Clinical Practice Guidelines
for the Assessment and Management of
Substance Use Disorders

The problem of psychoactive substance use disorders (SUDs) has reached epidemic proportions and it is a major public health concern in India. Clinical assessment and management of SUDs are obviously important, but there is a wide variability in clinical practice and deviance from evidence base. The members of the IPS Specialty Section on Substance Use Disorders felt that it would be a worthwhile venture to develop an updated set of Clinical Practice guidelines (CPGs) for assessment and management of SUDs. The present volume is the result of such endeavour.

The following areas are covered by these CPGs: **assessment** of SUDs in general, **alcohol** use disorders, **opioid** use disorders, **cannabis** use disorders, **sedative-hypnotic** use disorders, **tobacco** use disorders, **inhalant** use disorders, and **dual diagnosis**.

The development, refinement and finalization of these CPGs was the result of an arduous, long-drawn and rigorous process following a pre-defined iterative strategy involving progressively widening circles of peer review. The current Guidelines follow the Appraisal of Guidelines for Research and Evaluation II **(AGREE-II)** instrument.

Each chapter begins with a clinically useful "**Executive Summary**" that summarizes the key recommendations and issues. Individual "**Key Recommendations**" are mentioned at the end of each major subsection of the chapters.

The **primary target audience** for these CPGs is the practicing clinicians (especially psychiatrists but also non-psychiatric medical doctors and even non-medical professionals working in the area of SUDs). They should benefit from the Executive Summary and Key Recommendations to be applied in their clinical practice. The **secondary, but very important, audiences** include medical teachers, postgraduate students, and researchers. These CPGs provide a comprehensive compendium of updated knowledge that can be a rich resource for academic purposes of teaching, learning, and research. Finally, these might be of benefit to medical institutes and to policy makers to inform healthcare related decisions in the area of SUDs (e.g., the decision to fund and implement opioid substitution treatment programmes in an institute or in a state or even national basis).

CPGs are meant to **inform, assist and "guide"** the clinician, ***not*** ask them to sacrifice their autonomy of clinical judgment, nor to be oblivious of the individual patient's clinical situation and psychosocial context. With this caveat, if used for the correct purpose and in the correct manner, we hope that these CPGs should prove useful to both their primary as well as secondary readerships.

- Debasish Basu, P.K. Dalal (Editors)

Indian Psychiatric Society
Website : http://www.ips-online.org

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Editors
Debasish Basu, P.K. Dalal

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Clinical Practice Guidelines
for the Assessment and Management of
Substance Use Disorders

EDITORS
DEBASISH BASU
P. K. DALAL

Indian Psychiatric Society
Speciality Section on Substance Use Disorders

CLINICAL PRACTICE GUIDELINES FOR THE ASSESSMENT AND MANAGEMENT OF SUBSTANCE USE DISORDERS

Indian Psychiatric Society
Speciality Section on Substance Use Disorders
2014

Editors:

Debasish Basu
P.K. Dalal

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CLINICAL PRACTICE GUIDELINES FOR THE ASSESSMENT AND MANAGEMENT OF SUBSTANCE USE DISORDERS

INDIAN PSYCHIATRIC SOCIETY
SPECIALTY SECTION ON SUBSTANCE USE DISORDERS
2014

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CONTENTS

PREFACE

It gives me great pleasure to write the Preface of the book "Clinical Practice Guidelines for the Assessment and Management of Substance Use Disorders", published by the Indian Psychiatric Society.

Psychoactive substance use disorders take a heavy toll on the individuals, their families and the society at large. The situation has become very grim in India, with millions of people afflicted with these disorders. Along with the traditional substances like alcohol, opium and its derivatives, cannabis and tobacco, relatively newer substances like prescription drugs, injectable drugs, inhalants and others have made their entry in India and now pose a real threat. Management of these disorders, therefore, is an essential skill needed by all physicians and health professionals. Psychiatrists have to take leadership roles in this area. Substance use disorders are psychiatric disorders, and their management often requires a judicious combination of the right kind of knowledge, skills and attitude. Both pharmacological and non-pharmacological management, preceded by a comprehensive biopsychosocial assessment, are needed for this purpose.

Herein lies the problem, because the clinical management of substance use disorders is far from uniform and consistent. Clinical practice varies widely from country to country, region to region, sector to sector, and even centre to centre. The evidence for various methods and modalities for management is large, changing, and at times inconsistent. In the face of such heterogeneity, it becomes difficult for the practicing clinician to choose the right approach of management.

Clinical practice guidelines (CPGs) can be of substantial help in this situation. These are systematic statements, derived in a scientific manner, purported to assist and guide the clinicians in their decision making regarding management of specific clinical conditions. The previous CPGs developed by the IPS Task Force on substance use disorders were published in 2006. Things have changed since then, both in terms of prevalent patterns of use of substances and in terms of progress and clarifications made in their management. Thus it was imperative to update.

In this regard, the IPS Specialty Section on Substance Use Disorders has done a commendable job of producing an entirely new set of comprehensive

CPGs on various aspects of substance use disorders. The set of eight CPGs (assessment, alcohol, opioids, cannabis, sedative-hypnotics, tobacco, inhalants and dual diagnosis) is a rich and updated source of knowledge and skills. The authors have painstakingly collected the evidence, organized and rated them, and combining the evidence with the local situation and context, come up with their recommendations. The CPGs have been developed with a pre-planned scientific manner, on par with international standards.

This book should serve several purposes for several target users. The busy clinicians will find the Executive Summary and Key Recommendations useful for guiding their practice. The medical teachers and postgraduate students will find the literature review a goldmine of knowledge. The policy makers and administrators will find the Key Recommendations helpful in prioritizing their policies and funding resources. Finally, the researchers and academicians will find this book a reservoir of ideas (especially where areas of uncertainties remain) for future research and academic work.

I congratulate the IPS Specialty Section on Substance Use Disorders on this important and mammoth task well accomplished. I also thank the Publication Committee of IPS for publishing this voluminous book with great care. It was my dream to start a series of "IPS Publications", which should be a rich resource to clinicians, teachers, students, academicians, researchers, administrators and policy makers. I am very happy to see my dream come true with this important publication today!

Professor Dr. Indira Sharma

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FOREWORD

My hearty congratulations to Dr. M.S.Reddy, Chairperson, and Dr. Lalit Batra, Convenor of IPS Publication Committee for bringing out a book on "Clinical Practice Guidelines for Substance Use Disorders"

I am sure that this book would serve its prime purpose of identifying patients with substance use disorders and improve outcomes of various treatment procedures. I know that this book would be revered as a reference book in mental health care settings.

Fiat Lux

With wishes,

Dr. T.V.Asokan
President Elect,
Indian Psychiatric Society

SECRETARY'S MESSAGE

I am happy to learn IPS publication committee is publishing the clinical practice guideline of Substance used Disorder. The IPS Task Force on Substance Use Disorder under the leadership of Prof. PK Dalal and Prof. Debasish Basu who have done a tremendous job on this matter.

I hope this publication will help to benefit of our members for dealing drug abuse cases in future.

I also thank prof. Roy Abraham Kalliyavalil, Immediate Past President of our society who gave the continuous support and encouragement to the IPS task Force in last year to develop the practice guideline. I also thank to Prof. Indira Sharma, President, Indian Psychiatric Society for her interest to publish this guideline in time.

With wishes,

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CLINICAL PRACTICE GUIDELINES FOR THE ASSESSMENT AND MANAGEMENT OF SUBSTANCE USE DISORDERS

Indian Psychiatric Society
Speciality Section on Substance Use Disorders
2014

CLINICAL PRACTICE GUIDELINES FOR THE ASSESSMENT AND MANAGEMENT OF SUBSTANCE USE DISORDERS : OVERVIEW OF IPS GUIDELINES 2014

Debasish Basu
P.K. Dalal

On behalf of IPS-SS-SUD

2014

The problem of psychoactive substance use disorders (SUDs) has reached epidemic proportions and it is a major public health concern in India. Substance abuse is associated with problems of physical and mental ill health, accidents and crimes, impaired quality of life, productivity loss, economic waste, etc. These problems lead to tremendous burden on the individual, family, society and the nation.

Clinical assessment and management of SUDs are obviously important, but there is a wide variability in practice. There is often a lacuna between evidence base and actual practice. Thus, it is imperative to develop updated and evidence-based clinical practice guidelines (CPGs) in this area. The Indian Psychiatric Society (IPS) constituted a Task Force on CPGs in 2004. The Task Force produced a series of CPGs between 2005 and 2008, covering all the major groups of psychiatric disorders, published in four volumes, including one volume containing SUDs, which was published in 2006.[1] These are available as books as well as downloadable PDFs from the Indian Journal of Psychiatry website.

The guidelines for management of SUDs, however, require periodic updating based on new evidence and practice trends. It is more than seven years that the previous CPGs were published. Thus, the members of the present IPS Specialty Section on Substance Use Disorders (IPS-SS-SUD) felt that it would be a worthwhile venture to develop a fresh series of CPGs on assessment and management of SUDs. The present volume is the result of such venture and endeavour.

The Process of Development of these CPGs

The following were the areas decided for development of CPGs: assessment of SUDs in general, alcohol use disorders, opioid use disorders, cannabis use disorders, sedative-hypnotic use disorders, tobacco use disorders, inhalant use disorders, and dual diagnosis management.

Although all the members of the IPS-SS-SUD were variably involved in the process of development and/or refinement of the each of the CPGs, one senior author (a Faculty Member of a teaching medical institute with special interest and expertise in SUDs) was designated as the "Lead Author" for each of these CPGs. They co-opted another contributor, not below the rank of a Senior Resident in psychiatry and working in the area of SUDs, as the

second author. These two authors developed their respective CPG assigned to them.

In the process of development, we were guided by: (a) an extensive review of the relevant literature, including Indian data wherever available in published and retrievable form; (b) pre-existing recent guidelines in this area; (c) an awareness of the local needs and priorities whenever applicable (e.g., the need to focus on smokeless tobacco use in India); (d) need to balance the rigor and extensiveness of data coverage with the pragmatic considerations of condensing and filtering the data for practical use by clinicians; (e) need to rate the category of evidence and the strength of recommendations as per internationally accepted norms;[2] and (f) the Appraisal of Guidelines for Research and Evaluation II (AGREE-II) instrument.[3] These (strength of evidence and recommendations, and AGREE-II instrument, with degree of compliance displayed by most of these CPGs) are mentioned in the Appendix, and have been followed throughout all the CPGs. Much of these 'guidance on guidelines' was influenced by the published feedback obtained from a section of Indian psychiatrists on the previously published set of CPGs by IPS[4], and their comparison with other international guidelines.[5]

The process was initiated in September 2011, following the approval of the proposal by the Executive Council (EC) of IPS. After the first draft was prepared by the Lead Author and Co-Author, it was circulated to the Members of IPS-SS-SUD for critical review of format, content and application. The comments received from this "Core Group" peer review formed the basis of further revision of the draft document. After an iterative process of revisions, the next-level drafts were then sent to nine pre-identified senior experts in addiction psychiatry in India for "external peer review". Following their comments and further revision if needed, the pre-final drafts were then posted on the e-ips webgroup for viewing and comments by the entire e-ips web community. The final drafts of the CPGs were then sent to all IPS EC members for review, comments and approval. As the final step in this long-drawn process, the CPGs were approved by the EC of IPS in its Annual Meeting in 2013. Following this approval, the CPGs were edited and fine-tuned for consistency in pattern and formatting.

It can thus be appreciated that the development, refinement and finalization of these CPGs on SUD was the result of an arduous, long-drawn and rigorous

process following a pre-defined iterative strategy involving progressively widening circles of peer review.

The Organization of the Book Chapters and the CPGs

Following this overview chapter, the next chapter is on assessment of SUDs in general. It contains three assessment proformas as actually used in the three leading institutes of India, to serve as potential templates for others to follow or adapt suitably according to local needs. This is followed by six chapters on specific substances, arranged according to their order of appearance in the ICD-10 (alcohol, opioids, cannabis, sedative-hypnotics, tobacco and inhalants). CPGs on stimulants and hallucinogens have not been incorporated, nor on 'club drugs' or 'new psychoactive substances', because we had to prioritize the content according to the currently existing predominant patterns of substance use in India. However, the scenario of substance use is always a fluid one, and newer drugs, including cocaine and other stimulants, and the so-called 'club or rave' drugs, have made entry into select circles of substance users in India. A future revised edition of this book may therefore add new CPGs on these SUDs as well. The final chapter is on assessment and management of dual diagnosis disorders, which are combinations of SUDs with non-SUD psychiatric disorders.

Each chapter begins with a clinically useful "Executive Summary" that summarizes the key recommendations and issues. Individual "Key Recommendations" are mentioned at the end of each major subsection of the chapters, occasionally also marking areas of present uncertainty. These summary points and recommendations come with the grading of evidence and strength as mentioned in the Appendix of this chapter.

While not always possible or feasible, we have attempted to maintain a degree of uniformity and consistency in the structure and format across all the chapters. Each chapter is subdivided into several sections and subsections, which are numbered hierarchically in a numerical-point scheme (1, 1.1, 1.1.1, etc.) so that navigation along these subsections becomes easier and more meaningful for the reader. Scope and methodology including search strategies have been mentioned. Special attention has been paid to locate and highlight Indian studies and the applicability of the recommendations to the Indian situation. Certain special populations or situations have also been mentioned at the end of each chapter. Finally, along with pharmacological therapies, a conscious emphasis has been placed on non-

pharmacological (psychosocial, cognitive and behavioral) interventions as well, to the extent possible.

Potential Readership, Utility, Scope, and Limitations of these CPGs

These are Clinical Practice Guidelines; hence the primary target audience for these CPGs is the practicing clinicians (especially psychiatrists but also non-psychiatric medical doctors and even non-medical professionals working in the area of SUDs). They should benefit from the Executive Summary and Key Recommendations to be applied in their clinical practice. Whoever is further interested can look up the relevant literature cited in the text as and when needed.

The secondary, but very important, audiences include, among others, medical teachers, postgraduate students, and researchers. These CPGs provide a comprehensive compendium of updated knowledge that can be a rich resource for academic purposes of teaching, learning, and research. Finally, these might be of benefit to medical institutes and to policy makers to inform healthcare related decisions in the area of SUDs (e.g., the decision to fund and implement opioid substitution treatment programmes in an institute or in a state or even national basis).

Like any CPG, along with their potential utility as outlined above, their scope and limitations need to be kept in mind so as to avoid their misuse, and encourage their correct use. Ever since the Institute of Medicine in 1990 defined CPGs as "systematically developed statements to assist practitioner and patient in decisions about appropriate health care in specific clinical circumstances",[6] the benefits, lack of benefits, and potential harms have been hotly debated, and the debate continues till date.[7-11]

Without going into details of these 'pros and cons' debates, our humble submission to the readers and potential users of this book and its individual chapters is: please remember that CPGs are "guidelines", ***not*** mandates or obligatory standards required by law or by an institute, though mandates may later be derived from them as a policy matter. CPGs are meant to inform, assist and "guide" the clinician, not ask them to sacrifice their autonomy of clinical judgment, nor to be oblivious of the individual patient's clinical situation and psychosocial context. Neither do we claim that these CPGs cover everything under the sun related to SUDs. We had to necessarily prioritize the content and coverage of the areas, and, in this process, some sections might have been missed.

A final and most important issue in developing CPGs is ethical, i.e., potential conflicts of interests of the developers of CPGs, both financial and professional.[12-14] In this regard, our statement is as follows:

(a) The individual authors of these CPGs, as well as the entire IPS-SS-SUD members, are Faculty members or Senior Residents working in medical teaching institutes of eminence and repute, with no substantive ties of any nature with any pharmaceutical industry.

(b) The medicines and interventions mentioned for treatment of various SUDs are named in their generic form and not as any individual brand or proprietary names.

(c) All the authors have individually signed a declaration of "No Conflict of Interest" Form.

(d) The CPGs have undergone several rounds of internal and external peer reviews as detailed above.

(e) The CPGs are published by the Publication Committee of the IPS. The members of IPS-SS-SUD as well as the individual authors have no knowledge of the source of funding for the printing, publication or dissemination of this book. Similarly, the Publication Committee had no role in shaping or influencing the contents of these CPGs in any manner. In that sense, we have adopted a 'double-blind' approach to any financial aspects related to printing, publication and dissemination of these CPGs.

(f) It must be noted, however, that our group of CPG authors did not include any non-psychiatric professional expert in data review. Nor did we include any non-physician experts/patient representative/ community stakeholders. These may be considered as limitations in the current CPGs,[13,14] but we do not believe that these omissions are so serious as to invalidate or seriously hamper the summary recommendations of these CPGs.

With this statement of the scope, declarations and limitations as a 'disclaimer', we would like to end by reiterating that if used for the correct purpose and in the correct manner, we hope that these CPGs should prove useful to both their primary as well as secondary readerships.

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Appendices

Appendix 1. AGREE-II instrument, and compliance of CPGs developed by IPS-SS-SUD

AGREE II Item	**CPGs of IPS-SS-SUD 2014**
Overall objective(s) of the guideline	To develop evidence-based clinical assessment and management options for selected substance use disorders.
The population (patients, public, etc.) to whom the guideline is meant to apply	Patients with substance use disorders and dual diagnoses.
The target users of the guideline	The primary target users of these guidelines are practicing clinicians (especially psychiatrists but also non-psychiatric medical doctors and even non-medical professionals working in the area of SUDs). The secondary, but very important, target users include medical teachers, postgraduate students, researchers and policy makers at various levels.

Systematic methods used to search for evidence	Existing guidelines, systematic reviews, RCTs and other clinical trials, and various observational studies were identified from PubMed, EMBASE, Google Scholar and other database searches, from the Cochrane Database as well as from guidelines and identification by experts in the field.
The methods for formulating the recommendations	This guideline is based on the synthesis and interpretation of available evidence obtained from studies across the world, especially in light of the Indian context, rating them on strength of evidence and combining this strength with the perceived importance and relevance in the Indian context to finally arrive at specific key recommendations as well as identifying current areas of uncertainty where applicable.
The health benefits, side effects, and risks have been considered in formulating the recommendations	Yes
There is an explicit link between the recommendations and the supporting evidence	Yes
A procedure for updating the guideline is provided	No, not at this stage. However, these CPGs may be updated every 5-7 years, or specific added or modified recommendations may be made available online if major changes in evidence are witnessed in specific areas.

The recommendations are specific and unambiguous	Yes. However, these are not algorithmic or "cook-book recipe" recommendations to be followed blindly. Rather, major principles are recommended, which have to be applied along with clinical judgment in individual circumstances.
The different options for management of the condition or health issue are clearly presented.	Yes, to the extent possible.
Key recommendations are easily identifiable.	Yes
The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes, usually but not in very instance.
The guideline describes facilitators and barriers to its application.	This issue has not been specifically addressed in these CPGs.
The potential resource implications of applying the recommendations have been considered.	This issue has not been specifically addressed in these CPGs.
Competing interests of guideline development group members have been recorded and addressed.	All authors declared "No conflicts of interest."

Appendix 2. Categories of Evidence and Strength of Recommendations (followed throughout these CPGs).[2]

Categories of evidence

Ia: evidence from meta-analysis of randomised controlled trials

Ib: evidence from at least one randomised controlled trial

IIa: evidence from at least one controlled study without randomisation

IIb: evidence from at least one other type of quasi-experimental study

III: evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies

IV: evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Strength of recommendations

A: directly based on category I evidence

B: directly based on category II evidence or extrapolated recommendation from category I evidence

C: directly based on category III evidence or extrapolated recommendation from category I or II evidence

D: directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

S: Standard of care

CLINICAL PRACTICE GUIDELINES (CPG) FOR THE CLINICAL ASSESSMENT OF SUBSTANCE USE DISORDERS

Debasish Basu
Kavita Nagpal

On behalf of IPS-SS-SUD

2014

ABBREVATIONS USED

AGREE - Appraisal of Guidelines for Research & Evaluation
AUDIT - Alcohol Use Disorders Identification Test
MAST - Michigan Alcoholism Screening Test
SADQ - Severity of Alcohol Dependence Questionnaire
SADD - Short Alcohol Dependence Data Questionnaire
ADS - Alcohol Dependence Scale
ASI - Addiction Severity Index
CDP - Comprehensive Drinker Profile
RTQ - Revised Fagerström Tolerance Questionnaire
FTND - Fagerström Test for Nicotine Dependence
DAST - Drug Abuse Screening Test
OSI - Opiate Treatment Index
SODQ - Severity of Opiate Dependence Scale
BDEPQ - Benzodiazepine Dependence Questionnaire
LDQ - Leeds Dependence Questionnaire
SDS - Severity of Dependence Scale
SDSS - Substance Dependence Severity Scale

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EXECUTIVE SUMMARY

1. Introduction – Substance use and related disorders are highly prevalent worldwide and are a cause for significant morbidity and mortality. Despite this it continues to be under diagnosed by health care practitioners. Assessment of these disorders is thus essential for screening at risk population, for diagnosis and to assess severity, associated comorbidities, social support and resources available for comprehensive management of the patient.

2. Methodology - Clinical practice guidelines for assessment of substance use disorders aims to target all practising psychiatrists and other mental health professionals. *Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument II* has been used as a template for formulation of these guidelines to the extent possible. Overall there is scarcity of data regarding assessment of substance use disorders. Current guidelines are largely based on American Psychiatric Association (APA) guidelines and the assessment forms used in three Indian reputed institutes, i.e., NDDTC, AIIMS, Delhi; DDTC, PGIMER, Chandigarh; and CAM, NIMHANS, Bangalore.

3. Assessments – Clinical assessment remains the mainstay. Laboratory tests and structured and unstructured instruments should be used to complement clinical assessment for comprehensive patient care**.**

3.1 Clinical assessment – It is the most important assessment for patients with substance use and related disorders. Detailed exploration regarding substance use should include initiating and maintaining factors, quantity and pattern of use, impact of substance use on various spheres of patient's life, previous attempts of successful and unsuccessful abstinence, details of past interventions, comorbid medical and psychiatric illnesses, motivation to quit substance and insight into illness. Along with these, relevant aspects of past, personal and family history should be explored and noted. In addition to detailed history, complete physical and mental status examination is warranted for correct diagnosis and comprehensive management of the patient.

A direct, empathetic and non judgmental attitude of healthcare provider will facilitate the process of clinical assessment.

3.2 Laboratory assessment – In general laboratory tests alone cannot diagnose dependence. Most of the commonly used laboratory parameters in case of substance use are non specific and at best can only assist clinical assessment in diagnosis. Laboratory parameters can reflect the effects of continued substance on patient's body. During assessment of alcohol use the laboratory parameters commonly assessed are blood alcohol concentration, mean corpuscular volume, liver function tests including alanine and aspartate amino transferase, gamma glutamyl transferase and carbohydrate deficient transferrin (CDT) levels. Although not routinely done, expired air carbon monoxide and blood levels of nicotine and cotinine and salivary levels of cotinine are tests for nicotine use. Drug analysis in urine can reflect the presence of other drugs like cannabis and opioids.

3.3 Instrument based assessment - Instrument based assessments have the advantage of being non invasive and non expensive. However such information in these questionnaires can be easily feigned and depends on coherent thought process, intact insight and overall mental status. Hence these instruments should be used only as an adjunct to clinical assessment. Various instruments are available which can be used for screening as well as to assess severity of dependence.

4. Special group – Children and adolescents: Substance use should be included in the differential diagnosis of any adolescent presenting with behavioural, educational and psychosocial problems. Alcohol and cannabis are two commonly used substances in adolescents. While assessing adolescents for substance use, features suggestive of psychological dependence should be given more emphasis as opposed to physiological dependence which is equally important in adults. Rapport building with general open ended questions with gradual progression towards more specific questions regarding substance use is the key to obtain detailed history.

1. INTRODUCTION

1.1 NEED FOR ASSESSMENT

Substance use and related disorders are highly prevalent worldwide. Studies report that despite estimated lifetime prevalence of 10.3%, substance abuse and dependence are routinely under-diagnosed by health care providers [1]. It has been found that prevalence of substance use is greater among people with mental illness as compared to general population [2]. Substance use and related disorders are widespread in Indian population as well. A meta-analysis of studies revealed an overall substance use prevalence of 6.9/1000 for India with urban and rural rates of 5.8 and 7.3/1000 population respectively [3].Substance use and related disorders have been linked to various health, occupational, psychological and social problems [4] and significantly increase morbidity and mortality [5]. Early diagnosis and intervention is thus of paramount importance.

1.2 PURPOSE OF ASSESSMENT

Assessment of substance use and related disorders needs to done because of following reasons:

(a) In view of high morbidity and mortality associated with substance use disorders it is pertinent to screen people for substance use disorders and intervene early. All patients undergoing psychiatric evaluation should be screened for substance use. Individuals attending other hospital services should also be enquired about substance use especially those who are at high risk either due to high genetic loading, occupational or environmental factors and/or personality attributes.

(b) For diagnosing substance use disorders.

(c) To assess severity of substance use disorders.

(c) To assess associated physical and psychiatric comorbidity.

(d) To assess motivation, support and resources available so that necessary pharmacological and psychosocial interventions can be planned.

(e) To assess patient's clinical state and functioning during follow up.

1.3 COMMONLY USED SUBSTANCES, AND DIAGNOSTIC CRITERIA

ICD-10 encompasses 10 different classes of drugs in substance related disorders. These include alcohol, opioids, cannabinoids, sedative-hypnotics,

cocaine, other stimulants including caffeine, hallucinogens, tobacco, volatile substances, and other psychoactive substance [6]. DSM-5 includes similar drugs except that these drugs have been categorized differently, e.g., cocaine has been subsumed under the category of stimulants and caffeine has been provided with a separate category[7]. ICD-10 diagnostic criteria for harmful use and dependence and DSM-5 criteria for substance use disorder respectively are mentioned below.

1.3.1 ICD-10 describes harmful use and dependence as follows:

Harmful use - Defined as a pattern of psychoactive substance use that is causing damage to health. The damage may be physical or mental. The diagnosis requires that actual damage should have been caused to the mental or physical health of the user.

Dependence - A cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value.

A definite diagnosis of dependence should usually be made only if three or more of the following have been present together at some time during the previous year:

1. A strong desire or sense of compulsion to take the substance.
2. Difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use.
3. A physiological withdrawal state when substance use has ceased or been reduced, as evidenced by the characteristic withdrawal syndrome for the substance or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms.
4. Evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses.
5. Progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects.
6. Persisting with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking,

depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm [6].

DSM-IV had mentioned the criteria for dependence and abuse. However, DSM-5 has abolished the category of "abuse" and combined abuse and dependence into one single category called "Substance Use Disorder".[7]

1.3.2 DSM-5 criteria for "Substance Use Disorder" are as follows:

A problematic pattern of substance use leading to significant impairment or distress as manifested by at least two of the followings, occurring within a 12 month period:

1. Substance is often taken in larger amounts or over a longer period of time than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
3. A great deal of time is spent in activities necessary to obtain substance, use substance or recover from its effects.
4. Craving, or a strong desire or urge to use substance.
5. Recurrent substance use resulting in failure to fulfill major role obligations at work, school or home.
6. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by effects of substance.
7. Important social, occupational or recreational activities are given up or reduced because of substance use.
8. Recurrent substance use in situations which are physically hazardous.
9. Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by substance.
10. Tolerance, as defined by either of the following:
    (a) A need of markedly increased amounts of substance to achieve intoxication or desired effects.

(b) A markedly diminished effect with continued use of the same amount of substance.

11. Withdrawal, as manifested by either of following:

(a) The characteristic withdrawal syndrome of substance.

(b) Same substance or closely related substance is taken to relieve or avoid withdrawal symptoms.

Substance use disorder is further specified as mild, moderate or severe depending on the number of criteria met [7].

2. SCOPE AND METHODOLOGY

Clinical practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances. Target users of our guidelines are all practicing psychiatrists and mental health professionals. To maintain a high standard and quality for these guidelines we have used the *Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument II* as a template for this exercise as far as possible [8]. It must be understood, however, that no external "evidence" is possible to generate in order to formulate these guidelines for clinical assessment. Rather, the guidelines and recommendations are based on clinical expertise and experience, precedence from existing guidelines and assessment forms available, and good medical practice (**i.e., most of the recommendations in this CPG are of "S" category – Standard of Care).**

Detailed searches were run on the search engines including PubMed, Google and Google Scholar using several combinations of the words "Assessment", "Evaluation", "Screening", "Monitoring", "Patient Workup", "Format", "Interview", "Structured", "Clinical", "Laboratory", "Biochemical", "Scales", "Instruments", "Substance", "Addiction", "Dependence", "Abuse", and individual substances. In addition, we obtained (with permission from the respective Heads of Departments) soft copies of the detailed clinical assessment proformas used for patients with substance use disorders in National Drug Dependence Treatment Centre (NDDTC), All India Institute of Medical Sciences (AIIMS), New Delhi; Centre for Addiction Medicine (CAM), Department of Psychiatry, National Institute of Mental Health & Neuro Sciences (NIMHANS), Bangalore; and Drug De-addiction & Treatment Centre (DDTC), Department of Psychiatry,

Postgraduate Institute of Medical Education & Research (PGIMER), Chandigarh, and examined them critically for content and form. Existing Guidelines were also examined in details. The recommendations are based on a combination of all these sources.

3. TYPES OF ASSESSMENT

Detailed assessment is of paramount importance for patient with substance dependence. Although various other parameters like laboratory tests and various structured and unstructured scales are available for assessment, clinical assessment remains the mainstay. Laboratory tests and assessment instruments can be used to complement clinical assessment for better patient care.

3.1 CLINICAL ASSESSMENT

Comprehensive clinical assessment mandates detailed history with complete physical examination and mental status examination. History is the most important first step in evaluation of substance use related disorder. It should be obtained from multiple informants including specifically patient and his/her caregivers which may be family members, friends, neighbours, etc. A general guideline of history taking, physical examination and mental status examination is as follows.

3.1.1 Detailed history

Detailed history is the first step in clinical assessment of patients with substance dependence and should include following:

- Socio demographic details – Includes name, age, gender, marital status, education, occupation, religion, type of family, socioeconomic status and residence.
- Details of informants – Name, relationship to patient and other demographic details. Reliability and adequacy of information gathered should be assessed.
- Chief complaints with duration according to each informant should be enlisted in chronological order. Generally a total of 2 - 6 main complaints are chosen among the list as chief complaints and they should include information regarding substance intake and its pertinent psychiatric consequences. Occasionally there may be discrepancy between complaints enumerated by patient and caregiver which can provide important insight into patient's motivation to remain abstinent from

substance and insight among other things and should be explored further during detailed exploration.

- Onset of symptoms (abrupt, acute, sub-acute or insidious), precipitating factor and course of illness (continuous, fluctuating or episodic) should be assessed.
- A systematic inquiry into current and past substance use should be made. This includes age at first use, circumstances around onset of drug use, effect of drug perceived at the time of first use and subsequently, preparation used, quantity and frequency of use. Special emphasis on route of drug administration should be placed in case injectable mode is suspected when inquiry regarding injecting practices and possibility of using shared needles should be explored in detail. Enquiry should be made regarding usual setting of substance use (where, with whom, how much) and the course of substance use, fluctuations in the pattern of use, reason for fluctuations and association with life events. Ascertain whether patient has developed craving, tolerance, loss of control and/or withdrawal symptoms and if so then at what age and whether patient fulfills criteria for dependence as per ICD 10 and/or DSM 5. Pattern and quantity of drug used in preceding few days, severity of associated withdrawal symptoms and time elapsed since last dose have important treatment implications. In case of polydrug abuse history needs to be explored in detail for each drug and possibility of combining drugs should be assessed. Ascertain use of over-the-counter medications and prescription medications use in patient.
- If there were any past attempts of abstinence then additional history regarding duration of abstinence, reasons for abstinence, factors promoting or favouring abstinence, details of pharmacological or psychosocial treatment during this period if any, level of socio occupational functioning achieved, circumstances leading to lapse and then further relapse, individual reaction towards past abstinence attempts should be explored. Current motivation for quitting substance should be assessed as per accordance with Prochaska and Diclemente stages of pre-contemplation, contemplation, preparation, action and maintenance/relapse [9].
- Screen for comorbid physical illnesses, e.g., gastritis, jaundice, peripheral neuropathy, hepatitis, history of self harm behaviour and infections (e.g., thrombophlebitis, oropharyngeal infections, fungal

infections, tuberculosis, sexually transmitted infections like HIV, etc) which is commonly found in patients with substance dependence.

- Assess for marital, social, financial, legal and occupational consequences secondary to substance abuse.
- Detailed evaluation for presence of any other psychiatric diagnosis which may be independent or related to substance use should be done.
- Past history of treatment both pharmacological and psychosocial interventions including setting, contexts (voluntary or involuntary), duration of treatment, adherence to treatment, doses used in case of pharmacological interventions, response separately with each intervention in terms of both abstinence from substance or reduction in drinking days and changes in socio occupational functioning during treatment.
- Past history of any psychiatric, general medical or neurological illness should be assessed.
- Family history should include three generation pedigree, socio demographic details about caregivers and significant others, family history of any psychiatric illness, substance abuse vs. dependence and any major general medical and neurological illness, family size, living condition, general home environment, interpersonal relationship, attitude towards substance use, major life events.
- History of high risk behavior, e.g., unprotected sexual exposure, multiple sexual partners, gambling etc. should be given due emphasis in patients with substance use. Other important details in personal history include early birth and development history, educational and occupational history, sexual and marital history and social support.
- Externalizing traits (e.g., impulsivity, inattention, hyperactivity, conduct symptoms and oppositional defiant symptoms) and internalizing traits (e.g., anxious avoidant, social anxiety) act as contributing or susceptibility factors in initiation and/or maintenance of substance use and should be explored. Antisocial personality traits should be enquired.

3.1.2 Physical Examination

Detailed general physical and systemic examination should be done in all cases. Some non specific features may be present in early stage of substance use disorders in the form of injury sustained under influence of substance

use, alcohol smell in breath, signs of intoxication such as gait abnormalities, slurred speech, sedation, dilated or constricted pupils, and excoriated skin (due to scratching), track marks, and skin abscesses. Over time specific features including substance withdrawal symptoms appear which aid in the diagnosis. These are

- Signs of alcohol withdrawal include anxiety, tremors, nausea, vomiting, agitation, paroxysmal sweats, tactile disturbances, visual disturbances, auditory disturbances, clouding of consciousness, headache [10].
- Features of opioid withdrawal includes muscle aches, lacrimation, sweating, rhinorrhoea, nausea, vomiting, diarrhea, increased blood pressure, tachycardia, yawning, insomnia or anxiety, restlessness or irritability, piloerection, increased sensitivity to pain and craving for opioids.

  Some physical features ensue after persistent use of substance over a significant period of time. Early recognition and management is mandatory for comprehensive care of patients with substance dependence. These are as follows:

- Malnutrition including cachexia, but also obesity.
- Systemic infections including cellulites, sexually transmitted disease (e.g., HIV, hepatitis B and C), tuberculosis, bacterial endocarditis.
- The myriad systemic effects of excessive alcohol use includes delirium, seizures, signs of liver enlargement or failure, ascites, anemia, thrombocytopenia, bleeding, myopathy, cardiomyopathy, nystagmus, lateral nerve palsy, peripheral neuritis and dermatitis.
- Thrombosed veins and track marks due to repeated injectable drug use and chronic sinus/nasal problems. Worsening of bronchitis can occur due to marijuana or cocaine smoking.
- In pregnant woman abruptio placenta, premature birth, low gestational size and neonatal withdrawal syndrome can occur.

3.1.3 Mental status examination

General scheme of mental status examination is as follows:

- General appearance and behaviour – Level of consciousness and orientation can provide valuable clue regarding degree of substance withdrawal and intoxication. General demeanour of patient, degree of

eye-to-eye contact and rapport to be assessed. Abnormal movements, e.g., tremors, can be a useful tool to assess substance withdrawal.

- Psychomotor activity – Can be affected in substance related delirium (e.g., hypoactive or hyperactive) or substance related mood disorder etc.
- Speech – Spontaneity, tone, tempo and volume of speech, relevance, coherence, reaction time and prosody to be noted.
- Thought – In form and stream of thought assess for circumstantiality, tangentiality, thought block, incoherence, verbigeration, word salad, neologism and perseveration. Referential/persecutory ideations and delusions, hypochondriacal beliefs, depressive cognitions, death wishes and suicidal ideation, expansive/grandiose ideation and delusions are evaluated in content of thought. Possession of thought includes thought alienation, obsession and compulsions.
- Mood - Both subjective and objective components, with range, reactivity, congruence to thought process and appropriateness to environment to be assessed along with mood lability.
- Perception – Includes sensory distortions and deceptions. Both of these phenomena can occur under influence of drugs. Sensory distortions commonly occur under substance intoxication and sensory deceptions like illusions and hallucinations can occur under both substance intoxication and withdrawal.
- Assessment of detailed cognitive functions is of paramount importance, especially when substance related cognitive impairment is suspected during intoxication, Korsakoff amnesic state or substance induced dementia etc. Domains to be assessed include orientation, attention and concentration, memory, intelligence, abstraction and judgment. Comprehensive evaluation of cognitive function is mandatory not only for accurate diagnosis but it also has treatment implications and may determine prognosis.
- Insight – It has important treatment implications. Patient understanding of substance dependence and other associated substance induced or independent psychiatric disorder if any, to be assessed separately. Reasons for seeking treatment and goals envisaged.

- Motivation – As per Prochaska and Diclemete's classification the stages of motivation are pre-contemplation, contemplation, preparation, action and maintenance/relapse [9]. Patient's motivation can also be assessed in terms of poor, superficial and good/fair. Poor motivation is failure to perceive any problem at all regarding amount, frequency or pattern of substance consumption or its control and/or denying any substance-related functional impairment and/or refusing professional help. In superficial motivation patient admits that there are substance problem but ascribes it to external or rationalizing internal problem rather than trying to understand it as an internal process of dependence and/or minimizes substance-related complications and/or acknowledges need for treatment but often for some physical or mental complications of substance dependence rather than for the dependence itself. Fair/good is defined as having an insight about the basic nature of the problem's a 'dependence' or 'addiction' and/or appreciating the extent and severity of substance-related complications and ability to link them with substance as the causative factor, and/or feeling the need of treatment not just for the complications but basically for the dependence itself. Although patient's motivation varies with time, stage of motivation in which patient is currently in has immense treatment implications. For example, a patient who is in precontemplation /contemplation or poor/ superficial phase of motivation is less likely to continue prescribed medications and would benefit from motivation enhancement therapy rather than from relapse prevention counseling. Apart from psychosocial intervention patient's stage of motivation can also influence choice of long term medications for promoting abstinence from substance; for example, deterrents like disulfiram when used in combination with psychosocial interventions in motivated patients can be quite good at promoting and maintaining abstinence but may not be an appropriate choice in patients with poor motivation.

3.1.4 Skills and attitude

Substance use and related disorders are associated with huge societal stigma. People with substance use experience stigma not only from general public but also during their encounters with health care providers including many psychiatrists as well. Negative attitudes of health care providers arising out of early experiences can significantly affect therapeutic alliance. Due to these reasons such patients may be ashamed, in denial, ambivalent and

resistant to change. Substance use disorders are akin to chronic medical illnesses like diabetes and hypertension and long lasting relapsing and remitting course is often a rule rather than exception. Having a medical model for substance use disorders is likely to change medical practitioner's attitude towards such patients. A direct, empathic, non judgmental and compassionate attitude is likely to keep patient in treatment loop and improve overall treatment outcome.

KEY RECOMMENDATIONS

- Clinical assessment is the mainstay for the diagnosis and further management of patients with substance use and related disorders.
- Detailed history, thorough physical examination and complete mental status examination is required for comprehensive assessment of patients with substance use disorders.
- Assessment should be individualized and pertinent areas specific to each particular patient should be evaluated in detail.
- A direct, empathic, non judgmental and compassionate attitude is the key to keep patient in treatment loop and improve overall treatment outcome.

Our guidelines are based on American Psychiatric Association guidelines[11] and guidelines for assessment for substance use and related disorders used in AIIMS [12], PGI [13] and NIMHANS [4]. Assessment forms of three leading Indian institutes, i.e., AIIMS, PGI and NIMHANS have been added in the **APPENDIX** as examples of detailed assessment. Although these forms can be a useful guide for clinical evaluation of patients with substance use and related disorders, it is recommended that every institute should try to develop their own assessment forms based on their needs, resources and prioritization.

3.2 LABORATORY ASSESSMENT

Although assessment of laboratory parameters is not mandatory for diagnosing patients with substance use and related disorders, they can complement clinical assessment in diagnosis and to assess effects of substance on patient's body. Common laboratory tests of some of abused drugs are mentioned below.

3.2.1 Blood alcohol concentration

It is an easy, non invasive method for quantifying alcohol concentration in blood which measured in milligrams per 100ml of blood. It is analysed using breathalyser and is a measure of alcohol concentration in end expiratory air. It provides good insight into acute body burden of alcohol [14] but is insensitive to differentiate between acute or chronic consumption of alcohol, binge drinking or long term alcohol abuse [15]. Hence it is useful to diagnose intoxication but may not be useful to diagnose dependence.

3.2.2 Liver function test

Although liver is particularly susceptible to effects of alcohol, deranged liver function tests are neither specific nor sensitive to alcohol abuse [16]. Most of parameters measured routinely in liver function tests indicate liver damage that may or may not be due to alcohol use. Nevertheless liver function test forms an important part of assessment in patients with alcohol related problems as it is commonly affected during heavy drinking and is a pertinent factor determining treatment options. Other indicators of liver damage secondary to alcohol include gamma glutamyl transferase and carbohydrate deficient transferrin. Enzyme gamma glutamyl transferase is a non specific indicator of liver damage as it is also found in blood and brain. It is elevated in about 60-80 % of patients with alcohol abuse [17]. Its level in blood rises before elevation in liver enzymes. It has a half life of 14-26 days [18]. Carbohydrate deficient transferrin (CDT) levels are related specifically to amount of alcohol consumed and alcohol metabolism. Its levels return to normal after a period of abstinence. CDT has half life of about 15 days [18]. Combination of CDT with enzyme gamma glutamyl transferase may further increase sensitivity without reducing specificity [19].

3.2.3 Mean Corpuscular Volume (MCV) – It is one of the indirect biomarkers of alcohol use like liver function test and detects the effects of alcohol on organ system or body biochemistry. It also increases in variety of other reasons apart from alcohol and it takes 2 to 4 months to normalize.[20]

3.2.4 Carbon monoxide (CO)

Expired air carbon monoxide monitoring is the most convenient and economical measure of nicotine intake. With a relative short half life of 4-5 hours, for the most accurate readings its levels are best measured during end of the day. At a cutoff point of 8ppm its sensitivity to correctly identify

people with active tobacco use is around 66 to 97%. Its levels positively correlate with number of self reported cigarettes per day [21].

3.2.5 Nicotine and Cotinine

Nicotine and cotinine (metabolic byproduct of nicotine) can be measured in blood, urine and saliva. Due to variable metabolism in different people, for accurate reflection of nicotine levels both nicotine blood levels and elimination rate should be measured. Nicotine levels are measured in plasma about 6-7 hours after smoking when it tends to plateau. With longer half life of 6-16 hours as compared to nicotine, cotinine is generally a preferred measure of nicotine exposure. Salivary cotinine is the most accurate index of nicotine but is expensive and involves complicated laboratory assessment. Its value correlates with number of cigarette smoked per day [22].

3.2.6 Urine analysis

It detects the presence or absence of drugs and its specific metabolites; however, it may not indicate dosage or time of drug administration or extent of any drug effect on the body [23] . Semi quantitative urine analysis may be done in which concentration of substance in urine can be monitored over time. Various factors influence urine drug analysis including dose of drug consumed, frequency of use and rate of metabolism.

KEY RECOMMENDATIONS

- Laboratory assessment measures are not mandatory for diagnosing patients with substance use and related disorders.
- However, some of these assessments are necessary for evaluation of physical consequences of substance use or for detecting presence of substances in body fluids.
- Some laboratory measures used are non specific and can be deranged in variety of other disorders.
- Most of the commonly used laboratory tests at best reflect acute burden of substance use on body.
- Laboratory tests should be used as an adjunct to clinical assessment for comprehensive management of patients.

3.3 INSTRUMENT-BASED ASSESSMENT

Instrument based assessments have the advantage of being non invasive and non expensive. Some of these instruments can be relatively rapidly

applied and are self reporting questionnaires or require minimal or no special training for administration. However such information in these questionnaires can be easily feigned and depends on coherent thought process, intact insight and overall mental status [24]. Various assessment questionnaires for alcohol, nicotine and other drugs are mentioned below.

3.3.1 Assessment of alcohol use

Table 2 lists instruments used for screening of alcohol use and Table 3 mentions instruments used for assessment of severity of alcohol dependence.

Table 2. Screening instruments (full form of abbreviations mentioned earlier)

S.No	Instrument	Brief description	Time needed	Specific Training needed	Sensitivity	Specificity
1	AUDIT	Comprehensive 10-item brief screening instrument. Provides information on alcohol hazardous, harmful use, abuse and dependence.Cross culturally valid [25].	2-5 min	No	61	90
2	MAST	24-item screening instrument designed to identify and access alcohol abuse and dependence [26] Shortened 13 item and 10 item versions are available [27][28]. Does not discriminate between past and present drinking.	10 min	No	91	76
3	CAGE	4-item screening instrument designed to identify and assess potential alcohol abuse and dependence. Particularly useful in geriatric population and can be easily used in primary health settings [29].	<1 min	No	84	95

		Screening instrument which was developed specifically to identify at risk drinking in pregnant women [30].				
4	TWEAK	Was developed to identify at risk drinking in pregnant women [31]. Later was noted to be a sensitive instrument to identify alcohol problems in general population also [32].		No	79	83

Table 3. Instruments to assess severity (full form of abbreviations mentioned earlier)

S.No	Instrument	Brief description	Time needed	Specific Training needed	Sensitivity	Specificity
1	SADQ-C	20-item scale designed to measure severity of alcohol dependence. Has five subscales – physical withdrawal symptoms, affective withdrawal symptoms, craving and withdrawal relief drinking, consumption and reinstatement [33].	5 - 10 min	No		
2	SADD	15-item self report questionnaire which is used to measure the severity of alcohol dependence. Focuses on behavioural and subjective aspects of alcohol dependence than on withdrawal symptoms of dependence [34].	< 5min	Self report quest-ionnaire		
3	ADS	25-item self-report questionnaire designed to		No		

		measure severity of alcohol dependence [35].It is also a useful instrument to measure alcohol dependence in women [36].				
4	ASI	155-item multidimensional structured interview for assessing alcohol and drug dependence. Assesses frequency of use without addressing quantity of use [37] [38]. Useful instrument to assess alcohol abuse vs. dependence in women too[39].	30 - 60 min	Yes	94	96
5	CDP	88-item structured instrument that provide extensive information which is useful for the assessment and treatment of alcohol problems [40].	2 h	Yes		

3.3.2 Assessment of nicotine use

Instruments used for assessing severity of nicotine dependence are mentioned below in Table 4.

Table 4. Instruments used for assessing severity of nicotine dependence (full form of abbreviations mentioned earlier)

S.No	Instrument	Brief description	Time	Specific	Sensitivity	Specificity
1	RTQ	10-item questionnaire designed to measure the severity of nicotine dependence [41].				
2	FTND	It consists of 6 items from the RTQ. It assesses the severity of nicotine dependence, tolerance and withdrawal. Items covered			68	81

		include number of cigarettes smoked, smoking topography, smoking to relieve nicotine withdrawal and difficulty in refraining from smoking [42].				

3.3.3 Assessment of other drug use

Measures to screen and to assess quantity and frequency of drugs other than alcohol and nicotine are listed in Table 5.

Table 5. Assessment of other (general) drug use (full form of abbreviations mentioned earlier)

S.No	Instrument	Brief description	Time needed	Specific Training needed	Sensitivity	Specificity
1	DAST	20-item screening instrument designed to identify individuals with drug abuse problems (excluding alcohol) in past 12 months. It includes some features of dependence syndrome and a range of emotional and behavioural problems associated with drug abuse [43].	< 5min	No	96	
1	OSI	It is a structured instrument which provides comprehensive measure of drug misuse. It measures outcome in six independent domains namely drug use, HIV risk taking behavior, criminality, social functioning, health status and psychological assessment [33].	20 - 30 min			
3	SODQ	5-section questionnaire which assesses opiate		No		

		dependence. Apart from assessing pattern and quantity of drug use it is useful to evaluate four aspects of dependence – physical and affective withdrawal, withdrawal relief drug taking and rapidity of reinstatement after abstinence [44].				
4	BDEPQ	30-item questionnaire for measuring dependence on benzodiazepines, sedatives and hypnotics. It has incorporated psychological dependence among other measures of dependence [45].				
5	LDQ	10-item, multiple choice self completion questionnaire which is used to assess dependency on a variety of substance. It is most sensitive to detect psychological dependence[46].		Self comple-tion questio-nnaire		
6	SDS	5-item questionnaire used to measure the degree of dependence on a variety of drugs. It focuses on psychological aspects of dependence. [47].				
7	SDSS	It is semi-structured clinical interview designed to obtain a measure of severity of DSM-IV substance use disorders. Useful to assess dependence on a variety of substances over past one month [48].	30 - 45 min	Yes		

KEY RECOMMENDATIONS

- Instrument based assessments have the advantage of being non invasive and non expensive.
- Separate instruments for screening and for assessing severity of dependence are available.
- Some assessments are time consuming and requires specialist training for their application.
- Since information in these can be feigned and depends on the mental status of patient so instrument based assessments should be used to complement clinical assessment and not as a sole measure on its own.

4. SPECIAL GROUP – CHILDREN AND ADOLESCENTS

Substance use should be included in the differential diagnosis of any adolescent who exhibits behavioural, educational and psychosocial problems. Pediatricians and other mental health professionals have significant role in identifying children and adolescents with substance use disorders. Studies also indicate that the average age at first use is around 12 to 14 years, alcohol and cannabis are two common drugs of abuse and adolescents tend to use multiple drugs. Regarding alcohol consumption it has been found that although adolescents typically drink less than adults, they tend to engage more in binge drinking behavior and hence are more likely to experience acute effects of alcohol in the form of intoxication and hangover rather than more chronic effects. Physiological dependence symptoms ex withdrawal etc are less likely to be present in adolescents [49]. Accordingly, it would be more appropriate to assess for repeated episodes of binge drinking, loss of control, psychological craving and academic and interpersonal problems resulting from alcohol use while evaluating adolescent with substance use disorders. AUDIT has been shown to be superior to other instruments for assessing alcohol problems in adolescents.[50]

As per American Medical Association Guidelines for adolescent health prevention (GAPS) every adolescent should be screened annually for risk behavior like substance abuse and sexuality [51]. However, the relevance of this recommendation in the Indian setting is uncertain.

Rapport building using open ended questions with gradual progression towards more specific questions regarding pattern and quantity of substance

use is the key to obtain detailed history regarding substance use. As evaluating any patients with substance use, comorbidity should be assessed while evaluating adolescent with substance abuse. The most common psychiatric symptom seen in the adolescent who has a substance use disorder is depression. Careful evaluation of possible family history of substance abuse should be done as substance abuse in family is the major risk factor for substance abuse in adolescents.

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APPENDICES: CASE ASSESSMENT PROFORMA OF AIIMS, PGIMER & NIMHANS

1. NDDTC, AIIMS FORM

Out-patient Case History Proforma

National Drug Dependence Treatment Centre (NDDTC), Ghaziabad
All India Institute of Medical Sciences (AIIMS), New Delhi)

OPD Reg no: Date of detailed workup:

Socio-demographic details

Name: Age: Sex:

Religion: Marital Status: Education:

Occupation: Current living arrangement:

Address:

Distance from NDDTC:

Informants:

Quality of Information: Adequate: Reliable:

Chief complaints:

Information on drug use:							
S No	**Substance**	**Age of onset**	**Age of daily use**	**Age of dependence**	**Currently pattern of use-dependent pattern (Yes/No)**	**Currently pattern of use-abuse/ harmful use (Yes/ No)**	**Dependent Pattern of use in past-Yes/No**
1.							
2.							
3.							
4.							
5.							
6.							
7.							
8.							
9.							
10.							

Current pattern of drug use (past 1 month)					
S No	**Substance**	**Usual dose**	**Maximum dose**	**Frequency of use**	**Last dose**
1.					
2.					
3.					
4.					
5.					
6.					
7.					
8.					
9.					
10.					

Injecting Drug Use : Yes/No

If Yes, then

S No	**Substances**	**Age at first use**	**Total duration of use**	**Sharing Yes/No**	**Current use**	**Understanding of risks associated including that of HIV/AIDS**	**HIV testing done Yes/No**	**If yes, results, if available (with consent only)**
1.								
2.								
3.								
4.								

High risk sexual behaviour:

Multiple sexual partners	Sex with FSW	Unprotected intercourse	Understanding of risks associated including that of HIV/AIDS	History suggestive of STI	HIV testing done	If yes, reactive/ non-reactive

Complications/dysfunctions due to substance use:		
Nature of complication	**Present/ Absent**	**Remarks**
Physical		
Psychological		
Familial		
Social		
Financial		
Occupational/academic		
Legal		

Abstinence attempts (Treatment seeking in past, Successful attempts in cumulative duration in terms of overall drug use in dependent pattern, Reason of relapse)				
Year of attempt	**Motivating factors**	**Medical help sought or not**	**Duration of abstinence**	**Reason for relapse**

Past medical and psychiatric history

Family history (Only to focus on family dynamics in brief, family history of psychiatric illness or substance use, parental conflict or family member attitude towards drug seeking behavior, Treatment effort by parents, Environment regarding drug use in locality)

Personal history

Birth & developmental history:

Behavioural problem in childhood (Conduct/ ADHD symptoms):

Academic history:

Occupational history:

Marital history:

Sexual/ menstrual history:

Temperamental traits/ Pre-morbid personality:

General physical examination and systemic examination

Mental status examination

Motivation for quitting:

Reason for quitting:

Stage of change:

Locus of control:

Diagnosis (Provisional/ tentative/ definitive):

Salient features/ issues in case:

Management plan/advice:

Signature of the resident
Discussed with the consultant

2. PGIMER FORM

DRUG DE-ADDICTION & TREATMENT CENTRE
DEPARTMENT OF PSYCHIATRY
POSTGRADUATE INSTITUTE OF MEDICAL EDUCATION & RESEARCH
CHANDIGARH

PATIENT INTAKE RECORD

Date DDTC No. CR No.

NAME OF THE PATIENT

IDENTIFYING DATA (Age, Sex, Marital Status, Education, Occupation (and current occupational status), Religion, Type of Family, Name of the City *I* District.

INFORMANTS

Relationship	Name	Reliability (Ability to report, familiarity with patient), adequacy
1.		
2.		
3.		

(RELIABLE / ADEQUATE)
COMPLAINTS WITH DURATION
1.
2. .
3.
4.
5.
6.

ONSET, PRECIPITATING FACTOR AND COURSE

2
HISTORY OF PRESENT ILLNESS

I. HISTORY OF SUBSTANCE USE

1. First contact with any substance

   a) Circumstances of first use

   b) Drug and its preparation

   c) Setting and social reaction

2. Course of use of the primary drug (s)

   a) Drug, preparation, route, frequency and quantity

   b) Usual setting and usual time

   c) General effect

   d) Tolerance and Withdrawal

   e) Course of intake, fluctuations over time, reasons for fluctuation, association with life events, physical, social and legal consequences.

   f) Periods of abstinence-reasons, dates, duration, withdrawal symptoms, how relapsed

LIFE CHART

3

4

3. Drug-related problems (encircle the ones applicable: add details)

a) Health : Bad trips, unpleasant effects; physical and psychological illnesses; accidents and their severity; delirium tremens, liver/ gastric disease; weight loss; sexual problems; blackout; fits; delusions, hallucinations.

b) Occupation : Regularity & efficiency; absenteeism; normal promotions; job changes; transfer/ suspension; dismissal; complaints/ warnings.

c) Finance: Source and amount of earnings; drug-related expenses and how they were covered (debts and losses; misappropriation; theft etc.)

d) Legal : Criminal/Undesirable activities, circumstances and outcome; arrest; prosecution; conviction; response of person and family to these.

e) Family : Impaired I.P.R.; responses of different family members to:- drug use, complications abstinences, treatment and outcome; role-performance, expectations, difficulties, support.

f) Marital : (if applicable) : Impaired I.P.R.; separations; impending divorce; completed divorce ; psychiatric problems of spouse; attempts at suicide; death of spouse.

g) Social: Impaired I.P.R.; restriction of social circle; undesirable incidents in social circumstances; social ostracism.

6

4.	Name of the Substance	Substance 1	Substance 2	Substance 3	Substance 4
	Duration of use				
	Duration of Dependence				

5. History of treatment and its response.

6. Last intake-drug (s), dose, routes, date, time. Withdrawal effects and response to them.

II. NON-DEPENDENT USE OF OTHER DRUG(S)

- Drug(s) preparation, route, frequency, quantity.
- Fluctuation over time

III. OTHER PSYCHIATRIC HISTORY If any (history suggestive of independent psychiatric illness).

7

PAST HISTORY

a) Medical, including injuries and operations.

b) Psychiatric: Dates, diagnosis or salient features, treatment. Interim history in case of a previous psychiatric illness, specific enquiry into completeness of recovery and socialization/personal care in the interim period.

FAMILY HISTORY Family tree/ Pedigree

Parents : (Age, education, occupation, general personality and relationship with patient. If deceased age at, date and cause of death) [Any H/o substance abuse]

Father :

Mother :

Siblings: Age, sex, education, occupation, marital status, drug abuse.

1.

2.

3.

4.

5.

6.

8

Family history of mental iIIness, including mental retardation, epilepsy, alcoholism, drug dependence or abuse, suicide, renouncing the world: In grand parents, parents, uncles, aunts, first cousins, siblings and children.

General home situation in patient's childhood, relationship between parents, socioeconomic status, interpersonal relationship, attitude to alcohol/ drug abuse. Major life events

PERSONAL HISTORY

Date and place of birth. Home or hospital delivery ?
Prenatal, natal and postnatal complications, if any.

Early development : Age at weaning, developmental milestones (explore at least age at first word, three-word sentences and walking), neurotic traits (nail-biting, bedwetting, phobias). Illnesses and injuries in childhood, conduct problems.

Educational history: Age at starting schooling, highest class completed, performance in school (give chronologically for each important exam), disciplinary problems, peer relationship and group 'participation, hobbies, special abilities, reasons for discontinuing.

9

Occupational history - Jobs held in chronological order. Give dates; adjustment with peers and superiors, specific difficulties, promotions, reasons for change of jobs.

Sexual and marital : Age at menarche, reaction to it and menstrual cycles, sex education, masturbation and associated guilt feeling. Marriage: how arranged, date of marriage, age and occupation of the spouse, general and sexual adjustment, ages and sex of children, sexual problems, if any.

10

Religious: Religion and sect, level of participation, any sudden changes in interest in religion.

Present living situation : The residence, who all live with the patient, sharing of income, expenses, kitchen; domestic conflicts, overall social class. In case of married women, details of the in-law's family.

Social support :

0 Poor (No support from family, network or society)
1 Minimal (Support from only one source)
2 Fair (Support from two sources, e.g. family and network)
3 Good (Support from multiple sources, inadequate amount regarding all aspects, e.g. financial instrumental, emotional)

PREMORBID PERSONALITY

Personality traits: passive Vs. active, assertive; introvert Vs. extrovert. Is sociable, anxious and worrisome, compulsive, depressive, suspicious? Hobbies and interests, eating, sleep and excretory habits (anything remarkable?) Anti-social behaviour independent of substance abuse.

11

PHYSICAL EXAMINATION

General: Appearance, body built and nutrition, any evidence of pallor, icterus, oedema,lymphadenopathy, needle marks, vein thrombosis, smell of alcohol, signs of intoxication currently.

Fundus

CVS (apex beat, regularity, heart sounds, murmurs)

Chest (Expansion on the two sides, percussion, adventitious sounds).

Abdomen (Tenderness, mass, bowel sounds)

CNS (Cranial nerves, motor and sensory system, rigidity, involuntary movements, superficial reflexes, DTR's, cerebellar functions)

Current Withdrawal Profile (Recent history and examination) (Mark the ones applicable)

General: Anxiety, restlessness, agitation, irritability, tremors, headache, sweating, anorexia, nausea, vomiting, insomnia, pupil size and reactivity.

Pulse_____*I* mt.

BP_____ mmHg,

Alcohol: Hallucinations, delusions, delirium, disorientation, amnesia, nystagmus, slurred speech, cognitive impairment.

Opiates: Lacrimation, rhinorrhea, diarrhoea, yawning, aches & pains, muscle twitchings, gooseflesh, hot and cold flushes.

Any other:

12

MENTAL STATUS EXAMINATION

1. **General appearance, attitude and behaviour :** General demeanour; whether tidy and well-kempt, aware of surroundings, cooperative in this examination.

2. **Rate and form of psychomotor activity :** Speed and amount of verbalization, pressure of thought and flight of ideas, motoric tension, posture and movements, mannerisms, grimacing, posturing, catatonic features.

3. **Affect :** Subjective feeling tone; objective assessment of resting affect, and its fluctuations in the context of topics being discussed; flat, anxious, depressed, elated, inappropriate and labile affect.

4. **Thought form & content and Perception :** circumstantiality, tangentiality, thought block, incoherence, verbigeration, thoughts, word-salad, neologism, perseveration, Ideas of reference, delusions, obsessions, hypochondriacal, depressive and suicidal ideas, hallucinations.

5. Cognitive functions : Level of consciousness, Orientation to time, place and person; Memory- immediate, recent and remote; Serial 7's, digit-span, counting forwards and backwards; general knowledge, calculation, similarities, proverb interpretation; (Appropriateness of judgement in face of realistic problems.)

Motivation

0 Poor [defined as i) failure to perceive any problem at all regarding amount, frequency or pattern of alcohol consumption or its control, ii) denying any alcohol-related functional impairment, iii) refusing professional help]

1 Between 0 and 2

2 Superficial/ [defined as i) admitting there was an alcohol problem but ascribing it to external (e.g "friends', "Society pressure") or rationalizing internal problem (e.g., "tension") rather than trying to understand it as an internal process of dependence. ii) minimizing alcohol-related complications, and iii) acknowledging need for treatment but often for some physical or mental complications of alcohol dependence ("pain. "insomnia", tension",) rather than for the dependence itself].

3 Between 2 and 4

4 Fair/good [defined as i) haivng an insight about the basic nature of the problem's a 'dependence' or 'addiction', ii) appreciating the extent and severity of alcohol-related complications and ability to link them with alcohol as the causative factor, and iii) feeling the need of treatment not just for the complications but basically for the dependence itself.

6. Insight : Patient's understanding and assessment of the alcohol/drug dependence, associated illness and problems (nature, course treatment and outcome). Reasons stated for seeking treatment (in descending order of importance) and the goals envisaged.

14

DIAGNOSTIC FORMULATION :

Salient positive and important negative findings in the mental illness, including the history and the mental status. History of alcohol/drug intake (whether meets criteria for abuse of dependence) and its related problems. Behavioral formulation.

15

Drug De-addiction & Treatment Centre, Department of Psychiatry, PGIMER, Chandigarh

HIV/HBV/HCV-RELATED RISK QUESTIONNAIRE

Name:
DDTC No.:
Date of data intake:

Section A. Screening question: Have you ever had experience with injectable drugs? Y/N [If NO, skip to Section B.]

First time: ..... Last time:..... Approx. no. : .....

1. Route of abuse : IV/IM/SC/mixed

   First time: ..... Last time:..... Approx. no. : .....

2. Have you ever shared needle with others?

   First time: ..... Last time:..... Approx. no. : .....

3. Have you ever shared syringes?

   First time: ..... Last time:..... Approx. no. : .....

4. Have you ever shared mixer/ vials/ cotton?

   First time: ..... Last time:..... Approx. no. : .....

5. Have you ever shared any of the above items with person with known STD (+ve for HIV/HBV/HCV/ other STD)?

   First time: ..... Last time:..... Approx. no. : .....

6. Have you ever reused needle/ syringe used by other persons?

   First time: ..... Last time:..... Approx. no. : .....

7. Have you ever received injectables from non-registered practitioner ("RMP", quacks, etc)

   First time: ..... Last time:..... Approx. no. : .....

Section B. Have you received any other form of injections or needle procedures on your body like tattooing, piercing of body parts, etc. **Y/N**

if yes, details (what, when, by whom, probability of use of shared equipment):

16

Section C. Have you ever received transfusion of blood/plasma/blood products? Y/N

If yes, First time: ..... Last time:..... Approx. no. : .....

Section D. Screening question: Have you ever had sex with any person? Y/N

[If NO, skip to Section E.]

1. Have you had sex with multiple partners?
   If yes: Protected/ unprotected

2. Have you had sex with commercial sex workers?
   If yes: Protected/ Unprotected

3. Have you had sex with strangers?
   If yes: Protected/ Unprotected

4. Have you had sex with a known drug abuser?
   If yes: Protected/ Unprotected

5. Have you had sex with person with known STD (+ve for HIV/ HBV/ HCV/ other STD)?
   If ye : Protected/ Unprotected

6. Have you had homosexual experience?
   If yes : Protected/ unprotected

7. Have you had premarital experience?
   If yes : Protected/unprotected

Section E. Screening question : Have you ever got yourself tested for any STD (HIV/HBV/HCV/ other STD)? Y/N

[If NO, terminate here.]

If yes:

	HIV	HBV	HCV	Others (specify)
Year				
Result known?				
If known, status				
Any other				
remarks				

17

DEPENDENCE CRITERIA (DSM IV)	PSYCHOACTIVE SUBSTANCE(S)			
	1	2	3	4
(1) Substance taken over long periods or larger amounts than intended				
(2) Unsuccessful effort/ persistant desire to Cut/Control Substance use				
(3) Withdrawal a. Characteristic withdrawal syndrome				
b. Substances taken to relieve or avoid withdrawal				
(4) Tolerance				
a. Need for increased substance for desired effect				
b. Deminished effect with same amount.				
(5) Important social/ occupational/ Recreational activities given up				
(6) Continued substances use despite knowledge of persistant physical/ psychological problems				
(7) Time spent to obtain the substance				
(a) Desire/ compulsion for use				
(b) Impaired control (onset/termination/level)				
(c) Withdrawal (withdrawal state/use for relief)				
(d) Tolerance				
(e) Neglect of alternative pleasures/ interests; increased time spent				
(f) Persistence despite harm				

18

PROVISIONAL DIAGNOSIS AND TREATMENT PLAN

COMMENTS OF THE CONSULTANT

FINAL DIAGNOSIS

INVESTIGATIONS AND TREATMENT ADVISED

Consultant's Signature
(Name in BLOCK LETTERS)

Resident's Signature
(Name in BLOCK LETTERS)

Followup ratings of drug-related problems

Area of functioning	Severity of Complications				Ratings		
	Nil (0)	Mild (1)	Moderate (2)	Severe (3)	1 mth	3 mth	6 mth
Health	No Complications	At least one health related complications	2 health related complications	>2 health-related complications			
Occupation	No Problem	Irregularity/inefficiency/ Absenteeism	Job changes/ Transfer	Suspensions/dismissal Chronic joblessness			
Finance	No Problem	Spending upto 25% salary of income on alcohol-related expenses	Spending more than 25% income	Serious debts, losses/ Misappropriate/thefts/ Embezzlement, robbery			
Legal	No Problem	Public Intoxication	Caught for drunk driving or violent brawls	Imprisonment, Public prosecution due to alcohol-related offence			
Family	No Problem	Strained intrpersonal relation (IPR)	Disrupted family functioning	Family ties broken; Disowned by family			
Marital	No Problem	Strained IPR	Episodes of separation	Divorce			
Social	No Problem	Impaired IPR	Restriction of social circle	Social ostracism			
TOTAL SCORE (OUT OF)							

20

FOLLOW-UP NOTES

Focus on

1. Drug use (medical/non-medical), reasons, circumstances, route, dose, frequency, duration, effects, management.
2. Health, work, financial, legal and family, I.P.R.-status, changes, reasons and responses.
3. Withdrawal effect-details, how managed, course.
4. Motivation.

3. NIMHANS FORM

CENTRE FOR ADDICTION MEDICINE, NIMHANS, Bangalore – 29

Sociodemographic details		DATE OF REGISTRATION
		P. No.
NAME	AGE (yrs)	SEX: 1.Male ☐ 2. ☐emale 3.Sexual Minorities
LANGUAGES SPOKEN: ☐ ☐ ☐ 1- Kannada 2- Tamil 3- Telugu 4- Malayalam ☐ 5 Hindi ☐ 6- English ☐ 7- Others	ECONOMIC STATUS 1.APL ☐ 2.BPL ☐ MONTHLY INCOME: Rs.....	
YEARS OF FORMAL EDUCATION: EDUCATIONAL STATUS: 1- Nil 2-Iliterate/No formal education 3- Primary (1-5 years) 4 - School (6-10 years), 5-Higher Secondary(PUC) 6- Graduate 7- Post- graduate 8-Professional 9- No Information ☐	CURRENT OCCUPATION: 1-Unemployed 2-Farmer 3-Unskilled 4- Semiskilled- (peon, domestic servant etc.) 5-Skilled-(plumber, carpenter, welder etc.) 6- Clerical 7- Professional 8-Business 9-Student 10-Home Maker, 11. Health Professionals. (a. Doctors, b. Nurse, c. Pharmacist, d. Other) ☐	
MARTIAL STATUS CURRENT 1. Single never been married ☐ 2. Married, living with spouse ☐ 3.Married separated ☐ 4.Divorced ☐ 5.Widowed ☐ 6. Living in relation ☐		

ADDRESS: Contact Address (Self): Mobile: Email:	Alternate Contact Address/support persons address:
REFERRAL: 1- Self 2- Family 3- Physician etc , 4- Psychiatrist 5- Emp ☐ , 6- Police 7- Ex-patient, 8. NGO 9- Others	**INFORMANT/S** (Relation with the patient):
(OPTIONAL) **RELIGION**: 1- Hindu, 2- Muslim, 3- Christian, 4- Others **COMMUNITY**/ Caste, Sub caste etc (For genetic studies) ☐	
Details:	

Substance use history – Current Use (see coding in the bottom of the Table)				
use (Last 6 months)	**Quantity – typical/day**	**Frequency**	**Quantity- Last use**	**Last use [days/weeks back]**
Spirits	30mlx			
Others				

Tobacco, Cigarettes, Beedies	Numbers			
Tobacco-SMT (Smokeless tobacco)	No. of pouch			
Cannabis –	Joints x			
Cannabis-Hashish				
Heroin: Chased / I.V	Grams/day			
Pentazocine **Proxyvon** **Codeine**	Caps x Bottles x			
Benzodiazepine **ALPRZ/ LZM/DZM** **Type :** **Route: Oral / IV**	Number of Dose:			
BZDZ- DZM etc	10mg x			
Non-BZDZ (Zolpidem, Zaleplon etc.)	10mg x			

Inhalants • **Erazex** • **Glues** • **Others(specify)**	No. of bottles x			
Cocaine				
Methamphetamine				
Others (specify)				

Frequency: 1= Daily / almost daily; 2 = 3-4 times /week; 3= 1-2 times/ week; 4=One to three times a month; 5=Less than once a month; 6=Never in the last 6 months

Substance Use History **Lifetime Use & Consequence**	**ALC**	**TOB**	**CANN**	**OPI**	**BZD**	**INH**	**OTH**
PATTERN OF USE: 1. similar amounts everyday, unable to abstain except due to unavailability - no money etc. **2.** Episodically with significant gaps in between; use for ≥2days without sobering up. **3.**Use infrequently/ when available	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐
AGE AT FIRST USE (Yrs)							
INITIATION: 1- Self ☐ 2- Peer ☐ 3- Others ☐							

REASON:

1- Experiment ☐ 2-Peer infl ☐ 3- Adults' infl ☐ 4- Myths ☐ 5-Relieve –ve Mood/stress/ boredom ☐

6- Enhance +ve mood ☐ 7- others (specify) ☐

INITIAL AMOUNT **Units/no. of joints or cigarettes/No. of tablets/ grams of opioid**							
TOLERANCE: 50 % more to give same effect 1.Yes 2.No	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
LOSS OF CONTROL: Use after deciding not to or use more 1.Yes than intended ? 2.No	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
SALIENCE: Given up / greatly reduced important activities while using 1.Yes /recovering from effects for several days or more 2.No	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
CRAVING: **Irresistible urge/** 1.Yes **strong desire for alcohol/drugs –** **could not manage without it –** couldn't think of anything else **2.No**	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Substance Use History Lifetime Use & Consequence							
	ALC	**TOB**	**CANN**	**OPI**	**BZD**	**INH**	**OTH**
EARLY MORNING USE: Ever needed/ taken just after 1.Yes getting up in the morning 2.No	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐

CIRCUMSTANCE OF USE : 1.Usually alone 2. Usually in company 3. No fixed pattern	○ ○ ○	○ ○ ○	○ ○ ○	○ ○ ○	○ ○ ○	○ ○ ○	○ ○ ○
CONTINUED USE DESPITE HARM							

WITHDRAWAL SYMPTOMS: If simple withdrawal discuss

SIMPLE WITHDRAWAL – (for most of the day for 2 days or more)

A 1.Hands trembling			**B** 1.Tears & Yawning			**C** 1.Agitation/ panic		
2.Unable to Sleep			2.Running nose			2.Fatigue		
3.Feel anxious			3.Goosebumps			3.Excess sleep		
4.Feel depressed			4.Sweating			4.Hunger		
5.Irritable			5.Muscle spasms					
6. Fast heart beat			6.Abdominal cramps					
7.Sweating			7.Fever & chills					
8.Nausea / Vomiting			8.Loss of appetite					
9.Feel physically weak								
10.Headaches								
11.Fidgety / Restless								

Age when two or more of these problems occurred together 3 times or more? **Years**

Did (this/these) problem(s) interfere with your functioning at work, school, or home? 1. Yes ☐ 2.No ☐

Relief drinking/use: Takes a drink/ more drugs to relieve withdrawal symptoms 1.Yes ☐ 2.No ☐

HALLUCINOSIS (hearing voices or seeing things that other people were not able to hear or see) Yes/No

If yes describe:

SEIZURES

1= On stopping/ decreasing ☐

2= Started even when drinking at the usual rate ☐

Fits occurred due to overdose or high doses of drug (Specify drug):

1. Yes ☐ 2. No ☐

Last time? (days lapsed)

Age, first time this happened? **years**

Last time? (days lapsed)

How many times did this happen?

Type: 1.Generalised tonic clonic ☐ 2.Focal/complex ☐

3. Focal/ complex –Generalised ☐

Seizure:	**When**	**Type**	**Last Time**	**Treated**
Withdrawn				
Overdose				
Independent				

Past history of independent seizures

1.Yes ☐ 2.No ☐

Family history of seizures

1.Yes ☐ 2.No ☐

Current / prior treatment

1.Yes ☐ 2.No ☐

On ≥3 occasions taken a drink to prevent/ control 1.Yes ☐ 2.No ☐	

DELIRIUM TREMENS:	**DETAIL DESCRIPTION**
1.On stopping/ decreasing ☐ 2. Started even when drinking at the usual rate ☐ **1.Altered sensorium** 1.Yes ☐ 2.No ☐ **2.Hallucinosis** 1.Yes ☐ 2.No ☐ 1.Auditory ☐ 2.Visual ☐ 3.Multimodal ☐ **3.Coarse tremors** 1.Yes ☐ 2.No ☐	

Age at first episode of DT?	Recent Episode
No. of episodes	
SUSPICIOUSNESS / DELUSIONAL JEALOUSY	

WERNICKE-KORSAKOFF 1.Yes ☐ 2.No ☐	
PERIPHERAL NEURITIS 1.Yes ☐ 2.No ☐	
MYOPATHIES 1.Yes ☐ 2.No ☐	
OVERDOSE 1.Yes ☐ 2.No ☐	
HIGH RISK BEHAVIORS 1.Yes ☐ 2.No ☐	
HR Sexual behaviours ☐	
Gambling ☐	

PHYSICAL INJURIES :

1.Yes ☐ 2.No ☐

Severity-

1 - Usual ☐ 2- Significant ☐
3- Severe ☐

Frequency:

1 -None ☐ 2- Frequent ☐
3-Infrequent ☐

HEAD INJURIES:

1.Yes ☐ 2.No ☐

1- None ☐ 2-Significant ☐
3- Severe ☐

MEDICAL

Gastritis

1.Yes ☐ 2.No ☐

Peripheral neuritis

1.Yes ☐ 2.No ☐

Jaundice

1.Yes ☐ 2.No ☐

PSYCHIATRIC

Psychosis

1.Yes ☐ 2.No ☐

Cognitive deficits

1.Yes ☐ 2.No ☐

INFECTIONS

1.Yes ☐ 2.No ☐ a.Thrombophlebitis ☐ b.Oropharyngeal infections ☐ c.Fungal infections/ STDs ☐		
DELIBERATE SELF HARM ☐ 1.Yes ☐ 2.No Attempts- 1 None ☐ 3. Multiple ☐ 2 Single ☐ Last attempt: Intentionality: 1-Low ☐ 2-High ☐ Lethality: 1-Low ☐ 2-High ☐		
CO-MORBID PROBLEMS		
PHYSICAL/ MEDICAL		
SYSTEMIC ILLNESS 1.Yes ☐ 2.No ☐ **Hypertension** 1.Yes ☐ 2.No ☐ **Diabetes** 1.Yes ☐ 2.No ☐		

INFECTIONS 1.Yes ☐ 2.No ☐ **Tuberculosis** ☐ **HIV** ☐ **Fungal** ☐ **Other** ☐		
PSYCHIATRIC		
Bipolar disorder 1.Yes ☐ 2.No ☐		
Depressive disorder 1.Yes ☐ 2.No ☐		
Schizophrenia 1.Yes ☐ 2.No ☐		
Anxiety disorders 1.Yes ☐ 2.No ☐		
Cognitive deficits- 1 -Nil ☐ 2- Significant ☐ 3- Severe ☐		

Other 0 ☐ 1 ☐	
CONSEQUENCES – PERSONAL, INTERPERSONAL, LEGAL	
PERSONAL	
COGNITIVE-EMOTIONAL 1- None ☐ 2- Loss of esteem/ dysphoria ☐ 3-Loss of motivation ☐ 4-Despair ☐	
ECONOMIC 1- No impact ☐ 2- Significant impact on earnings ☐ 3- Severe impact – requiring major support, loans or support of others ☐	
OCCUPATIONAL 1- None ☐ 2- Poor performance ☐ 3 –Absenteeism ☐ 4 - Job loss/ discontinued studies ☐	
INTERPERSONAL	
PARENTS & SIBLINGS **CONFLICT / FAMILY TENSION** 1-Not more than usual ☐ 2- Significant ☐ 3 Severe ☐ **VIOLENCE – PHYSICAL**	

1 –None ☐ 2- Frequent ☐ 3-Infrequent ☐	
SPOUSE **MARITAL DISHARMONY:** 1-Not more than usual ☐ 2- Significant ☐ 3- Severe ☐ **VIOLENCE – PHYSICAL:** 1 –None ☐ 2- Frequent ☐ 3 –Infrequent ☐ **CO-DEPENDENCE:** 1 -Not more than usual ☐ 2- Significant ☐ 3- Severe ☐	
CHILDREN **REDUCED ACCESS TO RESOURCES** (Food, education, clothes etc) 1 -Not more than usual ☐ 2- Significant ☐ 3- Severe ☐ **VIOLENCE – PHYSICAL** 1-None ☐ 2- Frequent ☐ 3-Infrequent ☐	
FRIENDS-NEIGHBORS Conflict: 1- usual ☐ 2- Significant ☐ 3- Severe ☐	

PREVIOUS ATTEMPTS AT ABSTINENCE (2 WEEKS OR MORE / TREATMENT)	
Substance use	
Previous attempts to control 1- General medical ☐	

2- Gen. psychiatric ☐ 3- Self help groups ☐ 4- Deaddiction facilities ☐ 5- Traditional healers ☐	
Previous medications: 1. DS ☐ 2. Anti-craving ☐ 3. Others ☐4. Name	
Max. abstinence	
Reason for relapse	
Attempts at self abstinence	
CONTRIBUTING / SUSCEPTIBILITY FACTORS	
EXTERNALISING BEHAVIORS **Impulsivity:** 1-Not more than usual ☐ 2- More than usual ☐ 3- Much more than usual ☐ **Inattention** 1-Not more than usual ☐ 2-More ☐ 3-Much more ☐ **Hyperactivity** 1-Not more than usual ☐ 2-More ☐ 3-Much more ☐ **Conduct Problems** 1-Not more than usual ☐ 2-More ☐ 3-Much more ☐ **Opposing-defiant behaviour** 1-Not more than usual ☐ 2-More ☐	

3-Much more ☐	
INTERNALIZING BEHAVIOR SPECTRUM **Generalised anxiety** 1-Not more than usual ☐ 2-More 3-Much more **Social anxiety** 1-Not more than usual 2-More 3-Much more **Phobias** 1-Not more than usual 2-More 3-Much more	
DEVELOPMENTAL **Poverty** 0-No; 1- Significant **Deprived neighbourhood** 0 1 **Aborted schooling** 0 1 **Poor family support** 0 1	
FAMILY HISTORY OF USE	Alcohol, tobacco & other drugs; significant illness
Family History Positive / Negative for Alcohol/ Drug Dependence **Father side: Total no : Use** **Mother side: Total No. Use:** **Likely Dependence:** **Likely Dependence** **Family History Positive / Negative for other Psychiatric diagnosis:** **Psychosis:** **Mood:**	
Suicide: **Personality disorder:**	

THREE GENERATION GENOGRAM

Diagnosis: **Substance**		
	Early **Late**	onset Dependence – **Alcohol – Opioid – Benzodiazepine –Inhalant- Cannabis – Multiple drug -**
		Nicotine dependence
Family loading		High / Low (No. of Relatives Affected 1st___ 2nd degree__
Co-morbid psychiatric		Axis I Axis II
Associated Medical Problems		

LOCUS OF IMMEDIATE MANAGEMENT(Tick which is applicable)			
In-patient admission		**Out-patient treatment**	
1.Severe / complicated withdrawal	☐	1.Mild withdrawal	☐
2.Failed OP attempts at abstinence/ likely to fail	☐	2.Good social support	☐
3.High risk of DSH	☐	3. Refused admission	☐
4.Poor social supports	☐	4. No beds	☐
5.Comorbid medical/ psychiatric problems	☐	5. Severe medical problems,	☐
6. From far-away	☐	referred elsewhere	
7. Highly motivated	☐		
8. Respite care	☐		

Investigations(Tick which is applicable)

1. Liver function tests & Biochemistry

R.Glucose	F. Glucose	PP Glucose	Urea	Creatinine	Total Protein	Albumin	Globulin	A/G Ratio	

Total Bilirubin	Direct bilirubin	Alk Phos	SGOT	SGPT	GGT	Sodium	Potassium	Chloride	

Urine Screen

Cannabis	Opioid	Cocaine	Benzo	

2.

Hb	RBC	PCV	N	L	B	E	M	MCV	ESR Any thing else

3. USG :

4. CT/MRI:

5. EEG:

6. Virology

Hb_sAG	HIV	VDRL	Tuberculosis		

WITHDRAWAL And SEVERITY

Scale (As per drug of use)	Last Intake	Score Days 1 2 3 4 6 10 14
CIWA COWS SADQ		

Severity of Alcohol Dependence Questionnaire (SADQ)

NAME AGE P no

The 20 Items of the SADQ are all scroes as follows:

0 = Never; Allmost Never at all

1= Sometimes ;slightly

Have you drunk any alcohol in the past six months? YES/ NO

During the past six months

1. The day after drinking alcohol, I woke up feeling sweaty.

Almostnever ***Sometimes*** ***Often*** ***Nearly Always***

2. The day after drinking alcohol, my hands shook first thing in the morning.

Almostnever ***Sometimes*** ***Often*** ***Nearly Always***

3. The day after drinking alcohol, my whole body shook violently first thing in the morning if I didn't have a drink.

Almostnever ***Sometimes*** ***Often*** ***Nearly Always***

4. The day after drinking alcohol, I woke up absolutely drenched in sweat.

Almostnever ***Sometimes*** ***Often*** ***Nearly Always***

5. The day after drinking alcohol, I dread waking up in the morning woke up absolutely drenched in sweat.

Almostnever ***Sometimes*** ***Often*** ***Nearly Always***

6. The day after drinking alcohol, I was frightened of meeting people first thing in the morning. .

Almostnever ***Sometimes*** ***Often*** ***Nearly Always***

7. The day after drinking alcohol, I felt at the edge of despair when I woke. .

Almostnever ***Sometimes*** ***Often*** ***Nearly Always***

8. The day after drinking alcohol, I felt very frightened when I woke up at the edge of despair when I woke. .

Almostnever ***Sometimes*** ***Often*** ***Nearly Always***

9. The day after drinking alcohol, I liked to have an alcohol drink in the morning.

Almostnever ***Sometimes*** ***Often*** ***Nearly Always***

10. The day after drinking alcohol, I always gulped my first few alcoholic drinks down as quickly as possible.

Almostnever ***Sometimes*** ***Often*** ***Nearly Always***

11. The day after drinking alcohol, I drank more alcohol in the morning to get rid of the shakes.

Almostnever ***Sometimes*** ***Often*** ***Nearly Always***

12. The day after drinking alcohol, I had a very strong craving for a drink when I woke up.

Almostnever ***Sometimes*** ***Often*** ***Nearly Always***

13. I drank more than a quarter of a bottle of spirits in a day (OR 1 bottle of wine OR 7 beers)

Almostnever ***Sometimes*** ***Often*** ***Nearly Always***

14. I drank more than half a bottle of spirits per day (OR 2 bottles of wine OR 15 beers)

Almostnever ***Sometimes*** ***Often*** ***Nearly Always***

15. I drank more than one bottle of spirits per day (OR 4 bottles of wine OR 30 beers)

Almostnever ***Sometimes*** ***Often*** ***Nearly Always***

16. I drank more than two bottles of spirits per day (OR 8 bottles of wine OR 60 beers)

Almostnever ***Sometimes*** ***Often*** ***Nearly Always***

Imagine the following situation:

1. You have **hardly drunk any alcohol for a few weeks.**

2. You then drink **very heavily** for **two days.**

How would you feel the **morning after** those two days of heavy drinking?

17. I would start to sweat.

Not At All ***Slightly*** ***Moderately*** ***Quite a Lot***

18. My hands would shake.

Not At All ***Slightly*** ***Moderately*** ***Quite a Lot***

19. My body would shake.

Not At All ***Slightly*** ***Moderately*** ***Quite a Lot***

20. I would be craving for a drink

Not At All ***Slightly*** ***Moderately*** ***Quite a lot***

Total Score:

Scores from 1 – 20: Mild alcohol dependence

Scores from 21 – 40: Moderate alcohol dependence

Scores of over 40 : Severe alcohol dependence

Fagerstrom Addiction Scale

Fagerstrom Addiction Scale for Smokers	**Modified Fagerstrom Questionnaire for Smokeless Tobacco Users**
1. How soon after you wake in the morning do you smoke or first use tobacco? a. Within 30 minutes **1** b. More than 30 minutes **0**	1. After a normal sleeping period, do you use smokeless within 30 minutes of waking? a. Yes 1 b. No 0
2. Do you find it difficult not to use tobacco where tobacco is forbidden? a. Yes **1** b. No **0**	2. Do you use smokeless tobacco when you are sick or have mouth sores? a. Yes 1 b. No 0
3. Which of all the times you use tobacco during the day is the most satisfying? a. First thing in the morning **1** b. Any other time **0**	3. How many times do you use per week? a. Less than 2 0 b. More than 2 1 c. More than 4 2
4. How many cigarettes do you smoke a day? a. 1-15, light smoker **0** b. 16-25, moderate smoker **1** c. 26 or more, heavy smoker **2**	4. Do you intentionally swallow your tobacco juices rather than spit? a. Never 0 b. Sometimes 1 c. Always 2
5. Do you use tobacco more in the morning than the rest of the day? a. Yes **1** b. No **0**	5. Do you keep a dip or chew in your mouth almost all the time? a. Yes 1 b. No 0
6. Do you use tobacco when you are sick enough to have to stay in bed? a. Yes **1** b. No **0**	6. Do you experience strong cravings for a dip or chew when you go for more than two hours without one? a. Yes 1 b. No 0
7. What is the tar/nicotine rating of the brand you smoke? a. Low tar, 1-8 mgs **0** b. Medium tar, 9-16 mgs **1** c. High tar, 15 or more mgs **2**	7. On average, how many minutes do you keep a fresh dip or chew in your mouth? a. 10-19 minutes 1 b. 20-30 minutes 2 c. More than 30 minutes 3
8. How often do you inhale? a. Occasionally **0** b. Often **1** c. Always **2**	8. What is the length of your dipping day (total hours from first dip/chew in a.m. to last dip/chew in p.m.)? a. Less than 14.5 hours 0 b. More than 14.5 hours 1 c. More than 15 hours 2
	9. On average, how may dips/chews do you take each day? a. 1 - 9 1 b. 10 - 15 2 c. >15 3
Your score =	Your score =
The highest possible score = 11 The closer to zero your score, the less dependent you are on tobacco. The higher the score, the more strongly you are addicted.	The highest possible = 16 The closer to zero your score, the less dependent you are on tobacco. The higher the score, the more strongly you are addicted.

Clinical Opiate Withdrawal Scale	
Patient's Name:_____ Date and Time ____/____/____:_____ Reason for this assessment:	
Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset**: *over last ½ hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 Multiple episodes of diarrhea or vomiting
Sweating: *over past ½ hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 No tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/ muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing Assessment: _____
Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal	
For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.	

To be filled by therapist (Psychosocial) for the admitted patients

LONG TERM PLAN

MOTIVATION	
Motivational Interviewing and Education	No of Sessions:
RELAPSE PREVENTION TRAINING	
Triggers and Strategies Prepare for relapse	No of Sessions:
LIFESTYLE MODIFICATION	
Unchaining habits Positive highs Structuring ADL	No of sessions:
REMEDIATION	
Group therapy attended Any other interventions	No of Sessions:
ENLISTING SOCIAL SUPPORT	
Spouse/ relative to supervise medication Prompt help-seeking after first use Survivor's groups	1: Yes 2: No
FOLLOW-UP Status (Separate form)	1: Yes 2: No

Regular follow up personally or over telephone/email/post	
	1: Yes 2: No
3 monthly follow up review	
Clinical status	
6 monthly follow up review	1: Yes 2: No
Clinical status	

Follow up

Date of Discharge:

No.	Date	Status	Intervention	Discussed with
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				

9.				
10.				
11.				
12.				
13.				
14.				
15.				
16.				
17.				
18.				
19.				
20.				

Admission Counseling and Consent

Date Time:

The inpatient programme at the de addiction centre ,NIMHANS is a 3-4 weeks programme. it consist of

a. **Counseling** to the individual with addiction as well as to the family members. Counseling includes motivation you to change,identify factors that may lead to relapse and helping you learn methods to effectively prevent relapse.counseling also helps you to identify your goals and develop the strengths to achieve these goals

b. **Group meetings** will be held everyday in order to discuss issues related to your addiction and recovery

c. **Meditation :**As appropriate,medication will be used to treat any alcohol /drugs and to help in preventing relapse

d. **Family counseling:** It is necessary that one or more significant family members are actively involved in the treatment.They are expected to meet the treating team on a regular basis,and attend counseling session as advised

_____agree that I will actively co operate with the treating team during my admission

I agree that I will not use alcohol or any unprescribed drug my stay.I understand That I may be subjected to the random checks for alcohol/drugs as part of the Deaddiction Centre policy.

I will comply with the rules and regulations of the centre

Violation of any of the above may necessitate discharge /transfer to another ward

Individual's signature

Relative's signature

Signature of the Psychiatric Social Worker

GROUP SESSIONS

Name P No

Session is defined as a focused interview/therapy of atleast half an hour or more**

Sl no	Date	Theme	Resident psychiatry	Staff DAC (PSW/CP)	Post Graduate (PSW/CP/NURSE)

**PLEASE ENTER THE SESSION

INDIVIDUAL SESSIONS

Name P No

Session is defined as a focused interview/therapy of atleast half an hour or more**

Sl no	DATE	THEME	Resident psychiatry	Staff DAC (PSW/CP)	Post Graduate (PSW/CP/NURSE)

FAMILY SESSIONS

Name P No

Session is defined as a focused interview/therapy of atleast half an hour or more**

Sl no	Date	Theme	Resident psychiatry	Staff DAC (PSW/CP)	Post Graduate (PSW/CP/NURSE)

**PLEASE ENTER THE SESSION

CLINICAL PRACTICE GUIDELINES (CPG) FOR THE MANAGEMENT OF ALCOHOL USE DISORDERS

Subodh B.N.
Umamaheswari V.

On behalf of IPS-SS-SUD

2014

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EXECUTIVE SUMMARY

Alcohol use disorders show an increase trend in India not only among male but also in women. They affect different aspects of life of a person (medical, legal, financial, interpersonal etc.,) and their family members. As Alcohol Dependence Syndrome (ADS) is a chronic relapsing and recurring condition, patients with ADS will require a comprehensive multipronged care for continuous and prolonged period of time. An integrated Bio-psychosocial approach to care is needed to address several aspects of the treatment. An active collaboration with the family while planning and delivering treatment is required. Management of the ADS should be sensitive to the needs and empirically titrated to the patient's response and progress.

The main goal of treatment is to maintain abstinence and if not possible decrease the frequency and severity of relapses and maximize functioning in between. The goals of treatment vary according to time frame, across individual patients and can be revised from time to time. It has been broadly divided into short term and long term goals. The short goals are management of intoxication, management of withdrawal symptoms, motivation enhancement, treatment of acute medical sequel and crisis intervention. Long term treatment goals are relapse prevention, maintain abstinence, occupational rehabilitation, social reintegration, abstinent life style and improving the quality of life of a person. This guideline will focus on the evidence available for the management of intoxication, management of withdrawal symptoms, and management of alcohol dependence. Goals of treatment should be set and agreed between the patient and the clinician.

Assessment of Alcohol use disorders:

A thorough and good assessment will help in diagnosing, establishing rapport, motivating the person and in formulating the plan of the management. The goal of assessment also varies in different phases of the treatment. During the first contact it is to establish rapport, diagnosis and plan of management, and during intervention it is monitoring the progress and assessing abstinence. The goal also depends on the context, motivation of the client and cooperativeness of the client. If

the client is uncooperative the aim of assessment is to retain the client in the treatment. During this time the information can be collected in pieces and information can be added when patient is co-operative.

A detailed assessment should include substance related factors (age of initiation, frequency, amount, tolerance, craving, withdrawal symptoms, salience, last dose, motivation, consequences of substance use), history of other substance use, physical and psychiatric comorbidity if any, abstinent related factors (past abstinence, duration, reasons for relapse, past treatment/s, methods used for controlling craving). It also includes history of high risk behaviours, presence of any externalizing disorders, physical and psychiatric comorbidity, family history of substance abuse and psychiatric illness, assessing social support, current living arrangements and reasons for current visit. A thorough physical examination to assess for intoxication, withdrawal symptoms and look for evidence of physical damage due to alcohol use or other substance use. Investigations are used to confirm the presence of the alcohol, assess the degree of the physical damage and to confirm the presence of sexually transmitted disorders.

Short term Management

The short term management is aimed towards medical stabilisation and engaging patient in process of recovery. The management of alcohol intoxication should include general assessment as described in assessment with particular emphasis placed on physical status, mental status, substance use history and associated consequences. The acute effects of alcohol generally subside with time and they do not warrant any specific treatment. Specific pharmacological treatment is necessary when there is a history of recent use of other substance use and with respiratory depression. If simple intoxicated state general measures like reassurance and maintain in a safe and monitored environment do decrease external stimulation and to provide orientation is necessary. Adequate hydration and nutrition should be provided. Patients with past history of complicated withdrawal, and prolonged heavy drinking there is a need to monitor complicated withdrawal state.

Management of alcohol withdrawal (AW) requires constant monitoring of signs and symptoms of withdrawal. The goals of the AW are:

a) To relieve patient's discomfort, prevent the occurrence of more serious symptoms, and forestall cumulative effects that might worsen future withdrawal; b) To utilise the withdrawal treatment opportunity to engage patients in long-term management. The symptoms of AW may range in severity from mild tremors to convulsions and delirium. The signs and symptoms of alcohol withdrawal appear between 6 to 48 hrs after the cessation or reduction of heavy, prolonged ingestion of alcohol. The assessment should include general assessment as described in assessment with particular emphasis placed on time elapsed since last use, concomitant use of other substance use, the presence or absence of concurrent general medical or psychiatric disorders, and past complicated withdrawal syndromes. Pharmacological management is the treatment of choice in withdrawal state. Benzodiazepines are efficacious in reducing signs and symptoms of withdrawal (A); fixed-dose regimens are recommended for routine use with symptom-triggered dosing reserved for use only with adequate monitoring (D). The evidence for the use of acamprosate in alcohol withdrawal is confusing. Some trials have shown that when given along with Benzodiazepines during withdrawal they improved outcome (Ib), whereas some trials (Ib) have shown that they indeed worsen the outcome when given during the beginning of detoxification (A). Baclofen – Evidence is insufficient for its use in alcohol withdrawal (A). Both short acting and long acting Benzodiazepines are effective in preventing primary and secondary seizure prevention (A). Some evidence to suggest the use of carbamazepine in prevention of seizures in alcohol withdrawal but evidence is insufficient to recommend the use of carbamazepine (A). Benzodiazepines are more effective in preventing delirium, and in reducing mortality in alcohol withdrawal delirium (A). High index of suspicion should be maintained as Wernicke-Korsakoff's syndrome (WKS) does not present with all signs and symptoms. All suspected cases to be given parental thiamine (D). Patient at risk for WKS or suspected cases should be treated with 100 mg of intramuscular or oral thiamine before any glucose intake (D). In Indian setting suspected or high risk cases of WKS parental thiamine to be given for fortnight along with oral preparation of 100-200 mg of thiamine (D).

Long term Management

Alcohol dependence is a chronic illness with lapses and relapses. Medications and psychosocial strategies are used for promoting abstinence and preventing relapse in patients with alcohol dependence. All the pharmacological agents used in alcohol use disorders have been studied along with psychosocial interventions. Hence patients should use whichever psychosocial approach they think beneficial or is available along with pharmacological agents.

Pharmacological interventions: Pharmacological agents have been found to be effective in management of alcohol dependence. Disulfiram is effective if taken under supervision. Disulfiram can be offered as a treatment option for patients who intend to maintain abstinence (A). Acamprosate better than placebo in maintaining abstinence and in preventing relapse (A); Acamprosate reduces heavy drinking in patients who have relapsed (A). Naltrexone reduces return to heavy drinking by reducing lapse to relapse, but does not improve the abstinence rate (A). Long acting Injectable form of Naltrexone has been used to overcome poor adherence (B). Baclofen has a higher rate of abstinence and decreases anxiety (A). Baclofen holds promise and should be first line of management in patients with moderate to severe cirrhotic liver disease (D). Topiramate reduces the percentage of heavy drinking days (A). SSRIs' effectiveness is less consistent in non depressed patients (A). SSRIs are generally used for patients with comorbid depression (B). SSRIs worsen outcome in early onset, family history of alcoholism (D). Ondansetron was found effective in early onset group (D).

Non-Pharmacological interventions: Interventions like Motivation Enhancement Therapy (MET) / Motivation Interviewing and Brief intervention (BI) have been found to be effective (A). They can be given in different setup by different professionals. A brief MET of 4 sessions has been found to be as effective as or better than other therapies for alcohol dependence. The effects have been improved when combining with medications (A). Cognitive Behavior therapy based therapies along with medications have found to be effective in relapse prevention, alcohol use (A). Family therapies along with medication have found to be better in reduction of alcohol, relapses and this has

also been found effective in Indian setup (A). AA or other 12 step approaches have found to be effective method for management but was not found to better than other treatments in reducing alcohol use and achieving abstinence (A). Psychosocial therapies differing widely in conceptual framework, intensity, duration, and location have minimal long-term difference between inpatient/residential treatment and outpatient counseling approaches, found approximately equivalent (and reasonably good) outcomes with both brief, non-intensive treatments and intensive treatments for moderately severe alcoholics (A). Combined pharmacological and non-pharmacological intervention is effective than either alone (A).

Special populations:

Pregnancy provides an opportunity to think about the alcohol related problems. In pregnant women non-pharmacological treatments should be treatment of choice (C). When needed drugs can be used after discussing with the pregnant women about pros and cons and taking an informed decisions and close monitoring of the pregnancy (C).

In young people with problems with alcohol use has shown that school based interventions, family based interventions and multipronged interventions have found to effective in medium and long term (A). Young children should also be assessed for psychiatric comorbidity and managed accordingly (C).

Brief intervention (BI) has been found to be effective in decreasing alcohol use in people with problematic alcohol users in different settings (A). The benefits of brief intervention were similar in clinical setting and in research settings and with person providing the intervention (A).

1. INTRODUCTION

Alcohol use disorders (AUDs) represent a most serious health problem worldwide and also in India with major social, interpersonal and legal interpolations. Globally alcohol dependence syndrome (ADS) ranks 5th and 3rd on the list of preventable causes of morbidity and mortality respectively.[1] It contributes substantially to the health care costs of most nations.

1.1 Epidemiology

Alcohol use disorders show an increased trend in developing countries like India as evident in NFHS 3 when compared to NFHS 2 and they are becoming major public health problem.[2,3,4] The National Household Survey was the first systematic effort in the country to document the nationwide prevalence of drug use. In this, alcohol (21.4%) was the primary substance use apart from tobacco. 17% to 26% of alcohol users qualified to ICD 10 diagnosis of dependence translating into an average prevalence of about 4%. There was a marked variation in alcohol use prevalence in different states of India.[5] It has been estimated that there are nearly 70 million alcohol users which include 12 million users who are dependent on alcohol not including millions of social drinkers in India. Nearly 30- 35% of adult men and approximately 5% of adult women consume alcohol (Male to Female ratio being 6:1).[4] In India currently the most important and significant changes seen in alcohol using population is age of initiation into alcohol, increase in female alcohol use and signature pattern of alcohol intake.[2,6,7,8] In India age at first use of the alcohol has reduced from 28 years during the 1980s to 17 years in 2007.[4] More number of women is using alcohol regularly and heavily.[4,6,7,8] It has been consistently observed in many studies that more number of people who take alcohol regularly (mostly solitarily) and heavily to the point of intoxication. This pattern of use is also called as signature pattern of alcohol use in India.[2,4,6,7]

1.2 Consequence of Alcohol Use disorders

Alcohol use disorders affect different aspects of life of a person (medical, legal, financial, interpersonal etc.,) and their family members. Alcohol use disorders are associated with high mortality and morbidity in India. They have been reviewed extensively in several reviews.[2,4,7]

2. SCOPE AND METHODOLOGY OF THE GUIDELINE

2.1 Brief Overview

Over the years there has been a change in the way AUDs has been understood and managed. This has led on to better management of AUDs with positive results. Despite this many AUDs patients are not managed properly and this appears to be due to lack of efforts to adapt existing treatments to suit the specific needs of the Indian patients and their family. This may be due to low level of awareness, beliefs about alcoholism, lack of trained personnel, lack of community resources, and inadequate access to health care. The need to develop treatment tailored made to suit needs of individual patients and match the existing resources has been voiced and very little has been achieved till now. The current document is a step towards formulating certain principles to guide the treatment of the ADS in the Indian context. The current document aims to set down certain minimum evidence based standards that need to be taken into account in managing patients with ADS and their family.

2.2 Scope of the Guidelines

These guidelines are neither comprehensive nor definitive. Psychiatrists caring for patients should consider the evidence base but not be limited by the recommendations made, as patients are cared in a number of different settings in our country. In the present form the guidelines are particularly applicable to De-addiction centres, and General hospital psychiatric centres. In this article we are not going to discuss about evidence base for management of dual diagnosis which is a separate guideline.

2.3 Methodology of Guideline development

The guideline seeks to summarise the recent data available on major treatments available for people with AUDs which might assist practitioners to ensure minimum standards of care. Relevant literature was identified through a PubMed literature search for publications related to this guideline. Searches were conducted; using the keywords like “Alcohol abuse OR Alcohol dependence OR Alcohol use” The search yielded 257102 references till 29th Sep 2013. The search was restricted to human studies, written in the English language, and had abstracts, of which 6041 were randomized controlled trials and 776 were meta-analyses. Evidence tables were developed for these results. A second MEDLINE literature search, using

PubMed, on the same keywords using filter 'last 10 years' yielded 60381 references, of which 3206 were randomized controlled trials and 586 were meta-analyses. Similarly, when filter was changed to 'last 5 years', the search yielded 32207 references of which 1753 were randomized controlled trials and 393 were meta-analyses. Additionally, bibliography of relevant articles and other guidelines like APA,[9] NICE,[10,11] BAP,[12] WHO guideline for treatment of alcohol use disorders were also searched. The Cochrane databases were also searched for relevant meta-analyses. The summary of treatment recommendations is keyed according to the level of evidences.

3. REVIEW OF TREATMENT MODALITIES

3.1 General Issues

While treating patients with ADS several factors should be taken into consideration. As ADS is a chronic relapsing and recurring condition patients will require a comprehensive continuous care for prolonged period. An integrated Bio-psychosocial approach to care is needed to address several aspects of the treatment. An active collaboration with the family while planning and delivering treatment is required. Management of the ADS should be sensitive to the needs and empirically titrated to the patient's response and progress. The main goal of treatment is to maintain abstinence and if not possible decrease the frequency and severity of relapses and maximize functioning in between. The specific goal depends on the stage at which patient's visits the clinic.

3.2 Treatment Aims / Goals

The aims of treatment of alcohol dependence syndrome are

- Promote complete abstinence
- Stabilize acute medical (including alcohol withdrawal) and psychiatric conditions, as needed
- Increase motivation for recovery
- Initiate treatment for chronic medical and psychiatric conditions, as needed
- Enhance coping and relapse prevention skills
- Improve occupational functioning, social support and assist in integrating to society as needed

- Promote maintenance of recovery through ongoing participation in structured treatment or self-help groups

The goals of treatment vary according to time frame, across individual patients and can be revised from time to time. It has been broadly divided into short term and long term goals. The short goals are management of intoxication, management of withdrawal symptoms, motivation enhancement, treatment of acute medical sequel and crisis intervention. Long term treatment goals are relapse prevention, maintain abstinence, occupational rehabilitation, social reintegration, abstinent life style and improving the quality of life of a person. This guideline will focus on the evidence available for the management of intoxication, management of withdrawal symptoms, and management of alcohol dependence. We have tried to indicate clearly the aims of each treatment. Goals of treatment should be set and agreed between the patient and the clinician.

3.3 Assessment of Alcohol use disorders:

Detailed assessment guidelines are provided in the specific chapter on assessments. This section briefly recapitulates the main points especially relevant to alcohol use disorders.

3.3.1 Brief Overview

The assessment is very important as it forms the first point of contact and a thorough and good assessment will help in diagnosing, establishing rapport, motivating the person and in formulating the plan of the management. The goal of assessment also varies in different phases of the treatment. During the first contact it is to establish rapport, diagnosis and plan of management, and during intervention it is monitoring the progress and assessing abstinence. The goal also depends on the context, motivation of the client and cooperativeness of the client. If the client is uncooperative the aim of assessment is to retain the client in the treatment. During this time the information can be collected in pieces and information can be added when patient is co-operative.

3.3.2 Clinical History

A detailed assessment should include substance related factors such as age of initiation, frequency, amount, tolerance, craving, withdrawal symptoms, salience, loss of control, persistent despite harm, last dose, motivation, consequences of substance use (physical, psychological, financial, Family

problems, vocational and legal), history of other substance use, physical and psychiatric comorbidity if any, abstinent related factors such as past abstinence, duration of abstinence, reasons for relapse, past treatments (pharmacological or non-pharmacological or both), methods used for controlling craving. It also includes history of high risk behaviours, presence of any externalizing disorders, physical and psychiatric comorbidity, family history of substance abuse and psychiatric illness, assessing social support, current living arrangements and reasons for current visit.

3.3.3 Physical Examination

A thorough physical examination to assess for intoxication, withdrawal symptoms and look for evidence of physical damage due to alcohol use or other substance use. A thorough mental status examination and look for psychopathology in case of co-morbid psychiatric conditions. Psychological or neuropsychological testing can be done for some individuals with history of cognitive impairment.

3.3.4 Instruments

Scales provides ways to structurally assess the individuals with alcohol use disorders. Some scales such as CAGE,[13]ASSIST,[14] CIWA-Ar[15] can be used to assess to make diagnosis, for intoxication, and withdrawal symptoms.

3.3.5 Investigations

Investigations are used to confirm the presence of the alcohol, assess the degree of the physical damage and to confirm the presence of sexually transmitted disorders. Investigations such as liver function test, hemogram, GGT, Serum B12, Ultrasound abdomen, VDRL, HIV in high risk cases can be used. In some cases, neuropsychological tests can be used to assess the cognitive function.

4. MANAGEMENT OF ALCOHOL INTOXICATION

4.1 Management of ethanol toxicity

Alcohol intoxication is commonly encountered in clinical settings particularly medical emergency settings. The signs and symptoms of intoxication include slurred speech, lack of coordination, unsteadiness of gait, impairment in attention and concentration and in severe cases coma and stupor. Diagnosis of intoxication can be made according to the criteria

set up in ICD-10[16] or DSM-5.[17] The clinical assessment should include general assessment as described in assessment with particular emphasis placed on physical status, mental status, substance use history and associated consequences. If breath analysers are available the BAC can be measured and noted in the clinical history. The acute effects of alcohol generally subside with time and they do not warrant any specific treatment. Specific pharmacological treatment is necessary when there is a history of recent use of other substance use and with respiratory depression. In simple intoxicated state general measures like reassurance and maintain in a safe and monitored environment to decrease external stimulation and to provide orientation are necessary. Adequate hydration and nutrition should be provided. Patients with past history of complicated withdrawal, and prolonged heavy drinking there is a need to monitor complicated withdrawal state.

4.2 Management of methanol toxicity

In India there are reports of the ingestion of the adulterated alcohol leading on to hooch tragedies. As methanol is the most common ingredient in the adulterated alcohol in this guideline we will briefly discuss about the management of methanol toxicity. In methanol intoxication common symptoms are visual disturbances (like decreased visual acuity, photo-phobia, and blurred vision), and abdominal pain. Some patients also present with neurological abnormalities, Kusmaul's breathing, impaired cardiac function, and hypotension. Visual disturbances and abdominal pain are found in 37 to 72% of patients.[18,19] In methanol intoxication immediate gastric lavage, induced emesis, or use of activated charcoal to remove alcohol from gastrointestinal tract needs to be initiated within 30 to 60 min after ingestion of alcohol. If facilities are available Administration of ethanol or fomepizole (not available in India) to delay or prevent generation of toxic metabolites can be done. If facilities are available dialysis (hemo/peritoneal) helpful in removing unmetabolized alcohol and possibly toxic metabolites and delivering base to patient to ameliorate metabolic acidosis. Although ethanol has never been approved by the Food and Drug Administration for this purpose, it has been used in the treatment of methanol and ethylene glycol intoxication for many years.[20-23]

5. MANAGEMENT OF ALCOHOL WITHDRAWAL AND DETOXIFICATION

5.1 Withdrawal state

Alcohol withdrawal syndrome usually occurs in physically dependent individuals who discontinue or reduce alcohol use after a period of regular and heavy use. The symptoms of alcohol withdrawal (AW) may range in severity from mild tremors to convulsions and delirium. Mild AW can cause pain and suffering; severe AW can be life-threatening.

5.1.1 Simple withdrawal state

The signs and symptoms of alcohol withdrawal appear between 6 to 48 hrs after the cessation or reduction of heavy, prolonged ingestion of alcohol. Initial symptoms may include gastrointestinal distress, anxiety, irritability, elevated blood pressure, tachycardia, and autonomic hyperactivity. These initial symptoms of alcohol withdrawal intensify and then diminish over 24-48 hrs. The symptoms would be normally abating over duration of 5-7 days. The factors which predict the severity of a withdrawal syndrome include 1) time elapsed since last use, 2) concomitant use of other substance use, 3) the presence or absence of concurrent general medical or psychiatric disorders, and 4) past complicated withdrawal syndromes.

5.1.2 Complicated withdrawal state

The syndrome of severe alcohol withdrawal includes delirium tremens and seizures (complicated withdrawal). Withdrawal seizures ('rum fits') occur within 12 to 72 hours of alcohol cessation, characterized by major motor (generalized tonic clonic) seizures that occur during withdrawal in patients who normally have no seizures and have normal EEGs. In 60% of patients, the seizures are multiple (in burst of 2 to 6), but only 3% of patients go on to develop status epilepticus. About 30-40% of patients with alcohol withdrawal seizures progress to DTs.

Delirium tremens (DT) is most severe neurological complication of alcohol withdrawal occurring in 5% of patients is associated with high mortality rate. It usually begins after 2 to 5 days of sudden reduction/stoppage of alcohol use. It may also triggered by infection, illness, or head injury in people with a history of alcohol abuse. It is characterized by usual alcohol withdrawal symptoms, *plus* reduced level of consciousness, disorientation in time, place and person (non-recognition of close family and friends),

impairment in recent memory, disruption of the sleep-wake cycle with insomnia or daytime sleepiness, transient hallucination, delusion and evening worsening of symptoms, with severe agitation and coarse tremors of limbs and body. In addition to above the patient may have ataxia, autonomic disturbances and mild pyrexia. No specific findings on physical examination are diagnostic for DTs. It is a Medical emergency with mortality rate of 20-50 % of patients if not treated, and at times 5-10% mortality even with treatment. Delirium tremens complications may include dehydration, arrhythmias, hypotension, renal failure and pneumonia.

5.2 Treatment Goals

Management of Alcohol withdrawal state has the following goals

- To relieve patient's discomfort, prevent the occurrence of more serious symptoms, and forestall cumulative effects that might worsen future withdrawal.
- To utilise the withdrawal treatment opportunity to engage patients in long-term management

5.3 Treatment regimens for alcohol withdrawal

Alcohol withdrawal is managed only through pharmacological methods. The pharmacological agent which can be called as an 'ideal' agent should be effective in relieving the symptoms of alcohol withdrawal and also should prevent alcohol withdrawal seizures and delirium. It should be safe in overdose, with benign side effect profile, less drug-drug interaction, tolerability, and suppress drinking during and after alcohol withdrawal.[24]

5.4 Treatment settings

Alcohol withdrawal can usually be managed in outpatient settings. However, in certain conditions inpatient management of withdrawal is preferred, for example, when the patient 1) Is confused or has hallucinations; 2) Has a previous history of complicated withdrawal; 3) Has epilepsy or a history of fits; 4) Is undernourished; 5) Has severe vomiting or diarrhoea; 6) Is at risk of suicide; 7) Has severe dependence coupled with unwillingness to be seen daily; 8) Has a previously failed home-assisted withdrawal; 9) Has an acute physical or psychiatric illness; 10) Has multiple substance misuse and 11) Has a home environment unsupportive of abstinence.

5.5 Pharmacological agents:

There are several systemic reviews, metanalysis and guidelines which have reviewed various pharmacological agents used in managing alcohol withdrawal states. The agents are directed towards reducing CNS hyperexcitability and restoring physiological homeostasis. The common groups of drugs used are Benzodiazepines, anticonvulsants and other groups of drugs as described below.

5.5.1 Benzodiazepines:

Benzodiazepines are a class of sedative medications used to treat anxiety, insomnia and seizures. Because of cross tolerance between alcohol and benzodiazepines, they are used for alcohol withdrawal symptoms.

5.5.1.1 Evidence base

Several meta-analyses and systematic reviews have consistently shown that benzodiazepines are better than placebo in reducing the severity of withdrawal, prevention of delirium and withdrawal seizures and thereby leading on to higher success rate of detoxification and entering into long term programmes.[25-29] Several recent guidelines also recommended benzodiazepines as first line of treatment of alcohol withdrawal.[9-12] It can be clearly seen that benzodiazepines has a strong role in medication assisted withdrawal management in alcohol withdrawal syndrome.

5.5.1.2 Comparison between different benzodiazepines

Several studies which compared different benzodiazepines have consistently shown that all benzodiazepines are equally effective in management of the simple alcohol withdrawal state.[28,30-32] Some studies have shown that long acting benzodiazepines are effective in preventing seizures and delirium.[25,27-28] The benefits have to be weighed up against their risk in elderly and those with liver damage. Short acting benzodiazepines such as oxazepam and lorazepam are preferred in liver damage, in elderly and in people with cognitive disorders. Short acting benzodiazepines are preferred in liver disease as they undergo glucuronide conjugation in liver.[33] The short acting benzodiazepines because of their short half live have to be used frequently to manage withdrawal symptoms.[34-36]

5.5.1.3 Dosing patterns

Several studies have been conducted on dosing pattern of the benzodiazepines in alcohol withdrawal state. The benzodiazepines have been

used as fixed dose schedule, front loading schedule, and symptom triggered dosing. Symptom triggered dosing was found to be effective in faster control of symptoms and lesser dosing of benzodiazepines.[37] A metananlysis of 3 RCT's concluded that comparison of fixed-schedule versus symptom-triggered regimens, favor symptom-triggered regimens MD -1.10 [-3.27, 1.07] for CIWA-Ar scores at the end of treatment.[28] Recently a prospective RCT has shown no difference in loading protocol or symptom triggered protocol in CIWA-Ar score, Systolic blood pressure and dose.[38] Some studies have also showed that symptom-triggered self-medication was as safe as fixed-schedule medication in treating outpatients with mild to moderate withdrawal symptoms.[39-40] Some studies and guidelines have recommended use of fixed dosing in general care in community and symptom triggered dosing preferred when close observation is possible.[10,12,41] Overall, there is some evidence to indicate the superiority of symptom-triggered regimens when feasible; however, there is still no final word on the best method of benzodiazepine use in alcohol withdrawal state.

5.5.1.4 Indian Study

An Indian study also found that there is no difference in the benzodiazepines and they are equally effective in management of the simple alcohol withdrawal state. A RCT found that lorazepam and chlordiazepoxide were comparable in attenuating effects on uncomplicated withdrawal.[32]

5.5.2 Anticonvulsants

Anticonvulsants as they reduce glutamate overactivity and risk of brain toxicity during withdrawal they have been thought as a desirable alternative to benzodiazepines.

5.5.2.1 Evidence base

The use of anticonvulsants in withdrawal state has been studied in several studies[42-46] and considered in systematic reviews and metanalysis.[24-26,47] Studies have shown that anti glutamatergic drugs like memantine, topiramate or lamotrigine were efficacious in treating alcohol withdrawal similarly to diazepam.[48] Carbamzepine has been found to be efficacious in treating AWS and it is similar to lorazepam and oxazepam.[44] Other anticonvulsants, like oxcarbazepine, levetiracetam, pregabalin, have been found effective compared to placebo.[49-51] A Recent Metanalysis of 56 studies stated there is insufficient evidence for use of anticonvulsants in the treatment of alcohol withdrawal. It also states that anticonvulsants have limited side effects and they are effective for some symptoms such as seizures.[29]

5.5.2.2 Prophylactic use

The prophylactic use of anticonvulsants such as Phenytoin is not recommended except in cases of co-occuring seizure disorder and alcohol use.[52-55] Thus the role for anticonvulsants in alcohol withdrawal therefore still remains unclear except in cases of Alcohol withdrawal seizures.

5.5.3 Baclofen

Baclofen is a selective GABA B receptor agonist and in animal studies it was found to decrease alcohol withdrawal signs.[56]

5.5.3.1 Evidence base

In a randomised trial baclofen was efficacious in treatment of uncomplicated AWS comparable to that of the "gold standard" diazepam.[57] In a prospective, randomized, double-blind, placebo-controlled clinical study baclofen was associated with a significant reduction in the use of high doses of benzodiazepine (lorazepam) in the management of symptomatic alcohol withdrawal symptoms.[58] There is one small study which has shown 86% prophylactic success rate for alcohol withdrawal symptoms with Baclofen.[59] However a Cochrane review concluded that evidence of recommending baclofen for Alcohol withdrawal symptom is insufficient and better designed RCTs are recommend to prove its efficacy and safety.[60] Further studies that are double-blinded placebo controlled are needed to support or refute the usefulness of Baclofen for alcohol withdrawal.

5.5.4 Acamprosate

It stabilizes the chemical alterations in the brain in alcohol dependence by its antagonist action on NMDA receptor and agonist action on GABA Type A receptor.

5.5.4.1 Evidence base

The studies of Acamprosate in withdrawal state have shown contradictory results. In some studies it was found that acamprosate along with benzodiazepines improved symptoms[61] and in some studies when given at the beginning of detoxification they have worsened the symptoms.[62]

5.5.5 Other agents

There are several other medications which have been used in the management of the withdrawal state like beta-blocker (propranolol), and $\alpha(2)$-agonists (clonidine).[63-64] In a randomized double blind study Food supplements containing D-phenylalanine, L-glutamine and L-5-hydroxytryptophan have

found to alleviate withdrawal symptoms.[65] There is limited evidence currently of these agents in withdrawal stage.

5.6 Alcohol withdrawal - related Seizures

Several studies and metanalysis have consistently found that benzodiazepines reduce withdrawal severity and the incidence of seizures and delirium.[25,52,55] A systemic review concluded that both short acting (lorazepam) and long acting (diazepam) benzodiazepines are effective in primary or secondary seizure prevention. There is some evidence to suggest use of carbamazepine in prevention of the seizures in alcohol withdrawal state but evidence is insufficient to recommend its use.

5.7 Alcohol withdrawal - delirium tremens (DT)

Delirium tremens has high mortality and morbidity and hence its recognition and treatment is very important. Because DT's are more likely to occur in patients who have co-occurring medical illnesses, the recognition and aggressive treatment of such illnesses is paramount.

5.7.1 General measures for management of DT

All cases of DT should be managed as inpatient in hospital. The general measures like maintaining water and electrolyte balance, correcting metabolic disturbances, nutritional supplement and administering medication should be done as appropriate. The patient should be kept under close supervision at all times. Safe and protective environment should be provided.

5.7.2 Specific measures for management of DT

A metanalysis of 9 prospective controlled trials showed that benzodiazepines are more effective than neuroleptics in reducing mortality in alcohol withdrawal delirium.[66] There are case series of use of Baclofen, Ethyl alcohol, Lamotrigene and magnesium in alcohol withdrawal delirium and evidence is insufficient to recommend their use.[66-68]

5.8 Alcohol related Brain Disorders

Alcohol use disorders in some proportion of the cases are associated with preventable and irreversible conditions like Wernicke's encephalopathy and Korsakoff's syndrome. Initially they were considered as two separate entity but nowadays they are considered as unitary entity called as Wernicke–Korsakoff syndrome (WKS). Wernickes encephalopathy is an acute condition which in proportion of cases proceeds to Korsakoffs syndrome.

There is a need for high degree of suspicion in high risk cases (those with diarrohoea, vomiting, physical illness, weight loss, poor diet, malnutrition cases) and adequate assessment and diagnosis is still a challenge.

5.8.1 Wernicke's encephalopathy (WE)

Wernicke's Encephalopathy is an acute neuro-psychiatric condition caused by an insufficient supply of thiamine (Vitamin B1) to the brain.

5.8.1.1 Clinical characteristics of WE

The diagnosis of WE have been proposed with only two of the classic triad (ophthalmoplegia, ataxia, confusion) and dietary deficiencies.[69] A presumptive diagnosis can be made if we have evidence of ophthalmoplegia, ataxia, acute confusion, memory disturbance, unexplained hypotension, hypothermia, coma, or unconsciousness in patients with alcohol dependence.[70] A high risk of suspicion has to be kept in patients who are found to be using large quantity of alcohol users (drinking >15 units per day for a month or more) and where there is evidence of recent weight loss or vomiting or diarrhoea or malnutrition or peripheral neuropathy or chronic ill health. The treatment of Wernicke's syndrome is a medical emergency requiring treatment on a highly supervised medical unit.

5.8.1.2 Management of WE

There are no RCT of the use of thiamine in WE. It is recommended that all suspected cases of WE and high risk cases it is recommended to give parental thiamine as they are absorbed faster. Patients at risk of Wernicke-Korsakoff's syndrome or suspected cases should be treated with 100mg of intramuscular or oral thiamine before any glucose intake. There is no consensus on how long thiamine has to be used in WE or in high risk cases. The British National Formulary recommends 200-300 mg of thiamine daily for treatment of severe deficiency.[71] In Indian setting it is recommended that all the suspected or high risk cases of WE parental thiamine be given for fortnight along with oral preparation of 100-200mg of thiamine. In all cases of alcohol detoxification it is recommended to start oral thiamine for minimum of three months.

5.8.2 Korsakoff syndrome

If Wernicke's encephalopathy is undiagnosed or inadequately treated, it is likely to proceed to Korsakoff's Syndrome. The best treatment for

Korsakoff's Syndrome is timely recognition of Wernicke's Encephalopathy and appropriate intervention and prevention.

5.8.2.1 Clinical features of Korsakoff syndrome

The diagnosis of korsakoff's syndrome is made if we have Severe anterograde amnesia (memory is not transferred from short- to long-term memory storage), Retrograde amnesia and Cognitive deficits.

5.8.2.2 Management of Korsakoff syndrome

Once cognitive impairment or Korsakoff's syndrome is evident and adequate thiamine replacement has been given, little additional pharmacotherapy to ameliorate cognitive impairment has been shown to be effective.

5.8.3 Dosage of thiamine:

Insufficient evidence available from randomized clinical trials in regards to the dose, frequency, duration, and route of administration of thiamine both for the prophylaxis against Wernicke Korsakoff syndrome and for the treatment of Wernicke korsakoff syndrome.[72] A review recommends 200 mg thrice daily thiamine before any carbohydrate in high risk cases and the overall safety of thiamine is good.[73]

Alcohol withdrawal: Key Recommendations:

- Benzodiazepines are efficacious in reducing signs and symptoms of withdrawal (A); fixed-dose regimens are recommended for routine use with symptom-triggered dosing reserved for use only with adequate monitoring (D)
- The evidence for the use of acamprosate in alcohol withdrawal is confusing. Some trials have shown that when given along with Benzodiazepines during withdrawal they improved outcome(Ib), whereas some trials (Ib) have shown that they indeed worsen the outcome when given during the beginning of detoxification (A)
- Baclofen – Evidence is insufficient for its use in alcohol withdrawal (A)

Seizures:

- Both short acting and long acting Benzodiazepines are effective in primary and secondary seizure prevention (A)

- Some evidence to suggest the use of carbamazepine in prevention of seizures in alcohol withdrawal but evidence is insufficient to recommend the use of carbamazepine (A)

Delirium

- Benzodiazepines are more effective in preventing delirium, and in reducing mortality in alcohol withdrawal delirium (A)

Key uncertainties

- The role of Serotonergic agents, food supplements in alcohol withdrawal – evidence is insufficient
- What is the appropriate regimen for maximum symptom control, reducing risk of complications, preventing neuroinflammation and brain damage?

Alcohol related brain disorder:

- High index of suspicion should be maintained as WE does not present with all signs and symptoms
- All suspected cases to be given parental thiamine (D)
- Patient at risk of Wernicke-Korsakoff's syndrome or suspected cases to be treated with 100 mg of intramuscular or oral thiamine before any glucose intake (D)
- **Indian setting:** Suspected or high risk cases of WE parental thiamine to be given for fortnight along with oral preparation of 100-200 mg of thiamine (D)

Key Uncertainties:

- About the exact dose, duration, route of administration not so clear?
- Role of prophylactic thiamine to prevent WE?
- Treatment of persistent symptoms of Korsakoff syndrome in the long term?

6. MANAGEMENT OF ALCOHOL DEPENDENCE

Alcohol dependence is a chronic illness with lapses and relapses. Medications and psychosocial strategies are used for promoting abstinence

and preventing relapse in patients with alcohol dependence. All the pharmacological agents used in alcohol use disorders have been studied along with psychosocial interventions. Hence patients should use whichever psychosocial approach they think beneficial or is available along with pharmacological agents.

6.1 Pharmacological agents:

The pharmacological agents have been broadly classified as aversive (deterrent) agents and anticraving agents. Disulfiram is the only aversive agent and all other agents like acamprosate, naltrexone, topiramate, baclofen etc., are used as anticraving agents.

6.1.1 Disulfiram:

6.1.1.1 History & Mechanism of Action

Disulfiram is the first pharmacological agent approved by FDA in 1951 for alcohol dependence. It is being used for more than 50 years and it is the cheapest pharmacological agent available in India at this time. Disulfiram is the only drug which is used for complete abstinence of alcohol dependence. Disulfiram is a irreversible inhibitor that blocks aldehyde dehydrogenase, causing accumulation of acetaldehyde if alcohol is consumed, resulting in nausea, sensation of heat in head & neck, hypotension, flushing, and palpitations. This deters people from drinking along with disulfiram.[74] Recently it has also been found that disulfiram blocks dopamine-b-hydroxylase in the brain, which in turn leads to increase in dopamine and reducing noradrenaline, contributing to its clinical effects in alcoholism or cocaine addiction.[75]

6.1.1.2 Evidence base

Many of the earlier controlled trials which were conducted with disulfiram have not demonstrated any advantage of disulfiram over placebo in achieving total abstinence, delaying relapse, or improving social stability.[74] A review (systematic/ metanalysis) of older trials report that disulfiram is no better than placebo in preventing lapse to drinking.[11,76-77] These studies were done a decade earlier and not as rigoursly undertaken. The problem is also due to deterrent effect of the DER and people who are entering the trial should be informed of the reaction and proper blinding is difficult. Recently there are several studies which have showed that ‘supervised’ disulfiram use was found to better than placebo, naltrexone, acamprosate, lengthening time to

relapse and maintaining abstinence on short term abstinence rate.[78-81] Clinician who are using disulfiram for many decades believe that those who are motivated, have less impulsivity, intelligent and whose craving is dependent on internal and external cues are better candidates for disulfiram use and in them abstinence rate is better.

6.1.1.3 Dosage and Precautions

Disulfiram is prescribed usually in doses of 250mg/day. In some studies higher doses (500mg/day) of disulfiram was found to be useful.[82] Disulfiram can be started only when body is alcohol free for at least 24 hr. Patients must also be warned about potential for a reaction with alcohol for up to 7 days after stopping disulfiram. It is recommended to start disulfiram safely in patient desires to start on after explaining about medications during abstinence period. Disulfiram should never be used without patient's knowledge and consent. The patients using disulfiram also should be informed to avoid all forms of alcohol containing items (like after shave, pickles etc.,). There are no absolute contraindications for Disulfiram use except in patients who are unmotivated. The commonly reported side effects with disulfiram are drowsiness and gastric irritation. There are several reports showing safety of disulfiram in a wide range of patients, including those with psychosis[12] and hepatitis C.[83] So the clinician using disulfiram should not be excessively afraid of using disulfiram due to its reaction. The person using disulfiram should be carry a card containing information about disulfiram, drugs and food items to be avoided, DER, management of DER and give to medical professional when he visits them in clinic or emergency.

6.1.1.5 Duration of use

There is no evidence to guide how long to prescribe disulfiram, An open prospective study lasting 9 years reported that 2 years of treatment with disulfiram or calcium carbimide resulted in overall abstinence rates of 50%.[84] In some studies disulfiram has been used safely even for 15 years.[85-86] The guiding principle to stop disulfiram is when patient and therapist mutually agree and patient is confident of remaining abstinence. It is advisable to continue disulfiram for duration of one year.

6.1.1.5 Indian Studies

In India disulfiram is still the most commonly used as it is cheap and easily available. Disulfiram in Alcohol use disorders in Indian context is a useful treatment particularly when compliance with the drug regimen is overseen

by family members.[87] Recently there are well designed RCTs on disulfiram has consistently found that 'supervised' disulfiram use was found to better than placebo, naltrexone, acamprosate, lengthening time to relapse and maintaining abstinence on short term abstinence rate.[78-80]

6.1.2 Naltrexone:

6.1.2.1 History and Mechanism of action

Naltrexone is one of the most widely studied medications with a strong efficacy base in alcohol dependence. Naltrexone, an opiate receptor antagonist, is thought to act by preventing the opiate receptor mediated euphoric and rewarding effects of alcohol.[88-89] It also diminishes the rewarding aspects of alcohol induced dopamine release, thus blunting the subsequent craving for alcohol.[90-91]

6.1.2.2 Evidence base

There are several systematic reviews and meta analysis which have consistently concluded that that oral naltrexone significantly reduces return to heavy drinking, probably by reducing 'lapse to relapse', but does not necessarily improve cumulative or continuous abstinence rates compared to placebo.[11,92-93] Some interesting findings have emerged after post hoc analysis of several trials in alcoholism. Naltrexone was consistently found to be useful in people with family history of alcohol dependence.[94-96] Secondary analysis of COMBINE study has shown that Naltrexone has better outcome in Type A alcoholism (Babor classification) compared to Type B.[97] Long acting Injectable form of Naltrexone has been used to overcome poor adherence. A 6 month trial, XR-NTX (190mg & 380 mg monthly) reduced the rate of heavy drinking compared with placebo and the response rate significantly increased at higher rate.

6.1.2.3 Dosage and Precautions

Oral Naltrexone is given at dose of 50mg/day in nonopioid-abusing patients, and it can also be given while the patient is using alcohol. Higher doses (100mg/day or 150mg/day) have not been found to be much more efficacious compared to standard dose. Injectable forms are used in the dose of 190mg & 380 mg per month. Both formulations of Naltrexone have been associated with mild and transient side effects, including CNS-related symptoms (headache, fatigue, dysphoria) and gastrointestinal problems (nausea, vomiting, abdominal pain). The most common side-effects are nausea and

sedation.[93] Hepatic toxicity has been reported with Naltrexone, but it is rare in the usual doses.

6.1.2.4 Duration of use

There is no consensus on minimum duration of Naltrexone use in alcohol dependence. Majority of the efficacy studies were conducted for 3 - 6 months. A study has shown that longer duration of Naltrexone use (six months) had better alcohol related drinking outcomes compared to shorter duration (three months).[98] A recent guideline has recommended Naltrexone use for six months.[12] There are few studies which have looked into persistence of the effects after stopping Naltrexone. The earlier studies have shown that the effects would last for 14 or 16 weeks[99,100] but recent evidence from COMBINE showed that benefit continued for up to one year.[101-102]

6.1.3 Acamprosate:

6.1.3.1 History and Mechanism of Action

Acamprosate (calcium acetylhomotaurinate) is a synthetic molecule with a chemical structure similar to that of the endogenous amino acid N-acetyl homotaurine a small highly flexible with analogy to many amino acids most notably glutamate, gaba aminobutyric acid, aspartate, glutamate and taurine.[103-105] Acamprosate precise mechanism of action is still under investigations, but it is hypothesized that it acts as a functional glutamatergic NMDA antagonist.[106] It acts at the regulator site of receptor and reduces hyperglutamatergic state and reestablishes the homeostasis.[105,107]

6.1.3.2 Evidence base

Several systematic reviews and meta analysis which have consistently shown that acamprosate is better than placebo in maintaining abstinence and in preventing relapse.[77,107-111] Recently there are three reasonably large studies which have shown negative results with Acamprosate.[101,112-113] In a recent Cochrane meta analysiswhich included 24 RCTs it was found that when compared to placebo acamprosate was shown to signicantly reduce the risk of any drinking RR 0. 86 (95% CI 0. 81 to 0. 91) and to signicantly increase the cumulative abstinence duration MD 10. 94 (95% CI is 5.08 to 16.81).[114] Some meta analysis or systematic reviews (but not all) have shown that acamprosate can reduce ‘heavy drinking’ in patients who have relapsed.[111,115]

When comparison were made between Acamprosate and Naltrexone COMBINE study in USA found that naltrexone (100mg) with medical management alone or in combination with combined behavioral interventions resulted in greater improvements than placebo or medical management alone, whereas acamprosate (3gms) showed no evidence of additional efficacy in any combination.[101] In a recent metanalysis (Three trials) concluded that there was no superiority of one or the other drug on return to any drinking, return to heavy drinking and cumulative abstinence duration.[114] The studies which have combined Acamprosate and Naltrexone conferred no additional benefit to naltrexone but improved outcomes compared with acamprosate.[116-117]

6.1.3.3 Dosage and Precautions

Acamprosate is available in 333mg pills and doses depend on the weight of the patient and it ranges from 999 mg/day to 1998mg/day. Acamprosate is generally well tolerated, with gastrointestinal disturbance (e.g. nausea, diarrhea) being the most common side effects reported.[11,111] Acamprosate is not metabolized in liver[118] and is excreted unchanged in kidney.[119] It can be given safely to a wide number of patients with physical comorbidity, although with caution or even contraindicated in those with severe liver and renal impairment.

6.1.3.4 Duration of use

Acamprosate currently has be recommended to be used for a year as effect size of abstinent rate increased from 3 months (1.33) to 6 months (1.5) and 12 months (1.95).[11,120] The benefits of acamprosate was observed to last for 3 – 12months after stopping of the medication.[114]

6.1.3.5 Indian studies

There are very few studies comparing Naltrexone with acamprosate in India. In a retrospective chart review done in north India comparing Acamprosate with Naltrexone it was found that acamprosate combined with family and social support had a modest effect on short-term outcome compared to Naltrexone.[121]

6.1.4 Baclofen:

6.1.4.1 History and Mechanism of Action

Baclofen a stereo selective gamma aminobutyric acid B receptor (GABA) agonist which is used in management of central muscle spasms for several

decades. Baclofen has been found to inhibit the release of several neurotransmitters, including dopamine, noradrenaline, glutamate and serotonin. Preclinical evidence in rats has shown that baclofen can suppress alcohol withdrawal signs in physically made dependent on alcohol.[56] (Colombo 2000).

6.1.4.2 Evidence base

In a RCT conducted in cirrhotic patients Baclofen was observed to be effective when compared to placebo (71% vs 29%).[122] A recent RCT reported no such effects when compared with that of placebo in increasing abstinence.[123] A recent systematic review of three prospective RCT concluded that compared with placebo, those who were on Baclofen had higher rates of abstinence and low anxiety scores.[124]

6.1.4.3 Dosage and Precautions

Baclofen used in the dose of 30-60mg/day in alcohol dependence patients. There is some evidence from secondary analysis of the trials showing higher doses (60mg/day) superior to lower dose.[125] Baclofen holds promise and should be first line of management in patients with moderate to severe cirrhotic liver disease.

6.1.5 Topiramate:

6.1.5.1 History and Mechanism of Action

Topiramate is used in the treatment of epilepsy and prevention of headache has recently been tested in alcohol dependence. Topiramate reduces mesolimbic activity of dopamine by facilitation of the neurotransmitter gamma-aminobutyric (GABA) inhibitory action in its non-benzodiazepine receptor and the reduction of the glutamate excitatory action in the alpha-amino-3 hydroxy-5 metylisoxazole-4 propionic (AMPA) receptor and the kainate receptors.[126-128]

6.1.5.2 Evidence base

Several RCTs have consistently shown that topiramate (up to 300 mg/day) has been shown to improve the percentage of heavy drinking days, maintain abstinence, harmful drinking consequences, physical health and quality of life.[129-132] A meta analysis of 3 placebo controlled studies have shown that topiramate was more efficacious than placebo in reducing the percentage of heavy drinking days (23.2%, 95% CI: 15.7 to 34.4), increasing

the number of days of abstinence (mean difference: 2.9 days, 95% CI: 2.5 to 3.3). There were two RCTs comparing Topiramate with Naltrexone. One study showed that number of alcohol-dependent patients who remained abstinent over 12 weeks were significantly greater in those receiving topiramate (titrated to 300 mg/day) compared with either naltrexone or placebo.[133-134] Another study for six months found Topiramate (~200mg/day) and Naltrexone (50mg/day) were equally effective, with almost half maintaining abstinence.[135]

6.1.5.3 Dosage and Precautions

Topiramate has been used in the dose of 150mg-300mg/day. The side effects found in trials include paraesthesia, anorexia, insomnia, and difficulty with concentration.[134] The prescribing clinician should keep these troubling side effects in mind while prescribing topiramate. The optimal dosage and duration of Topiramate use needs still much research.

6.1.6 Selective Serotonin Reuptake inhibitor (SSRI):

SSRIs have been used in the management of alcohol dependence. Studies which have used SSRIs in trials have been less consistent in non depressed patients.[136-137] Sertraline (100mg/day) along with Naltrexone (50mg/day) did not improve the drinking outcome, when compared with naltrexone alone.[138-139] However another study, found that the combination was effective when compared with naltrexone alone as most of the subjects were depressed.[140] These drugs are generally used for individuals with comorbid depression. Sertraline, fluoxetine and escitalopram have been so far studied.[137,141] There are some literature to suggest that SSRIs are not beneficial and in some studies worsens outcome in early onset, family history positive alcoholics.[136,137, 142]

6.1.7 Other agents: There are several other drugs which have been studied and used in alcohol dependence. Some of these agents have been found useful in RCTs, some in open label studies and in few meta analysis has also been used. These drugs should not be used as first line of drugs in alcohol dependence and more evidence of efficacy of these drugs is necessary.

GHB a GABA-B agonist has shown efficacy in alcohol dependence syndrome. A Cochrane analysis of 13 RCTs concluded that compared to placebo GHB is better in preventing relapse and craving in detoxified alcoholics during 3 months of follow-up. Because of the risk of developing

addiction, and the misuse or abuse of this drug it should be used only under strict medical surveillance.[143]

Ondansetron an 5-HT 3 receptor antagonist has been found to be effective in alcohol dependent patients particularly in early onset group.[144]

Antipsychotics have been used in alcohol dependence cases. Recently Aripiprazole has shown efficacy similar to Naltrexone.[145-146] There are reports of quetiapine, olanzapine, Amisulpride, Flupenthixol, Haloperidol and clozapine improving drinking outcomes.[147-152] A recent multisite clinical trial showed no efficacy for quetiapine compared with placebo at reducing alcohol consumption in heavy-drinking alcohol-dependent patients.[153] Studies with TCA's in alcohol dependence patients has shown that patients with alcohol use disorders and depression benefit but not those with alcohol use disorders in the absence of depression.[154]

There are preliminary reports of useful of Pregabalin, oxcarbazepine and tiagabine in alcohol dependence.[155-157]

6.2 PSYCHOSOCIAL INTERVENTIONS

These include a variety of non-pharmacological strategies for management of alcohol dependence. Several efficacy trials have shown that structured specific therapies have better outcome compared to less defined supportive counselling. No particular psychotherapy has been found consistently to be better, than others in alcohol use disorders. Better results have been found when psychosocial therapies are combined with pharmacological medications. The commonly used psychosocial interventions are Motivation Enhancement therapy (MET), cognitive behavioral therapies (CBT), Behavioral therapies, group therapies, family therapies, Twelve Step Facilitation (TSF) therapy and relapse prevention counselling.

6.2.1 Goals of Psychosocial therapies

Psychosocial therapies in alcohol use disorders have the following goals

- Enhance efficacy of pharmacotherapy
- Achieving sustained drug free status
- Providing the relationship
- Change of life style
- Improved quality of life

6.2.2 Motivation Enhancement:

Motivation of the patient with substance use disorders to change their behaviours can be done in any stage of the treatment. There has been a great deal of research on different therapies to motivate patients with substance use disorders. The two therapies which have been well studied are Motivation Enhancement Therapy and Brief intervention.

6.2.2.1 Motivation Enhancement Therapy

Motivation Enhancement Therapy aims at maximizing the patient's intrinsic desire to change of substance use using motivational interviewing techniques.

6.2.2.1.1 Basic Principle

It is a brief therapy which uses an empathic, nonjudgmental, and supportive approach to examine the patient's ambivalence about changing substance use behaviors. MET can be used at any stage of the treatment.

6.2.2.1.2 Evidence base

It has been found to be efficacious in studies.[158-160] The Project MATCH, in which four MET sessions given as a stand-alone treatment either initially or as part of post hospitalization care were comparable to 12 sessions of CBT or Twelve Step Facilitation therapy (TSF), with benefits of treatment persisting through 3 years of follow-up.[161] Several reviews and metanalysis studies have shown that Motivational interviewing/MET has been found to be effective in reduction of alcohol use post intervention in alcohol abuse/ dependence.[162-167]

6.2.2.2 Brief Intervention

Another strategy called brief intervention (BI) has also been used for motivation enhancement using motivational interviewing techniques.

6.2.2.2.1 Basic Principle

It is a brief therapy consisting of Feedback, personal Responsibility, Advice, Menu, Empathy and Self efficacy which is summarised as acronym FRAMES. Requires much lesser time, can be carried out in primary health care setting, and is cost effective. The BI can be given by general physician, nurses, and psychologists in a short period of time.

6.2.2.2.2 Evidence base

The Mesa Grande project, which reviewed 361 controlled clinical trials (CCTs) (a three-year update), found BIs to be the most effective psychosocial

treatment in treating AUDs.[168] In several reviews and meta analysis it has been found consistently that BI has reduced alcohol consumption, and are as effective as more intensive treatments.[158,169-172]

6.2.3 Cognitive Behaviour Therapy (CBT):

6.2.3.1 Basic Principle

The therapies are based on the social learning theories aimed at improving self-control and social skills.

6.2.3.2 Evidence base

The cognitive behavioural therapies have consistently showed to reduce drinking and patients who have mastery over behavioural self control measures and cognitive behavioural stress management techniques have shown better outcome than control.[173-177]

6.2.4 Relapse Prevention counselling (RPC):

6.2.4.1 Basic Principle

Relapse prevention is a treatment approach in which CBT techniques are used to help patients develop greater self-control over alcohol use behaviors to avoid relapse.

6.2.4.2 Evidence base

Studies in Alcohol use disorders have consistently shown that people who have better coping strategy for internal and external stressors, learn from previous lapses and have mastery over self control measures have better outcome.[173,177]

6.2.5 Behavioural Therapies (BT):

6.2.5.1 Basic Principle

Behavioural therapies based on learning theories and positive reinforcements for target behaviours have been found to be effective.[178]

6.2.5.2 Evidence base

Aversive therapies have not found to be useful.[177] Community reinforcement approach which usually includes conjoint therapy, training in job finding, counselling focused on alcohol-free social and recreational activities, monitoring of disulfiram use has been found to be effective.[178]

6.2.6 Group Therapies:

6.2.6.1 Basic Principle

Group therapies helps in making efficient use of therapist time. All the therapies can be given in groups. It helps in decreasing the stigma and encourages people to discuss about their problems.

6.2.6.2 Evidence base

Group therapies involving assertive techniques, social skill training, family focussed therapy, and motivation enhancement has been shown to be effective.[177]

6.2.7 Family therapies:

6.2.7.1 Basic Principle

Alcohol use disorders are associated with disturbance in the family. Studies have shown dysfunctional families, families with high expressed emotions leads to substance use in patient and not able to maintain abstinence. Family plays an important role in patient's problem of drug abuse and in particular it is very important in the Indian context.

6.2.7.2 Evidence base

In particular, behavioral marital therapy has demonstrated efficacy and cost-effectiveness.[180-183]

6.2.7.3 Indian Study

In a recent study conducted in South India it has been found that individuals randomly assigned to dyadic relapse prevention (that is involvement of both patient and family members in the intervention) consistently performed better than those assigned to treatment as usual, and individual relapse prevention in terms of reduction in quantity of alcohol, drinking days, and number of days with dysfunction in family, occupational, and financial dimensions.[184]

6.2.8 Self help group approach and 12 step oriented programme:

6.2.8.1 Basic Principle

Most widely used self help groups are 12 step approach which are part of steps in Alcohol Anonymous (AA). AA or other 12 step approaches offers emotional support and a model of abstinence for people recovering from alcohol dependence.

6.2.8.2 Evidence base

In Project MATCH study, Twelve Step Facilitation (TSF)-based aftercare was more effective than that using CBT for outpatients who did not show psychiatric symptoms and was of comparable efficacy for those with psychiatric symptoms. At 1-year follow-up, patients rated as high in seeking meaning of life fared better with TSF compared with MET and CBT, and patients with high social support for abstinence had better drinking outcomes at 1- and 3-year follow-up.[161] A Cochrane review reviewed eight trials involving 3417 people concluded that available experimental studies did not demonstrate the effectiveness of AA or other 12-step approaches in reducing alcohol use and achieving abstinence compared with other treatments. They also concluded that AA may help patients to accept treatment and keep patients in treatment more than alternative treatments, though the evidence for this is from one small study that combined AA with other interventions and should not be regarded as conclusive.[185]

6.2.8.3 Indian Study

A five year follow-up study of 150 patients treated for alcohol dependence using a primarily Alcoholics Anonymous approach reported a modest outcome (16.5% remaining abstinent). It was also suggested by the authors that one year outcome is a good predictor of the 5 year outcome.[186]

6.2.9 Comparison of different therapies: It has been found from two large RCTs conducted in different continents (USA & UK) that psychosocial therapies differing widely in conceptual framework (MET, CBT, TSF, Social Behavior and Network Therapy), intensity, duration, and location have minimal long-term difference between inpatient/residential treatment and outpatient counseling approaches. The trials also found approximately equivalent (and reasonably good) outcomes with both brief, non-intensive treatments (MET) and intensive treatments (CBT, TSF, and SBNT) for moderately severe alcoholics.[187-188]

6.3 Combined Pharmacological therapies and psychosocial interventions

Research has demonstrated repeatedly that utility of pharmacological therapies can be enhanced when combined with psychosocial interventions. The beneficial effect of psychosocial interventions with Naltrexone has been studied for several psychosocial strategies in alcohol dependence with none having clear advantage over other. Cognitive Behavioral Theraphy (CBT) has a beneficial interaction with naltrexone and to be superior to supportive

therapy, and motivational enhancement therapy, and equal to medical management.[101,189] In Disulfiram treatment effectiveness is enhanced when adherence is encouraged through AA, group therapy and contingency management.[190-192] There are several well conducted reviews which have shown the efficacy of pharmacological and psychosocial treatments for relapse prevention in alcoholism.[120,193-194] In COMBINE study which examined whether acamprosate or Naltrexone individually or together provided any benefit in addition to standard medical management or more intensive combined behavioural intervention showed that all groups showed improvement in drinking outcomes, naltrexone with medical management alone or in combination with CBI resulted in greater improvements than placebo or medical management alone, whereas acamprosate showed no evidence of additional efficacy in any combination. A recent multicentre AHEAD randomized trial using both medications and psychosocial managements was associated with fewer alcohol problems.[195] As can be seen most of the literature shows that effectiveness of the pharmacological management can be improved by combining with psychosocial intervention, and all patients of alcohol dependence should be managed with some form of psychosocial interventions.

Key Recommendations: preventing relapse, maintaining abstinence

Pharmacological interventions: Pharmacological agents have been found to be effective in management of alcohol dependence.

- Disulfiram is effective if taken under supervision. Disulfiram can be offered as a treatment option for patients who intend to maintain abstinence (A).
- Acamprosate is better than placebo in maintaining abstinence and in preventing relapse (A); Acamprosate reduces heavy drinking in patients who have relapsed (A)
- Naltrexone reduces return to heavy drinking by reducing lapse to relapse, but does not improve the abstinence rate (A)
- Long acting Injectable form of Naltrexone has been used to overcome poor adherence (B)
- Baclofen produces a higher rate of abstinence and decreases anxiety (A)
- Baclofen holds promise and should be used as the first line of management in patients with moderate to severe cirrhotic liver disease (D)

- Topiramate reduces the percentage of heavy drinking days (A)
- SSRIs effectiveness is less consistent in non depressed patients (A). SSRIs are generally used for patients with comorbid depression (B)
- SSRIs may worsen outcome in early onset, family history positive alcoholism (D)
- Ondansetron may be effective in early onset group (D)
- Antipsychotics improves drinking outcome (D)

Non-Pharmacological interventions: Non-pharmacological interventions have been found to be effective in management of alcohol dependence.

- Combined pharmacological and non pharamacological intervention is effective than either alone (A)
- Interventions like Motivation Enhancement Therapy (MET) / Motivation Interviewing and Brief intervention (BI) have been found to be effective (A). They can be given in different setup by different professionals. A brief MET of 4 sessions has been found to be as effective as or better than other therapies for alcohol dependence. The effects have been improved when combining with medications (A)
- Cognitive Behavior therapy based therapies along with medications have found to be effective in relapse prevention, alcohol use (A).
- Family therapies along with medication have been found to be better in reduction of alcohol relapses and this has also been found effective in Indian setup (A)
- AA or other 12 step approaches have been found to be effective method for management but was not found to better than other treatments in reducing alcohol use and achieving abstinence (A)

Key uncertainties

- Predictors of response to a particular drug?
- How long the drug to be prescribed?
- How long the non-pharmacological therapies have to be prescribed?

7. SPECIAL POPULATIONS

7.1 Pregnancy & Breast Feeding

7.1.1 Brief Overview

Alcohol use during pregnancy has adverse effect on the health of the pregnant mother, fetal and child growth, and course of pregnancy. Alcohol consumption during pregnancy is the most widely recognized cause of severe mental and developmental delay in the baby. The most well established syndrome is Fetal Alcohol spectrum disorders (FASD). FASD is characterized by typical facial features, growth retardation, intellectual dysfunction.[196] Pregnancy provides a window of opportunity for women to seek treatment for their problems with alcohol out of concern for their unborn child. This also provides the treating doctor an opportunity to advise the pregnant women to think about their substance use.

7.1.2 Management

Recent metanalysis one on pharmacological therapy and another on psychosocial interventions in alcohol dependence concluded that there are no randomised control trials in pregnant women. They have also opined that there is a need for high quality research to determine the effectiveness of the therapy.[197-198] The goal of the treatment in pregnant women is to stop the alcohol use during pregnancy, treat the co-occuring medical or psychological problems, monitoring the pregnancy closely, motivation the pregnant women to be in the treatment during pregnancy and also post partum periods, and closely monitoring infant and child growth and intellectual development post delivery. Psychological therapies which aim to maintain abstinence during pregnancy should be the first line of therapy. If they are not successful pharmacological therapies like disulfiram, Naltrexone, Acamprosate can be used. They should be used after completely explaining the pros and cons about the drugs, continuing pregnancy and effects on the children.

7.2 Young age group

7.2.1 Brief Overview

Alcohol and substance use problems are a major issue in the developed countries. In India also this is going to become a major problem as age at first use of the alcohol is reducing.[4]

7.2.2 Management

Most adolescents with alcohol use disorders also have one or more co-occurring psychiatric disorders, such as conduct disorder and/or major depression, although ADHD, anxiety disorders, bipolar disorder, etc., The clinician who is treating them should assess for comorbidity and manage them accordingly.

There are several strategies which have been used and found to be successful in the problematic substance users. Systematic reviews and metanalysis studies have found that school based programmes, family based programmes and multipronged prevention programmes have found to be useful in medium and long term. There was no evidence to show that multiple components are more effective than interventions with single components. The studies also mentioned that there are large variations in the studies included and majority of the studies have come from the developed countries.[199-201]

7.2.3 Indian studies

An Indian study which included 4776 adolescents has showed that school based interventions for adolescents with problematic substance use is effective.[202]

7.3 Co-morbidity

There is high comorbidity of psychiatric problems in alcohol use disorder patients. Please refer to the chapter on dual diagnosis for management guidelines for such patients.

7.4 Problematic alcohol user:

7.4.1 Brief Overview

Problematic alcohol users refer to any user who has problem with alcohol use which may be physical, psychological, social consequences etc. It includes hazardous use of alcohol, harmful use of alcohol and alcohol dependence. Management of alcohol dependence has already been discussed and here we will be talking about management strategy available for hazardous alcohol use and harmful alcohol use. Hazardous use is a term given by World Health Organisation (WHO) to pattern of substance use which carries with it a risk of harmful consequences to the substance users. These consequences may be damage to physical or mental health, or social consequences to the substance users or others. Harmful use of alcohol as defined by ICD-10 refers to use of alcohol leading physical and psychological

harm to the individual. In India it has been estimated that more than 50% of regular alcohol users also fall into the category of hazardous drinking. This pattern of use causes contributes significantly to social problems (increased violence, Interpersonal problems, etc.,), physical (accidents etc.) and psychological illness, high risk sexual behaviors under intoxication, injury and death. These problem users do not come to the de-addiction centres and will be visiting the primary health care.

7.4.2 Management

Screening for alcohol use and brief intervention by the treating person can decrease considerable morbidity and mortality. Brief intervention (BI) used for motivation enhancement using motivational interviewing techniques has been described above in the section of motivation enhancement section. The BI can be given by general physician, nurses, and psychologists in a short period of time (5-15min) and is cost effective. The Mesa Grande project, which reviewed 361 controlled clinical trials (CCTs) (a three-year update), found BIs to be the most effective psychosocial treatment in treating AUDs.[159,203] The systematic reviews have shown that effectiveness of BI improved when people who were dependent on alcohol were excluded.[172,204-205] Several Metanalysis have consistently found that BI in primary care settings has been effective in decrease in the alcohol use.[206-208] A recent metanalysis of 29 controlled trials from various developed countries, settings (24 trials in general practice or 5 trials in emergency setting) of 7000 participants showed that after one year or more, people who received the brief intervention drank less alcohol than people in the control group. The benefits of brief intervention were similar in the normal clinical setting and in research settings with greater resources and with person providing the intervention. Longer counselling had little additional benefit. The effects were not significant in women after one year as compared to men on alcohol use.[209] All the people who are working in the Primary care to be trained for giving BI which will reduce a large mortality and morbidity.

Key Recommendations in special populations:

- Pregnancy provides an opportunity to think about the alcohol related problems. In pregnant women pharmacological treatments should be treatment of choice (C). When needed drugs can be used after discussing with the pregnant women about pros and cons and taking an informed decisions and close monitoring of the pregnancy (C)

- In young people with problems with alcohol use has shown that school based interventions, family based interventions and multipronged interventions have found to be effective in medium and long term (A). Young children should also be assessed for psychiatric comorbidity and managed accordingly (C).
- Brief intervention (BI) has been found to be effective in decreasing alcohol use in people with problematic alcohol users in different settings (A). The benefits of brief intervention were similar in the normal clinical setting and in research settings and with person providing the intervention (A).

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CLINICAL PRACTICE GUIDELINES (CPG) FOR THE MANAGEMENT OF OPIOID USE DISORDERS

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On behalf of IPS-SS-SUD

2014

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EXECUTIVE SUMMARY

Opioids figure among the substances associated with most severe problems. Opioid dependence is a chronic, relapsing disorder amenable to medical treatment. In India, Opioids have been used for centuries as medicines as well as for recreational purpose. However in recent years, the problem of opioid use – particularly through the injecting route – has assumed an entirely new dimension in India. This document seeks to review the available evidence regarding treatment of opioid use disorders and present some guidelines which are expected to aid Indian clinicians in clinical decision making and provide evidence-based services and care to their patients.

A thorough **assessment** is an essential first step for making a diagnosis and formulating a treatment plan, tailored to the identified needs of the patient. The goals of treatment of opioid use disorders include:

- *Abstinence from using opioids*
- *Retention in Treatment*
- *Reduction in the frequency and severity of substance use episodes*
- *Improvement in psychological, social, and adaptive functioning*
- *Reduction of harm associated with drug use (without reduction in drug use per se)*

Treatment settings

Treatment for opioid use disorders can be provided in a variety of treatment settings. Contrary to the popular misconception, hospitalization is required only for a minority of patients with specific indications for the same. Most patients can be managed in outpatient settings.

Management of opioid use disorders: General Principles

These include:

- *Motivation Enhancement*
- *Establishing and maintaining a therapeutic framework and alliance*

- *Assessing safety and clinical status*
- *Pharmacological management*

Managing intoxication / Overdose

The classic triad of severe opioid intoxication / overdose includes *coma, severely depressed respiration, and pinpoint pupils*. Overdose is a medical emergency which is managed by ensuring clear airways and breathing, and other supportive measures. **Naloxone** is the specific antidote, which can be administered, i.v., i.m. or even sub-cutaneous. The dose is 0.8 mg and usually the response is dramatic. Patients should however be monitored and observed after regaining consciousness.

Withdrawal Management (detoxification)

- The pharmacological treatment of choice for opioid detoxification is an agonist medication with long duration of action. With the available evidence reviewed, buprenorphine sublingual tablets is the most strongly recommended agent in India.
- The adequate dose and duration may vary from patient to patient and should be guided by withdrawal status of the patient, determined clinically.
- Most patients are likely to be stable in the range of buprenorphine 6 mg per day which can be tapered off within next 7-10 days.
- Depending upon the availability, other agonist medications like methadone can also be considered. Experience for methadone as agent for detoxification is yet to be accumulated in India.
- In cases where agonists cannot be used, clonidine treatment can be recommended, but only in the inpatient settings with careful monitoring of side effects (particularly hypotension).
- The phase of detoxification should be utilized for preparing the patients for a longer term treatment which is aimed at prevention of relapse and rehabilitation.
- Ultra rapid detoxification is not recommended owing to unnecessary expenses, risks involved and no extra benefits.

Agonist maintenance treatment / Opioid Substitution Treatment:

- Agonist maintenance treatment is preferred as the long-term treatment of choice for long-duration opioid users with severe dependence, with high risk of relapse and for those who are willing to comply with the requirements.
- Owing to its safety profile, evidence-base and experience in India, buprenorphine should be the preferred agent for the purpose.
- Buprenorphine induction involves administering the first dose in the relative opioid-free state (i.e. when patient is in mild withdrawals) and observation of the patient for 2 hours. The first day's dose is usually 4-6 mg.
- Depending on the response to first days' dose, dose can be titrated upwards or downward based on clinical parameters.
- For an effective treatment, it is essential to maintain the patients on optimum dose (i.e. the dose on which patients experience no *withdrawals*, no *craving*, and no *reinforcement on taking illicit opioids*). Most Indian patients are likely to be stable on daily dose of sublingual buprenorphine 8-10 mg/day.
- Since agonists are liable to be diverted and have abuse liability, the administration of agonist medications for the purpose of maintenance treatment should be supervised and observed, to the extent possible.
- Buprenorphine-naloxone combination is a relatively safer option which can be considered as 'take-home' medications, in the settings where it is available.
- In settings where methadone is being used as an agent, the process of induction would involve administering lower doses in the beginning (10 to 20 mg per day on first three days) and subsequent dose increments of about 5 mg every third day (owing to accumulation of methadone in the body).
- Though Indian experience is limited, it is expected that most Indian patients would require stabilisation dose of methadone between 40 and 80 mg per day.

- As yet it is difficult to choose between buprenorphine and methadone as maintenance treatment in the Indian context. Methadone offers the advantage of being a pure agonist and consequently better subjective experience for patients. However, the process of slow induction of dose of methadone coupled with its relatively higher risk of overdose makes buprenorphine a more convenient option. The relative cost of treatment per day per patient of methadone and buprenorphine are yet to be determined.
- Along with optimum dose, adequate duration of treatment and retention in treatment are crucial factors, which determine outcome of OST. The decision regarding duration of treatment and treatment-completion (i.e. tapering of agonist maintenance medication to make patient opioid free) should only be arrived at in consultation with the patient and involves evidences that patient is stabilized, is leading an illicit opioid-free life and is socially and occupationally rehabilitated. Till such criteria are evident, the agonist maintenance treatment should continue, if required, for very long duration (running into years).
- Switching to use of another substance such as alcohol or cannabis (substitute dependence) remains a possibility in opioid dependent patients undergoing long-term treatment. Clinicians should remain careful and vigilant about this.
- In many settings, agonist maintenance treatment involves some programme management requirements. Availability of adjunct psychosocial treatment is an essential part of package of agonist maintenance treatment.

Antagonist (Naltrexone) treatment:

- Long term treatment with oral naltrexone is indicated for opioid dependent patients with a relatively shorter duration of opioid use, less severe dependence, high motivation, better social and occupational status, and good social support.
- Induction with naltrexone requires a totally opioid free state (at least three days of confirmed abstinence from short acting opioids, determined clinically). Confirming opioid-free state with naloxone challenge test is a good practice (though not mandatory).

- The dose of oral naltrexone is 50 mg per day. Owing to its long duration of action, it can also be administered, 100 mg every alternate day or 150 mg every third day.
- Involving family members for supervising naltrexone administration is a good practice.
- Though naltrexone is safe in general, to avoid risk of hepatotoxicity, liver function tests should be monitored at baseline and during the course of therapy (every three months).
- Confirming abstinence by other sources of information besides self-report, (family members, urine screening) is a good practice.
- Owing to limited evidence-base and controversies, depot preparations of naltrexone are not recommended.
- Switching to use of another substance such as alcohol or cannabis (substitute dependence) remains a possibility in opioid dependent patients undergoing long-term treatment. Clinicians should remain careful and vigilant about this.
- Availability of adjunct psychosocial treatment is an essential part of package of naltrexone treatment. Since there is risk of loss of tolerance and consequent risk of opioid overdose in the event of relapse, all patients should be educated about it.
- Along with optimum dose, adequate duration of treatment and retention in treatment are crucial factors, which determine outcome of long term treatment with naltrexone. The decision regarding duration of treatment and treatment-completion (i.e. stopping naltrexone) should only be arrived at in consultation with the patient and involves evidences that patient is stabilized, is leading an illicit opioid-free life and is socially and occupationally rehabilitated. Till such criteria are evident, the treatment should continue, if required, for very long duration (running into years).

Psychosocial Interventions:

- Most psychosocial interventions have been described in general terms. It is the task of therapist to tailor them according to the needs of particular patient.

- While choice of psychosocial interventions will be guided largely by the availability of therapeutic skills, some essential psycho therapeutic interventions should be provided to ALL patients in combination with pharmacotherapy. These are: Motivation Enhancement / Motivation Interview, Psycho-education and Relapse Prevention.

Special Population Groups

Women in pregnancy and lactation present with specific clinical needs. Agonist maintenance treatment is the preferred treatment option during pregnancy and lactation. Though most guidelines discourage agonist maintenance treatment for *adolescents* and minors there is growing evidence that this treatment approach can be effective and safe for adolescents as well. Outcome of ART is improved in *HIV positive individuals* on agonist maintenance treatment with methadone or buprenorphine. The help-seeking behaviour of *chronic pain patients* can be easily misconstrued as addiction. Agonist maintenance treatment has been found to be effective even for *prison inmates*.

1. Introduction

Substance use is a complex problem having multiple medical and social ramifications. It affects not only the user and their families but all sections of the society. [1] Opioids have been used for analgesic and other medicinal purposes for hundreds of years, but they also have a long history of misuse for their psychoactive effects. Continued opioid use can lead to development of opioid use disorders like abuse and dependence. Heroin is the most popular opioid, associated with abuse and dependence, all over the world. However, there is growing public health concern about prescription opioids, which have significant abuse liability, and are increasingly being used for nonmedical purposes. It is now being accepted that opioid dependence is a chronic, relapsing disorder amenable to medical treatment and intervention.[2]

1.1. Opioids: History

World: Crude opium or alcoholic solutions of opium have been used for at least 3,500 years. Thomas Syndeham noted medicinal property of opium in 1680. In the 1800s, morphine and codeine were isolated from opium, they gradually replaced crude opium for medicinal purposes. The first semi-synthetic opium derivative (diacetylmorphine or heroin) was introduced into medicine in 1898 and marketed as an effective cough suppressant. The first purely synthetic morphine-like opioids, meperidine and methadone were introduced into medical practice in the 1940s. The term opioid was coined to include the opiates, the semisynthetic drugs produced from opium derivatives, and totally synthetic agents bearing little chemical resemblance to morphine. Opioid withdrawal was first recognized in 1700 and addiction was common by the middle of the 19th century, particularly among white middle-class women who were given opiates for various ailments like neurasthenia to cough and post childbirth ailments. At the same time, the use of opioids by the intravenous route with the newly introduced hypodermic needle and syringe was also recognized. Thereafter multiple laws came to regulate opioid use in western countries like Pure Food and Drug Act of 1906 and Harrison Narcotics Act of 1914. [2]

India: Opium poppy has been cultivated in India since the 10th century. The *'Dhanvanatari Nighantu'* an ancient Indian medical treatise of the 10th

century lists opium as a remedy for a variety of ailments. In the early part of 16th century, opium was cultivated in India as a federal monopoly during the Moghul period. The *'Ain-e-Akbari'*, a historical record of the times and period of Moghul Emperor - *Akbar* (1556 to 1605AD) states that opium was cultivated in all the provinces of North India scattered over an area of more than one million sq. km. After the decline of Moghuls, the Britishers controlled opium production from year 1773. After independence the Indian Government checks and monitors its production and usage.[3] (IV)

Habitual use of opium has been reported in India in the early 19th century. However, little attention was paid to the effects of opium on regular user. Opium cultivation by Indian farmers was a major source of revenue in the 19th Century. The Opium Act of 1857 and 1878 provided the legislative basis for strict control of opium and its use in India. The first formal enquiry on the prevalence of opium use was made in 1893 and subsequently in 1895. These two Royal Commissions examined over 700 witnesses from all sections of the society and looked into various patterns of use of opium. The commission concluded that opium smoking was rare but oral consumption was quite prevalent. It was seen that the practice of giving opium to infants was quite common. Smoking of opium in religious ceremonies was also reported. The recommendations led to the formation of British Government's Opium Policy which was continued till 1947.Chopra & Chopra (1965) [4] (IV) investigated the effects of regular opium eating among subjects in 1935. Study revealed that moderate users of opium were by and large healthy. However, a minority was regular users and needed long term care and supervision. The British recognized this and allowed registration of opium users so that they could get their quota of opium from licensed shops maintained by the Government. Thus, there has been a long standing history of not only opioid addiction in India, but also managing this addiction through providing access to opioids in a regulated fashion, akin to the agonist maintenance treatment of today.

After gaining independence in 1947, India prohibited non-medical use of various narcotic substances as a part being signatory to various international conventions including Single Convention on Narcotic Drugs (1961). Thus, fresh registration of opium users was gradually discouraged and hence the number of registered opium addicts decreased from 200,000 in 1956 to 570 in 2003 and only 44 in 2004. [5] (IV)

1.2. Epidemiology

Worldwide, some 12 to 21 million people used opiates (0.5-0.8%) and about three quarters of them used heroin in 2010. Though the prevalence of opioid use may be low in the general population, opioids are more often associated with the 'problem drug use' [6] (IV). In India, as per the National House Survey (NHS), current prevalence of opiates was 0.7% among males. [7] (III). This translates into as many as two million opioid users in India. Clearly the problem is enormous in its dimensions. A study conducted [8] (III) in Chandigarh (N=59470) found prevalence of opioid use to be 0.4%. Another study [9] (III) conducted in rural population (n=2415) of Lucknow found prevalence of drug use to be 21.4/1000. Among them prevalence of opioid use was 1.4%. In another study carried out simultaneously with NHS, data from treatment centres (Drug Abuse Monitoring System-DAMS) revealed that amongst all patients reporting for treatment, about 9% were opium users. They were concentrated in certain states of India. [7] (III). Basu et al. (2012) conducted retrospective chart review of three decades and found prevalence of opiate use were ranging between 37-53% among treatment seekers. They found that subjects presenting for the treatment of opioid dependence were 36.8% (n=204), 42.9% (n=809) and 53.2% (n=2219), respectively for the three decades (P<0.001). The proportion of subjects using natural opioids decreased over the three decades, with a concomitant emergence and/or increase of newer and prescription opioids such as buprenorphine, codeine and dextropropoxyphene. [10] [III] Similarly National drug dependence treatment centre (NDDTC), AIIMS, New Delhi reported the data collected through Drug abuse monitoring system (DAMS) from 55 government deaddiction centres between 2006-2009. The prevalence of opiates use was 41-43%, and among opiates prevalence of heroin use was (15-17%), opium (11-14%), and other opiates (13-15%). [11] [III]

1.3. Consequences of opioid use

Opioid dependence imposes a significant economic burden on society, not only in terms of directly attributable health-care costs (e.g. treatment and prevention services, and other health-care use), but also in terms of its impact on other budgets (notably social welfare and criminal justice services). Opioid dependence also has an effect on productivity, due to unemployment, absenteeism, and premature mortality. Studies in industrialized countries have attempted to place an economic value on the aggregate impact of these

consequences, with findings of from 0.2 to 2% of a country's gross domestic product (GDP). [12-14] (IV)

Box 1: Injecting Drug Use: A new dimension to harms associated with opioid use

Injecting drug use (IDU) has been strongly associated with HIV, accounting for 30% of HIV infections outside sub-Saharan Africa, and up to 80% of cases in some countries in eastern Europe and central Asia. [15] Once it enters a drug-using population, HIV can spread rapidly, and new epidemics of HIV infection mediated by intravenous drug use are occurring in sub-Saharan Africa. [16] Unsafe injecting practices associated with injecting drug use have also led to a global epidemic of hepatitis C. An estimated 130 million people are infected with hepatitis C, with 3–4 million people newly infected each year (CDC, 1998). Unsafe injection practices are the main route of transmission, accounting for an estimated 90% of new hepatitis C infections. In countries with a low prevalence of HIV, opioid dependent individuals have been found to have an annual mortality of 2–4% per annum, or 13 times that of their peers. [17] In India too, among all risk groups, prevalence of HIV is highest among IDUs (9.19%). [18] There are pocket of very high prevalence of Hepatitis C (60-90%), other wise the range is moderate (30-50%) among Indian IDU populations.[19]

1.4. Pharmacology of opioids: A Brief outline

The term opioid is referred in a generic sense to all drugs natural or synthetic which bind with the opioid receptors in the brain. There are *internal or endogenous opioids*, which are produced inside the body, and *external opioids* include either natural opium alkaloids or semi-synthetic and synthetic compounds having morphine like activity.

1.4.1. Endogenous opioids

There are three genetically distinct families of endogenous opioid peptides which have been identified: enkephalins, endorphins and dymorphins. Each family is derived from distinct precursor polypeptides, the pro-enkephalin, pro-opiomelanocortin (POMC) and pro-dynorphin. These peptides have characteristic anatomical distribution. [20] More recently, another distinct family of opioid peptides was identified, termed endomorphins. These appear to have a high affinity and specificity for the receptor and produce analgesia in mammals. [21]

1.4.2. Exogenous opioids

The exogenous opioids have been classified by Reisine and Pasternak (1996) [20] in the following ways:

A. According to the source

- Natural opium alkaloids - morphine, codeine.
- Semisynthetic opiates - diacetylmorphine (heroin), ethylmorphine, pholcodeine.
- Synthetic compounds - pethidine, fentanyl, methadone, Dextropropoxyphene, sulfentanil, synthetic opioid peptides like DAMGO**,** CTOP**,** DALCE**,** etc.

B. According to the action on the opioid receptor

- Opioid agonists - they bind to opioid receptors and mimic the effect of morphine, heroin, and methadone.
- Opioid antagonists - These drugs binds to opioid receptors but do not mimic the effect of morphine. They are devoid of intrinsic activity and inhibit action of morphine eg. Naloxone and naltrexone.
- Partial agonists - Even at full saturation of the receptor these compounds have less than the maximal effect obtained with morphine, the full agonist e.g. Buprenorphine, pentazocine.

1.4.3. Opioid receptors

In order to understand the physiologic factors underlying opioid addiction, it is first necessary to understand the function of opioids and opioid receptors. An opioid agonist is any exogenous substance that binds specifically to any of several subtypes of opioid receptor and that produces some action. Although many opioids produce actions similar to that of morphine (a prototypical μ-opioid receptor agonist), others may bind to various receptor subtypes in a pattern that is distinct from that of morphine, producing a dissimilar profile of actions, and may not suppress the morphine abstinence syndrome. Several opioid receptor types have been described and characterized. Three of these, μ, δ, and κ, have been recognized for some time. More recently, a fourth receptor type, OFQ/N (ORL-1), has been accepted as part of an extended family of opioid receptors. All of the opioid receptor types, including OFQ/N, are typical G-protein–coupled receptors. [2]

Most opioid drugs associated with opioid abuse and dependence are μ receptor agonists, which exert action primarily at receptors on neural tissues in the CNS, the autonomic nervous system. These actions produce effects that include analgesia, respiratory depression, miosis, changes in mood, indifference to anticipated distress, drowsiness, decreased ability to concentrate, changes in endocrine and other functions regulated by the hypothalamus, and increased tone of smooth muscle in the gastrointestinal (GI) tract. In contrast, κ receptor agonists, such as U-50,488, produce some dysphoria and no significant pupillary change but still induce analgesia [2].

1.5. Opioid Use Disorders

The term "substance use disorder" encompasses a number of different substances and disorders (i.e., abuse, dependence, intoxication, withdrawal, and psychiatric syndromes and disorders that result from substance use). Substance abuse and substance dependence are two disorders that are frequently encountered, and their criteria are applicable across substances. The criteria are mentioned in the chapter on assessment.

1.6. Course and outcome of opioid use disorders

Cohort studies of dependent illicit opioid users show that although a significant proportion (10–40%) is abstinent at follow-up, most continue to use illicit opioids. [22-25] (I) Contact with treatment is one factor associated with recovery from opioid dependence; other factors include personal motivation, religion, spirituality, family and employment. [24]

The usual measures of treatment outcome in addition to abstinence—legitimate work, crime, drug use, family relationships, and psychological adjustment—are best predicted by different pretreatment variables. Thus, pretreatment history of high levels of criminal activity most accurately predicts post treatment criminal activity, and previous stable work history is more predictive of post treatment gainful employment. Severity of psychological problems at the beginning of treatment, however, is a predictor of outcome on all dimensions. Opioid addicts with the least severe psychological problems appear to respond better to all treatments on all outcome measures. [2]

2. Scope of this guideline / How to use this guideline

This document aims to provide helpful and pragmatic guidelines for Indian clinicians such as psychiatrists and general practitioners involved in

providing treatment to people with opioid abuse or harmful use and dependence. However, the guidelines should also be of interest to other practitioners in the opioid addiction, non- specialists, patients and their families. This revision was undertaken to update the guidelines in the light of new evidence focusing on areas not covered by guidelines published since the original IPS guidelines.

2.1. How were the guidelines developed? Evidence categories and strength of recommendations

Relevant literature was identified through a PubMed literature search for publications related to this guideline. Searches were conducted, using the keywords like "opiate abuse OR opiate dependence OR opiate use OR opioid abuse OR opioid dependence OR opioid use OR heroin abuse OR heroin dependence OR heroin use." The search yielded 64142 references. The search was restricted to human studies, written in the English language, and had abstracts, of which 10080 were randomized controlled trials and 357, were meta-analyses. Evidence tables were developed for these results. A second MEDLINE literature search, using PubMed, on the same keywords using filter 'last 10 years' yielded 24548 references, of which 4500 were randomized controlled trials and 294 were meta-analyses. Similarly, when filter was changed to 'last 5 years', the search yielded 12913 references of which 2237 were randomized controlled trials and 185 were meta-analyses. Additionally, bibliography of relevant articles and other guidelines like APA, NICE, BAP, WHO guideline for treatment of opioids were also searched. The Cochrane databases were also searched for relevant meta-analyses. The summary of treatment recommendations is keyed according to the level of evidences.

3. Assessment

Specific guidelines about conducting assessment and diagnosis in substance use disorders have been developed and are a part of this document. In this section, we present some salient issues specific to assessment in cases of opioid use disorders.

3.1. Clinical History

- The most important tool at the disposal of clinicians for assessment of a case of opioid use disorders is a thorough clinical history. A systematic inquiry into the mode of onset, quantity, frequency, and duration of substance use; the escalation of use over time; the motivation for use;

the specific circumstances of the individual's substance use ; the desired effect of the substance used; the most recent dose of each substance used; last dose of each substance used; assess for intoxication and withdrawal symptoms. A clinician should also determine if the individual meets DSM-IV-TR/ICD-10 criteria for abuse or harmful use or dependence for opioid and any other substance used. Assessment should routinely include questions about the use of multiple substances. [27]

- A history of any prior treatment for a substance use disorder, including the characteristics of the treatment such as setting; context (e.g., voluntary or involuntary); modalities used; duration and, if applicable, dose of treatment; adherence to treatment; and short-term (3-month), intermediate (1-year), and longer-term outcomes as measured by subsequent substance use, level of social and occupational functioning achieved, and other outcome variables. Previous efforts to control or stop substance use outside of a formal treatment setting should also be discussed. For individuals who had previous treatment or periods of abstinence, additional history may include the duration of abstinence, the factors that promoted or helped sustain abstinence, the impact of abstinence on psychiatric functioning, the circumstances surrounding relapse (e.g., whether the relapse was related to withdrawal symptoms, exacerbation of a psychiatric disorder, or psychosocial stressors), the individual's attitude toward prior treatment, non treatment experiences, and expectations about future treatments. When a clinician is attempting to ascertain an individual's current medication use, he or she should specifically ask about prescribed and non prescribed medications, including vitamins and herbal products. [23]
- A complete family and social history, including information on familial substance use or other psychiatric disorders; social factors contributing to the development or perpetuation of the substance use disorder (e.g., social facilitation of substance use); financial or legal problems; social supports, including peer relationships; school or vocational adjustment; and other functional impairments. It is important to determine whether and how household members and friends have supported or interfered with prior attempts at abstinence.
- Individual preferences, motivations, and barriers for treatment. Individuals vary in their treatment preferences regarding pharmacotherapy, group therapy, individual therapy, and self-help

treatments. Working with the individual's preferences is likely to lead to better treatment adherence and outcomes. [24] For individuals who have a co-occurring psychiatric disorder, exacerbation of psychiatric symptoms can be an additional barrier. [28,29] (II)

3.2. Clinical examination

- A comprehensive general medical and psychiatric history, including mental status and physical examination, to ascertain the presence or absence of co-occurring psychiatric or general medical disorders as well as signs and symptoms of intoxication or withdrawal. Psychological or neuropsychological testing may also be indicated for some individuals (e.g., to assess an individual's level of cognitive impairment). Clinicians may also note the signs of chronic opioid use (e.g. needle track marks in injecting drug users, burn finger tips in heroin chasers).

3.3. Investigations

- Qualitative and quantitative blood and urine screening for substances of abuse and laboratory tests for abnormalities that may accompany acute or chronic substance use. These tests may also be used during treatment to monitor for potential relapse.
- Screening for infectious and other diseases often found in opioid-dependent individuals especially injectable drug user (IDU) (e.g., human immunodeficiency virus [HIV], tuberculosis, hepatitis).

3.4. Instruments

- These tools consist of a set of questions designed to assess one or more domains associated with drug abuse. This provides a more structured way of assessment of an individual. Several rating scales and instruments exist to assess different domains. Some of these instruments have high sensitivity so that they can be used for screening purpose. Instruments with high degrees of specificity confirm the diagnosis of substance use disorder. Some instruments may require training to enable the individual to administer the particular instrument.

4. Goals of treatment

4.1. Treatment retention and substance use reduction or abstinence as initial goal of treatment

The ideal outcome for most individuals with substance use disorders is total

cessation of substance use. Nonetheless, many individuals are either unable or unmotivated to reach this goal, particularly in the early phases of treatment and/or after a relapse to substance use. Such individuals can still be helped to minimize the direct and indirect negative effects of ongoing substance use. For example, reductions in the amount or frequency of substance use, substitution with a less risky substance, and reduction of high-risk behaviors associated with substance use may be achievable goals when abstinence is initially unobtainable. [30,31] (IV) Engaging an individual to participate and remain in treatment that may eventually lead to further reductions in substance use and its associated morbidity is a critical early goal of treatment planning and is often enhanced by motivational interviewing techniques. [32] (IV)

4.2. Reduction in the frequency and severity of substance use episodes

Reduction in the frequency and severity of substance use episodes is a primary goal of long term treatment. [33] (IV) The individual is educated about common types of substance use triggers, such as environmental cues, stress, and exposure to a priming substance. [34, 35] (IV) The individual is then helped to develop skills to prevent substance use; these skills include identifying and avoiding high-risk situations as well as developing alternative responses to situations in which substance use may occur.

4.3. Improvement in psychological, social, and adaptive functioning

Substance use disorders are associated with impairments in various areas of life. For optimal outcome, the treatment of a substance use disorder may also include strategies that target repair of damages or losses that resulted from the individual's substance use; aid in developing effective interpersonal, vocational, and proactive coping skills; and enhance familial and interpersonal relations that will support an abstinent lifestyle. It is particularly important to provide comprehensive treatments when individuals have co-occurring psychiatric or general medical conditions that significantly influence relapse risk (e.g., chronic pain, depression, anxiety, impaired cognition, and impulse control disorders). [36-38] (IV)

Box 2: Concept of Harm reduction

One of the recent approaches to look at addressing drug problems is the 'harm reduction' approach. It is defined as 'policies, programmes and practices that aim primarily to reduce the adverse health, social and economic and legal consequences of the use of legal and illegal

psychoactive drugs without necessarily reducing drug consumption'. [39] With a harm-reduction approach, drug users are enabled to progress towards reduced harm and improved health at a speed which is more acceptable and realistic for them. Importantly, it does not stigmatize those who practice high-risk behaviours, recognising that such behaviours result from various complex social, environmental, economic, cultural and personal factors. The aim of harm reduction strategies is to keep drug users alive, well and productive until treatment works or they grow out of their drug use and can be reintegrated into society. With a harm reduction approach, the emphasis is on short-term practical, attainable goals, as opposed to idealistic and utopian yet unattainable goals. [40-42] (IV)Though there are multiple harms associated with substance use, in practice, the phrase 'harm reduction' is most often applied to those strategies which are aimed at reducing one particular harm associated with drug use, namely HIV/ AIDS. It is a well-known fact that Injecting Drug Users (IDUs) remain at a very high risk for acquiring and transmitting HIV infection through sharing and reuse of unsafe injecting equipment. [43,44] (IV) A host of strategies have been developed to reduce this risk:

- Outreach programs and peer education
- Needle and syringe programs.
- Drug substitution programs

There is huge body of evidence supporting the efficacy and effectiveness of these interventions in reducing the risk of HIV among drug users, and bringing them closer to mainstream in order to achieve a healthier life. [45] (IV)

5. Treatment settings

5.1. Factors affecting choice of treatment setting

Individuals should be treated in the least restrictive setting that is likely to prove safe and effective. Decisions regarding the site of care should be based on the individual's:

- capacity and willingness to cooperate with treatment
- ability for self-care
- social environment (which may be supportive or high risk)

- need for structure, support, and supervision to remain safe and abstinent
- need for specific treatments for co-occurring general medical or psychiatric conditions
- need for particular treatments or an intensity of treatment that may be available only in certain settings
- preference for a particular treatment setting.

Patients should be moved from one level of care to another on the basis of these factors; the decision to move to a less intensive level of care should consider these factors plus the clinician's assessment of a patient's readiness and ability to benefit from the less restrictive setting. [27]

5.2. Hospitals

The range of services available in hospital-based programs typically includes emergency detoxification and stabilization during withdrawal; assessment and treatment of general medical and psychiatric conditions; group, individual, and family therapies; psychoeducation; motivational counseling; and social service facilitation of follow-up care in available community services. [46,47] The available data do not support the notion that hospitalization per se has specific benefits over other treatment settings beyond the ability to address treatment objectives that require a medically monitored environment. [48,49] (IV)

There is consensus (e.g., American Society of Addiction Medicine (ASAM) patient placement criteria) that individuals in one or more of the following categories may require hospital-level care:

- Individuals with drug overdoses
- Individuals are at risk for a severe or complicated withdrawal syndrome
- Individuals with acute or chronic general medical conditions
- Individuals with a documented history of not engaging in or benefiting from treatment in a less intensive setting
- Individuals with marked psychiatric comorbidity who are an acute danger to themselves or others
- Individuals manifesting opioid use or other behaviors who are an acute danger to themselves or others

- Individuals who have not responded to less intensive treatment efforts and whose opioid use disorder(s) poses an ongoing threat to their physical and mental health

5.3. Partial hospitalization programs and intensive outpatient programs

Partial hospitalization and intensive outpatient programs can provide an intensive, structured treatment experience for individuals with substance use disorders who require more services than those generally available in traditional outpatient settings. Although the terms "partial hospitalization," "day treatment," and "intensive outpatient" programs may be used nearly interchangeably in different parts of the world, the ASAM patient placement criteria [46] define structured programming in partial hospitalization programs as 20 hours per week and in intensive outpatient programs as 9 hours per week. Partial hospitalization programs provide ancillary medical and psychiatric services, whereas intensive outpatient programs may be more variable in the accessibility of these services. Some patients enter these programs directly from the community. Alternatively, these programs are sometimes used as "step-down" programs for individuals leaving hospital or residential settings who are at a high risk of relapsing because of problems with motivation, the presence of frequent cravings or urges to use a substance, poor social supports, immediate environmental cues for relapse and/or availability of substances, and co-occurring medical and/or psychiatric disorders.

5.4. Residential treatment

Residential treatment is indicated primarily for individuals who do not meet clinical criteria for hospitalization but whose lives and social interactions have come to focus exclusively on substance use and who currently lack sufficient motivation and/or substance-free social supports to remain abstinent in an ambulatory setting. For these individuals, residential facilities provide a safe and substance-free environment in which residents learn individual and group living skills for preventing relapse. As in the case of hospital-based programs, residential treatment programs frequently provide psychosocial, occupational, and family assessment; psychoeducation; an introduction to self-help groups; and referral for social or vocational rehabilitative services. The duration of residential treatment should be dictated by the length of time necessary for the patient to meet specific criteria that would predict his or her successful transition to a less structured, less restrictive treatment setting (e.g., outpatient care).

5.5. Therapeutic communities

Individuals with opioid or multiple substance use disorders may benefit from referral to a long-term residential therapeutic community. These programs are generally reserved for individuals with a low likelihood of benefiting from outpatient treatment, such as individuals who have a history of multiple treatment failures or whose profound impairment in social relational skills or ability to attain and sustain employment impede adherence to outpatient treatment. [47] (III) Rather than viewing substance abuse as an illness (as defined by the disease concept), therapeutic community theory views it as a deviant behavior; that is, it is seen as a symptom of pathological development in personality structure, social relating, and educational and economic skills. [52] The therapeutic community milieu provides individual, social, and vocational rehabilitation through the community method of social learning. It is a highly structured, substance-free community setting in which the primary interventions are behavioral modeling, supportive peer confrontation, contingency management, community recreation, and work therapy designed to facilitate adherence to social norms and substance-free lifestyles. [53] (III) Data regarding the effectiveness of traditional long-term (2-year commitment) therapeutic communities are limited by the fact that only 15%–25% of individuals admitted voluntarily complete a program, with maximum attrition occurring in the first 3 months. [54,55] (III); (I) Retention rates differ with program sites [56] (I), and retention lengths predict outcomes on abstinence and lack of criminal recidivism indexes, with 2-year post completion success rates at 90% for graduates, 50% for dropouts completing >1 year, and 25% for dropouts completing <1 year. [53,54]

Concerns have been expressed that, at many places TCs are being implemented by individuals with dubious qualifications and reports of serious human right violations in many such centres keep springing-up. [57]

5.6. Community residential facilities

Community residential facilities are commonly known as “halfway houses” or “sober houses,” with the former typically offering more structure and supervision. They provide an outpatient substance-free housing environment as a transitional setting for individuals in recovery who are not yet able to manage independent housing without a significant risk for relapse. Some studies have shown that for patients with multiple service needs (e.g., vocational, housing, transportation), the provision of stable housing in the form of long-term community residential facilities leads to significantly

improved substance use outcomes.[58-60] (III) This benefit has been demonstrated for adult substance users of both sexes. Community residential facilities show more variability in substance use outcomes for youth and adolescents [61] (IV); this may be related to inadequate matching of services to individual needs. There is no published account of community residential facilities in India.

5.7. Aftercare

Aftercare occurs after an intense treatment intervention (e.g., hospital or partial hospitalization program) and generally includes outpatient care, involvement in self-help approaches, or both. Research on aftercare has examined different treatment models, including eclectic, medically oriented, motivational, 12- step, cognitive-behavioral, group, and marital strategies.

5.8. Outpatient settings

Out patient treatment settings includes mental health clinics, integrated dual-diagnosis programs, private practice settings, primary care clinics, and substance abuse treatment centers, including opioid treatment programs. In addition to medication therapies, outpatient treatments with strong evidence of effectiveness include CBTs (e.g., relapse prevention, social skills training), MET, behavioral therapies (e.g., community reinforcement, contingency management), psychodynamic therapies/IPT, self-help manuals, behavioral self-control, brief interventions, case management, and group, marital, and family therapies.

5.9. Case management

Case management, by definition, exists as an adjunctive treatment. The goals of case management interventions are to provide advocacy and coordination of care and social services and to improve patient adherence to prescribed treatment and follow-up care. [62] (IV). In India however, Case management approaches are yet to evolve.

5.10. Legally mandated treatment

Treatment of substance use disorders may be legally mandated under a variety of circumstances, including substance-related criminal offenses. In the western countries, Drug court programs recognize the effectiveness of diverting offenders with lesser drug related convictions from correctional facilities into court-mandated community programs for the treatment of substance use disorders. [63] A recent issue of the journal, 'WHO bulletin'

has argued against the legally mandated treatment stating that "In countries with compulsory centres, the detention of people who use drugs often occurs without sufficient due process, legal safeguards or judicial review, and there are frequent reports of physical and sexual violence, forced labour, sub-standard conditions, denial of health care, and other violations of human rights in such state-sanctioned centres".[64] In India, though there are provisions of treatment in lieu of jail as punishment under the NDPS Act (1985), a structured system of legal referral for drug offenders is yet to evolve.

Prison as treatment setting: Drug use is overrepresented in prisons and remains endemic among incarcerated populations. Opioid use remains one of main drugs of abuse in prison population. Further, there are strong bilateral links between opioid abuse or dependence, and criminal behavior. Substance use problems are considered in prison settings separately because of their magnitude, severity and implications on society. [65] Hence, prisons are ideal place of treatment of opioid dependence. Opioid maintenance programmes in prisons reduces opioid use, injecting, and sharing of injecting equipment. Such programmes consistently promote treatment entry and retention after release from prison, and generally too are associated with reduced opioid use. [66]

5.11. Employee assistance programs

Employee assistance programs (EAPs) provide an employment-based treatment setting and referral platform for employees with substance use disorders. EAPs differ according to workplace size and location. A critical difference for substance use treatment received through an EAP versus through an alternate community outpatient setting is the definition of successful intervention outcome. Whereas most community settings define successful outcome as a reduction of substance use and related medical and social problems, an EAP defines and measures success primarily through job performance. [67] EAPs are cost-effective in the short term management. [68, 69] (IV); In India, while there is some experience with programs based on EAP principles for ALCOHOL use disorders (implemented by NIMHANS and AIIMS for workplace settings), specifically for opioid use disorders there is no data on experiences.

6. MANAGEMENT OF OPIOID USE DISORDERS

Successful treatment of opioid use disorders may involve the use of multiple specific treatments, the choice of which may vary for any one individual over time, and may involve clinicians and professionals from a variety of backgrounds. Management entails the ongoing process of choosing from among various treatments, monitoring patients' clinical status, and coordinating different treatment components. The frequency, intensity, and focus of management must be tailored to meet each patient's needs, and the type of management is likely to vary over time, depending on the patient's clinical status.

6.1. General principles of management

6.1.1. Motivating change

In recent years, there has been a great deal of research and clinical emphasis on the clinician's role in motivating patients with substance use disorders to change their behaviors. Motivational interviewing techniques [70] (IV) involve the use of an empathic, nonjudgmental, and supportive approach to examining the patient's ambivalence about changing addictive behaviors. Understanding the patient's stage of readiness to change [71] allows the clinician to determine what motivational strategies are most appropriate for the patient at that time.

6.1.2. Establishing and maintaining a therapeutic framework and alliance

An essential feature of management of patients with a opioid use disorder is the establishment and maintenance of a therapeutic alliance wherein the clinician empathically obtains the necessary diagnostic and treatment-related information, gains the confidence of the patient and perhaps significant others, and is available in times of crisis. Within the context of this alliance, the primary goal of treatment is to help the patient learn, practice, and internalize changes in attitudes and behaviors that are conducive to relapse prevention. [72,73] (IV); The strength of the therapeutic alliance has been found to be a significant predictor of outcome. [74]

6.1.3. Assessing safety and clinical status

The psychiatric assessment establishes a diagnosis and provides a baseline determination of a patient's clinical status. Ongoing evaluation of the patient's safety is also critical, as the patient's clinical status may change

over time. It is particularly important to assess patients for suicidal or homicidal thoughts or other dangerous behavior. Baseline blood and urine testing are helpful in the detection of drug used by patient and also early assessment of physical damage by drug.

6.2. Pharmacological management

6.2.1. Managing intoxication / Overdose

Opioid intoxication can vary in severity. In severe cases of opioid overdose, there is usually coma, severely depressed respiration, and pinpoint pupils. There may be gross pulmonary edema with frothing at the mouth, but X-ray evidence of pulmonary changes is seen even in less severe cases. Mild to moderate opioid intoxication usually does not require treatment. An uncomplicated overdose with a short-acting opioid that has a relatively short half-life, such as heroin, may be treated in an emergency department, with release after a few hours. Overdose with longer-acting opioids such as methadone, however, requires closer inpatient observation for a minimum of 24–48 hours.

Box 3: Diagnostic Guidelines for Opioid Intoxication (ICD-10)

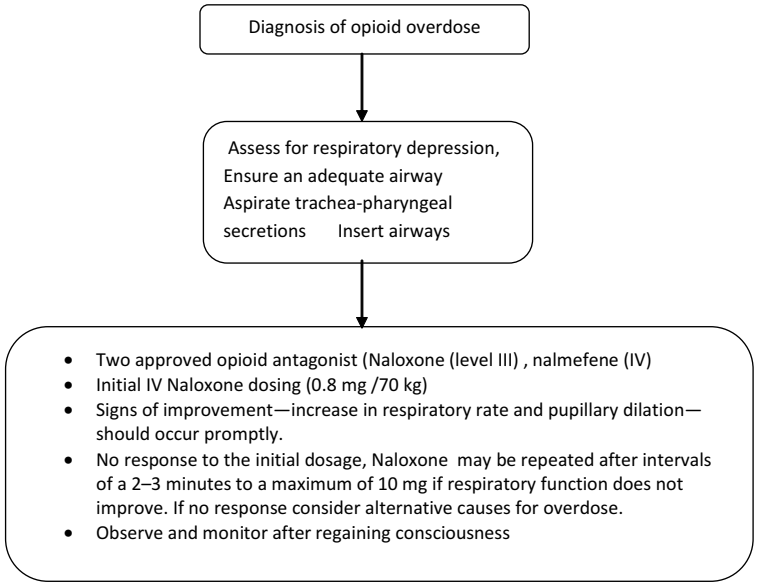
A. There must be dysfunctional behavior, as evidenced by at least one of the following:

1. apathy and sedation
2. disinhibition
3. psychomotor retardation
4. impaired attention
5. impaired judgment
6. interference with personal functioning

B. At least one of the following signs must be present:

1. drowsiness
2. slurred speech
3. pupillary constriction (except in anoxia from severe overdose, when pupillary dilatation occurs)
4. decreased level of consciousness (e.g., stupor, coma)

Box 4: Algorithm for Management of opioid overdose (Two approved opioid antagonist (Naloxone (III), nalmefene (IV). [75]



6.2.2. Managing withdrawal (Detoxification)

An opioid-dependent individual may undergo opioid withdrawal rather than the maintenance treatment (described later) if, the patient has a relatively short history of opioid abuse, younger age, good social support, no maintenance treatment program is available locally, or the patient desires to not be restricted by the requirements of maintenance medication. Some patients successfully maintained on a medication such as methadone or buprenorphine will also want to undergo medically supervised withdrawal (see section on Long-term / agonist maintenance).

The goal of opioid tapering is to minimize acute withdrawal symptoms and help patients transition to long-term treatment for opioid dependence. The use of standard rating scales for withdrawal can help guide dosing in an objective and routine manner.

6.2.2.1. Buprenorphine

Buprenorphine is a partial μ agonist and k antagonist. It binds tightly to and dissociates slowly from the opioid receptors. It is a long acting, highly

lipophilic opiate and 25-50 times more potent than morphine (in analgesic action). It has higher affinity and low intrinsic activity to μ receptor. Buprenorphine can substitute for morphine or heroin and can block the effects of other opioids. [76- 78] However at very high levels of μ agonist physical dependence, particularly if the patient is still under the influence of μ agonist, it may precipitate withdrawal. [79]

6.2.2.1.1. Inpatient opioid withdrawal management with buprenorphine

Patients can be stabilized on a relatively low dose of daily sublingual buprenorphine (e.g., 8 mg/day), with the goal of suppressing opioid withdrawal symptoms. The dose can be decreased in increments of 0.4 to 2 mg/day over several days. Because buprenorphine has a long duration of action, minimal withdrawal symptoms are seen during the dose reduction. However, some clinicians report that withdrawal symptoms can appear several days after the last dose of buprenorphine, after a patient is discharged from an inpatient setting.

In the Meta analyses conducted by Cochrane data base involving Twenty-two studies with 1736 participants, the major comparisons were with methadone (5 studies) and clonidine or lofexidine (12 studies). Five studies compared different rates of buprenorphine dose reduction. Severity of withdrawal is similar for withdrawal managed with buprenorphine and withdrawal managed with methadone, but withdrawal symptoms may resolve more quickly with buprenorphine. It appears that completion of withdrawal treatment may be more likely with buprenorphine relative to methadone (RR 1.18; 95% CI 0.93 to 1.49, P=0.18) but more studies are required to confirm this. Relative to clonidine or lofexidine, buprenorphine is more effective in ameliorating the symptoms of withdrawal. Patients treated with buprenorphine stay in treatment for longer (SMD 0.92, 95% CI 0.57 to 1.27, $P < 0.001$), and are more likely to complete withdrawal treatment (RR 1.64; 95% CI 1.31 to 2.06, $P < 0.001$). At the same time there is no significant difference in the incidence of adverse effects, but drop-out due to adverse effects may be more likely with clonidine. [80] (Ia)

6.2.2.1.2. Outpatient opioid withdrawal management with buprenorphine

If buprenorphine is used for the outpatient treatment of opioid withdrawal, then procedures similar to those described for methadone should be followed. The tablet form combined with naloxone is preferred. For example, patients

should be initially stabilized on a daily dose (probably 8–32 mg/day) of buprenorphine that suppresses opioid withdrawal and results in abstinence from illicit opioid use. Dose reductions should then occur gradually over a period of 10–14 days.

6.2.2.1.3. Withdrawal Management with Buprenorphine: Indian evidence

Buprenorphine has been found to be an effective agent for management of opioid withdrawal symptoms [81,82] (Ib) In a single blind randomized study at National Drug Dependence Treatment Center, AIIMS, New Delhi, 22 patients were detoxified with either clonidine (0.3-0.9 mg) orally or buprenorphine (1.2 mg) sublingually. It was seen that subjects on clonidine had a significantly greater number of subjective symptoms following morphine injection at 2 and 6 hrs post injection and subjects on buprenorphine had a significantly lower number of objective symptoms following morphine injection at ½ and 2 hrs post injection. It was also seen that patients on clonidine had a significantly greater degree of liking for morphine injection as compared to placebo while no significant difference in degree of liking between placebo and morphine injection was seen in patients on buprenorphine.

6.2.2.2. Methadone

Methadone is highly effective in ameliorating the symptoms of opioid withdrawal.

6.2.2.2.1. Inpatient opioid withdrawal management with methadone

Initially, patient is stabilized on a daily methadone dose that is determined by the patient's response based on objective withdrawal sign. Once the stabilization dose is determined (usually 40–60 mg/day and sometimes less), methadone can be tapered by 5 mg/day. In inpatient settings, detoxification from heroin or other short-acting opioids can usually be completed within 7 days, but a more gradual tapering will result in a smoother clinical course.[23]

A Meta-analysis has been conducted by Cochrane data base which included twenty three trials involving 2467 subjects. Comparing methadone versus any other pharmacological treatment they observed no clinical difference between the two treatments in terms of completion of treatment, [relative risk (RR) 1.08;95% CI 0.97 to 1.21)] and number of participants abstinent at follow-up [RR 0.98 ; 95% CI 0.70 to 1.37)]. It was impossible to pool

data for the degree of discomfort for withdrawal symptoms and adverse events but the results of the studies did not show significant differences between the considered treatments. These results were confirmed also when they considered the single comparisons: methadone with: adrenergic agonists (11 studies), other opioid agonists (eight studies), anxiolytic (two studies), paiduyangsheng (one study). Comparing methadone with placebo (two studies) more severe withdrawal and more drop outs were found in the placebo group. The results indicate that the medications used in the included studies are similar in terms of overall effectiveness. [83] (Ia).

6.2.2.2.2. Outpatient opioid withdrawal management with methadone

Outpatient opioid withdrawal uses a higher initial dose of methadone and occurs over a longer period of time. The goal of using a higher initial dose of methadone is to help dependent individuals end illicit opioid use. Because studies have suggested that slow tapers are associated with better outcomes, methadone should be tapered gradually over a period of weeks. Many patients tolerate methadone reductions to 20– 30 mg/day with little difficulty, but further dose reductions may lead to increasing withdrawal distress. Even with gradual reductions in the dose, such distress may be difficult for some patients to tolerate and may be accompanied by high dropout and relapse rates during this later phase of withdrawal. [27] There has been no Indian experience with using Methadone for detoxification (inpatient or outpatient) so far. However, the recent introduction of Methadone in India adds a promising agent at the disposal of clinicians for treating their patients with opioid dependence.

6.2.2.3. Alpha-2 adrenergic agonists (Clonidine)

Clonidine is a centrally acting á2-adrenergic antihypertensive medication that effectively decreases the noradrenergic hyperactivity associated with opioid withdrawal. Clonidine reduces withdrawal symptoms such as nausea, vomiting, diarrhea, cramps, and sweating but, unlike methadone, does little to reduce other – more distressing – symptoms such as muscle aches, insomnia, distress, and drug craving. As a nonopioid medication, clonidine has some advantages over opioid for withdrawal. For example, clonidine does not produce opioid-like tolerance or dependence or the post methadone rebound in withdrawal symptoms. [84] (Ib). In addition, patients completing a course of clonidine-assisted withdrawal can immediately be given an opioid antagonist (e.g., naltrexone) if indicated. The disadvantages of clonidine

include its aforementioned inability to improve certain opioid withdrawal symptoms, associated hypotension that can be profound despite the use of low doses of this medication, and its possible sedative effects. Contraindications to the use of clonidine include acute or chronic cardiac disorders, renal or metabolic disease, and moderate to severe hypotension.[85] ((Ib)

6.2.2.3.1. Inpatient opioid withdrawal management with Clonidine

On the first day of clonidine-aided detoxification, a clonidine dose of 0.1 mg three times daily (totaling 0.3 mg per 24 hours) is usually sufficient to suppress signs of opioid withdrawal. If the patient's blood pressure falls below 90/60 mm Hg, the next dose should be withheld, after which tapering can be resumed while the patient is monitored for signs of withdrawal. In the case of short-acting opioids such as heroin, clonidine-aided withdrawal usually takes 4–6 days. Other medications may be used along with clonidine to treat withdrawal symptoms.

In general, clonidine-assisted detoxification is better to carry out and monitor in inpatient settings. Clonidine-induced sedation is also less of a problem for inpatients.

In the Meta analyses conducted by Cochrane data base twenty-four studies, involving 1631 participants, were included. Twenty-one were randomised controlled trials. Thirteen studies compared a treatment regime based on an alpha2-adrenergic agonist with one based on reducing doses of methadone. Diversity in study design, assessment and reporting of outcomes limited the extent of quantitative analysis. Alpha2-adrenergic agonists are more effective than placebo in ameliorating withdrawal, however have higher rates of adverse effects. Though, they are associated with significantly higher rates of completion of treatment as compared to placebo. For the comparison of alpha2-adrenergic agonist regimes with reducing doses of methadone, there were insufficient data for statistical analysis, but withdrawal intensity appears similar to or marginally greater with alpha2-adrenergic agonists. No significant difference was detected in rates of completion of withdrawal with adrenergic agonists compared to reducing doses of methadone, or clonidine compared to lofexidine. Clonidine is associated with more adverse effects than reducing doses of methadone. Lofexidine does not reduce blood pressure to the same extent as clonidine, but is otherwise similar to clonidine. [86] (Ia).

6.2.2.3.2. Outpatient opioid withdrawal management with Clonidine

It is usually recommended to avoid outpatient detoxification with clonidine considering treatment requires careful dose titration and clonidine overdoses can be life-threatening.

6.2.2.3.3. Withdrawal management with clonidine: Indian evidence

Usefulness of clonidine for opioid detoxification was described by various authors in 1980s as there was no alternative available for opioid detoxification and clonidine emerged as the only choice for detoxification in view of its antiadrenergic activity. [87-89] However, with considerable clinical experience of more than two decades at many centres, it can be safely stated that first choice for opioid withdrawal management should be a long-acting opioid agonist such as buprenorphine.

6.2.2.4. Slow release oral morphine (SROM).

Slow release oral morphine (SROM), a natural derivative of opium and a mu receptor agonist, is relatively cheap with long duration of action. This medication is being routinely used in the treatment of cancer pain. [90] Compared with short acting, immediate release morphine, SROM has the advantage of single dosage, decreased sleep disturbance and increased medication compliance.

It has been found to be most effective in doses of 60 mg daily. A higher dose is needed sometimes to control craving and withdrawal symptoms. A dose of up to 180mg – 240 mg can be administered and the effects last for up to 12 – 24hours. Strict monitoring is required as morphine produces chemical dependence and the patient may try to escalate the dose, use other narcotics concomitantly or even divert the prescribed morphine to the illicit market.[1]

No evidence is available for use of slow release oral morphine (SROM) for detoxification, although it has been used for detoxification of opioid dependent patients, who were not able to tolerate detoxification with buprenorphine in absence of availability of methadone in India. (IV)

Box 5: Dextropropoxyphene (Special Mention)

It is an oral opioid agonist. Following metabolism, it gives rise to propoxyphene and nor-propoxyphene. The accumulation of nor-propoxyphene in the body gives rise to toxicity [20]. **However, in the**

recent past, Government of India has banned the manufacturing, distribution and sale of Dextropropoxyphene.

1.1.1.1.1. Inpatient opioid withdrawal management with Dextropropoxyphene

Dextropropoxyphene can also be used for management of opioid withdrawal symptoms in absence of other Buprenorphine or methadone. However, it is less effective in management of opioid withdrawal symptoms. Usually dose required are 6-12 capsules of Dextropropoxyphene (65 mg) initially and tapered off after the third day in inpatient setting.

1.1.1.1.2. Outpatient opioid withdrawal management with Dextropropoxyphene

In India, many centres were using it as treatment agent for out-patient detoxification due to its easy availability and low cost. Usually dose required are 6-12 capsules of Dextropropoxyphene (65 mg) initially and tapered off after the 1-2 weeks in outpatient setting.

Several studies reported that the patients who were on propoxyphene had more withdrawal symptoms, early drop out and abused heroin more than patients on methadone. [91, 92] (Ib) Overall propoxyphene is less effective than methadone as a maintenance agent and serious toxicity limits its therapeutic usefulness. It also has significant abuse potential and produces dependence. (IV)

6.2.2.5. Use of other medications

Some clinicians and treatment programs have used medications targeting the symptoms of opioid withdrawal as the primary means for treating this condition. For example, sedative hypnotics or anxiolytics are used to treat insomnia and/or anxiety, antiemetics are prescribed to treat nausea and vomiting, NSAIDs are provided for muscle cramps, and antispasmodics are used to treat gastrointestinal cramping. There are limited controlled data about the use of such medications for the treatment of opioid withdrawal.

Box 6: Rapid / ultra rapid detoxification (SPECIAL MENTION)
The combined use of clonidine and naltrexone for rapidly withdrawing patients from an opioid has been demonstrated to be safe and effective.

Essentially, naltrexone-precipitated withdrawal is avoided by pretreating the patient with clonidine. This technique is most useful for opioid dependent patients who are in transition to narcotic antagonist treatment. The limitations of this method include the need to monitor patients for 8 hours on the first day because of the potential severity of naltrexone-induced withdrawal and the need for careful blood pressure monitoring during the entire detoxification procedure. However, relapse rates with naltrexone maintenance are high. A related technique is to withdraw a patient from an opioid while the patient is maintained under general anesthesia. This technique has been called ultra-rapid opioid detoxification and has included naltrexone maintenance after the acute withdrawal is completed. Although some small uncontrolled studies have reported good long-term outcomes with this method, it appears to be no more effective than methadone detoxification in achieving beneficial outcomes such as maintenance of abstinence. [93] (Ib) In addition, complications associated with such rapid withdrawal procedures (e.g., general anesthesia) coupled with the lack of better long-term results suggest that the procedure should not be commonly used. [85]

Withdrawal Management (detoxification:) Summary

- *The pharmacological treatment of choice for opioid detoxification is an agonist medication with long duration of action. With the available evidence reviewed above buprenorphine sublingual tablets is the most strongly recommended agent in India.*
- *The adequate dose and duration may vary from patient to patient and should be guided by withdrawal status of the patient, determined clinically.*
- *Most patients are likely to be stable in the range of buprenorphine 6 mg day which can be tapered off within next 7-10 days.*
- *Depending upon the availability, other agonist medications like methadone or d-propoxyphene can also be considered. While experience for methadone as agent for detoxification is yet to be accumulated in India, there is plenty of clinical experience with d-propoxyphene.* ***However, in view of the recent government ban on manufacture and use of dextropropoxyphene in India, it is no longer legally available and in any case cannot be recommended.***

- *In cases where agonists cannot be used, clonidine treatment can be recommended, but only in the inpatient settings with careful monitoring of side effects (particularly hypotension).*
- *The phase of detoxification should be utilized for preparing the patients for a longer term treatment which is aimed at prevention of relapse and rehabilitation.*
- *Ultra rapid detoxification is not recommended owing to unnecessary expenses, risks involved and no extra benefits.*

6.2.3. Long term pharmacotherapy

6.2.3.1. Agonists (Opioid maintenance treatment)

Agonist maintenance eliminates drug hunger and produces cross-tolerance or blockade so that the person would not experience any narcotic or euphoric effects if they were to self–administer the illicit drug. [94]

The specific objectives of agonist maintenance treatment are

- to reduce illegal and other harmful drug use,
- improve the patient's health and well-being,
- reduce the risk of transmission of blood-borne infectious diseases,
- reduce death and other medical morbidities associated with drug use,
- reduce crime committed by patients,
- facilitate an improvement in the patient's occupational and social functioning,
- improve the economic status of patients and their families
- to achieve abstinence from drug use, including cessation of the substitution treatment.

This approach to treatment is also known by a variety of names: Opioid Substitution Treatment (OST), Oral Substitution Treatment, Metahdone / Buprenorphine Maintenance Treatment (MMT / BMT), or Medication Assisted Treatment (MAT) [95]

6.2.3.2. Methadone as agonist maintenance treatment

6.2.3.2.1. Introduction

Methadone is a synthetic narcotic analgesic compound developed in Germany just prior to World War II. Dole and Nyswander (1965) [96] proposed methadone as an effective maintenance agent. In 1972 Food and Drug Administration (FDA) in US approved its use as maintenance agent for opioid dependence. Since then methadone has gained widespread popularity

and is currently being used as treatment for opioid dependence in a number of countries throughout the world.

Upon acute administration, methadone acts as a typical μ receptor agonist and produces euphoria, analgesia, and other typical morphine-like effects. However, upon long-term oral administration, methadone displays several interesting properties making it a very useful maintenance agent. These properties include (i) its reliable absorption and bioavailability after oral administration, (ii) the delay of peak plasma levels until 2 to 6 hours after ingestion, and (iii) the binding to tissues that creates a large reservoir of methadone in the body. This large reservoir, along with slow action, protects patients against sharp peaks in euphoria. The reservoir also results in minimum withdrawal. Thus, this makes it possible to administer with a once-a-day regime. The mean plasma half-life ranges from 22 to 56 hours in methadone-maintained patients. [2] (II)

6.2.3.2.2. Treatment outcome

Many studies have consistently demonstrated that methadone treatment reduces mortality, and decreases illicit drug use, criminal activity, health-care cost, unemployment and accidental overdoses among opioid dependent individuals. Significant differences in effectiveness across programs have been observed; these are largely due to the characteristics of patients treated. However, certain program features tend to make some programs more effective than others. The average retention rate for a group of methadone clinics participating in a national prospective study in USA was 81 percent at 1 month, 67 percent at 3 months, and 52 percent at 6 months. [2] (II)

Evidence indicates that methadone programme prevents many opioid injectors from getting HIV [97,98] and there is substantial evidence that not just needle use but sharing are reduced when opioid dependent IDUs receive methadone treatment. A one year follow up study (National treatment outcome research study) has shown that injecting, sharing needles and having unprotected sex substantially decreased by methadone maintenance. [99]

In one of the large prospective cohort studies, over 18 months, the odds of HIV infection were 5.4 times greater among those who were not in maintenance treatment compared with those who were in treatment. [100] Socially productive behaviour as measured by employment, schooling or home making also improve with length of time in treatment. [101] Overall methadone maintenance is cost-beneficial. [102]

The meta-analysis on methadone maintenance by Cochrane database [103] included Eleven randomised clinical trials, and two were double-blind. There were a total number of 1969 participants. The sequence generation was inadequate in one study, adequate in five studies and unclear in the remaining studies. The allocation of concealment was adequate in three studies and unclear in the remaining studies. Methadone appeared statistically significantly more effective than non-pharmacological approaches in retaining patients in treatment and in the suppression of heroin use as measured by self report and urine/hair analysis (6 RCTs, RR = 0.66 95% CI 0.56-0.78), but not statistically different in criminal activity (3 RCTs, RR=0.39; 95%CI: 0.12-1.25) or mortality (4 RCTs, RR=0.48; 95%CI: 0.10-2.39). (Ia)

6.2.3.2.3. Dosing

Minimum effective dose found in the western studies is 60 mg / day. A dose below 50 mg enhances the risk of patient drop-out. [104] In a study of six clinics in the United States, there was an inverse relation between methadone dosage (over the range from 20 to 80 mg daily) and the percentage of patients using heroin. Although some programs persist in using low doses that have been shown to correlate with high dropout rates and continued heroin use, their number has decreased as data on the importance of adequate dosage have become more generally accepted. Duration of treatment is also important as treatments lasting less than 90 days usually have little or no impact; consequently, retention in treatment is critical. In general longer the duration of treatment and retention in treatment, better the outcome.

Higher doses on the other hand lead to longer retention and greater reduction in illicit opioid use. [105, 106] (Ib) There are wide variations in rates of methadone metabolism. Indeed, some experts also suggest measuring methadone plasma levels to determine daily dosage. It appears that an average methadone serum level of 400 ng/mL is adequate, and that levels of less than 150 ng/mL are likely to be associated with withdrawal or drug hunger. [2] However because of its resource-intensive nature, most treatment guidelines do not recommend routine monitoring of serum methadone levels. [2]

- **Preparation of methadone:** It is available in tablet and liquid preparation. Usual formulations are 5mg/ml of liquid and 5 mg / 10 mg / 20 mg tablets.

- **Induction:** Patients should be assessed for suitability for methadone treatment. Patient should be supplied with verbal and written information about all aspects of the maintenance treatment. The dose should be titrated according to the clinical effect in the individual patient.

Methadone can be initiated in an individual with well-established current physiological dependence at a dose of 20 to 30 mg. If there is doubt regarding degree of an individual's tolerance to opioids, an initial dose of 10 mg is indicated. The maximum allowable first dose is usually 30 mg, and the maximum total dose for the first day of treatment is 40 mg. Dose escalation should be done in small increments (usually 5 to 10 mg at a time) under close physician supervision until an optimum maintenance dose is achieved. Given methadone's long half-life, it is advisable to observe the patient for at least 3 to 4 days before an additional dose increase is provided.

Box 7: The optimum dose of Methadone (or any other agonist for maintenance treatment) is achieved when:

(1) the patient evidences **no withdrawal** signs or symptoms throughout the 24-hour dosing period,

(2) the patient reports an **absence of craving** for opioids,

(3) adequate cross tolerance is obtained such that the patient experiences little or **no reinforcement** from use of other opioids, and

(4) self-report and urine testing indicate the **absence of illicit opioid use**.

6.2.3.2.4. Adverse effects

Methadone shares the adverse effects and toxic potential of other opioid agonists. Hence, the usual precautions of opioid agonist therapy should be observed. Common side effects of opioids include sedation, constipation, sweating, nausea, dizziness, and hypotension. During methadone maintenance, most adverse effects disappear over the course of several weeks. However, constipation and excessive sweating often persist even with long-term methadone administration. Methadone in moderate to high doses can impair cardiac conduction, prolong the QT interval, and, in rare instances, lead to torsades de pointes. Some patients would also complain of decreased libido; and sexual dysfunction.

Severe intoxication or overdose with methadone constitutes a medical emergency. Opioid overdose leads to potentially fatal respiratory depression from direct suppression of respiratory centers in the midbrain and medulla. For severe cases, the administration of the pure opioid antagonist naloxone in combination with general supportive measures is indicated (see: management of opioid intoxication). Owing to the long half-life of methadone, repeat administration of naloxone may be necessary.

6.2.3.2.5. Methadone for OST: Indian experience:

Methadone has been launched only recently in India, and at the time of developing these guidelines is being implemented as a pilot project at five sites in India. The initial clinical experiences are encouraging; however, the adequate dose for Indian patients is yet to be determined. Early experiences indicate that most Indian patients would require dose ranging between 40 and 80 mg / day. In the early experiences, no serious adverse events or toxicity has been noted. Notably, the Indian experience has been gathered at the variety of locations (Punjab, New Delhi, Mumbai, Manipur), variety of treatment settings (Medical college hospitals, District hospitals, Community Clinic) and variety of patients (Pharmaceutical Opioid injectors, Pure Heroin injectors and Brown-sugar injectors).

6.2.3.3. Buprenorphine as agonist maintenance agent

6.2.3.3.1. Introduction

Buprenorphine is a partial μ agonist and k antagonist. It binds tightly to and dissociates slowly from the receptors. It is a long acting, highly lipophilic opiate and 25-50 times more potent than morphine (in analgesic action). It has higher affinity and low intrinsic activity to μ receptor. At low doses Buprenorphine produces morphine like subjective, physiological and behavioral effects. These include analgesia, sedation, pupillary constriction and euphoria. Because of higher affinity of Buprenorphine for the mu receptor, full agonists cannot displace it and therefore will not exert an opioid effect on receptors already occupied by Buprenorphine. This effect is dose related, as shown by Comer et al. (2001) [107] in a study demonstrating that a single 16 mg dose of the sublingual Buprenorphine tablet was more effective than the 8 mg dose in blocking the reinforcing effects of heroin. When given sublingually morphine like subjective effects reached a ceiling at about 8-16 mg whereas 32 mg dose often produced slightly lower scores indicating there was a ceiling dose, beyond which no greater effect was observed. [108]

Buprenorphine is less effective by oral route and its bio-availability by this route is 15% but when administered sublingually, its bio-availability increases to 51%. [101] There is no limit in sublingual absorption and plasma concentration is linearly related to dose. Peak blood levels are achieved after 5 minutes when administered through I.V. route and 2 hours when administered sublingually. [20] It is metabolized in liver by glucoronide conjugation and N-dealkylation and has an active metabolite norbuprenorphine. [16] Elimination half-life of I.V. Buprenorphine is 3.21 hours and for sublingual Buprenorphine is 27.2 hours. [109] Following three times daily chronic sublingual dosing of 0.4 mg, steady state levels were achieved at about 4 days. About 96% of the circulating drug is bound to plasma proteins. [20] Metabolites are detected in urine but most of the drug is excreted unchanged in faeces. [110, 20]

6.2.3.3.2. Treatment outcome

Nine studies between 1992 and 1999 compared the effect of Buprenorphine as against methadone. Sample size varied from 40-225 and duration of therapy varied from 6-52 weeks. The doses of Buprenorphine varied between 2-8 mg and that of methadone varied between 25-80 mg. These studies indicated that high dose methadone was most effective. It seems that high dose of Buprenorphine 8 mg/day is equal in efficacy to methadone as a maintenance agent but at low doses (2 mg or less), the efficacy of Buprenorphine is less. However, it was also reported that the difference between efficacy of 4 mg and 8 mg daily dose of Buprenorphine was marginal. [111- 114] (Ib) Comer et al (2001) [99] concluded that 16mg Buprenorphine reduced heroin abuse more relative to 8mg.

The meta-analysis on Buprenorphine maintenance by Cochrane database[115] (IA) included Twenty four studies and reported that buprenorphine given in flexible doses was significantly less effective than methadone in retaining patients in treatment. For methadone doses between 20 and 35 mg were “low dose” and doses between 60 and 80 mg were “high dose.” For Buprenorphine, “low dose” included 2 to 4 mg and “high dose” included 6 to 12 mg. It was seen that low dose Buprenorphine was not superior to low dose methadone. High dose Buprenorphine did not retain more patients than low dose methadone, but suppressed heroin use better. High dose Buprenorphine was inferior in suppression of heroin use over high dose methadone. The study concluded that Buprenorphine is an effective intervention for use in the maintenance treatment of heroin dependence, but is not more effective than methadone at adequate doses.

Simoens et al (2005) [116] (IA) conducted a systematic review to synthesize and critically appraise the evidence on the effectiveness of community maintenance programmes with methadone or Buprenorphine in treating opiate dependence. They took systematic review of databases, journals and the grey literature from 1990-2002. They included community-based, randomized controlled trials of methadone and/or Buprenorphine for opiate dependence involving subjects who were aged 18 years old or over. Trials were set in a range of countries, employed a variety of comparators, and suffered from a number of biases. The evidence indicated that higher doses of methadone and Buprenorphine were associated with better treatment outcomes. Low-dose methadone (20 mg per day) was less effective than Buprenorphine (2-8 mg per day). Higher doses of methadone (>50-65 mg per day) was slightly more effective than Buprenorphine (2-8 mg per day).

Sung and Conry (2006) [117] in a review of studies till February 2005 reported that Buprenorphine as maintenance treatment is effective, but not more effective than methadone.

Giacomuzzi et al (2006) [118] with use of a randomized study design compared opioid addicts at admission with slow-release oral morphine, methadone, and sublingual Buprenorphine maintenance program participants after 6 months of treatment. Both the Buprenorphine and the methadone maintenance group showed significantly more favourable values than opioid clients at admission for stomach cramps, muscular tension, general pain, feelings of coldness, heart pounding, runny eyes, and aggressions. Patients receiving slow-release oral morphine treatment generally showed the least favourable Quality Of Life scores compared with patients at admission or sublingual buprenorphine and methadone clients. Patients in the sublingual buprenorphine or methadone program showed nearly the same Quality Of Life scores. The buprenorphine and the methadone maintenance group showed significantly more favourable values than opioid clients at admission regarding leisure time, finances, mental health, and overall satisfaction. Similar findings were reported in other studies with follow up till 12th month, [119] and findings of methadone having an earlier onset in Quality of Life scores than buprenorphine though both later showed nearly same Quality Of Life scores. [120]

Connock et al. (2007) [121] in a systemic review compared methadone to buprenorphine maintenance treatment and concluded that a fixed dose of Methadone Maintenance Treatment (MMT) or Buprenorphine Maintenance

Treatment (BMT) has superior levels of retention in treatment and opiate use than placebo or no treatment, with higher fixed doses being more effective than lower fixed doses. Retention in treatment was superior for flexible MMT than flexible BMT dosing. There was no significant difference in serious adverse events with MMT compared with BMT.

Boothby and Doering (2007) [122] in a systemic review reported that buprenorphine, buprenorphine-naloxone, and methadone are similarly efficacious for the treatment of opioid-dependent patients. Buprenorphine-naloxone has less potential for abuse and diversion. The adverse-effect profiles for buprenorphine, buprenorphine-naloxone, and methadone are similar.

The meta-analysis on Buprenorphine maintenance versus Placebo or methadone maintenance by Cochrane database [123] (IA) included twenty four randomised clinical trial studies (4497 participants), all but six were double-blind. Results were almost similar to Cochrane metaanalysis conducted by same authors in 2004.

6.2.3.3.3. Dosing

In the analgesic dose range, morphine 10 mg, i.m. is equivalent to 0.4 to 0.6 mg of Buprenorphine sublingually. [109] For the treatment of opioid dependence, approximately 4 mg of sublingual Buprenorphine is equivalent to daily dose of 40 mg of oral methadone. [124]

In a study carried out by AIIMS Drug Dependence Treatment Centre (in the initial years of buprenorphine usage as maintenance treatment), most patients did remarkably well while on 1.2 - 2 mg s/l dose per day over 6-8 months.[125] However, the optimal maintenance dose among Indian patients is 5.9±2.4 (described later).[94] Alternate day dosing and twice weekly dosing are feasible option in buprenorphine maintenance.

- **Induction:** Patients who are assessed as suitable for buprenorphine treatment should be supplied with verbal and written information about all aspects of the maintenance treatment-what to expect and what not to expect, and their rights and responsibilities. The dose should be titrated according to the clinical effect in the individual patient. Procedure for buprenorphine (s.l) administration: First and foremost is the establishment of diagnosis of opioid dependence clinically and optional confirmation by urine screening for recent opioid consumption. After that 2mg to 4mg of s/l buprenorphine is given to the patient. The patient is observed for 2 hours and another 2 mg

may be given on day 1 if withdrawal symptoms persist after 2 hours. Dose increments can be done every day by 2 mg/day. In most patients daily dose of 4 to 8 mg of buprenorphine is sufficient. However as in Methadone the criteria for determining dose adequacy remain the same, i.e. control of withdrawals, control of craving and blocking of effect of illicit opioids.

6.2.3.3.4. Adverse effects

Primarily seen effects are sedation, drowsiness and constipation including other effects of μ opioid agonist in general. [126] The side effects reported by Harcus et al, (1979) [127], after surveying 8137 non-dependent subjects were – nausea (8.8%), vomiting (7.4%), drowsiness (4.3%), sleepiness (1.9%), dizziness (1.2%), sweating (0.98%), headache (0.55%), confusion (0.53%), light-headedness (0.38%), blurred vision (0.28%), significant euphoria (0.28%), and dry mouth (0.11).

The post marketing surveillance of higher strengths of Buprenorphine (0.4 and 2 mg) in India showed that the subjective symptoms most often reported by the subjects were: generalized weakness (48.9%), sense of high (44.5%), muscle aches (39.5%), yawning (38.5%), relief from pain (37.2%), constipation (33.1%), lacrimation (26.1%), craving (26.6%), anxiety (18.9%) and sleeplessness (18.9%). Many symptoms including giddiness, light-headedness, drowsiness, blurred vision, vomiting, pre-mature ejaculation, low libido, poor appetite and postural giddiness were reported though the number was less than 10 per cent. Some had however, reported better sexual performance and increased appetite. Buprenorphine treatment was found to be safe and devoid of major side effects in the study. [128]

6.2.3.3.5. Buprenorphine as maintenance treatment: Indian Experience

De et al. (2001) [129] in a double blind randomized controlled trial compared different doses of sublingual buprenorphine (2 and 4 mg/day) in an inpatient setting for long term pharmacotherapy among opiate dependent subjects at the Drug Dependence Treatment Centre, AIIMS, New Delhi. Altogether twenty-two subjects were included in the study and analysis of withdrawal symptom profile, sedation and euphoria, craving, side-effects, global rating of wellbeing and analysis of plasma level of buprenorphine were carried out. The results indicated that both 2mg and 4mg dose of buprenorphine were effective in pharmacotherapy of opioid dependence without significant difference as compared by different measures used in the study.

Mohan and Ray (1997) [125] did a quasi-experimental study of community based treatment with Buprenorphine of heroin dependence in an urban slum of Delhi. A total of 108 heroin users were included and given 1.2-1.8 mg/ day Buprenorphine for 6-11 months along with psychosocial intervention. Assessment was done at 6, 9 and 11 months. It was seen that 70% subjects improved with no use or very little use of heroin. No heroin use was seen at 11 months among 62% of subjects. Addiction Severity Index (ASI) scores showed an improvement in drug, alcohol, legal, family and psychological domains.

In the community based treatment conducted by the De-addiction Centre, AIIMS in an urban slum area, 1.2 mg and 1.8 mg Buprenorphine was provided in two/three divided doses for period of 6-11 months for 108 male subjects with heroin dependence. At follow up about 70% had improved indicating no use or very little use of heroin. [125] Dhawan and Sunder (2008) [130], in a brief overview of buprenorphine substitution in India, have concluded that buprenorphine substitution programs have been successful in decreasing the harm associated with drug use, as well as decreasing the drug use per se and improving the quality of life.

In another study carried out by AIIMS in Nagaland, 54 opioid dependent patients on Buprenorphine maintenance were followed up to for 6 months. There was significant improvement in 'drug and family domain of addiction severity index (ASI) and subjective wellbeing scale as reported by Dhawan and Sunder (2008). [130]

Similarly, treatment centre of TT Ranganathan clinical Research Foundation, Chennai, found improvement in buprenophine maintained patient in their drug use pattern, life functioning, general health, high risk behaviour, crime rate and arrests as reported by Dhawan and Sunder (2008) [130]

Kumar from Chennai reported the use of Buprenorphine in 250 injecting opioid users. At one year follow-up, significant risk reduction was observed for injection related risk behaviours as reported by Dhawan and Sunder (2008). [130]

SHARAN, a Delhi based NGO provided Buprenorphine substitution for 447 IDUs between February 1995 and January 1997. Of these, 148 (33%) had stopped injecting while 158 (35%) had reduced the frequency of injecting and sharing of equipment as reported by Dhawan and Sunder (2008). [130]

Considering the HIV prevalence among injecting drug users in Manipur and Nagaland, an NGO established thirteen drop-in-centres (DIC) across the two states to deliver opioid substitution treatment with sublingual buprenorphine for 1200 injecting drug users. Within a short span of time the treatment was found to be attractive to the clients. The intervention was reported to be acceptable to the drug users, the families, the communities, religious as well as the militant groups. The average maintenance dose reported was 4–8 mg per day. [131]

Armstrong et al, (2010) prospectively collected from all clients enrolled in an OST program in Manipur and Nagaland between May 2006 and December 2007 using standardised questionnaires. Of all clients enrolled in OST during the month of May 2006 (n = 713), 72.8% remained on treatment after three months, and 63.3% after six months. Statistically significant ($p = 0.05$) improvements were observed in relation to needle sharing, unsafe sex, incidents of detention, and a range of quality of life measures. [132]

In a multisite study, involving 231 opioid dependent individuals Dhawan et al reported that the mean dose required was 6 mg per day. By six months of treatment the mean number of days, illicit opioids were used in the past month were reduced to less than two. There was a significant reduction in injecting as well as sharing of injecting equipment. Addiction severity scores were significantly decreased and measures of quality of life were significantly improved. Most patients and their family members expressed satisfaction with the treatment. [133]

In an operational research conducted by National Drug Dependence Treatment Centre, (AIIMS) data was collected through two methods: (a) an email based questionnaire method in which 42 OST centres selected for the study – spread nationwide - responded, and (b) one-to-one interview of 192 OST clients located across 22 centres. About 70% clients reported residing within five km range of the OST centre, 95% reported having to spend 15 minutes or less for travel to OST centre, and 90% reported having to spend 50 Rupees or less for their OST intake daily. About 3/4th of the doctors reported that they were fully trained and confident on the core clinical issues related to OST implementation. Only about 50% of the counsellors felt fully trained and confident on various topics of OST. The centres reported that the mean dose of buprenorphine on which most of the clients are stabilised is 6 mg/day. In the data from client interview, mean dose of buprenorphine for the last month, as collected from record review, was 4.4

mg/day, and 75% were receiving 6 mg/day or below. About 89% of clients reported that they were satisfied with the dose of buprenorphine being provided to them. [134]

6.2.3.4. Buprenorphine- naloxone combination

6.2.3.4.1. Introduction

The fact that buprenorphine tablets can be diverted and subsequently injected means that it cannot be made available for widespread use. One of the strategies to combat the problem of diversion and injection could be to use a combination of sublingual buprenorphine-naloxone tablets which have a minimum risk of being injected. [135] The addition of naloxone, with its relatively poor sublingual bioavailability, will result in Buprenorphine effect predominantly by the sublingual route. However, abuse via the parenteral route will result in a predominant naloxone effect. Buprenorphine and naloxone in a ratio of 4:1 produced significant opioid antagonist like effects. [136, 137]

6.2.3.4.2. Treatment outcome

In a review [138] this combination was found to be effective and advantageous over methadone. This combination product has recently been introduced in France as an outpatient treatment agent for opioid dependence. Prohibiting factor could be cost of naloxone. In some studies it has been shown to have similar abuse liability by s/l route in recently detoxified individuals who abuse heroin. [139]

There is evidence from naturalistic setting, post-dispensing surveillance studies that diversion of buprenorphine/naloxone does occur, but that it is less prevalent than diversion of buprenorphine alone. [140,141] (III) There is evidence that the buprenorphine/naloxone combination is less likely to be injected than buprenorphine alone, although some individuals do inject it. [142] (III)

A randomized, active-drug controlled, parallel-group trial consisting of a 2-day, double-blind, double-dummy induction phase followed by 26 days of open-label treatment with BNX was reported by Amas et al, 2012. [143] (Ib) They found that direct buprenorphine/naloxone induction was a safe and effective strategy for maintenance treatment of opioid dependence. Response to high-dose direct buprenorphine/naloxone induction appears to be similar to indirect buprenorphine-to-buprenorphine/naloxone induction and was not associated with reports of intravenous buprenorphine/naloxone misuse.

Study conducted by Comer et al, 2010 [144] found that Buprenorphine/naloxone combination has lower intravenous abuse potential than buprenorphine alone, particularly when participants received higher maintenance doses and lower buprenorphine/Naloxone challenge doses. Buprenorphine/naloxone may be a reasonable option for managing the risk for buprenorphine misuse during opioid dependence treatment.

6.2.3.4.3. Dosing

Buprenorphine-Naloxone combination is available in 2 mg/0.5 mg and 8 mg/2 mg dosages. Essentially the dosing remains same as for plain buprenorphine.

6.2.3.4.4. Adverse effects

The adverse effects of buprenorphine – naloxone combination are not different from the adverse effects of buprenorphine alone.

6.2.3.4.5. Buprenorphine-Naloxone as maintenance treatment: Indian Experience

In India, buprenorphine-naloxone combination has been available for some years now but only in highly regulated manner (like buprenorphine tablets) and is meant only for dispensing through recognized drug treatment centres. The clinical experience with hundreds of patients over the years suggests that it is a safe combination and can be safely dispensed to patients as take-home (as opposed to buprenorphine or methadone which are supposed to be dispensed only as daily observed treatment). A research study or trial involving buprenorphine-naloxone combination however is still not available from India. A Post marketing Surveillance study is available as an evidence of safety of this product in Indian patients.[145]

Box 8: OST Programme of India under National AIDS Control Organization, using Buprenorphine

India has a concentrated but growing HIV-epidemic among Injecting Drug Users (IDUs) with 7% IDUs being HIV positive. The National AIDS Control Programme has adopted the strategy of Targeted Interventions (TIs) for preventing HIV, which provide various harm-reduction services such as Peer-based-Education, Needle-Syringe-Exchange, condom-promotion, abscess-management, referral-linkage and Opioid Substitution Therapy (OST).

The OST programme of NACO is meant only for Opioid dependent individuals who are also current injecting drug users. Essential elements of the programme are requirement of adequate infrastructure, facilities for proper assessment and diagnosis of patients and dispensing of medications (buprenorphine) as a directly observed treatment. For this purpose the patients are required to attend the clinic daily. Psychosocial interventions as well as linkage and referral services for other health and psychosocial needs are essential parts of the package.

As on September 2013, about 130 OST centres are implementing buprenorphine-based OST in India. While about 51 OST centres, are based in NGO settings, rest are in government hospitals which provide the clinical OST services in collaboration with linked NGOs which provide the outreach and field-based services. Owing to dearth of psychiatrists, general physicians are being trained to provide services under the supervision of psychiatrists, through systematically designed training systems and resource materials. Systems are also in place for monitoring, evaluation, accreditation and on-site mentoring of service providers.

The Indian experience suggests that Buprenorphine based OST programmes can be implemented at a large scale in even resource-limited, non-specialist health settings. [146-149]

6.2.3.5. LAAM (levo-alpha-acetyl-methadol)

6.2.3.5.1. Introduction

LAAM a μ-opioid agonist is a synthetic congener of methadone. It has good oral bio-availability and longer half- life than methadone. [150] The half-life is 48-96 hours which is mainly due to its active metabolites, nor-LAAM and Dinor-LAAM with half life 48 hours and 96 hours respectively. Although LAAM is similar to methadone in its pharmacological actions, it is converted into the active metabolites nor-acetylmethadol and di-nor-acetylmethadol that have long biological half-lives (e.g., 48 to 96 hours for di-nor-acetylmethadol). Consequently, LAAM can be given as infrequently as three times a week, thereby reducing the inconvenience of attending a clinic daily to ingest the drug and simultaneously reducing concerns about illicit diversion. LAAM can only be provided through directly observed treatment, and a relatively small number of patients were treated with LAAM when it

was available. Its limited use was probably due to the restriction on its use, along with concerns about LAAM's safety.

6.2.3.5.2. Treatment outcome

Doran et al, 2006 [151] (IIb) conducted a study involving 551 participants. A total of 272 patients (49%) received methadone maintenance, 238 (43%) received buprenorphine maintenance and 41 (7%) participants received levo-alpha-acetyl-methadol (LAAM). A total of 63% of participants in the methadone maintenance group were in treatment in the third month, with an average treatment episode lasting 69 days. This compares with 51% of participants in the buprenorphine maintenance group with an average treatment episode of 60 days and 71% of participants in the LAAM group with an average treatment episode of 75 days. The results of the cost-effectiveness analysis suggested that, for the primary outcome measure of imputed change in heroin-free days, compared with methadone maintenance, LAAM was the most cost-effective treatment, followed by buprenorphine maintenance. No statistically significant differences were found in the cost-effectiveness of methadone maintenance, buprenorphine maintenance and LAAM.

6.2.3.5.3. Dosing

It can block the effect of opioids for upto 72 hours so it is usually given thrice weekly and weekend dose is increased 20-40% more than other day doses to cover the weekend. Usual starting dose is 20-40 mg/day with supplemental methadone 5-20 mg/day and weekend dose of 80-90 mg. [152]

6.2.3.5.4. Adverse effects

After LAAM was approved in the Unites States and Europe, cases of arrhythmias associated with LAAM use were reported to the FDA and European authorities. It was found that some patients developed prolonged QT intervals when treated with LAAM and that a potentially fatal arrhythmia (torsade de pointes) could occur. These case reports resulted in the decision to withdraw LAAM from the European market altogether. In the United States, the FDA revised LAAM's label to include a black-box warning about its potential to cause prolongation of the QT interval and the recommendation that LAAM be reserved for use as a second-line agent for the treatment of opioid dependence. The manufacturer subsequently ceased distribution in the United States after the black-box warning. Despite these safety concerns,

LAAM was a useful agent for some patients. Anecdotal reports from patients treated with LAAM indicate that they feel a more level pharmacological effect, when asked to compare LAAM to previous experience with methadone. However, since it is no longer available LAAM is more of an academic interest at this time.

6.2.3.6. Slow release oral morphine (SROM)

6.2.3.6.1. Introduction

Slow release oral morphine (SROM), a natural derivative of opium and a mu receptor agonist, is relatively cheap with long duration of action. Compared with short acting, immediate release morphine, SROM has the advantage of single dosage, decreased sleep disturbance and increased medication compliance.

6.2.3.6.2. Treatment outcome

SROM has been used as a maintenance agent in methadone intolerant individuals dependent on opioid with favourable results in countries such as the UK, Austria and Australia. [153-156] (III)

Recent systemic review conducted by Jegu et al, 2011[157] (IIb) identified 13 articles corresponding to nine clinical trials considering the use of SROM for substitution treatment. Among them, only one was a randomized trial and one was a controlled not randomized trial. All other studies were uncontrolled. Retention rates were good (from 80 to 95%) with SROM maintenance, but similar retention rates were obtained with methadone. Most of the studies showed that quality of life, withdrawal symptoms, craving and additional drug consumption improved with SROM. However, there was no comparison with other maintenance drugs. As most of the studies assessing SROM efficacy were uncontrolled, there is no definite evidence that SROM is an effective alternative to methadone for substitution treatment.

6.2.3.6.3. Dosing

It has been found to be most effective in doses of 60 mg daily. A higher dose is needed sometimes to control craving and withdrawal symptoms. A dose of up to 180mg – 240 mg can be administered and the effects last for up to 12 – 24hours. Strict monitoring is required as morphine produces chemical dependence and the patient may try to escalate the dose, use other narcotics concomitantly or even divert the prescribed morphine to the illicit market.[1]

6.2.3.6.4. Adverse effects

Adverse effects are similar to other opioid agonist

6.2.3.6.5. SROM as maintenance treatment: Indian Experience

In India too, SROM has been tried for opioid dependent patients as a maintenance agent at NDDTC, AIIMS, New Delhi. It has been found to be a safe drug with minimal side effects and can be administered in once a day dosage. Patients showed definite improvement, with a decrease in heroin consumption, improved functioning and a decrease in illegal activities. [158,159] (III) However compared to buprenorphine and buprenorphine-naloxone, clinical experience with sustained release morphine as opioid agonist maintenance agent is limited in India.

Box 9: Heroin as maintenance agent for heroin dependence Over the last decade, several studies and trials have been conducted to test the efficacy of pharmaceutical heroin for treating the most recalcitrant heroin users. Four countries (Switzerland, Netherlands Germany and Spain) have successfully conducted studies on its efficacy and drawn conclusions; some other countries are in the process of conducting heroin trials and awaiting results or scheduled to start trials soon.There is a some evidence that heroin maintenance programme helps stabilize those heroin dependent users who are unresponsive to other treatment by improving physical and mental health, increases social integration, reduces high risk behaviour, prevents overdose, reduces dependence on street heroin and reduces involvement in illegal activities. For some patients heroin maintenance programme has shown to be the first step towards MMT or even abstinence. Heroin maintenance programme has also been clearly shown to be a cost effective intervention for the treatment of resistant heroin users. [160-164] The meta-analysis on heroin maintenance versus placebo or methadone maintenance by Cochrane database. [165] (Ia) included Eight studies involving 2007 patients. Five studies compared supervised injected heroin plus flexible dosages of methadone treatment to oral methadone only and showed that heroin helps patients to remain in treatment (valid data from 4 studies, N=1388 Risk Ratio 1.44 (95%CI 1.19-1.75) heterogeneity P=0.03), and to reduce use of illicit drugs. Maintenance with supervised injected heroin has a not statistically significant protective effect on mortality (4 studies, N=1477 Risk Ratio 0.65 (95% CI 0.25-1.69) heterogeneity P=0.89),

but it exposes at a greater risk of adverse events related to study medication (3 studies N=373 Risk Ratio 13.50 (95% CI 2.55-71.53) heterogeneity P=0.52). Results on criminal activity and incarceration were not possible to be pooled but where the outcome were measured results of single studies do provide evidence that heroin provision can reduce criminal activity and incarceration/imprisonment. Social functioning improved in all the intervention groups with heroin groups having slightly better results. If all the studies comparing heroin provision in any conditions vs any other treatment are pooled the direction of effect remain in favour of heroin.However, needless to mention, heroin maintenance treatment is a controversial treatment approach. In India, it cannot be recommended to be used for any therapeutic indication.

6.2.3.7. Injectable opioid / Supervised Injection (Special Mention)

6.2.3.7.1. Introduction

Injectable opioid treatment (IOT), also known as heroin-assisted treatment (HAT), has a long history, which is remarkable for variations between national jurisdictions. It was used in many parts of the UK during the twentieth century, although many had commented on the lack of evidence underpinning treatment. During the past few years a number of studies have expanded the evidence base considerably. [165] (Ia). In addition to the main findings below, it is of note that study reports contain detailed description of what constitutes optimized oral treatment, and that patients randomised to optimized oral treatment also show improvement over baseline, in a group often selected for treatment resistance.

6.2.3.7.2. Treatment outcome

Injectable diamorphine: Several open-label RCTs of on-site diamorphine provision compared with oral methadone.[26] There is increased retention in IOT/ HAT compared with control groups; reductions in self-reported illicit heroin use, and improved outcomes in terms of quality of life or health outcome measures in these studies. One study reported improved outcomes in relation to reduced consumption of alcohol. [166] (Ib). The Cochrane review by Ferri et al. (2011) (Ia) [165] concluded that evidence suggested heroin alongside methadone for long-term, treatment refractory opioid users reduced

illicit substance use and criminal activity and possibly reduced mortality and increased retention in treatment. However, due to the higher rate of serious adverse events, injectable heroin is an option for those that have failed previous maintenance treatments.

A number of the studies have reported longer-term follow-up outcomes – the study from the Netherlands demonstrates continued retention at 4 years of 55.7%. Those who continued HAT treatment also had fewer health problems and were more likely to have stopped illicit drug and excessive alcohol use. [167] (III). The German study also demonstrates improved long-term retention. [168] (III). Inclusion criteria are typically those who have failed on oral opioid treatment, although the recent German study [169] (Ib) included a group that was not currently on oral treatment. Controlled studies are now necessary to examine whether diamorphine treatment could be considered as one of several options in treating severely opioid-dependent patients, regardless of previous maintenance treatment experience. Research reports also include cost utility analyses. The study in the Netherlands [170] (Ib) analysed costs of addiction treatment, other health treatment, law enforcement and victim costs and found increased quality-adjusted life years (QALYs) per patient-year and a cost saving in the diamorphine group. However, the outcomes reported remain limited by a relative reliance on self-reported illicit drug use, with only two studies including biological measures. The illicit drug outcome in the German trial included urine and hair data but supplemented with self-report where these were not available. The recently reported UK study, RIOTT, had a reduction in urine tests positive for illicit heroin as the primary outcome measure. Some studies provide data about the frequency of serious adverse events [171,172] (III), with a lower mortality rate among the treatment group in a Swiss study compared with mortality of Swiss opioid users in the general population.

Injectable methadone: The UK randomised study, RIOTT [173] (Ib), included an arm in which participants were randomised to receive injectable methadone. These subjects did not show the benefits demonstrated in the injectable heroin arm.

Injectable hydromorphone: The North American study included an arm in which participants received hydromorphone to inject, rather than diamorphine. Results were equivalent, and the place of oral hydromorphone is being evaluated in a follow-up trial. [174] (Ib).

6.2.3.7.3. Dosing

The mean daily dose of heroin was 442 mg with an additional 8 mg of methadone (mean daily dose over all heroin treatment days). [175] (Ib) The study aimed to assess the efficacy of the prescription of intravenous diacetylmorphine (DAM) with daily methadone versus oral methadone with medical and psychosocial support. The average DAM dosage used was 274.5 mg/day (range: 15-600 mg), and an average methadone dosage was 42.6 mg/day (range: 18-124 mg). The daily methadone dosage in the control group was 105 mg/day (range: 40-180 mg). [176] (Ib)

6.2.3.7.4. Adverse effects

A total of 315 serious adverse events were reported during the 12-month study period: 177 among 124 participants in the heroin group and 138 among 88 participants in the methadone group. Of the 58 adverse events possibly, probably or definitely related to the heroin medication, 41 occurred within a few minutes of injection, 31 of these events were related to respiratory depression. (Haasan et al, 2007) [175] Maintenance with supervised injected heroin has a not statistically signicant protective effect on mortality (4 studies, N=1477 Risk Ratio 0.65 (95% CI

0.25-1.69) heterogeneity P=0.89), but it exposes at a greater risk of adverse events related to study medication (3 studies N=373 Risk Ratio 13.50 (95% CI 2.55-71.53) heterogeneity P=0.52). [165]

Needless to mention, injection heroin maintenance is not recommended for implementation in India.

Agonist maintenance treatment / Opioid Substitution Treatment: Summary

- *Agonist maintenance treatment is preferred as the long-term treatment of choice for long-duration opioid users with severe dependence, with high risk of relapse and for those who are willing to comply with the requirements.*
- *Owing to its safety profile, evidence-base and experience in India, buprenorphine should be the preferred agent for the purpose.*
- *Buprenorphine induction involves administering the first dose in the relative opioid-free state (i.e. when patient is in mild withdrawals) and observation of the patient for 2 hours. The first day's dose is usually 4-6 mg.*

- *Depending on the response to first days' dose, dose can be titrated upwards or downward based on clinical parameters.*
- *For an effective treatment, it is essential to maintain the patients on optimum dose (i.e. the dose on which patients experience no withdrawals, no craving, and no reinforcement on taking illicit opioids). Most Indian patients are likely to be stable on daily dose of sublingual buprenorphine 8-10 mg/day.*
- *Since agonists are liable to be diverted and have abuse liability, the administration of agonist medications for the purpose of maintenance treatment should be supervised and observed, to the extent possible.*
- *Buprenorphine-naloxone combination is a relatively safer option which can be considered as 'take-home' medications, in the settings where it is available.*
- *In settings where methadone is being used as an agent, the process of induction would involve administering lower doses in the beginning (10 to 20 mg per day on first three days) and subsequent dose increments of about 5 mg every third day (owing to accumulation of methadone in the body).*
- *Though Indian experience is limited, it is expected that most Indian patients would require stabilisation dose of methadone between 40 and 80 mg per day.*
- *As yet it is difficult to choose between buprenorphine and methadone as maintenance treatment in the Indian context. Methadone offers the advantage of being a pure agonist and consequently better subjective experience for patients. However, the process of slow induction of dose of methadone coupled with its relatively higher risk of overdose makes buprenorphine a more convenient option. The relative cost of treatment per day per patient of methadone and buprenorphine are yet to be determined in India.*
- *Along with optimum dose, adequate duration of treatment and retention in treatment are crucial factors, which determine outcome of OST. The decision regarding duration of treatment and treatment-completion (i.e. tapering of agonist maintenance medication to make patient opioid free) should only be arrived at in consultation with the patient and involves evidences that patient is stabilized, is leading an illicit opioid-*

free life and is socially and occupationally rehabilitated. Till such criteria are evident, the agonist maintenance treatment should continue, if required, for very long duration (running into years).

- *In many settings, agonist maintenance treatment involves some programme management requirements. Availability of adjunct psychosocial treatment is an essential part of package of agonist maintenance treatment.*

6.2.3.8. Antagonist treatment

6.2.3.8.1. Oral naltrexone

6.2.3.8.1.1. Introduction

Naltrexone is rapidly and completely absorbed following oral administration and reaches peak plasma concentration within an hour. It has high first pass metabolism and oral bioavailability is 60%, with 20% of the drug being bound to plasma proteins. Naltrexone undergoes first-pass metabolism in the liver via glucuornic acid conjugation with transformation to the active metabolite 6-beta naltrexol. The half-life of this drug is about 4 hours and that of its active metabolite is 10-12 hours. Naltrexone is a non-specific opiate antagonist that binds to all three opiate receptors sites as a function of dose administered. The pharmacological duration of naltrexone is longer than might be predicted by the plasma kinetics. The plasma half-life of naltrexone is 4 hours, but the duration of opioid receptor blockade is much higher and a 50 mg dose of naltrexone blocks 25 mg of heroin for 24 hours, 100 mg for 48 hours and 150 mg for 72 hours. This pharmacodynamic property of naltrexone makes it easy to be administered in simple and convenient regimens.

6.2.3.8.1.2. Treatment outcome

Patients involved in meaningful relationships, employed full time, or attending school and living with family members are most likely to benefit from naltrexone treatment. Follow up of naltrexone treated patients indicates that 30-40% are opioid free for 6 months after terminating treatment. However, naltrexone treatment has a very high early dropout rate. Only 10-20% take naltrexone for 6 months or longer, although certain specific motivated populations like addicted professionals and former prisoners on probation have significantly higher rates of accepting naltrexone and remaining in treatment. This may be due to the fact that naltrexone has no reinforcing properties of its own and is perceived as a subjectively neutral

drug that prevents addicts from getting high. Kirchmayer and colleagues in 2002 [177] (Ia) systematically reviewed controlled clinical trials and concluded that there was insufficient evidence to justify naltrexone use in the maintenance of addicts, except to decrease the possibility of incarceration of prisoners treated with combined behavior therapy and naltrexone. However a meta-analysis of fifteen studies involving 1071 patients in 2006 found significant heterogeneity in the efficacy of naltrexone. [178] (Ia) The authors attributed this to the potential moderating effect of treatment retention. This study concluded that retention was the key variable for understanding the mechanisms of the effect of naltrexone in opioid dependence and that the drug may be effective if the retention rate is increased above a certain level.

Another Meta-analysis included 26 randomised controlled trials (RCTs) and the results suggest that naltrexone as maintenance therapy may be better than placebo in terms of retention in treatment, but this was not statistically significant. Another meta-analysis of seven included RCTs gave the relative risk (RR) of loss of retention in treatment in the naltrexone arm as 0.94. The pooled hazard ratio (HR) reported in five of the RCTs for retention in treatment data followed up to 35 weeks was calculated as 0.90 in favour of naltrexone and also did not reach statistical significance. The risk of drug abuse in naltrexone versus placebo, with or without psychological support given in both arms, gave a pooled RR of 0.72, which was a statistically significant difference in favour of naltrexone. The pooled HR from three RCTs for opioid relapse-free rates was significantly different from placebo in favour of naltrexone 0.53; however, this fell off over time and may be of limited clinical significance. The RR of re-imprisonment while on naltrexone therapy showed results in favour of naltrexone in the combined two studies of parolees or people on probation, but the number of participants was small. One study of 52 participants found that the difference in improvement score for risky sexual behaviour in the naltrexone group compared with the placebo group was not statistically significant. The adverse events data reported showed no significant difference between the naltrexone and placebo arms. The quality of the nine RCTs of interventions designed to increase retention with naltrexone was poor to moderate; however, all three different modalities of enhanced care showed some evidence of effectiveness. [179] (Ia)

The Cochrane reviewers [180] (Ia) concluded that there was no significant difference in treatment retention for people treated with naltrexone with or

without adjunctive psychosocial therapy compared with placebo with or without psychosocial therapy (six studies, RR 1.43, 95% CI 0.72–2.82). There was a significant reduction in illicit heroin use as assessed by urinalysis (six studies RR 0.72; 95% CI 0.58–0.90) but the difference was not statistically significant when comparing the studies of naltrexone versus placebo only. Naltrexone with psychosocial treatment showed reduced re-incarceration rates compared with psychosocial treatment alone (two studies RR 0.47, 95% CI 0.26–0.84) but the sample size was small.

6.2.3.8.1.3. Dosing

Naltrexone is available in 50 mg tablets and the recommended daily dose is 50 mg per day. Initiating naltrexone maintenance requires that the patient be opiate free. So patients should be detoxified and should be abstinent from short acting opiates (e.g. heroin) for about 3 days and from longer acting opiates (e.g. methadone) for about 7 days or more as judged by self report, urine toxicology screening test and Naloxone Challenge test.

Box 10: Naloxone testing for residual dependence (Naloxone Challenge test)

It has been advocated that an intravenous or subcutaneous challenge of 0.4-0.8 mg of Inj. Naloxone be given prior to the administration of naltrexone to test for residual opioids so that withdrawal signs and symptoms are not precipitated. A positive test indicative of residual opioids would consist of typical signs and symptoms of opiate withdrawal. These include yawning, abdominal cramps, irritability, anxiety, chills etc. These signs and symptoms often last only 30-60 minutes and in such a situation naltrexone should be withheld for at least 24 hours.[86]

Intravenous:

Inject 0.2 mg naloxone.

Observe for 30 seconds for signs or symptoms of withdrawal.

If no evidence of withdrawal, inject 0.6 mg of naloxone.

Observe for an additional 20 minutes.

Subcutaneous:

Administer 0.8 mg naloxone.

Observe for 20 minutes for signs or symptoms of withdrawal.

Note: The naloxone challenge test should not be performed in a patient showing clinical signs or symptoms of opioid withdrawal, or in a patient whose urine contains opioids. Naloxone Challenge Test is NOT MANDATORY for induction of naltrexone if clinicians are reasonably certain of patients' opioid-free status and no risk of precipitated withdrawals.

Naltrexone Induction: When the required period of abstinence from opioids is complete, naltrexone can be initiated carefully in the dose of 25mg and if no withdrawals occur after 1 hour then another dose of 25 mg is given. The recommended dosage subsequently is 50mg/day. After the first 1-2 weeks, it is usually possible to graduate the patient (50, 75, 100 mg on subsequent days) to three doses per week **(**100mg on Mondays and Wednesdays and 150mg on Fridays). It may also be give in the dosing regimen of 100mg every other day or 150 mg every third day. As compliance is often poor, these flexible dosage regimens make it possible to supervise the ingestion of naltrexone from the treatment centre (directly observed treatment.) Progress in treatment is determined by psychosocial parameters (e.g finding a job, job performance) and absence of drug abuse as confirmed by urine tests. [94]

6.2.3.8.1.4. Adverse effects

It has few side effects. Most patients report no symptoms at all and the profile of reported adverse effects includes gastrointestinal distress (nausea, vomiting, diarrhoea, and abdominal pain), anxiety, restlessness, dysphoria, mild hypertension, headache and insomnia. It has been suggested that some effects might be attributed to a mild, temporary abstinence syndrome influenced by naltrexone's complete opiate blockade.

The potential for hepatotoxicity at high doses has been raised as a more serious concern. However convincing reports of elevated liver function test results have been limited to patients receiving 250mg to 300mg daily, five to six times higher than the recommended maintenance dosage for opiate dependence.

As a precaution, patients should receive a full battery of liver function tests prior to receiving naltrexone, and it is *contraindicated* in patients with liver failure, persons who are taking opiate agonists or acute hepatitis and caution should be used in patients with severe renal impairment. [94]

6.2.3.8.2. Naltrexone implant / depot preparations

6.2.3.8.2.1. Introduction

An injectable extended release form of naltrexone is available in the United States and was registered by the FDA in the USA for the treatment of opiate addiction in 2011. The implant releases over one month. Various implants are available in many countries, including the USA, Germany, Russia and China. [181] These were most often a compacted pellet of naltrexone in a magnesium stearate matrix and also usually act for one month. At one time such implants contained triamcinolone in order to reduce local tissue reactions. One such implant comes from the George Sherman pharmacy in New Jersey and is marketed in Russia as Prodetoxone. [182] This is the only registered NI in the world. [183] Two different Chinese implants are available, and are active for 5 and 10 months respectively. Since 2000 the "Go Medical" group in Perth has compounded naltrexone implants based on the polylactide-polyglycolide microsphere technology. Two randomized trials have been conducted using this device. [184, 185] Versions of this implant are now available lasting twelve months and development is proceeding towards a version that will last 24 months. It is widely agreed that serum levels of 1–1 ng/mL of active naltrexone are required to effectively block opiate use. Pharmacokinetic data is available which shows that this occurs for the respective periods quoted for each device. Various other naltrexone implants are under development in the USA.

6.2.3.8.2.2. Treatment outcome

Six recent clinical trial data from several continents have uniformly provided dramatic evidence of the potent, dose-related and highly significant efficacy of NI, with minimal or manageable accompanying toxicity and safety concerns. The opiate-free lifestyle is attained significantly more often with NI adjusted O.R. = 6.00 (95% C.I.3.86–9.50). Other drug use and drug craving are also rapidly reduced. [186]

Naltrexone can be used to treat opioid dependence, but patients refuse to take it. Extended-release depot formulations may improve adherence, but long-term adherence rates to depot naltrexone are poor. Study conducted by Everly et al, 2012 [187] (Ib) used employment-based reinforcement of adherence to depot naltrexone in unemployed opioid-dependent adults. They found that Contingency participants accepted significantly more naltrexone injections than Prescription participants (81% versus 42%), and were more

likely to accept all injections (66% versus 35%). At monthly assessments (with missing urine samples imputed as positive), the groups provided similar percentages of samples negative for opiates (74% versus 62%) and for cocaine (56% versus 54%).

An RCT of 56 patients given a 6-month naltrexone implant versus usual aftercare found naltrexone was associated with significantly fewer days of heroin use in the 6-month follow up Period. [188] (Ib) In an RCT of 60 patients, Comer et al. (2006) [189] (Ib) found improved retention in treatment for injectable sustained-release naltrexone compared with placebo, and that retention was higher for those given higher dose naltrexone. Superior effects on abstinence from illicit drugs were not demonstrated. An RCT of 70 patients reported that a naltrexone implant significantly reduced relapse to heroin use and resulted in higher blood naltrexone levels compared with oral. [184] (Ib) In a comparison of two separate trials (one of oral naltrexone and one of injectable sustained-release naltrexone), Brooks et al. (2010) [190] (IIb) concluded that patients with severe baseline heroin use showed better outcomes when treated with oral naltrexone and intensive psychosocial therapy (behavioural naltrexone therapy), while those with less severe baseline heroin use showed better outcomes with injectable naltrexone. However, these conclusions are uncertain as they are drawn from a comparison of the interventions in two separate, though concurrent, trials. [190] (IIb) Others have reported that many patients did not accept a second injection [191], and plasma levels of naltrexone implants have been shown not to remain at the targeted levels for the intended time. [184]

6.2.3.8.2.3. Dosing

Injectable naltrexone preparations are administered intramuscularly in the gluteal region. Three different formulations, containing naltrexone-loaded microspheres of polymers of polylactide (Naltrel®) or polylactide-co-glycolide (Vivitrol) have been clinically tested, with dosages ranging from 75 to 400 mg. [192-195] The polylactide-coglycolide polymer formulation Vivitrol® containing 380 mg of naltrexone received United States Food and Drug Administration (FDA) approval for treatment of alcohol dependence in April 2006 and for relapse prevention in OD patients after detoxification treatment in October 2010. [196] This formulation releases naltrexone at levels above 1 ng/mL for about 4–5 weeks,70 with no need to adjust the dosage to weight, age, gender, or health status. [197]

6.2.3.8.2.4. Adverse effects

Concerns have been raised whether naltrexone is associated with higher mortality due to suicide or overdoses. One study reported that risk of death appeared low during naltrexone treatment; however, it was higher post-treatment compared with methadone. [198] (III) Studies using the implant have shown reduced opioid overdoses. [199] (III)) and similar mortality to methadone. [200] (III) There were no untoward side-effects except initial discomfort associated with the injection of depot naltrexone. [192]

Open level study regarding safety, and tolerability of a depot formulation of naltrexone in alcoholics conducted by Galloway et al, 2005 [194]. (IIa) Over the course of the study all 16 subjects had 1 or more adverse events. A total of 15 subjects had injection site adverse reactions. Three subjects experienced drainage from their injection site. The drainage fluid of 2 of the subjects was available for culture and in both cases did not grow out any organisms. Of the 198 adverse events reported, 17 were rated severe: nausea, flatulence, gastrointestinal pain, fatigue, lethargy, somnolence (2 reports), depression, irritability, headache (4 reports from 3 subjects), back pain, injection site mass, injection site pain and elevated GGT. There were no serious averse events.

It must be noted that many experts have raised concerns over interpretation of findings of trials involving extended-release naltrexone and in fact have questioned the process of granting approval by FDA to these products. It has been commented that trial data on patients receiving naltrexone extended-release for treatment of *alcoholism* may have been used to extrapolate its safety in patients with *opioid* dependence – disregarding the risk of potentially fatal opioid overdose in patients who take opioids after losing tolerance (which occurs after some months of naltrexone therapy). Indeed, many trials of depot or extended-release naltrexone have been conducted in countries where agonist maintenance treatment is not available (which seemingly justifies a comparison with placebo). [201]

Antagonist (Naltrexone) treatment: Summary

- *Long term treatment with oral naltrexone is indicated for opioid dependent patients with a relatively shorter duration of opioid use, less severe dependence, high motivation, better social and occupational status, and good social support.*

- *Induction with naltrexone requires a totally opioid free state (at least three days of confirmed abstinence from short acting opioids, determined clinically). Confirming opioid-free state with naloxone challenge test is a good practice (though not mandatory).*
- *The dose of oral naltrexone is 50 mg per day. Owing to its long duration of action, it can also be administered, 100 mg every alternate day or 150 mg every third day.*
- *Involving family members for supervising naltrexone administration is a good practice.*
- *Though naltrexone is safe in general, to avoid risk of hepatotoxicity, liver function tests should be monitored at baseline and during the course of therapy (every three months).*
- *Confirming abstinence by other sources of information besides self-report, (family members, urine screening) is a good practice.*
- *Owing to limited evidence-base and controversies, depot preparations of naltrexone are not recommended.*
- *Switching to use of another substance such as alcohol or cannabis (substitute dependence) remains a possibility in opioid dependent patients undergoing long-term treatment. Clinicians should remain careful and vigilant about this.*
- *Availability of adjunct psychosocial treatment is an essential part of package of naltrexone treatment. Since there is risk of loss of tolerance and consequent risk of opioid overdose in the event of relapse, all patients should be educated about it.*
- *Along with optimum dose, adequate duration of treatment and retention in treatment are crucial factors, which determine outcome of long term treatment with naltrexone. The decision regarding duration of treatment and treatment-completion (i.e. stopping naltrexone) should only be arrived at in consultation with the patient and involves evidences that patient is stabilized, is leading an illicit opioid-free life and is socially and occupationally rehabilitated. Till such criteria are evident, the treatment should continue, if required, for very long duration (running into years).*

Box 11: Choosing long term pharmacotherapy for opioid dependence: Agonist or Antagonist?

Very often clinicians will find themselves in situations where a long-term pharmacotherapy for managing opioid dependence appears necessary to prevent the risk of relapse. However, choosing between agonist and antagonist treatment may be a clinical dilemma. In general, maintenance treatment with agonist or antagonist represents two different approaches to treatment. While on the face of it a common thread does run across the two approaches: *taking medications to stay away from drugs*, however, the philosophy behind both the approaches is different. The agonist maintenance treatment involves maintaining the patients on safer, legal, longer-acting opioids so that use of illicit opioids for withdrawal symptoms or craving can be avoided. Antagonist treatment on the other hand is about keeping the patients off-opioids so that any reinforcement from use of illicit opioids can be avoided. Antagonist treatment does not offer any relief from the distressing protracted withdrawal symptoms, while the agonist treatment does. Thus for choosing between antagonists and agonists the following points may come in handy for the clinicians:

- In general, the amount and strength of evidence-base is much stronger for agonist maintenance treatment as opposed to antagonist treatment.
- Patients with certain kinds of profile are better suited for **antagonist treatment**:
  - Shorter duration and lesser severity of opioid dependence
  - High motivation
  - Better social support
  - Higher levels of education; professionals; white-collared occupation
  - Patients with co-morbid alcohol use disorders for whom treatment with anti-craving agents may be indicated (see CPG for alcohol use disorders)
  - Patients who express a desire for remaining opioid-free
- Patients with certain kinds of profile are better suited for **agonist treatment**
  - Longer duration and more severity of opioid dependence
  - Uncertain motivation; expressing difficulty to remain off-opioids

- High risk of relapse as judged by the clinician (based on past history and/or existing life-style and presence of risk factors)

- Finally, the choice of treatment modality will also be guided by availability of treatment. Agonist maintenance treatment is often a part of systematic, regulated programme whereby agonist medications are dispensed under supervision. Naltrexone, on the other hand, can be prescribed to patients and can be obtained from pharmacies.

6.3. Psychosocial treatment

6.3.1. Role of psychosocial treatments

Psychosocial treatments for substance use disorders attempt to counteract compulsive substance use by bringing about changes in patients' behaviors, thought processes, affect regulation, and social functioning. Although the techniques and theories of therapeutic action vary widely across the different approaches reviewed below, they all address one or more of a set of common tasks: 1) enhancing motivation to stop or reduce substance use, 2) teaching coping skills, 3) changing reinforcement contingencies, 4) fostering management of painful affects, and 5) enhancing social supports and interpersonal functioning. [202] A central challenge for clinicians treating individuals with substance use disorders is that the core symptom, compulsive substance use, at least initially results in euphoria or relief of dysphoria, with the aversive and painful effects of substance use occurring some time after the rewarding effects.

A host of psychosocial treatments are available. Many of these are generic in nature i.e. they are not specifically meant for a particular category of substance use disorders. Here we largely discuss psychosocial interventions which form a treatment package for opioid dependence.

6.3.2. Relation of psychosocial treatments to pharmacotherapy for substance use disorders

Research has demonstrated that the utility of pharmacotherapies for substance use disorders may be limited unless they are delivered with adjunctive psychotherapy. For example, naltrexone Maintenance for opioid dependence is plagued by high rates of premature dropout [203,204] that can be lessened by concurrent behavioral or family therapy. [205] Methadone maintenance for opioid dependence is the most successful pharmacological

treatment of a substance use disorder, with substantial evidence of its impact on treatment retention and associated reductions in opioid use and illegal activity. [206] However, cross-program effectiveness varies widely in relation to the quality and amount of ancillary psychosocial services delivered. [200] Moreover, McLellan et al. 1993 [207] have shown that methadone maintenance alone yields acceptable results for only a small fraction of patients and that outcome is enhanced in proportion to the intensity of concomitant psychosocial services. More recently, a meta-analysis (28 trials, 2945 participants), confirmed that that adding any psychosocial support to maintenance treatments improve the number of participants abstinent at follow up (with no differences for the other outcome measures). Data do not show differences between different psychosocial interventions also for contingency approaches, contrary to all expectations. [208] (Ia) but recent Cochrane meta-analysis concluded that adding any psychosocial support to standard maintenance treatments do not add additional benefits. Data do not show differences also for contingency approaches, contrary to all expectations. It should be noted that the control intervention used in the studies included in the review on maintenance treatments, is a program that routinely offers counselling sessions in addition to methadone. [209] (Ia)

6.3.3. Types of psychosocial interventions

6.3.3.1. Psycho-education (Individual / Group)

Individual Psycho educational groups are designed to educate clients about substance abuse, and related behaviors and consequences. Group Psycho-education therapy works well because it engages therapeutic forces—like affiliation, support, and peer confrontation—and these properties enable clients to bond with a culture of recovery. Another advantage of group modalities is their effectiveness in treating problems that accompany addiction, such as depression, isolation, and shame. Groups can support individual members in times of pain and trouble, and they can help people grow in ways that are healthy and creative. Formal therapy groups can be a compelling source of persuasion, stabilization, and support. Group therapy can provide a wide range of therapeutic services, comparable in efficacy to those delivered in individual therapy.

Psycho-educational Model - Psycho educational groups are designed to educate clients about substance abuse, and related behaviors and consequences. This type of group presents structured, group-specific content, often taught using videotapes, audiocassette, or lectures.

Old studies from India have reported that psychoeductional groups have been found to facilitate recovery in alcohol and drug dependence. [210]

6.3.3.2. Cognitive-behavioral therapy

CBTs for the treatment of substance use disorders are based on social learning theories regarding the acquisition and maintenance of the disorder. [211] These therapies target two processes conceptualized as underlying substance abuse: 1) dysfunctional thoughts, such as the belief that the use of substances is completely uncontrollable, and 2) maladaptive behaviors, such as acceptance of offers to use drugs. Early versions of this approach [212,213] were derived from cognitive therapy for depression and anxiety by Beck and Emery [214] and placed primary emphasis on identifying and modifying dysfunctional thinking patterns. Other adaptations of this approach have broadened the focus of therapy to help the patient master an individualized set of coping strategies as an effective alternative to substance use. [211, 215]

In individuals who are receiving methadone maintenance, CBT is efficacious in reducing illicit substance use and achieving a wide range of other treatment goals. The benefits of CBT in combination with drug counseling are equivalent to those of drug counseling alone or drug counseling plus supportive-expressive psychotherapy in patients with low levels of psychiatric symptoms; however, in the presence of higher degrees of depression or other psychiatric symptoms, supportive-expressive therapy or CBT has been shown to be much more effective than drug counseling alone. [212, 216-218] CBT may also help reduce other target symptoms or behaviors (e.g., HIV risk behaviors) in opioid-using individuals. [219] Group based relapse prevention therapy, when combined with self-help group participation, may also help recently detoxified patients reduce opioid use and criminal activities and decrease unemployment rates. [220]

6.3.3.3. Motivational enhancement therapy(MET)

Motivational enhancement therapy (MET), a widely used brief substance use intervention, offers one low-cost potential approach for addressing the need for more effective treatments for African Americans. MET fits within the framework of stages of change theory [221], with particular emphasis on personal assessment feedback within the overall clinical style of motivational interviewing (MI), a “client-centered, directive method for enhancing intrinsic motivation to change by exploring and resolving ambivalence”. [222] The basic MI principles are expressing empathy, developing discrepancy,

avoiding argumentation, rolling with resistance, and supporting self-efficacy. MI/MET consists of two phases: building motivation for change and strengthening commitment to change. [222] MET is the longer-term follow-up to an initial brief intervention strategy. It continues the use of motivational interviewing and moves a patient closer to a readiness to change substance use behaviors. [222, 223] It combines techniques from cognitive, client-centered, systems, and social-psychological persuasion approaches and may be provided by trained clinicians in substance abuse facilities, mental health clinics, and private practice offices.

Most of studies on MET are patients with alcohol and cannabis use disorders; very few studies have been conducted on opioid use disorders.

However the study conducted as a secondary analysis of a randomized clinical trial conducted by the Clinical Trials Network of the National Institute of Drug Abuse, addressed this knowledge gap by examining the efficacy of motivational enhancement therapy (MET) compared with counseling as usual (CAU) among 194 African American adults seeking outpatient substance abuse treatment at 5 participating sites. The findings revealed higher retention rates among women in MET than in CAU during the initial 12 weeks of the 16-week study. Men in MET and CAU did not differ in retention. However, MET participants self-reported more drug-using days per week than participants in CAU. [224] (Ib)

Cochrane review conducted to assess the effectiveness of motivational interviewing (MI) for substance abuse on drug use, retention in treatment, readiness to change, and number of repeat convictions. They included 59 studies with a total of 13,342 participants. Compared to no treatment control MI showed a significant effect on substance use which was strongest at post-intervention standardised mean difference (SMD 0.79) (95% CI 0.48 to 1.09) and weaker at short SMD 0.17 (95% CI 0.09 to 0.26], and medium follow-up SMD 0.15 (95% CI 0.04 to 0.25]). For long follow-up, the effect was not significant SMD 0.06 (95%CI-0.16 to 0.28). There were no significant differences between MI and treatment as usual for either follow-up post-intervention, short and medium follow up. MI did better than assessment and feedback for medium follow-up SMD 0.38 (95% CI 0.10 to 0.66). For short follow-up, there was no significant effect. [225] (Ia)

6.3.3.4. Behavioral therapies

Behavioral therapies are based on basic principles of learning theory [226], which deals with the role of externally applied positive or negative

contingencies on learning or unlearning of behaviors. The shared goals of behavioral therapies are to interrupt the sequence of substance use in response to internal or external cues and substitute behaviors that take the place of or are incompatible with substance use. There are two broad classes of learning theory-based treatments:1) those that are based on classical conditioning and focus more on antecedent stimuli such as cue exposure therapy [227] those that are based on operant conditioning and focus more on consequences such as community reinforcement therapy. [228]

6.3.3.5. Contingency management

Contingency management therapy involves introducing rewards for therapeutically desired behaviors (e.g., attending therapy sessions, providing substance-negative urine samples) and/or aversive consequences for undesirable behaviors (e.g., failure to adhere to clinic rules). [229-231] (Ib)

Contingency management approaches are beneficial in reducing the use of illicit substances in opioid-dependent individuals who are maintained on methadone. [232-234] Although other reinforcers or rewards (e.g., vouchers for movie tickets or sporting goods) may be provided to patients who demonstrate specified target behaviors (e.g., providing drug-free urine specimens, accomplishing specific treatment goals, attending treatment sessions), methadone take-home privileges are a commonly offered and effective incentive that is made contingent on reduced drug use. [235-238]

6.3.3.6. Community reinforcement

The community reinforcement approach (CRA) is based on the theory that environmental reinforcers for substance use perpetuate substance use disorders and that, at the same time, patients with substance use disorders lack positive environmental reinforcers for sober activities and pleasures. [239] CRA aims to provide individuals with substance use disorders with natural alternative reinforcers by rewarding their involvement in the family and social community; thus, family members or peers play a role in reinforcing behaviors that demonstrate or facilitate abstinence. [228]

The review was conducted on Community Reinforcement Approach in the treatment of opioid dependence. It covers the use of CRA with both methadone maintenance patients and patients withdrawing from opioids. The data reviewed in the use of CRA in combination with methadone maintenance shows improvement in a number of areas. These include the reduction of opioid use, as well as other drugs of abuse, improved legal

status, less psychiatric symptoms, and improved vocational and social functioning. CRA coupled with vouchers can assist in retaining patients in treatment long enough to improve opioid detoxification rates from buprenorphine and coupled with naltrexone may sustain abstinence. [240](Ia)

The therapist-delivered and computer-assisted CRA plus vouchers interventions produced comparable weeks of continuous opioid and cocaine abstinence (M = 7.98 and 7.78, respectively) and significantly greater weeks of abstinence than the standard intervention in randomized, controlled trial.[241] (Ib)

In this multi-center, naturalistic study, the effectiveness of naltrexone maintenance combined with the Community Reinforcement Approach (CRA) was investigated in detoxified, opioid-dependent patients (N=272). Patients were recruited from methadone maintenance programs. With intention-to-treat analysis, 10 months of treatment yielded abstinence rates of 28% and 32% at 10 and 16 months after detoxification. The cumulative abstinence rate at 16 months was 24%. Quality of life, craving, general psychopathology, use of other psychoactive substances, and addiction severity of the abstinent group significantly improved when compared to the relapsed group. [242] (IIb)

The efficacy of the community reinforcement approach was compared to standard counseling in opiate-dependent patients on methadone maintenance. One hundred eighty subjects were randomized to three treatment conditions: standard, CRA, and CRA with relapse prevention (CRA/RP). Of these, 151 subjects were followed up 6 months after intake. Since few of the RP sessions had been concluded at the 6-month follow-up, the two CRA groups were combined for analyses. Weekly urinalysis drug screens and Addiction Severity Index (ASI) scores at intake and 6 months were compared. The combined CRA groups did significantly better than the standard group in the following areas: consecutive opiate-negative urinalysis (3 weeks), and the 6-month ASI drug composite score. These results support the benefit of adding CRA strategies to the treatment of patients who are opiate dependent and on methadone maintenance. [243] (Ia)

6.3.3.7. Cue exposure and relaxation training

Cue exposure treatment involves exposing a patient to cues that induce craving while preventing actual substance use and, therefore, the experience of substance-related reinforcement. [244] Cue exposure can also be paired

with relaxation techniques and drug-refusal training to facilitate the extinction of classically conditioned craving. [245, 246]

6.3.3.8. Aversion therapy

Aversion therapy involves coupling substance use with an unpleasant experience such as mild

electric shock, pharmacologically induced vomiting, or exaggerated effects of the substance. This treatment seeks to eliminate substance use behaviors by pairing them with punishment. However such treatment approaches should not have any place in modern times.

6.3.3.9. Relapse prevention (Facilitating adherence to a treatment plan and preventing relapse)

Relapse prevention emerged as a way of helping the individual with a substance use disorder maintain change over time. Factors associated with achieving initial change (i.e., abstinence) differ from those associated with the maintenance of change over time. Relapse prevention generally refers to two types of treatment strategies. First, relapse prevention may be incorporated in any treatment aimed at helping an individual with a substance use problem maintain abstinence once substances are stopped. Second, specific coping skills-oriented treatments

Carroll,1996 [247] reviewed 24 randomized controlled trials on the effectiveness of relapse prevention among smokers (12 studies), alcohol abusers (6 studies), marihuana abusers (1 study), cocaine abusers (3 studies), the opiate addicted (1 study), and other drug abusers (1 study). It was reported that the strongest evidence for efficacy of relapse prevention is with smokers and concluded that there is good evidence for relapse prevention approaches compared with no-treatment controls [and that] outcomes where relapse prevention may hold greater promise include reducing severity of relapses when they occur, durability of effects after cessation. Clients with higher levels of impairment along dimensions such as psychiatric severity and addiction severity appear to benefit most from relapse prevention when compared to those with less-severe levels of impairment.

6.3.3.10. Family therapy

Family therapy may be delivered in a formal, ongoing therapeutic relationship or through periodic contact. Goals of family therapy include obtaining information about the patient's current attitudes toward substance

use, treatment adherence, social and vocational adjustment, level of contact with substance-using peers, and degree of abstinence, as well as encouraging family support for abstinence, maintaining marital and family relationships, and improving treatment adherence and long-term outcome. [248-251] They may also include behavioral contracting to maintain treatment (e.g., contracting with a partner for disulfiram treatment) or increasing positive incentives associated with sober family activities. Even the brief involvement of family members in the treatment program can enhance treatment engagement and retention.

Family therapy has been demonstrated to enhance treatment adherence and facilitate implementation and monitoring of contingency contracts with opioid-dependent patients. [251, 252]

6.3.3.11. 12 Step / SHGs / NA

Self-help groups, such as Narcotics Anonymous, are beneficial for some individuals in providing peer support for continued participation in treatment, avoiding substance-using peers and high-risk environments, confronting denial, and intervening early in patterns of thinking and behavior that often lead to relapse. Because of the emphasis on abstinence in the 12-step treatment philosophy, patients maintained on methadone or other opioid agonists may encounter disapproval for this type of pharmacotherapy at Narcotics Anonymous meetings.

Psychosocial Interventions: Summary

- *Most psychosocial interventions have been described in general terms. It is the task of therapist to tailor them according to the needs of particular patient.*
- *While choice of psychosocial interventions will be guided largely by the availability of therapeutic skills, some essential psycho therapeutic interventions should be provided to ALL patients in combination with pharmacotherapy. These are: Motivation Enhancement / Motivation Interview, Psycho-education and Relapse Prevention.*

6.4. Special patient groups

6.4.1. Females patients with opioid use disorders

In general, as elsewhere in the world, opioid use disorders is predominantly a male phenomenon in India with very few women using drugs or presenting for treatment for drug use disorders. Issues related to substance use among

women however are increasingly being recognized and this particular group of patients presents some unique clinical challenges.

6.4.1.1. Pregnancy

Possible effects of opioid use and the related lifestyle on the course of the pregnancy include preeclampsia, miscarriage, premature rupture of membranes, and infections. Possible short- and long-term effects on the infant include low birth weight, prematurity, stillbirth, neonatal abstinence syndrome, and sudden infant death syndrome. [253, 254] Approximately 50% of the infants born to women with opioid dependence are physiologically dependent on opioids and may experience a moderate to severe withdrawal syndrome requiring pharmacological intervention. However, when socioeconomic factors are controlled for, mild to moderate neonatal withdrawal does not appear to affect psychomotor or intellectual development. [248]

Methadone maintenance improves infant outcomes relative to continued maternal heroin use. Methadone is preferred treatment for opioid dependent pregnant women. [255-257] Although the long history of methadone use in pregnant women makes this medication the preferred pharmacotherapeutic agent, a growing body of evidence suggests that Buprenorphine may also be used. Jones et al. 2005 [258] (Ib), in a randomized, double-blind, double-dummy, flexible dosing, parallel-group controlled trial, compared 4–24 mg/day sublingual buprenorphine to 20–100 mg/day oral methadone, with treatment starting in the second trimester of pregnancy. Although the study was limited by its small sample size, buprenorphine and methadone showed comparable outcomes in terms of neonatal abstinence syndrome

Minozzi et al, 2008 [259] (Ia) conducted cochrane review on maintenance agonist treatments for opiate dependent pregnant women. They included three RCT with 96 pregnant women. Two compared methadone with buprenorphine and one methadone with oral slow morphine. For the women there was no difference in drop out rate RR 1.00 (95% CI 0.41 to 2.44) and use of primary substance RR 2.50 (95% CI 0.11 to 54.87) between methadone and buprenorphine, whereas oral slow morphine seemed superior to methadone in abstaining women from the use of heroin RR 2.40 (95% CI 1.00 to 5.77).For the newborns birth weight, APGAR score and NAS (neonatal abstinence syndrome studies did not find any significant difference).

6.4.1.2. Breast feeding

According to the recent literature, addicted women, substituted with methadone or buprenorphine are allowed to breast feed their newborns. The advantages of breast feeding revail the risks of an infant opiate intoxication caused by methadone or Buprenorphine. [260] (IIa) OST is not contra-indicated for breast-feeding. Breast-feeding should be encouraged. [261] In a recent study (Ilett et al, 2012) [262] on the estimated dose exposure of the neonate to buprenorphine and its metabolite norbuprenorphine via breast milk during maternal buprenorphine substitution treatment, seven pregnant opioid-dependent women taking buprenorphine (median, 7 mg/day; range, 2.4-24mg) and who intended to breastfeed, were recruited. After lactation was established, several milk samples were collected from each subject over a 24-hour dose interval, and buprenorphine and norbuprenorphine concentrations were measured by liquid chromatography-tandem mass spectrometry. They found that the dose of buprenorphine and norbuprenorphine received via milk is unlikely to cause any acute adverse effects in the breastfed infant. (III)

6.4.2. Younger age group (Children and adolescence)

Most adolescents with substance use disorders also have one or more co-occurring psychiatric disorders, most often conduct disorder and/or major depression, although ADHD, anxiety disorders, bipolar disorder, eating disorders, learning disabilities, and other axis II disorders are also common. [263-265] Many adolescents with substance use disorders also have preexisting and concurrent impulsive, oppositional, self injurious, and suicidal symptoms or syndromes. [266] Treatment should also address these problems, with treatment of the substance use disorders and coexisting psychiatric symptoms occurring simultaneously.

A retrospective cohort study was conducted on 100 consecutive heroin-dependent adolescents who sought these treatments over an 8-year recruitment period. Half of the patient group remained in treatment for over 1 year. Among those still in treatment at 12 months, 39% demonstrated abstinence from heroin. The final route of departure from the treatment program was via planned detox for 22%, dropout for 32%, and imprisonment for 8%. The remaining 39% were transferred elsewhere for ongoing opiate substitution treatment after a median period of 23 months of treatment. [267](III)

Outcome of methadone and buprenorphine substitution treatment in adolescents is unclear. Most guidelines discourage clinicians for considering agonist maintenance treatment for adolescents, though age less than 18 years is not an absolute contraindication for agonist maintenance treatment. If there appears to be considerable risk of relapse in an adolescent in the absence of agonist maintenance, this treatment can be considered for adolescents, in conjunction with other appropriate psychosocial interventions.

6.4.3. Medical co-morbidity and sequelae of substance use disorders

Opioid used by inhalation route leads to bronchitis and other pulmonary infection. The injection of opioids may result in the sclerosing of veins, cellulitis, abscesses, or, more rarely, tetanus infection. Other life-threatening infections associated with opioid use by injection include bacterial endocarditis, hepatitis, and HIV infection. HIV infection rates have been reported to be as high as 60% among individuals dependent on heroin in some areas of the United States. Tuberculosis is a particularly serious problem among opioid using individuals especially who inject drugs. In addition to the presence of life-threatening infections, opioid dependence is associated with a death rate as high as 1.5%–2% per year from overdose, accidents, injuries, or other general medical complications. [27]

One particular con-morbidity / sequelae of opioid use worth discussing is HIV infection and AIDS among Opioid dependent IDUs. There has been a long-held myth that drug users are poorly compliant to treatment and since poor compliance to ART enhances the risk of developing resistance, access to ART has been limited for HIV positive IDUs. In many countries as many as two thirds of HIV positive individuals are IDUs, but less than 25% of them receive ART. [268] Many recent studies have indicated that agonist maintenance programs improve the outcome of ART in HIV positive individuals. [269-272] Consequently, agonist maintenance should be seriously considered in all HIV positive opioid dependent individuals, including those for whom ART is indicated.

6.4.4. Patients with chronic pain conditions

Kouyanou et al, 1997 [273] in the UK, used DSM-III-R criteria in chronic-pain patients and found opioid abuse in 3.2%, opioid dependence in 4.8%. Other groups have reported much higher rates of substance abuse in such patients: Maruta et al, 1979 [274], in the pre-DSM-III era found 24% drug dependence, 41% drug abuse; Reid et al, 2002 [275] reported prescription

opioid abuse by 24– 31%; however, any attempt to measure prevalence is wholly dependent on the definitions.

Researchers divided the patients into two groups according to whether the treating physician suspected them of being addicted to their prescribed opioids. Those who were judged to show addictive behaviour, such as unauthorized dose escalations or 'doctor shopping', were noted to have significantly more unrelieved pain than the non-addicted group. This raised the possibility that what appears to be addiction in some chronic pain patients is the same as the 'pseudo-addiction' reported in patients with cancer whose pain is unrelieved, and whose addictive behaviours disappear once pain relief is achieved. [276] Inadequacies of the diagnostic criteria for substance dependence in both DSM-IV and ICD-10, - when applied to chronic pain patients - have also been pointed out. Firstly, in long-term opioid treatment, one or both -tolerance and withdrawal - are likely to develop, but in cases of pain management these are not necessarily pathological. [277] Secondly, in the chronic-pain patient, the behavioural criteria (e.g. increasing importance of acquiring and using the drug, compulsion to use, impaired control, reduced social or recreational activities) could be construed as a manifestation of therapeutic dependence—attempts to secure pain-relief. [278] Chronic pain by its nature reduces peoples' desire and ability to socialize or remain active. Additionally, for those with unrelieved pain, the 'doctor shopping' (desperate visits to multiple practitioners, the quest for analgesic drugs), can give a false impression of addiction.

A Cochrane review was conducted by Noble et al, 2010 [279] (Ia) on the long-term opioid management for chronic noncancer pain. They included 26 studies with 27 treatment groups that enrolled a total of 4893 participants. Twenty five of the studies were case series or uncontrolled long-term trial continuations, and the other was an RCT comparing two opioids. They found that many patients discontinue long-term opioid therapy (especially oral opioids) due to adverse events or insufficient pain relief; however, weak evidence suggests that patients who are able to continue opioids long-term experience clinically significant pain relief. Whether quality of life or functioning improves is inconclusive. Many minor adverse events (like nausea and headache) occurred, but serious adverse events, including iatrogenic opioid addiction, were rare.

6.4.5. Prison population

Drug use is overrepresented in prisons and remains endemic among

incarcerated populations. [280] It has been estimated that around three quarters of people in prison had alcohol or other drug-related problems, and more than one-third may be opioid dependent. [281] Some level of drug use may often continue in prison and the prisoners may then go on to share drug injecting equipment and have unprotected sex, both inside prison and back in the community [282, 283] thus posing a threat to public health. Substance abuse may be present either prior to prison entry, develop or get exacerbated in prison and persist after release from prison. Substance use problems should be considered in prison settings separately because of their magnitude, severity and implications on society. [65]

A large number of studies from around the world report high levels of injection drug use in prisoners [284,285] including female prisoners. [286, 287] Urinalysis of arrested felons in major cities nationally showed that the percentage of males and females, respectively, who tested positive for opiates ranged from 12% - 25% and 13% - 23% in 2003. [288] Drug using prisoners may be continuing a habit acquired before incarceration or may acquire the habit in prison.

Baseline vulnerability survey in prisons conducted in three south Asian countries found that 86% from Sri Lanka, 63% from India and 72% from Nepal have ever had drugs in prisons. In India and Sri Lanka, most of the inmates used heroin and cannabis and in Nepal, the drug of choice was heroin. [289] Focused thematic study of drug abuse among prison population [7] conducted on 6800 individuals admitted to an NGO treatment in Tihar Jail, Delhi found that between 75% and 82% of the entire prison population were heroin users. A study in Bangalore prison found lifetime prevalence of opioids was 0.6% and injecting use 0.2%. [290]

Systemic review was conducted on the effectiveness of opioid maintenance treatment in prison settings. Twenty-one studies were identified: six experimental and 15 observational. OMT (Opioid maintenance treatment) was associated significantly with reduced heroin use, injecting and syringe-sharing in prison if doses were adequate. Pre-release OMT was associated significantly with increased treatment entry and retention after release if arrangements existed to continue treatment. For other outcomes, associations with pre-release OMT were weaker. Four of five studies found post-release reductions in heroin use. Evidence regarding crime and re-incarceration was equivocal. There was insufficient evidence concerning HIV/HCV incidence. There was limited evidence that pre-release OMT reduces post-

release mortality. Disruption of OMT continuity, especially due to brief periods of imprisonment, was associated with very significant increases in HCV incidence. [291] (Ia)

A longitudinal cohort study In New South Wales, Australia, concluded that opioid substitution treatment after release from prison has reduced the average risk of re-incarceration by one-fifth [292] (III). A pilot randomized controlled trial of buprenorphine for opioid dependent women in the criminal justice system was conducted by Cropsey et al, 2011[293] (Ib) Analyses showed that buprenorphine was efficacious in maintaining abstinence across time compared to placebo. At end of treatment, 92% of placebo and 33% of active medication participants were positive for opiates on urine drug screen (Chi-Square=10.9, df=1; $p<0.001$). However, by the three month follow-up point, no differences were found between the two groups, with 83% of participants at follow-up positive for opiates.

Various studies demonstrated that oral naltrexone was effective in reducing opioid use and preventing recidivism among offenders under federal supervision. However, a RCT of oral naltrexone for treating opioid-dependent offenders. This study provides limited support for the use of oral naltrexone for offenders who are not closely monitored by the criminal justice system. [294] Another study compared the effects of naltrexone implants and methadone treatment on heroin and other illicit drug use, and criminality among heroin-dependent inmates after release from prison. Intention-to-treat analyses showed reductions in both groups in frequency of use of heroin and benzodiazepines, as well as criminality, 6 months after prison release. [295] (Ib)

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CLINICAL PRACTICE GUIDELINES (CPG) FOR THE MANAGEMENT OF CANNABIS USE DISORDERS

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EXECUTIVE SUMMARY

INTRODUCTION

Cannabis has an enduring reputation as being relatively harmless, but evidence continues to accumulate that cannabis use can be associated with a number of psychosocial and physical health problems. Moreover, there is a rising trend of cannabis use throughout the world. Thus it is important to synthesize the limited research evidence available for the treatment of cannabis use disorders into treatment guidelines.

METHODOLOGY

The index clinical practice guideline is expected to address treatment issues related to cannabis use disorders, namely, cannabis intoxication, withdrawal and dependence. The *Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument II* has been used as a template for this exercise. Strength of evidence is decided on the methodology and generalizability of the studies and the consistency and applicability of the results. Though the recommendations of this guideline are largely based on available research evidence, an effort has been given to make it more clinically meaningful and contextually relevant. At the end of each section, areas which are controversial and need to be researched further are described. Overall both quantitatively and qualitatively treatment of cannabis use disorders is understudied. Hence the recommendations made from these evidences should be considered in the light of this inevitable limitation.

PHARMACOLOGICAL TREATMENT OF CANNABIS USE DISORDERS - The obvious initial step for the treatment of cannabis use disorders is to identify the presenting state or diagnosis of the patient. Because treatment differs on various phases, like intoxication, withdrawal and for relapse prevention.

Pharmacological treatment for cannabis intoxication- Intoxication is usually mild and self-limiting, and does not normally require pharmacological treatment. Rarely, intoxication can manifest with

severe anxiety and panic attack like symptoms and Psychotic symptoms. Treatments for cannabis intoxication focus on alleviating the usual symptoms of intoxication or the rarer but nevertheless significant symptoms of anxiety and panic. In those severe but rare occasions, atypical antipsychotics (like olanzapine) for cannabis intoxication induced psychosis and benzodiazepines for acute episodes of anxiety can be considered. Propranolol can be tried as an alternative treatment for acute anxiety episodes.

Pharmacological treatment for cannabis withdrawal- Symptoms of cannabis withdrawal are largely non specific and mostly begin during the first week of abstinence and resolve after a few weeks. Based on the limited research available with regard to the pharmacological management of cannabis withdrawal, a concrete recommendation is still elusive. Despite the absence of available published evidence, benzodiazepines are the most commonly and effectively used pharmacological agents as per the authors' clinical experience and expertise. Dronabinol and baclofen are the two other alternatives for cannabis withdrawal. Antidepressants like nefazodone can be used largely to alleviate mood symptoms of cannabis withdrawal. Though not clearly defined, possibly these medications are to be given at least for a week and should then be titrated according to the level of symptomatic distress.

Pharmacological treatment for cannabis dependence - Though no single medication has been shown to be unequivocally effective in cannabis dependence, a few treatment strategies like agonist substitution, antagonist therapy, and modulation of other neurotransmitter systems have already tried. Tweaking of the neurotransmitter system i.e. neuro-modulation appears to be the most efficacious amongst all these. Buspirone has emerged as a reasonable first choice; fluoxetine, N-acetylcysteine and baclofen are the other alternatives. As in other phases, duration of treatment is not well defined and needed to be researched further. Preferably, pharmacotherapy should always be advised in conjunction with psychosocial intervention.

Psychosocial treatment of cannabis use disorders- Psychosocial interventions in the context of cannabis are directed towards

maintaining abstinence. Broadly speaking, psychotherapy for cannabis dependence has its origins in psychotherapy for substance dependence in general and there are a handful of RCTs of motivational enhancement therapy (MET) and cognitive-behavioural therapy (CBT) available for cannabis dependence. These place psychosocial interventions as the main stay of treatment with reasonably good quality evidence base. Brief MET intervention which has possibly the strongest evidence can be delivered even in the primary care or in the community settings. CBT is the second alternative form of treatment which can also be tried. Combining CBT and MET either from the outset or in case of failure of either of these intervention is a well supported alternative. Other interventions like contingency management and family therapy also have been researched and are found to be effective. In the absence of concrete and substantial evidence for pharmacotherapy, psychosocial interventions should be tried in all cases of cannabis dependence. In view of the scarcity of the mental health professional in countries like India, brief MET could well be the best possible bet.

1. INTRODUCTION

Cannabis sativa, or the Indian hemp plant, is the source of a number of products known collectively as cannabis.[1] The term cannabis includes *Bhang*, the term for the cut and dried large leaves and stems of the plant; *Ganja*, which refers to the buds and flowering tops of the female plant; and *Charas* (*Hashish)*, the resin that coats the young leaves and flowering heads of the plant. Cannabis is typically smoked (*Ganja* and *Charas*) or eaten (*Bhang*). The concentration of Ä9-tetrahydrocannabinol (THC), the most active cannabinoid in cannabis preparations, may range from 0.5% to 3% in *Bhang*, while *Ganja* may contain 3-5% THC. *Charas (Hashish)* contains 5-8% THC.

THC, the primary psychoactive compound in cannabis is a highly lipophilic molecule that readily crosses the blood-brain barrier. THC acts through CB1 cannabinoid receptor which mediates its psychological and behavioral effects. CB1 cannabinoid receptors are found in brain regions known to be involved in mood, perception, motor control, and memory formation. Therefore, THC exerts its influence in all these parameters. In chronic users, THC in detectable in urine up to 11 weeks after last use. Due to highly lipophilic nature of THC, it accumulates in the fatty tissues and may be detectable in blood for several days; traces may persist for a few weeks. [2]

During the late 1960s, cannabis emerged from relative obscurity to become the most common illicit drug used in the United States, and has remained so ever since. While over the next few decades, use is decreasing in the developed world, it appears to be stable or increasing in developing countries and some indigenous communities. [3]

In India, cannabis is one of the most commonly ‘abused’ substances since prehistoric time. The National Household Survey of Drug Use in the country is the first systematic effort to document the nation-wide prevalence of drug use. Alcohol (21.4%) was the primary substance used (apart from tobacco) followed by cannabis (3.0%). The Drug Abuse Monitoring System (DAMS), which records the lifetime and current substances of abuse in patients attending government de-addiction centres, found cannabis as the primary substance of use in 11.6% of cases. The number, though lesser than alcohol and opioids, is still substantial. Moreover, the figure is likely to be an

underestimate as DAMS is expected to tap only the severely ill, treatment seeking subset of the entire pool of the drug-abusing population in India. [4,5]

Despite having an enduring reputation as being relatively harmless, evidence continues to accumulate that cannabis use can be associated with a number of psychosocial problems. Early exposure to cannabis has been demonstrated to be an independent risk factor for continued cannabis use, other drug use, juvenile offending and unemployment.[6] Also, a significant relationship has been demonstrated between the degree of cannabis use and the likelihood to commit certain violent crimes.[7] Further, an association between cannabis use and risky sexual behavior has been found. [8, 9] Marijuana use is common and can be problematic in individuals with other psychiatric disorders, including major mood, anxiety, and personality disorders. [10-13] Especially, cannabis use can precipitate initial episodes of psychosis in vulnerable individuals [14] and is associated with an earlier age at first psychotic episode in male patients with schizophrenia. [15] Cannabis is also regarded as the gateway substance as its abuse or dependence is highly associated and usually predates other substance dependence. [16]

Though most cannabis users do not require and do not seek treatment, cannabis is important from a public health perspective due to the large numbers of people who use the drug and become dependent with the consequent problems associated with use. Treatment seeking is further less in countries like India where cannabis has been used since time immemorial and has some degree of sociocultural sanction. The Narcotic Drugs and Psychotropic Substances (NDPS) Act 1985, the legislative instrument for drug abuse control in India, does not consider *Bhang* under its ambit, and imposes lesser degree of punishment for *Ganja*, which reflects an indirect evidence of its cultural acceptability in our country.[17]

Despite the prevalence and consequences of cannabis dependence, it remains relatively understudied compared with other substances of abuse.[18] To date, there have been only a few controlled clinical trials for the treatment of cannabis dependence. Though Indian psychiatric society (IPS) has already published a guideline on cannabis use disorders in 2006, it needs to be updated in view of rapidly expanding frontiers in the areas of research in substance use disorders. The objective of the current guideline is to study the available evidence, determine its strength and finally to recommend practical treatment options especially suited to the Indian context.

2. SCOPE AND METHODOLOGY OF THE GUIDELINE

Clinical practice guidelines ('guidelines') are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances. The authors have tried to maintain a high standard and quality for these guidelines. Thus, the *Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument II*[19] has been used as a template for this exercise as far as possible. AGREE instrument is a tool that assesses the methodological rigor and transparency in which a guideline is developed. We have prepared this guideline in accordance to AGREE II, the newer revised version. Our aim is to follow a structured and rigorous development methodology, to conduct an internal assessment to ensure that their guidelines are sound, and to evaluate guidelines by other groups for potential adaptation to our own context. [20]

We have used the term *cannabis use disorders* to include cannabis intoxication, withdrawal and dependence. [21] These have been dealt with separately. We have excluded other conditions associated with Cannabis use such as Affective or Psychotic disorders as these are specialized areas and are not directly relevant to the scope of the guideline. Dual diagnosis is covered in a separate chapter.

3. TREATMENT SETTINGS

Treatment for cannabis dependence usually occurs in an outpatient setting, either individually or in groups. Inpatient treatment is most likely to occur if the individual is hospitalized for another psychiatric disorder, including another substance use disorder.

4. PHARMACOLOGICAL TREATMENT FOR CANNABIS USE DISORDERS

A number of pharmacologic agents have been studied for their potential as treatments of cannabis dependence. These pharmacotherapy studies have primarily looked at a medication's effects on cannabis abstinence, intoxication, or withdrawal largely in non-treatment-seeking heavy THC users. There are fewer outpatient treatment studies that have investigated pharmacologic agents to treat cannabis-dependent individuals with and without co-morbid psychiatric conditions. So far, no medication has been shown broadly and consistently effective; none has been approved by any national regulatory authority. Medications studied have included those that alleviate symptoms of cannabis withdrawal (e.g., dysphoric mood,

irritability), those that directly affect endogenous cannabinoid receptor function, and those that have shown efficacy in treatment of other drugs of abuse or psychiatric conditions. [21]

4.1 Treatment of cannabis intoxication

Cannabis intoxication is a syndrome recognized in DSM-IV [21] and ICD-10 [22], with both psychological and behavioral (euphoria, relaxation, increased appetite, impaired memory and concentration), and physical (motor incoordination, tachycardia, orthostatic hypotension), manifestations. Intoxication is usually mild and self-limiting, not requiring pharmacological treatment. [23] Rarely, intoxication can manifest with severe anxiety and panic attack like symptoms and Psychotic symptoms. There are also reports of death by brain infarction - especially among teenagers - following the acute use of marijuana [24, 25] as well as of cases of patients with severe sequelae resulting from this complication. [26] Similarly, there are reports of coma in children induced by the accidental intake of cannabis [27], in addition to cases of cardiac arrhythmia [28-32], acute myocardial infarction [33], and transitory ischemic attacks. [26] There also exists strong evidence that cannabis use can have major detrimental effects on the course of the illness when patients with a pre-existing psychotic condition continue to use the drug. [34] In addition to worsening the outcome and exacerbating the symptoms, cannabis use by people with psychosis can lead to sudden behavioral disturbances such as increased proneness to violence, criminal activity, suspiciousness, and hallucinations. [35] Treatments for cannabis intoxication focus on alleviating the usual symptoms of intoxication or the rarer but nevertheless significant symptoms of anxiety and panic.

Although scarce, the evidence on pharmacological interventions for the management of cannabis intoxication suggests that propanolol and rimonabant are the most effective compounds to treat the physiological and subjective effects of the drug. Benzodiazepines have also been found to have efficacy in intoxication induced anxiety symptoms especially panic attacks. Further studies are necessary to establish the real effectiveness of these medications, as well as the effectiveness of other candidate compounds to counteract the effects of cannabis intoxication, such as cannabidiol.

Studies based on the efficacy of various treatment options for cannabis intoxication have been highlighted in **Table 1**.

Table-1 Pharmacological management for cannabis intoxication

Study	N	Dose/day; duration of use	Design	Results
Sulkowski A *et al.*, 1977 [36]	6	Propranolol-120 mg	Uncontrolled trial (investigational); single dose of propranolol	Pretreatment with propranolol blocked cannabis induced physiological, cognitive and psychological effect
Berk et al., 1999 [37]	30	Olanzapine Vs Haloperidol-10 mg; 4 weeks	Randomized Double-blind trial	Both the medications were equally efficacious in reducing cannabis intoxication induced psychotic symptoms; Haloperidol causes more EPS
Heustis et al., 2001 [38]	63	Rimonabant-90 mg	Randomized Double-blind Placebo-controlled cross-over in laboratory samples	Blocked acute psychological and physiological effects of smoked marijuana without altering THC pharmacokinetics
Heustis et al., 2007 [39]	42	Rimonabant-40 mg followed by 90 mg; for 2 weeks	Randomized Double-blind Placebo-controlled cross-over in laboratory samples	Acute physiological effects of smoked cannabis was blocked by both; Effect of both the doses are similar (effect measured by visual analogue scale)

Recommendation

- Cannabis intoxication is usually mild and self limiting. Mostly it does not warrant pharmacological intervention.
- Pharmacological treatment becomes meaningful in the presence of severe and distressing anxiety or psychotic symptoms induced by cannabis intoxication.
- Antipsychotics (preferably atypical antipsychotics) can be considered in cannabis intoxication induced psychosis. (B)
- Role of benzodiazepines in acute anxiety episodes is well established. Extrapolating this evidence and from the clinical experience of the authors, acute anxiety produced during the time of cannabis intoxication

could be treated with benzodiazepines like Alprazolam or Lorazepam.(D)

- Propranolol (60-120 mg) has little evidence base but can be considered as an alternative. (D)
- Symptoms of cannabis intoxication usually last for 3-4 hours and longer in case of chronic heavy users and after oral ingestion. Taking clue from these facts, though is not studied formally, duration of pharmacological treatment for cannabis intoxication should not exceed more than a day.

Rimonabant 40 mg or 90mg/day is found to be efficacious; however, its use is prohibited in India and most other countries due to its probable association with increased suicidality and other psychiatric adverse effects. Hence it cannot be recommended as of now.

Key uncertainties

- Only scarce literature is available in the context of cannabis intoxication. The studies have small sample size and mostly were not done in a representative sample.

4.2 Treatment of cannabis withdrawal

Both human laboratory and clinical outpatient studies have established the reliability, validity and time course of the cannabis withdrawal syndrome [40, 41] and the cannabis withdrawal syndrome has been proposed for inclusion in DSM-V. [42] Some US studies suggest that about half of patients in treatment have reported symptoms of the cannabis withdrawal syndrome. [43-46] The main symptoms of cannabis withdrawal are anxiety, irritability, depressed mood, restlessness, disturbed sleep, G-I symptoms, and decreased appetite. Symptoms are largely non specific and mostly begin during the first week of abstinence and resolve after a few weeks. Because symptoms of cannabis withdrawal may serve as negative reinforcement for relapse to cannabis use in individuals trying to abstain [41, 47], pharmacological treatment aimed at alleviating cannabis withdrawal might prevent relapse and reduce dependence.

Till date two strategies were used to treat cannabis withdrawal. One approach is cross-tolerant (cannabinoid CB1 receptor) agonist substitution to suppress the withdrawal syndrome (analogous to using an opiate to suppress heroin withdrawal). This approach can be implemented using synthetic THC

(dronabinol), which is legally marketed in many countries as an oral medication for appetite stimulation and suppression of nausea and vomiting owing to chemotherapy. Another approach, which has been evaluated in human laboratory studies, tries to alleviate symptoms of cannabis withdrawal (e.g., dysphoric mood, disturbed sleep) by influencing the brain circuits that mediate these symptoms, using medications already approved for other psychiatric conditions. Mood stabilizers and antidepressants were studied under this approach. Table 2 depicts the results of these approaches. [48]

Table 2 Pharmacological management for cannabis withdrawal

Cannabinoid receptor agonists- Synthetic THC (Dronabinol)				
Study	N	Dose/day; Duration of use	Design	Results
Haney *et al.*, 2004 [49]	11	10 mg; 15 days	Randomized Double-blind Placebo-controlled in laboratory samples	Reduced withdrawal (mood, psychomotor task, appetite and sleep as outcome)
Budney *et al.*, 2007 [50]	8	30, 90mg; 5 days	Randomized Double-blind Placebo-controlled in laboratory samples	Reduced withdrawal; higher dose more efficacious
Levin and Kleber 2008 [51]	2	10-50 mg	Case studies	Mixed
Levin et al., 2010 [47]	156	40 mg; 1 week (original study for 12 weeks aiming at measuring abstinence)	Randomized Double-blind Placebo-controlled in laboratory samples	Reduced withdrawal
Antidepressants and Mood stabilizers				
Haney *et al.*, 2001 [52]	10	Bupropion-300 mg	Randomized Double-blind Placebo-controlled	Worsening of withdrawal
Haney *et al.*, 2003a [53]	7	Nefazodone-450 mg; 26 days	Randomized Double-blind Placebo-controlled	Improvement in anxiety and muscle pain in subjective rating scale

Haney *et al.*, 2004 [49]	7	Divalproex-1500 mg	Randomized Double-blind Placebo-controlled	Worsening of withdrawal
*Levin *et al.*, 2004 [54]	25	Divalproex-1500 mg	Randomized Double-blind Placebo-controlled in clinical samples	No effect

* Indicates studies in treatment seeking population

Recommendations

- Based on the limited research available with regard to the pharmacological management of cannabis withdrawal, a concrete recommendation is still elusive.
- Though is not researched, benzodiazepines are the most commonly prescribed medications in cannabis withdrawal and as per our clinical experience, the results of such intervention is encouraging. Dose and duration of Benzodiazepine use are based on response and clinical judgment. (D)
- Dronabinol (20-60 mg/day) can be prescribed in divided doses for about 7-10 days depending on the duration of the withdrawal symptoms. (C)
- Lofexidine (2.4 mg/day) in combination with Dronabinol (60 mg/day) or Nefazodone alone (450 mg/day) are other alternatives. (D)
- Baclofen 40 mg/day in divided doses for 1 week is another treatment alternative. (D)

Key uncertainties

- Duration of treatment is not well defined.
- Dosages of various medications used so far are highly variable and arbitrary.

4.3 Treatment for cannabis dependence

No medication has been shown broadly effective in the treatment of cannabis dependence, nor is any medication approved for this condition by any regulatory authority. Ongoing research is evaluating 3 major strategies for treatment: Agonist substitution, antagonist, and modulation of other neurotransmitter systems.

One strategy to treat drug dependence is long-term treatment with the same agonist drug or with a cross-tolerant drug to suppress withdrawal and drug

craving. This approach is successfully used in the treatment of tobacco (nicotine) dependence (nicotine itself) and opiate dependence (Methadone, Buprenorphine). It is being studied for treatment of cannabis dependence using synthetic THC.

The antagonist approach uses long-term treatment with a CB1 antagonist to prevent patients from experiencing the pleasurable reinforcing effects of cannabis use, resulting in extinction of drug-seeking and drug-taking behavior. CB1 receptor inverse agonist, rimonabant, marketed as an appetite suppressant (but currently withdrawn from most world markets because of psychiatric adverse effects especially suicidality), has been tried with some success.

Another strategy is modulation of other neurotransmitter systems to reduce the reinforcing effects of and craving for cannabis. This strategy has been implemented using a variety of medications approved for other psychiatric conditions. Antidepressants (Fluoxetine, Bupropion, Nefazodone), Mood stabilizer, (Valproate), Anxiolytics (Buspirone) and drugs for attention deficit disorder (Atomoxetine) were studied under the strategy of neuromodulation. Though almost all medications (except Valproate, Atomoxetine) were found to be well tolerated, except Buspirone which has shown some promise, other medications mostly failed to live up to their expectations. [57] Till date, research conducted on various pharmacological management for cannabis dependence, has been mentioned in table 3.

Table 3 Pharmacological management for cannabis dependence

Cannabinoid receptor agonists- Synthetic THC (Dronabinol)				
Study	N	Dose/day & duration	Design	Results
Levin and Kleber 2008 [50]	2	10-50 mg	Case studies	Reduced use but not abstinence
*Levin et al., 2011 [47]	156	40 mg; 8 weeks	Randomized Double-blind Placebo-controlled in laboratory samples	Did not improve abstinence but improved treatment retention

Neuromodulation				
*McRae *et al.*, 2006 [58]	10	Buspirone- 60 mg; 12 weeks	Open label	Reduced craving and irritability
*McRae *et al.*, 2009 [59]	50	Buspirone- 60 mg; 12 weeks	Double-blind, Placebo-controlled	Reduced cannabis use
*Cornelius *et al.*, 2005 [60]	22	Fluoxetine- 20-40mg	Randomized Double-blind Placebo-controlled	Reduced cannabis use
*Cornelius *et al.*, 2010 [61]	70	Fluoxetine- 20mg	Randomized Double-blind Placebo-controlled	No effect
*Carpenter *et al.*, 2009 [62]	106	Nefazodone/ Bupropion- 300 mg/ 150 mg; 13 weeks	Randomized Double-blind Placebo-controlled	No effect
*Levin et al., 2004 [54]	25	Valproate- 1500-2000mg; 6 weeks	Randomized Double-blind Placebo-controlled	No effect and poorly tolerated
*Tirado *et al.*, 2008 [63]	13	Atomoxetine- 25-80 mg; 12 weeks	Open label	Reduction in cannabis use but adverse events
*McRae-Clark *et al.*, 2010 [64]	36	Atomoxetine- 25-80 mg; 12 weeks	Double-blind, Placebo-controlled	No effect
Shafa et al, 2009 [65]	36	Entacapone- 200 mg; 12 weeks	Open label	Reduced craving but no effect on abstinence
Gray *et al*., 2010 [66]	24	N-acetylcysteine- 1200 mg; 4 weeks	Open label	Reduced self-reported use, but not urine cannabinoid levels
Cooper and Haney, 2010 [67]	29	Naltrexone- 25-100 mg	Double blind Placebo-controlled	Enhanced subjective effects of cannabis

Haney *et al.*, 2007 [68]	21	Naltrexone- 12 mg; 6 weeks	Double blind Placebo-controlled	Mixed results
Haney *et al.*, 2003b [69]	23	Naltrexone-50mg; 6 weeks	Double blind Placebo-controlled	Enhanced subjective effects of cannabis
Haney *et al.*, 2010 [70]	11	Baclofen-60/90 mg Or Mirtazapine-30 mg	Randomized Double-blind Placebo-controlled	No effect
*Nanjayya et al, 2010 [56]	6	Baclofen 40 mg; monthly assessment	Open label clinical trial in *treatment seeking population*	Range of abstinence from 1 to 13 months
Cannabinoid receptor antagonist- Rimonabant				
Huestis *et al.*, 2007 [39]	42	90 mg; 2 weeks	Double blind parallel groups	attenuated subjective effects after 8 but not 15 days (transient effect)

*Indicates studies in treatment seeking population

Recommendations

- Buspirone in doses up to 60 mg/day for at least 12 weeks period has come out to be a reasonable first choice. (B)
- Fluoxetine (20-40 mg/day) is another alternative with a weaker evidence base. (D)
- Entacapone (200 mg) and N-acetylcysteine (1200 mg) for variable duration (1-3 months) could reduce cannabis use but possibly has no proven role so far in maintaining abstinence. But real clinical experience with these agents is minimal.(C)
- Emerging evidence of Baclofen (40 to 60 mg/day) would be another reasonable treatment option. (D)

As with the treatment of any substance dependence, duration of medication use is also arbitrary in cannabis dependence. An empirical trial of one year is a reasonable duration.

Key uncertainties

- Duration of treatment is not well defined.
- Even studies which have shown some positive results, generalization of those are limited by inadequate statistical power.
- Most of the studies have included psychosocial management in conjunction with pharmacotherapy, hence the relative contribution of each of these approaches are difficult to ascertain.

5.1. PSYCHOSOCIAL TREATMENT FOR CANNABIS USE DISORDERS

A variety of psychosocial interventions have been studied in cannabis dependence. Early work in treating cannabis dependence drew from anecdotal experience and advocated exercise, eating well, pulmonary care, addressing insomnia, conducting a behavioral risk assessment, and 12-step programs.[71, 72] Broadly speaking, psychotherapy for cannabis dependence has its origins in psychotherapy for substance dependence in general. In the past 15 years, a handful of RCTs of motivational enhancement therapy (MET) and cognitive-behavioural therapy (CBT) for cannabis dependence, in which outcomes are confirmed by urinalysis for cannabinoids or collateral validation, have been performed in the USA [73, 74] and Australia [75]. Other interventions like contingency management, as well as community and family interventions were also manualized and studied. Because the underpinnings of these therapeutic models are complementary, researchers have been less focused on treatment superiority and more on identifying effective combinations.

5.1 Motivational enhancement therapy (MET)

MET involves a relatively nondirective intervention approach and is delivered in 45- to 90-minute individual sessions. MET is designed to help resolve ambivalence about quitting and strengthen motivation to change. Therapists use a motivational style of interaction to guide the patient toward commitment and action to change. Techniques used include expression of empathy, reflection, summarization, and affirmation of self-efficacy, exploration of pros and cons of drug use, rolling with resistance, and forging

a goal plan when ready. Duration of MET has ranged from 1 to 4 sessions. MET has been shown to improve cannabis related outcomes among treatment-seeking adults, non-treatment seekers, and individuals with co-occurring disorders. There have been efforts to computerize motivational interventions, simplify them for use in community settings and busy primary practices, and utilize them in inpatient settings for patients with significant co-occurring disorders. Studies of brief motivational interventions in adolescents show only minimal impact on cannabis use outcomes. [76]

5.2 Cognitive behavior therapy (CBT)

CBT for marijuana dependence has typically been delivered in 45- to 60-minute individual or group counseling sessions. The overall focus is the teaching of coping skills relevant to quitting marijuana and coping with other related problems that might interfere with good outcome. Such coping skills include functional analysis of marijuana use and cravings, development of self-management plans to avoid or cope with drug-use triggers, drug refusal skills, problem-solving skills, and lifestyle management. Each session involves analysis and discussion of recent marijuana use or cravings, brief didactic introduction of a coping skill, role-playing, interactive exercises, and practice assignments. [77] The duration of CBT has ranged from 6 to 14 sessions. CBT was not superior to MET, but the synergies offered compelling rationale to integrate them.

5.3 Contingency management (CM)

CM treatments can vary in many respects, but the central feature common to all of them is the systematic application of reinforcing or punishing consequences in order to achieve therapeutic goals. With regard to treatment of SUDs, CM most commonly involves the systematic application of positive reinforcement to increase abstinence from drug use (confirmed by urine screening in cannabis), an approach referred to as *abstinence reinforcement therapy,* but also to facilitate other therapeutic changes, including retention in treatment, attendance at therapy sessions, and compliance with medication regimens. Typically, CM is used as part of a more comprehensive treatment intervention. CM is not a replacement for motivational enhancement or skill building, but can be used to augment the decisional balance among patients who would not otherwise be ready to address their substance use. In accordance with this, studies consistently show that, although not effective in isolation, CM reliably augments treatment outcomes of other effective psychotherapies. [78, 79]

5.4 Family and systems interventions

The family systems approach views substance abuse as a major organizing principle for patterns of interactional behavior within the family system. A reciprocal relationship exists between family functioning and substance abuse, with an individual's drug and alcohol use being best understood in the context of the entire family's functioning. According to family systems theory, substance abuse often evolves during periods in which the individual family member is having difficulty addressing an important developmental issue (e.g., leaving the home) or when the family is facing a significant crisis (e.g., marital discord). During these periods, substance abuse can serve to 1) distract family members from their central problem or 2) slow down or stop a transition to a different developmental stage that is being resisted by the family as a whole or by one of its members. Multidimensional family therapy (MDFT), comprehensive systems therapy that targets the functioning of the individual within the context of his or her environment has been studied in cannabis dependence. [80] MDFT more often than not is used in conjunction with other psychosocial treatment especially CBT and MET.

Other psychosocial treatment like the twelve step facilitation and supportive-expressive psychotherapy, though well researched in the context of other substance use disorders, does not have any evidence base in relation to cannabis.

5.5 Combined psychosocial treatment

To date, the largest therapy trial targeting cannabis dependence is the Cannabis Youth Treatment (CYT) study. The focus of this large multisite study was to identify and test the effectiveness, cost, and cost-benefit of five psychotherapies for cannabis dependence, and to develop manual-guided treatments that could be used in clinical venues. [81-84] The five treatments tested were:

- Five sessions that included two motivational enhancement therapy and three cognitive behavioral therapy sessions (MET/CBT5)
- Twelve sessions that included two motivational enhancement therapy and ten cognitive behavioral therapy sessions (MET/CBT12),
- Family support network (FSN), a multi-component treatment designed to be added to MET/CBT12,

- The adolescent community reinforcement approach (ACRA), which is comprised of 10 individual sessions and four sessions with the caregivers to educate them how to support the adolescent's abstinence, and
- 12 sessions of a multidimensional family therapy (MDFT), which is a family-focused therapy designed to work individually with adolescents and their families.

The CYT study was performed as two separate clinical trials. The "incremental" trial compared the three incrementally more intense treatments: MET/CBT5, MET/CBTI2, and FSN (which is added to MET/CBT12). The "alternative" trial compared treatments which varied in both type and length: MET/CBT5, ACRA, and MDFT. The investigators recruited 600 adolescent cannabis users and randomized them into the aforementioned categories. Follow-up data were obtained at three, six, nine, and twelve months. The two clinical outcomes were days of abstinence between the randomization date and the 12-month follow-up interview, and whether the adolescent was in recovery (defined as reporting no substance use, abuse, or dependence problems while living in the community) at the end of the study. The team reported that in both the incremental and alternative trials, each treatment condition increased the number of subjects in recovery and days of abstinence, but that in neither trial did one treatment show greater effectiveness than any other. In a second analysis, it was found that MET/CBT5 and MET/CBT12 in the incremental trial and ACRA and MET/CBT5 in the alternative trials was more cost-effective treatments.

A second large multisite trial that has been completed recently is the Marijuana Treatment Project (MTP). [85, 86, 74] It evaluated 450 subjects who met DSM-IV criteria for cannabis dependence and who used cannabis for at least 40 of the past 90 days. Participants were randomized to one of three treatment arms: a two-session motivational enhancement intervention that occurred over five weeks, a nine-session treatment lasting three months that added cognitive behavioral therapy and case management to the motivational enhancement sessions, and a delayed treatment control (DTC) group. The investigators gathered self- and collateral report data at four and nine month follow-up periods and performed a brief self-report phone check-in at 15 months. The DTC group only had a four-month follow-up assessment. The researchers found that both treatment groups had comparable rates of improvement that were larger than those seen in the DTC group. Also, at the four- and fifteen-month follow-up (but not the

nine-month follow-up), the nine-session treatment group was more likely to report being abstinent than the two-session group, which in turn was more likely to report being abstinent than the DTC group.

Therefore, these studies point towards superior role of combination psychosocial intervention and a relatively long term engagement with the treatment facilities. Table 4 demonstrates studies on psychosocial management for cannabis dependence.

Table 4 Psychosocial management for cannabis dependence.

Motivational enhancement therapy (MET)				
Study	N	Number of sessions; duration	Design	Results
Walker *et al.*, 2011 [87]	310	4	Randomized trial in *self referred adolescents*; follow up after 3 months and 12 months	MET intervention was reported to have significantly fewer days of cannabis use and negative consequences
Walker DD et al., 2007 [88]	97	2	Randomized trial in *non treatment seekers*; follow up at 3 months	Significantly reduced cannabis use
Martin et al., 2008 [89]	40	2	Randomized trials in *non treatment seekers*; follow up after 3 months	Greater reduction in cannabis use
Cognitive behaviour therapy (CBT)				
Copeland et al., 2001 [75]	229	1 and 6	Randomized trial *in treatment seekers*; follow up after ~ 8 months	CBT6>CBT1; both significantly more effective than WL control

Contingency management (CM)				
Kadden et al., 2007 [79]	214	9; weekly sessions	Randomized; three groups (MET+CBT Vs MET+CBT+CM Vs CM)	MET+CBT+CM had the maximum abstinence rate
Budney et al., 2000 [90]	60	3	Randomized; two groups (MET+CBT+CM Vs MET + CBT)	Greater patients in MET+CBT+CM group were abstinent
Budney et al., 2006 [78]	90	6; 14 weeks duration	Randomized; three groups (CM Vs CM+CBT Vs only CBT); follow up at the end of 1 year	CM improves efficacy of CBT

Recommendations

- Evidences obtained so far are based on the out patient population. Hence the extent to which it can be generalized to the inpatient group is questionable. (A)
- 1-4 sessions of MET as a sole intervention could well be the first possible option as psychosocial management of cannabis dependence. Brief MET intervention can be delivered even in the primary care or in the community settings. (A) CBT is the second alternative form of treatment which can also be tried. (B) Combining CBT and MET either from the outset or in case of failure of either of these intervention is a well supported alternative. (A)
- Contingency management (CM) should always be used in conjunction with either CBT or MET or both. (B)
- Family systems therapy for cannabis dependence is in early stage of development, but in patients with demonstrable and significant family pathology, systems therapy could be a worthwhile alternative if used judiciously in combination with other psychosocial treatment. (B)

Due to paucity of definite evidence of efficacy or effectiveness of pharmacological interventions, psychosocial treatment can play an important role in the management of cannabis dependence. Hence it can be recommended.

Key uncertainties

- Countries like India in which majority of the treatment of substance use disorder is clinic based and where there is a substantial scarcity of mental health professionals, effective delivery of psychosocial management remains elusive.
- Issue like cost effectiveness of these psychosocial interventions have not been researched extensively. Therefore, the rationale of implementing psychosocial intervention in a country with existing resource inadequacy could be questioned.

6. CAVEATS OF THE PROPOSED GUIDELINE

Concerns have emerged as to whether results from tightly controlled trials, generalize to patients commonly seen in community settings. [91-94] It has been suggested that some exclusion criteria in clinical trials are overly restrictive, provide little additional patient safety or internal validity [95, 96], and severely limit the generalizability of study results. The National Institute on Drug Abuse has consistently stressed the need to increase the generalizability of clinical trials. [97] In a study of a large representative sample of US adult population, it was found that approximately 80% of the community sample of adults with a diagnosis of cannabis dependence would be excluded from participating in clinical trials by one or more of the common eligibility criteria. [98] Therefore, Clinical trials should carefully evaluate the effects of eligibility criteria on the generalizability of their results. Even in efficacy trials, stringent exclusionary criteria could limit the representativeness of study results. The included studies were too heterogeneous and could not allow drawing up a clear conclusion. The studies comparing different therapeutic modalities raise important questions about the duration, intensity and type of treatment. The generalizability of findings is also unknown because the studies have been conducted in a limited number of localities with fairly homogenous samples of treatment seekers.

Unlike the concern related to the generalizability of research findings which is universal, the other major concern is actually limited to this proposed guideline. Practically all research evidence on which this guideline is based on, are taken and adopted from either the US or other developed countries. The extent to which these findings could be extrapolated for the purpose of the guideline is questionable. In India and countries alike, much more research is needed in the entire area of substance dependence in general and cannabis dependence in particular.

7. SUMMARY

Cannabis is a frequently used drug that causes dependence in a relatively small percentage of its users. However, given the large number of people who have used cannabis, the number of cannabis-dependent individuals is significant. There is no way of predicting a priori which casual user will develop a dependence syndrome and suffer the myriad and severe consequences attendant to this affliction. Given these realities, effective treatments for cannabis dependence are needed. Cannabis withdrawal is gaining recognition as a clinically significant component to marijuana dependence. Human laboratory data indicate that oral THC, alone or in combination with lofexidine, shows promise inn the treatment of withdrawal. The treatment trials conducted to date for cannabis dependence have failed to produce long-term marijuana abstinence, and relapse rates observed for marijuana are comparable to those observed for other drugs, indicating that marijuana dependence is not easily overcome. It is clear that more behavioral and pharmacological treatment options for marijuana-dependent individuals are needed. Promising medications in marijuana-dependent or co-morbidly affected patients include buspirone, fluoxetine and newer dopamine or glutamate agonists. Larger confirmatory studies will need to be conducted for these medications. Behaviorally based outpatient treatments have demonstrated efficacy for cannabis dependence in adults and adolescents. The specific types of treatment (CBT, MET, CM) evaluated in clinical trials are similar to and appear to produce similar effect sizes as those used for other substance dependence problems. The cannabis literature includes 2 notable innovations: the integration of MET/CBT, and the use of CM with adolescents to specifically target drug (cannabis) use.

The next few years look very promising for finding effective treatments for different phases of marijuana dependence. Combinations of different behavioral interventions with medications hold great promise for helping patients to remain abstinent and to resume a high degree of functioning.

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CLINICAL PRACTICE GUIDELINES (CPG) FOR THE MANAGEMENT OF SEDATIVE-HYPNOTIC USE DISORDERS

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2014

CONTENTS

EXECUTIVE SUMMARY

Sedatives and hypnotics are chemically diverse group of medications, which include benzodiazepines, barbiturates, "Z-group" and other newer sedative-hypnotic drugs. They are primarily used for sleep, anxiety and seizure disorders. In current clinical practice, because of their favourable clinical profile, use of benzodiazepines and Z-group drugs outnumbered barbiturates in most of the indications. Sedatives and hypnotics are often misused by the people and thus cases of intoxication, dependence and withdrawal state pose a serious challenge worldwide. We have developed a clinical practice guideline based on existing evidence, with emphasis on available Indian data, to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances e.g. acute intoxication, harmful use, dependence and withdrawal state due to use of sedatives and hypnotics, with additional reference to special populations.

Management of benzodiazepine use disorders

1. Management of Benzodiazepine Intoxication

The benzodiazepines have a large margin of safety in contrast to the barbiturates when taken in overdoses. The symptoms of overdose include drowsiness, lethargy, ataxia, some confusion and mild depression of user's vital signs. Gastric lavage is only indicated where presence of lethal co-ingestant is suspected (D, S). Supportive medical care and flumazenil is the mainstay of treatment of acute intoxication with benzodiazepines but in mixed overdoses and benzodiazepine dependent patients role of flumazenil is controversial where it can precipitate seizure (B).

2. Management of Benzodiazepine Dependence

There are three overlapping types of benzodiazepine dependent populations: therapeutic dose dependence, prescribed high-dose dependence and recreational benzodiazepine users.

- **Management of benzodiazepine dependence in 'therapeutic dose' users**

  In cases of early/mild benzodiazepine dependence minimal

interventions such as advisory letters or General Practitioner advice should be offered to the patient (A). Gradual dose reduction of prescribed benzodiazepine which may last for several weeks is recommended where benzodiazepine dependence is established (A). Switching to a long half-life benzodiazepine from a short half-life benzodiazepine before gradual taper should only be reserved for patients having problematic withdrawal symptoms on reduction (D). Individuals with insomnia and panic disorder may be benefitted from additional psychological therapies which increase the effectiveness of gradual dose reduction (B). Use of additional pharmacotherapy is of no value *per se* (A). However, medications such as antidepressants, melatonin, valproate, carbamazeoine and flumazenil can be considered on an individual basis (C).

- **Management of benzodiazepine dependence in high-dose and/or illicit drug users**

  There is no consensus regarding the role of maintenance benzodiazepines in illicit drug users though some patients can be helped (D). Even in very high dose benzodiazepine users 30 mg of diazepam is shown to be sufficient enough to control withdrawal symptoms including withdrawal seizures (D). Use of benzodiazepines in patients co-dependent on alcohol and/or opioids should be avoided (D). Carbamazepine may be another option instead of benzodiazepines to control withdrawal symptoms (C). In some dependent users reduction of high-dose use to a therapeutic dose level may be a useful therapeutic option (D).

3. Management of Benzodiazepine Withdrawal State

Various methods have been adopted to manage benzodiazepine withdrawal including gradual dose reduction of the agent of dependence, substituting the short acting benzodiazepine with a long acting one, or with Phenobarbital substitution (C). Flumazenil is now being explored as a potential agent for controlling benzodiazepine withdrawal symptoms (C). Role of antiepilectics in cases of benzodiazepine withdrawal seizures are highly debated, although some authorities have recommended the use of valproate and carbamazepine (D).

4. Benzodiazepine Use in Special Population

- **In pregnancy and lactation**

  Benzodiazepines and its metabolites freely cross the placenta and excreted in breast milk. If used in first trimester there is risk of teratogenicity (e.g. cleft palate) and if used in high or prolonged doses in the third trimester it may precipitate fetal benzodiazepine syndrome. Use of certain benzodiazepines (e.g. diazepam, alparazolam) during lactation can cause lethargy, sedation, and weight loss in infants. Chlordiazepoxide is considered to be relatively safe whereas alprazolam should be avoided during pregnancy and lactation (S). Whenever it is essential to use, it should be at the lowest effective dosage for the shortest possible duration (S).

- **In older adults**

  Use of benzodiazepine in older adults increases the risk of falls, fractures, cognitive decline and untimely death. Most of the studies of benzodiazepine discontinuation in elderly populations have usually involved patients in general practice or outpatient settings and patients who have 'therapeutic dose' dependence. In older adults minimal intervention or graded discontinuation along with psychological interventions seem to be effective (A).

- **In children and adolescence**

  Detoxification with diazepam without any maintenance therapy is the mainstay of treatment (D).

Management of Barbiturates Use Disorders

1. Management of Barbiturate Intoxication/ Overdose

Systematic data regarding management of barbiturate intoxication are lacking. Patients with barbiturate intoxication should be managed in indoor setting (S). Gastric lavage, supportive medical treatment, forced alkaline dieresis are the mainstay of treatment (S). Hemodialysis and hemoperfusion may be required in cases of severe intoxication. No specific antidotes are available for barbiturates overdose.

2. Management of Barbiturate Dependence and Withdrawal

Barbiturate withdrawal symptoms are qualitatively similar to the

symptoms that occur with other sedatives-hypnotics and alcohol. However, they generally appear somewhat later and are clinically more variable depending upon the individual agent, its half life, route of administration etc. Withdrawal symptoms last for three to fourteen days. Barbiturate withdrawal seizures and delirium develop between third and eighth day of discontinuation.

3. Pharmacological Interventions

Three basic strategies are employed to treat barbiturate dependence. First, the agent of dependence if tapered off slowly but is not commonly practiced nowadays (C). Second, existing barbiturate of abuse is substituted with a long acting barbiturate which is then reduced gradually and is preferred by most of the physicians (C). Third, an anticonvulsant can be started in place of existing barbiturate but its use has remained highly controversial.

4. Psychosocial Interventions

Little research has been conducted with regard to psychosocial interventions in barbiturate dependence. However, cognitive restructuring, implementation of adaptive coping strategies, systematic desensitization, problem solving, individually or in groups can be tried along with pharmacological treatment. Underlying primary illnesses should be properly addressed (S).

Management of Z-Group and Other Newer Sedative-Hypnotic Drugs Use Disorders

Z-group and other newer sedative-hypnotic drugs are chemically unrelated but pharmacologically similar to benzodiazepines, acting selectively through GABA receptors. This category includes zolpidem, zopiclone, eszopiclone, zaleplon etc. Ramelteon is a newer agent in this class which is a synthetic melatonin agonist selectively acting on MT1 and MT2 receptors. USFDA has approved these drugs for treatment of insomnia characterized by difficulty with sleep onset. Although initially denied, several case reports documented their abuse potential, mostly when used in supra-threshold doses. Clinical features are almost similar to other agents of the sedatives-hypnotics group. There is no standard management protocol for this group itself. Treatment is usually in the line of other sedative-hypnotic drugs(S).

1. INTRODUCTORY SECTION

1.1. INTRODUCTION

Sedatives and hypnotics are used to treat a wide variety of disorders, including sleep disorders, anxiety disorders, epilepsy, manic episodes, depression, symptoms of alcohol withdrawal, and rapid tranquilisation. However, in most cases, they are indicated for short term use only (two to four weeks) in the management of anxiety and insomnia and when used appropriately, do not present any problems to the patient. Nevertheless, use is not always appropriate and when used for longer duration it may lead to the development of physical and psychological dependence. There may be occasions, however, where, long term use is justified. For example, in patients whose quality of life is much improved with a benzodiazepine, where withdrawal causes severe distress and in patients with epilepsy or spasticity.

Medications included in the category of sedatives and hypnotics are of 3 types – barbiturates, benzodiazepines and others which include Z- drugs. In 1955, Hoffmann-La Roche chemist Leo Sternbach serendipitously identified the first benzodiazepine, chlordiazepoxide (Librium). [1] After introduction into medical practice by Randall et al. in 1960, benzodiazepine quickly displaced barbiturates and other sedative hypnotics in most indications of their use. [2] Their high therapeutic ratios compared to barbiturates, widespread efficacy, favorable side effect profile and lack of induction of liver enzymes made them one of the most widely prescribed drugs. Later Z-drugs came into vogue but usage of benzodiazepines in clinical practice remains quite high. [3] While benzodiazepine substance dependence and abuse can occur, the overwhelming weight of epidemiological evidence suggests that this is a problem only for a very small minority of patients (0.6% for abuse and 0.5% for dependence among users) and that the rates of abuse of benzodiazepines are significantly lower than the rates of abuse of food. [4] NIMH survey (1979) revealed that 15% of benzodiazepine users take it for greater than one year and about 0.6% take it for 4 month -1 year. Prevalence in general population in 1981 varied from 7.4-17% and 9.6-16%. [5, 6] Indian studies show that the use of benzodiazepine in general population ranges from (3.5-53.5%) and use in student population range from 3.5 - 61%. [7]

1.2. SCOPE AND METHODOLOGY OF DEVELOPING THE GUIDELINE

Clinical practice guidelines ('guidelines') are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.

In this guideline we mainly cover the management of acute intoxication, harmful use, dependence and withdrawal state due to use of sedatives and hypnotics, with additional reference to special populations. In general we will be following the ICD-10 classification for mental and behavioural disorders as our point of reference.[8] The discussion on management will mainly focus on benzodiazepines due to its magnitude of use in clinical practice, availability of scientific data and importance in comorbid psychiatric and other substance use disorders. Barbiturates, Z-drugs and a relatively newer molecule, ramelteon, will be touched upon at the end. In this guideline 'acute intoxication' means, a transient condition following the administration psychoactive substance, resulting in disturbances in level of consciousness, cognition, perception, affect or behaviour, or other psychophysiological functions and responses; 'harmful use' means, a pattern of psychoactive substance use that is causing damage to health, the damage may be physical or mental; 'dependence syndrome' means, a cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value; and 'withdrawal state' means A group of symptoms of variable clustering and severity occurring on absolute or relative withdrawal of a substance after repeated, and usually prolonged and/or high-dose, use of that substance. We have excluded other conditions associated with sedatives and hypnotics use such as Affective or Psychotic disorders as these are specialized areas and are not directly relevant to the scope of the guideline.

1.3. DATA SEARCH METHODOLOGY

The data search strategies for this review included electronic databases as well as hand-search of relevant publications or cross-references. The electronic search included PUBMED and other search engines (e.g. Google Scholar, PsychINFO). Cross-searches of electronic and hand search key references often yielded other relevant material. Besides this, British Institute of Psychopharmacology (BAP) guidelines, National Institute for Clinical Excellence (NICE) guidelines, National Health Services (NHS) guidelines,

and reviews from Cochrane database were very much helpful. The search terms used, in various combinations, were: benzodiazepine, sedatives, hypnotics, z-drugs, dependence, intoxication, withdrawal, treatment, management.

2. MANAGEMENT OF MENTAL AND BEHAVIOURAL DISORDERS DUE TO USE OF BENZODIAZEPINES

2.1. MANAGEMENT OF BENZODIAZEPINE INTOXICATION

The benzodiazepines in contrast to the barbiturates and the barbiturate like substances have a large margin of safety when taken in overdoses. The ratio of lethal to effective doses is approximately 200 to 1 or higher. Flurazepam, had the highest fatal toxicity index of any benzodiazepine (15.0), followed by temazepam (11.9), vs. benzodiazepines overall (5.9) taken with or without alcohol. [9] An Australian study of overdose admissions between 1987 and 2002 found alprazolam, which happens to be the most prescribed benzodiazepine in the U.S. by a large margin, to be more toxic than diazepam and other benzodiazepines. [10] Even when grossly excessive amount (>2 gms) are taken in suicide attempts the symptoms include only drowsiness, lethargy, ataxia, some confusion & mild depression of user's vital signs. When confronted with a case of isolated benzodiazepine intoxication the following steps should be followed:

- **Decontamination:** Ipecac syrup is contraindicated for prehospital or hospital use because of the risk for CNS depression and subsequent aspiration with emesis. Gastric lavage is not recommended but may be considered if the presence of a lethal co-ingestant is suspected and the patient presents within 1 hour of ingestion. Single-dose activated charcoal is recommended for GI decontamination in patients with protected airway who present within 4 hours of ingestion. It is important to remember that isolated oral BZD overdose is relatively benign exposure (eg, prolonged sedation), and aspiration of activated charcoal can significantly worsen clinical outcome, sometimes resulting even in death.
- **Assisted ventilation:** If present respiratory depression may be treated with assisted ventilation
- **Flumazenil:** Flumazenil is a competitive benzodiazepine receptor antagonist and should be used cautiously because it has potential to precipitate benzodiazepine withdrawal in chronic users, resulting in

seizures. Flumazenil administration is contraindicated in mixed overdoses (eg, tricyclic antidepressants) because benzodiazepine reversal can precipitate seizures and cardiac arrhythmias. Ideal indication for flumazenil use is isolated benzodiazepine overdose in benzodiazepine-naive patients, particularly if overdose is iatrogenic in nature. Flumazenil reverses the sedative, and implicit and explicit memory effects of benzodiazepines, as well as their effects in time-space, orientation-collaboration, and psychomotor performances without accompanying tranquilizing properties. [11] Intravenous injection of 0.1 mg to 0.3 mg over a period of 30 seconds is the most effective and safe mode to elicit optimal arousal, but additional boluses are usually required until consciousness is adequately established or a predetermined maximal dose (2 to 5 mg) is reached. [11] A study by Weinbroum et al. found Flumazenil to be a valid diagnostic tool for distinguishing pure benzodiazepine from mixed-drug intoxication or nondrug-induced coma. [12] Flumazenil was effective in preventing recurrence of benzodiazepine-induced coma. Respiratory insufficiency was reversed after its administration. Furthermore, Flumazenil was safe when administered cautiously, even in patients with coma caused by a mixed overdose of benzodiazepine plus tricyclic antidepressants (IIa). However, a survey on flumazenil in emergency department failed to find any beneficial effect in adult patients and advocated cautious use of the same. [13] A recent survey in UK found flumazenil to be effective and associated with a low incidence of seizure in management of cases with benzodiazepine overdose (III). [14]

Recommendations: benzodiazepine intoxication

- Gastric lavage in cases of acute intoxication with benzodiazepines is only indicated where presence of lethal co-ingestant is suspected(D, S).
- Barring mixed overdoses and benzodiazepine dependent patients, Flumazenil is an effective antidote of acute intoxication with benzodiazepines (B).

Key uncertainties:

- Only scarce literature is available in the context of benzodiazepine intoxication.
- Role of Flumazenil in benzodiazepine intoxication is still doubtful as its use is not supported by robust database.

2.2. MANAGEMENT OF BENZODIAZEPINE DEPENDENCE

There are three overlapping types of benzodiazepine dependent populations:

Therapeutic dose dependence

The 'therapeutic dose' users include patients who have been prescribed benzodiazepines usually on a long-term basis for a disorder such as anxiety or insomnia but who do not abuse their prescription. The size of this population is estimated at 500,000 to 1 million in the UK, 4 million in the US and several million worldwide. [15, 16] It is likely that at least 50% of these users are dependent.

Prescribed high-dose dependence

A minority of patients who start on prescribed benzodiazepines escalate their dosage excessively. At first they may persuade their doctors to increase prescriptions, but on reaching the prescriber's limits, they may attend several doctors or hospital departments to obtain further supplies. When other sources fail they may resort to 'street' benzodiazepines. [17]

Recreational benzodiazepine use

These are the patients who misuse their prescription and/or use illicit benzodiazepines, often in high doses. This may include benzodiazepines purchased via the internet. [18] The size of this population is unknown but estimates suggest about 200 000 people in the UK alone (population 55 million) and similar or higher proportions in the US, Europe, Australia and other countries. [17] Abuse of benzodiazepines is often associated with other substance abuse (e.g. to 'come down' from stimulants or to enhance the effect of opioids). It is important to establish the presence or absence of dependence to help determine whether pharmacological treatment is appropriate. Use patterns in high-dose abusers include once-daily dosing to maximise effect, seeking euphoric or sedative effects, escalating dosages, 'binge' use and very high self reported doses. The withdrawal syndrome can be severe. The literature and evidence base on the management of 'therapeutic dose' dependence is far more extensive and systematic than for the management of benzodiazepine dependence in illicit, high dose users. Transferring the management principles from the 'therapeutic dose' literature to illicit drug users is affected not only by the differing clinical picture, but also by the need to avoid abuse and diversion of any prescribed medication.[19]

Table 1: Approximate therapeutic equivalent doses of benzodiazepines

Benzodiazepine	Common therapeutic use	Approximately equivalent dosage(mg)	Elimination half life (active metabolite) in hrs
Alprazolam	Antianxiety	0.5	6-12
Chlordiazepoxide	Antianxiety	25	5-30 (36-200)
Clonazepam	Anticonvulsant	0.5	18-50
Diazepam	Antianxiety	10	20-100 (36-200)
Flunitrazepam	Hypnotic	1	18-26 (36-200)
Flurazepam	Hypnotic	15-30	40-250
Loprazolam	Antianxiety	1	6-12
Lorazepam	Antianxiety	1	10-20
Lormetazepam	Hypnotic	1	10-12
Nitrazepam	Hypnotic	10	15-38
Oxazepam	Antianxiety	20	4-15
Temazepam	Hypnotic	20	8-22

2.2.1. Management of benzodiazepine dependence in 'therapeutic dose' users

Management of benzodiazepine dependence includes minimal interventions, gradual dose reduction and gradual dose reduction with additional psychological or pharmacological treatments. A stepped approach can be considered, moving through minimal interventions to gradual dose reduction and then additional therapies aimed at specific symptoms. Minimal or brief interventions include general practitioners (GPs) sending a letter advising patients of the need to reduce their benzodiazepine prescription, and provision of booklets on self-help strategies. In primary care populations, minimal interventions were more effective than routine care in achieving cessation of benzodiazepine use (three studies, OR = 4.37, CI= 2.28–8.40) increasing the success rates from 5% to 22% (Ia). [20] Another meta analysis also arrived at the same conclusion (three studies, RR = 2.1, CI= 1.5-2.9)(Ia). [21]

2.2.1.1. Gradual dose reduction alone

Dose-reduction schedules frequently last several weeks, although there is wide variation from abrupt discontinuation to discontinuation over a year or more (Ia). [22] One review has recommended withdrawal in < 6 months. [23] Gradual dose reduction is preferable to abrupt discontinuation of benzodiazepine (Ia). [24] Switching from a short half-life benzodiazepine to a long half-life benzodiazepine before gradual taper does not receive much support, but may be useful if reduction of short half-life benzodiazepine causes problematic withdrawal symptoms. [24,25] In primary care patients who had failed to cease benzodiazepine use with minimal intervention, gradual dose reduction was more effective than routine care in achieving cessation of use (51% vs. 15%) (1b). [26] At 15-month follow-up 36% of those who received gradual dose reduction were abstinent based on benzodiazepine prescription data, compared with 15% of those who received routine care (Ib). [27]

2.2.1.2. Gradual dose reduction and additional psychological therapies

Additional psychological therapies increase cessation rates compared with both routine care (three studies, OR = 3.38, CI 1.86– 6.12) and gradual dose reduction alone (seven studies, OR = 1.82, CI 1.25–2.67) (Ia). [20] These studies employed some form of group CBT as a part of psychological intervention. Compared with gradual dose reduction alone, additional psychological intervention seemed particularly beneficial in patients using benzodiazepines for insomnia and panic disorder (Ib). In a primary care study, Baillargeon et al. (Ib) reported that 77% of patients with chronic insomnia withdrew from benzodiazepines with gradual dose reduction and group CBT compared with 38% with gradual dose reduction alone (OR = 5.3, CI 1.8–16.2). [28] The effect persisted at 12-month follow-up. Morin et al. found similar results in their study of older adults with chronic insomnia (Ib). [29] For panic disorder patients attempting to stop benzodiazepines, successful discontinuation was significantly greater in the gradual dose reduction plus CBT group, than the gradual dose reduction alone group (76% vs. 25%, $p < 0.005$) (Ib). [30] A pilot study of CBT delivered via the internet for cessation of benzodiazepine use found good acceptability amongst participants but limited take-up (IIb). [31] Gradual dose reduction plus additional pharmacotherapy has shown no benefit compared with gradual dose reduction alone in a meta-analysis (14 studies, OR = 1.30, CI 0.97–1.73) (Ia). [20] This metaanalysis involved 11 different

pharmacotherapies. Four of the pharmacotherapies showed significant effects on benzodiazepine discontinuation rates in single studies (1b). Garfinkel et al. reported discontinuation rates of 77% with the addition of melatonin compared with 25% with gradual dose reduction alone (IIb). [32] Rickels et al. added sodium valproate, trazodone or placebo to a benzodiazepine taper (Ib).[33] At 5 weeks post-taper, 79% of sodium valproate and 67% of trazodone, but only 31% of placebo patients were benzodiazepine free. These differences were not maintained at 12 weeks post-taper. Adjunctive paroxetine in patients without major depression increased discontinuation rates compared with gradual dose reduction alone (46% vs. 17%) (Ib).[34] However, in patients in primary care with depression, adding paroxetine to gradual dose reduction did not increase benzodiazepine discontinuation rates above gradual dose reduction and placebo, with two-thirds in each group ceasing benzodiazepine use. In both groups depressive ratings improved with no significant effect of paroxetine, but paroxetine did have a beneficial effect on anxiety symptoms (Ib).[35] Within the meta-analysis the odds ratio for these two paroxetine studies was significant (OR = 1.73, CI 1.01– 2.96) (Ib).[20] Two studies of imipramine with conflicting results were not reported in the meta-analysis. In patients with generalised anxiety disorder and long-term benzodiazepine use, imipramine increased discontinuation rates compared with placebo (83% vs. 37%, $p < 0.01$). Buspirone also increased discontinuation rates but non-significantly compared with placebo (68% vs. 37%, $p < 0.06$) (Ib).[36] However, in patients with panic disorder and long-term benzodiazepine use, imipramine or buspirone did not significantly increase discontinuation rates (Ib).[37] Flumazenil (a benzodiazepine antagonist) reduced withdrawal symptoms and craving compared with an oxazepam taper over 8 days in benzodiazepine-dependent patients. Flumazenil-treated patients also had greater abstinence rates post detoxification (Ib).[38] A flumazenil infusion has also been shown to be a safe and effective treatment for benzodiazepine withdrawal (III).[39] A Cochrane review by Denis et al. found that, propanolol, dothiepin, buspirone, progesterone or hydroxyzine were of no benefit for managing benzodiazepine withdrawal or improving benzodiazepine abstinence (Ia).[24] Carbamazepine although might have some promise as an adjunctive medication for benzodiazepine withdrawal, particularly in patients receiving benzodiazepines in daily dosages of 20 mg/d or more of diazepam (or equivalents). Usefulness of carbamazepine as adjunctive therapy was highlighted by another review also (Ib).[23]

2.2.2. Management of benzodiazepine dependence in high-dose and/or illicit drug users

There is little evidence to guide practitioners in the management of this often difficult-to-treat population. Patients should be assessed to determine why they are using benzodiazepines, and alternative treatment strategies be employed for problems such as anxiety and insomnia. The presence of alcohol or other illicit drug abuse or dependence should be determined. Benzodiazepine abuse is frequent amongst heroin users and those in opioid substitution treatment. [40-42] Ongoing current benzodiazepine use is associated with concurrent poorer clinical outcomes in this population (III). [43] Prescribing of benzodiazepines during opioid substitution treatment is common, despite a lack of research to support this (III). [44] Such prescribing can often slip into de facto maintenance despite the lack of evidence for this. Use of benzodiazepines in combination with opioids is associated with increased opioid toxicity and performance deficits (III). [45, 46] Vorma et al. evaluated gradual dose reduction with CBT versus an unspecified standard withdrawal regime in high dose benzodiazepine users (Ib). [47] There was no significant difference in discontinuation rates (13% experimental group vs. 27% control group, OR 0.4 (0.1–1.5), $p = 0.20$). Over half the users in each group were able to reduce their dose by > 50% (54% vs. 59%). Reductions to therapeutic dose levels were maintained (Ib)). [48] McGregor et al. conducted an RCT of fixed gradual dose reduction (5–10 mg reduction per day) versus symptom triggered diazepam taper methods during inpatient benzodiazepine withdrawal treatment in 44 high-dose benzodiazepine users (Ib). [49] There were no significant differences in abstinence rates (27% gradual dose reduction vs. 18% symptom triggered). Both groups showed a reduction in benzodiazepine dosage of 86% to around 14 mg which was maintained at 1 month post-discharge. Liebrenz et al. have proposed the need to evaluate agonist substitution treatment in high-dose benzodiazepine dependence, where individuals have not been able to undergo withdrawal. [50] However, they recognize this need to be balanced against the risks, particularly in regard to negative effects on cognition and memory. An example of slow withdrawal schedule in a high dose benzodiazepine user is given below (Table 2) (IV):

Table 2: Withdrawal from high dose (6mg) alprazolam with diazepam substitution (6mg alprazolam is approximately equivalent to 120mg diazepam) [51]

	Morning	**Midday/Afternoon**	**Evening/Night**	**Daily Diazepam Equivalent**
Starting dosage	alprazolam 2mg	alprazolam 2mg	alprazolam 2mg	120mg
Stage 1 (one week)	alprazolam 2mg	alprazolam 2mg	alprazolam 1.5mg diazepam 10mg	120mg
Stage 2 (one week)	alprazolam 2mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 3 (one week)	alprazolam 1.5mg diazepam 10mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 4 (one week)	alprazolam 1mg diazepam 20mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 5 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	alprazolam 1mg diazepam 20mg	110mg
Stage 6 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	alprazolam 0.5mg diazepam 20mg	100mg
Stage 7 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	Stop alprazolam diazepam 20mg	90mg
Stage 8 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	alprazolam 1mg diazepam 10mg	diazepam 20mg	80mg
Stage 9 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	alprazolam 0.5mg diazepam 10mg	diazepam 20mg	80mg
Stage 10 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	Stop alprazolam diazepam 10mg	diazepam 20mg	60mg
Stage 11 (1-2 weeks)	Stop alprazolam diazepam 20mg	diazepam 10mg	diazepam 20mg	50mg
Stage 12 (1-2 weeks)	diazepam 25mg	Stop midday dose; divert 5mg each to morning and night doses	diazepam 25mg	50mg
Stage 13 (1-2 weeks)	diazepam 20mg	--	diazepam 25mg	45mg
Stage 14 (1-2 weeks)	diazepam 20mg	--	diazepam 20mg	40mg

In an open study in methadone-maintained benzodiazepine dependent patients, clonazepam was substituted for their benzodiazepine of choice. Patients were then either detoxified from or maintained on clonazepam, and outcome measured was self reported illicit benzodiazepine use. Illicit benzodiazepine use was reduced in the maintenance group compared with the detoxification group (III). [52] Wickes et al. described five case studies of

clobazam maintenance in methadone-maintained patients with mixed results (III). [53] Clobazam was reported by the patients as being less sedating than diazepam. Other small studies in benzodiazepine-dependent methadone maintained patients have examined community reduction and contingency management. McDuff et al. reported that 12 out of 22 patients misusing primarily alprazolam completed an outpatient reduction procedure which averaged 7.8 weeks (III). [54] Contingency management with rewards for benzodiazepine-free urines showed some success. However, results were not maintained at the end of the contingency phase (III). [55] In clinical practice some services have used carbamazepine for inpatient benzodiazepine detoxification in opioid dependence, particularly when the benzodiazepine use has been illicit. There is some evidence to support carbamazepine in attenuating the withdrawal symptoms from benzodiazepines (IIb). [56-58] In practical terms for illicit drug users, there should be an extended assessment of their benzodiazepine use, dependence and needs with resistance to requests for immediate prescriptions. Benzodiazepines should be detected in serial drug screens. If a benzodiazepine prescription is to be issued, there should be a clear treatment plan outlining the goals and time frame of treatment. A single, long-acting benzodiazepine should be prescribed and initiated on a daily dispensing basis. Doses greater than 30 mg diazepam equivalent per day should rarely be prescribed. [59] Reduction schedules should be negotiated at the outset. In high-dose users, reducing to a 'therapeutic' benzodiazepine dose level may be an appropriate first aim, because of the high relapse or drop-out rates with detoxification (Ib). [47-49] Once this has been achieved and there is sufficient psychosocial stability, further reductions or detoxification can occur. For drug users on 'maintenance' benzodiazepine prescriptions, the treatment should be reviewed, including medication compliance with drug screening, and ideally a gradual dose reduction plan put in place.

Below is a summary of points which need to be considered when drawing up benzodiazepine withdrawal schedule (adopted form Ashton, 2002) (IV)[60]

- Design the schedule around your client's symptoms. For example, if insomnia is a major problem, prescribe most of the dosage at bedtime; if getting out of the house in the morning is a difficulty, prescribe some of the dose in the morning.
- When switching over to diazepam, substitute one dose at a time, usually starting with the evening or night-time dose, then replace the other

doses, one by one, at intervals of a few days or a week. Unless one is starting from very large doses, there is no need to aim for a reduction at this stage; simply aim for an approximately equivalent dosage. After achieving this one can start reducing the diazepam slowly.

If, however, client is on a high dose, such as 6mg alprazolam (equivalent to 120mg diazepam), one may need to undertake some reduction while switching over, and may need to switch only part of the dosage at a time (see Table 7). The aim is to find a dose of diazepam which largely prevents withdrawal symptoms but is not so excessive as to make the client sleepy.

- Diazepam is very slowly eliminated and needs only, at most, twice daily administration to achieve smooth blood concentrations. If your client is taking benzodiazepines three or four times a day it is advisable to space out the dosage to twice daily once he/she is on diazepam.
- The larger the dose one is taking initially, the greater the size of each dose reduction can be. One can aim at reducing dosage by up to one tenth at each decrement. For example, if your client is taking 40 mg diazepam equivalent you could reduce at first by 2-4mg every week or two. When you are down to 20mg, reductions could be 1-2mg weekly or fortnightly. When you are down to 10mg, 1mg reductions are probably indicated. From 5mg diazepam some people prefer to reduce by 0.5 mg every week or two.
- There is no need to draw up your withdrawal schedule right up to the end. It is usually sensible to plan the first few weeks and then review and if necessary amend your schedule according to your progress.
- As far as possible, never go backwards. You can stand still at a certain stage in your schedule and have a vacation from further withdrawal, but try to avoid ever increasing the dosage again.
- Avoid prescribing extra tablets in times of stress. Teach your client to gain control over his/her symptoms. This will give him/her extra confidence that he/she can cope without benzodiazepines.
- Be cautious about your client compensating for benzodiazepines by increasing his/her intake of alcohol, cannabis or non-prescription drugs. One can suggest other drugs for particular symptoms, but do not prescribe the sleeping tablets like zolpidem, zopiclone or zaleplon as they have the same actions as benzodiazepines.

- Getting off the last tablet: Stopping the last few milligrams is often viewed as particularly difficult. This is mainly due to fear of how one will cope without any drug at all. In fact, the final parting is surprisingly easy. People are usually delighted by the new sense of freedom gained. Do not be tempted to spin out the withdrawal to a ridiculously slow rate towards the end (such as 0.25mg each month). Take the plunge when you reach 0.5mg daily. Some people after completing withdrawal like to carry around a few tablets with them for security "just in case", but find that they rarely if ever use them.
- If for any reason you do not (or did not) succeed at your first attempt at benzodiazepine withdrawal in your client, you can always try again. The good news is that most long-term benzodiazepine users are successful after the first attempt. Those who need a second try have usually been withdrawn too quickly the first time. A slow and steady benzodiazepine withdrawal is nearly always successful.

Recommendations: benzodiazepine dependence

Management of benzodiazepine dependence in 'therapeutic dose' users

- In cases of early/mild dependence minimal interventions such as advisory letters or General Practitioner advice should be offered (A).
- Gradual dose reduction of prescribed benzodiazepine is recommended where dependence is established (A).
- Switching to a long half-life benzodiazepine from a short half-life benzodiazepine before gradual taper should only be reserved for patients having problematic withdrawal symptoms on reduction (D).
- Individuals with insomnia and panic disorder may be benefitted from additional psychological therapies which increase the effectiveness of gradual dose reduction (B).
- Use of additional pharmacotherapy such as antidepressants, melatonin, valproate, and flumazenil can be considered on an individual basis (C).

Management of benzodiazepine dependence in high-dose and/or illicit drug users

- Existing evidence do not support maintenance prescription of benzodiazepines in illicit drug users, although it may reduce illicit benzodiazepine use in some patients (D).

- Carbamazepine may be used instead of benzodiazepines to control withdrawal symptoms (C).
- Doses greater than 30 mg diazepam is rarely necessary, and this is sufficient to prevent benzodiazepine withdrawal symptoms including withdrawal seizures in very high dose benzodiazepine users (D).
- Reduction of high-dose use to a therapeutic dose level may be a useful therapeutic objective in some dependent users (D).
- Clinicians should remember the potential risks of benzodiazepine prescribing in patients co-dependent on alcohol and/or opioids (D).

Key uncertainties:

- Available literature is ambiguous about the optimal speed or duration of gradual dose reduction. It is still unclear whether there is any role for benzodiazepine agonist maintenance therapy like in cases of opioid dependence.

2.3. MANAGEMENT OF BENZODIAZEPINE WITHDRAWAL STATE

The long term use of benzodiazepines or other sedative hypnotics at dosage above the therapeutic dose range produces physical dependence and all drugs have similar withdrawal symptoms that may be severe and life threatening. Therapeutic doses of benzodiazepines taken daily for months to years may also produce physiological dependence. A summary of benzodiazepine withdrawal syndromes is given in table 3.

Table 3: Characteristics of syndromes related to benzodiazepine withdrawal [61]

Syndrome	Signs and symptoms	Time course	Response to reinstitution of benzodiazepine
High-dose withdrawal	Anxiety, insomnia, nightmares, major motor seizures, psychosis, hyper pyrexia, death	Begins 1 -2 days after a short acting benzodiazepine is stopped; 3-8 days after a long-acting benzodiazepine is stopped	Signs and symptoms reverse 2-6 hours after a hypnotic dose of a benzodiazepine

Symptom rebound	Same symptoms that were present before treatment	Begins 1 -2 days after a short acting benzodiazepine is stopped; 3-8 days after a long-acting benzodiazepine is stopped; lasts for 7-17 days	Signs and symptoms reverse 2-6 hours after a hypnotic dose of a benzodiazepine
Protracted, low dose withdrawal	Anxiety, agitation, tachycardia, palpitations, anorexia, blurred vision, muscle spasms, psychosis, increased sensitivity to sounds and light, paresthesia	Signs and symptoms emerge 1 -7 days after a benzodiazepine is reduced to below the usual therapeutic dose	Signs and symptoms reverse 2-6 hours after a hypnotic dose of a benzodiazepine
Symptom reemergence	Recurrence of the same symptoms that were present before taking a benzodiazepine (e.g., anxiety, insomnia)	Symptoms emerge when benzodiazepine is stopped and continue unabated with time	Sings and symptoms reverse 2-6 hours after usual therapeutic dose of a benzodiazepine

Adopted from; David E Smith, Donald R Wesson: Benzodiazepines and other sedative-hypnotics: Textbook of treatment of substance use disorders: American Psychiatric Press 1999.

The ways of managing benzodiazepine withdrawal state are many:

- To use decreasing dosages of the agent of dependence. With a slow gradual withdrawal program the success rate is 88-100 percent [62]
- To substitute the short acting benzodiazepine with a long acting one (e.g. diazepam or chlordiazepoxide) during the process of gradual withdrawal (as shown in table 7) [49]
- To substitute Phenobarbital or some other long acting barbiturates for the addicting benzodiazepine & gradually withdraw the substituted medication. In a review of medical records, 3-day fixed-dose phenobarbital taper for benzodiazepine dependence was found to be safe and effective where no fall, seizures or injuries were reported (III).[63] However, in a comparison study, a rapid detoxification using benzodiazepines was found to be superior to a phenobarbital rapid detoxification (III). [64] The rationale for using phenobarbital is as follows: phenobarbital is long acting hence little change in blood levels between doses; lethal doses are many times higher than toxic doses;

signs of toxicity (sustained nystagmus, slurred speech & ataxia) are easy to observe; low abuse potential; intoxication usually does not produce disinhibition; excreted primarily through kidneys, is non toxic to liver, and can be used in the presence of significant liver disease. [65]

- Flumazenil has been successfully tried for protracted benzodiazepine withdrawal (III). [66] A recent case series emphasizes the role of subcutaneous flumazenil infusion in the management of acute benzodiazepine withdrawal. Data indicated that, patients subjective benzodiazepine withdrawal symptoms were well managed, with significant reduction in psychological distress seen over the duration of treatment (III).

Benzodiazepine withdrawal seizures have occurred with short, medium, and long half life benzodiazepine, if discontinued abruptly. Withdrawal seizures usually occur in patients who have been taking these medications for long periods of time and at high doses. Seizures have also been reported with less than 15 days of use and at therapeutic dosage. Almost all the withdrawal seizures reported were grand mal seizures. The severity of seizures can range from a single episode to coma and death. [67] The role of anticonvulsants in benzodiazepine withdrawal seizure has been poorly addressed. Pages and Ries suggested that valproate and carbamazepine can be used (IV). [68]

Recommendations: benzodiazepine withdrawal state

- Benzodiazepine withdrawal can be treated by gradually decreasing the dosage of the agent of dependence, substituting the short acting benzodiazepine with a long acting one, or with Phenobarbital substitution (C).
- Flumazenil can be effective in the treatment of benzodiazepine withdrawal (C).
- Valproate and carbamazepine can be used in the management of benzodiazepine withdrawal seizure (D).

Key uncertainties:

- Sparse literature is available which has systematically addressed the issue of management of benzodiazepine withdrawal. Role of Flumazenil in the treatment of benzodiazepine withdrawal is not supported by any robust evidence and long term outcome is also not known. Although some agencies have recommended the use of valproate and

carbamazepine in the management of benzodiazepine withdrawal seizure, their actual role is not clear.

2.4. BENZODIAZEPINE USE IN SPECIAL POPULATION

2.4.1. In pregnancy and lactation

Benzodiazepines and metabolites freely cross the placenta and accumulate in fetal circulation. It is advisable to avoid use in the first trimester because of risks of teratogenicity (association with incidence of cleft palate). High doses or prolonged use by the mother in the third trimester may precipitate fetal benzodiazepine syndrome including floppy infant syndrome, impaired temperature regulation and withdrawal symptoms in the newborn. In cases of severe anxiety, low-dose chlorpromazine may be considered as an alternative to benzodiazepine, for which it is advisable to seek specialist advice. [69]

Benzodiazepines are excreted in breast milk in levels sufficient to produce effects in the newborn, including sedation, lethargy, and poor temperature regulation. Metabolism in infants is slower especially during the first 6 weeks and long acting benzodiazepines can accumulate. [69]

The available literature suggests that it is safe to take diazepam during pregnancy but not during lactation because it can cause lethargy, sedation, and weight loss in infants. The use of chlordiazepoxide during pregnancy and lactation seems to be safe. Avoidance of alprazolam during pregnancy and lactation would be prudent. To avoid the potential risk of congenital defects, physicians should use the benzodiazepines that have long safety records and should prescribe a benzodiazepine as monotherapy at the lowest effective dosage for the shortest possible duration (IV). [70]

2.4.2. In older adults

There are ongoing concerns about inappropriate prescribing of benzodiazepines to older adults. [71] In older adults benzodiazepine use has been associated with increased risk of falls, cognitive decline, fractures, and mortality. [72-76] Many of the studies of benzodiazepine discontinuation in elderly populations have usually involved patients in general practice or outpatient settings and patients who have ‘therapeutic dose’ dependence. [20] In these studies minimal interventions (1a) and graded discontinuation (1b) have proven effectiveness. The addition of psychological interventions to graded discontinuation has shown increased effectiveness compared with

gradual dose reduction alone, and may be particularly beneficial where there is problematical insomnia (Ia). [20, 27]

Recommendations: in older adults

- Based on the above evidences it can be recommended that, therapeutic dose benzodiazepine users should be offered minimal interventions or graded discontinuation along with psychological interventions depending on the clinical picture (A).

2.4.3. In children and adolescence

For benzodiazepine dependence, maintenance prescribing is not recommended and detoxification with diazepam is recommended (IV).[77, 78]

3. MANAGEMENT OF MENTAL AND BEHAVIUORAL DISORDERS DUE TO USE OF BARBITURATES

3.1. INTRODUCTION

More than a century ago, chemical introduction of barbituric acid began with a German scientist Adolf von Baeyer in 1864 [79] and the clinical introduction of first barbiturate, diethyl-barbituric acid as a hypnotic was made possible by another two German scientists, Josef Freiherr von Mering and Emil Fischer. [80] Since 1903, a large number of barbiturate derivatives have been manufactured for medical use and marketed with huge promise both in clinical as well as economic grounds. [81] During 1930s and 1940s medical use of the barbiturate derivatives grew dramatically worldwide extending its arms as an anti-convulsant [82] and anesthetic agent. [83,84] By then people started getting taste of another side of these multi-coloured pills and it became popular as a 'downer' drug which hit the streets as well. Its injectable preparations became notorious for fatal overdoses, even deaths, [85-87] which claimed celebrities like Jimi Hendrix and Marilyn Monroe. Nazis utilized it during Second World War as a means for euthanasia. Many national & international health organizations raised their voices to restrict the access to these drugs. The use of barbiturates without a medical doctor's prescription became illegal in many courtiers. After the beginning of psychopharmacological revolution with the discovery of chlorpromazine (1952) and chlordiazepoxide (1960), therapeutic use of barbiturates began to decline. Popularity of barbiturates in pop culture fell dramatically by mid 1980s because of greater supply of another 'downer' drug, heroin.

Overall data regarding management of barbiturate overdose/intoxication, dependence and withdrawal state are sparse. Data are mostly in the form of retrospective chart review, comparative studies, case reports and case series. Indian data is almost nonexistent. Therefore, recommendations are mainly based on literature available from abroad.

3.2. PHARMACOLOGY OF BARBITURATES

Barbituric acid (2,4,6-trioxohexahydropyrimidine) is synthesized by condensation of urea and malonic acid and barbiturates are substituted derivatives of barbituric acid (malonylurea). Further substitution of side chains with alkyl or aryl groups on the fifth carbon of the barbiturate ring produces the pharmacologically active barbiturates. Replacement of 'O' with 'S' at second carbon yields thiobarbiturates which enhances their lipid solubility and potency in exchange of their half lives.

Barbiturates reversibly depress the activity of all excitable tissues of the body with special vulnerability of CNS, mediated by inhibiting transmission of GABA acting at $GABA_A$ receptors. Non-anesthetic doses preferentially suppress polysynaptic responses either postsynaptically (at cortical and cerebellar pyramidal cells, the cuneate nucleus, substantia nigra, and thalamic relay neurons), or presynaptically (in the spinal cord). In lower doses it has GABA-facilitatory action (by increasing the life time of chloride channel opening) and in higher doses GABA-mimetic action (by enhancing BZD binding to its receptors) in comparison to benzodiazepines which have only GABA-facilitatory action. Barbiturates enhance extracellular DA levels in both nucleus accumbens and neostriatum, with more pronounced effects in nucleus accumbens which is dose-dependent; low doses enhance DA efflux, whereas high doses inhibit. Barbiturates also block the AMPA receptor and Na^+ and K^+ channels, inhibit calcium dependent release of various neurotransmitters resulting in increase the duration of the receptor response to GABA and extend the depressed condition of the cell.

Barbiturates are well absorbed from GIT, widely distributed all over body, cross BBB, placenta and secreted in breast milk depending on their lipid solubility. Termination of action of barbiturates in the body occurs by the process of redistribution in the body, metabolism in the liver (oxidation, alkylation, conjugation etc.) and excretion via kidney. Commonly used barbiturates compounds and their pharmacological properties are listed below (Table 4).

Table 4: Commonly used barbiturates

Barbiturates compounds	Route of adminis-tration	Elimination half life (in hours)	Withdrawal equivalency to 30 mg of Phenobarbital	Common therapeutic use
Amobarbital	IM, IV	10-40 (short acting)	100	Insomnia, preoperative sedation, emergency management of seizures
Butabarbital	Oral	35-50 (short acting)	100	Insomnia, preoperative sedation
Butalbital	Oral	35-88 (medium acting)	100	Marketed in combination analgesics
Mephobarbital	Oral	10-70 (long acting)	NA	Seizure disorders, daytime sedation
Methohexital	IV	3-5 (ultra-short acting)	NA	Induction and maintenance of anesthesia
Pentobarbital	Oral, IM, IV, Rectal	15-50 (short acting)	100	Insomnia, preoperative sedation, emergency management of seizures
Phenobarbital	Oral, IM, IV	80-120 (long acting)	30	Seizure disorders, status epilepticus, daytime sedation
Secobarbital	Oral	15-40 (short acting)	100	Insomnia, preoperative sedation
Thiopental	IV	8 -10 (ultra-short acting)	NA	Induction/maintenance of anesthesia, preoperative sedation, emergency management of of seizures

3.3. PATTRN OF USE OF BARBITURATES

With declining trend of barbiturates uses and misuses, epidemiological data on this area falls drastically both in national and international domain in last few decades. Most of the data are on sedatives and hypnotics as a whole rather on barbiturates itself. Several case reports have been reported sporadically. Various common patterns and recent trends of barbiturate abuse that have been reported in vulnerable groups are mentioned below:

- Individuals with emotional inadequacy, comorbid psychiatric illness, personality disorders or psycho-social maladjustment are more likely to become dependent with barbiturates. Recently reported data shows in spite of downward trends of barbiturates use still there is significant intake of barbiturates use as non-medical use of prescription drugs in adolescent [88] and female population. [89] In United States high school surveys suggest that illicit use of barbiturates by adolescents has increased gradually during the

1990s, with slightly more than 7% of high school seniors reporting having used this class of drug in 1995. [90]

- Several analgesics (e.g. Fiorinal, Sedapap etc.) were marketed in combination with barbiturates, are still widely prescribed in medical practice for better pain relief, and are often becoming the source of iatrogenic dependence. [91]
- Barbiturates ("downer'') are also used in "mixed addiction" to counteract the troublesome effects of the primary substances (e.g. alcohol, heroin, methamphetamine, cocaine etc.).
- Short acting intravenous barbiturates (e.g. secobarbital, pentobarbital) are common drugs of abuse because of the 'high' they produce.
- Purchasing barbiturates from internet is now a common trend and an important source of problems related to barbiturates which can not be monitored predictably.
- Moreover barbiturates are still a common method of suicide in all vulnerable age groups.

3.4. CLINICAL FEATURES OF BARBITURATE INTOXICATION, ABUSE, DEPENDENCE AND WITHDRAWAL SYNDROME

Clinical features of barbiturate intoxication, abuse, dependence and withdrawal syndrome are mostly similar to that of benzodiazepine as mentioned in the benzodiazepine section. In barbiturate section we will mainly focus on additional features and issues.

3.4.1. Barbiturate Intoxication / Overdose

Both suicidal and accidental cases of barbiturate overdose are commonly reported. Children are in particular risk of fatal overdoses. Manifestation of overdose are due to excessive CNS depression, patients become flabby with induction of coma, shallow and failing respirations, fall of blood pressure, cardiovascular collapse, renal shutdown and bullous eruptions.

There are classic reports of fatal overdose due to the "automatism phenomenon", whereby the patient would take his or her dose, only to forget that he or she had already taken it, given the amnesic effect of the drug, and take it again, this process being repeated several times. [92]

Lethal dose varies according to individual agents, its lipid solubility, route of administration and degree of tolerance of the individual. It is 2-3 gm for

more lipid soluble agents and 5-10 gm for less lipid soluble, phenobarbitone. Ratio of therapeutic to lethal doses varies between 1:3 and 1:30 (average 1:10).

3.4.2. Barbiturate Abuse

Individuals who are not taking barbiturates for a long time, even a small dose of barbiturates decreases anxiety, increases feelings of fatigue, dizziness, lightheadedness, lethargy, sluggishness, incoordination, difficulty in thinking, poor memory, slowness in speech and comprehension, faulty judgment, disinhibition of sexual and aggressive impulses. Hostility, argumentativeness, moroseness, occasionally paranoid and suicidal ideation are the other potential symptoms. Other neurological symptoms are nystagmus, diplopia, strabismus, ataxic gait, hypotonia, diminished superficial reflexes, and positive Romberg's sign. On regular intake persons get an experience of a state of "high," which is described as being similar to *alcohol intoxication* and which reinforce them to abuse barbiturates.

3.4.3. Barbiturate Dependence and Withdrawal Syndrome

Patients who are taking long acting barbiturates orally, daily for a month or more above the upper therapeutic ranges should be presumed to be physiologically dependent and in need of medically managed detoxification. In case of short acting or ultra-short acting agents physiological dependence can be induced even within several days with continuous infusion. Sudden discontinuation from these states leads to withdrawal symptoms. Symptoms are qualitatively similar as with other sedative–hypnotics and alcohol, however, they generally appear somewhat later and is clinically more variable depending upon the half life (more intense for short acting or ultra-short acting agents), doses and duration of barbiturate use. Mild to moderate withdrawal symptoms are common, characterized by uneasiness, postural hypotension and dizziness, anorexia, vomiting, anxiety, insomnia, muscle weakness and twitching, coarse tremor, myoclonic jerks, EEG changes. With short-acting agents (e.g., pentobarbital, secobarbital), withdrawal symptoms typically begin 12–24 hours after the last dose and peak in intensity between 24 and 72 hours and with long-acting drugs (e.g., Phenobarbital) they peak on the fifth to eighth day. Symptoms may develop more slowly in patients with liver disease or in the elderly because of slowed drug metabolism. Severe withdrawal reactions are characterized by seizures and delirium. The barbiturate withdrawal seizures usually occur between 24 and 115 hours after discontinuation with its peak on second or third day. About 60% of the

patients subsequently have a delirium resembling delirium tremens which develop between third and eighth day of discontinuation and is characterized by disorientation to time and place but not to person and hallucinations, predominantly of visual type. Fatal hypothermia develops in few cases during withdrawal phase as a major complication resulting in deaths. The duration of withdrawal syndrome lasts for three to fourteen days, mostly resolved by eighth day.

3.5. DETECTION AND ASSAY OF BARBITURATES IN BIOLOGICAL SPECIMENS

Indication: Other than forensic use, assay of barbiturate in biological specimens is indicated for diagnostic purpose e.g. to assess the cause of intoxication and to estimate the degree of barbiturate use in last few days including the abstinence status. [93]

Biological specimens: Urine is the sample of choice, as most of the metabolites of barbiturates are excreted through kidney and can be detected for a longer time in urine than in blood. Blood assay is a useful additional method, though other biological specimens (e.g. saliva, hair) have not been universally accepted. [93]

Collection of sample: Urine should be collected in clean, sealed and labeled glass container, supervised by trained authorized personnel who will maintain the confidentiality and it should be kept or transported in dark and cool (32-38 degree C) environment. Plastic containers or rubber stoppers may absorb non-polar metabolites and should be avoided.

Methods used: Commonly practiced methods for screening are radio-immunoassay (RIA), enzyme-immunoassay (EIA), fluorescence polarization immunoassay (FPIA), latex agglutination inhibition etc. and for confirmation are thin layer chromatography (TLC), gas chromatography (GC), high performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GC-MS) etc.

Interpretation: Barbiturates generally can be detected in urine for 24 hours after use of short acting agents such as pentobarbital and secobarbital, but much longer for the long acting agents such as phenobarbital, up to 14 days or more, depending on the doses and pattern (chronic vs acute) of use of drugs, pH of the urine, co-substance use, methods used for assay etc. [94] Blood concentration should be interpreted with caution, toxic effects may come even in lower concentration depending on the degree of tolerance,

presence of respiratory and cardiovascular diseases, use of other CNS depressants, route of administration etc.

3.6. MANAGEMENT OF BARBITURATE INTOXICATION/ OVERDOSE

As already indicated, data concerning management of barbiturate intoxication are in the form of expert opinions, chart reviews and case reports. Therefore, the evidences and recommendations has been merged together to make the topic concise.

- Patients with barbiturate intoxication should be hospitalized immediately; should be treated in intensive care setting to monitor the vital signs and CNS activities (S). Sudden and rapid deterioration of vital signs is a rule rather exception. Target should be to keep the patient alive till the barbiturates are eliminated from body.
- Routine gastric lavage should be done for all patients (S). One or two packs of activated charcoal should be administered through nasogastric tube to stomach to prevent further absorption from intestine.
- Supportive medical treatment should be instituted to maintain Airway, Breathing & Circulation (ABC). An intravenous fluid line, preferably a central line should be established. Infusion of fluid and vasopressor, dopamine in the dose of renal vasodilatation should be started to maintain the blood volume.
- Forced alkaline diuresis should be started with infusion of mannitol and sodium bicarbonate (S).
- Hemodialysis and hemoperfusion (preferably through a column of activated charcoal or other absorbants) is very helpful, both for long and short acting barbiturates.
- No specific antidotes are available for barbiturates, use of analeptics or CNS stimulants may deteriorate further by inducing convulsions and subsequently death.
- Acute barbiturate intoxications are often superimposed over chronic barbiturate dependence. In these cases whenever patient recovers from coma, every effort should be made to ascertain if he has been taking large doses of barbiturates daily, he should be mildly reintoxicated with barbiturates and then gradual reduction should be started as described above (IV). [95]

3.7. MANAGEMENT OF BARBITURATE DEPENDENCE

Treatment setting: Whether treatment should start from OPD setting or patient should be admitted, it depends upon few parameters e.g. the pattern of use, doses and duration of barbiturate intake, severity of withdrawal symptoms, tolerance, presence of comorbid physical or mental illness, associated with other substance intake, social support, past H/O treatment etc.

Indication for admission in hospital (IV) [91, 96]

- Patients who have taken more than 0.4 g/d of secobarbital or an equivalent amount of another barbiturate for 90 days or longer, or 0.6 g/d or an equivalent dose for 30 days or longer
- Who have had withdrawal seizures or delirium
- Patients whom phenobarbital loading has been planned
- Using several drugs including opioids
- Uncontrolled use
- Failed outpatient treatment
- Active medical complications
- Serious psychiatric morbidity
- Poor social support
- Patient's willingness to undergo detoxification in hospital

3.7.1. Pharmacological Interventions

There are ***three basic strategies*** to treat physical dependence on barbiturates, they are as follows:

3.7.1.1. Decrease the dose of barbiturate of dependence or abuse gradually:

In this approach, the drug of dependence is withdrawn gradually (IIa). [97] It is an appropriate method for low dose dependence and for long-acting barbiturates but not suitable for short-acting agents, where patients can have behavioural disinhibition and signs of intoxication. Moreover giving an addict their drug of abuse, even in a therapeutic context, may reinforce patients. This approach is not commonly practiced nowadays (B, C).

3.7.1.2. Substitute long-acting barbiturates for the existing barbiturate of abuse and gradually withdraw the long-acting one:

Several methods are commonly practiced.

First method: Initially try to assess the level of tolerance. If a patient presents with signs of barbiturate intoxication, once clinical features of intoxication has subsided and withdrawal symptoms are just appearing, an intermediate-acting barbiturate (e.g., pentobarbital, 0.2 to 0.4 g orally every 4 to 6 hours) is started to stabilize the withdrawal symptoms and stabilization dose is determined as per table 5.[19] Estimated daily dose is then continued for next 2-3 days in divided doses to stabilize the patient and then gradually taper off with daily dose reduction of around 10% of the stabilization dose. Over pentobarbital, phenobarbital has several advantages e.g. a slower elimination rate, a larger therapeutic window, effective anticonvulsant activity etc. So, for this method phenobarbital can be substituted for pentobarbital in equivalent doses (table 10). [98-101]

Table 5: Pentobarbital test dose procedure for barbiturate withdrawal[98]

Symptoms after test dose of 200 mg of oral pentobarbital	Estimated 24 hours pentobarbital dose (mg)	Estimated 24 hours phenobarbital dose (mg)
Level I: Asleep but could be aroused with no withdrawal symptoms	Not required	Not required
Level II: Mild sedation, slurred speech, ataxia and nystagmus.	500-600	100-200
Level III: Patient is comfortable, no sedation, may have nystagmus.	800	250
Level IV: No drug effect	1000-1200	300-600

Adopted from Ewing JA, Bakewell WE. Diagnosis and management of depressant drug dependence. Am J Psychiatry 1967; 123: 909.

Second method: In this method, on the basis of patient's reporting about the doses of barbiturates (with or without other sedatives including alcohol) required dose of phenobarbital or equivalent hypnotic dose is calculated and same dose is continued for next 2-3 days, followed by gradual dose reduction of 30-60 mg of phenobarbitone or equivalent doses in every 2-3 days (C).

Disadvantages of the second method

- There is uncertainty about the dosage. Published equivalencies are only approximations with significant individual pharmacokinetic and dynamic variations and cross tolerance between different hypnotic drugs are not complete as observed in animal studies.
- Reinforcement of drug-taking behaviour through the repeated administration of barbiturates
- Difficulties in assessing the clinical state
- Patients history is often not much reliable

Third method: In this method, a loading dose of phenobarbital is titrated till signs of mild level intoxication come to determine the actual extent of drug use, the severity of physical dependence and to prevent severe withdrawal reaction. No additional drug is required because of the special property of phenobarbitone, known as "pharmacokinetic umbrella". Because of its long half-life it allows CNS for gradual adaptation to a drug-free state and prevents the reappearance of withdrawal symptoms. [102]

Doses of 120 mg are given every 1 to 2 hours until three of five signs - nystagmus, drowsiness, ataxia, dysarthria and emotional lability - appear or, in symptomatic patients, the withdrawal signs and symptoms disappear. Before giving each subsequent dose patients should be assessed carefully for signs of intoxication and of the therapeutic effect. In some cases, hourly dose titration may be required for up to 15 to 20 hours with the median loading dose of 1440 mg (mean 23.4 and standard deviation 7.1 mg/kg) and median plasma concentration of 150 micromol/L (ranging from 57 and 308 micromol/L). Possibilities of developing seizures and delirium are remote with this method. After only 3 days of direct medical supervision patients can be discharged or send for rehabilitation. [103] In acutely ill patients intravenous phenobarbital (0.3 mg/kg per minute) can be given. [99] Those who require lower doses (less than 7 mg/kg or 480 mg) are not sufficiently dependent and do not require full loading therapy or further treatment (B). [102] Monitoring of Phenobarbital concentrations can be used to reassure the patient from the start that the treatment is working well and that the need for additional doses can be determined.

The loading dose technique has other advantages e.g. manipulative drug-seeking behaviour of patients are minimum and alley undue anxiety of the

patient, staff members and even in respond to nonspecific signs of the patient during detoxification. [98]

For persons who are taking analgesic in combination with butalbital, a loading strategy has been described. If the person takes less than ten tablets (e.g. Fioricet) per day, the dose should be reduced by one tablet in every 2-3 days, can be stopped successfully (C). If patient's information seems to be unreliable, a loading dose of phenobarbitone of 120 mg to be started hourly guided by a rating scale to monitor the signs of intoxication. In one study using this strategy, mean number of phenobarbitone dose required was 9.7 ranging from 7 to 14 and within a day the process of detoxification was completed. [103]

3.7.1.3. Substitution with an anticonvulsant: Role of anticonvulsant in barbiturate withdrawal is controversial and not commonly practiced. In patients with comorbid seizure disorders, anticonvulsants may have some help.

3.7.2. Psychosocial Interventions

Literature is deplete of any study concerning specific psychosocial intervention for barbiturates dependence or abuse itself. But, there are some instances where psychosocial intervention may be of some help for barbiturates dependence or abuse directly or indirectly. Transmitting a sense of control over withdrawal symptoms and linking the symptoms of anxiety to environmental & intrapsychic stressors led to successful withdrawal and reduced relapse rate. For this purpose, in uncomplicated withdrawal, during and after detoxification with pharmacological treatment, cognitive restructuring, implementation of adaptive coping strategies, systematic desensitization, problem solving, individually or in groups can be tried. Underlying primary symptoms or illnesses (e.g. anxiety disorder, sleep disturbance) for which barbiturates were initially started should be properly addressed either by psychological means or changing to safer alternatives.

The moral choice in prescribing barbiturates: In our clinical practice, we can never do without sedative-hypnotic drugs but we do appear to be able to do without barbiturates except for certain specific indications e.g. in the treatment of epilepsy. It is for us as doctors to see that we are sufficiently wise to control the use of these compounds, using the safest of the hypnotics when absolutely necessary for the shortest possible period.

3.8. Management of Neonatal Barbiturate Withdrawal

Desmond et al. in 1972 first described neonatal barbiturate withdrawal as a state of jitteriness, excessive crying and alteration of the sleep pattern, vomiting and deficient sucking in neonates started within 30 min to 14 days (median 6 days) after birth. [104] Bleyer and Marshall added another serious symptom, convulsions, with EEG changes resembling changes seen in adult barbiturate withdrawal. [105] Unlike neonatal narcotic withdrawal, intrauterine growth retardation and neonatal jaundice were less commonly observed in neonatal barbiturate withdrawal with better Apgar scores. Withdrawal symptoms are unrelated to the dose or type of barbiturate, but are probably dependent on the duration of exposure. In case of short duration of intake of barbiturate only in the latter part of pregnancy for the prevention of hyperbilirubinaemia of the newborn, withdrawal symptoms are less likely. No apparent residual damage following withdrawal has been reported. Diagnosis is facilitated by a history of barbiturate use in pregnancy, and such a history should be sought when neonatal behaviour is suggestive of withdrawal. Frequent feeds, adequate warmth and diminished environmental provocation suffice in controlling symptoms in some infants, while others require sedation (S). Phenobarbital is effective; a dose in excess of the recommended anticonvulsant dose would probably be most effective. This should be reduced over a few months (S). One of the first signs of improvement is the infant's ability to sleep for longer periods.

4. MANAGEMENT OF MENTAL AND BEHAVIOURAL DISORDERS DUE TO USE OF Z-GROUP AND OTHER NEWER SEDATIVE-HYPNOTIC DRUGS

Nonbenzodiazepine hypnotic agents were developed to minimize the adverse effects of benzodiazepines. These hypnotics bind to the $á_1$, $á_2$, and $á_3$ subunits of the gamma-aminobutyric acid type A ($GABA_A$) receptor complex. Initially these compounds were thought to have less abuse liability relative to benzodiazepines, and recommended for short term sleep disturbance. In last decade increasing number cases has been reported with their abuse potential. Commonly prescribed Z-group and other newer sedative-hypnotic drugs are listed below (Table 6).

Table 6: Z-group and other newer sedative-hypnotic drugs

Active ingredient	International (National Brands)	Initial doses		Half-life (hrs)
		Adults	Older adults	
Zolpidem (Extended release)	Ambient (Stilnoct, Sove-IT)	10 (12.5) mg	5 (6.25) mg	2.2 (2.8)
Zaleplon	Sonata	10 mg	5 mg	1
Zopiclone	Imovane	7.5 mg	3.75 mg	5-6
Eszopiclone	Lunesta (Fulnite, Bexomer)	2-3 mg	1-2 mg	6
Ramelteon	Rozerem (Ramitax)	8 mg	8 mg	1.36

4.1. ZOLPIDEM

Zolpidem is a hypnotic drug of imidazopyridine group, chemically unrelated to the benzodiazepines, but its pharmacologic profile is similar to a benzodiazepine, acting selectively through omega 1 receptors of GABA-A. [106, 107] In higher doses this selectivity is lost. Unlike the benzodiazepines, zolpidem has little effect on the stages of sleep in normal human subjects. The drug is as effective as benzodiazepines in shortening sleep latency, prolonging total sleep time in patients with insomnia, suppress REM sleep to a lesser extent than benzodiazepines. Its sedative effects are reversed by the benzodiazepine antagonist flumazenil. Zolpidem is rapidly absorbed and has a short half-life ($T_{1/2}$ = 2.2 hours). Its sedative effects are additive with alcohol. It is recommended by FDA for treatment of short term insomnia.

Initial several trials including RCTs showed that if used in therapeutic doses, sudden discontinuation of zolpidem treatment after 2 to 4 weeks was not associated with withdrawal symptoms. [108, 109] However, zolpidem dependence is now well known. [110, 111] Several case reports described withdrawal symptoms including insomnia, anxiety and epileptic attacks soon after abrupt discontinuation of zolpidem, especially if taken in suprathreshold doses [112, 113], and also after parenteral use [114]. In one case series of seven cases of zolpidem abuse, it was reported that almost half of them did not even feel any sedative effects of zolpidem despite incremental doses, rather experienced stimulating and euphoric effects. [115] Females were found to have a significantly higher serum zolpidem concentration than men at equivalent dosage which is one of the susceptibility factors associated with adverse effects of zolpidem in females. [116] From India few cases [117, 118] of zolpidem withdrawal delirium were reported. In one [117] such case of a zolpidem-naive alcohol-dependent person, delirium occurred at slightly higher than recommended dose of zolpidem prescribed for insomnia during

alcohol detoxification. Delirium was reported even after taking first doses of 5 mg of zolpidem in an 86-year-old white woman. [119]

4.2. ZALEPLON

Zaleplon is a pyrazolopyrimidine, another non-benzodiazepine agent, binds to the omega-1 receptor with zolpidem like effect on sleep. FDA approved it for marketing in the United States in 1999. Several animal studies [120, 121] suggested about its abuse potential similar to triazolam. Peak plasma concentration occurs about 1 hour following oral ingestion. It is rapidly metabolized with a half-life of about 1 hour. A study comparing memory and cognitive effects of triazolam, zolpidem, and zaleplon showed that zaleplon (10 or 20 mg) demonstrated no evidence of cognitive impairment 8.25 hours after the dose, whereas triazolam (0.25) and zolpidem (20 mg, recommended therapeutic dose is 5 to 10 mg) showed measurable cognitive impairment. [123] A recent case report described intranasal zaleplon abuse by snorting pulverized capsules for its mood lifting effect. [122]

4.3. ZOPICLONE

Zopiclone is another Z-group hypnotic belonging to the cyclopyrrolone class. Its mode of action and hypnotic properties are similar to zolpidem and zaleplon. Though rebound insomnia and abuse potential of zopiclone are much less than benzodiazepines, but it's addictive non-medical use has been reported with occasional tolerance and psychological craving. [123]

4.4. RAMELTEON

Ramelteon is a synthetic melatonin agonist which selectively acts on MT1 and MT2 and has been approved by the USFDA for treatment of insomnia characterized by difficulty with sleep onset. It acts on the sleep regulatory mechanisms within the suprachiasmatic nucleus. It is available as an 8 mg tablet, which should be taken approximately 30 minutes prior to bedtime. The FDA approval contains no limitation on how long the medication may be prescribed. Though considered as a 'no abuse' drug for insomnia, its rampant use in recent years may cause serious problem in future.

MANAGEMENT OF ABUSE OR DEPENDENCE OF Z-GROUP AND OTHER NEWER SEDATIVE-HYPNOTIC DRUGS

There is no standard management protocol for this group itself. Treatment is usually in the line of other sedative-hypnotic drugs. However, clinical, patient and clinician variables influence treatment decision.

5. SUMMARY

Though sedatives and hypnotics are one of the most commonly prescribed and abused pharmacological agents over the decades, little effort has been made to develop a systematic plan to combat with the complications arising out of its non-medicinal/recreational use. Use of barbiturates has seen a steady decline, whereas use of benzodiazepines and other newer sedatives-hypnotics are on the rise. In day to day clinical practice, patients presenting with sedatives-hypnotics intoxication, dependence and withdrawal state challenges the skills of emergency physician. Research has mainly focused on management of benzodiazepine dependence and withdrawal, whereas, other areas have been largely neglected. Indian data is almost non-existent. Minimal interventions, gradual dose reduction and psychological therapies (CBT), all have been successfully tried in the management of benzodiazepine dependence in therapeutic dose users. Substitution with a long acting benzodiazepine with gradual taper and carbamazepine seem to work in cases of high-dose and/or illicit users. In cases of benzodiazepine withdrawal syndrome, phenobarbital substitution and flumazenil can be effective. Flumazenil still has a central role in uncomplicated benzodiazepine intoxication. Newer sedatives and hypnotics including z-drugs and ramelteon are not completely devoid of addictive potentials; cases of dependence and withdrawal seizures have been reported in literature.

With the progress of neuroscience as a whole and neuropsychopharmacolgy in particular we will probably be in a better state in next few decades to address the caveats in benzodiazepine research. In future, we can hope for better sedatives-hypnotics with less abuse potential; can hope for better antidotes to counter their dreaded effects in cases of overdose; can devise more effective strategies to mitigate the withdrawal symptoms; and last but not the least, can hope to conduct more meaningful research to provide us with systematic data in this relatively neglected but very important topic.

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CLINICAL PRACTICE GUIDELINES (CPG) FOR THE MANAGEMENT OF TOBACCO USE DISORDERS

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On behalf of IPS-SS-SUD

2014

CONTENTS

EXECUTIVE SUMMARY

Tobacco use is a major cause of preventable death and disease in India. Thirty five percent of adults in India use some form of tobacco. Smokeless tobacco use is more common than smoking both in male and females.

Tobacco cessation should be offered to tobacco users at every opportunity by a physician. Psychiatrists, in view of their training on bio-psycho-social models and counseling skills, are very well placed to provide this intervention. Psychiatrists can also play an important role in managing patients with severe nicotine dependence, training physicians and other health professionals and can also provide inputs into existing tobacco cessation programs.

Behavioral support and Counseling

Counseling is an integral part of any tobacco cessation programme. Studies from India suggest that a significant number of tobacco users who receive counseling are able to reduce or quit tobacco use. The commonly used 5 As model (Ask, Advise, Assess, Assist and Arrange)is a popular brief intervention approach for tobacco cessation. Brief personalized counseling focusing on health impact, fixing a quit date and physician support have been found to be helpful (RR 1.66). There is a dose-response rate in counseling. More intensive counseling (duration as well as number of sessions) is associated with better outcome. The psychiatrist is well placed to offer intensive counseling. Psychiatrists can provide support for craving management, coping skills, problem solving, life style changes etc. that will help to minimize relapses. Psychiatric co-morbidity needs to be recognised and effectively managed.

Nicotine Replacement Therapy

Nicotine replacement therapy (NRT: Gum, Patch, Spray, Inhaler) is a safe and effective treatment for dependence on both forms of tobacco. NRT dose is dependent on the severity of tobacco use i.e. the amount of tobacco and how early one uses in the morning. Use of adequate

dosage and duration of NRT is associated with better outcome. The likelihood of tobacco abstinence with NRT in case of smoking is one and half time (RR 1.58) greater than placebo. Although all forms of NRT are more or less equally effective in smoking, the best result is with nasal spray. NRT can be initiated during the smoking reduction phase and for a person who is not completely motivated to quit immediately. Combining the patch with a shorter acting NRT like gum is associated with higher success rate.

For smokeless tobacco dependence, gum and patches have been studied and found to be effective. In India, addition of gum has also increased the abstinence rate among tobacco chewers. There are only a few studies focusing on treatment effectiveness for chewing tobacco as most of the studies of smokeless tobacco have been among *snus* users (in Europe and USA).

Non-Nicotine Pharmacotherapy

Antidepressants like bupropion and nortriptyline are found to be effective in tobacco use, particularly smoking. Sustained release Bupropion increases the abstinence rate by more than one and half times (RR: 1.69) compared to placebo. This effect is independent of its antidepressant property. The drug is beneficial in attenuating post cessation weight gain. In India, bupropion has been used for tobacco cessation and found to be beneficial in both smoker and chewers. Combining bupropion with NRT increases the odds of quitting. Although a safe medication, it is not advisable in persons with seizure disorders. It is contraindicated in pregnancy.

Nortriptyline is as equally effective as bupropion. Its use is limited in view of tricyclic- associated side effects. Yet, because of its cost effectiveness and efficacy, nortriptyline can be an appropriate choice for cessation treatment in our country.

Nicotine Partial Receptor Agonists

Varenicline, a selective nicotine partial agonist, is definitely effective for smoking cessation and likely to be useful for smokeless tobacco. The sustained abstinence rate for varenicline is twice (RR 2.27) that of placebo and one and half times compared to bupropion (RR 1.52).

Two important adverse events, though very low in occurrence, i.e., behavioral change and cardiac events, have raised concerns. While cardiac events have been found to occur rarely, the patient on varenicline must be monitored for any behavioral change, though recent studies seem to allay this concern. Cytisine, a partial nicotine receptor agonist, is a low cost drug that has been reported to be effective in smoking. There is a need for more studies on its safety and efficacy.

Other drugs

Among other agents, clonidine has been found to have some evidence for effectiveness in tobacco cessation, but in view of the well-known side effect of orthostatic hypotension, its use must be closely monitored.

Other Interventions

Use of technologies like Internet, telephone counseling/follow up, quit line etc. has been found to be helpful in tobacco cessation in the West. Some of them (e.g. telephone) have potential use in India, to increase the quit rate. Recently a national quit line has been launched by the Government of India.

Conclusion

Tobacco cessation needs a multi-pronged approach. The psychiatrist can substantially contribute and play a key role in cessation.

1. INTRODUCTION

Tobacco use, a human created epidemic, kills one third of the people who use it. Across the world, smoking is the most common form of tobacco use. In India, both smoking as well as smokeless tobacco is used among all age groups. In 2002, 50% of the people killed from tobacco use were from developing countries. In the next two decades, unless urgent action is taken, the number might double and 70% of deaths are likely to be from developing countries. Tobacco related deaths will be more than 8 million in 2030 which is more than the total number of deaths from malaria, maternal and major childhood conditions, and tuberculosis combined.[1]

1.1 Tobacco in India

35% of adults in India use tobacco. Among them 21 percent adults use only smokeless tobacco, 9 percent only smoke and 5 percent smoke as well as use smokeless tobacco. More people in India use smokeless tobacco than smoking forms (**Table 1**). Nearly one in two adult males (48%) and one in five adult females (21%) are tobacco users. Nearly two in five (38%) adults in rural areas and one in four (25%) adults in urban areas use tobacco in some form.(Source GATS India 2010[2]).

Table 1: Gender difference in use of tobacco[2]

	Smoking (%)	Smokeless (%)
Male	24	33
Female	3	18

Tobacco related mortality in India is very high. It increases the number of premature deaths. In a national representative sample, smoking was associated with twice as many deaths among both men and women. Smoking was associated with reduction of median survival rate by 6-8 years. Excess deaths among smokers, as compared with nonsmokers, were chiefly from tuberculosis and from respiratory, vascular, or neoplastic diseases.[3]Although there is no systematic study, it is estimated that 8.3 million cases of coronary artery disease and chronic obstructive airway diseases are also attributable to tobacco each year.[4]

The association of smokeless tobacco with oral cancer is very high. The use

of *Gutkha* is associated with coronary vasoconstriction and significant hemodynamic alterations.

1.2 Facts regarding Nicotine Use and Dependence

There are certain important features with tobacco use which makes it highly addictive.

- Nicotine, the addictive component of tobacco, binds to midbrain nicotine cholinergic receptors and releases a surge of dopamine.
- Dopamine, a neurotransmitter of reward pathway, is responsible for reinforcing effect of nicotine.
- Delivery of nicotine from tobacco plays a significant role in its repeated use. Immediately following inhalation, smoking delivers a bolus of nicotine in cerebral arterial circulation. Use of smokeless tobacco produces slower delivery of nicotine.
- Much of the ''relaxation and pleasure'' associated with nicotine use may simply be a brief interruption of withdrawal symptoms, including restlessness, anxiety, depression, irritability, impatience, difficulty concentrating, insomnia, and increased appetite.
- Nicotine dependence is a chronic relapsing medical disorder like ulcerative colitis or diabetes.
- While all physicians need to manage and provide brief advice, they should network with experts who can effectively help in the management of dependence which is often associated with multiple relapses.

Tobacco dependence is characterized by craving, tolerance and withdrawal as well as continued use despite harm. Other features of dependence like salience, significant socio-occupational dysfunction etc. are not prominent. The severity of tobacco dependence (physical) can be assessed by enquiring about the number of cigarette smoke/pouch of smokeless tobacco per day and how early one needs to use tobacco after wake up. Fagerstrom Test for Nicotine Dependence (FTND)[5] is a simple and useful six item scale to assess the severity of smoking. This scale is also modified for use in smokeless tobacco.[6]

1.3 Tobacco Cessation and Guidelines

Aggressive tobacco control has been associated with substantial benefit. It has been estimated that if adult consumption were to decrease by 50% by the year 2020, approximately 180 million tobacco-related deaths could be avoided[7]. Cessation of tobacco use at any time in life has been found beneficial. Control of the tobacco epidemic and tobacco cessation needs multiple approaches including taxation, regulation and prevention of tobacco use as well as the physician's offer for help. Studies from the USA have shown that the combined approach of tax increase, increase in smoke-free areas along with the physician's help for cessation has led to a reduction in tobacco use[8].

Spontaneous quit attempts in the Indian population are very low and it has been suggested that only 2% of users quit on their own[3]. However, one third of tobacco users had made a quit attempt in the previous year. Among persons who sought a health consultation, less than 50% were asked or advised to quit tobacco and less than 10% provided any form of counseling or pharmacotherapy[2]. Misconceptions held by the physician can also hinder intervention. In a study from South India, about one-third of doctors believed that smoking only becomes harmful when the number of cigarettes per day is 6 or more.[9] Smokeless tobacco users are even less likely to have received any intervention.

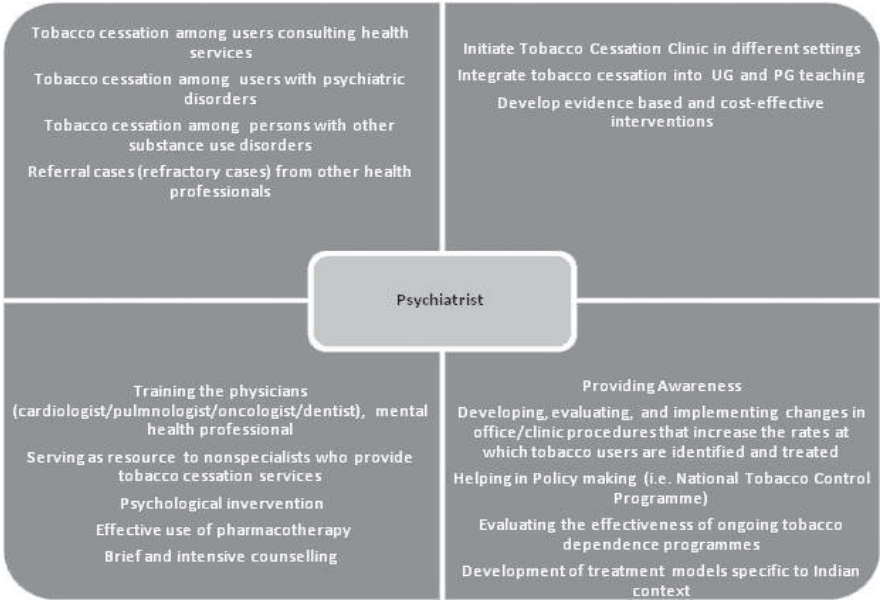
Thus, in India, most physicians miss the opportunity to advise their patients on the risks of continuing tobacco use and the benefits of cessation. More importantly, patients with tobacco dependence who are unable to stop by themselves are not even advised to stop, let alone assisted with pharmacotherapy. Providing simple counseling with proper use of pharmacotherapy, when required, is cost-effective in many Indian settings rather than specialized and more intensive counseling.[1,4,10]

There are existing guidelines for tobacco cessation developed in India and are already been used. They are *Tobacco Dependence Treatment Guidelines* by Directorate of Health Services (DGHS), Ministry of Health and Family Welfare[11] , Manual for tobacco cessation by DGHS, Ministry of Health and Family Welfare[6,12]*Helping People Quit Tobacco: A manual for doctors and dentists.*[1]Apart from this, the tobacco cessation clinics established under Ministry of Health and Family Welfare, have developed different manuals and guidelines for tobacco cessation or specific interventions for cessation.[4,13]

These are general guidelines for physicians. The current guidelines for psychiatrists incorporate this and in addition include guidelines for more specialized care. The guidelines in this chapter have also updated the Indian Psychiatric Society guidelines of 2006.[14]

1.4 Psychiatrist's Role in Tobacco Cessation

Tobacco cessation needs to be aggressively promoted by all the health professionals (both general physicians as well as specialists, i.e., pulmonologists, dentists, cardiologists, internal medicine practitioners, etc.). In substance use disorders (including alcohol, cannabis, opioids, benzodiazepines), the psychiatrist is often the primary health care provider. Thus, psychiatrists, in view of their training in both biological and psychosocial aspects of addiction are better equipped to assist persons dependent on tobacco. Psychiatrists are also better placed for diagnosing and intervening for concomitant psychiatric as well as other substance use disorders among tobacco users. However, studies showed that psychiatrists offered smoking cessation counseling only in 12.4% of the visits from psychiatric patients who smoked.[15]No pharmacotherapy was offered. This study from USA suggests that psychiatrists are assuming that the general physician will take care of smoking cessation, thereby missing opportunities to offer smoking cessation counseling to their patients.[15]



2. SCOPE AND METHODOLOGY

Clinical practice guidelines ('guidelines') are systematically developed statements to assist the practitioner and patient regarding decisions about appropriate health care in specific clinical circumstances. The *Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument II*[16, 17] has been used to a certain extent as a template for this exercise.

Categories of strength of evidence for causal relationships (including treatment) and strength of recommendations are taken from Treating tobacco use and dependence: 2008 update, published by the US Dept of Health and Human Services. This is the most cited meta-analysis for the treatment of nicotine use disorders.[18]

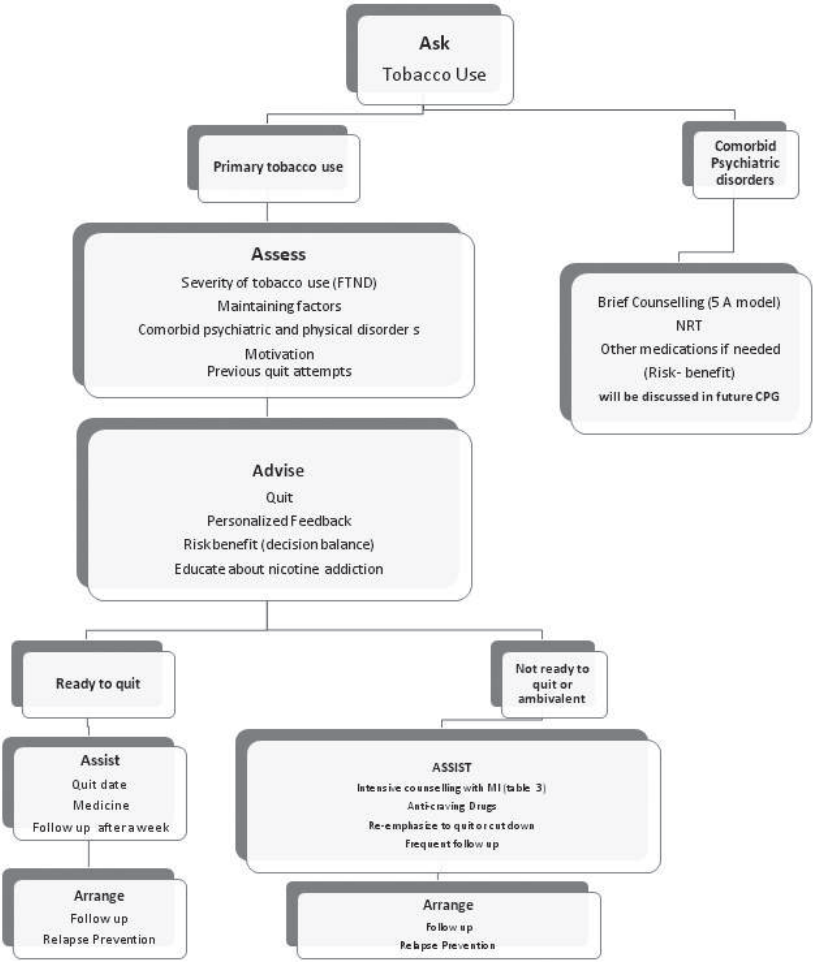
The evidence for developing this CPG was gathered from multiple sources: existing guidelines, systematic reviews, RCTs/clinical trials, and various observational studies. These were identified from PubMed, EMBASE, Google Scholar, Cochrane Database as well as from guidelines by experts in this field. This guideline is based on the synthesis and interpretation of available evidence obtained from studies across the world, especially in light of the Indian context, rating them on strength of evidence and combining this strength with the perceived importance and relevance in the Indian context to finally arrive at specific key recommendations as well as identifying current areas of uncertainty where applicable.

3. BEHAVIORAL INTERVENTIONS AND COUNSELING

Counseling is the simplest form of intervention for tobacco cessation. This helps in increasing the motivation to quit and enhances the ability to handle the urge to use tobacco.

Various counseling strategies ranging from brief intervention to more in-depth counseling have been developed for physicians and such resources applicable in developing countries are now available (Reference: Helping People Quit Tobacco: A manual for doctors and dentists[1], Tobacco Treatment Dependence Guidelines[11]).

An outline of tobacco cessation intervention by a Psychiatrist (This is a generic one and can be modified as per patient's need)



FTND: Fagerstrom test for Nicotine dependence (smoking and smokeless)

MI: Motivational Interviewing (Developing discrepancy, Decision balance, self-efficacy, etc.)

3.1 Brief Intervention

Brief Intervention has been found very effective in the practice of smoking cessation. This intervention does not need much expertise and can be delivered by any health professional, preferably the treating doctor

irrespective of the settings. As the name suggests, the intervention is brief and simple.[1]

The important steps of intervention are[1]:

a. Advise all current tobacco users to quit

All physicians should advise their clients to quit tobacco. Simple advice to quit by the physician has been shown to increase the quit rate (OR 1.3, 95% CI 1.1-1.6) compared to placebo or no intervention.[18]The advice should be strong, relevant and personalized. It has been seen that specific advice linked to the patient's clinical condition works best.

Example: For a tobacco user recently diagnosed as hypertension…. (Hypertension, and CVD are known to worsen by continued tobacco use)

"Your blood pressure is high. I would like to monitor it before considering putting you on any medication. Right now, you will need to be careful with your diet, and make sure you learn how to handle tension. Your blood pressure control can get worse if you continue to use tobacco. Even if I need to put you on treatment for blood pressure in the future, remember that the treatment will be more effective if you stop using tobacco.."[1]

b. Educate about the addiction

It is important to understand that addiction is a brain disease and having craving, withdrawal symptoms are part of this illness.

c. Provide Brief Counseling

Making sure that help is available in case of any difficulty increases person's confidence. This also consists of fixing a quit date, making environmental manipulations, tackling withdrawal symptoms and handling relapses.

d. Offering Medications

Evidence is accumulating that providing medications improves the outcome even in the person who is not contemplating for complete quitting.

e. Follow up:

It is important to have a regular contact with the person.

3.2 Minimal intervention is also helpful

In a country like India, there is a pressure of time as well as a lack of expert counselors. In case of tobacco intervention, a minimal intervention lasting less than 3 minutes increases overall abstinence rates. At the same time more intensive intervention (more time spent) is likely to provide increase in abstinence rates. Four or more sessions are associated with better outcome as per the metaanalysis.[18]

3.3 Psychiatrist: Intensive Counseling

The psychiatrist, a mental health professional is well placed to provide intensive and multiple sessions counseling for tobacco cessation compared to of the brief counseling that is offered by physicians. This involves comprehensively addressing various psychosocial issues, multiple visits for a longer duration and involvement of other mental health professionals, i.e., psychologist or psychiatric social worker. Intensive interventions produce higher success rates than do less intensive interventions and there is a strong dose- response relation between counseling intensity and quitting success. In addition, the tobacco dependence interventions offered by specialists i.e. psychiatrist, represents an important treatment resource for patients even if they have already received tobacco dependence treatment from their own physician.[18]

The major components of intensive counseling are increase in duration of each session and multiple sessions that include detailed assessment and counseling (**Table 2**).

3.4. Motivational interviewing (MI)

The main component of MI is tilting the balance towards quitting tobacco. This can be achieved by discussing the issues with respect to advantages/ disadvantages of using and stopping tobacco. Developing discrepancy, eliciting motivational statements i.e. why should you quit? Expressing empathy, avoiding argumentation and supporting self-efficacy are important steps in MIs. This needs multiple sessions of counseling. The aim is to motivate the person for complete quitting or decrease the tobacco use. It is useful to provide educational booklet and keeping a future appointment for the tobacco users who are not currently willing to quit. (**Table 2**)

Table 2 : Enhancing motivation: a practical approach[19]

Stage of motivation	What will help	What psychiatrist can do
Pre-contemplation: Person does not want to stop using tobacco	Providing information about tobacco use and the benefit of quitting (Educational booklet)Helping the person to speak about tobacco use and also its impact to the people around including himself	Avoid confrontation.Educate about tobacco and other substances (in case he is abusing)Focus on rapport building.Encourage and appreciate any expression of the desire to quit tobacco (even in future)
Contemplation: Acknowledges that there is a problem. Is considering costs and benefits of tobacco use	Assessment of the client'sfeelings and thoughts abouthis/her tobacco use behavior	Facilitate (also provide further inputs) the analysis of pros and cons.Help in realistic appraisal ofthe good and bad things about continued use of tobacco.
Determination/ Preparation: Making decision to quit tobacco and feels the need to do something to it.	Choosing to give up tobacco and committing to specific goals	Reaffirm person's ability to make the change. (self-efficacy)
Action: Takes action to stop using tobacco	Achieving the goals by taking concrete steps.	Help him/her lay a definite plan of action

3.5 Relapse Prevention

Relapse is very common in tobacco use disorders. Hence relapse prevention is an integral part of psychosocial counseling. It is a state where an individual returns back to the previous pattern of tobacco use. There are multiple factors that can trigger relapses. Some of the common factors are mood (positive or negative), peer pressure, cues (internal and external), craving etc. (**Table 3**)

Table 3: Components of relapse prevention and intensive psychosocial counseling [18, 20]

Techniques	Examples
Identify the high risk relapse situations	Mood state, peer i.e. being around other tobacco users, drinking alcohol
Craving management	Identify the craving, using distraction, deep breathing, drinking glass of water, use chewing gum or cinnamon, urge surfing etc.
Increase in problem solving ability and coping skills	Learning cognitive strategies and behavioral interventions to reduce the cues. Anticipate the negative or trigger situations and work accordingly .
Life style changes	Time management to reduce stress, Improve quality of life. Keeping oneself busy. Staying in non-smoking locations.
Cognitive	Increase self-efficacy i.e. "I can do it" Encourage self visualisation as a non-tobacco user. Communicate care and concern. Instill confidence and explain the addictive nature of tobacco. Encourage to take credit and feel good for not using tobacco.

Psychiatrists are also well placed to address psychiatric comorbidities which may be an important reason for continuation of tobacco use.

Table 4: The comparison of efficacy of non-pharmacological therapies [8, 18, 21]

Type of intervention	Strength of evidence	Risk ratio (95% CI) (Placebo / no treatment:1)	No. of trials
Smoking cessation counseling			
Individual	**A**	1.39 (1.24-1.57)	22
Group	**B**	1.98 (1.60-2.46)	13
Telephone quit line	**B**	1.37 (1.26-1.50)	9
Physician intervention			
Brief advice to quit	**A**	1.66 (1.42-1.94)	17
Brief counseling	**A**	1.84 (1.60-2.13)	11

3.6 Use of Modern Technology

Telephone based intervention for tobacco cessation has been found to be effective. This can be a "quitline" or a proactive counseling process. Telephone based counseling has the advantage of easy accessibility, assured privacy and convenience. Proactive counseling, i.e., the counselor should initiate the call as well as fix the timing, make a planning as well as remind the client is more effective than providing only self help material[22] or a quitline.[23] The positive part of this approach is that proactive telephonic counseling increases the abstinence rates both in passive or actively recruited smokers.[24]

Internet based counseling is emerging as a treatment option in developed countries. Most of the internet based counseling also includes an offer NRT if required. Also, there is a component of telephone counseling incorporated in this. There is heterogeneity in different methods and studies in this area. To be effective, the counseling has to be tailored for the client and frequent automated contact is to be ensured.[25]

KEY RECOMMENDATIONS: COUNSELING

- *Counseling irrespective of intensity, type and frequency is effective (A)*
- *Brief intervention even lasting for few minutes is effective (A)*
- *Brief advice to quit by physician increases the chance to quit (A)*
- *Proactive telephonic counseling is better than ordinary quitlines (B)*

- *Tailor-made web-based counseling might be helpful (B)*
- *For people who are not very keen to quit, a clinician advice can enhance motivation and future attempt to quit (A)*
- *Combined pharmacotherapy and behavioral support increase smoking cessation (A)*

4: PHARMACOTHERAPY

Pharmacotherapy aims to reduce the intensity and quantity of tobacco use. The most effective drug is that which significantly reduces the craving, particularly in situations where tobacco is accessible. A unique issue in a country like India and others in South East Asia is that tobacco products are available in different forms apart from smoking. The common non-smoking forms are chewing tobacco *i.e. Gutkha, Khaini, Zarda, pan,* inhalation forms, *i.e. snuff* or paste forms i.e. *gudhakhu*. Gutkha contains tobacco along with areca nut. Studies from South East Asia suggest that areca nut dependence is also not uncommon.[26-28]

The literature regarding the efficacy of pharmacological agents has been mostly from cigarette smokers. There are a few emerging studies on smokeless tobacco particularly from *snus* users from Europe and USA. There is paucity of treatment studies on chewing tobacco (Gutkha, khaini). However, experience of tobacco cessation clinics in India in the last ten years on over 30,000 patients (predominantly smokeless users) suggests that adding pharmacotherapy improves the likelihood of tobacco cessation.[13]

4.1: Nicotine Replacement Therapy (NRT)

Nicotine Replacement Therapy (NRT) delivers nicotine which is safe and non-toxic. There are three predominant mechanisms by which NRT works, i.e., it reduces withdrawal symptoms, partially reduces the reinforcing effects of tobacco-delivered nicotine, and may provide some effects for which the patient previously relied on tobacco, such as sustaining desirable mood and attention states, making it easier to handle stressful or boring situations, and managing hunger and body weight.[29] NRT comes in five forms: gum, patch, lozenge, inhaler and spray. (**Table 5**) Nicotine patch has to be used once a day whereas others are to be used at different intervals.

The 4mg gum is available against prescription whereas the 2mg gum is available as over the counter.

Table 5: Nicotine Replacement Therapy used for tobacco cessation [8, 30-

Preparation	Dosage	Administration	Adverse effects	Advantage	Disadvantage
Nicotine Gum *2mg, 4mg* (Flavored with mint and that one similar to chewing tobacco)	*< 25 cig= 2mg every 1-2 hrly > 25 cig = 4mg every 1-2 hrly* (maximum: 24 gums/day) Duration: 12 wks Wk 1-6:1 piece every 1-2 h Wk 7-9: 1 piece every 2-4 h Wk 10-12: 1 piece every 4-8 h	*Chew and Park Method* (Chew until a tingling/peppery taste is obtained and park in the gap between gum and inner cheek. Continue till the sensation stops i.e. around 30 min) No drink 30 minute before or after the gum. Gum can be kept more than one hour in mouth.	Usually Safe Mouth Irritation, Jaw fatigue, Dyspepsia hiccup	Effective in controlling withdrawal symptoms. Concomitant use of tobacco does not cause any significant problem. Can be initiated without complete stoppage of tobacco use. User can control nicotine dose.	No significant anti-craving property while not using
Nicotine Patch 21mg, 14mg, 7 mg	*>10 cigarettes/day* d: 21 mg/day *<10 cigarettes* per d: 14 mg per d Duration : 10-12 wk Wk 1-6:21 mg/day or 14mg/day Wk 7-9: 14 mg/day or 7mg/day Wk 10-12: 7mg/day	Apply in clean, dry and non-hairy part of the body. Press the patch over the skin and press down on the margin. One patch per day. Do not stop using patch abruptly.	Local skin reactions (erythema,pruritus, burning), headache, sleep problem (insomnia/dreams)	Easy, as once per day use. Provides steady nicotine level.	Slow release of Nicotine. User cannot alter nicotine level in case of breakthrough craving. Can combine gum or any other NRT along with patch
Nicotine Lozenge 2mg, 4mg	*1st cigarette <30 min after waking: 4 mg* *1st cigarette >30 min after waking: 2 mg* Duration: 12 week Wk 1-6: 1 lozenge every 1-2/hours Wk 7-9: 1 lozenge every 2-4 hours Wk 10-12: 1 lozenge every 4-8 hours Maximum: 20 lozenges per day	Dissolve in mouth over 20–30 min. Do not bite or chew. No drink 30 minute before or after the gum.	Hiccups or heart burn	Similar to gum. Can be used with people having dental problems	No role in craving
Nicotine Inhaler 10-mg cartridge delivers 4 mg of nicotine per spray	*Usual: 6-16 cartridges per d* *Initially: 1 cartridge every 1-2 h* Duration: 12-24wks Taper in last 6-12 wks	Inhaled through the mouth. Patient should inhale into back of throat or puff in short breaths. Not inhaled into the lungs (like a cigarette) but puffed as if lighting a pipe; Open cartridge retains potency for 24 h. No food or beverages 5 min before or during use.	Mouth and throat irritation	Delivers nicotine rapidly. Mimics the *"hand to mouth"* ritual of a cigarette user. Controls the nicotine delivery.	Frequent puffing. Device is visible while using.
Nicotine Nasal spray	*1 spray (1 mg nicotine) in each nostril* Initial treatment is 1–2 doses per h, as needed. Typical dosing is 8–40 doses/d. Duration : 12-24wks	Nasal administration	Nasal irritation	Very fast delivery of nicotine Most rapid delivery of nicotine	Local irritation to nasal mucosa

NOTE: *There are no specific guidelines for the quantity of gum to be used for bidis and smokeless tobacco.*

4.1.1 Effectiveness of NRT

The recent meta-analysis collating data from 132 RCT studies with over 40,000 participants observed that NRT significantly increases the likelihood of tobacco abstinence compared with placebo (risk ratio [RR] 1.58; 95% CI, 1.50–1.66). The overall risk of long term smoking abstinence with different forms of NRT varies from 1.43 for gum to 2.02 for nasal spray (details in the **Table 6**).[21,32] NRT when used in the proper dose and duration, increases the long term abstinence by 50-70% irrespective of treatment setting or type of counseling or type of behavior therapy.

4.1.2 Initiation of NRT

The initial dose and type of NRT depends on the number of cigarette and how early a person takes first smoke as soon as he wakes up in the morning. There are two methods of advising to quit. One is "cold turkey" and the other is gradual reduction over a two week period. The NRT is usually initiated two weeks prior to target quit date.[33]

4.1.3 Smoking Reduction

Initiating nicotine patch during the phase of smoking reduction in preparation for a target quit date, has been shown to be effective and may improve self-efficacy for quitting. A meta-analysis including seven RCTs (2767 patients) reported that NRT and behavioral counseling is likely to double long term quit rate compared to placebo.[32,34] There is evidence that NRT can be effective when given without behavioural support [35]

4.1.4 Dose and Duration of NRT

Smokers using more than 25 cigarettes per day or with a Fagerstrom score for nicotine dependence (FTND)[5] (scale to measure the severity of nicotine addiction) of $\geq$6 are generally defined as highly dependent. This group needs a higher initial dose of NRT. Nicotine gum of 4mg is significantly effective in this group. However, a higher nicotine dose patch has not been found to be significantly effective compared to lower dose of patch.[21]

Once started, NRT should be used for a minimum of 8-12 weeks and then as long as necessary. Once the tobacco cessation is maintained, the NRT can be tapered as mentioned in **Table 5**.

NRT can also be used with the goal of reduction of smoking rather than complete quitting as mentioned above. In this scenario, the immediate goal

can be to reduce cigarette consumption by at least 50%, and the quitting goal should be reviewed after 3 months.[36]

Most of the guidelines recommend use of NRT for 12 weeks or less. The recent studies have looked at the long term continuation of NRT and the effect on cessation. An RCT comparing 6 months versus 8 weeks showed that longer treatment with nicotine patch was superior.[37]

4.1.5 Adverse effects of NRT

NRT use is usually well tolerated. The three most commonly reported adverse effects of NRT in observational studies were headache, nausea and/or vomiting, and other gastrointestinal symptoms. Orally administered NRT was associated with mouth and throat soreness, mouth ulcers, hiccoughs and coughing. Pooled evidence specific to the NRT patch found an increase in skin irritation (OR 2.80; 95% Cl, 2.28-3.24). Coughing has been observed to be more likely with nicotine nasal spray and nicotine inhaler (OR=2.89; 95% CI, 1.92–4.43).[38]

There was no statistically significant increase in anxiety or depressive symptoms associated with NRT use, making it a safer option in comorbid psychiatric disorders.[38]

4.1.6 Combination of NRTs

The delivery of NRT varies as per the formulation. The standard practice is to prescribe a single NRT. The combination of long acting nicotine patch (slow release, one in 24hours) along with a short acting formulation (gum, spray, inhaler) has been found to be effective. The short acting NRTs help in controlling urges and are thereby likely prevent breakthrough tobacco use in the background of nicotine steady state maintained by long acting NRT. A meta-analysis of NRT combinations compared with either NRT monotherapy or no NRT reported an advantage for combination NRT (RR 1.35; 95% CI, 1.11–1.63)[11,21,32] Combination of nicotine lozenges + patch and bupropion + lozenge was found to be effective than monotherapy. This beneficial effect is seen both in research and as well as in primary medical settings.[39, 40]

The effectiveness of NRT appears to be largely independent of the intensity of additional support provided to the individual.[21]

In a large tobacco cessation clinic based study from India, use of NRT was reported to be 10% (2,362 out of 23,320 patients) along with behavior counseling.[13]

Non Nicotine Pharmacotherapy

4.2 Antidepressants

Nicotine withdrawal produces a depression like state and can precipitate a depressive syndrome. Nicotine may have antidepressant effects that maintain smoking, and antidepressants may substitute for this effect. A number of antidepressants including bupropion, doxepin, fluoxetine, imipramine, moclobemide, nortriptyline, paroxetine, sertraline, tryptophan and venlafaxine have been studied. The best evidence has emerged for two antidepressants: bupropion and nortriptyline.[41]

4.2.1 Bupropion

Bupropion is an atypical antidepressant that has been associated with attenuation of the withdrawal symptoms and decreases the rewarding effect associated with smoking. This is achieved through antagonizing the nicotine receptor sites and inhibiting the reuptake of dopamine and nor-epinephrine.[42] Sustained release bupropion is commonly used for tobacco cessation.

Effectiveness

Systematic reviews and meta-analyses collating data from 49 RCT studies recommend bupropion as being efficacious for smoking. When used as the sole pharmacotherapy in 36 RCTs (n=11,140), bupropion significantly increased long-term (e>6 months) smoking abstinence (RR=1.69; 95% CI, 1.53–1.85). But there is insufficient evidence regarding addition of bupropion with standard dose or high dose NRT with regard to increase in benenfit[41,43].

Bupropion is equally effective for tobacco cessation in patients who are depressed or predisposed to depression as well as those who are not depressed.[44] An RCT of 199 smokers with either current or past depression, bupropion or placebo was added to nicotine patch and group cognitive behavioral therapy. Abstinence was associated with increased depressive symptoms, regardless of bupropion treatment. Bupropion appeared to have no effect for improving smoking abstinence when added to nicotine patch and behavioral support for smokers with current depressive symptoms or past depression.[45]

Dose and adverse effects

The recommended dose is 150 mg at initiation, increased to 150mg twice a day in a week's time. Bupropion is to be initiated a week to 10 days before the planned quit date.

Although an effective medication, its wide acceptance and use have been limited by side effects that include anxiety, headache, insomnia, and irritability and a rare propensity to induce seizures (contraindicated in prior history of seizure), estimated to occur in 1 out of 1000 patients. RCTs do not report any severe side effects except risk of seizure. Pharmacovigilance reports from post marketing surveillance of 6,98,000 people who have received bupropion for smoking cessation reported a total of 475 serious adverse events (SARs), including 21 deaths. Seizures, angioedema and serum sickness-like reactions were the most frequently reported SARs. The median time to onset of the adverse effects was within 2 weeks of treatment initiation indicating that prescribers should monitor patients exposed to bupropion more carefully during the first 2 weeks of treatment.[46]

Earlier studies had reported unexpected increase in blood pressure as an adverse effect of bupropion. A recent RCT of 4 weeks of placebo or bupropion (in doses of 150, 300, or 400 mg per day) suggests that blood pressure elevations are not common.[47]

Indian studies

The studies from India have not consistently found bupropion effective among smokers.

Two clinic based studies among treatment seekers for chest ailments (open ended and one small RCT) reported effectiveness for bupropion compared to counseling. In a clinic based study in India, 372 patients were provided counseling and 87 patients received bupropion along with the counseling. The study found higher abstinence rate in the medication group. This was an open label non-randomized study.[48] In a small RCT for seven weeks, 30 smokers were randomized to either 300mg bupropion sustained release or placebo for seven weeks. They were followed up initially weekly and then monthly till the end of 16 weeks. The continuous abstinence rate between the two groups was not significant after 4 weeks. The point abstinence rates did not differ significantly at each week.[49]

Findings from 23,320 patients who visited the Tobacco Cessation Clinic across the country suggest that bupropion is the most common medication prescribed to them (less than 20.2%).[13]

4.2.2 Nortriptyline

Nortriptyline, a tricyclic antidepressant has been used for smoking cessation.

The data from four RCTs suggest results similar to that of bupropion (four trials, OR 2.34, 95% CI 1.61 to 3.41) i.e. doubling the chance of quitting. Although a tricyclic, nortriptyline was not associated with any significant side effects in these four small trials.

Nortriptyline is economical and its once-a-day dosing makes it a potentially useful drug that is probably underutilized. Its use has been limited by common side effects, including drowsiness, dry mouth, dizziness, constipation, and cardiac dysrrhythmias in susceptible patients. Typically, nortriptyline is begun 10 to 28 days in advance of the anticipated quit date and titrated from a starting dose of 10 to 25 mg a day to 75 to 100 mg daily.

4.2.3 *Other antidepressants*

There were six trials of selective serotonin reuptake inhibitors: four of fluoxetine, one of sertraline, one of paroxetine, one of venlafaxine and one trial of the MAOI. None of these detected significant long-term benefits for tobacco cessation.

4.3 Nicotine partial receptor agonists

The use of nicotine partial receptor agonists has been a recent addition for the treatment of smoking cessation. Nicotinic receptors, densely present in the ventral tegmental area of the midbrain, play a vital role in the activation of the reward system and dopamine release. This reinforces the process of nicotine addiction. Agonist drugs help people to stop smoking both by maintaining moderate levels of dopamine to counteract withdrawal symptoms (acting as an agonist) and reducing smoking satisfaction (acting as an antagonist). There are three agents in this group: varenicline, cytisine, and dianicline. Varenicline has been in use for the last six years but is expensive. Cytisine is cheaper and is being used in countries like Bulgaria and Poland for the last 40 years.[50]

4.3.1 Varenicline

Effectiveness

Systematic reviews and meta-analyses collating data from 14 RCT studies involving 6166 people recommend that varenicline is effective for smoking.[51] Continuous or sustained abstinence at six months or longer for varenicline at standard dosage versus placebo showed an RR of 2.27 (95% CI 2.02 to 2.55). A low or variable dose of varenicline was twice more effective than placebo.

Compared to bupropion, the abstinence rate at the end of one year from varenicline was better (OR 1.52, 95% CI 1.22 to 1.88, 3 RCT, 1622 people). Varenicline was found to be slightly superior to NRT in two trials (RR of 1.13, 95% CI 0.94-1.35; 2 trials, 778 people).

Recent studies also report the robust effectiveness of varenicline in smokers with smoking related disorders i.e. COPD and CVD. The study involving 714 smokers with stable CVD,[52] the abstinence rates with varenicline was 6 time higher at the end of 12 weeks and continuous abstinence rate for end of year was three times more. In a similar multicentred study on COPD patients[53], the abstinence rate was 8 times higher for the initial period (9-12wks) and 4 times greater at a later period (9-52wks) compared to placebo.

The effectiveness of varenicline beyond 12 weeks and role in subsequent relapse prevention is not clear.

Dose and Adverse effects

Varenicline is usually started a week before the quit date. It is started at 0.5 mg daily for 3 days and then increased to twice daily for 4 days. The medication is then increased to its recommended dose of 1 mg, twice daily. The usual duration is for 3 months and can be continued for the subsequent 3 months if required (if there is partial improvement).

The most common adverse effect reported is nausea. This decreases with the slow titration of the medication. There are two important recent warnings i.e., cardiac events and behavioural change with varenicline. A meta-analysis reported a small but statistically significant increase in serious cardiovascular adverse events, i.e., ischemia, arrhythmia, congestive heart failure, sudden death or cardiovascular-related death in subjects receiving varenicline[54] (varenicline 1.06% vs. placebo 0.82%; OR1.72; 95% CI, 1.09–2.71). In view of low absolute increase in risk for serious cardiovascular events, compared with the large benefit for smoking cessation, current opinion appears to suggest varenicline may be used in stable CVD.[32]

An increased risk of behavioral change, agitation, depressed mood and suicidal ideation has been reported with varenicline. However, a recent meta-analysis (11 clinical trials with over 10,000 participants, 7000 of whom received varenicline) and post-marketing surveillance (80,660 smokers attempting to quit, 10,973 with varenicline) did not show any increased psychiatric or behavioral change. The mood changes are comparable to that of NRT.[51, 55, 56]

Still, in view of possible links of varenicline to serious side effects i.e. depressed mood, agitation and suicide, patients need to be in regular observation for mood status.

There is a need for a long term study (>12 weeks) with regard to its efficacy in smoking and independent community based study for the associated side effects.[51]

Severe Mental Illness

In a prospective 12 week open ended study among 112 smokers (>10cig/day) with schizophrenia,[57] varenicline was found to be effective in reducing the urge and reduction in withdrawal symptoms. Fifty-three participants (47.3%) achieved e>2 consecutive weeks biochemically-verified continuous tobacco abstinence at week 12, and 38 participants (34%) achieved e>4 consecutive weeks of continuous abstinence at week 12. There was decrease in depressive and psychotic symptoms during the study period. The limitations were of small sample size and high attrition rate (33%).

One RCT among smokers with schizophrenia and schizoaffective disorder reported that varenicline was well tolerated and associated with higher smoking cessation rates compared to placebo at the end of 12 weeks.[58] The open label studies done among persons with known schizophrenia and mood disorders has not shown any serious adverse effects.[57]

4.3.2 Cytisine

Cytisine, a partial agonist, is similar to varenicline in its mechanism. This drug has been in use for quite some time in countries like Bulgaria and Poland. There are at least 10 studies, including 3 placebo controlled reporting its effectiveness.[59]A recent 12 weeks RCT compared cytisine to placebo. The rate of sustained 12-month as well as 7-day point prevalence of abstinence at the 12-month follow-up was significantly high in the cytisine group compared to placebo. The primary outcome, abstinence for 12 months after treatment ended, was 8.4 percent in Cytisine compared to 2.4 percent in placebo group. Cytisine was prescribed for 25 days i.e. six 1.5-mg tablets per day (one tablet every 2 hours) for the first 3 days, five tablets per day for 9 days (days 4 through 12), four tablets per day for 4 days (days 13 through 16), three tablets per day for 4 days (days 17 through 20), and two tablets per day for the final 5 days (days 21 through 25).[50] Cytisine, a low cost

drug, may increase the abstinence rate but there is a need for further studies to establish its effectiveness and safety.[51]

4.4 Clonidine

Clonidine is an alpha 2 adrenergic agonist and primarily used for hypertension. It suppresses the withdrawal symptoms of nicotine and probably has anti-craving property also, although the exact mechanism is not known. Apart from oral use, the transdermal form has also been tried for tobacco cessation. The overall effectiveness from 6 RCTs was OR: 1.89 (95% CI 1.30 to 2.74).[60] In spite of the beneficial effect close to other agents, its use is restricted because of side effects especially sedation, fatigue, orthostatic hypotension, dizziness, and dry mouth.[61]

Table 6

Type of intervention	Strength of evidence	Risk ratio (95% CI) (Placebo / no treatment:1)	No. of trials
Any NRT		1.58 (1.50 to 1.66)	132
Nicotine gum	A	1.43 (1.33-1.53)	53
Nicotine Patch	A	1.66 (1.53-1.81)	41
Nicotine Spray	A	2.02 (1.49-3.73)	4
Nicotine Inhaler	A	1.90 (1.36-2.67)	4
Nicotine Lozenge	B	2.00 (1.63-2.45)	6
Bupropion Sustained Release	A	1.69 (1.53-1.85)	36
Varenicline	A	2.27 (2.02-2.55)	14
Nortriptyline	A	2.03 (1.48-2.78)	6
Clonidine	A	1.63 (1.22-2.18)	6

Key Recommendations: Pharmacotherapy[18, 32, 36, 39, 41, 51]

KEY RECOMMENDATIONS: PHARMACOTHERAPY

- *Interventions that combine pharmacotherapy and behavioural support increase smoking cessation success compared to minimal intervention or usual care (A)*
- *Pharmacotherapy for tobacco dependence treatment is safe, effective and significantly increases the chance for long-term*

smoking abstinence compared with quit attempts unaided by pharmacotherapy (A)·

- *NRT is very safe and should be offered to all in proper dose and for duration (A)*
- *The effectiveness of NRT appears to be largely independent of the intensity of additional support provided to the individual (A)*
- *Combination of multiple form of NRT (long duration i.e. Patch) with short duration (gum/spray) increase smoking abstinence (B)*
- *NRT should be considered as an aid to smoking reduction even if the person has not firmly decided to quit (A)*
- *Bupropion and nortriptyline are effective agents for smoking cessation (A)*
- *Bupropion is effective irrespective of whether the person is currently or history of depression.*
- *Varenicline is most effective agent for smoking cessation (one and half time more than bupropion and twice more than NRTs) (A)*
- *Varenicline association with neuropsychiatric and behavioral change is a concern (A)*
- *Varenicline can be used inpatient with stable psychiatric disorder under close monitoring (B)*
- *Nortriptyline, clonidine and cytisine may be the low cost treatment options (C)*

5. SMOKELESS TOBACCO: A MAJOR CONCERN IN INDIA

5.1 Introduction

Smokeless tobacco (SLT) use is on rise in developing countries including India. Even in developed countries, its use has not decreased, unlike smoking. Smokeless tobacco is used in various forms in different countries.[62]

In India, the use of smokeless tobacco is higher than smoking. In the West i.e. Europe and USA, the predominant form of SLT is Snus. The major problem of SLT is the presence of carcinogens i.e. tobacco specific

nitrosamines. In India more than 50% of oral cancer is attributable to intake of smokeless tobacco.

In India, the data has shown that 35% smokeless tobacco users had tried to quit in past 1 year and 46% wanted to quit the tobacco.

5.2 Intervention

Pharmacological treatment of SLT has been derived from the medication used from smoking. Nicotine gum, patch and lozenge, varenicline and bupropion SR have been evaluated for the treatment of SLT users. Nicotine replacement therapy (4 studies on patch, 2 studies on gum, 2 studies on lozenges) demonstrated the overall effectiveness as odds ratio 1.4 (95% CI 0.91-1.42) compared with placebo for increasing long term (>6 months) tobacco abstinence rates. This is less than that that achieved in the treatment of smoking. Despite this limitation, nicotine patch and gum have shown consistently significant decrease in withdrawal symptoms.[62, 63]

Varenicline has been shown to significantly increase the continuous abstinence rate as well as point prevalence rate among snus users (Odds Ratio [OR] 1.6, 95% CI 1.08 to 2.36). There needs to be further studies (current evidence is only from 2 RCTs) as well as from tobacco chewers.

Bupropion use has not been associated with better abstinence rate compared to placebo in two published RCTs (OR 0.86, 95% CI 0.47 to 1.57).[64, 65] Behavioral intervention incorporating either telephone counseling, an oral examination and feedback about any SLT induced mucosal changes, or both, are likely to improve the outcome.[63]

In summary, along with behavioral counseling, NRT increases short term abstinence and varenicline seems useful for long term abstinence. But the effect size is less than that of smoking. There is a need for further trials in this area to in order to reach any firm conclusions.

In a multicenter naturalistic study of 23320 patients from India, 65.5% were reported as chewers. These groups were poor and less educated than smokers. All of them receive some form of behavioral counseling. The use of nicotine gum as well as bupropion was low. At the end of six-week follow up, 36% had either quit tobacco or reduced the use by 50%. Less than 20% received pharmacotherapy. Among men, use of smokeless tobacco and younger age were associated with good outcome. Behavioural counseling combination with pharmacotherapy was more useful. Having longer term contact was

associated with better outcome and increasing the motivation to quit tobacco in Indian setting.[4, 13]

KEY RECOMMENDATION: SMOKELESS TOBACCO

- *Most research is on "Snus" and no study on chewing tobacco· Varenicline and NRT are shown to be effective (A)*
- *NRT increases short-term abstinence but only varenicline seems effective in long term abstinence (B)*
- *Bupropion not significantly associated with increased tobacco abstinence (B)*
- *Behavioral counseling and long term follow up increases the abstinence rate in chewing tobacco (B)*

6. SPECIAL CONDITIONS

6.1 Pregnancy and Breast Feeding

All pregnant women should be advised to stop quitting in view of the detrimental effect on the fetus. Counseling is the first line of intervention. NRT should be considered if the counseling or behavioral intervention fails. The use of bupropion or varenicline[66] is not recommended.

6.2 Co-morbidity (Psychiatric Disorder)

Patients with schizophrenia as well as other severe mental disorders smoke more than the general population. Although the studies from India had showed the prevalence of smoking is not more than the general population, smoking related morbidity and mortality in patients who smoke can be prevented by offering smoking cessation.

Bupropion has been found effective as well as safe in smokers with schizophrenia. Meta-analytic studies comparing bupropion with placebo showed that smoking cessation rates after bupropion were significantly higher than placebo at the end of treatment RR of 2.84 (seven trials, N=340; 95% CI 1.61 to 4.99). The effectiveness of NRT or psychosocial intervention is not proven.

Prospective reports, case series and case reports suggest that use of varenicline in stable patients with schizophrenia or schizoaffective disorder is safe.[57,58] Although there are reports of increased use of varenicline among

patients with psychiatric illnesses, it needs careful monitoring as there are also reports of exacerbation of psychosis and worsening of mood symptoms with varenicline.[67]

7. CONCLUSION

Individual counseling along with use of nicotine gum for tobacco cessation has been in practice for quite some time. Recent and better understanding in neurobiology has paved the way for development of partial nicotine receptor agonists. In spite of this, the treatment outcome has been modest. One of the major challenges has been lack of wide spread use of tobacco cessation interventions.

Psychiatrists can play a major role in tobacco cessation. Well designed controlled studies show that behavioral and pharmacological interventions are effective. The challenge in our country is implementation of evidence based strategies i.e. counseling, motivational interviewing and use of different pharmacotherapies. One option is to provide brief counseling and offer nicotine replacement therapy to all the tobacco users. Intensive psychosocial intervention as well as medication like bupropion, varenicline etc. can be considered in specialized settings.

In view of the huge tobacco related morbidity, the psychiatrist can play an important role in training human resources, i.e., physicians, dentists, nurses, counselors to deliver low cost brief psychosocial interventions.[23]

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CLINICAL PRACTICE GUIDELINES (CPG) FOR THE MANAGEMENT OF INHALANT USE DISORDERS

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On behalf of IPS-SS-SUD

2014

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EXECUTIVE SUMMARY

The non-medical use of inhalants for their mind-altering effects is currently a worldwide problem. However, inhalant use disorders continue to be under-researched both in western and Indian settings, though there has been some progress in recent times. Based on the existing data, the current impression is that inhalant use occurs mostly in economically deprived children but increasingly, children from other socioeconomic strata are now being seen in treatment settings. The general view is that inhalant use is on the rise and is not limited to the metropolitan cities only but is becoming more widespread. Ink eraser fluid, petrol and glue have been some of the inhalants used in India. Literature suggests that risk factors for inhalant abuse are child abuse, family instability, lower socioeconomic status, dropping out of school, delinquency, suicidal behaviour and anti-social personality and many of the above mentioned factors have been reported in Indian studies as well.

A substantial proportion of inhalant users who report to treatment settings are inhalant dependent as per the few studies conducted in the country. The diagnostic criteria in DSM IV (unlike ICD-10) do not list withdrawal symptoms as diagnostic criteria although several studies including some of the Indian studies have reported withdrawal symptoms. Inhalant withdrawals are experienced by regular users of inhalants, usually within 24 hours of cessation. Often, the withdrawal symptoms are mild, and comprise of psychological and few physical symptoms, which may last from 2-5 days. Craving for inhalants may last for a few weeks. The variations in the nature of withdrawal symptoms according to specific inhalant products and types need to be examined more closely.

General principles of management

Care must be taken not to violate the patient's rights at any stage of treatment. Patients should be treated with respect and dignity by the treating professional as well as staff members. Only the safe and effective treatment options must be offered based on evidence and

expert consensus. Every attempt must be made to ensure confidentiality. Any private or personal information disclosed in confidence to the treating professional should not be disclosed to parents (unless there is a genuine threat to safety).

Ideally the adolescents using inhalants and other drugs should be treated in a specialist setting, with services geared towards younger people (except for occasional or early users who may receive intervention in community settings). The patients using inhalants may receive various levels of care, ranging on a continuum of service intensity from brief, early intervention, out-patient treatment, intensive out-patient treatment, residential/in-patient treatment and medically managed intensive in-patient services.

Out-patient treatment is particularly suitable for patients:

(a) If the use is occasional or less frequent
(b) If the use is of shorter duration (few months)
(c) If there is mild or moderate dependence
(d) If the treatment is being sought for first time, no prior failed attempts
(e) If there is no significant health damage
(f) If there is no concurrent abuse/dependence on other substances
(g) If the functioning at school or home is relatively preserved
(h) If there is a good social support system
(i) If patient stays in close proximity of treatment services

Inpatient treatment covering the extended detoxification period may help to regain some control over the behavior, and help the patient to deal with cues and cravings. In-patient treatment is more appropriate:

(a) If there is a severe dependence
(b) If the patient is using inhalants for a prolonged duration (few years)
(c) If there are multiple failed abstinent attempts in the past
(d) If there are significant health complications
(e) If there is a concurrent use of multiple other substances

(f) If there is severe dysfunction at home or school

(g) If the family support is absent/minimal, and/or presence of familial psychopathology interfering with treatment and care

(h) Geographical distance from treatment centre

The goal of treatment in case of inhalant users is complete abstinence. This is especially in view of severe and life-threatening health risks which may occur with single or repeated use of inhalants. However, it is also acknowledged that inhalant users are one of most elusive, and difficult groups to retain in treatment. Therefore, while working for an ultimate goal of abstinence, these users must also be provided with the necessary health education aimed at harm minimization in order to reduce the risks associated with inhalants.

Immediate goals may be establishment of rapport, detoxification and intervention for a psychosocial and medical crisis. Short-term goals may include management of co-morbid conditions and re-integration with family. Long-term goals consist of relapse prevention, vocational skills acquisition or an improvement in overall quality of life. After the initial phase of treatment lasting few weeks, the long term psychosocial treatment can be initiated once the patient is comfortable and more receptive. It should be continued for a prolonged duration, possibly as long as 2 years.

Assessment

Purpose of assessment in inhalant users is to assess the severity of inhalant use, detect medical/psychiatric symptoms, make a diagnosis, assess for cognitive deficits, assessment for health damage and formulation of a management plan. The detailed assessment should be commenced only if the patient is comfortable, and not in acute intoxication or withdrawal state. Screening for inhalant use must be employed in all health care and community settings Assessment of patients using inhalants should include a thorough history and examination, assessment for psychiatric comorbidites, assessment of health damage, neuropsychological assessment and laboratory investigations (to detect inhalants, if available).

Management of Inhalant Intoxication

The treatment recommendations have been summarized below :

- Basic supportive case should be offered to all inhalant users
- Ensure safety
- Careful monitoring of the intoxicated patient should be done on a frequent basis till symptoms resolve, on following parameters:
  - blood pressure
  - pulse rate
  - respiratory rate
  - temperature
  - oxygen saturation
  - orientation to time, place, person
  - level of consciousness
  - changes in mood and behavior
- Environment should be calm, quiet and reassuring, with minimal stimulation (to reduce the risk of cardiac arrhythmias and arrest which may be precipitated by undue alarm)
- Speak in a calm, non-threatening voice
- Physical restraints should not be used
- Use of sedatives should be avoided as they can potentiate the inhalant effects, unless it is absolutely necessary to ensure safety or reduce severe agitation
- Paracetamol may be given for headache, if required
- Complications, if any, resulting from inhalant use (e.g. metabolic acidosis) must be treated by specific treatment measures after appropriate referral/consultation
- Emergency medical care should be arranged or provided immediately if there are any danger signs e.g. breathing difficulty, circulatory failure, loss of consciousness.
- Patient can be discharged from medical care (under supervision of a guardian) when the symptoms have fully recovered (usually < 4-6 hours if uncomplicated) and there is no discernible

abnormality in orientation, alertness, mood, behavior, vitals and motor functions.

- Advise the family member or caregiver to keep monitoring the patient for at least 24 hours

Treatment Recommendations for Inhalant Withdrawals

Available literature on existence of inhalant withdrawals is recent and still emerging. There is an insufficient published literature on treatment of inhalant withdrawals. Specific treatment recommendations for this section were formulated mainly on the basis of clinical experience, expert opinions and consultation with expert recommendations in other parts of the world [IV].

The treatment recommendations [D] have been summarized below:

- Ensure a quiet and supportive environment
- Advice to minimize the stimulation for patient, in order to reduce anxiety and agitation
- Ensure adequate rest and sleep
- Ensure hydration, by means of adequate oral fluids; and regular meals.
- Pharmacological treatment should be on symptomatic basis only, with close monitoring.
- Analgesics (e.g. paracetamol, ibuprofen) can be given for headache or somatic pain/s.
- Benzodiazepines (e.g. lorazepam) may be used to manage the anxiety, agitation and sleep disturbances, however their use should be restricted to a short period. Gradual taper is advised to minimize the discomfort to patient.
- In case of in-patients, monitor the vitals regularly (blood pressure, pulse rate, respiratory rate, temperature) and supervise the need and effects of medications.
- Monitor for any sudden change in patient's state (hallucinations, seizures, breathing problems, hypervigilance, unusual agitation etc.), which may need immediate medical assessment and referral.

Inhalant withdrawal symptoms can be managed by basic supportive care and symptomatic medical management. Majority of patients who use inhalants can be treated in the out-patient setting, with frequent follow up visits in the initial phase of treatment. Admission may be required (with attendant, if the patient is minor) particularly for patients who have a co morbid mental or physical disorder or are polydrug users. Plan of management should be governed by the patient report, account of family member/s and objective assessment by the clinician.

Treatment Recommendations for Psychosocial Treatment

Most studies on psychosocial intervention in inhalant users are case series or uncontrolled studies. Only one randomized controlled trial (CBT based brief intervention compared to simple education) is available. However, four types of interventions appear to merit a closer examination for inhalant users: CBT based brief intervention, family therapy, activity-based programmes and Indigenous-led residential approaches. Extrapolating from literature on adolescent substance use disorder, three approaches, which are (a) Family Therapy, (b) Cognitive Behavioral Therapy (CBT), and (c) Motivational Enhancement Therapy/CBT (MET/CBT) have shown the best outcomes in adolescent substance use disorder. No clinical trials or case series were available specific to use of Brief intervention/ Motivational Interviewing (BI/MI) for inhalant users. Evidence for effectiveness of BI/MI can be extrapolated from several methodologically sound studies demonstrating its effectiveness for adolescent substance use. Harm reduction, although is not considered as a mainstream treatment approach in the context of inhalant use, can be one of the steps to reduce the risks associated with inhalant use. It has also been incorporated in other clinical guidelines as well and includes the following messages-

- Do not use inhalants with a bag on the head (*bagging*) to avoid suffocation
- Avoid using inhalants in secretive, enclosed spaces e.g. cupboards as consciousness may be lost due to inadequate oxygen supply

- Avoid use of inhalants when you are smoking or near a lit cigarette or lighter
- Do not drive (for the next several hours) after using inhalants
- Avoid concomitant use of other drugs to prevent overdose
- Avoid using inhalants while alone
- Use inhalants from small bottles with small surface areas to minimize exposure
- Do not use inhalants immediately before exercise or physical exertion to reduce risk of arrhythmias and sudden death
- If someone is using inhalants, do not unnecessarily alarm or chase or try to hold them if they are struggling, to reduce risk of sudden death which is more common if heart rate is elevated
- A family member or peer who has used inhalants must be closely monitored for at least 6 hours to ensure his/her safety.
- Call emergency medical services if the person shows unusual symptoms or behavior, e.g. agitation, seizure, disorientation or loss of consciousness.

In order to formulate the recommendations for psychosocial intervention evidence from studies on inhalant users, extrapolated evidence from adolescent substance use treatment, expert consensus based recommendations were taken into consideration.

The key recommendations are:

- Psychosocial treatment should be offered to all inhalant users[S]
- Brief Intervention, using motivational interviewing, should be provided to all inhalant users, as and when, there is an opportunity or contact with health professionals [B]
- Targeted education must be provided to all inhalant users (and their families) aimed at provision of information about the harmful effects of inhalants, harm minimization, management of intoxication and resources to get more information [S]

- Consider cognitive-behavioral therapy (CBT)-based brief interventions for patients with inhalant use disorders [Ib, A]
- Consider family-based approaches for all patients with inhalant use disorders, wherever family is available [IIb, B]
- Life-skills based approaches should be employed for all inhalant users, preferably in a group setting, alongside other interventions [IIb, B]
- Supportive psychotherapy should be provided to patients with inhalant use disorders. [IIb, B]
- General (patient-centered) counseling and Narrative therapy can be used for patients with inhalant use disorders. [IV, D]
- Participation in activity- and engagement-based approaches should be encouraged, wherever feasible, alongside other interventions[III, C]
- Residential rehabilitation approaches may be used only for chronic, heavy users or poly substance users, when other treatment interventions have been unsuccessful. [IV, D]

Applicability

Given the paucity of evidence base, it will be difficult to comment on which of these approaches Family therapy/CBT/Life skills/Supportive psychotherapy may be preferred in a given patient. In a clinical setting in India, avenues for receiving training related to the above mentioned approaches is an important clinical consideration. Familiarity in dealing with clinical issues in adolescents with psychiatric disorders or in adult substance users are important, however there may be important differences. The role of family in adolescent substance users is much more important than adult substance users. The dependence of the child on the family for meeting his physical needs is much more pronounced in children. In children who come from the lower socioeconomic strata, the parents very often lack the psychological orientation to understand psychosocial intervention as a treatment modality and are looking for "pills" as treatment. Besides this, frequent visits to the clinic for psychosocial intervention can be challenging

for them because it may entail losing a days' wages. In spite of these constraints, it is possible to engage the patient and the family in the treatment process. It is important for this purpose to identify one or more key family members who can be educated about the nature of the disorder, the treatment process and recovery.

When dealing with underprivileged children living on the streets who constitute a substantial percentage of inhalant users, family members are often absent and NGOs may play the role of surrogate guardians.

Treatment Recommendations for Long term pharmacotherapy

Available literature on pharmacological treatment of inhalant use disorders is almost non-existent and only two isolated case studies are there (one on Lamotrigine and one on Buspirone). There is an insufficient evidence for using a pharmacological agent for long term treatment.

Management of Co morbid conditions

There is no research study for treatment of co morbid mood and anxiety disorders, and only one retrospective study for treatment of co morbid conduct disorder. Treatment of inhalant-induced psychotic disorder has been described in a few case reports and one randomized controlled trial. [I] However, it was considered that haloperidol has been, more or less, replaced by use of atypical antipsychotics over the past decade. Therefore, the findings from this randomized trial may not be relevant or applicable in current context especially since carbamazepine may have a range of adverse effects of its own.

In absence of a evidence base, following recommendations are made on basis of expert consensus/opinions/experiences. [IV]

- The management of inhalant-induced psychiatric disorders should be guided by the same general principles as in management of dual diagnosis patients. Generally, these patients should be treated by a specialist.
- Careful history should be taken to assess for psychiatric conditions with onset during childhood and adolescence e.g. attention deficit/ hyperactivity disorders, learning disorders, oppositional defiant disorder, conduct disorder etc.

- In view of a high prevalence of psychiatric comorbidites, the mental state examination should be carefully conducted in all chronic inhalant users to look for any evidence of mood, anxiety, psychotic or cognitive symptoms.
- Inhalant-induced psychiatric disorders are likely to subside with supportive treatment and maintenance of abstinence. Specific psychotropic medications are not warranted, unless the symptoms are severe, risky or life-threatening.
- Inhalant users are more likely to have underlying neurological damage, and consequently, may be more susceptible to develop tardive dyskinesia and other adverse effects with use of typical antipsychotics. Typical anti-psychotics may be avoided for treatment of psychotic disorders in inhalant users.
- All medications must be started at low dose and increased only gradually (*start low, go slow*) with close monitoring, as chronic inhalant users may have neurological, cognitive, renal, hepatic or other impairments, which could be worsened.
- Careful consideration must be done for choice of a particular medication, including the full range of adverse effects, possible interactions with other drug/s. other substances of abuse or its impact on comorbid health condition/s in an inhalant user.

1. SCOPE AND SEARCH STRATEGY

1.1 Scope

This Practice Guideline aims to provide evidence-based and pragmatic guidelines for management of patients with inhalant use disorders. The practice guidelines are meant to facilitate the treatment decisions primarily in clinical or hospital settings. However, some interventions as described later have been found to be useful in the community settings as well.

The Guideline has reviewed the interventions which are in common clinical use as well as those with limited or only emerging evidence. Wherever the data was limited, some extrapolations had to be made from literature on treatment interventions for adolescent substance use. Such extrapolations and key areas of uncertainty have been clearly indicated in the document. As inhalant use is primarily seen in younger population (children and adolescents), relevant issues pertaining to assessment and treatment of adolescent patients have been briefly mentioned. However, a detailed discussion on management of adolescent substance use was out of the scope of this guideline. The guideline deals primarily with management of Inhalant use disorders, though a brief sub-section (3.7) has been included to cover treatment of inhalant induced psychiatric conditions.

1.2 Search Strategy

Relevant literature was identified through a MEDLINE literature search, using PubMed. Literature was searched for a period between Jan 1950 and Nov 2012 restricting to human studies using Search string#1 (inhalant OR solvent OR volatile-substance OR toluene OR correction-fluid OR glue OR petrol OR gasoline OR nitrites OR aerosol OR anesthetic gas OR nitrous oxide) AND Search string#2 (use OR misuse OR abuse OR harmful use OR dependence OR addiction OR intoxication OR withdrawal OR tolerance OR craving). This yielded a total of 22,744 references covering the MeSH terms and all search fields. Search was repeated after adding the Search string # 3 (assessment OR investigation OR treatment OR intervention OR management OR detoxification OR counseling OR therapy OR care OR rehabilitation), which yielded a total of 11,382 references and when search was restricted to title/abstract, there were 652 references. With “Inhalant abuse” as a subject heading/ descriptor (found under Substance-related

disorders in MeSH database), a total of 280 references were retrieved. Available search results were filtered for article types (meta-analysis, systematic reviews, randomized trials, controlled clinical trial, clinical trial etc) in order to identify the methodologically robust articles. References were screened for retracted status of any article.

In addition, the Cochrane Database for Systematic Reviews was searched. IndMED was searched for additional studies from India. A manual search was conducted through the reference lists of selected papers and book chapters. The websites of the key institutes and organizations working in the field of substance use disorders were also visited to look for additional resources.

Duplicate, irrelevant or over inclusive entries were discarded. Relevance and importance of the studies towards the guideline was evaluated after going through title/ abstract of the references.

2. BACKGROUND INFORMATION

2.1. Introduction

The non-medical use of inhalants, also referred to as solvent abuse or volatile substance abuse, is currently a worldwide problem. Inhalants are breathable chemical vapors or gases that can be abused for their psychoactive (mind-altering) effects. These are available as cheap household or commercial products (such as glue, ink eraser fluid or petrol) which contain a variety of hydrocarbons, ethers, ketones and alkyl halides. In the Indian context, it appears that the ink eraser fluid (*correction fluid*), petrol and glue are commonly used inhalants; and ink eraser fluid is probably the commonest of them. [1-3]

Unlike other substances, inhalants are defined solely by their route of administration. They can be used by various modes of administration: sniffing/snorting (inhaling through the nose), bagging (inhaling from a bag that contains the substance), huffing (soaking a rag with the substance, placing the rag in the mouth and inhaling), or dusting (spraying directly into the mouth or nose).

Inhalants can be classified into four broad types, [4] as follows:

- *Volatile solvents* are liquids that vaporize at room temperature if left in unsealed containers. Paint thinner, gasoline, correction fluid, felt-tip markers, nail polish remover and glue are some of examples.

- *Aerosols* are sprays that contain propellants and solvents. Common aerosols include paint, deodorant, hair products, fabric protector.
- *Gases* are substances such as refrigerants and medical anesthetics, gases found in butane lighters, air conditioning units, and propane tanks.
- *Nitrites* are a special class of inhalants which include amyl nitrite, butyl nitrite (*'poppers')* or cyclohexyl nitrite (*'room odorizers'*). Nitrites differ from other inhalants in their action (vasodilatation and muscle relaxation) and their use as sexual enhancers rather than euphoric agents. For these reasons, nitrites are often not considered with other inhalants. In view of significant differences in their properties and profile of users, it may be best to study them separately from other inhalants.

The effects of inhalants resemble that of other CNS depressants e.g. alcohol. Initial effects comprise of stimulation, disinhibition and euphoria. These sensations may be followed by hallucinations and then a general depression including slurred speech and disturbed gait, dizziness, disorientation, and drowsiness or sleep within seconds to minutes.[5] Further drowsiness and headache can persist for hours because of residual intoxication. The intoxication with inhalants occur rapidly and is relatively short-lived. Some users may self-administer inhalants repeatedly or continuously to maintain intoxication.[6] Absorption takes places primarily via the respiratory tract and distribution occurs by absorption to white adipose tissue, adrenals, skin, kidneys, liver, lung and brain. Toluene is one of common constituent in many abused products. The major pathway of toluene metabolism involves cytochrome P-450, alcohol dehydrogenase and aldehyde dehydrogenase resulting in hippuric acid as the major urinary metabolite and ortho- and para-cresol as minor metabolites. An average elimination half-life for toluene from breath is 25 minutes and from adipose tissue is 0.5-2.7 days. However, blood concentration becomes undetectable after few (4-10) hours, though urine hippuric acid may be detectable for a slightly longer period. [7,8]

2.2 Epidemiology

2.2.1 International

Use of inhalants by younger population has been reported worldwide and is quite common in some countries.. The 2003 World Youth Report reported that in the 1990s, among 41 countries providing information on prevalence of inhalant abuse among young people (various age ranges between 12-29 years), 10 countries reported rates of 10%–20%, 15 reported rates between

5%-10%, and 16 reported rates lower than 5%. 9 The World Drug Report for the year 2005 stated that 11 countries reported an increase from the previous year. [10] However, data on inhalant abuse is often lacking and not collected in National Surveys.[11]

Prevalence is highest among young people from socioeconomically deprived and marginalized groups, including certain aboriginal communities in certain countries. High rates are also reported among school-going population in certain countries such as US and Brazil. [12] In US, 10- 20% of adolescents surveyed annually report a lifetime history of volatile solvent or inhalant use.[13] Data from some of the developed nations show that inhalants are among the first drugs used by young people and the age of onset is in early teens usually.[11]

Inhalant use is reported mostly in children or adolescents, and only a few studies have commented on its use in adults. The past-year prevalence of inhalant use disorder among adult par-ticipants in the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions was found to be 0.02 percent.[6] Previous studies have also shown that current prevalence was low in adults (0.4% in 26-34 year age-group as compared to 1.6% in 12-17 year age-group). [14] Adults who had inhalant use disorder were less educated, had received treatment for emotional or psychological problems and had a coexisting alcohol use disorder. [11]

2.2.2 Indian scenario

The magnitude of inhalant use in the country is not well known. Earlier descriptions from India were in the form of case studies [15] expressing a growing concern over the problem of inhalant use. [16] The National Household Survey on Drug Use in India that studied the population aged 12-60 years did not identify inhalant use in the general population. [17] However, inhalants are known to be very commonly used by vulnerable populations, e.g., street children.

In a study on drug use among street children in Bangalore, Benegal et al. [18] reported that 76% smoked tobacco, 45.9% chewed tobacco, 48% inhaled volatile substances, 42% drank alcohol, 15.7% smoked cannabis, and 2% ingested opioids. Various other studies from India have documented inhalant use as one of the common substance of use in street children. [19,20] A recent study which assessed 174 children in juvenile observation homes at Hyderabad found a prevalence of 35% for whitener use along with concurrent use of other substances.[21]

Inhalants use has also been reported by children from other socioeconomic strata. Some of the inhalant users are school-going children or out-of-school children living with their families. A school based study from Manipur with a sample of more than 1000 students from 17 government/private higher secondary schools found that last one year use of solvents was 4% among school children. [22] Recently collected data for drug use among treatment seekers in government, NGO and private sector in India showed that current use of inhalants in last one month was reported by 3-5% of treatment seekers from across the three sectors. [23] This prevalence among treatment seekers is higher than the previous data (last 4 years) on treatment seekers from Government de-addiction centres which showed that inhalant users constituted 1-2% of treatment seekers. Another study describing the profile of inhalant users from a drug treatment centre provides some more information.[2] The inhalant users were unmarried males with the mean age of 19 years, unemployed (43%), students (38%), urban nuclear family (86%), middle socioeconomic status (76%), and many of them had a poor social support (62%).

In a yet unpublished data from a tertiary care centre in north India, it was seen that the inhalant users seeking treatment at the specialist de-addiction clinic for over a ten-year period showed an increase that peaked in 2006, and then stabilized at 1-3% of new cases annually.[24]

Overall, there is inadequate information about the prevalence of inhalant use in India. Based on the existing data, the current impression is that inhalant use occurs commonly in economically deprived children, and children from other socioeconomic strata may also be users and are being increasingly seen in treatment centres.

2.3. Clinical correlates

Overall, risk factors for inhalant abuse have been identified as child abuse, family instability, being in foster care, lower socioeconomic status, dropping out of school, delinquency, suicidal behaviour and anti-social personality. Psychiatric co-morbidity and the family history of substance dependence were present in 26.4% and 32.9% of treatment seeking subjects. (n=87). [24] Similarly high rates of family history of substance use disorders and psychiatric comorbidity have been reported from some other studies in India.[25,26] Low levels of parental education and plans not to complete college were significant correlates of adolescent inhalant abuse in the Monitoring the Future Survey in US.[27] Numerous studies have identified strong

associations between inhalant use and comorbid psychiatric disorders, although it is not clear whether this relationship is causal. Suicidal ideas are also commonly observed especially among those with diagnoses of inhalant abuse and dependence. [13]

Data from a study in a tertiary drug treatment centre from India has also revealed that almost half of the cases (48%) had a family history for substance dependence and all cases had impairment in the family and educational/ occupational domains.[2] A study on situation assessment of inhalant use in street children in Delhi, India found that inhalant use in street children as compared to non-users was associated with greater unsupervised exposure to street life, less education, less contact with NGOs, more exposure to unsafe situations and fights, more drug using friends.[3] Studies have also found high substance use among family members, history of physical abuse, presence of stepparents, migrant status and association with delinquent peers was associated with inhalant use in street children. [3, 28]

2.4 Course and outcome

Most inhalant users appear to discontinue inhalants eventually, as rates of lifetime use are much higher than last one year use. Lifetime use reported in higher grades of school is less than that reported in lower grades, suggesting that many of those who start using inhalants early may have dropped out of school. [6] A small proportion of users may continue chronic use of inhalants well into their twenties. [11] Perron and Howard [29] found that adolescent volatile substance users who were younger, or who had friends and/or siblings who were volatile substance users were more likely to report intentions to continue use. Initiation of inhalants by age 14 was associated with a five- to six-fold increase in risk for inhalant dependence.[30] Early initiation is also associated with increased risk of heroin use, injecting drug use, other drug use and antisocial behavior. [13] Sharp et al.[31] has described four main categories of inhalant abusers, as follows:

(a) Transient social user: short history of use; use with friends; average intelligence

(b) Chronic social user: long history of use 5+ years; daily use with friends; minor legal involvement; poor social skills; limited education; brain damage

(c) Transient isolate user - short history of use; solo use

(d) Chronic isolate—long history of use 5+ years; daily solo use; legal involvement; poor social skills; limited education; brain damage.

3. MANAGEMENT OF INHALANT USE DISORDERS

Section 3.1 General Principles of Management

The management of inhalant users should follow the same general principles as those followed for treatment of substance use disorders [32,33] and especially for the adolescent substance use treatment.[34-36] Certain issues specific to inhalant use need a special consideration.

3.1.1 Ethical principles, confidentiality and consent

The patients using inhalants should receive care as per the standard ethical principles. Care must be taken not to violate the patient's rights at any stage of treatment. Inhalant users may be more vulnerable to rights violation in view of following reasons:

- Patients using inhalants are generally minors, who may not be aware of their rights
- The social or family support is often absent
- Chronic users may have impaired cognitive functions, make it difficult to understand or evaluate the nature and need of treatment
- These patients may be viewed as deviants and at times, may be treated in a stigmatizing manner even in health care settings

Care must be taken to safeguard patient's interests and respect for privacy. Patients should be treated with respect and dignity by the treating professional as well as staff members. Only the safe and effective treatment options must be offered based on evidence and expert consensus. Every attempt must be made to ensure confidentiality. Any private or personal information disclosed in confidence to the treating professional should not be disclosed to parents (unless there is a genuine threat to safety).

If an adolescent seeks consultation on his/her own, effort must be made to approach and engage the parents (or guardians) after patient's approval. Admission must, however, proceed only after a valid consent from the parents (or legal guardians) has been obtained, and if they are willing to accompany the patient throughout the ward stay. However, an adolescent who is

unwilling to get admitted for inhalant or drug use must not be admitted, even if parental consent is present.

3.1.2 Treatment settings and levels of care

Ideally the adolescents using inhalants and other drugs should be treated in a specialist setting, with services geared towards younger people (except for occasional or early users who may receive intervention in community settings). The patients using inhalants may receive various levels of care, ranging on a continuum of service intensity, [37] as follows:

1. Early intervention services, which comprise brief intervention in a health care or community settings (opportunistic)
2. Outpatient treatment services, with periodic follow-up visits (weekly)
3. Intensive outpatient, in which adolescents attend treatment or day-care facility during the daytime (daily basis)
4. Residential/ in-patient treatment services (few weeks to few months)
5. Medically-managed intensive inpatient, which is most appropriate for adolescents with substance use, medical, and/or psychiatric problems warranting intensive, supervised care.

A critical issue in treatment of inhalant use is whether inpatient or outpatient treatment is the more appropriate. While there are no clear-cut guidelines for this, certain clinical considerations may facilitate the decision. Out-patient treatment is particularly suitable for patients:

(a) If the use is occasional or less frequent
(b) If the use is of shorter duration (few months)
(c) If there is mild or moderate dependence
(d) If the treatment is being sought for first time, no prior failed attempts
(e) If there is no significant health damage
(f) If there is no concurrent abuse/dependence on other substances
(g) If the functioning at school or home is relatively preserved
(h) If there is a good social support system
(i) If patient stays in close proximity of treatment services

However, it is to be noted that several common clinical correlates associated with inhalant use may interfere with out-patient treatment. The families of the inhalant abusers often have high rates of psychopathology, including substance use and chaotic relationships, providing little/no support for patient

recovery. Many a times, inhalant users are living away from home or on streets, making it difficult to abstain as an out-patient. The strong and influential peer group often seen in inhalant users may make behavior change unlikely in an outpatient setting. The easy availability of variety of solvent products at home or in the vicinity may make abstinence harder. As a group, solvent abusers are very impulsive and elusive, making treatment compliance very difficult. [38]

Inpatient treatment covering the extended detoxification period may help to regain some control over the behavior, and help the patient to deal with cues and cravings. In-patient treatment is more appropriate:

(a) If there is a severe dependence
(b) If the patient is using inhalants for a prolonged duration (few years)
(c) If there are multiple failed abstinent attempts in the past
(d) If there are significant health complications
(e) If there is a concurrent use of multiple other substances
(f) If there is severe dysfunction at home or school
(g) If the family support is absent/minimal, and/or presence of familial psychopathology interfering with treatment and care
(h) Geographical distance from treatment centre

3.1.3. Treatment goals

The goal of treatment in case of inhalant users is *complete abstinence*. This is especially in view of severe and life-threatening health risks which may occur with single or repeated use of inhalants. The long term management plan should be geared to achieve abstinence from use of inhalants and improvement in familial, social and academic functioning.

However, it is also acknowledged that inhalant users are one of most elusive and difficult groups to retain in treatment. They may 'go in and out' of the treatment services, often being pressurized or coaxed into treatment by family pressure. The motivation to quit inhalants is low, especially as they may not perceive any harm associated with use of common 'innocuous' household products. The cognitive immaturity and low risk perception during the adolescent psychosocial development stage further contributes to low motivation. At times, the children living on streets may cite use of inhalants and other drugs as a survival strategy for a difficult life, using inhalants to cope with hunger or cold or bullies. Therefore, while working for an ultimate

goal of abstinence, these users must also be provided with the necessary health education aimed at harm minimization (see box 5. section 3.5.3) in order to reduce the risks associated with inhalants.

Goals may be classified as immediate, short-term and long-term goals. Immediate goals may be establishment of rapport, detoxification and intervention for a psychosocial and medical crisis. Short-term goals may include management of co-morbid conditions and re-integration with family. Long-term goals consist of relapse prevention, vocational skills acquisition or an improvement in overall quality of life.

3.1.4. *Phases of treatment*

A thorough assessment (as described in section 3.4.) must precede and guide management. In the *early phase* of management of inhalant users, two issues that require particular attention are (a) medical management for health damage, if any (b) detoxification (management of withdrawals, if any).[38] Depending on severity of inhalant use, there may be complications in a number of body systems, including the brain, heart, lungs, kidneys, liver, and blood (see box 3. section 3.2.4), which need a thorough assessment, management and multiple referrals. There may also be some withdrawal symptoms which are generally non-specific, although craving may be prominent, and require supportive care. Inhalants are lipophilic and can stay in fatty tissue of the body for weeks; therefore detoxification periods could extend for a month[39] or even more. Unless the patient is comfortable, it will be difficult to engage him/her in the therapeutic aspects of treatment Patient may also have some mistrust, resistance and dilemmas for treatment in the initial phase, which need to be resolved. Therefore, in the initial phase, emphasis should be on:

- building a therapeutic alliance
- basic supportive care (rest, nutrition, calm environment etc)
- use of analgesics and sedatives, if required
- general counseling
- involvement of family
- provision of education to patient (and families)

Patients may be allowed to observe group sessions but not required to participate in the initial phase. After the initial few weeks, the *long term psychosocial treatment* can be initiated once the patient is comfortable and

more receptive. Inhalant users often have a multitude of problems in various spheres of life: academic, legal, social, and family issues, either as risk factors or consequences of inhalant use. Further, cues and cravings may lead to frequent relapses. Therefore, therapy may need to be continued for a prolonged duration, possibly as long as 2 years. [38]

3.1.5 Special treatment considerations

Patients using inhalants should receive multi-disciplinary care (psychiatrists, psychologists, social workers, trained nurses) aimed at a comprehensive psychosocial management, preferably for a long duration.

Certain issues merit a special consideration in management of inhalant abusers.[38,40] These have been summarized below:

- The inhalant-using population is still largely hidden and elusive, rarely seeking treatment on their own. It is important to have a network of referral sources such as the school counselors, welfare organizations, law enforcement officials, homeless shelters etc which can screen and refer the patient for help. They can also provide brief intervention for occasional inhalant users.
- Adolescence, as a psychological development stage, is often characterized by sense of invincibility, low risk perception, rebelliousness, influence of role models and experimentation. Therefore, adolescent inhalant users need a careful and sensitive handling during the interview, with a respect to their privacy and autonomy. While interviewing young children with inhalant use, the questions should be framed in a developmentally appropriate language. Projective techniques and play can be used in assessment and therapy of young children.
- While physical examination is a part of the standard protocol for substance users, but it attains a special importance in case of inhalant abusers. There are a number of specific medical complications which must be assessed in various organ systems (as described in section 3.2.4.). Therefore, the need to conduct a thorough general physical and systemic examination cannot be over-emphasized.
- Assessment of co morbid psychiatric conditions must be form a part of the assessment. Special attention must be given to pre-existing attention-deficit disorders, learning disorders etc which may have lead to academic

underperformance and dropping out of school, consequently increasing the risk of inhalant or substance use. The evaluation must also focus on presence of any mood or psychotic symptoms induced by inhalants.

- Chronic prolonged inhalant use can lead to a variety of neuropsychological deficits, which are indicated by history and more clearly evident on formal assessment. Assessment and monitoring of the persistent deficits, if any, after abstinence from inhalants may help in planning educational/vocational aspects. Alternately, it is also possible that pre-existing comorbidities e.g. learning disabilities, attention deficit disorders may lead to academic underperformance.
- The psychological interventions for inhalant users should be kept as brief (e.g., 20-minute sessions as opposed to standard 45-60 minutes) sessions, which require less complexity of thinking at least in the initial few months. This is because the attention span and other cognitive functions are often impaired to a varying degree.
- Extensive involvement of the family is required compared to other substance use disorders, in view of younger age of patients. There are a variety of possible ways in which family can facilitate the treatment process: by ensuring compliance, monitoring patient's behavior, enforcing the behaviorally based approaches at home, minimization of negative expressed emotions or undue criticisms and support the rehabilitation of the patient in society. Further, many a time, the families of inhalant users may be dysfunctional, and there is a need for thorough assessment of family structure and dynamics prior to planning the management.
- Emphasis should be placed on retry into school and school re-adjustment issues; vocational skills training for older inhalant abusers to promote self-sufficiency should be part of the management. In this context, it is useful for a treatment facility to have liaison with various community and educational resources which may be mobilized and utilized in the rehabilitation process.
- Inhalant users often lack the basic life skills since they have initiated the drug use from a very young age, at times as early as 7-8 years. Usually, they drop out of school and spend most of time with drug using peers. There is absent or minimal parental support, and even if family is supportive, inhalant users often spend little/no time with family

members. Therefore, they are likely to be deficient in essential life skills, which may complicate the recovery and re-integration process. The treatment of inhalant users should focus on imparting life skills training which can help the patients to manage their personal affairs and handle problematic situations efficiently

- Peers have a powerful influence on adolescent drug use. Usually the peer clusters or peer groups of inhalant abusers are engaged in anti-social activities e.g. stealing, pick-pocketing etc as part of a spectrum of deviant behaviors. Assessment must consider the structure, norms and dynamics of the peer group. If accessible, then an attempt is often made to reach out to the peers and engage them in treatment.
  At times, it is necessary to work towards building an alternate group of non-drug using friends in the course of therapy.
- Extensive aftercare and follow-up period, extending as many as 2 years, is advisable. While a large proportion of inhalant users drop out of treatment much early, however those who are compliant must be offered continual care for a prolonged time.

3.1.6 Treatment approaches

Common psychosocial approaches used for treatment of inhalant users are broadly the same as in adolescent substance use treatment. These have been aptly summarized by Winters et al,[41] as follows:

1. Family-based therapy: It attempts to reduce the drug use and problem behaviors in adolescents by addressing the mediators and risk factors in the family, such as faulty communications, and maladaptive family patterns. Research demonstrates that family relations are predictors of drug abuse and related antisocial behaviors.[42] However, adolescent drug abuse and behavior problems can change as a result of changes in the family relations and family patterns of interactions.
2. Individual and group therapy: As the name implies, these refer to psychosocial therapeutic sessions delivered either to an individual or a group of individuals. Although both are used, group therapy is the more prevalent treatment modality in the context of adolescent substance users. [43] The common therapeutic approaches in individual and group therapy which have been researched are as follows:

   (a) Cognitive Behavioral Therapy (CBT)

(b) Brief Intervention/Motivational Interviewing (BI/MI)

(c) Contingency Management Reinforcement Approach.

3. Twelve-step programs: Self-help approach organized around the basic tenets of Alcoholics Anonymous

4. Therapeutic community (TC): It is based on self-help principles and experiential knowledge of recovery community. [44] TCs tend to be long-term residential treatment programs that often implement a wide variety of therapeutic techniques, including (but not limited to) individual counseling sessions, family therapy, 12-step techniques, life skills techniques, and recreational techniques for adolescents. [45]

Effective pharmacotherapies are not yet available for inhalant use disorders.

3.1.7 Components of effective treatment

In order to review the treatment services for inhalant users, Jumper-Thurman [39] had provided a set of questions (Box 1), which can provide insight into what constitutes an effective treatment program for inhalant abusers.

Box 1: What constitutes effective treatment for inhalant abusers?

- *Do you outreach to referral sources about inhalant abuse? Inhalant abusers are a hidden population, rarely seeking treatment on their own*
- *Do you rigorously assess for inhalant abuse? Do you know what products are being used and how they are used? Do you understand patterns of abuse so you can pursue a conversation with a client who may be reluctant and embarrassed to discuss use?*
- *Does your program allow for adequate detoxification? Depending on length of use and type of product used, detoxification from the acute effects of solvents and gases may last few weeks.*
- *?Do you thoroughly assess for cognitive functioning, neurologic damage, and physical effects? In some treatment populations, abusers have been found to have higher rates of physical and sexual abuse.*
- *?Does treatment include specific inhalant focused components? Do you provide education about harms of inhalants? Some abusers have started as early as elementary school. Do you address life skills*

issues? Do you take into account cognitive deficits by using briefer (20 minutes) and more concrete interventions?

- *?Does family involvement include education about inhalants, removing inhalants from the home, and the extra support and supervision that inhalant abusers and their families may need?*
- *Are inhalants accessible in your treatment program? Do you have a policy about commonly used inhalants e.g. dry erase markers, correction fluid*
- *Is your staff knowledgeable about inhalant abuse? Do they have realistic expectations for recovery? In order to effectively treat inhalant abuse, counselors need to understand the unique aspects of the problem, including a slow rate of recovery.*
- *Does your aftercare planning take into account the special problems of inhalant abuse? Has a school-based counselor been included in the plan?*

Source: Jumper-Thurman et al. [39]

Section 3.2. Assessment of patients using inhalants

The general principles for assessment of adolescent substance users [34] should be followed in case of adolescents using inhalants as well. Purpose of assessment in inhalant users is to assess the severity of inhalant use, detect medical/psychiatric symptoms, make a diagnosis, assess for cognitive deficits, assessment for health damage and formulation of a management plan. The detailed assessment should be commenced only if the patient is comfortable, and not in acute intoxication or withdrawal state.

In general, the assessment and treatment of adolescent substance use is a three-phase process as described by Kaminer.[46] The initial screening phase involves identification of health disorders, psychiatric problems, and psychosocial maladjustment. Based on the screening phase, some adolescents are required to go through the second phase, which includes an extensive assessment necessary for initiating integrated problem-focused and comprehensive treatment. This assessment provides a diagnostic summary which identifies the adolescent's treatment needs within specific life domains such as: substance use, psychiatric status, physical health status, school adjustment, vocational status, family function, peer relationship,

leisure and recreation activity, and legal situation. The third phase involves the preparation and implementation of an integrative management plan determining which patients respond best to what treatments.

3.2.1 Screening

Many a times, the diagnosis of inhalant abuse relies almost entirely on a high index of suspicion. Children and adolescents using inhalants may present to a variety of health professionals e.g. psychiatrists, pediatricians, family physicians, primary care physicians and a variety of health settings. However, research suggests that clinicians appear to have a low index of suspicion for inhalant use and related problems. [47] Inhalant use must be suspected especially if there are one or more clinical pointers as shown in box 2.

Box 2: Clinical pointers for suspected inhalant use

- *Any discernible or unusual odor or stains on fingernails, body parts or clothes*
- *Presence of sniffer's rash around nose and mouth, rhinorrhea, injected sclera*
- *Appears to be under influence of a drug (e.g. drowsiness, incoordination)*
- *Deterioration in physical appearance*
- *A recent change in child' behavior*
- *Drop in school performance/ frequent absenteeism*
- *Impairments in attention, memory or other cognitive functions*
- *Secretive behavior regarding actions and possessions*
- *Unusual borrowing/stealing of money from home or friends*

Only few attempts have been made to develop specific instruments to screen and assess for the inhalant use and related problems, and these are not in common use (e.g. Ogel et al, [48] Yeniden inhalant use severity scale). Howard and colleagues [49] have prepared Volatile Solvent Screening Inventory (VSSI) and Comprehensive Solvent Assessment Interview (CSAI) (see Howard et al,[49] supplementary data), though the psychometric properties for the same are not available. The VSSI is freely available, requires approximately 20 minutes to complete, and assesses past-year and lifetime frequency of use of 55 inhalant chemicals and products, medical history, demographic

characteristics, current psychiatric symptoms, suicidal thoughts and attempts, trauma history, temperamental traits such as impulsivity, and the frequency and nature of antisocial behavior in the prior year. The CSAI is also free, requires 20 to 90 minutes to complete (depending on the extent of the reported history of inhalant use), and assesses reasons for starting and stopping inhalant use; typical modes, locations, contexts and subjective effects of use; adverse acute consequences of inhalant intoxication; perceived risks of inhalant use; estimated likelihood of future use; sibling and friends' inhalant use; and DSM-IV inhalant abuse and dependence criteria. [49,50]

In absence of valid screening instruments for inhalants, adolescents can be screened for use of substance/s using CRAFFT questionnaire,[51] which is a brief, reliable tool for adolescent substance abuse screening (available at Center for Adolescent Substance Abuse Research: *http://www.slp3d2.com/rwj_1027/webcast/docs/screentest.html*.)

If screening indicates the possibility of an early or infrequent inhalant use, brief intervention should be carried out after initial assessment. More detailed assessment and interventions are warranted for regular, frequent or chronic use, or in the presence of co morbid conditions.

3.2.2 Thorough history and examination

Besides the immediate reasons for presentation, a thorough history should cover following aspects: nature, type, frequency, duration, mode of administration of inhalants and/or co-occurring substance use, reasons for initiation/continuation, acute effects, withdrawals (if any), tolerance, craving, time spent on drug use, neglect of alternate activities, drug-using peer group (if any), consequences of drug use (physical, psychological, familial, school, social, legal), abstinence attempts, comorbid psychiatric/medical disorders (present/past), family history, personal history (including educational/vocational and sexual history) and pre-morbid temperament/ personality. Assessment of family dynamics, inter-personal relationships and communication styles is required for child/adolescent inhalant users seeking treatment. General physical and systemic examination should be conducted diligently in all users and any discernible abnormality recorded. Mental state examination should be conducted routinely in all inhalant users covering aspects of alertness and orientation, behavior, speech, affect/mood, thought, perception, and higher cognitive functions (attention and concentration, memory, intelligence, abstraction, judgment, insight.

3.2.3 Assessment for psychiatric comorbidities

History and mental state examination should specifically look for presence of any psychiatric comorbidity. If co-morbid Axis I disorders e.g. depression, psychosis, conduct disorder, attention deficit, learning disorders or Axis II disorders e.g. borderline intelligence, personality disorders are suspected, they should receive a detailed psychiatric assessment, including a careful delineation of their relationship to inhalant or other drug use. Psychiatric screening instruments can be applied to detect the co-morbidity. The Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) is a brief structured diagnostic instrument for current DSM-IV & ICD-10 psychiatric disorders and suicidality, [52] and might be used. However, it must be mentioned here that there are no specific instruments or studies to guide the psychiatric assessment of inhalant users.

3.2.4. Assessment of health damage

Solvents are easily absorbed from the blood into lipid-rich/fatty tissues, including white matter of brain. [53] Chronic inhalant abuse significantly damages the heart, lungs, kidney, liver, and peripheral nerves. [54] Continued, chronic inhalant abuse has been associated with neurological damage. [55,56] Various health complications related to use of inhalants have been shown in box 3. Neurological toxicity is the most recognized adverse effect of chronic inhalant abuse because of damage to myelin sheath and neuronal membranes due to lipophilic chemicals. Common findings on brain imaging include enlarged ventricles, widened cortical sulci, and cerebral, cerebellar, or brain stem atrophy, [57] which may be irreversible.

Therefore, a comprehensive clinical assessment must be performed in order to assess for possible health damage (see box 3) associated with inhalant use. Laboratory tests and imaging studies (including MRI brain) should be performed, if indicated. Specialist referral and consultation must be sought for a medical complication.

Inhalants have a propensity to cause harmful effects on fetus if the exposure continues during pregnancy. Children exposed to inhalants during pregnancy have been reported to be small at birth, had craniofacial abnormalities similar to fetal alcohol syndrome and showed deficits in cognitive, speech, and motor skills in later life, as evident from a review of over 100 case–reports described in literature. [58] Withdrawal signs for exposed newborns have been documented, which consist of high-pitched crying, sleeplessness, hyperactive Moro reflex, tremor and hypotonia, and difficulty in feeding. [59]

Box 3: Medical complications of Inhalant use

Organ system	Complications
Neurological	Encephalopathy (acute/chronic), cerebellar ataxia, cranial and peripheral neuropathies, parkinsonism, tremor, visual loss/optic neuropathy, white matter degeneration
Neuropsychiatric & neuropsychological	Apathy, dementia, depression, psycho-sismemory deficits, deficits in attention and executive functions,
Cardiovascular	Dysarthymias, hypoxic-induced heart block, myocardial fibrosissudden sniffing death syndrome (due to sudden release of catecholamines resulting in ventricular fibrillation)
Respiratory	Cough, wheezing, dyspnoea, emphysema, pneumonitis, Goodpasture's syndrome
Abdominal	Hepatotoxicity, nausea and vomiting
Renal	Acid-base disturbance, acute renal failure, renal tubular acidosis, Fanconi's syndrome
Haematological	Aplastic anemia, bone marrow suppression, leukaemia
Dermatologic	Burns, contact dermatitis, peri-oral eczema
Reproductive / Fetal exposure	Low fertility, Increased risk of abortion, possible neonatal withdrawals, low birth weight and craniofacial abnormalities, growth retardation and cognitive/speech/ motor deficits in later life

Source: Reference no. [5, 31,57]

3.2.5. Neuropsychological assessment

Evidence from research studies have shown neuropsychological impairments in chronic inhalant users, including impaired attention, speed of information processing, psychomotor coordination, learning and memory, executive abilities (including working memory), as well as tests of verbal intelligence. [60-63] Commonly observed neuropsychological deficits are also consistent with white matter pathology as seen in a recent meta-analysis of neuropsychological and neuroimaging studies.[63] This indicates the need to study the particular factors mitigating or increasing the risk of neuropsychological impairments, including the type of product/s used, co-occuring substance use and a host of other factors.

A detailed neuropsychological assessment should be routinely conducted for all chronic inhalant abusers. The neuropsychological assessment should be done in the initial few weeks after the patient is comfortable, and should be repeated after a few months of abstinence in order to look for residual cognitive impairments.

3.2.6. Laboratory investigations

A patient presenting with acute inhalant intoxication or suspected inhalant use should be investigated for complete hemogram, biochemical parameters (serum electrolytes, calcium and phosphorous levels, hepatic and renal profiles), acid-base assessment and cardiac/muscle enzyme analysis. [8,47]

The diagnosis of inhalant use disorders should be primarily based on clinical history and examination, as laboratory tests may not detect many inhalants due to their short half-life. Toluene can be measured in serum. Hippuric acid, a major metabolite of toluene, can be detected in urine samples for longer periods and may be useful to monitor the patient for abstinence. It may, however, cause false positive results as it is normally produced from certain food products containing benzoic acid preservatives. Simultaneous analysis of hippuric acid to creatinine ratio can reveal toluene use.[64]

Certain precautions must be taken during collection of samples. Inhalants tend to volatilize from the collected samples, urine should be collected in a tightly sealed glass container (with little/no air space) and immediately refrigerated till urinalysis. Inhalants have a tendency to bind to plastic containers, which should not be used. Urinalysis is usually done by gas chromatography, followed by mass spectroscopic (GC-MS) procedures.

Research from the occupational toxicology and inhalant abuse literature suggests that bioassays for hippuric acid, o-cresol levels, and benzylmercapturic acid may eventually be useful urinary markers of toluene abuse. [8] It is advised that laboratory tests to detect inhalants may be done only in centres, where such infrastructure and expertise is available, keeping their limitations in mind.

3.2.7. Diagnosis

The diagnostic criteria in current classificatory systems have been shown in Table 3. A total of 6 criteria have been listed for Inhalant dependence in DSM-IV compared to 7 for other substance use disorders and does not list inhalant dependence.

Research suggests that prevalence of inhalant dependence was about equal for ICD-10[65] and DSM-IV TR[66] diagnostic criteria, though more users received ICD-10 harmful use diagnosis compared to DSM-IV TR Inhalant abuse. Howard and Perron[50] found that 46.9% of the adolescent solvent users had a diagnosis of inhalant use disorders (18.6% abuse; 28.3% dependence), while others[67,68] have reported a lower percentage (18.4%) of inhalant use disorders among inhalant users. In a study on treatment seekers in India, a substantial portion of inhalant users were inhalant dependent (81%). Craving was more common (90%) than withdrawal (57%).[2]

Table 3: Diagnostic criteria in ICD-10 and DSM IV TR

ICD-10 Mental and Behavioral Disorders due to Substance Use (F18.Volatile Solvents)	DSM-IV TR Criteria for Substance Use Disorders
Harmful Use (F18.1) The diagnosis requires that actual damage should have been caused to the *mental* or *physical* health of the user.Should not be diagnosed if dependence is present	304.60. Inhalant AbuseA. A pattern of substance use leading to significant impairment or distress, as manifested by one or more of the following during in the past 12 month period: 1. Failure to fulfill major *role obligations* at work, school, home 2. Frequent use of substances in situation in which it is *physically* hazardous 3. Frequent *legal* problems (e.g. arrests, disorderly conduct) for substance abuse

	4. Continued use despite having persistent or recurrent *social or interpersonal problems* B. The symptoms have never met the criteria for substance dependence for this class of substance
F18.2 – Dependence syndromeThree or more of the following have been present together at some time during the previous year: (a) a *strong desire* or sense of compulsion to take the substance; *(b) difficulties in controlling* substance-taking behaviour in terms of its onset, termination, or levels of use; (c) a physiological *withdrawal state* when substance use has ceased or been reduced (d) evidence of *tolerance*, such that increaseddoses of the psychoactive substances are required in order to achieve effects originally produced by lower doses (e) progressive *neglect of alternative pleasures* or interests, increased amount of time necessary to obtain or take the substance or to recover from its effects;(f) persisting with substance use despite *clearevidence of overtly harmful consequences*	305.90. Inhalant Dependence† Maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period: 1. Tolerance 2. Use in larger amounts or over a longer period than was intended 3. Persistent desire or unsuccessful efforts to cut down or control substance use 4. A great deal of time is spent in activities necessary to obtain or use the substance , or recover from effects 5. Important social, occupational, or recreational activities are given up or reduced. 6. Use continued despite knowledge of a persistent or recurrent physical or psychological problem

† A total of 6 criteria have been listed for Inhalant dependence in DSM-IV TR compared to 7 for other substance use disorders.

3.2.8 . Special considerations in assessment

Besides what has been discussed in preceding sub-sections, few more issues need a consideration during the assessment of inhalant users,[69] as follows:

- Adolescents who experiment with inhalants may stop them after using once or a few occasions are transient users, and may never meet the

formal criteria for diagnosis of inhalant use disorders (even though in view of risks, such users would be candidates for brief interventions).

- Use of multiple substances may occur together or sequentially in adolescent patients experimenting with various drugs. Use of other gateway drugs e.g. alcohol, tobacco, cannabis in addition to inhalants is common. The abuse or dependence on other substances must be carefully established through a proper history and examination, and co-occurring substance use must be considered in diagnosis and management.
- Anti-social behaviors may be frequently seen in the context of inhalant use. Careful assessment must be done to assess if such behaviors were present before or after onset of use of inhalants.
- The sexual history, including high-risk sexual behaviors, should be taken from all patients. If indicated, laboratory investigations to rule out sexually transmitted infections (including HIV-ELISA) may be considered. Possibility of sexual abuse should be considered in vulnerable users e.g. street children using inhalants and other substances.
- Menstrual history should be taken in all post-pubertal/married female inhalant users and if indicated, a urine pregnancy test may be undertaken with patient's consent.

Section 3.3. Management of Inhalant Intoxication

3.3.1 Inhalant Intoxication

Inhalant intoxication should be considered for all young persons showing an acute onset of behavioral changes, coupled with a characteristic odor of organic solvents or surrounding paraphernalia suggestive of inhalant use.[69] The diagnostic criteria for Inhalant Intoxication, as specified in DSM IV TR[66], are shown in Box 4. ICD-10 has a corresponding diagnostic category for intoxication of volatile solvents, but do not specify the diagnostic criteria.[67]

The intoxication of Inhalant resembles that of alcohol intoxication in terms of clinical presentation.[31] The early stages are characterized by a sense of euphoria, 'rush', light-headedness, disinhibition and excitable behavior. As the person continues to use, there may be dizziness, ataxia, incoordination and blurred vision. High doses may cause disorientation, delirium, loss of consciousness, stupor or coma. Death can occur during the course of inhalant

intoxication as a result of cardiac arrhythmias (ventricular fibrillation), cardiac arrest, asphyxia, aspiration, seizures or accidents. In the presence of co-occurring substance use e.g. alcohol, clinical there may be a more rapid decline and patient may be stuporous.

Box 4: DSM-IV TR diagnostic criteria for Inhalant Intoxication

A. Recent intentional use or short-term, high-dose exposure to volatile inhalants .

B. Clinically significant maladaptive behavioral or psychological changes that developed during or shortly after inhalant use or exposure.

C. Two (or more) of the following signs, developing during, or shortly after, inhalant use or exposure:

1) dizziness
2) nystagmus
3) incoordination
4) slurred speech
5) unsteady gait
6) lethargy
7) depressed reflexes
8) psychomotor retardation
9) tremor
10) generalized muscle weakness
11) blurred vision or diplopia
12) stupor or coma
13) euphoria

D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

Source: Reference no.[66]

The onset of intoxication is begins shortly after the inhalation of volatile solvents, as they are rapidly absorbed through the pulmonary membranes and quickly distributed into brain and other lipids.[69] Usually, inhalants have a short half-life, though the effects of inhalant intoxication may last for a few hours or less. It must be noted that acute intoxication has been studied mostly among toluene users, and it is possible that inhalant users may abuse products with an array of chemicals causing unpredictable or additive effects.

Garland et al.[70] assessed the inhalant intoxication experiences of 267 low-, moderate-, and high-frequency inhalant users. Aversive experiences such as depressed mood, suicidal ideation, and chest pain were commonly reported by high-frequency users. High-frequency users also experienced significantly more euphoria, talkativeness, and grandiosity during inhalant intoxication than low-frequency users. Low-frequency inhalant users reported predominately hedonic experiences during inhalant intoxication, whereas high-frequency users reported a mixture of hedonic and aversive experiences.

Another study by Garland et al.[71] evaluated the adverse consequences of acute inhalant intoxication in 279 adolescent inhalant users under residential care. Results of this study indicated that high-risk behaviors and adverse outcomes experienced during episodes of inhalant intoxication were common. Certain risky behaviors and consequences, such as engaging in unprotected sex or acts of physical violence while high on inhalants, were dramatically more common among high-frequency users than low-frequency users.

3.3.2 Summary of Evidence

No controlled clinical trials for inhalant intoxication are available. Two descriptive case series have discussed management of symptoms following acute exposure.[72,73] In a retrospective chart review for the patients who presented to a poison centre with exposure to methanol-containing carburetor cleaners (n=33), all patients had neurological symptoms, 64% had vomiting and 27% had metabolic acidosis after the exposure.[72] Metabolic disturbances resolved within 24 hours with only basic care. No patient required more aggressive treatment such as dialysis. In the recent study by Cámara-Lemarroy et al.[73] using chart review of 22 patients, the main clinical presentation was weakness as a result of hypokalemia, severe metabolic acidosis and five patients had renal tubular acidosis. Treatment comprised of supportive measures and aggressive potassium repletion, where indicated, following which complete recovery occurred.

Few other isolated case reports have described the management of symptoms or complications seen during course of intoxication. Gaynor[74] described case of a 20-year female presenting to an emergency department in an aggressive and self-harming state after inhaling petrol fumes. The author emphasized the importance of maintaining patient dignity, focusing on reducing patient arousal, and avoiding physical restraint if possible, and discussed the use of midazolam. Another case report[75] describes use of

carburetor cleaner for several hours by a 15 year male who started protracted vomiting with rapid respirations. Profound metabolic acidosis was detected. During the 40-minute air evacuation to a pediatric unit, he received 3 L/min of oxygen, ranitidine 50 mg intravenous piggyback and promethazine 12.5 mg intravenous slow push, after which he slept and showed improvement in emesis. On reaching pediatric hospital, he received emergent dialysis and was discharged after 48 hours. A case report[76] describes a 20-year inhalant user with a learning disability and seizures, whose mental and neurological status were closely monitored over one month of admission. Treatment consisted of charcoal, ipecacuanha and intravenous fluids with sodium bicarbonate and authors discuss the reversibility of psychiatric symptoms in the patient.

Rapid reversal of hypokalemia was achieved by use of hemodialysis in a patient with toluene induced hypokalemia, metabolic acidosis, respiratory failure and ventricular arrhythmia.[77] Another inhalant-using patient with acute generalized muscle weakness and hypokalemia was managed by intravenous potassium supplement and other basic supportive measures.[78]

3.3.3 Recommendations for Management of Inhalant Intoxication

The treatment recommendations based on expert opinions and expert consensus documents[79] have been summarized below:

- Basic supportive case should be offered to all inhalant users
- Ensure safety
- Careful monitoring of the intoxicated patient should be done on a frequent basis till symptoms resolve, on following parameters:
  - blood pressure
  - pulse rate
  - respiratory rate
  - temperature
  - oxygen saturation
  - orientation to time, place, person
  - level of consciousness
  - changes in mood and behavior
- Environment should be calm, quiet and reassuring, with minimal stimulation (to reduce the risk of cardiac arrhythmias and arrest which may be precipitated by undue alarm)

- Speak in a calm, non-threatening voice
- Physical restraints should not be used
- Use of sedatives should be avoided as they can potentiate the inhalant effects, unless it is absolutely necessary to ensure safety or reduce severe agitation
- Paracetamol may be given for headache, if required
- Complications, if any, resulting from inhalant use (e.g. metabolic acidosis) must be treated by specific treatment measures after appropriate referral/consultation
- Emergency medical care should be arranged or provided immediately if there are any danger signs e.g. breathing difficulty, circulatory failure, loss of consciousness.
- Patient can be discharged from medical care (under supervision of a guardian) when the symptoms have fully recovered (usually < 4-6 hours if uncomplicated) and there is no discernible abnormality in orientation, alertness, mood, behavior, vitals and motor functions.
- Advise the family member or caregiver to keep monitoring the patient for at least 24 hours

Section 3.4. Management of Inhalant Withdrawal Symptoms

3.4.1 Status of Inhalant Withdrawals in Current Diagnostic Systems

Withdrawal state is defined as symptoms which occur after cessation or reduction in the use of a substance after repeated, often prolonged use in high doses. In general, the occurrence of withdrawals is one of the indicators of dependence syndrome. [66] While withdrawal states are clearly identified for several substances of abuse e.g. alcohol or opioids, evidence for inhalant withdrawal state remains debatable.

In ICD-10, there is a provision to code withdrawal state of all the substances, including volatile solvents, but there is no specific text description.[65] There is no diagnosable withdrawal syndrome specified in the Diagnostic and Statistical Manual, 4th edition TR (DSM-IV TR).[66] Unlike other substances, the DSM-IV TR indicates that inhalants do not have an associated withdrawal syndrome among persons who meet criteria for inhalant dependence. The non-inclusion of inhalant withdrawal symptoms in the diagnostic criteria has been criticized by recent researchers.[80]

3.4.2 Summary of Evidence for Inhalant withdrawals

Evidence over past decade point towards the existence of inhalant withdrawal symptoms. Initial evidence had emerged mainly from case studies of heavy or dependent inhalant users reporting withdrawal symptoms,[81-83] as summarized in Table 3. In addition, it was seen in a sample of 30 inhalant users seeking treatment at adolescent de-addiction clinic, A.I.I.M.S. that nearly 73% reported withdrawal symptoms, with irritability, poor concentration, fatiguability, headache and insomnia, being the most common.[84] Another study from same setting also reported similar findings, with 79% users reporting one or more withdrawal symptoms, which were non-specific.[85]

Other researchers have compared the phenomenology and experiences of inhalant and other substance use disorders, describing a mild inhalant withdrawal syndrome based on relatively small samples. These studies showed inhalant users do experience restlessness, inattentiveness, anxiety, insomnia, and high levels of craving as part of withdrawals.[85, 86]

At least two studies that have specifically looked into existence of inhalant withdrawals using more robust methodology need a special mention. [88, 89] In a community based study of 162 adolescent or young adult inhalant users, [88] 12.3% of sample was found to have inhalant dependence, and withdrawal was the second most common inhalant dependence criterion to be met. Overall, 11.1% of sample reported experiencing withdrawal symptoms varying from 5.3% for nitrites to 11.9% for solvents. [Refer to Table 4 for commonly reported withdrawal symptoms].

More recently, Perron et al.[89] examined the prevalence of withdrawal symptoms among inhalant users using data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; 2001-02).[90] Approximately 47.8% of the persons who met criteria for inhalant dependence reported three or more inhalant-related withdrawal symptoms that were clinically significant. This was almost similar to that observed for cocaine dependence. Though it was a large-scale survey of representative population, the number of dependent inhalant users was small. In addition, preliminary and even questionable evidence in the form of case report suggests possible exacerbation of toxic encephalopathy in a patient after sudden discontinuation of mothballs in a regular user. [91] Similar worsening of the toxic neurological symptoms was seen shortly after hospitalization-imposed abstinence, suggesting possible role of withdrawal effects. It is to

be noted that both patients used mothballs by ingestion, and so technically they was not used as inhalants. However as mothballs are otherwise commonly abused by inhalation, and so were included in review for sake of comprehension and discussion.

To summarize available evidence, inhalant withdrawals are experienced by regular users of inhalants, usually within 24 hours of cessation. Often, the withdrawal symptoms are mild, and comprise of psychological and few physical symptoms, which may last from 2-5 days. Craving for inhalants may last for a few weeks. The variations in the nature of withdrawal symptoms according to specific inhalant products and types need to be examined more closely. Further work needs to be done on the assessment and construct validity of inhalant withdrawals before it can be considered for inclusion in classificatory systems.

Table 4: Summary of studies reporting inhalant withdrawals[92- 94, 1, 83, 2, 86-89]

Study reference	Study design	Sample	Withdrawal symptoms
Das et al, 1995 (India)	Case report	A 17 year female with 8 months of kerosene use by inhalation and ingestion	Anxiety, irritability, nausea, abdominal pain (lasted 5 days); Craving lasted 3 weeks
Pahwa et al, 1998 (India)	Case report	A 13 year old female using petrol	Irritability, nervousness and difficulty in sleep (lasting for 1-2 days)
Shah et al, 1999 (India)	Case series	9 subjects, aged 7-25 years using gasoline	Anhedonia, irritability, sleep disturbance, psychomotor retardation, dry mouth, lacrimation, craving, headache, palpitation (began 24 hours after cessation, lasting several days)
Basu et al, 2004 (India)	Case series	5 inhalant users, aged between 10-25 years	No specific withdrawals reported
Muralidharan et al, 2008 (India)	Case series	3 males, between 17-21 years of age	Craving, irritability, mood swings, dysphoria, aggression, anorexia
Kumar et al, 2008 (India)	Chart review	21 consecutive treatment seeking inhalant users	57.1% reported one or more withdrawal symptoms: irritability, subjective restlessness, observed restlessness, insomnia, tingling sensation all over the body, headache and poor concentration.
Kono et al, 2001; Miyata et al, 2004	Comparative studies	Comparison of small sample of inhalant users (n=6 & 30 respectively) with tobacco, alcohol & methamphetamine users	Mild withdrawal syndrome reported in the form of restlessness, inattentiveness, anxiety, insomnia and high levels of craving
Ridenour et al, 2007	Community based, observational study	162 inhalant users aged 15-25 years, using aerosols, gases, solvents or nitrites	12.3% of sample was dependent. 11.1% of sample experienced in decreasing order of frequency: Headaches Nausea or vomiting Anxiety Craving Fatigue, Trouble concentrating Hallucinations Runny eyes or nose Fast heart beat, depressed mood, trembling or twitching

Perron et al, 2011	Population based survey	Data from 2001-02 NESARC representative survey of 43,093 US adults 644 Inhalant Users, of which 21 had dependence	Following withdrawals were reported (among dependent users): Hypersomnia (63.6%) Fatigue(55.4%) Nausea(46%) Sweating or fast heart beat (45%) Depressed mood(42.2%) Anxiety (41.8%) Yawning(39%) Tremors(37.8%) Hallucinations(35.3%) Fever (33.9%) Runny eyes or nose(33%) Bad headache(30.9%) Insomnia(28.6%) Psychomotor retardation(27.1%) Restlessness(21.6%) Muscle ache(11%) Vivid dreams(7.7 %) Eat more or gain weight (4.8%) Seizure(2.4%)

3.4.3 Summary of Evidence for Treatment of Inhalant withdrawals

As the presence of inhalant withdrawals is only being recently acknowledged in published literature, consequently, the research on treatment options for inhalant withdrawals is quite limited. Further, many of the symptoms are non-specific and relatively short lasting, although craving may last longer. Thus, management of inhalant withdrawals requires more research attention.

No controlled clinical trials have been conducted. Evidence towards the treatment options for inhalant withdrawals is in the form of one case series and one case study. These are being summarized below:

- A case series[83] of three inhalant dependent users (17 yrs, 20 yrs, 21 yrs) who were admitted with non-specific withdrawal symptoms in form of irritability, insomnia and craving, and treated with 50 mg/day baclofen continued over 7-10 days of hospitalization. Marked reduction in craving and other withdrawal symptoms was noted within 48 hours and patients were asymptomatic at the time of discharge. Authors proposed Baclofen as a safe and effective treatment, possibly acting through its agonistic action on ã-amino butyric acid B receptors in ventral tegmental area of brain.
- A case study[95] of a 22 year old patient inhaling petrol for six months, reports the use of buspirone 40 mg/day for two months, which led to a marked reduction in frequency of use from first week up to 8 weeks. However, it is to be noted that the study does not specifically describe any withdrawals per se, but reports on the short-term efficacy of buspirone in achieving abstinence from inhalants in the given patient, possibly through a role in reduction of anxiety symptoms.

Based on above, there appears to be an insufficient evidence for a specific pharmacological agent for treatment of inhalant withdrawals.

There are no specific studies or case reports which have described the efficacy of non-pharmacological modalities for inhalant withdrawals.

3.4.4. *Treatment Recommendations for Inhalant Withdrawals*

Available literature on existence of inhalant withdrawals is recent and still emerging. There is an insufficient published literature on treatment of inhalant withdrawals.

Specific treatment recommendations for this section were formulated mainly on the basis of clinical experience, expert opinions and consultation with expert recommendations in other parts of the world [IV].

The treatment recommendations [D] have been summarized below:

- Ensure a quiet and supportive environment
- Advice to minimize the stimulation for patient, in order to reduce anxiety and agitation
- Ensure adequate rest and sleep
- Ensure hydration, by means of adequate oral fluids; and regular meals.
- Pharmacological treatment should be on symptomatic basis only, with close monitoring.
- Analgesics (e.g. paracetamol, ibuprofen) can be given for headache or somatic pain/s.
- Benzodiazepines (e.g. lorazepam) may be used to manage the anxiety, agitation and sleep disturbances; however, their use should be restricted to a short period. Gradual taper is advised to minimize the discomfort to patient.
- In case of in-patients, monitor the vitals regularly (blood pressure, pulse rate, respiratory rate, temperature) and supervise the need and effects of medications.
- Monitor for any sudden change in patient's state (hallucinations, seizures, breathing problems, hypervigilance, unusual agitation etc.), which may need immediate medical assessment and referral.

Inhalant withdrawal symptoms can be managed by basic supportive care and symptomatic medical management. Majority of patients who use

inhalants can be treated in the out-patient setting, with frequent follow up visits in the initial phase of treatment. Admission may be required (with attendant, if the patient is minor) particularly for patients who have a co morbid mental or physical disorder or are polydrug users. Plan of management should be governed by the patient report, account of family member/s and objective assessment by the clinician.

Section 3.5. Psychosocial Interventions for Inhalant Use Disorders

3.5.1. Summary of evidence from studies on inhalant users

Although the earliest reports can be traced back to three decades, [96, 97] the research studies have remained quite sparse and disconnected to each other. Evidence from available studies on efficacy of psychosocial interventions among inhalant users has been presented in Table 5. Studies which had inhalant users as a tiny fraction of a larger sample of juvenile offenders or substance users, were considered to be important for inclusion only if the specific outcomes pertaining to inhalant users have been provided.

Assessing the quality of the evidence, most of the studies are either uncontrolled or descriptive case series, and only one randomized controlled trial is available. Sample sizes have ranged from mostly small (8-19) to a few with moderate-sized samples (35-81) and one unpublished data source with a larger sample of 154 adolescents. A range of interventions have been tested across various studies, from supportive psychotherapy to activity- and engagement-based programmes to residential rehabilitation. Most of studies have been conducted in an isolated manner and not much attempt has been made to replicate the previous findings. Outcomes were variably defined and the inhalant use parameters were self-reported in almost all studies. Many of the approaches were multi-modal and no two interventions appear to be sufficiently homogeneous to support a meta-analysis. Two systematic reviews have been conducted to assess the treatment interventions for inhalant use disorders, and their findings are summarized below:

- A Cochrane review [98] aimed to search and determine risks, benefits and costs of a variety of treatments for inhalant dependence or abuse. Selection criteria included randomized controlled trials or controlled clinical trials. A comprehensive literature search (1966-2010) was undertaken, however no randomized or controlled clinical trials could be found. Therefore, no specific recommendations could be made for the treatment of inhalant dependence or abuse.

- A systematic review [99] concerning psychosocial interventions for volatile substance use was conducted for a range of study types, published between 1980 and 2010. A total of 19 studies covering a range of psychosocial interventions were identified, but were generally of low evidentiary levels and no clear conclusions could not be supported.

More recently, the first and only Randomized Controlled Trial (RCT) for psychosocial interventions among inhalant users has been conducted.[100] It aimed to assess the efficacy of cognitive behavior therapy (CBT) based brief intervention among a sample of hospitalized male adolescents (13-18 years) with a DSM-IV diagnosis of 'volatile substance dependence', or 'polysubstance dependence with preference to volatile substances'. The study sample comprised of 62 adolescents allocated randomly to experimental or control group (n=31 each). Both groups received the standard single session, educational program and participated in vocational training which was offered to all patients. In addition, the experimental group participated in a CBT-based brief intervention with a focus on psychoeducation, which was delivered over three sessions. The length of hospitalization period was subject to the adolescents own decisions. At one year of follow- up, the rate of volatile substance discontinuation was significantly higher (÷2 = 11.8, p = .01) in the experimental (n=26) compared to the control group. (n=23). Few subjects were not traceable at follow-up. This randomized study provides evidence [I] supporting the role of CBT based brief intervention as an effective treatment modality for inhalant dependence.

Based on above evidence, four types of interventions appear to merit a closer examination for inhalant users: CBT based brief intervention, family therapy, activity-based programmes and Indigenous-led residential approaches.[99, 100] **(Table 5)**

3.5.2. Summary of evidence for extrapolations from adolescent substance use treatment

Given the scarcity of methodologically robust studies on inhalant users, some insights can be gained from the literature on adolescent substance use treatment, which can be carefully and meaningfully extrapolated to inhalant users.

It must be commented here that a comprehensive search for treatment interventions in adolescent substance users was outside the purview of this practice guideline. Only the key studies, including reviews, systematic

Table 5: Studies assessing the efficacy of psychosocial interventions among inhalant users [100- 104, 96, 97, 105- 108, 18, 3, 109]

Reference	Study design	Sample	Intervention	Time at assessment	Outcome
Ögel et al, 2011 (Turkey)	Randomized controlled trial	62 adolescents, hospitalized dependent users	CBT-based brief intervention - 3 sessions (experimental group) vs a single session of education only (control group)	1 year post-treatment	Abstinence rates significantly higher in experimental group (51.6%) compared to study group (16.1%)
Burns et al, 1995, (Australia)	Pre/post test case series	55 current and ex-sniffers, including 27 petrol sniffers aboriginal community setting	Employment and skills training (in conjunction with substitution of petrol with aviation gasoline as fuel supply in community)	20 months after intervention	Significant increase in employment rates (7% to 63%) among petrol sniffers; significantly less mean blood lead levels; reduction in sniffing related crime
Cheverton et al, 2003 (Australia)	Descriptive case series	8 homeless adolescents / young adult inhalant users	Activity and engagement programme (2 weeks daily arts training followed by a performance project)	4 weeks	Abstinence achieved in all but one
Butt , 2004 (Australia)	Descriptive case series	Sample of 24 adolescents, of which 19 were inhalant users. 6 completed pre/post psychosocial assessments & rest rated retrospectively by staff	Activity based education programme ('Get Real Challenge'). Total of 14 activities e.g. rock climbing, deep sea fishing included , with 3-14 participants in each	Average of 4 months in six users who completed assessments	Marked reduction in inhalant use frequency ; Improvement in those who participated in 3 or more activities
Coleman et al, 2001 (Canada)	Pre/post test case series	N=78 inhalant users, aged between 7-19 years, both genders 70% co-occuring substance use	Residential drug treatment and aftercare; Individual, group and family therapy	Nearly 2 years	49% abstinent during treatment but majority left before completion of treatment; 70% relapsed
Framrose, 1982 (UK)	Descriptive case series	41 adolescent solvent users and their families , of which 35 could be engaged	Family therapy – structural approach for milder (1/3rd) and strategic approach for those with severe problems (2/3rd)	6 months	Improved family functioning and cessation of solvent use in 74% of sample
O' Connor et al, 1982 (UK)	Controlled clinical study	6 adolescent inhalant users and 6 matched controls	Hypnosis and suggestion techniques in study group Counseling in both groups	15 weeks	Study group- all six ceased to use inhalants at end-point Control group- cessation in 1/3rd and reduction in 1/3rd

Sakai et al, 2006 (US)	Pre/post test case series	80 adolescent substance users, of which 34 had ever used inhalant 14 could be diagnosed as inhalant use disorders (7 current users)	Residential treatment program based on modified therapeutic community (6-12 months) Multi-modal approach (medication, individual & family counseling, vocational skills/education, behavioral principles)	2 years post-admission	Inhalant use decreased, with only one adolescent reporting use in past month
Taymur et al, 2011 (Turkey)	Single group pre/post quasi-experimental study	17 adolescent inhalant users, with 53% having crime-related/legal problems	Once-a-week individual supportive psychotherapy	6 months	All were abstinent at end-point; 4 had a regular job and 4 attended school regularly
Simpson, 1997 (US)	Pre/post test case series	Of total sample of 175 mexican american adolescents, 61 inhalant users (weekly, monthly or experimental)	Youth advocacy programme (counseling, life skills, activities)	1 years and > 4 years post-admission	Decrease in number of inhalant users at 1 year and significant drop at 4 years
Unpublished data (source: Dell et al, 2011 (Canada)	Pre/post test case series	154 youth (reflecting 40% of total clients admitted between 2007-09)	Residential, spiritually grounded treatment; Elements of positive psychology and indigenous culture	3- & 6 months post-treatment	Abstinence: 50% at 3 months and 74% at 6 months ; Improved school attendance and reduced legal difficulties
Benegal et al, 1998 (India)	Single group pre/post quasi-experimental study	Of total 321 street children, 81 were inhalant users , whose pre/post data was available	Experimental brief intervention using animated video & workbook in group setting (2-3 sessions) – for sensitization and Life Skills	3 months after intervention	78% stopped or reduced the use of solvents
Ray, Dhawan et al, 2009 (India)	Single group pre/post quasi-experimental study	100 street children	Psychosocial intervention package – focusing on Life Skills	Immediately after Intervention	Improvement in inhalant use, hygiene, drug refusal skills, money management, living arrangements
Ray, Dhawan et al, 2011 (India)	Single group pre/post quasi-experimental study	100 street children (≤ 18 years), Pre/post data available for 75	6-session intervention package – focusing on Life Skills delivered over 3 days in group setting	3 months after intervention	Reduced quantity & frequency of use , Increased contact with families, and improved functioning

reviews and meta-analysis in adolescent substance users have been referred to. No effort was made to search the adult literature which was not deemed to be relevant as inhalants are primarily abused at a younger age.

To assess comparative effectiveness of different types of treatment programs for adolescents with substance use disorders, Lipsey and colleagues have conducted a total of three meta-analysis, which included the Controlled

Clinical Trials, Single Group Pre/Post Studies and Treatment Provider Data respectively. [110,111] A consistent pattern emerged showing overall positive effects for all kind of treatment models compared with comparison conditions. However, three approaches, which are (a) Family Therapy, (b) Cognitive Behavioral Therapy (CBT), and (c) Motivational Enhancement Therapy/CBT (MET/CBT) tended to show the best outcomes in meta-analyses of controlled studies as well as single group pre/post studies. Individual counseling was less effective than all other treatment types with which it was compared. A prior systematic review had studied the out-patient treatment effectiveness of adolescent substance abuse using only RCTs (n=17). The results showed especially positive treatment effects for multidimensional family therapy (MDFT), Functional Family Therapy (FFT), and Cognitive Behavioral Therapy (CBT). [112]

Although several evidence-based and empirically supported treatments have been found to be effective, those that incorporate family-based intervention consistently provide the most positive treatment outcomes for adolescent substance users with conduct problems.[113] This evidence is important as a high prevalence of conduct problems is often seen among inhalant users [67, 105] who may benefit from family based therapies.

Robust evidence from RCTs of CBTs[114] indicates that Group and Individual CBT were associated with significant and clinically meaningful reductions in adolescent substance use. The evidence for Group Therapy is particularly important, as it helps to clear some of dilemmas surrounding the aggregation of problematic youths into a single group treatment setting.

Research studies have consistently shown the effectiveness of motivation enhancement and brief interventions for substance-using adolescents. Two systematic reviews are available for the effectiveness of brief interventions[115] and motivational interviewing[116] respectively in substance-using adolescents. Small but significant effect sizes were found for substance use outcomes. Another systematic review of early interventions, employing brief interventions strategies, in adolescent substance users had found similar effect sizes for a range of behavioral outcomes. [117] In a randomized trial for substance using adolescents in school setting, the brief intervention group that included a parent session exhibited greater and more consistent intervention effects compared with the condition in which only the adolescent client received services. [118]

Contingency management approaches have received some research attention in the literature on adolescent substance use treatment, [119-122] and could be a potentially promising technique for adolescent substance abusers. [123]

3.5.3 Psychosocial Interventions for Inhalant Use Disorders

It should be mentioned here that the treatment for inhalant users is often multi-modal and multi-component, and one or more of the following interventions is used depending on their suitability, feasibility and availability of expertise. Only those approaches that have shown some promise for management of inhalant use or substance use disorder in general are discussed in some detail below.

Brief Intervention/Motivational interviewing (BI/MI)

A brief intervention can be defined as a treatment strategy in which structured therapy of short duration (typically few minutes) is offered with the aim of assisting an individual to cease or reduce the use of a psychoactive substance. (WHO lexicon of drugs and terms [124]) Although a range of interventions are referred to as brief interventions, we restrict the discussion to Brief Intervention based on Motivational Interviewing principles (BI/MI). Typically, BI/MI begins with a screening process followed by a brief advice and counseling.

BI/MI can be used as a main strategy for opportunistic intervention in early or occasional users who may present to a health care setting for a problem related or unrelated to inhalant use. Adolescents who experiment with inhalants may stop them after using once or a few occasions (transient users), never meeting the criteria for diagnosis of inhalant use disorders. Such adolescents are candidates for Brief Intervention in addition to health education. Even for heavy users, brief interventions may help to identify and encourage them to seek treatment and referral, though eventually they will require more intensive interventions. [125] Brief Intervention can be delivered by physicians, nurses, social workers or health workers in a variety of settings and also be school counselors in school settings.

Motivational interviewing is a non-confrontational, client-centered approach, which is employed. [126] There are six elements critical to a brief intervention, which are summarized as the acronym FRAMES:

- **F**eedback is given about personal risk or impairment (using information gained from questionnaire scores or blood investigations)

- **R**esponsibility for change is placed on the patient.
- **A**dvice to change is given in clear terms
- **M**enu of alternative treatment options is offered
- **E**mpathic style is followed
- **S**elf-efficacy is encouraged

No clinical trials or case series were available specific to use of BI/MI for inhalant users. Evidence for effectiveness of BI/MI can be extrapolated from several methodologically sound studies demonstrating its effectiveness for adolescent substance use. Adolescent substance users are more focused on immediate concerns and BI/MI should take this into consideration. Brief Intervention, using motivational interviewing, should be provided to all inhalant users, as and when, there is an opportunity or contact with health professionals. [B]

Robust evidence is available for a CBT-based brief intervention (three 1-hour sessions) which was found useful in a sample of hospitalized inhalant dependent users, however it has been considered under the cognitive behavioral approaches.

Health education (and harm minimization)

Health education is based on the health promotion model, where individuals are empowered to assume more control over improving one's own health. [127] Universal education aimed at prevention of inhalant and other drug use among adolescent population is out of scope of this clinical practice guideline. What is being discussed here is targeted education, aimed at inhalant users who are at risk for a variety of health complications.

Targeted health education can be delivered to individuals or group of individuals and their families in clinical settings, or communities experiencing high rates of inhalant-related deaths. It must be provided in a simple, locally understandable language with due cultural considerations. Targeted health education for inhalant users and their families should cover the following areas:

- Provision of information about the short-term and long-term harmful effects of inhalants
- Minimization of harm/s or risk/s associated with inhalant use (harm minimization)

- Basic management of intoxicated individual (peer or family member)
- Information about various resources for knowledge and help regarding inhalant use

Harm reduction, per se, is not considered as a mainstream treatment approach in the context of inhalant use unlike many other substances. Although abstinence is the safest and most advisable option, several users are not motivated to quit and may continue to use inhalants along with treatment. In this context, harm minimization, through provision of education, can be one of the steps to reduce the risks associated with inhalant use. Harm reduction in the context of Inhalant use has been described by d'Abbs and MacLean, [128] and also has been incorporated in national framework for addressing inhalant use in Australia. [79, 129]

Harm minimization involves: (a) making the environment or surroundings safer for the user, and (b) altering the practices by which inhalants are used to minimize the risks, including fatality. Key messages which should be incorporated in the targeted education/harm minimization session are shown in box 5.

No clinical trials or case series were available specific to role of health education in inhalant users. Even though several studies on inhalant users included education as part of a multi-modal intervention, but no conclusions could be made about its specific effects on treatment outcomes. Based on expert opinions and consensus, it is recommended that Targeted education must be provided to all inhalant users (and their families) aimed at provision of information about the harmful effects of inhalants, harm minimization, management of intoxication and resources to get more information.

Box 5: Key messages aimed at harm minimization for inhalant users (and their families)

- Do not use inhalants with a bag on the head (*bagging*) to avoid suffocation
- Avoid using inhalants in secretive, enclosed spaces e.g. cupboards as consciousness may be lost due to inadequate oxygen supply
- Avoid use of inhalants when you are smoking or near a lit cigarette or lighter
- Do not drive (for the next several hours) after using inhalants

- Avoid concomitant use of other drugs to prevent overdose
- Avoid using inhalants while alone
- Use inhalants from small bottles with small surface areas to minimize exposure
- Do not use inhalants immediately before exercise or physical exertion to reduce risk of arrhythmias and sudden death
- If someone is using inhalants, do not unnecessarily alarm or chase or try to hold them if they are struggling, to reduce risk of sudden death which is more common if heart rate is elevated
- A family member or peer who has used inhalants must be closely monitored for at least 6 hours to ensure his/her safety.
- Call emergency medical services if the person shows unusual symptoms or behavior, e.g. agitation, seizure, disorientation or loss of consciousness.

Psychological therapies

Cognitive-behavioral therapy (CBT) has been shown to be effective in treating adolescent substance use disorders. [110] Both Group and Individual CBT are associated with significant and clinically meaningful reductions in adolescent substance use. [114] Cognitive-behavioral therapy based approaches in substance using adolescents should have certain common features, [114, 130, 131] as follows:

- Employing motivation-enhancing techniques to establish a strong treatment alliance and improve treatment engagement and retention
- Performing a functional analysis to identify patterns of inhalant use, skills deficits, and dysfunctional attitudes and thoughts
- Enhancing coping strategies to effectively deal with craving and negative moods
- Strengthening problem-solving and communication skills and the ability to anticipate and avoid high risk situations; and
- Identifying enjoyable activities incompatible with drug use/alternate recreational pursuits.

New skills and coping strategies are initially taught and practiced during therapy sessions, then applied to the patient's daily life in 'homework'

assignments, with a review of successes and setbacks the following week.[130] Typically, the sessions are delivered on a weekly basis, ranging between 5-16 sessions.

However, CBT-based brief interventions, typically between 1-4 sessions, have also been used as stand-alone approaches or part of ongoing care.[35] Recently, an RCT[100] supported a higher efficacy of CBT-based brief intervention compared to simple education among adolescents with inhalant dependence. [I] The cognitive behavioral treatment had a focus on psychoeducation. and consisted of three sessions. During the first session, patients were informed about dependency and harmful effects of volatile substances. The second session was about high-risk conditions and on how to cope with the cravings. During the third session, adolescents were trained on how to resist drug offers and how to cope with emergency conditions.

Individual and Group CBT are both effective treatment options for adolescents with substance use disorders. Cognitive-behavioral therapy (CBT)-based brief interventions should be considered for patients with inhalant use disorders [Ib, A].

Apart from CBT, *Supportive psychotherapy* has been found to be effective in at least one quasi-experimental study [IIb] by Taymur et al. [106] Weekly individual supportive psychotherapy was implemented for adolescents with inhalant abuse. Issues focused during individual supportive psychotherapy included:

- positive and negative life events in family
- expectations and disappointments about family
- information about substance abuse
- educational levels and expectations from education
- communication styles in interpersonal relationships
- positive and negative life events in interpersonal relationships
- evaluation of problem solving skills and its restructuring
- expectations from the future
- creating alternatives about what can be done in the future.

Contingency management has been tried for adolescent substance use treatment. [123, 132] In this approach, substance use is conceptualized in the framework of operant behavior, which is amenable to change via the same processes and principles as other types of human behavior. Adolescents often enter treatment because their parents, school, or the judicial system

require it. In this scenario, contingenecy interventions may offer clear incentives and positive reinforcers for quitting, which are designed to enhance motivation to abstain. Further, the referral agents that bring adolescents into treatment (families, schools, legal authorities) are also potential sources for the implementation of contingency management strategies. Such interventions could be effective additions or alternatives to clinic-based treatments [123] of adolescent substance users and need to be researched in a systematic manner.

Person-centered general counseling, as described by Carl Rogers, may be used for patients. Although it is often incorporated as one of components in a treatment program, but specific evidence for person-centered counseling for inhalant users has not been evaluated. Its recommendation is based primarily on expert consensus and expert opinions. Person-centered general counseling is a non-directive approach to psychotherapy, which is based on premise that person may be able to understand the cause of their problems after reflecting on their thoughts and feelings. Therefore, this form of therapy does not recommend any particular course of action to the patient and instead, assists him/her to take responsibility for themselves. [133]

Narrative therapy is an informal approach, which can be of assistance for adolescent patients who may show resistance to traditional psychotherapies. It involves an informal interactive conversation with the adolescent to help him/her in gaining insight into life's experiences through the use of stories. Stories can be about an individual's skills, desires, friendships or work, and Narrative therapy explores how the adolescent forms and links these stories to make meaningful conclusions. [134, 135]

In an intervention developed in India for out-of-school/street children with inhalant use (box 6), [109], story-telling method has been included in one of sessions, as follows: The children are shown six pictures based on which they are expected to build a story. The six scenes depict the child a) with the family b) on the railway station (running away from home) c) with his new peer group d) using inhalants e) depicting problems due to drug use – social, legal or health related and lastly, f) a blank picture that has to be filled up by the child depicting what should happen to change the outcome to a more desirable one. The last blank card facilitates processing.

Family based approaches

Family-based treatment is the most thoroughly studied behavioural treatment modality for adolescent substance abuse with proven effectiveness. [110, 136]

Family therapy is based on the assumption that dysfunctional family dynamics contribute to adolescent substance use and related problems. In practice, clinicians perform a functional analysis to identify problematic behaviors, family dynamics and relationship patterns which are targeted with restructuring interventions. Parents are taught about the monitoring skills and basic behavioral management principles to improve their adolescent's behavior and reduce drug abuse together with strategies to improve overall family functioning and sustain the gains of treatment. [130]

Of the specific models, that have emerged as 'well established' interventions include Multidimensional Family Therapy (MDFT) and Functional Family Therapy (FFT) in a meta-analytic synthesis of adolescent substance use treatments. [112] Three additional family models – Brief Strategic Family Therapy (BSFT), Behavioural Family Therapy (BFT) And Multisystemic Therapy (MST) – were classified as 'probably efficacious'. In another comprehensive review of outpatient treatments, [136] ecological family therapy (including MDFT and MST) have shown evidence of treatment superiority in the highest quality studies. Specific discussion on principles and protocol of family therapy is out of scope of this guideline and readers are requested to consult relevant references, [137, 138] and other resources.

The family-based approaches should be considered for all patients with inhalant use disorders, wherever family is available [IIb, B]

Even when family therapy is not feasible, an attempt must still be made to engage and involve the family in treatment process. A range of *family interventions* should be used in routine clinical care of adolescents, including family education (including information on harm minimization) and family counseling. The aims of family-inclusive clinical practice are:

- provision of information to family members and caregivers
- ensure their involvement in treatment process and care
- seek their help to enforce behavioral strategies at home
- minimize expressed emotions
- make the family environment and relationships conducive to recovery of inhalant users

Activity and engagement based approaches

Therapeutic programmes for young people have frequently made the use of recreation or activity-based strategies to engage them in therapeutic relationships, develop skills and provide alternatives to inhalant use.

At least two descriptive studies are available for inhalant users supporting the use of activity based approaches. [102, 103] Cheverton et al. [102] had used two weeks daily arts training followed by a performance project to engage homeless street children, with consequent reduction in inhalant use and improved functioning. Butt [103] had described the Get Real Challenge (GRC), which was an activity based programme for volatile substance misusers from indigenous communities of Australia, majority of whom used other substances. The program provided alternative activities for inhalant users in the form of beach-day, deep sea fishing, cultural evening, outdoor excursions etc where meals were also provided. Participation in at least 3-5 sessions was found to be optimal.

Participation in activity- and engagement-based approaches should be encouraged, wherever feasible, alongside other interventions [III, C]

Life Skills based approaches

Life skills are abilities for adaptive and positive behavior, which enable the individual to deal with problems and challenges of life. [139] It is assumed that as the life skills are gained, a person gains more problem solving behaviors which improves the capacity to deal with problem behaviors, including drug use.

Several treatment approaches have used various life skills as one of the components of a multi-modal intervention. For example, the intervention by Ray et al.[109] for Inhalant using children incorporated activities aimed at money management. It uses a game with fake money bills, where the child is asked to plan how he would spend his income under various heads. The exercise is designed to allow the children to reflect on various possible ways of spending money and thus, increase options of spending money on constructive and healthy options. It may be especially useful for street children who often do not have concept of managing money and end up using all day's income on using inhalants and other drugs.

Box 6: Intervention for out-of-school/street children with Inhalant use developed in India

The six sessions of the intervention are delivered in groups of 5-10 children over five half days (or 2-3 full days). Intervention uses role play, forum theatre, story-telling and other innovative and engaging methods to deliver the sessions.

The themes of the sessions are as follows:

1. Functional analysis of pro-social activities and substance use behaviour
2. Motivation enhancement and harm reduction
3. Life skill Training (drug refusal skills and enhancing self-esteem)
4. Health management and knowledge of harms or perceived benefits of inhalant use
5. Money management and healthy recreational pursuits
6. Relapse Prevention and role of networks and family in preventing relapse

Source: Ray, Dhawan et al, 2011

Residential rehabilitation

Residential rehabilitation programmes addressing substance misuse in adolescents are often multi-modal and incorporate a range of components such as counseling, education and life skills. Sakai et al.[105] reported on a 6-12 month residential treatment program that utilizes a modified therapeutic community for adolescents with inhalant use and related problems. It included specialist services, individual and family counseling, onsite school for individualized instruction focusing on vocational and educational objectives. The program utilized a behavioral approach, providing rewards for positive behavior and consistent, fair, punitive consequences for misbehavior.

Indigenous-led residential rehabilitation for inhalant users has been reported from Canada (unpublished source) [108], which is culturally based treatment approach based on the elements of positive psychology, including resiliency theory and emotional intelligence, and grounded in an Indigenous cultural understanding. Specific strategies included ceremonial feasts, elder's teaching, among others. Coleman et al.[104] reported on a federal residential treatment programme for indigenous inhalant users in Canada, which included therapy, access to specialist services and traditional healing practices and ceremonies. Another model practiced in Australia, is the *out-station model of rehabilitation*, which is run by indigenous people, aimed at the young people of the community and has following features: physical remoteness, good food and *kanyirninpa (elder's helping in nurturing and learning of the young people through culturally approved teachings)* usually

lasting between 16-20 weeks. [140] However, the rigorous evaluations of these programs have not been done so far.

Evidence for efficacy of residential rehabilitation approaches is mainly based on descriptive studies, unpublished sources and expert consensus documents. [IV] Therefore, it may be used only for chronic, heavy users of inhalants (with or without multiple substance use) for whom other treatment options have shown multiple failures. [D]

3.5.4. Summary of Treatment Recommendations

In order to formulate the recommendations for this sub-section, following were considered:

i) Evidence from studies on inhalant users, summarized in sub-section 3.5.1

ii) Extrapolated evidence from adolescent substance use treatment, summarized in sub-section 3.5.2

iii) Expert consensus based recommendations in other settings, in particular Australia and United States

iv) Expert opinions based on clinical experiences in Indian adolescent treatment settings

The recommendations have been discussed alongside the specific treatment interventions in the previous sub-section, but key recommendations are summarized here for benefit of readers:

- Psychosocial treatment should be offered to all inhalant users [S]
- Brief Intervention, using motivational interviewing, should be provided to all inhalant users, as and when, there is an opportunity or contact with health professionals.[B]
- Targeted education must be provided to all inhalant users (and their families) aimed at provision of information about the harmful effects of inhalants, harm minimization, management of intoxication and resources to get more information. [S]
- Consider cognitive-behavioral therapy (CBT)-based brief interventions for patients with inhalant use disorders [Ib, A]
- Supportive psychotherapy should be provided to patients with inhalant use disorders. [IIb, B]

- General (patient-centered) counseling and Narrative therapy can be used for patients with inhalant use disorders. [IV, D]
- Participation in activity- and engagement-based approaches should be encouraged, wherever feasible, alongside other interventions [III, C]
- Consider family-based approaches for all patients with inhalant use disorders, wherever family is available [IIb, B]
- Life-skills based approaches should be employed for all inhalant users, preferably in a group setting, alongside other interventions [IIb, B]
- Residential rehabilitation approaches may be used only for chronic, heavy users or poly substance users, when other treatment interventions have been unsuccessful. [IV, D]

Other key issues that need to be remembered while managing adolescent inhalant users is the associated high rates of co morbid psychiatric disorder including conduct disorder and the impairment in neuropsychological functioning that is associated with inhalant use. It is generally believed that inhalant use should be treated in an inpatient setting with admission for more than a month. Also, due to the attention deficits in inhalant users, any kind of psychosocial intervention that is carried out has to be conducted as brief sessions of 15-20 minutes duration. These general principles of treatment have been described earlier (refer section 3.1.)

Applicability

Given the paucity of evidence base, it will be difficult to comment on which of these approaches Family therapy/CBT/Life skills/Supportive psychotherapy may be preferred in a given patient. In a clinical setting in India, avenues for receiving training related to the above mentioned approaches are an important clinical consideration. Familiarity in dealing with clinical issues in adolescents with psychiatric disorders or in adult substance users are important, however there may be important differences. The role of family in adolescent substance users is much more important than adult substance users. The dependence of the child on the family for meeting his physical needs is much more pronounced in children. In children who come from the lower socioeconomic strata, the parents very often lack the psychological orientation to understand psychosocial intervention as a treatment modality and are looking for “pills” as treatment. Besides this, frequent visits to the clinic for psychosocial intervention can be challenging

for them because it may entail losing a days' wages. In spite of these constraints, it is possible to engage the patient and the family in the treatment process. It is important for this purpose to identify one or more key family members who can be educated about the nature of the disorder, the treatment process and recovery.

When dealing with underprivileged children living on the streets who constitute a substantial percentage of inhalant users, family members are often absent and NGOs may play the role of surrogate guardians.

Section 3.6. Pharmacological Interventions for Inhalant Use Disorders

The pharmacological interventions for inhalant withdrawals have been covered elsewhere and present section deals with pharmacological interventions for treatment of inhalant use disorders.

3.6.1 Summary of evidence for pharmacological treatment of Inhalant Use Disorders

No controlled clinical trials are available for pharmacological treatment of inhalant use disorders. Available evidence is in the form of two isolated case studies, which are being summarized below:

- A case study [82] reported a 21-year old male patient who used inhalants regularly for four years. He met the diagnosis of Inhalant Dependence, in addition to depressive and anxiety disorders, NOS as per DSM IV TR. He had received a course of individual and behavior psychotherapy for 2 months, which was not effective. Subsequently, he was given a trial of lamotrigine (25 mg/day), increased to 100 mg/day within 2 weeks. After receiving this treatment for 4 weeks, the patient had been able to resist his craving for inhalants and avoid use of inhalants. Patient was on same dose of medication for 6 months, without any use of inhalants.
- A case study [95] of a 22 year old patient inhaling petrol for six months, reports the use of buspirone 40 mg/ day for two months, which led to a marked reduction in frequency of use from first week up to 8 weeks. Psychosocial treatment remained the same before and during use of buspirone. The study reports on the short-term efficacy of buspirone in achieving abstinence from inhalants in the patient.

Various hypotheses have been proposed for use of these pharmacological agents. The site of action of inhalants is not completely understood, but

recent studies suggest that ion channels that regulate neuronal excitability may become more sensitive after use of inhalants. [141] Lamotrigine has been hypothesized to stabilize glutamate mediated neuronal excitability.[82] In contrast, Buspirone is a serotonin agonist, which has been described as an anxiolytic. Because of buspirone's serotonergic efficacy with additional anxiolytic efficacy, it is hypothesized that it might reduce fear and anxiety due to dependency, which may be the initial reason for consuming inhalants. [95] It must be emphasized here that the field needs more research to arrive at specific pharmacotherapies for treatment of inhalant use disorders.

At present, there is insufficient evidence for using a pharmacological agent for treatment of inhalant abuse/dependence.

3.6.2. *Treatment Recommendations for Inhalant use disorders*

Available literature on pharmacological treatment of inhalant use disorders is almost non-existent. There is an insufficient evidence for using a pharmacological agent for long term treatment.

Section 3.7. Management of Comorbid Psychiatric Conditions

It must be noted that the Inhalant induced disorders (as opposed to Inhalant use disorders) do not come in the purview of this practice guideline. However, it was decided that a sub-section on treatment for inhalant-induced disorders should be included here for comprehensive discussion and for pragmatic reasons, as specific attention has rarely been devoted to them elsewhere.

Readers are advised to consult the literature on management of comorbid mental and substance use disorders [131,142] for general principles and issues pertaining to assessment, diagnosis and treatment in such cases.

3.7.1. Review of evidence for Comorbid Conditions

Chronic inhalant users are likely to have an increased association with mood disorders, especially depression and suicidality, anxiety disorders, psychotic disorders, conduct disorders and personality disorders. [67, 143]

Mood and anxiety disorders: In a sample of inhalant users (n=664) derived from nationally representative U.S survey, a high lifetime prevalence of DSM-IV mood (48%), anxiety (36%), and personality (45%) disorders was found, with 70% of users fulfilling criteria for at least one of disorders. [144] Among a sample of adult inhalant dependent users, the prevalence of Axis I disorders was 72.3% for lifetime major depression, 41% for major

depression-current, 24% for dysthymic disorder, 20.5% for inhalant-induced depressive disorder, 27.7% for panic disorder, 30% for PTSD, 36.1% for social phobia and 20.5% for generalized anxiety disorder, which was higher compared to other substance dependent users and non-users. [145]

Suicidality: Several studies have found elevated rates of suicidal ideation. In the U.S national comorbidity survey, among persons with inhalant use disorders, 67.4% had thought about committing suicide and 20.2% had attempted suicide. [146] In a prospective longitudinal study, 147 early-onset of inhalant use signaled modestly excess risk of suicide attempt among female users (RR = 2.2; p = 0.05). The severity of inhalant use was positively associated with histories of suicidal ideation and suicide attempts. [148]

Psychotic disorders: Evidence for psychotic disorders has mainly emerged from several isolated case reports. [149-153] and few observational studies. [154] It appears that inhalant-induced psychotic disorder is a common diagnosis in some geographical locations e.g. Mexico City where inhalants are widely consumed. [155]

A case report from India [156] described psychotic symptoms in the form of delusions of reference and persecution, bizzare delusion, voices commenting on his actions and hoarding garbage and dead crows which persisted for 3 years in a chronic inhalant dependent user, and remitted after abstinence. Positive symptoms in the form of delusions (including first rank) and hallucinations appear to more common compared to negative symptoms, [157] though one study has suggested amotivational syndrome to be a characteristic feature of patients suffering from inhalant-induced psychosis.

Okudaira et al [154] compared the three sub-groups (psychosis, dependence, abuse) of inhalant abusers. Patients in the psychosis group had a higher prevalence of family history of schizophrenia and past history of multiple drug abuse. However, when patients with inhalant induced psychosis were compared to schizophrenia patients in a separate study, there was no significant difference in family history. [158] This study, using principal component analysis, also indicated that inhalant-induced psychotic disorder is a discernable syndrome, distinct from schizophrenia. There has been debate about the reversibility of psychotic symptoms associated with inhalants, with some reports suggesting an irreversible psychosis [150,159] others suggest a sustained psychosis for a long time [160, 161] and some others reporting a complete recovery after abstinence. [156]

Conduct problems and Anti-social behaviors: Studies from residential clinical settings have found higher rates of inhalant use (36.7%) among youths with antisocial behaviors [49] and higher rates of conduct disorder among inhalant users. [67] Few general population surveys have also examined the association of inhalant use with adolescent [162] as well as adult 144 antisocial behaviors. In a nationally representative sample of inhalant users, [163] a higher lifetime levels of childhood and adult anti-social behaviors were seen in inhalant users compared to non-users. The inhalant users who were dependent were significantly more likely, compared to non-dependent users, to have reported bullying behavior, starting physical fights, using dangerous weapons, physical cruelty to people, staying out all night without permission, running away, and frequent truancy in childhood, as well as greater deceitfulness, impulsivity, irritability/aggressiveness, recklessness, and irresponsibility in adulthood.

Attention deficit disorders: The association of childhood attention deficit disorders with adolescent and adult substance use disorders is well established. [164, 165] Only few of such studies have focused specifically on inhalant users. In a longitudinal cohort study of children aged 7-18 years recruited from general population, hyperactivity-inattention symptoms alone accounted for the risk of subsequent lifetime use of other drugs including stimulants, opiates, inhalants and sedatives (OR=2.72, p=0.02) in male subjects. [166] In an unpublished study from a tertiary care Indian setting, [84] a high prevalence (16.6%) of attention deficit/hyperactivity disorders was found, indicating the need for more clinical and research attention

Learning problems: No specific studies are available on prevalence of specific learning disorders in inhalant users. Even in research studies on comorbidites in substance use disorders, most large scale surveys have restricted their coverage to major disorders. Many of commonly used instruments e.g. MINI-KID, CIDI do not assess for specific learning disorders, thus limiting the available research findings. CASA [167] proposes that learning disorders may be a risk factor for substance use problems. Children with learning disabilities are at greater risk of school failure and often experience difficulty, frustration , low self-esteem, peer rejection, engaging in negative and disruptive behaviors, and a desire for peer acceptance, all of which can act as a risk factor for substance use. However, the research base is rather minimal.

At times, the differentiation between independent co-morbid disorders and inhalant-induced disorders may be quite difficult, as highlighted in the case report from India, [168] one may need revisions in diagnosis after a longitudinal period of observation and follow-up.

3.7.2. Summary of Evidence for pharmacological treatment for Comorbid Psychiatric Conditions

Available evidence is in the form of isolated case studies, which are summarized in table 6. Additionally, a case study by Shen[82] has described a patient with inhalant dependence, depressive disorder NOS and anxiety disorder NOS who received lamotrigine (100 mg/day), with complete abstinence from inhalants for six months. Lamotrigine was hypothesized to have stabilized the glutamate-mediated neuronal excitability, possibly caused by inhalants. An alternate hypothesis could be possible role of lamotrigine in treating depressive symptoms, with a consequent reduction in inhalant use. However, surprisingly latter hypothesis was not at all discussed by authors and no specific attention was given to mood/anxiety symptoms in case report. So, this case report was not included in the summary table.

Table 6 : Summary of evidence for treatment of comorbid psychiatric conditions[156,169,170, 171]

Study reference	Study design & sample	Diagnosis	Treatment/ Intervention	Outcome
Rao et al, 2009 (India)	Case report 23-year male	Volatile solvent dependence Solvent-induced schizophrenia like psychotic disorder Toxic maculopathy	Supportive care Use of diazepam as required	Psychotic symptoms subsided within 2 weeks of abstinence Visual impairment persisted
Misra et al, 1999 (U.S)	Case report 25-year male	Inhalant dependence Inhalant induced psychotic disorder	Risperidone (2 mg/day)	Resolution of psychotic symptoms Abstinence maintained at 12 weeks follow-up Improved functioning
Erdogan et al, 2010 (Turkey)	Retrospective case analysis N=7 adolescents	Inhalant abuse & Conduct disorder	Aripiperazole (5-20 mg)	No side-effects which warranted cessation 4/7 patients abstinent at 3 months of treatment Significant improvement in mean CGI scores at 6 months
Hernandez et al, 1998 (Mexico)	Randomized controlled trial N= 40 males admitted patients	Inhalant dependence Inhalant-induced organic mental state (DSM IIIR)	Carbamazepine (920±336.5mg) or Haloperidol (21.7±10.6 mg) for 5 weeks	Nearly half patients responded in each group Carbamazepine appears to have comparable efficacy to haloperidol in inhalant induced psychosis, with fewer adverse effects

3.7.3. Treatment Recommendations

There is no research study for treatment of co morbid mood and anxiety disorders, and only one retrospective study for treatment of co morbid conduct disorder.

Treatment of inhalant-induced psychotic disorder has been described in a few case reports and one randomized controlled trial. [I] The trial by Hernandez et al. [171] compared carbamazepine to haloperidol for treatment of psychotic disorder and found both to be equally efficacious. It was concluded that carbamazepine may be a better choice given the adverse effect potential of haloperidol in inhalant users who may have neuronal damage. However, it needs to be pointed out that haloperidol has been, more or less, replaced by use of atypical antipsychotics over the past decade. Therefore, the findings from this randomized trial may not be relevant or applicable in current context especially since carbamazepine may have a range of adverse effects of its own. The study was, therefore, not deemed to be suitable to guide the treatment recommendations, even though it was a randomized trial.

In absence of a evidence base, following recommendations are made on basis of expert consensus/opinions/experiences. [IV]

- The management of inhalant-induced psychiatric disorders should be guided by the same general principles as in management of dual diagnosis patients. Generally, these patients should be treated by a specialist.
- Careful history should be taken to assess for psychiatric conditions with onset during childhood and adolescence e.g. attention deficit/ hyperactivity disorders, learning disorders, oppositional defiant disorder, conduct disorder etc.
- In view of a high prevalence of psychiatric comorbidites, the mental state examination should be carefully conducted in all chronic inhalant users to look for any evidence of mood, anxiety, psychotic or cognitive symptoms.
- Inhalant-induced psychiatric disorders are likely to subside with supportive treatment and maintenance of abstinence. Specific psychotropic medications are not warranted, unless the symptoms are severe, risky or life-threatening.

- Inhalant users are more likely to have underlying neurological damage, and consequently, may be more susceptible to develop tardive dyskinesia and other adverse effects with use of typical antipsychotics. Typical anti-psychotics may be avoided for treatment of psychotic disorders in inhalant users.
- All medications must be started at low dose and increased only gradually (*start low, go slow*) with close monitoring, as chronic inhalant users may have neurological, cognitive, renal, hepatic or other impairments, which could be worsened.
- Careful consideration must be done for choice of a particular medication, including the full range of adverse effects, possible interactions with other drug/s. other substances of abuse or its impact on comorbid health condition/s in an inhalant user.

4. FUTURE DIRECTIONS

Inhalant use disorder continues to be an under-researched area, though some progress has been seen over the past decade. There are several challenges to be overcome by this sub-specialty, which is still in its nascent stages. The public health perspective for inhalant use is totally lacking in most countries, including India. Inhalant users continue to remain a largely hidden population, with very few treatment seekers. The absence of requisite expertise, child-friendly services or specific pharmacotherapies make it difficult to retain patients. Consequently, there is a need to broaden and strengthen research base on key aspects of inhalant use disorders, which can guide the service provision and policy development.

Evidence regarding various aspects of inhalant use disorders is either low-grade or non-existent. Large part of research on management is comprised of case reports (which were not counted towards recommendations), case series or treatment data from program evaluations (possibly for funding, and consequently, not as rigorous as a planned scientific research). Barring a few, there are hardly any randomized controlled studies in the field. Future research should, therefore, place a higher emphasis on methodological rigor, using more robust study designs and methods. Specific areas for future research are discussed below:

- Inhalants are a heterogeneous group which have various types (e.g. volatile solvents, aerosols), and multiple products (e.g. correction fluid,

gasoline) and ingredients (e.g. toluene, 1,1,1-trichloroethane) within each type. There is a need to understand the relative differences between the various inhalants in terms of their acute or chronic effects, toxicity, health effects, withdrawals, and the clinical implications of these differences, if any.

- Inhalants are primarily a drug of abuse during childhood and adolescence, when neuro-maturation is not yet complete. There is a need to investigate the neurobehavioral consequences of exposure to inhalants during this developmental period.
- More epidemiological studies are needed to document the prevalence and patterns of inhalant use in general population and high-risk groups, especially in Indian settings.
- The inhalant–related mortality data need to be documented systematically as it remains under-reported in India. Similarly, there is minimal data on health complications and HIV prevalence among inhalant users.
- More prospective studies are needed to understand the trajectories of inhalant use disorders, including factors affecting initiation, course and outcome.
- There is an urgent need to develop and validate the screening tools and clinical rating instruments to assess the severity of inhalant use. There is a complete absence of standardized and validated tools to assess and measure outcomes of inhalant use disorders.
- There is a need to develop a consensus on the various outcome parameters for interventions used for inhalant use disorders, which will facilitate comparison of various studies.
- Carefully planned studies are required to establish the presence and nature of withdrawal syndrome, which is still controversial
- Many of the treatment programs are multi-modal in nature, and it is difficult to comment on the relative efficacy of each component, limiting their applicability (unless one uses the whole package). There is a need to discern the key effective components of these multi-modal treatment programs. Individual treatment modalities should also be systematically studied to know their efficacy.
- The psychosocial interven-tions which have been found to be effective in rigorously conducted studies elsewhere (e.g. CBT-based brief

intervention), need to be studied and replicated in Indian patient population. Similarly, family-based approaches which have been found to be effective in adolescent substance use treatment need to be tested and adapted for adolescent inhalant users in Indian settings.

- Brief Intervention based on motivational interviewing principles has been widely tested for many other substances of abuse, but there is a need to document its effectiveness for early or occasional inhalant users in various health care or community settings.
- There is a need to evaluate the efficacy of indigenous models of care for inhalant users in a more rigorous manner. More low-cost, low-resource models of care should be developed for Indian settings and their efficacy tested in carefully planned research studies.
- No specific pharmacotherapy is yet available to treat inhalant use disorders. More pre-clinical and basic science research is needed to study the various possible sites of action for inhalants, which can eventually provide a clue for novel pharmacological agents.
- In view of high rates of psychiatric comorbidity, it is important to study the effective treatment interventions for co morbid inhalant use and psychiatric disorders.
- More research attention should be paid to special population groups among inhalant users e.g. street children, who may differ in risk factors, course, prognosis and long-term consequences, and may require interventions more suited to their needs and background.
- Qualitative studies can be planned to understand the user experiences of inhalants, and issues of stigma and help seeking aspects. Though it is not scientifically a rigorous design, but it can help to provide some important and new perspectives which may not be tapped with quantitative research studies.
- Women inhalant users have been grossly under-represented in research, though some evidence suggests that they do exist. There is a need to document the extent and prevalence of inhalant use among females, and study the reproductive adverse effects, including the effects of fetal exposure.
- Cross-national, multi-site research studies should be planned to look for differences in risk factors, correlates, course and outcome of the

inhalant use disorders in geographically and culturally distinct settings. The diversity of sample would also enhance the generalizability of findings.

- The public health burden and impact on communities with high prevalence of inhalant use need to be documented.
- Research evidence (in addition to expert consensus) is needed if harm-minimization can or should be adopted as one of the alternate approaches. Further, more research is needed to explore product substitution at a commercial/community level to reduce health effects or to deter the user. Many such interventions have been tried with some success in Australia (e.g. replacing leaded with unleaded gasoline to reduce health effects, or replacing standard gasoline with aviation gasoline which produce unpleasant side-effects), however feasibility and implementation in Indian settings need to be evaluated.
- Research is need to develop preventive strategies for inhalant use, testing their efficacy, cost-effectiveness, and exploring their linkage with adolescent substance use prevention and adolescent mental health services.

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CLINICAL PRACTICE GUIDELINES (CPG) FOR THE MANAGEMENT OF DUAL DIAGNOSIS

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2014

CONTENTS

EXECUTIVE SUMMARY

The term 'dual diagnosis' refers to the co-occurrence of substance use disorder along with another psychiatric disorder. Large scale epidemiological studies suggest that substance use disorders are highly concurrent with other psychiatric disorders. Co-occurrence of psychiatric disorder along with a substance use disorder worsens the course and outcome of the patients with these disorders, and is associated with longer hospital stays, poorer recovery, greater risk of having medical illnesses, and greater risk of suicide and violence.

In patients with dual diagnosis history should be explored in detail and relevant physical examination should be conducted (S). Psychiatric disorder and substance use disorder related scales and instruments can be applied to patients with dual diagnosis with minor caution (B). Due to association with medical illnesses, relevant investigations should be done in patients with dual diagnosis (D). Motivational interview as an add-on measure may improve retention into treatment for substance abuse (A). Modification of motivational interviewing techniques in view of dual diagnosis may improve outcomes in certain substances of abuse (C)

Antipsychotics are effective for patients with dual diagnosis, and it reduces psychotic symptoms as well as substance use (A). Olanzapine, risperidone, aripiprazole, quetiapine, flupenthixol and clozapine have demonstrated efficacy through at least one open label trial/ controlled trial (C). Clozapine seems be more effective than other antipsychotics in treatment of dual diagnosis psychotic disorders (C). Patients with dual diagnosis are at increased risk of having extra-pyramidal side effects (A). Bupropion and varenicline are efficacious in smoking cessation in dual diagnosis patients (A). Nicotine replacement is efficacious for dual diagnosis nicotine dependent patient (B). Naltrexone is useful in patients with alcohol dependence and psychotic disorder (A). Baclofen and disulfiram may potentially induce psychosis in dual diagnosis patients (D). Attention should be paid towards drug interactions and impact of concomitant medical illnesses on drug metabolism while prescribing (D).

Antidepressants are efficacious in major depression or dysthymic disorder with alcohol use disorder (A). SSRIs are as efficacious as

tricyclic antidepressants in patients with depression and substance use disorder (A). Single agent antidepressants are as useful as combination agents in patients with depression and substance use disorder (B). Venlafaxine is efficacious in patients with depression and cocaine abuse (C). Atomoxetine and pemoline may be efficacious in patients with ADHD and substance use disorder (C). Paroxetine useful in patients with concurrent alcohol use disorder and social anxiety disorder (A). Lithium and valproate may be efficacious in reducing substance use and controlling affective symptoms in patients with bipolar disorder and substance use disorder (B). Acamprosate and naltrexone reduces substance use in alcohol use disorder ad substance use disorder (A).

Among the psychotherapeutic modalities, therapeutic community useful for patients with dual diagnosis (A). Twelve step approaches for psychiatric disorders and substance use disorders may be useful (B). Dual focused or integrated CBT better than single focused CBT in dual diagnosis patients (A). CBT, contingency management and integrated psychotherapeutic programs are useful in patients with psychotic dual diagnosis (A). Dialectical behaviour therapy may be useful in patients with borderline personality disorder and substance, but evidence is conflicting (B). Contingency management may improve vocational rehabilitation (A).

Integrated treatment of dual diagnosis is associated with better outcomes rather than serial or parallel treatment (A). Assertive community treatment has shown benefits compared to standard care of patients with dual diagnosis (A). High service intensity is associated with better substance use, family and social outcomes (C). Training of service providers can improve staff self-efficacy and knowledge of dual diagnosis, but may not translate into better patient outcomes (B). Jail diversion services may reduce time spent in jail without increasing public safety risk (B). Immediate benefits of jail diversion services may not translate for long term benefits (B). Contingency management is useful for homeless dual diagnosis population (A). Therapeutic community shows better outcomes than treatment as usual for homeless dual diagnosis population (A).

Treatment of each dual diagnosis patient needs to be individualized based upon unique characteristics of the patient.

2. INTRODUCTION

2.1 Concept of dual diagnosis

The term ‘dual diagnosis’ has been defined in different ways by different workers and researchers. For the purposes of the present guidelines, ‘dual diagnosis’ refers to the co-occurrence of substance use disorder along with another psychiatric disorder. Other similar terms which refer to the presence of concurrent substance use disorder and psychiatric disorder include chemical abuse and mentally illness (CAMI), substance abusing mentally ill (SAMI), mentally ill chemical abusers (MICA), mentally ill substance abusers (MISA), co-occurring substance use and mental disorders (COD).[1,2]

The concerted clinical and research focus on dual diagnosis has emerged as a result of different prioritization, philosophy and modalities of treatment substance use disorders and other psychiatric disorders. While a volitional component is often implied for the genesis of substance use disorders, such a prerogative is not implied for the genesis other psychiatric disorders.[3] The service delivery formats of substance use disorder and other psychiatric disorder treatment also differ. It has been seen that substance use disorders and other psychiatric disorders co-occur with each other more frequently than by chance, and pose specific challenges. Hence there is a requirement to understand and select the treatment modalities that can best fit these dual diagnosis patients.

There is a wide range of ‘dual diagnosis’ patients if one considers the permutations and combinations of psychiatric and substance use disorders that are possible. For sake of convenience, the dual diagnosis disorders can be classified into psychotic dual diagnosis and the other dual diagnosis, based on the presence and type of primary psychiatric diagnosis. Table 1 shows that commonly encountered psychiatric disorders and the substances along with the type of substance use disorders encountered. For example a patient may have schizophrenia and alcohol dependence syndrome. These guidelines present a broad overview of management aspects of various forms of dual diagnosis.

Table 1: Dual diagnosis combinations

Representative psychiatric disorders	Substances of use	Substance use disorder
Schizophrenia	Alcohol	Harmful use
Schizoaffective disorder	Tobacco	Dependence
Bipolar disorder	Opiates	Intoxication
Major depression	Cocaine	Withdrawal
PTSD psychosis	Cannabis	Substance induced
Panic disorder amnesic state	Volatile solvents	Substance induced
Generalized anxiety disorder psychosis	Sedative hypnotic	Residual and late onset
Somatisation disorder	Stimulants	
Personality disorders	Hallucinogens	

2.2 Epidemiology

In the worldwide literature, substance use disorders have been found to be highly concurrent with other psychiatric disorders. Large scale epidemiological studies have found that substance use disorders co-occur with other psychiatric disorders like anxiety and depressive disorders than expected by chance. The Epidemiological Catchment area study notes that odds ratio of having a substance use disorder in those with mental disorder is 2.9.[4] The National Comorbid Survey also reported that alcohol and drug use disorders are quite often comorbid with other psychiatric disorders.[5] The National Epidemiologic Survey on Alcohol and Related Conditions suggests that substance use disorders were more common with anxiety and depressive disorders.[6] Studies focusing on particular disorders like schizophrenia also have found high comorbidity of psychiatric disorders and substance use disorders.[7,8]

There have been a few studies on epidemiology of dual diagnosis from India. In one of the earliest studies from India, the rates of substance abuse in mentally ill patients was about two times of that of non-psychiatrically ill population.[9] Other studies have focused upon clinic based population and have reported high rates of psychiatric illnesses in alcohol and opiate abusers.[10,11] One study has reported the typology of psychiatric illnesses across different substance use disorders of patients encountered in a de-

addiction service over a period of 11 years.[12] Thus co-occurrence of substance use disorder and another psychiatric illness is quite frequent and merits attention.

2.3 Importance of Dual Diagnosis

Since the epidemiological studies suggest that substance use disorders concur with psychiatric illnesses quite commonly, encountering dual diagnosis patients would be an expectation rather than a rarity. A considerable proportion of patients attending a de-addiction service or a psychiatric treatment facility may be suffering from dual diagnosis disorders.[12,13]

Co-occurrence of psychiatric disorder along with a substance use disorder worsens the course and outcome of patients with these disorders. It has been seen that dual diagnosis is associated with longer hospital stays and poorer recovery.[14,15] Dual diagnosis patients are also at greater risk of developing medical illnesses like Hepatitis C and HIV.[16] Also, suicide attempts and violence are more common in such patients.[17,18] They are more likely to have psychosocial adversities like homelessness. Hence, overall prognosis of patients of dual diagnosis is poor.

Clinicians having specific expertise in treatment of either substance use disorders or psychiatric illnesses may have some difficulties while dealing with patients having dual diagnosis. Dealing with patients with dual diagnosis requires competencies which can be obtained through training and experience of managing such patients. Hence, it has been suggested that dual diagnosis should be incorporated into the training programs of psychiatry residents [19]

2.4 Specific difficulties faced in patients with dual diagnosis

Many unique challenges are faced while managing patients with dual diagnosis. Firstly, patients with dual diagnosis may have poor motivation for treatment and hence may not engage in the treatment process effectively when compared to other patients. Secondly, when a patient has both psychiatric illness and a substance use problem, which of them should be tackled first or whether both should be addressed together may pose as a clinical query. Thirdly, it may be a point of contention whether a substance use specialist or a general practicing psychiatrist should manage these patients. Analogous to the question is which kind of setting should be utilized to manage these patients needs, as de-addiction facilities and general psychiatric facilities may have different viewpoints of treatment, staffing

patterns, and manner of admissions. Fourthly, regarding the issue of involuntary treatment which is at times initiated for patients with psychotic or severe affective disorders, whether substance use disorder should also be forcibly addressed during such 'involuntary' treatment may raise concern. Fifthly, patients with dual diagnosis may perceive benefits to their psychiatric symptoms with substance use and hence may face re-emergence of psychiatric symptoms as treatment of substance use disorder is initiated. This may predispose them to be less compliant to treatment. Sixthly, dual diagnosis patients may have significant medical comorbidities which may require urgent or sustained attention. Seventhly, pharmacological treatments for psychiatric disorder and substance use disorder may have significant pharmacodynamic and pharmacokinetic interactions between themselves. Hence, being aware of these interactions may help avert side effects and rationalize treatment regimen. Eighthly, psychotherapeutic interventions applicable for patients with psychiatric disorders may require considerable modifications while being used with dual diagnosis patients. And lastly, patients with dual diagnosis may have additional difficulties in rehabilitation due to issues of homelessness and poor social supports. Due to all of the above, overall treatment of patients with dual diagnosis may require modifications from perspectives of both substance use disorders and psychiatric disorder.

3. SCOPE AND METHODOLOGY OF THE GUIDELINE

3.1 Overview

Management of dual diagnosis has been considered particularly challenging as focus needs to be laid upon both the psychiatric illness as well as substance use disorder. The manner and the framework in which the services are provided are of considerable importance in the management of the cases of dual diagnosis. The mental health care service systems in India present many challenges for effective management of dual diagnosis. These guidelines aim to offer suggestions to clinicians who manage patients having substance use disorders along with other psychiatric illnesses.

3.2 Scope of the Guidelines

These guidelines are aimed primarily for clinicians who deal with patients with comorbid substance use disorders and other psychiatric illnesses. The guidelines provide a general framework for management of patients with

dual diagnosis, but clinicians should keep in mind the specific characteristics of the patients and the treatment setting, and look at further evidence base before applying these guidelines for individual patient. These guidelines are meant for application by trained clinicians, both psychiatrists as well as other physicians who encounter patients with dual diagnosis. The guidelines are primarily applicable for de-addiction centre and general hospital treatment settings, though can be used for other settings like general outpatient settings too. The guidelines are management focused and carry recommendations for clinicians.

3.3 Methodology of Guideline development

The guideline attempts to collate the findings from studies relating to dual diagnosis and draw recommendations from them. Relevant literature was identified through a PubMed literature search for publications related to this dual diagnosis. The searches were carried out in September 2013. Using MESH keyword of "Diagnosis, Dual (Psychiatry)", 2723 abstracts were identified. Of these, 350 were clinical trials and 192 were randomized controlled trials. Only English language peer-reviewed articles were included for the preparation of the guidelines. Further studies were identified through cross references and searching through other guidelines like that of NICE, Queensland Guidelines etc. The Cochrane databases were also searched for relevant meta-analyses. The treatment recommendations have been made in accordance to the level of evidence.

To maintain uniformity in standard and quality of guidelines, the Appraisal of Guidelines for Research & Evaluation II (AGREE II) Instrument was used in preparing the guidelines. The strength of recommendation was based upon the categories and impact of the published literature. The guidelines can be updated by following the research methodology after a period of time.

4. ASSESSMENT AND FORMULATION

4.1 General Issues

Treatment of dual diagnosis requires attention to the both the substance use disorder as well as the psychiatric illness. How much focus, time and effort should be expended on each of the disorder is best determined by the nature of the disorder, associated impairments and patient/ therapist preferences.

Substance use disorders by themselves can be of a wide variety encompassing a multitude of substances (alcohol, tobacco, opiates, cannabis etc) as well as variety of syndromes (abuse, dependence, intoxication, withdrawal, psychosis etc). Due to unique psychosocial circumstances and physical vulnerability, the effects of a particular substance use disorder (for e.g. alcohol abuse) may vary between individuals. Similarly, psychiatric disorders encompass a gamut of disorders from psychotic to affective to neurotic disorders. Even a well defined disorder like schizophrenia may have variable severity profile, course and response to treatment across patients, conferring considerable heterogeneity to dual diagnosis.

Based upon the severity of the substance use and psychiatric disorder, a four quadrant model for management has been suggested.[20] This helps to prioritize treatment focus for the co-occurring disorders and allocate resources appropriately. It must be recognized that treatment of substance use disorders as well as many psychiatric illness can be prolonged and may have multiple relapses over time. The treatment focus as well as modalities can be modified and changed over time based upon patient's conditions. An active collaboration with the family members can be helpful on the longer run to promote abstinence and control the psychiatric symptoms. **[Table 2]**

Table 2: Four quadrant model for prioritizing substance use and psychiatric disorder

High mental illness severity High substance use severity	High mental illness severity Low substance use severity
Low mental illness severity High substance use severity	Low mental illness severity Low substance use severity

4.2 Treatment Aims / Goals

The aims of treatment of dual diagnosis are:

- Address acute and life threatening conditions (substance intoxication and withdrawal, psychiatric symptoms like suicidality, medical illness)
- Promote abstinence from substance of use
- Control the symptoms of psychiatric disorder
- Address the comorbid medical illnesses if any

- Increase motivation for recovery
- Enhance coping and inculcate relapse prevention skills
- Improve socio-occupational functioning
- Promote maintenance of recovery through continued treatment and/or participation in self-help groups

The goals of treatment vary according to individual patient and can be modified and revised from time to time. The overall goals of treatment can be broadly divided into short term and long term goals. The short goals are management of intoxication, management of withdrawal symptoms, management of acute psychiatric symptoms, management of medical issues and motivation enhancement. Long term treatment goals are maintenance of abstinence, relapse prevention, control of psychiatric symptoms, and socio-occupational rehabilitation.

4.3 Deciding treatment setting

The decision of the treatment setting needs to be made based upon consideration of a number of factors. The various treatment settings that can be considered for the treatment of dual diagnosis include outpatient setting, inpatient setting, day care setting and others. These can be implemented in de-addiction facility, general psychiatric facility or a specialized dual diagnosis treatment setting. The decision about treatment setting needs to take care into account elements like:

- Acute psychiatric symptoms in the form of suicidality and active psychotic symptoms
- Violent behaviour of the patient
- Severity of withdrawal symptoms/ intoxication
- Associated medical illnesses
- Severity of substance dependence
- Prior abstinence attempts
- Motivation status of the patient
- Presence of social supports
- Patient and physician preference

4.4 Assessment of dual diagnosis

4.4.1 General overview

Comprehensive assessment of patients with dual diagnosis can help clarify the diagnosis and to make a management plan to keeping in consideration

different facets of the patient. Additionally, it gives an opportunity to establish rapport with the patient and enhance motivation for treatment. Assessment is usually a continuous process and new information/ observation may emerge later on. The aim of assessment varies during different phases of the treatment. While initial assessment pertains to engaging the patient into treatment and getting information to start the treatment process, subsequent assessments may focus upon fine tuning the management. Assessment can be conducted by using various sources for history, conducting a physical examination, using specific scales and instruments and conducting relevant investigations.

4.4.2 Clinical history

Clinical history of the patient can be obtained from multiple sources including the patient himself/herself, relatives and family members, medical records, co-workers and acquaintances and other agencies like law enforcement. Information should be obtained about different substances of abuse including the age of initiation, frequency and amount of use, development of features of dependence or harmful use, last dose, motivation, complications due to substance use in various domains (physical, psychological, financial, familial, vocational and legal), abstinent attempts and reasons for relapse. History of psychiatric illness should be ascertained including onset, progression and course of illness, symptom profile over the time period, severity of the psychiatric symptoms, and socio-occupational dysfunction caused by the illness. An attempt may be made to understand the relationship of the psychiatric disorder with the substance abuse disorder (whether substance use precede or succeed psychiatric disorder, whether substance abuse a consequence of attempt to self medicate and whether causal association exists between substance use disorder and psychiatric illness). Other aspects of the history like treatment history, medical history, family history, educational and occupational history, and personality profile can help gain valuable insights into the patient's background. The social supports and key figures in patient's life can also be assessed. Though the first contact may yield a considerable part of the history, crucial elements may also emergence later as patients may be uncooperative initially.

4.4.3 Physical examination

Detailed physical examination forms an important part of the comprehensive evaluation of the patient. A general physical examination followed by systemic examination of the organ systems can help to discern medical

illnesses as well as signs of intoxication and withdrawal. Type of substance use disorder and psychiatric illness may predicate the expected physical findings. For example, injecting drug user with antisocial personality may have injection marks, thrombophlebitis and features of HIV or HCV. On the other hand a smoker with schizophrenia may have features of Chronic Obstructive Pulmonary Disease.

4.4.4 Assessing risk

Dual diagnosis patients may be considered to have risk of suicide and violent behaviour. Suicidality should be assessed in a comprehensive manner and immediate precautionary steps should be taken whenever suicidality is present. The options may include immediate admission, 24 hour vigilance, arm-length monitoring, and institution of electroconvulsive therapy etc. Similarly, assessment of risk of violence should be ascertained and management for the same instituted. The options may include talking down the patient, distraction, immediate sedation, and restraint etc.

4.4.5 Instruments and scales

Various objective scales and instruments are available for application patients with substance use disorders (for example CAGE questionnaire, Drug Abuse Screening Test) as well as those with psychiatric illnesses (Positive and Negative Syndrome Scale, Hamilton Depression Rating Scale). These scales are useful for monitoring treatment over time and assessing the severity of problems. Some of these scales have been validated in patients with dual diagnosis also. Lykke et al[21] assessed 134 dual diagnosis inpatients using the Beck Depression Inventory, Beck Anxiety Inventory and Brief Psychiatric Rating Scale and found that Beck Depression Inventory and though disorder subscale of the Brief Psychiatric Rating Scale could be reliably used for dual diagnosis patients. Bender et al[22] modified the Short Inventory of Problems for application to patients with bipolar disorder and substance use disorder. Pantalon and Swanson[23] replicated the 4 factor structure of the University of Rhode Island Change Assessment questionnaire in a sample of 120 psychiatrically ill and dual diagnosis patients. Haver et al[24] assessed the applicability of Symptom Checklist 90 in a set of women with psychiatric disorder and alcohol use problems and found that the scale could be used for detecting psychiatric comorbidity.

Apart from screening instruments and severity scales, some diagnostic instruments are also available. The Psychiatric Research Interview for

Substance and Mental Disorders (PRISM) is a comprehensive diagnostic instrument that covers substance use disorders, psychiatric disorders and attempts to delineate substance induced disorders from independent disorders. The instrument has been validated and has been used in large epidemiological trials.[25] Other brief instruments like Mini International Neuropsychiatric Interview can also be used.[26]

4.4.6 Investigations

Investigations that would be conducted for patients with dual diagnosis would vary primarily according to the substance use disorder that is present. Patients with alcohol use disorders would typically require liver function tests, haemogram, and ultrasound abdomen. Those having injecting drug use of heroin, cocaine or methamphetamine may require tests for viral markers like HIV and Hepatitis B and C. Psychiatric disorders as well as medications for them may require additional investigations like blood sugar, serum lipids, serum lithium, electrocardiogram etc at the time of initiation as well as on follow up.

4.5 Motivation enhancement measures

Motivation enhancement assumes an important role in the management of patients with dual diagnosis as it does in the management of patient of substance use disorder. Patients may not consider or acknowledge the need for treatment of either of the disorders. Motivation enhancement measures attempt to inculcate insight towards problems in a non-confrontative manner. Motivational interviewing program has been modified for dual diagnosis patients to include skills like open-ended questions, refining reflective listening skills, heightening emphasis on affirmations, and integrating psychiatric issues into personalized feedback so that it becomes more applicable for this population.[27] This type of motivational interviewing has been compared with standard two session psychiatric interview in a randomized controlled trial and has been found better.[28]

Many researchers have evaluated the role of motivation interviewing in patients with dual diagnosis. Graeber et al[29] have found usefulness of motivational interviewing over educational program in reducing the number of drinking days in a sample of patients with schizophrenia and alcohol use disorders in a randomized controlled study. In a randomized controlled study it was found that motivational interviewing when added to standard treatment for dual diagnosis patients, it led to improved treatment adherence.[30]

Smeerdijk et al compared family motivational intervention to routine family support in parents of adolescents with cannabis use and recent-onset schizophrenia.[31] In this randomized controlled trial, they found that that patients' cannabis use significantly decreased in the family motivational intervention group. Hulse and Tait[32] did not find advantage of motivational interviewing over information packet in terms of admission for substance use or psychiatric problem related admissions over 5 years. Motivational interviewing in the group format has been compared to therapist attention control and has been found to be useful in promoting attendance to treatment and reducing alcohol consumption.[33] Attendance to motivational interviewing program itself been has been however found to be low.[34] Some studies have incorporated motivational interviewing as a part of a comprehensive set of strategies for dual diagnosis patients and have shown promising benefits.[35,36]

4.6 Recommendations for practice

- History should be explored in detail and relevant physical examination should be done for patients with dual diagnosis (S)
- Psychiatric disorder and substance use disorder related scales can be applied to patients with dual diagnosis with minor caution (B)
- Due to association with medical illnesses, relevant and clinically indicated investigations should be conducted in patients with dual diagnosis (D)
- Motivational interview as an add-on measure may improve retention into treatment for substance abuse (A)
- Family motivational intervention may reduce substance use for cannabis abusing adolescents who have recent onset schizophrenia (A)
- Modification of motivational interviewing techniques with respect to dual diagnosis may improve outcomes (C)

5. PSYCHOTIC DUAL DIAGNOSIS

5.1 Pharmacological measures

5.1.1 For psychiatric disorder

Treatment of primarily psychotic disorders usually requires the use of antipsychotics. The antipsychotics can be broadly divided into typical and

atypical neuroleptics based upon the side effect profile. Additional medications in the form of mood stabilizers (lithium, valproate etc), antidepressants (selective serotonin reuptake inhibitors, tricyclic antidepressants, etc.) and sedative hypnotics may be used in some of the patients.

Some amount of literature has accumulated over time about the use of antipsychotics for dual diagnosis patients. Littrell et al [37] in a 12-month open label trial of olanzapine combined with psychoeducation and self-help referral in patients with schizophrenia or schizoaffective disorder and co-occurring substance use disorders found that about seventy percent of patients attained early full remission from substance use disorders. In a 14 week comparative trial of olanzapine and risperidone in patients with schizophrenia and substance use disorders,[38] it was found that both drugs resulted in lowering rates of cocaine positive urines, but more so for the olanzapine group. Olanzapine also resulted in greater lowering the craving towards cannabis than risperidone. Two other studies compared olanzapine to haloperidol in patients with schizophrenia and cocaine abuse. While one of them suggested superiority of olanzapine over haloperidol in reducing craving of substance use,[39] the other did not demonstrate such benefits.[40]

Clozapine has been suggested to be associated with good outcomes in patients with dual diagnosis as it has been shown to curtail not only psychotic symptoms, but also substance use.[41] In an observational study, it has been suggested that clozapine may have superior effects in reducing psychotic symptoms and substance use than other atypical antipsychotics.[42,43] Efficacy of clozapine has been suggested to be higher than risperidone in a retrospective study.[44]

Aripiprazole has been shown to be efficacious for both schizophrenia and schizoaffective disorder in open label trials.[45,46] It has shown some promise in reducing cocaine craving in dually diagnosed individuals.[45] Similarly, quetiapine has also been found to have positive effects in reducing psychotic symptoms, as well as reducing the substance use in an open label study involving patients with schizophrenia spectrum disorders.[47] Flupenthixol depots have been suggested to have possible beneficial effects in patients with schizophrenia and alcohol use disorder.[48] In a trial comparing risperidone long acting injections to zuclopenthixol, it was seen that risperidone was more effective in improving substance abuse.[49]

The adverse effect profile of the medications needs to be considered in patients being prescribed medications to the patients with dual diagnosis as they may also be receiving other medications. Typical antipsychotics are more likely to cause extropyramidal side effects while atypical ones may cause derangement of metabolic parameters. It has been suggested that dual diagnosis patients on antipsychotics are more likely to suffer from extrapyramidal side effects when compared to those patients who do not have substance use disorder.[50] Baclofen may have additive effect on respiratory depression with sedative antipsychotics like clozapine and olanzapine. Also, patients with substance use disorders may have deranged liver and kidney functions, altering the metabolism of the medications and may require modifications of dosages.[2] Hence monitoring for these side effects and possible drug interactions should be done.

5.1.2 For substance use disorder

The acute treatment of management of withdrawals should be initiated along with the treatment of psychotic disorder. Commonly used agents for alcohol withdrawal would include chlordiazepoxide, diazepam and lorazepam; while opioid detoxification can be carried out using a regimen of opioid agonists or clonidine. The centre's or the clinician's preference would determine the type of medications used, but regular monitoring of withdrawal symptoms is should be done.

Many pharmacological options are available for maintenance treatment of substance use disorder in patients, in the form of anticraving agents like acamprosate and bupropion, agonists like buprenorphine, antagonists like naltrexone and deterrent agents like disulfiram. The type and combination of substance use disorder, and the patient preference may determine the type of treatment that is prescribed.

Bupropion has been found to be effective for smoking cessation in patients with schizophrenia in a meta-analysis.[51] Similarly, varenicline has been found to be efficacious in a double blind randomized controlled trial for smoking cessation for patients with nicotine dependence and schizophrenia.[52] Nicotine replacement including the form of 'electronic cigarettes' also has an important role in treatment of dual diagnosis patients with psychotic disorder.[53]

Naltrexone has been studied in patients with alcohol use disorders and schizophrenia. An open trial of naltrexone in patients with schizophrenia

and alcohol dependence has suggested a positive effect.[54] Two randomized placebo-controlled double-blind trials[55,56] also suggest that naltrexone may be helpful in decreasing alcohol use in patients with psychotic disorders and alcohol dependence. Though caution has been expressed about the use of disulfiram and baclofen in patients with psychosis due to risk of psychosis,[57,58] but a retrospective study with severe mental illness and alcohol use disorder suggests beneficial effects for the use of disulfiram in majority of the patients with no evidence of increased psychosis.[59] Patients with schizophrenia and opioid dependence can also benefit from opiate replacement therapy added to other treatment.[60]

5.2 Non-pharmacological measures

Many psychotherapeutic measures have been used in patients with psychosis and substance use disorders. Kemp et al[61] conducted a randomized controlled trial of four to six session brief Cognitive Behaviour Therapy (CBT) ('Stop using stuff') comparing it to treatment as usual in patients with psychotic dual diagnosis. Both groups improved across the trial, though CBT showed better results for decreasing alcohol and cannabis use. James et al[62] compared manualized group based 6 session intervention to single educational session for patients with psychotic disorder substance use disorder in a randomized controlled trial and found that 6 sessions intervention was better in terms of reducing psychopathology, chlorpromazine equivalent dose of antipsychotics, alcohol and illicit substance use, severity of dependence and hospitalization.

Barrowclough et al[36] compared routine care to an integrated treatment comprising of CBT, motivational interviewing, family or caregiver intervention in patients with schizophrenia and substance use disorder and found that integrated treatment program resulted in significantly greater improvement in patients' general functioning.

Tidey et al[63] compared contingency management to no intervention in patients with schizophrenia and tobacco dependence, and found biochemically confirmed nicotine usage to be decreasing significantly with contingency management. Mueser et al[64] compared family intervention for dual disorders to family psycho-educational program for patients with mental illness and substance use disorder . The authors found that characteristics of the relatives were the strongest predictors of successful initial engagement regardless of the type of intervention.

5.3 Recommendations for practice

- Antipsychotics are effective for patients with dual diagnosis, and it reduces psychotic symptoms as well as substance use (A)
- Olanzapine, risperidone, aripiprazole, quetiapine, flupenthixol and clozapine have demonstrated efficacy through at least one open label trial/ controlled trial (C).
- Clozapine seems be more effective than other antipsychotics in treatment of dual diagnosis psychotic disorders (C)
- Dual diagnosis patients are at increased risk of having extra pyramidal side effects (A)
- Attention should be paid towards drug interactions and impact of concomitant medical illnesses on drug metabolism (D).
- Bupropion and varenicline are efficacious in smoking cessation in dual diagnosis patients (A)
- Nicotine replacement is efficacious for dual diagnosis nicotine dependent patient (B)
- Naltrexone is useful in patients with alcohol dependence and psychotic disorder (A)
- Baclofen and disulfiram may potentially induce psychosis in dual diagnosis patients (D)
- CBT, contingency management and integrated psychotherapeutic programs are useful in patients with psychotic dual diagnosis (A).

6. OTHER DUAL DIAGNOSIS

6.1 Pharmacological measures

6.1.1 For psychiatric disorder

Other dual diagnosis conditions referred to in this section include patients with psychiatric disorders of major depression, bipolar disorder, anxiety spectrum disorders and mixed set of patients with any of the disorders.

A few meta-analyses have looked at efficacy of antidepressants in dual diagnosis of depression and substance use disorder. Iovieno et al[65] meta-analysed 11 trials of antidepressants in patients with major depression and

dysthymic disorder with concurrent alcohol use disorders and found that antidepressants were effective. In their meta-analysis of antidepressants in depression and substance use disorder Torrens et al[66] did not find significant advantages of SSRIs over tricyclic drugs. Hesse[67] did not find advantage of add-on psychosocial treatment to antidepressants in patients with depression and substance use disorder. Pedrelli et al[68] analysed efficacy of antidepressants over placebo in patients with major depression or dysthymic disorder and opioid dependence on methadone maintenance. The 4 trials identified did not have statistically significant difference in response rates between antidepressant and placebo.

Geller et al[69] in a double blind randomized controlled trial in patients with bipolar disorder and substance use disorder found lithium to efficacious for treatment of both the disorders. Valproate has been found to show improvement in affective symptoms and substance abuse in patients with bipolar disorder and substance use disorder in an open label study.[70] Brown & Gabrielson[71] conducted a double blind randomized controlled trial comparing citicoline to placebo in unipolar/ bipolar depression and methamphetamine dependence. It was seen that citicoline was better than placebo for depression, but no differences in methamphetamine usage was found. In another placebo controlled randomized controlled[72] citicoline added on to bipolar disorder and cocaine dependence resulted in improvement on tests of verbal memory and substance use outcome, though no differences in mood was discerned.

Davis et al[73] compared escitalopram monotherapy to an antidepressant combination (venalfaxine-XR + mirtazapine or escitalopram + bupropion-SR) in patients with major depression with and without substance use disorder. It was found that patients with major depression and concurrent substance use disorder were as likely to respond and remit to a single agent as to combination antidepressant. In an open trial venlafaxine has been found to be safe, well-tolerated, rapidly acting, and effective in treatment of patients with depression and cocaine abuse.[74]

McRae-Clark et al[75] tried atomoxetine in patients with attention deficit hyperkinetic disorder (ADHD) and cannabis dependence and found that atomoxetine may improve some ADHD symptoms but does not reduce cannabis use. Carpentier et al[76] in a double blind cross over trial of methylphenidate versus placebo in ADHD and substance use disorders found a significant reduction in ADHD symptoms in the first week in both

conditions, and no subsequent differences between the drug and placebo. Riggs et al[77] compared pemoline to placebo in a trial of patients with ADHD, conduct disorder and substance use disorder and found that pemoline was efficacious for ADHD but did not have an impact on conduct disorder or substance abuse.

Assessing quetiapine add on to divalproex/ lithium in bipolar disorder and alcohol use disorder patients in a double blind randomized controlled trial, Stedman et al[78] did not find greater improvement in measures of alcohol use with add-on quetiapine. Osuji et al[79] found that pregnenolone in bipolar or unipolar depression and substance use disorder may reduce Hamilton depression rating scale scores more than placebo. In an open trial, Martinotti et al[80] found that flexible doses quetiapine in patients with psychiatric illness and alcohol use disorder resulted in decreased alcohol consumption, craving, and psychiatric symptoms with a good level of tolerance.

In an open label trial, Brown et al,[81] found that nefazodone was associated with improvement in mood/anxiety and alcohol use, independent of each other in patients with major depression and alcohol dependence. Ciraulo et al[82] compared nefazodone to placebo in patients with depressive disorder and cocaine dependence in a randomized controlled study and found that nefazodone administration can reduce cocaine craving. Schmitz et al[83] however, in a double blind randomized study did not find advantage of fluoxetine over placebo in patients with major depression and cocaine abuse. Similarly, Gonzalez et al[84] found that patients with major depressive disorder and opioid dependence may respond better to behavioural treatments such as contingency management than to combination of desipramine and buprenorphine.

Mariani and Levin[85] found that levetiracetam was useful in reducing in alcohol consumption and anxiety symptoms in a case series of patients with anxiety and alcohol dependence. Muhonen et al[86] conducted a randomized controlled trial comparing memantine to escitalopram in patients with major depressive disorder and alcohol dependence and found that abstinence was high in both the groups during the study period. Comparison of paroxetine to placebo in a double blind placebo controlled study of patients with social anxiety disorder and alcohol use disorder suggests paroxetine to be useful.[87] Book et al[88] compared paroxetine to placebo for social anxiety and alcohol use disorder and found that paroxetine was superior to placebo in reducing social anxiety.

Antidepressants may be supplemented with benzodiazepines in patients with depressive or anxiety disorders. However, long term use of benzodiazepines may be associated with development of dependence. Also, it may not be clear as to whether certain side effects are due to antidepressants or due to substance use, and hence may complicate decision making. For example sexual dysfunction may be due to SSRIs or due to alcohol use or is present independently. It may be prudent to change/stop the medication and look for improvement in symptoms.

6.1.2 For substance use disorder

Withdrawal symptoms of alcohol dependence may be confused with symptoms of anxiety disorder, especially if the anxiety disorder had been present after the onset of substance use. Hence presence of anxiety symptoms after the end of detoxification may help in understanding the presence and relationship of anxiety disorder. Long term treatment of alcohol use disorder may require use of medications like acamprosate, naltrexone, baclofen and disulfiram. Similarly opioid dependence may be treated with opioid agonists and antagonists.

Witte et al[89] compared acamprosate to placebo when added to escitalopram in patients with major depression and alcohol use disorders in a randomized controlled trial and found that add-on acamprosate reduced number of drinking days. Brown et al[90] conducted a double blind randomized controlled trial of naltrexone add-on in patients with bipolar disorder and alcohol dependence and found trends of naltrexone reducing the number of drinking days. Gopalakrishnan et al[91] conducted an observational study of setraline with naltrexone and compliance enhancement therapy for late life depression and alcohol use disorder and found that full responders at 12-weeks had better outcomes of drinking status and depression. Petrakis et al[92] studied PTSD and alcohol use disorder patients and compared naltrexone and disulfiram to placebo, either singly or in combination. It was found that subjects with PTSD had better alcohol outcomes with naltrexone, disulfiram or combination than on placebo, and overall psychiatric symptoms of PTSD improved with all the treatments. Hence it seems that use of pharmacoprophylactic medications can be useful in reducing the substance use in patients with dual diagnosis.

6.2 Non-pharmacological measures

Various forms of psychotherapeutic interventions have been studied for dual diagnosis patients. The focus of intervention may differ between that of

substance use disorder (e.g. discussing about relapse prevention measures) and psychiatric disorders (e.g. exploring cognitive biases relating to self esteem). Many researchers have used integrated or combined therapies in which attention is paid to psychotherapeutic measures for both the conditions. Also, there may be differences in the manner and context of delivery of the interventions. Treatment for anxiety and depressive disorders may be conducted in outpatient setting, though therapeutic community may be quite suited to substance use disorders. The evidence relating to these interventions is discussed further.

Evidence from meta-analytic studies suggests that modified therapeutic community for substance use disorders and psychiatric disorders has significant beneficial effects on many outcome measures.[93] Another meta-analysis by Torchalla et al[94] suggests that psychotherapeutic integrated treatment for substance use disorders with trauma histories effectively reduces trauma symptoms and substance abuse, but was not superior than non-integrated treatment. Bogenschutz et al[95] report that twelve step approaches for psychiatric disorders and substance use disorders may be useful.

Ball et al[96] conducted a randomized controlled trial comparing dual-focused and single-focused individual therapy for personality disorder with concurrent substance use disorder. The study found that individual drug counselling resulted in more sustained reductions than dual-focus schema therapy in several symptoms for several personality disorders. Granholm et al[97] compared Integrated Cognitive Behavioral Therapy (ICBT) with Twelve-Step Facilitation (TSF) Therapy in a randomized trial of patients with depression and substance use disorders in veterans. The study found that patients with poor neuropsychological functioning had better substance use outcome in ICBT than in TSF. Hunter et al[98] compared dual focused CBT to treatment as usual in a randomized controlled trial involving patients of depression and substance use disorder and found that CBT resulted in improvement of depressive symptoms and substance use. Worley et al[99] in their observational study of patients with depression and alcohol, stimulant or marijuana dependence report that twelve step facilitation (TSF) was associated with lower rates of depression when compared to integrated CBT. A randomized control trial of depression and alcohol dependence[100] found that integrated focus of CBT (covering both depression and alcohol dependence) was associated with a greater reduction in drinking days and

level of depression. Computer based CBT with intensive motivational interviewing has been shown to be superior to brief intervention in a randomized controlled trial of patients with major depression and alcohol or cannabis misuse.[101] Weiss et al[102] found that integrated group therapy had greater reduction in substance use and greater decline in risk of mood episodes when compared to group drug counselling in patients with bipolar disorder and substance dependence. Weiss et al,[103] compared integrated group therapy versus group drug counselling in patients with bipolar disorder and substance use disorder. Patients with integrated group therapy had significantly fewer days of substance use during treatment and follow-up. Comparison of integrated group therapy to no intervention in patients with bipolar disorder and substance dependence revealed intervention to be associated with fewer days of drug use over the 6-month study period.[104]

Carpenter et al[105] compared Behavioral Therapy for Depression in Drug Dependence (BTDD) to structured relaxation intervention depression and opioid dependence in a randomized controlled trial and found that both interventions were equally efficacious. Agyapong et al[106] in their single blind randomized trial found that supportive text messaging tended to improve patient outcomes in dual diagnosis patients with major depression and alcohol use disorder. Markowitz et al[107] found interpersonal psychotherapy better for depression, whereas brief supportive psychotherapy was better for alcohol dependence in patients with depression and alcohol dependence.

Dialectical behaviour therapy has been compared to treatment as usual in a randomized controlled trial in patients with borderline personality disorder and substance dependence.[108] It has been found that dialectical behaviour therapy was associated with better outcomes in treatment of drug abuse. However, another randomized controlled trial on patients with borderline personality disorder and substance use disorder did not find superiority of dialectical behaviour therapy.[109] Gregory et al[110] conducted a randomized trial comparing optimized community care to dynamic deconstructive psychotherapy for patients with borderline personality and alcohol use disorder. It was seen that dynamic deconstructive psychotherapy had more sustained benefits than optimized community care.

Karaèiæ et al[111]observed that using transdiagnostic cognitive behaviour therapy for eating disorders mean alcohol intake of the heavy drinking subjects decreased without being specifically addressed by the treatment.

Kushner et al,[112] finds that hybrid CBT for panic disorder and alcohol use disorder was more effective in relieving participants' panic symptoms relative to controls.

Sonne et al[113] noted difficulty of quitting smoking increased with depression in randomized trial of cognitive behavioural group counselling added to nicotine patches for smoking cessation. Goti et al[114] found that brief intervention for dual diagnosis patients resulted in significant increase in overall knowledge about drugs and perception of risk over time. Kaminer et al[115] finds that CBT resulted in significant reduction in severity of substance use than with interactional group treatment in adolescents with psychiatric disorder and substance use disorder. Moggi et al,[116] suggests that general and substance-specific coping skills modestly improved over 1-year with psychiatric interventions and better results are obtained with 'dual diagnosis treatment climate' and 12-Step self-help groups.

Drebing et al[117] studied addition of contingency management along with vocational rehabilitation for psychiatric disorders and concomitant substance use disorders. Contingency management was associated with more intense job searches, faster transition to competitive employment, and greater initial abstinence rates. The same group also found enhanced incentives to Compensation Work Therapy (CWT) in dual diagnosis patients was associated with more job-search activities, higher wages and abstinence from psychoactive substances.[118] Contingency management for disability payments was associated with significantly less alcohol and drugs use and better money management in a randomized trial of dual diagnosis patients.[119] Bellack et al[120] found Behavioral Treatment for Substance Abuse in Severe and Persistent Mental Illness (BTSAS) superior to Supportive Treatment for Addiction Recovery (STAR) in patients with serious mental illness and substance use disorder in terms of laboratory confirmed abstinence, retention in treatment, and attendance at sessions.

A range of psychotherapeutic and non-pharmacological interventions are available for dual diagnosis patients, both in individual and group formats. Which of them is applied to a particular case depends upon individual patient characteristics and therapist expertise/ preference. Though some of the interventions tested in dual diagnosis patients have been highlighted above, the other modalities which have not yet been studied rigorously in dual diagnosis (like mindfulness training, art therapies, psychodynamic psychotherapy etc) can also be utilized in individual cases.

6.3 Recommendations for practice

- Antidepressants are efficacious in major depression or dysthymic disorder with alcohol use disorder (A)
- SSRIs are as efficacious as tricyclic antidepressants in patients with depression and substance use disorder (A)
- Single agent antidepressants are as useful as combination agents in patients with depression and substance use disorder (B)
- Venlafaxine efficacious in depression and cocaine abuse (C)
- Atomoxetine and pemoline may be efficacious in patients with ADHD and substance use disorder (C)
- Paroxetine useful in patients with concurrent alcohol use disorder and social anxiety disorder (A)
- Lithium and valproate may be efficacious in reducing substance use and controlling affective symptoms in patients with bipolar disorder and substance use disorder (B)
- Acamprosate and naltrexone reduces substance use in alcohol use disorder ad substance use disorder (A)
- Therapeutic community useful for patients with dual diagnosis (A)
- Twelve step approaches for psychiatric disorders and substance use disorders may be useful (B)
- Dual focused or integrated CBT better than single focused CBT in dual diagnosis patients (A)
- Dialectical behaviour therapy may be useful in patients with borderline personality disorder and substance, but evidence is conflicting (B)
- Contingency management may improve vocational rehabilitation (A)

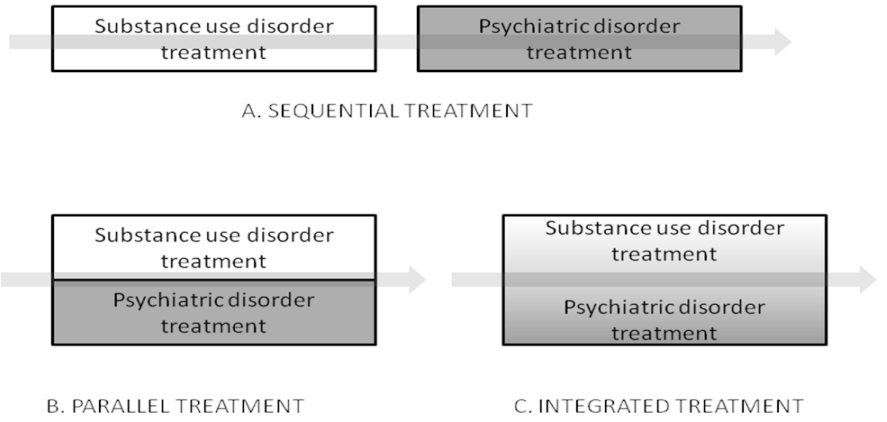
7. SERVICE DELIVERY RELATED ISSUES

7.1 Service delivery formats

The various service delivery formats for patients with dual diagnosis that has been proposed over time include sequential treatment (de-addiction treatment followed by psychiatric disorder treatment or vice versa), parallel

treatment (concurrent de-addiction treatment and psychiatric disorder treatment but by different service providers) and integrated treatment (concurrent de-addiction treatment and psychiatric disorder treatment but by same service provider).[1,121] These are depicted in **Figure 1.**

Figure 1: Service delivery formats



Of the three models, integrated treatment seems to be most beneficial for treatment of patients with dual diagnosis. Integrated treatment has been compared to standard hospital treatment in a population of patients with severe mental illness and alcohol dependence in a randomized controlled trial.[122] The researchers found that integrated treatment was associated with reduced chances of relapse in the first two months. Mangrum et al[123] compared the integrated treatment for dual diagnosis to parallel treatment for concurrent serious persistent mental illness and substance use disorder and found that integrated treatment resulted in greater reductions in psychiatric hospitalization and arrests. Morrens et al[124] in their comparative trial found that integrated treatment resulted in lesser dropouts than treatment as usual.

Assertive community treatment (ACT) extends the concept of integrated treatment further to provide community based services, intensive case management and provision of crisis services. Drake et al[125] in their controlled trial find that ACT is better than standard case management in terms of measures of substance abuse and quality of life. Similarly Frisman et al[126] found that ACT was better in reducing alcohol use and incarcerations for patients with ASPD.

Petersen et al[127] compared OPUS Treatment (a form of ACT) to standard treatment in patients with first episode psychosis with and without substance use disorder. The authors found that integrated treatment given by OPUS reduced substance abuse and improved clinical outcome in the substance abuser group. Fletcher et al[128] compared ACT to standard care and found that ACT was associated with higher consumer satisfaction and more stable housing. Manuel et al[129] found that ACT resulted in significant improvement in medication adherence when compared to standard clinical case management in a randomized controlled trial.

Timko and Sempel,[130] studied the relationship of intensity of treatment services with outcome for dual diagnosis patients in an observational study and found that high service intensity in the acute treatment phase was associated with better substance use, family and social outcomes. Womack et al[131] conducted a randomized controlled study comparing psychiatric case management to no case management and treatment as usual in sample of depressed substance users and suggested that psychiatric case management appeared effective in encouraging use of psychiatric referral services by the patients. Kay-Lambkin et al[132] tested stepped care approach in patients with depression and methamphetamine use and found that such an intervention resulted in less depression and less substance use over time. Farren and Mc Elroy[133] found that enrolment to dual diagnosis program in patients with affective disorder and alcohol use disorder resulted in reduction in the frequency and extent of drinking alcohol.

Models of psychiatric services or substance use facilities have less well studied in India. Despite the lack of structured community treatment programs, efficient and effective care can be provided by roping in the assistance of family members in treatment of the dual diagnosis patients. Family systems in India allow for family overview of treatment adherence, financial support, availability in times of crisis, and help in gaining vocational services. The camp approach can also be of use in Indian patients in delivering services to less accessible areas. Hence, modifications in service delivery parameters can be effectuated to help maximum number of patients.

7.2 Cost effectiveness related issues

A few cost based studies have been conducted in dual diagnosis patients regarding their treatment. Cleary et al[134] studied the cost-effectiveness of ACT for dual diagnosis patients comparing it to standard management in a randomized controlled trial and found that both the interventions were not

different from each other in terms of cost effectiveness. The cost of treatment and other indirect costs were assessed in a comparison of therapeutic community attendees, separators and treatment as usual patients in a sample of dual diagnosis patients.[135] The results suggest that retention into therapeutic community was associated with substantial financial costs, though other indirect costs reduced considerably. The treatment of dual diagnosis patients has been compared to non-dual diagnosis patients and has to be found on the higher side, suggesting the regular screening for dual diagnosis may help in reducing the complications of untreated psychiatric symptoms and hence increasing the costs.[136] Matching of severity of the illness to the intensity of intervention resulted in escalation of the costs of treatment according to a study conducted among veterans.[137] Patients with dual diagnosis from a randomised controlled trial of motivational intervention, individual CBT and family intervention were assessed for cost outcomes and it was suggested that there no differences in cost of treatment between the groups.[35]

7.3 Training of service providers

Initial literature in the area suggested cross-training between substance use and mental health professionals in chemotherapy, psychotherapy, abstinence from alcohol and other addictive drugs, 12-Step programs, spiritual issues, and milieu therapy.[19] Later studies attempted to identify how training programs to service provider personnel can help in better treatment delivery. Hughes et al, [138] and Johnson et al [139] reported findings from a study involving the training of case managers (COMO study) which randomized 79 case managers to training or control group from 13 London boroughs. Hypothesis that experimental group patients would spend fewer days in hospital and show reduced alcohol and drug consumption, were not confirmed in the study. However, improvements in Knowledge About Dual Diagnosis and Self-Efficacy Scale administered to the case managers were noted. The Combined Psychosis and Substance Use Programme (COMPASS)[140] study aimed to assess the needs of training of staff about psychotic dual diagnosis cases and to deliver training and competence. Following the receipt of training, the staff confidence significantly increased and remained high at 10 year follow up period. Lee et al[141] examined the applicability and benefits of implementation of screening and intervention module for mental health disorders among alcohol use disorder clients. Training and supervision focused on enhancing skills in detection of, and

intervention for, mental health conditions using a package 'PsyCheck'. A random file audit undertaken to examine changes in detection of mental health conditions suggested that intervention resulted in improved mental health detection and treatment by the clinicians. Hence training of service providers and staff may result in better patient management.

7.4 Recommendations for practice

- Integrated treatment of dual diagnosis is associated with better outcomes rather than serial or parallel treatment (A)
- Assertive community treatment has shown benefits compared to standard care of patients with dual diagnosis (A)
- High service intensity is associated with better substance use, family and social outcomes (C)
- Training of service providers can improve staff self-efficacy and knowledge of dual diagnosis, but may not translate into better patient outcomes (B)

8. SPECIAL POPULATIONS

8.1 Prison population

It has been suggested that a large proportion of prison population may be suffering from dual diagnosis.[142,143] Sullivan et al[144] compared dual diagnosis patients entering therapeutic community after being released from prison to no intervention, and found that intervention resulted in reduction in alcohol and drug use over time. In-jail treatment for dual diagnosis has been compared to diversion of patients to dual diagnosis treatment facilities. An observational study [145] finds that diversion services were more likely to have acute psychiatric symptoms and more likely to be diagnosed as psychosis not otherwise specified. Steadman and Naples[146] find that jail diversion of dual diagnosis patients reduces time spent in jail without increasing the public safety risk. Broner et al[147] finds from a large multi-site study that jail diversion services were related to immediate benefits to the patients, however it did not result in long term follow up. Thus if facilities are available, dual diagnosis patients should be treated in separate facilities rather than in the jails themselves.

8.2 Homeless population

Homeless dual diagnosis patients represent a specific subgroup which has been a focus of many studies. A randomized controlled study of 118 homeless

patients with PTSD and cocaine dependence found that high intensity contingency management has a positive impact on the PTSD symptoms also.[148] Tracy et al[149] in a randomized trial of 30 homeless patients found that contingency management was helpful in reducing alcohol and cocaine use over 4 weeks. A randomized controlled study evaluating the effect of abstinence contingent housing and work therapy as an add-on to behavioural day treatment suggests that greater abstinence rates were attained in the intervention group.[150] Data from an observational study suggests that behavioural interventions can be useful in reducing the occurrence of mood and anxiety disorders in patients with dual diagnosis.[151]

Calsyn et al[152] comparing ACT to Integrated treatment in a randomized controlled trial found that prior history of criminal activity rather than type of intervention predicted future criminal behaviour. French et al[153] compared therapeutic community to treatment as usual in a randomized controlled trial of homeless dual diagnosis patients and found that therapeutic community could be quite cost effective when the indirect costs are considered. Nuttbrock et al[154] conducted a randomized controlled trial of homeless dual diagnosis population comparing community residency to a therapeutic community program. The authors found that patients in the therapeutic community were more likely to be drug free and had lesser psychiatric symptoms. Drake et al[155] compared integrated mental health, substance abuse, and housing interventions to standard treatment in a quasi-experimental study of homeless dual diagnosis population. The authors found that integrated treatment resulted in fewer institutional days, more days in stable housing, better recovery from substance abuse and greater improvement of alcohol use disorders.

8.3 Recommendations for practice

- Jail diversion services may reduce time spent in jail without increasing public safety risk (B)
- Immediate benefits of jail diversion services does not last for a long period of time (B)
- Contingency management is useful for homeless dual diagnosis population (A)
- Therapeutic community shows better outcomes than treatment as usual for homeless dual diagnosis population (A)

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