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# Comorbidity of mental disorders and substance use: A brief guide for the primary care clinician

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# Comorbidity of mental disorders and substance use: A brief guide for the primary care clinician

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**Comorbidity of mental disorders and substance use:**
**A brief guide for the primary care clinician**

Author: Dr Andrea Gordon
Drug and Alcohol Services South Australia (DASSA)
Clinical Services and Research
Adelaide, South Australia


Additional copies can be obtained from:
National Mail and Marketing
11 Tralee Street Hume ACT
Tel: 02 6269 1000
Fax 02 6260 2770

**Internet sites**

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In order for the Guidelines to remain a useful and current resource for general practitioners, it was decided by the Department of Health and Ageing to review and update them.

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The revision of the original Guidelines was undertaken by Drug and Alcohol Services South Australia (DASSA) with Dr Andrea Gordon as the Author and coordinating Research Officer and Dr Chris Holmwood as the Project Manager.

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Ms Maxie Ashton (Seaton Mental Health Site, Central Northern Adelaide Health Service)

Associate Professor Michael Baigent (Department of Psychiatry, Flinders University)

Dr Peter Donohoe (Australian General Practice Network)

Dr Linda Gowing (DASSA) Evidence-Based Practice Unit/Discipline of Pharmacology, University of Adelaide)

Dr Les Koopowitz (Department of Psychiatry, University of Adelaide), and

Professor Jason White (Discipline of Pharmacology, University of Adelaide).

## Abbreviations

| | |
|---|---|
| AGPN | Australian General Practice Network |
| AOD | Alcohol and other drugs |
| ARBI | Alcohol related brain injury |
| CBT | Cognitive behavioural therapy |
| CYP 450 | Cytochrome P450 |
| DASSA | Drug and Alcohol Services South Australia |
| DSM-IV | Diagnostic and statistical manual |
| HIV | Human immunodeficiency virus |
| GAD | Generalised anxiety disorder |
| LSD | Lysergic acid diethylamide |
| MAO-I | Monoamine oxidase inhibitor |
| MDMA | 3,4 - methylendioxymethamphetamine |
| NRT | Nicotine Replacement Therapy |
| OCD | Obsessive compulsive disorder |
| PARC | Primary Mental Health Care Australian Resource Centre |
| PBS | Pharmaceutical Benefits Scheme |
| PTSD | Post traumatic stress disorder |
| RCT | Randomised controlled trial |
| SNRI | Selective noradrenaline re-uptake inhibitors |
| SSRI | Selective serotonin reuptake inhibitor |
| TBI | Traumatic brain injury |
| THC | Tetrahydrocannabinol |

## Contents

# Preface

The original comorbidity management guidelines were published in 2002 when it became apparent that there was a need for clinically relevant information concerning specific comorbidity patterns to be collated into one accessible resource. Most importantly, this resource provided clinicians with information on how best to manage individuals with comorbid mental disorders and substance use issues.

At the time, the information contained in the resource was based on clinician knowledge in the area and what management approaches were effective based on prior experience.

The updated guidelines provide a greater breadth of information on the same previously discussed topics and have a greater academic foundation.

The current guidelines also include information not previously included relating to brain injury, gambling, tobacco, inhalants and solvents.

# Introduction

Comorbidity or the co-occurrence of mental disorders and substance use disorders is common. The prevalence of comorbidity in the community and the complex interactions that occur between the two sets of disorders should raise doubts about the manner in which we continue to deal with each entity separately. Clinicians need to consider these problems as part of a whole complex of phenomena that are closely linked to one another.

There are significant problems with the management of people with comorbidity. There is a dearth of evidence about best practice. Specialist mental health or alcohol and other drugs (AOD) services, where they are available, are usually separated physically, administratively and philosophically. Only recently has training for general practitioners (GPs) become adequate for the problems that are faced on a day to day basis, either in the mental health field or the AOD field.

The original resource was developed as a result of work previously undertaken by PARC in 2001 with the development of a set of principles for the management of people with comorbidity.

The updating of these guidelines was undertaken in 2007–08 by Drug and Alcohol Services South Australia, through funding from the Australian Government under the National Comorbidity Initiative, to include the most current management principles obtained from the literature and clinical practice.

There is still a dearth of information available in the literature for some areas of comorbidity discussed in these guidelines. Therefore, management principles in these areas are based on what is currently thought to be reasonable clinical practice rather than on high levels of evidence. In addition, many people with comorbidity have more than one mental disorder and may have problematic use of several substances. This resource is a simple guide that provides a starting point for clinicians.

**Andrea Gordon and Chris Holmwood**

**Drug and Alcohol Services South Australia**

**2008**

# 1 Levels of evidence

## 1.1 Management approaches

**In these guidelines, the quality of scientific evidence supporting statements concerning clinical practice is indicated by the following indications of 'level of evidence':**

### *1.1.1 Level of evidence*

| | | |
|---|---|---|
| **** | STRONG | Systematic review of multiple randomised controlled trials (RCT) OR multiple RCTs with consistent findings. |
| *** | GOOD | At least one RCT or multiple comparative (non-randomised) studies with consistent findings. |
| ** | MODERATE | Any form of comparative (non-randomised) study. |
| * | SOME | Case series (single treatment group). |
| NO RATING | | No experimental studies – any statements are based on single case reports or clinical opinion/expertise. |

This system of rating the level of evidence draws on the system used by the National Health and Medical Research Council (NH&MRC) of Australia *(A guide to the development, implementation and evaluation of clinical practice guidelines.* Canberra: NH&MRC, 1999. www.nhmrc.gov.au/publications/synopses/cp65syn.htm), and the Australian National Council on Drugs (ANCD) (Monograph 4).

## 1.2 Drug interactions

**In these guidelines, the quality of scientific evidence supporting statements concerning drug interactions is indicated by different indications of 'level of evidence'.**

As it is unethical to conduct RCTs of drug interactions in clinical populations, it is not possible to base levels of evidence on clinical RCTs. As a result, the following 'level of evidence' statements have been formulated.

### *1.2.1 Level of evidence*

| | | |
|---|---|---|
| ✘✘✘ | DEFINITE | Multiple case reports or controlled pharmacological studies have confirmed interactions of the combination of these drugs.<br><br>Caution: if these drugs are administered in combination with one another, interactions will occur. Alternative treatment should be sought if appropriate. Should it be necessary to combine these drugs, patients should be monitored and doses adjusted as needed to prevent adverse events. |
| ✘✘ | LIKELY | Case reports indicate that interactions have occurred in a clinical situation.<br><br>Alternatives should be offered where appropriate. If the combination is to be administered, the individual should be monitored to confirm interactions and adjust treatment if necessary. |
| ✘ | THEORETICAL | Based on pharmacokinetic and pharmacodynamic properties of the drugs, there is a theoretical possibility that they may interact to cause a different effect if the drugs were administered individually OR in vitro, or animal studies suggest that there may be an interaction.<br><br>Individuals taking these combinations of drugs should be monitored. |

# 2 Management of people with comorbidity of mental disorders and substance use

Mental disorders and substance use occur together very frequently and can interact negatively on one another.

Little evidence is available to allow advice about safe levels of substance use in people with mental disorders. Safe levels of consumption in the general population may cause severe adverse effects in people with mental disorders[1,2]. The assumption should be that any substance use has the potential to cause deleterious effects on the comorbid mental disorder.

The management of comorbid mental disorders and substance use requires a long-term perspective. Actual clinician interventions may be brief or extended over a period of time. A doctor-patient relationship based on honesty, trust and respect will form the basis for effective therapy. Active listening skills and a patient-centred clinical method should be used to establish rapport and develop a common understanding of the problems and an agreed management plan.

## 2.1 Detection

The most common questions include:

- How to identify the presence of possible problems.
- Which problem to focus on first.
- Whether/how to address both problems concurrently[3].

Failure to detect all issues may contribute to poor treatment retention and outcomes[3].

When a patient presents with either a substance-use[1] related problem or a mental disorder then the clinician should routinely enquire about the other.

Comorbidity should be assumed to be present when progress or response to therapy for either mental disorders or substance use appears to be ineffective or not progressing as planned. Comorbidity should be actively sought and needs to be excluded.

## 2.2 Assessment

A full assessment often takes several consultations. This assessment should include determination of:

- The patterns of substance use.
- The day-to-day problems associated with substance use.
- The reasons for substance use.
- The effect that it might be having on the mental disorder.
- The nature of the mental disorder itself, diagnosis, previous treatments and responses to treatment.

1 Substance use: is intended to be a non-quantitative term for the consumption of a substance. The risk associated with the use may range from low to high. It does not necessarily imply dependent use.

2 Substance misuse: is a term for the consumption of a substance where the risk associated with the use is moderate or high, or where a substance is not being used for its intended therapeutic purpose, or use exceeds recommended therapeutic quantities.

3 Substance abuse is not a term favoured by the author but has been used in the context of information derived from publications using the DSM- IV diagnosis of substance abuse.

## 2.3 General management

Management should be based on the patient's readiness for change. This readiness for change might be different for the management of the substance use than for the mental disorder. For example, the patient may be ready to address their mental disorder and engage in treatment but not yet ready to alter their substance use, and vice versa.

Management should aim to increase the patient's awareness of the negative effect that the substance use and the mental disorder are having on each other.

Management should involve family or carers where appropriate.

## 2.4 Specific management

Detoxification should be offered as a first step to enable engagement in long-term approaches and decision making.

Specific management steps should include where appropriate:

- Provision of information.
- Structured problem solving.
- Motivational interviewing.
- Brief behavioural or cognitive approaches.

## 2.5 Pharmacological approaches

Clinicians should avoid using substances of dependence such as methadone unless these are used as part of a harm reduction plan.

Benzodiazepines should not be used for more than a few days. Generally, longer acting benzodiazepines are preferable.

Clinicians should consider whether the current medication for the mental disorder is adequate or causing side-effects as the patient may be self medicating with non-prescribed drugs to relieve symptoms or side effects.

The clinician should consider potential interactions between all substances used.

If there is drug-seeking behaviour, then engagement of the patient in a planned and limited prescribing program is required (e.g. Medicare Australia consent for all prescribing information to go to the one prescriber).

## 2.6 Referral

People with comorbid mental disorders and substance use frequently need care from several different disciplines. It is important that communication between all clinicians and service providers is coordinated. The use of a care plan in these instances is advisable.

Consider referral when:

- Self-harm risk or risk to others is present.
- Acute exacerbation of mental disorder occurs.
- Drug dependence with major associated problems (legal, health, social) is present.
- Complicated detoxification is anticipated.

It is important for GPs to develop links with local specialist mental health or AOD services (where they exist).

# 3 The common drug groups

## 3.1 Cannabis/hallucinogens

**Cannabis (marijuana, hash, grass, dope)**

**Lysergic acid diethylamide (LSD, acid)**

**Psilocybin (magic mushrooms)**

**Datura (angel's trumpet)**

**Anticholinergic drugs, (benztropine, benzhexol, orphenadrine)**

Cannabis is by far the most commonly used hallucinogen. Cannabis is derived from the hemp plant and contains the active substrate tetrahydrocannabinol (THC). THC exerts its effects via the central nervous system producing a mixture of hallucinogenic, delusional and depressant effects along with other centrally-mediated peripheral autonomic effects.

The drug is often used in group settings as it enhances sociability and at low doses causes a high that includes feelings of relaxation and happiness. In larger doses (larger amounts, parts of the plant with higher concentration, more potent cultivars), cannabis may produce effects similar to LSD.

LSD is a hallucinogenic or psychedelic drug. LSD and regular cannabis use can trigger underlying mental disorders and produce delusions, paranoia and schizophrenia-like states, particularly in people with a family history. These substances can also produce extreme anxiety states or panic attacks, not only while the person is under the influence of the drug, but for some time after.

Psilocybin causes similar effects to LSD; however, these effects are not usually as intense or long lasting. Anticholinergic drugs, e.g. benztropine, benzhexol or orphenadrine may be prescribed to alleviate extrapyramidal symptoms in patients with psychosis. However, these drugs may themselves lead to hallucinations and are therefore sometimes sold for recreational use. Several psychotropic drugs have less marked anticholinergic effects, e.g. tricyclic antidepressants or thioridazine, and may interact with prescribed or illicit drugs to produce an anticholinergic psychosis.

**Effects sought from the substance:**

*Cannabis:* Relaxation, increased appetite (and antiemetic effects), feelings of happiness, analgesia, sleepiness as well as feelings of sharpened sensory awareness. *Hallucinogens: (e.g. LSD and psylocybin):* Perceptual changes such as hallucinations.

**Associated harms:**

*Cannabis:* Hallucinations, anxiety, panic attacks, paranoia, nausea, impaired judgment and motor coordination, dependence, reduced motivation, persistent cognitive impairment while using the drug, acute and chronic lung problems.
*Hallucinogens (e.g. LSD and psylocybin):* Dissociation, disordered thought, flashbacks and frightening hallucinations and delusions which can lead to violence.

**Overdose:**

*Cannabis:* Risk is small.
*Hallucinogens (e.g. LSD and psylocybin):* LSD is not so much associated with overdose; however, a 'bad trip' may result in hallucinatory experiences which take on a menacing quality accompanied by paranoid delusions, often resulting in accidental or intentional self harm.

**Withdrawal:**

*Cannabis:* Unlikely although symptoms may include anorexia, disturbed sleep, irritability and moodiness.
*Hallucinogens (e.g. LSD and psylocybin):* There is little evidence of dependence, and therefore withdrawal, as drugs tend to be aversive rather than reinforcing.

**Psychological presentations commonly associated with use (likely to resolve on cessation of substance use):**

*Cannabis:* Depression[4-6], anxiety[6-13], precipitation of psychotic symptoms[2, 14, 15].
*LSD:* Precipitation of schizophrenia.

## 3.2 Alcohol

Alcohol (ethanol) is one of the most commonly used and misused substances. It is a depressant drug that slows down body reactions and general brain function. Alcohol is readily available and its excessive consumption has become part of Australian culture.

In Australia, the 12 month prevalence of harmful use of alcohol is 3.0% while the prevalence of dependence is 3.5%. Men are twice as likely to experience dependence compared with women.

The secondary effects of alcohol make it dangerous with motor vehicle accidents, alcohol-related violence (including domestic violence) and liver disease which are all major causes of morbidity and mortality.

The depressive effects of alcohol make it a significant risk factor in the development of mental health problems, particularly depression.

**Effects sought from the substance:** Relaxation and reduced social inhibition.

**Associated harms:** Slurring of speech, reduced motor-coordination, reduced vision and consciousness, liver disease, gastrointestinal disease, anaemia, malnutrition (thiamine deficiency), central nervous system disturbances (from psychosis through to dementia) and heart disease.

**Overdose:** Moderate risk of overdose. Alcohol becomes particularly dangerous when used in conjunction with other depressant substances (e.g. benzodiazepines).

**Withdrawal:** If dependence is established, then withdrawal effects include nausea and vomiting, agitation, tremor, sweating, hallucinations, and seizures. Withdrawal can be life threatening.

**Psychological presentations commonly associated with use (likely to resolve on cessation of substance use):** Depression[16, 17] and anxiety[10, 18-23].

## 3.3 Opioids

**Heroin, codeine, morphine, oxycodone, hydromorphone, buprenorphine, pethidine, dextropropoxyphene, methadone, tramadol***

Opiates are analgesic drugs derived from the opium poppy. The term 'opioids' includes both opiates (based on naturally occurring compounds) and synthetic compounds that act on opiate receptors.

Opioids are generally taken to produce a sense of wellbeing and to reduce the effects of stress and pain.

Opioids are addictive and habit forming. Regular use quickly creates tolerance leading the user to seek increasingly larger doses of the drug to achieve the same effect. Physical withdrawal effects, while very unpleasant, are rarely life-threatening.

Opioids are frequently injected. Harmful chemical contaminants used as cutting agents may include talc, glucose, quinine and strychnine.

**Effects sought from the substance:** Sense of wellbeing, reduction in stress and pain relief.

**Associated harms:** Respiratory depression, clouded mental functioning, nausea, vomiting, sweating, itchy skin, constipation, and lung complications (due to aspiration in overdose).

Problems associated with injecting drug use include: scarred or collapsed veins, abscesses, bacterial infections, blood borne viruses (e.g. hepatitis B and C, Human Immunodeficiency Virus [HIV]), thrombophlebitis, intravascular sepsis, endocarditis, accidental arterial injection and peripheral ischaemia.

Long-term opioid use can result in gonadal suppression, reduced bone density and increased osteoporotic fracture risk.

**Overdose:** Opioids carry a high risk of lethal overdose. Overdose results in respiratory and cardiovascular depression and loss of consciousness which leads to death. Tolerance to opioids develops rapidly resulting in the use of increasing amounts of unknown drug purity, heightening the risk of accidental overdose.

**Withdrawal:** In the dependent person, withdrawal is uncomfortable, somewhat resembling influenza. Features include rhinorrhea, lacrimination, shivers and sweats, pilo-erection, sleeplessness, restlessness and agitation, abdominal and general muscular pains, diarrhoea and nausea.

**Psychological presentations commonly associated with use (likely to resolve on cessation of substance use):** Depression[24-27] and anxiety[11, 25, 28, 29].

*atypical opioid with significant serotoninergic effect

## 3.4 Stimulants (including methamphetamine)

**Cocaine, dexamphetamine, methamphetamine (including crystal and ice), ecstasy (3,4 – methylenedioxymethamphetamine, MDMA), methylphenidate, ephedrine, pseudoephedrine (Sudafed)**

Stimulants are drugs that are purported to enhance sociability, confidence and alertness while reducing inhibition. The sensation of euphoria and wellbeing associated with the use of stimulants makes it highly sought after. However, these effects are usually only short lasting.

The physiological effects of stimulants include increased heart rate, blood pressure and temperature. Amphetamines, in general, reduce coordination, increase risk taking and are associated with an increase in the incident of road accidents.

**Effects sought by user:** Euphoria, empathy, enhanced sociability, increased energy level and stamina, and appetite suppression.

**Associated harms:** Tachycardia, hypertension, seizures, arrhythmias, increased risk taking including sexual activity and dangerous driving, paranoia, fear reduction, hallucinations, tremor, mydriasis, dehydration, diaphoresis, hyponatremia, acute renal failure, hypothermia, nausea, muscle cramping, jaw clenching, jitteriness, racing thoughts followed by periods of depression and low energy, anxiety, depression, paranoia and risk of suicide.

Injecting drug use is also associated with those risks described above for opioids. Problems associated with injecting drug use include: scarred or collapsed veins, abscesses, bacterial infections, blood borne viruses (e.g. hepatitis B and C, Human Immunodeficiency Virus [HIV]), thrombophlebitis, intravascular sepsis, endocarditis, accidental arterial injection and peripheral ischaemia.

Longer term structural brain changes result in memory problems, reduced problem solving ability, impaired concentration and personality change have been reported with heavy use.

**Overdose:** Low to medium risk of overdose for oral use. However, there is a high risk of overdose associated with smoking or injecting use.

**Withdrawal:** Depression, dysphoria, fatigue, exhaustion and somnolence and loss of appetite lasting up to two weeks.

Following prolonged use, insomnia, persistent craving, intense dreaming and irritability may ensue and last several weeks or months.

**Psychological presentations commonly associated with use (likely to resolve on cessation of substance use):** Psychosis[30-38], depression[39-54] and anxiety[11, 29, 43, 46, 50, 53-56].

## 3.5 Benzodiazepines

**Diazepam, temazepam, oxazepam, nitrazapam, alprazolam, flunitrazepam, lorazepam, clonazepam, midazolam**

Benzodiazepines are sedative drugs that may be prescribed to reduce symptoms associated with anxiety, encourage sleep or act as a muscle relaxant. Both prescribed and non-prescribed use of these medications is extremely common. Short-acting or rapidly-absorbed varieties (for example, alprazolam) produce a more immediate feeling of intoxication, are the most sought after by doctor shoppers and can be sold or exchanged on the street.

Benzodiazepines are often used in combination with alcohol, other benzodiazepines or other illicit drugs. Dependence may occur when benzodiazepines are taken in an attempt to medicate (self-medicate) symptoms that are associated with an undiagnosed mental disorder such as anxiety.

**Effects sought by user:** Euphoria, anxiolysis, skeletal muscle relaxation and sedation.

**Associated harms:** Drowsiness, confusion, disinhibition, impaired coordination and increased driving risk, light and sound sensitivity, forgetfulness or memory impairment, nausea, depression, digestive problems, tachycardia, apnoea, ataxia, hypotension and seizures.

When injected intravenously vein damage is common along with those harms associated with injecting drug use mentioned earlier. Problems associated with injecting drug use include: scarred or collapsed veins, abscesses, bacterial infections, blood borne viruses (e.g. hepatitis B and C, Human Immunodeficiency Virus [HIV]), thrombophlebitis, intravascular sepsis, endocarditis, accidental arterial injection and peripheral ischaemia.

When accidentally injected arterially, benzodiazepines can result in peripheral ischaemia and gangrene.

**Overdose:** Risk is variable depending on the strength of particular formulations. However, taken in large amounts and/or in-conjunction with other benzodiazepines or other substances (usually alcohol), there is a high risk of overdose, particularly in people with a high suicide risk. Overdose results in prolonged periods of sleep combined with respiratory and cardiovascular depression which can be fatal when combined with alcohol.

**Withdrawal:** There is an established withdrawal effect associated with the use of benzodiazepines. Likelihood of withdrawal is higher for stronger, shorter-acting types that are used for a long period of time. Withdrawal effects include anxiety, depression, problems with sleeping, irritability, palpitations and sensory disturbances. Seizures can occur with sudden withdrawal from more than 40mg/day of diazepam or diazepam equivalents.

**Psychological presentations commonly associated with use (likely to resolve on cessation of substance use):** Depression and rebound anxiety[57-59].

## 3.6 Inhalants/solvents

Inhalants and solvents are psychoactive drugs that are part of a class of volatile substances that give off gas or vapours at room temperature. They include a wide range of substances including petrol, spray paints and some glues as well as other chemicals such as butane.

The effects of inhalants or solvents vary greatly and depend on which substance is inhaled or sniffed. Most are absorbed rapidly and produce short-term effects similar to those of anaesthetics by depressing the central nervous system. When inhaled in sufficient concentrations, inhalants can cause intoxication and feelings of stimulation that are intense but usually only last a few minutes. This effect of intoxication can be extended for several hours by breathing in inhalants repeatedly. Repeated inhalations make users feel less inhibited and less in control. Users can lose consciousness with continued use.

Young people may use inhalants as they are cheaper and more easily accessible than alcohol. Long-term chronic inhalant users become difficult to treat due to cognitive impairment combined with multiple social and psychological issues.

**Effects sought by user:** Excitement, dizziness, exhilaration and feelings of self confidence.

**Associated harms:** Visual and auditory hallucinations, nausea, dullness, disorientation, loss of self control, blurred vision, drowsiness, lack of muscle coordination and slurring, red and watery eyes, cough, runny nose, short-term memory loss, mental confusion, thinking and learning problems, irritability, hostility, extreme tiredness, trembling, loss of control of fine movements, slowed reaction time, dizziness, chronic headaches, sinusitis and nosebleeds, spots/rash around the mouth and nose, indigestion and stomach ulcers, liver and kidney damage and hearing loss.

Permanent brain injury can occur from the use of solvents.

**Overdose:** More likely to occur with high concentration substances such as butane and occurs after repeated sniffing/inhalations in a single session. Tachyarrhythmias, heart failure and death can be directly induced within minutes of a session of repeated inhalation.

Delirium, fever, hallucinations, restlessness, seizures, confusion and unconsciousness can all occur with repeated sniffing. Death from hypoxia can occur through the displacement of oxygen in the lungs or by effects on haemoglobin oxygen binding.

**Withdrawal:** Headache, nausea, stomach and other muscle cramps, fatigue, tremors, hallucinations and visual disturbances, anxiety, depression, loss of appetite, irritation, aggressive behaviour and dizziness.

**Psychological presentations commonly associated with use (likely to resolve on cessation of substance use):** Paranoia and psychosis[60-62] and depression[63, 64].

For further information please consult:

National Directions on Inhalant Abuse Final Report[65].

http://www.health.vic.gov.au/drugservices/downloads/niat_report.pdf

## 3.7 Tobacco

Tobacco comes from the dried leaves of the tobacco plant with the majority of tobacco consumption in Australia being via cigarettes. After drying, the tobacco leaves are treated with a vast array of chemicals before being made into cigarettes. Many of the chemicals used to treat the tobacco leaves are carcinogenic.

Tobacco smoking is the leading preventable cause of premature death in Australia and causes more sickness and disease than any other drug, contributing to the death of over 15,000 Australians each year.

Nicotine is the pharmacologically active ingredient in tobacco. It is responsible for the addictiveness of cigarettes and other tobacco products and is highly toxic. Smoking tobacco delivers nicotine rapidly to the brain, contributing to its addictiveness. Its absorption causes nervous system stimulation, increased heart rate, raised blood pressure and constriction of small blood vessels.

**Effects sought by user:** Reduction of anxiety and tension and increased alertness.

**Associated harms:** Nausea, increased heart rate and blood pressure, cancer (especially lung, mouth and throat cancer), hypertension, ischaemic heart disease, chronic bronchitis, stroke and blindness.

Smoking harms nearly every organ in the body causing a wide range of diseases, many of which can result in the premature death of the smoker.

**Overdose:** Unlikely.

**Withdrawal:** Nicotine is highly addictive and produces a withdrawal syndrome characterised by craving, irritability, restlessness and anxiety, impaired performance of psychomotor tasks as well as difficulty concentrating, aggressiveness, frustration, sleep disturbances, depressed mood, decreased heart rate, increased appetite or weight gain.

Smokers claim they smoke to relax, reduce stress, increase alertness and concentration, regulate mood and control/lower body weight. However, it is difficult to separate these reported positive effects from the relief of nicotine withdrawal symptoms.

Withdrawal symptoms can last for two to three weeks; however, cravings may persist for months but at reduced frequency and intensity.

**Psychological presentations commonly associated with use (likely to resolve on cessation of substance use):** Not currently described.

For further information please consult:

*Smoking cessation guidelines for Australian general practice*[66].

http://www.quitsa.org.au/cms_resources/documents/AustralianGeneralPracticeGuidelineHandbook.pdf

# 4 Tobacco

## 4.1 Comorbidity with tobacco

- Smoking is much more common amongst people with mental disorders compared with those without a mental disorder in Australia.
- Smoking cessation strategies that are effective in the general population can be implemented and are effective at the same time as treatment for mental disorders.
- People with mental disorders are able to quit smoking if their mental disorder is under control and other psychotropic medication dosing remains stable.

While tobacco smoking rates have dropped significantly in the general community, the rate amongst people with mental illness is still very high.

This has been highlighted by a number of studies:

- *"People with psychotic illness: An Australian study 1997-98"* found that 73% of males and 56% of females with psychotic illness smoke tobacco and over 80% of these people smoke more than 20 cigarettes per day[67].
- Conversely, the National Survey of Mental Health and Wellbeing[68] found that 35% of smokers between 18–39 years had a mental disorder[69].

The incidence of smoking amongst those with a mental disorder appears to be culturally related and varies between countries[70].

### *4.1.1 Effects of tobacco on mental disorder*

There are many theories about why people with mental disorders have a high rate of tobacco use. Nicotine may help to:

- Relieve some of the symptoms of different mental disorders by:
  - Briefly improving auditory gating (the ability to block out irrelevant every day sounds, e.g. ticking clock) in smokers with schizophrenia[71] and other extrapyramidal side effects[2].
  - Reducing symptoms of anxiety and depression[72-75].
- Improve cognitive function[71, 76].
- Reduce side effects of some medications such as akathisia or restlessness[77].
- Suppress appetite in an attempt to lose weight in those with eating disorders[78-81].

Most of these effects are likely to be caused directly by nicotine. However, for some symptoms such as depression and anxiety, it can be difficult to separate the effects of nicotine from the relief of withdrawal[82-84]. While more recent research has enabled separation of withdrawal relief and direct effects of nicotine, nicotine withdrawal at times can present in a similar manner to some of the symptoms of the mental disorder (particularly depression and anxiety). As a result, it can occasionally be misinterpreted by the person with the mental disorder as well as the clinician and must be taken into consideration.

It is also likely that external social and environmental factors contribute significantly to, and account for, the high rates of smoking amongst individuals with mental disorders. These include higher rates of smoking amongst family, friends and within mental health services, the perceived role of smoking in relieving stress and as a coping mechanism, in aiding low self esteem and social mixing, and in dealing with boredom[70, 83]. In addition, people with mental disorders may have more difficulty quitting or reducing tobacco use because of limited support from health workers. They may have more difficulty coping with withdrawal symptoms and may lack the support and confidence needed to persist with their quitting efforts.

People with mental disorders have identified other effects of tobacco smoking including barriers to community involvement, accommodation difficulties, stigma and shame, the negative effects on appearance and other people, stained fingers and teeth, the smell of tobacco, and the added stress caused by living with an addiction[85-88].

As well as the serious impact on physical health, many people with mental disorders are spending a significant percentage of their income on cigarettes. As a result they have very little money for food, recreation, public transport, clothing and health care[85, 87, 89, 90].

The affordability of nicotine replacement therapy (NRT) and other treatments may, therefore, be a significant factor in restricting access. While the cost of NRT has been implemented so that it is more economical than continuing to smoke, the cost may be viewed in the same manner that clients perceive costs associated with methadone and buprenorphine dispensing. That is, individuals with mental disorders and substance use disorders are often unable to prioritise aspects of their life which include the inability to budget and rationalise treatment benefits. Therefore, they may perceive the cost of NRT to be prohibitive despite being a cheaper alternative than continuing to smoke.

A history of mental disorders does not necessarily mean, however, that individuals do not wish to quit smoking[91]. Evidence also suggests if the above mentioned factors such as demographics, diagnosis and concurrent medication are taken into account, smoking cessation strategies that are effective in the general population can be implemented and are effective at the same time as treatment for mental disorders****[92-101]. People with mental health disorders are able to quit smoking if their mental disorder is under control and other psychotropic medication dosing remains stable****[92, 99]. Improvements in anxiety and depression have also been observed in those who cease smoking[100].

### *4.1.2 Tobacco use in combination with other substance-use disorders*

Tobacco use amongst people with alcohol and other substance-use disorders may be as high as three times that of the general community[102, 103]. As comorbid tobacco consumption amongst individuals with other substance-use disorders (and mental disorders) is common, it is accepted as 'normal' by clinicians. As a result, individuals with other substance-use issues or mental disorders do not receive support to address tobacco consumption[70]. These people are often not asked about their tobacco use and little information is provided to them on the risks of smoking and benefits of quitting. They are also rarely offered the opportunity to quit.



Traditionally, the drug treatment culture has explicitly excluded smoking cessation treatments and dissuaded individuals from attempting cessation out of concern that concurrent treatment of multiple drugs of abuse is too difficult and may compromise sobriety. Tobacco use has few immediate consequences (including lack of direct psychoactive effects), and thus has not been a priority for treatment.

Yet, the use of tobacco accounts for greater morbidity than alcohol and all other drugs combined[104]. Among individuals treated for alcohol dependence, tobacco-related diseases were responsible for half of all deaths – greater than alcohol-related causes.

In a 24-year study of long-term users, the death rate among cigarette smokers was four times that of non-smokers. Although the magnitude of the problem of tobacco use in this patient population is clear, questions of when and how to best intervene remain[105].

However, evidence suggests that smoking cessation strategies can be implemented and are effective at the same time as treatment for alcohol and other drug use if patients are established and stable in treatment***[106].

Studies have shown that people with substance-use disorders are able to quit smoking especially if their other substance use is abating. Quitting smoking may also help control their use of other substances****[102, 107, 108].

### 4.1.3 Interactions between tobacco and therapeutic agents used for mental disorders

The hydrocarbons in cigarette smoke (not the nicotine) have been shown to increase the body's ability to metabolise some medications via the cytochrome P450 system, resulting in reduced plasma concentrations of these medications✖✖✖[109]. As a result, people who stop smoking may find that plasma levels of certain medications increase significantly.

Nicotine can significantly decrease plasma concentrations of antipsychotics, resulting in increased dosing requirements of these medications in known smokers[2].

The metabolism of the following medications is known to be affected by cigarette smoke: clozapine[110, 111], fluphenazine, haloperidol and olanzapine✖✖✖[112, 113]. Clinically, it is recommended that the plasma levels of these medications and the presence of side effects should be monitored before and after smoking cessation[114, 115].

Antipsychotics are known to lower seizure threshold and bupropion has been known to induce seizures and psychosis. Individuals receiving these two combinations of substances are therefore more vulnerable to seizures and should be monitored closely✖[2].

Please refer to P450 website to observe possible interactions between smoking and therapeutic agents:

http://medicine.iupui.edu/flockhart/table.htm

### 4.1.4 Implications for management

The World Health Organization (WHO) has recommended three broad strategies for assisting people to quit or reduce tobacco use[108]:

1. The routine delivery for all smokers of brief opportunistic intervention by health professionals.
2. Intensive support provided as a backup for brief intervention, including quit/reduce groups, coping skills information and support.
3. Pharmacological aids.

These three strategies are discussed in the following paragraphs.

All forms of treatment may require a degree of modification to accommodate those with mental disorders who have impaired cognitive ability.

**1. Brief intervention**

All smokers should be asked regularly about their tobacco use and offered at least brief intervention.

The *Smoking cessation guidelines for Australian general practice (*2004) recommended the 5As model for brief intervention[66]:

- **Ask** about smoking and keep an up-to-date record of smoking status.
- **Advise** smokers to stop smoking in a clear, straightforward and non-judgemental manner.
- **Assess** motivation to quit or reduce tobacco use.
- **Assist** the smoker by offering support and information about ways to quit/reduce, withdrawal symptoms, coping strategies, pharmacotherapy aids and other supports.
- **Arrange** follow-up if possible.

**2. Support**

Smokers need a range of cognitive and behavioural strategies to address their tobacco use. They may require:

- Support to plan their quitting attempt.
- Information regarding trigger situations and how to cope with them.
- Information regarding withdrawal symptoms and cravings.
- Help to identify and work through barriers to quitting.
- Relapse prevention skills.
- Coping skills.

Motivational interviewing is an effective way to help increase commitment to quitting.

The Stages of Change Model is a valuable model for assessing a person's readiness to change and suggests interventions targeted to the person's current stage in the Stage of Change. In the model the patient is at one of several stages relevant to changing their behaviour. The stages are:

- Precontemplation: the patient is not intending to change.
- Contemplation: the patient is thinking about changing.
- Determination: the patient has decided to change.
- Action: the patient is taking active steps towards changing.
- Maintenance: the changed behaviour has been established.
- Relapse: the patient has reverted to the previous behaviour.

Each stage requires a different intervention from the clinician.

For further information concerning motivational interviewing and stages of change models, please refer to:

*Putting prevention into practice: Guidelines for the implementation of prevention in the general practice setting*[116]:

http://www.racgp.org.au/Content/NavigationMenu/ClinicalResources/RACGPGuidelines/TheGreenBook/RACGPgreenbook2nd.pdf

**3. Pharmacological aids**

***Nicotine replacement therapy***

Nicotine replacement therapy (NRT) aims to replace some of the nicotine obtained from cigarettes. This reduces physical withdrawal symptoms when stopping smoking, helps the person resist the urge to smoke[84] and is acceptable in those with mental disorders****[93, 96]:

- It is available in patches, lozenges, inhalers, sublingual tablets and gum.
- It does not contain other toxic substances found in cigarettes, such as tar and carbon monoxide.
- It does not produce the dramatic surges of plasma nicotine concentrations.
- It does not produce dependence.
- It has been shown to increase quit rates by approximately 1.5–2 times, regardless of the setting[117].

**Combination NRT or high dose NRT**

People who are heavy smokers (smoke more than 20 cigarettes a day) can use combined treatments if they are still experiencing withdrawal symptoms and are unable to quit using a single type of NRT. For example, using a combination of a patch with gum, lozenge or inhaler may be more effective.

NRT is contraindicated and medical advice is recommended for people who;

- Have had a recent heart attack or stroke.
- Have ischaemic heart disease with current active angina.
- Experience cardiac arrhythmias.
- Are under the age of 12 years.

In addition, specific products are not recommended for some people, including:

- *Patches*: for those with severe skin disease or an allergy to the patch.
- *Lozenges*: for those with phenylketonuria.
- *Inhalers*: for those who are hypersensitive to menthol.
- *Gum*: for those who have difficulties chewing gum[84].

NRT for pregnant women and nursing mothers is indicated with precaution and medical advice should be sought regarding the appropriate product and dosage.

***Bupropion (Zyban)***

Bupropion is a non-nicotine oral therapy to assist smoking cessation. Its mechanisms of action are still unclear; however, it is thought to inhibit the reuptake of noradrenaline and dopamine. It has been shown to reduce the withdrawal symptoms associated with stopping smoking. In a number of clinical trials, bupropion demonstrated a significant effect in increasing long-term abstinence from smoking[66] as well as proving its effectiveness and acceptability for use in those with mental disorders****[94-97, 99].

The greatest risk associated with bupropion use is the lowering of the seizure threshold. Therefore, it should not be used by people with a predisposing risk factor for seizures unless the potential benefit of smoking cessation outweighs the increased risk of seizure[66, 108]. Predisposing risk factors for seizure include:

- Any seizure disorder, past or current.
- Concomitant use of medications known to lower seizure threshold, for example, antipsychotics, antidepressants (including SSRIs and tricyclics), antimalarials, tramadol, theophylline, systemic steroids, quinolones, sedating antihistamines✖.
- Excessive alcohol or benzodiazepine consumption✖.
- Withdrawal from alcohol or benzodiazepines.
- History of recent head injury.
- Diabetes treated with oral hypoglycaemics or insulin.
- Use of stimulants or anorectic products.
- Known central nervous system tumours.

In addition, major drug interactions occur with *monoamine oxidase inhibitors* (MAO-I) (both reversible and non-reversible). Therefore, bupropion should be avoided if these have been taken within the last 14 days.

Bupropion is further contraindicated, or its use needs be taken under strict consideration, in the following situations:

- Allergy to bupropion.
- Current or previous history of anorexia nervosa.
- Pregnant or breast-feeding women.
- Opioid dependence.
- Bipolar affective disorder, psychosis.
- Cardiac disease, hypertension.
- Renal disease.
- Liver disease.

For full prescribing information on bupropion, please see the Pharmaceutical Benefit Scheme (PBS) website:

http://www.pbs.gov.au/html/healthpro/home

***Varenicline (Chantix/Champix)***

Varenicline is a new non-nicotine oral therapy to assist smoking cessation and is the first approved nicotinic receptor partial agonist. It has been shown to be an efficacious and well-tolerated smoking-cessation pharmacotherapy that is superior to both placebo and bupropion in helping to maintain long-term abstinence from cigarettes***[118].

Varenicline interactions with other drugs appear to be minimal. However, the safety of the combination of varenicline and buproprion has not been established. The combination of varenicline and NRT has caused the discontinuation of treatment due to side effects such as nausea, headache, vomiting, dizziness dyspepsia and fatigue and should not be used.

The most common side effect of varenicline is nausea. This has been described as mild to moderate and often transient.

Varenicline is contraindicated, or its use needs be taken under strict consideration, in the following situations:

- Renal disease.
- Pregnant or breast-feeding women.

For full prescribing information on varenicline, please see the PBS website:

http://www.pbs.gov.au/html/healthpro/home

***Complementary therapies***

There is little evidence to suggest that complementary or alternative therapies such as acupuncture or hypnotherapy are effective in the management of smoking cessation.

There is no consistent evidence that shows that acupuncture (or any particular acupuncture technique) is superior in comparison to no treatment, other anti-smoking interventions, or sham acupuncture in the prevention of smoking[81].

Different types of hypnotherapy are used to try and help people quit smoking. Some methods try to weaken people's desire to smoke, strengthen their will to quit, or help them concentrate on a quit program. There are conflicting results for the effectiveness of hypnotherapy compared to no treatment or to advice against smoking. Hypnotherapy has not been shown to have a greater effect on quit rates than other interventions or no treatment at all.

For further information please consult:

*Smoking cessation guidelines for Australian general practice*[66]*:*

http://www.quitsa.org.au/cms_resources/documents/AustralianGeneralPracticeGuidelineHandbook.pdf

# 5 Depression and substance use

## 5.1 Depression

Depression is a debilitating disorder that disrupts relationships and daily lives and is one of the most common mental disorders[119]. Depression is more common in women than in men[68, 119].

People with depression may present as tearful and report that they feel sad, empty, hopeless and discouraged. Children and adolescents may present as irritable. Adults may also present as irritable and report concentration problems. People with depression may report loss of interest or pleasure in most activities, trouble sleeping, fatigue and problems with weight. Feelings of worthlessness and guilt may be associated with suicidal ideation.

To be diagnosed with major depression, a person must either have a depressed mood or a loss of interest or pleasure in daily activities consistently for at least a two week period. This mood must represent a change from the person's normal mood. Social, occupational, educational or other important functioning must also be negatively impaired by the change in mood.

## 5.2 Comorbidity with depression

- People with depression have high rates of comorbidity with other mental disorders and substance use disorders[17, 68, 119-122].
- Comorbidity in people with depression results in higher levels of impairment[119, 123] and increased severity and recurrence of depression[121, 122, 124].
- Depression and anxiety frequently co-exist[68, 119, 121, 122, 124].
- Psychosocial effects such as stigma, poverty and isolation associated with substance use may contribute to depression; depression also has the potential to predispose people to poverty, isolation and substance use[17].

### *5.2.1 General management approaches to comorbidity*

- Clinicians often find treatment of depression in the presence of substance dependence difficult. It is often unclear what the relationship is between the conditions and whether the depression is brought about by the substance dependence itself, or whether it is a primary depressive disorder, and therefore how best to approach treatment[125].
- Substance use or dependence should not preclude treatment of depression[125].
- In ideal circumstances, the patient should be assessed for persistent depression after a few weeks of abstinence in order to exclude depression related to withdrawal or due to the substance use itself[125].
- Antidepressants are more likely to be effective for primary depression in comparison to substance induced depression[125].
- Improvements in depression may result in short-term reductions in substance use; however, these reductions do not necessarily persist. Therefore, specific interventions for the substance use are also needed to increase the likelihood of long-term abstinence[125].

## 5.3 Major clinical issues with depression and cannabis/hallucinogen use

- Since cannabis use appears to be a predictor of depression, cessation of cannabis use is important as a first step so that depressive symptoms can be better evaluated.
- However, abstinence from cannabis is a difficult goal to achieve in cannabis dependent people.
- In the absence of other proven forms of treatment, CBT is, at present, the most widely employed form of treatment for cannabis use.

### *5.3.1 Effect of cannabis and other hallucinogens on depression*

- Depression is more common in people who use cannabis, particularly with those who commenced at a young age[4-6].
- There is little support for the self-edication hypothesis of cannabis being used to relieve symptoms of depression[4] and a greater evidence base suggesting cannabis to be a predictor of depression[126].
- The association between cannabis use and depression may be due to common factors that lead individuals to develop depression and use cannabis[4].
- Higher quantities of cannabis use predict more severe depressive symptoms[4].

### *5.3.2 Interactions between cannabis and hallucinogens and therapeutic agents for depression*

- Cannabis can exacerbate the sedative effects of tricyclic antidepressants which increases the risk of impaired driving and injury as well as overdose✖.
- LSD may induce a serotonin syndrome (Appendix 1) therefore, caution should be exercised when prescribing SSRIs or MAO-I✖[127].
- Cannabis and antidepressants are metabolised by CYP 450 enzymes which may result in the inhibition or induction of either drug group. Therefore, individuals should be monitored closely to ensure outcomes are appropriate✖.

### *5.3.3 Management approaches to comorbid depression and cannabis use*

- Since cannabis use appears to be a predictor of depression, cessation of cannabis use is important as a first step wherever possible so that depressive symptoms can be better evaluated.
- However, abstinence from cannabis is a difficult goal to achieve in cannabis-dependent people[128].
- In the absence of other proven forms of treatment, CBT is, at present, the most widely employed form of treatment for cannabis use✖✖✖✖[128].

## 5.4 Major clinical issues with depression and alcohol use

- Alcohol in large quantities has mood-depressant effects.
- A depression-like set of symptoms may emerge during or after alcohol withdrawal.
- In ideal circumstances, a period of abstinence should be trialled.
- Antidepressants are effective for the treatment of depression in those with alcohol-use disorders and have shown improvement in both depression and alcohol consumption.
- However, antidepressants are less effective in situations of continued heavy drinking or where depression is mainly alcohol induced.
- CBT in depressed alcohol dependent people is associated with decreased post-treatment alcohol use.
- Naltrexone or acamprosate can be used in combination with antidepressant medications and CBT.

### *5.4.1 Effect of alcohol on depression*

- Heavy alcohol use[17] and alcohol dependence[16] are associated with high rates of depression.
- Women more commonly drink in response to primary depression[129].
- Alcohol in large quantities has mood depressant effects and may worsen depressed mood if it is part of a Major Depressive Episode or a transient state in response to a stressor. Depression and alcohol use are therefore associated with increased risk of suicide[16, 129-131].
- The course of alcohol dependence in people with alcohol-induced depression is more severe when compared to those with depression that is independent of alcohol dependence[129].
- A depression-like set of symptoms may emerge during or after alcohol withdrawal[132].

### *5.4.2 Interactions between alcohol and therapeutic agents for depression*

- Alcohol can exacerbate the sedative effects of sedative antidepressants including tricyclics and mirtazepine used in the treatment of depression. Alcohol toxicity may occur through the inhibition of CYPs by antidepressants involved in the metabolism of alcohol✖[133].
- Interactions between antidepressants and acamprosate used to treat alcohol dependence are minimal as are interactions between antidepressants and disulfiram and naltrexone, also used to treat alcohol dependence✖[134].

### *5.4.3 Management approaches to comorbid depression and alcohol use*

- In order to fully assess the extent of depression, in ideal circumstances, a period of abstinence from alcohol should be trialled. It is worth noting that depressive symptoms may emerge both during and after alcohol withdrawal[130, 135].

- Where it is not possible to trial a period of abstinence from alcohol, the use of antidepressants is indicated. However, antidepressants will be less effective in situations of continued heavy drinking or where depression is mainly alcohol induced.
- Antidepressants will be most effective in those people with primary depression:
  - Antidepressant are effective for the treatment of depression in those with alcohol use disorders and have shown improvement in both depression and alcohol consumption***[130, 135-137].
  - SSRIs (fluoxetine and sertraline) are particularly well tolerated***[130, 135, 136] and may pose less risk of increased sedation than other forms of antidepressants.
  - Some studies of SSRIs used to treat alcohol dependent people have shown a worsening effect on alcohol consumption in certain subtypes, in particular those with early onset problem drinking***[138, 139]. Therefore, monitoring is required.
- CBT in depressed alcohol-dependent people is associated with decreased post-treatment alcohol use**[140].
- Treatments primarily aimed at alcohol dependence (in combination with SSRIs) are more effective under heavy drinking circumstances or when depression is alcohol induced****[134, 141-143].
  - Acamprosate and naltrexone are both effective in the management of alcohol dependence and maintaining abstinence****[141, 144].
  - Naltrexone may be more effective in those with higher depression scores***[144].
  - Naltrexone has been shown to be effective in reducing alcohol consumption in individuals who have been unable to abstain from alcohol consumption despite antidepressant treatment*[134].
  - Naltrexone in combination with antidepressants has been shown to reduce the number of days in which alcohol is consumed while in treatment***[145].

## 5.5 Major clinical issues with depression and opioid use

- Rates of depression decrease once people enter treatment for opioid dependence, in particular, maintenance pharmacotherapies.
- Fluvoxamine×××, fluoxetine××, norfluoxetine×× and paroxetine× can inhibit buprenorphine and methadone metabolism through inhibition of the CYPs involved in their metabolism.
- Carbamazepine is a potent CYP inducer and will induce the metabolism of methadone and buprenorphine as well as reduce plasma concentrations.
- If antidepressant medications are to be used, then non-sedating antidepressants (such as SSRIs) are preferable due to the risk of overdose mentioned above with tricyclic antidepressants.
- CBT provides additional benefit in combination with a maintenance therapy program in the treatment of depression in opioid users.

### 5.5.1 Effects of opioids on depression

- Depression is common among illicit opioid users[24-27]. Heavier illicit opioid use is associated with more severe depression[26].
- Rates of depression decrease once people enter treatment for opioid dependence, in particular maintenance pharmacotherapies[26, 146].
- Conversely, continued illicit opioid use affects adherence to treatment for depression in opioid dependent people[147].

### 5.5.2 Interactions between opioids and therapeutic agents for depression

- Fluvoxamine✖✖✖, fluoxetine✖✖, norfluoxetine✖✖ and paroxetine✖ can inhibit buprenorphine and methadone metabolism through inhibition of the CYPs involved in their metabolism[148-150]. This can result in an increase in plasma opioid pharmacotherapy concentrations and potential overdose. This can be a particular issue during induction onto methadone; however, the risk may persist even after stabilisation has occurred✖✖✖[151-155].
- Fluvoxamine is the most potent inhibitor of methadone and buprenorphine metabolism and is the most clinically relevant. Therefore, it should be avoided✖✖✖[150].
- Fluoxetine and paroxetine should also be avoided✖✖.
- Citalopram and sertraline are the least likely SSRIs to have cytochrome-mediated drug interactions; however, due to the theoretical potential for an interaction, caution should still be used and individuals monitored closely✖[156].
- Carbamazepine is a potent CYP inducer and will induce the metabolism of methadone and buprenorphine as well as reduce plasma concentrations✖✖[149, 157]. This has the potential to result in withdrawal and failure of retention in treatment****[158-160].
- There is an increase in sedation as well as risk of fatal overdose with opioid use and tricyclic antidepressants✖✖[161].

### 5.5.3 Management approaches to comorbid depression and opioid use

- It is important to consider the variety of factors that may be contributing to depressed mood in this group of people, e.g. chronic psychosocial stressors, the effects of substance dependence, and long-standing personality-related mood disturbances.
- Entry into a maintenance pharmacotherapy (buprenorphine or methadone) is associated with improvement in depression***[146].
- There is conflicting evidence on the efficacy of antidepressant medication amongst maintenance therapy populations****[162-165].
- If antidepressant medications are to be used, then non-sedating antidepressants (such as SSRIs) are preferable due to the risk of overdose mentioned above with tricyclic antidepressants.
- CBT provides additional benefit in combination with a maintenance therapy program in the treatment of depression in opioid users.

- In individuals who adhere to medication plans, naltrexone in combination with antidepressants is effective in improving depression and reducing illicit opioid intake***[142, 164, 166].
- In individuals who adhere to medication plans, naltrexone treatment is associated with reduced depression compared with methadone maintenance treatment***[164, 166].

## 5.6 Major clinical issues with depression and stimulant (including methamphetamine) use

- Depression is common amongst stimulant users, both in the days following heavy use and during withdrawal.
- Tolerance develops quickly to the positive effects of stimulant drugs when used to self medicate for depression, leaving the person at risk of dose escalation and dependence.
- Stimulant effects on sleep may worsen sleep-wake cycle disturbances associated with depression.
- Monoamine Oxidase Inhibitors (MAO-I) (either irreversible or reversible) are contraindicated in people using amphetamines or MDMA✖✖✖.
- Reductions in stimulant use improve symptoms of depression.
- If depression persists despite adequate withdrawal from stimulants, then treat as for primary depression.

### *5.6.1 Effects of stimulants on depression*

- Depression is common amongst stimulant users[40, 41, 43, 45, 49-51, 53, 54].
- In the days following use of stimulants, users report rebound depression, most likely due to monamine depletion[39, 47, 48].
- Depression is also present during the withdrawal phase from stimulants as well as for a significant period of time following abstinence[42, 44, 46].
- There is an association between depression and severity of stimulant use and dependence, with higher levels of use being more indicative of greater severity of depression[41, 44, 50, 52, 53, 56, 167, 168].
- Evidence suggests that depression precedes MDMA use in particular in most instances, supporting the self medication hypothesis in this case[40, 53, 55, 169-171].
- Evidence from animal studies suggests that serotonin producing neurons are damaged by heavy MDMA use[172] and that it is likely that at least some of these levels are achieved in humans who use MDMA[173-177].
- Tolerance develops quickly to the positive effects of these stimulant drugs[178] leaving the person at risk of dose escalation and dependence.
- Stimulant effects on sleep[171] may worsen sleep-wake cycle disturbances associated with depression.

### 5.6.2 Interactions between stimulants and therapeutic agents for depression

- Stimulant drugs are likely to exacerbate the effects of SSRI and SNRI antidepressants in particular (and vice versa) and may result in serotonin syndrome (Appendix 1)✖[127, 179, 180]. Patients should be warned of signs of serotonin syndrome and be monitored.
- MAO-Is (either irreversible or reversible) are contraindicated in people using amphetamines or MDMA. Deaths have been associated with concurrent use of moclobemide and MDMA✖✖✖[181, 182].
- Fluoxetine, norfluoxetine, paroxetine and sertraline are potential inhibitors of CYP 2D6 which metabolises MDMA and methamphetamine. This may result in elevated plasma concentrations leading to toxicity✖.

### 5.6.3 Management approaches to comorbid depression and stimulant use

- Reductions in stimulant use improve symptoms of depression[183]. Therefore, reductions and cessation of stimulant use should be encouraged.
- Treatment for depression should be commenced if use of stimulants is only occasional and there is established coexisting depression.
- If depression persists despite adequate withdrawal from stimulants, then treat as for primary depression.
- Formal drug detoxification should be considered if the person is dependent.
- There is little consistent evidence that antidepressants are beneficial in management of stimulant withdrawal[184].
- CBT can be used to address stimulant use and is effective***[49, 183].
- Care should be taken to select an appropriate antidepressant in order to minimise chances of drug interactions.



## 5.7 Major clinical issues with depression and benzodiazepine use

- Sedative and depressive actions as well as long-term use of benzodiazepines exacerbate the negative symptoms of depression such as lack of energy, negative cognitions and anhedonia.
- Benzodiazepine use should be restricted to a few days with a long acting benzodiazepine.
- Psychological and behavioural treatment can be effective in treating insomnia.
- CBT for depression is more effective if there is minimal sedation and anxiolysis due to the benzodiazepine use.
- If long-term benzodiazepine use is being considered, then this should be administered under close supervision.

### 5.7.1 Effects of benzodiazepines on depression

- Benzodiazepines are often prescribed to relieve some of the symptoms of depression such as insomnia[185] and agitation during the acute treatment phase.
- However, benzodiazepines also cause disruptions to and reductions in Rapid Eye Movement (REM) sleep[186, 187].
- Sedative and depressive actions as well as long-term use of benzodiazepines exacerbate the negative symptoms of depression such as lack of energy, negative cognitions and anhedonia[59].

### 5.7.2 Interactions between benzodiazepines and therapeutic agents for depression

- There is an increased risk of sedation and overdose with the combination of benzodiazepines and sedative antidepressants such as tricyclics and mirtazepine✖.
- Benzodiazepines and antidepressants are both metabolised by CYP 450 enzymes which may result in the inhibition or induction of either drug group. Therefore, individuals should be monitored closely to ensure outcomes are appropriate✖.
- Fluvoxamine will inhibit the metabolism of alprazolam, midazolam, triazolam and diazepam causing increased sedation and potential toxicity✖.
- Citalopram and sertraline are the least likely SSRIs to have cytochrome-mediated drug interactions✖.

### 5.7.3 Management approaches to comorbid depression and benzodiazepines

- Benzodiazepine use should be discouraged and cessation should be a long-term goal.
- Antidepressant medication (SSRIs or other non-sedating antidepressants) can be commenced with the patient still taking benzodiazepines.
- Tolerance quickly develops to the effects of benzodiazepines used during the treatment of depression (acute agitation, anxiety, panic and insomnia)[188].
- Benzodiazepine use should be restricted to a few days with a long-acting benzodiazepine[189].
- Psychological and behavioural treatment can be effective in treating insomnia***[190-192] associated with psychiatric disorders[193] and may reduce the need for benzodiazepine use during depression.
- CBT for depression will be more effective if there is minimal sedation and anxiolysis due to the benzodiazepine use.
- If large quantities of benzodiazepines (e.g. 40mg diazepam daily equivalent or more) are being consumed, then inpatient withdrawal to lower levels should be considered to avoid and manage seizure risk[194].
- If dependence has developed, then graduated withdrawal through slow reduction of dosage should be commenced****[194-196], possibly after transferring the patient onto a long acting benzodiazepine.

- If long-term benzodiazepine use is indicated, then:
  - This should be subject to a contract with the patient.
  - Authorities should be advised, including registration with the relevant local government health authority.
  - The seeking of additional benzodiazepines from other prescribers should be monitored (e.g. using the *Authority to release personal PBS claims information to a third party* form).
  - Daily or weekly dispensing of benzodiazepines should be considered and may assist with controlling use.

## 5.8 Major clinical issues with depression and inhalant/solvent use

- Depression and inhalant use often co-exist and both increase suicide risk.
- Inhalants can exacerbate the sedative effects of some antidepressants.
- Most antidepressants reduce seizure threshold and tricyclic antidepressants can cause cardiac arrhythmias – both complications of inhalant use.
- As with most other substances, inhalant users should be encouraged to try and reduce or cease use to observe whether depressive symptomatology resolves.

### *5.8.1 Effects of inhalants/solvents on depression*

- Depression and use of inhalants are positively correlated, particularly amongst adolescents[63, 64].
- Depression and inhalant use, and inhalant use alone are associated with increased risk of suicide[64, 197-200].

### *5.8.2 Interactions between inhalants/solvents and therapeutic agents for depression*

- Inhalants can exacerbate the sedative effects of some antidepressants including tricyclic antidepressants and mirtazepine✖.
- Most antidepressants reduce seizure threshold and tricyclic antidepressants can cause cardiac arrhythmias. Therefore, risks should be appraised prior to commencement✖.

### *5.8.3 Management approaches to comorbid depression and inhalant/solvent use*

- There appears to be no literature that sheds light on managing people with both depression and inhalant/solvent use related problems.
- As with most other substances, inhalant users should be encouraged to reduce or cease use to observe whether depressive symptomatology resolves.
- In general, with respect to inhalant/solvent use[65]:
  - Outline to users the harms associated with inhalant/solvent use.
  - Investigate polysubstance use as this is common.

- Standard CBT approaches to both sets of issues should be used, with particular attention to the development of:
  - Assertiveness skills (refusal skills).
  - Coping skills for controlling and managing emotions such as anger and sadness.
- Offer alternatives to inhalant use, for example, recreational activities.
- Community reinforcement approaches should be developed by mobilising the local health and welfare service system in individual care plans.
- Family interventions need to be considered, for example, increasing communication between the person and the family.
- Assertive outreach and follow-up may be required.

# 6 Anxiety disorders and substance use

## 6.1 Anxiety

In contrast to fear, which is a response to a realistic immediate danger, anxiety is a fearful response occurring in the absence of a specific danger or real threat. According to the National Survey of Mental Health and Wellbeing, anxiety disorders are the most common form of mental disorder in the population with a one-year prevalence of 9.7% in Australian adults[68].

The fear and worry associated with anxiety arises in response to a variety of specific triggers (fear of heights) more general triggers (e.g. crowds, shopping centres, being in trains or buses, meeting new people, or having to speak in public) or sometimes in response to general issues including finances, health or relationships and personal safety. In some cases, anxiety can arise suddenly and spontaneously without a discernable trigger, as is the case with panic disorder.

People with anxiety may find it hard to relax, concentrate and sleep, and may suffer physical symptoms such as heart palpitations, tension and muscle pain, sweating, hyperventilation, dizziness, faintness, headaches, nausea, indigestion, bowel disturbance and loss of sexual pleasure. These symptoms are accompanied by changes in thoughts, emotions and behaviour that substantially interfere with the person's ability to live and work.

More women than men experience anxiety disorders[68, 119, 121, 201]. Anxiety usually begins in early adulthood and is often, but not always, triggered by a series of significant life events.

### *6.1.1 Anxiety disorder subtypes*

**Panic disorder**

- This is characterised by recurrent panic attacks, which occur unexpectedly over at least a month. Panic attacks are diagnosed if there is a period in which there is a sudden onset of intense apprehension, fearfulness or terror commonly associated with feelings of impending doom. Symptoms such as shortness of breath, palpitations, chest pain or discomfort, smothering or choking sensations along with fear of losing control are experienced during these attacks.

**Agoraphobia**

- This is characterised by anxiety about, or avoidance of, places and situations from which escape may be difficult (e.g. elevators, buses, trains or trams or shopping centres), or in which help may not be available in the instance of experiencing a panic attack or panic like symptoms.

**Social phobia**

- This is characterised by clinically significant anxiety provoked by being exposed to certain types of social situations, commonly leading to avoidance of situations requiring socialising.

**Obsessive compulsive disorder (OCD)**

- This is characterised by obsessions that cause significant anxiety or distress and compulsions which serve to neutralise the associated anxiety or distress.

**Post traumatic stress disorder (PTSD)**

- This is characterised by re-experiencing of an extremely traumatic event accompanied by symptoms of increased arousal and avoidance of stimuli associated with the trauma.

**Generalised anxiety disorder (GAD)**

- This is characterised by at least six months of persistent and excessive anxiety or worry.

### *6.1.2 Management approaches to anxiety disorders*

- Anxiety disorders are treatable conditions, although as with all medical disorders, there is a spectrum of severity. Some are chronic. Anxiety disorders have a generally unappreciated high rate of morbidity and mortality[196].
- Discussions with the patient regarding treatment should involve both short- and long-term outcome goals[196].
- Treatment of the anxiety disorders vary depending on the nature of the condition and the circumstances of the individual. In most cases, CBT is first-line treatment****[202] and is cheaper and more effective than medication, especially in those individuals who have had little or no previous exposure to benzodiazepines.
- In the majority of situations, however, by the time people seek advice from a clinician they are not generally benzodiazepine naïve and the issue expands to management of anxiety as well as controlling benzodiazepine use.
- Patients taking benzodiazepines do not develop tolerance to their anxiolytic effects[196] which significantly contributes to the desire to continue with their use. Benzodiazepines are particularly best avoided as a long-term medication treatment in the elderly because of the risk of adverse effects.
- CBT is effective in reducing symptoms of anxiety****[202] and will be more effective if there is minimal sedation and anxiolysis due to benzodiazepine use[196].
- However, CBT can be and is effective when administered concurrently with benzodiazepine dose reductions****[202-204]. CBT has been shown to improve the likelihood of patients successfully tapering and ceasing benzodiazepine use when they also have an anxiety disorder***[204].
- Tricyclic antidepressants and SSRIs are equally effective and preferable to benzodiazepines because of problems with sedation and associated dependence and withdrawal.
- People with social phobias may show some treatment response with antidepressants, in particular SSRIs****[205-213]. People with OCD also respond well but require higher than normal doses[214-218].
- Benzodiazepines may be more useful than antidepressants for GAD, panic disorder and agorophobia *[196]. However, both anti-depressants and/or benzodiazpeines should only be used after other treatment approaches have been unsuccessful. That is, they should only be used as a third or fourth line of treatment when patient responses to other forms of management have been unsuccessful.

## 6.2 Comorbidity with anxiety disorders

- Anxiety frequently occurs in conjunction with other mental disorders, in particularly depression[10, 28, 58, 68, 123, 201, 219-224].
- Anxiety has also been shown to co-occur frequently with suicidality[28, 219] and somatisation disorders[123].
- The presence of anxiety as a comorbidity increases the level of impairment associated with the primary disorder[58, 123].
- Anxiety (particularly PTSD) is commonly seen in association with substance use[10, 11, 23, 28, 29, 68, 121, 196, 221, 224].
- The causal relationship between anxiety disorders and substance use (self-medication theories, substance-induced anxiety) are not clearly established[196].
- Anxiety is also a common feature of substance withdrawal[46, 194, 196].

## 6.3 Major clinical issues with anxiety disorders and cannabis/hallucinogen use

- Cannabis can induce anxiety or panic attacks especially in naïve users.
- In chronic users, cannabis tends to have the opposite effect and act more as an anxiolytic at the time of use.
- Individuals should be encouraged to reduce or cease using so that anxiety symptoms can be better evaluated. In many cases this will result in an overall reduction in anxiety symptoms once withdrawal has passed.
- Cannabis withdrawal commonly includes insomnia which can be prolonged. The longer term use of hypnotics to assist with sleeping is problematic due to tolerance development.
- In the absence of other proven forms of treatment, CBT is, at present, the most widely employed form of treatment for cannabis use.

### *6.3.1 Effects of cannabis and other hallucinogens on anxiety disorders*

- Anxiety is common in people who use cannabis and other hallucinogens, particularly for those who commenced use at a young age[6-13].
- Heavier or more frequent use of cannabis is a greater predictor of anxiety[6, 9, 12, 13].
- Cannabis can induce anxiety or panic attacks[6, 12, 13, 225] especially in naïve users.
- In chronic users, cannabis tends to have the opposite effect and act more as an anxiolytic at the time of use.
- It is also thought that anxiety may predispose people to cannabis use problems[7, 8].

### 6.3.2 *Interactions between cannabis and other hallucinogens and therapeutic agents for anxiety disorders*

- Cannabis can exacerbate the sedative effects of tricyclic antidepressants and benzodiazepines, which increases the risk of impaired driving and injury as well as overdose✖.
- LSD may induce a serotonin syndrome (Appendix 1); therefore caution should be exercised when prescribing SSRIs or MAO-I✖[127].
- Cannabis and antidepressants are metabolised by CYP 450 enzymes which may result in the inhibition or induction of either drug group. Therefore, individuals should be monitored closely to follow clinical response and to ensure that toxicity does not occur✖.

### 6.3.3 *Management approaches to comorbid anxiety disorders and cannabis use*

- Cannabis can induce anxiety symptoms, particularly in first time users. The effect is dose related. In addition, anxiety is a feature of cannabis withdrawal. People should be encouraged to reduce or cease using so that anxiety symptoms can be better evaluated. In many cases this will result in an overall reduction in anxiety symptoms once withdrawal has passed.
- Abstinence from cannabis is a difficult goal to achieve in cannabis dependent people[128].
- In the absence of other proven forms of treatment, CBT is, at present, the most widely employed form of treatment for cannabis use****[128].
- CBT is effective in reducing symptoms of anxiety***[196, 203]. CBT that focuses on coping mechanisms will be most effective if the individual has been using cannabis or other hallucinogens to self-medicate and cope with social anxiety situations.
- Treatment of acute anxiety associated with cannabis withdrawal can be treated with benzodiazepines; however, use should be minimised as those with substance use disorders are at a greater risk of abusing benzodiazepines[196].
- Cannabis withdrawal commonly includes insomnia which can be prolonged. The longer term use of hypnotics to assist with sleeping is problematic due to tolerance development[188].
- Psychological and behavioural treatment can be effective in treating insomnia***[190-192] associated with psychiatric disorders[193] and may reduce the need for benzodiazepine use during depression.

## 6.4 Major clinical issues with anxiety disorders and alcohol use

- Alcohol use and anxiety disorders frequently co-occur and exacerbate each other.
- Individuals should be encouraged to reduce or cease alcohol use so that anxiety symptoms can be better evaluated.
- Anxiety associated with alcohol withdrawal should be allowed to subside, before making a diagnosis of anxiety disorder.
- However, anxiety may be a feature of the post-withdrawal state lasting for several months (up to 12 months).
- SSRIs are also effective in alcohol dependent people with anxiety.
- CBT should be given prior consideration over benzodiazepine therapy.
- Disulfiram, naltrexone and acamprosate used to treat alcohol dependence are unlikely to interact with antidepressants if these are being used.
- Acamprosate, naltrexone and benzodiazepines do not appear to interact with one another.
- Successful treatment of either anxiety or alcohol use disorder with CBT does not necessarily result in a positive outcome for the accompanying comorbid disorder.
- Pharmacotherapies such as naltrexone, acamprosate and disulfram are effective in the management of alcohol dependence and maintaining abstinence and are effective in individuals with comorbid anxiety.



### *6.4.1 Effects of alcohol on anxiety disorders*

- Alcohol use and anxiety disorders frequently co-occur[10, 18-23].
- Problematic alcohol use and anxiety exacerbate each other, leading to increased severity of both the anxiety disorder and alcohol use[226].
- The short-term relief in symptoms that alcohol gives people with anxiety is a strong motivator for continued alcohol use[10, 18, 22, 226].
- However, as dependence develops, this ultimately leads to increased anxiety:
  - Alcohol withdrawal produces anxiety.
  - Excessive alcohol use can result in environmental situations or disruptions that cause anxiety[226].
- Higher anxiety sensitivity (people with increased levels of sensitivity to anxiety who do not have a diagnosable anxiety disorder) is highly predictive of alcohol use disorders[227].
- Higher levels of anxiety are more indicative of relapse to drinking alcohol[228].

### 6.4.2 Interactions between alcohol and therapeutic agents for anxiety disorders

- Alcohol can exacerbate the sedative effects of any sedative agents (including tricyclic antidepressants, mirtazepine, and benzodiazepines used in the treatment of anxiety✖.
- Alcohol toxicity may occur through:
  - The inhibition of CYPs by sedative antidepressant involved in the metabolism of alcohol✖[133].
  - An increase in sedation as a result of combinations of alcohol and benzodiazepines✖.
- Disulfiram used to treat alcohol dependence will increase the plasma concentrations of diazepam leading to possible increases in sedation and overdose✖.
- Disulfiram, naltrexone and acamprosate used to treat alcohol dependence are unlikely to interact with antidepressants if these are being used✖[229].
- Acamprosate, naltrexone and benzodiazepines do not appear to interact with one another✖[230].

### 6.4.3 Management approaches to comorbid anxiety disorders and alcohol use

- Due to the anxiety-provoking effect of alcohol, and vice versa, individuals should be encouraged to reduce or cease alcohol use so that anxiety symptoms can be better evaluated[226].
- Clinicians should allow sufficient time for anxiety associated with alcohol withdrawal to subside, before making a diagnosis of anxiety disorder[226, 231].
- However, anxiety may be a feature of the post-withdrawal state lasting for several months (up to 12 months).
- If large quantities of alcohol are being consumed, then inpatient withdrawal or detoxification with benzodiazepines should always be considered to avoid and manage seizure risk. Concerns about benzodiazepine dependence should not prevent controlled prescribing for withdrawal states.
- Benzodiazepine use should be monitored and minimised as those with substance use disorders are at a greater risk of abusing benzodiazepines[196].
- Successful treatment of either anxiety or alcohol use disorder with CBT does not necessarily result in a positive outcome for the accompanying comorbid disorder***[231]. That is outcomes for the two sets of problems are somewhat independent. However, CBT can be effective in:
  - Improving alcohol-related outcomes in people with anxiety and alcohol dependence and is more effective in those who drink less***[226, 231, 232].
  - Reducing symptoms of anxiety****[196, 202] in those with additional alcohol-related problems***[231]. CBT should be given prior consideration over benzodiazepine therapy.
- SSRIs may be effective in reducing anxiety****[205-218].
- SSRIs are also effective in alcohol dependent people with anxiety***[233] in situations where behavioural therapy is not possible or unsuccessful.
- Consistent with the situation with depression and alcohol dependence, SSRIs may even improve drinking outcomes in those with less severe alcohol dependence[220, 234].

- However, some studies of SSRIs used to treat alcohol dependent people have shown a worsening effect on alcohol consumption in certain subtypes, in particular those with early onset problem drinking***[138, 139] and therefore requires monitoring.
- Pharmacotherapies such as naltrexone, acamprosate and disulfram are effective in the management of alcohol dependence and maintaining abstinence, and are effective in individuals with comorbid anxiety****[141, 144, 235-237].

## 6.5 Major clinical issues with anxiety disorders and opioid use

- While opioids do not possess anxiolytic effects in the manner that benzodiazepines do, they do have the ability to enable the person to forget about the issues that may be causing them to feel anxious. An indirect short-term reduction in symptoms of anxiety may be a strong motivator for opioid use in those with anxiety disorders.
- Methadone itself has been shown to inhibit CYP3A4 which also metabolises many benzodiazepines. This has the potential to increase plasma concentrations of benzodiazepines and increase their sedative effects.
- Several deaths have been reported due to benzodiazepine use in conjunction with high dose buprenorphine and may be a result of similar metabolic interactions.
- Fluvoxamine***, fluoxetine**, norfluoxetine** and paroxetine* can inhibit buprenorphine and methadone metabolism through inhibition of the CYPs involved in their metabolism.
- Citalopram and sertraline are the least likely SSRIs to have cytochrome mediated drug interactions.
- If long-term benzodiazepine use is unable to be avoided, this should be monitored very closely.
- Acute opioid withdrawal is best managed using buprenorphine.
- If treatment of anxiety with antidepressants is required, this should involve non-sedating antidepressants such as SSRIs, taking into consideration their interaction effects.
- Longer acting maintenance pharmacotherapies such as methadone and buprenorphine potentially stabilise opioid plasma concentrations and reduce fluctuations in plasma concentration and levels of anxiety.



### *6.5.1 Effects of opioids on anxiety disorders*

- Those with anxiety disorders are significantly more likely to use opioids than those without anxiety disorders[11, 25, 28, 29].
- While opioids do not posses anxiolytic effects in the manner that benzodiazepines do, they do have the ability to enable the person to forget about the issues that may be causing them to feel anxious. An indirect short-term reduction in symptoms of anxiety may be a strong motivator for opioid use in those with anxiety disorders.

- People with anxiety disorders report more severe opioid dependency than those without anxiety[28].
- There is some debate as to whether anxiety can potentially have an adverse impact on the effectiveness of opioid maintenance pharmacotherapy[238, 239].

### 6.5.2 Interactions between opioids and therapeutic agents for anxiety disorders

- Methadone itself has been shown to inhibit CYP3A4✖✖[240, 241] which also metabolises many benzodiazepines. This has the potential to increase plasma concentrations of benzodiazepines and increase their sedative effect✖[242, 243].
- Several deaths have been reported due to benzodiazepine use in conjunction with high dose buprenorphine and may be a result of similar metabolic interactions✖✖✖[244-246].
- Fluvoxamine✖✖✖, fluoxetine✖✖, norfluoxetine✖✖ and paroxetine✖ can inhibit buprenorphine and methadone metabolism through inhibition of the CYPs involved in their metabolism[148-150]. This can result in an increase in plasma opioid pharmacotherapy concentrations and potential overdose. This can be a particular issue during induction onto methadone; however, the risk may persist even after stabilisation has occurred✖✖✖[151-155].
- Fluvoxamine is the most potent inhibitor of methadone and buprenorphine metabolism and is the most clinically relevant. Therefore, it should be avoided✖✖✖[150].
- Fluoxetine and paroxetine should also be avoided due to their possible effects on methadone metabolism✖✖.
- Citalopram and sertraline are the least likely SSRIs to have cytochrome-mediated drug interactions; however, due to the theoretical potential for an interaction, caution should still be used and individuals monitored closely✖[156].

### 6.5.3 Management approaches to comorbid anxiety disorders and opioid use

- Fluctuating plasma concentrations of short acting opioids such as heroin can exacerbate anxiety disorders due to the effects of withdrawal at times of low plasma concentration. Therefore, patients should be encouraged to reduce their use and, if possible, cease.
- Longer-acting maintenance pharmacotherapies such as methadone and buprenorphine potentially stabilise opioid plasma concentrations and reduce fluctuations in plasma concentration and levels of anxiety. However, relatively small changes in maintenance therapy concentrations can result in significant mood changes *[247].
- Acute opioid withdrawal is best managed using buprenorphine****[248]. However, benzodiazepines can be used if there is continuing residual anxiety. Their use should be minimised due to risk of misuse[196].
- If long-term benzodiazepine use cannot be avoided:
  - This should be subject to a contract with the patient.
  - Authorities should be advised, including registration with the relevant local government health authority.
  - The seeking of additional benzodiazepines from other prescribers should be monitored (e.g. using the *Authority to release personal PBS claims information to a third party* form).

  - Daily or weekly dispensing of benzodiazepines in conjunction with collection of methadone or buprenorphine doses should be considered and may assist with controlling use.

- If treatment of anxiety with antidepressants is required, this should involve non-sedating antidepressants such as SSRIs, taking into consideration their interaction effects.

## 6.6 Major clinical issues with anxiety disorders and stimulant (including methamphetamine) use

- Anxiety is common amongst stimulant users.
- MAO-Is (either irreversible or reversible) are contraindicated in people using amphetamines or MDMA due to risk of serotonin syndrome. Deaths have been associated with concurrent use of moclobemide and MDMA.
- Individuals should be encouraged to reduce or cease stimulant use so that anxiety symptoms can be better evaluated. In many cases this will result in an overall reduction in anxiety symptoms.
- CBT is also effective in reducing general symptoms of anxiety.
- CBT that focuses on coping mechanisms will be most effective in situations where the individual has been using stimulants to self medicate and cope with social anxiety situations.



### *6.6.1 Effects of stimulants on anxiety disorders*

- Anxiety is common amongst stimulant users[11, 29, 43, 50, 53, 54, 56].
- Anxiety also presents during withdrawal from stimulants[46].
- The incidence of anxiety increases following stimulant use[53].
- Anxiety and its severity is significantly associated with the extent of stimulant use, with higher stimulant use predicting greater severity of anxiety[50, 53, 55, 56].
- Individuals with childhood anxiety may have increased tendency to use stimulants, in particular ecstasy[55].

### *6.6.2 Interactions between stimulants and therapeutic agents for anxiety disorders*

- MAO-Is (either irreversible or reversible) are contraindicated in people using amphetamines or MDMA due to risk of serotonin syndrome (Appendix 1). Deaths have been associated with concurrent use of moclobemide and MDMA✖✖✖[181, 182].
- Stimulant drugs are likely to exacerbate the effects of SSRI and SNRI antidepressants (and visa versa) and may result in serotonin syndrome (Appendix 1)✖[127, 179, 180]. Patients should be warned of signs of serotonin syndrome and be monitored.
- Fluoxetine, norfluoxetine, paroxetine and sertraline are potential inhibitors of CYP 2D6 which metabolises MDMA and methamphetamine. This may result in elevated plasma concentrations leading to toxicity✖.

### 6.6.3 *Management approaches to comorbid anxiety disorders and stimulant use*

- Due to the anxiety-provoking effect of stimulants and the relationship to heavy use, individuals should be encouraged to reduce or cease stimulant use so that anxiety symptoms can be better evaluated. In many cases this will result in an overall reduction in anxiety symptoms.
- Treatment of acute anxiety associated with stimulant withdrawal can be treated with benzodiazepines. However, use should be minimised as those with substance use disorders are at a greater risk of misusing benzodiazepines[196].
- CBT is also effective in reducing general symptoms of anxiety****[196, 202, 203].
- CBT that focuses on coping mechanisms will be most effective in situations where the individual has been using stimulants to self medicate and cope with social anxiety situations.
- Citalopram and sertraline have the least CYP mediated drug interactions; however, all SSRIs are potential precipitators of serotonin syndrome in people using stimulants.

## 6.7 Major clinical issues with anxiety disorders and benzodiazepine use

- Tolerance to the sedative effects of benzodiazepines and dependence develops within a short period of time.
- It would appear that tolerance to the anxiolytic effects of benzodiazepines does not develop.
- Graded exposure is a highly effective component in the treatment of anxiety disorders. Patients taking benzodiazepines are unable to benefit from this approach if taking doses greater than 10mg diazepam equivalence and doses below this level may interfere with the person's ability to habituate.
- Benzodiazepine use should be discouraged and reduced, with cessation being a long-term goal, and alternative management strategies introduced.
- CBT is effective in reducing symptoms of anxiety and will be more effective if there is minimal sedation and anxiolysis due to benzodiazepine use.

### 6.7.1 *Effects of benzodiazepines on anxiety disorders*

- Due to their anxiolytic effects, benzodiazepines are one of the most commonly prescribed forms of pharmacotherapy in the treatment of anxiety symptoms[57, 58]. They are not, however, the recommended first-line treatment for anxiety disorders.
- Tolerance to the sedative effects of benzodiazepines and dependence develops within a short period of time.
- It would appear that tolerance to the anxiolytic effects of benzodiazepines does not develop[196].
- If short-acting benzodiazepines are used (e.g. alprazolam, oxazepam, temazepam), rapidly fluctuating drug plasma concentrations may exacerbate the symptoms of the anxiety disorder.
- Patients prescribed benzodiazepines for anxiety disorders may be less responsive to and less willing to accept psychological therapies than those who are not.

### 6.7.2 Interactions between benzodiazepines and therapeutic agents for anxiety disorders

- There is an increased risk of sedation and overdose with the combination of benzodiazepines and sedative antidepressants such as tricyclics and mirtazepine✖.
- Benzodiazepines and antidepressants are both metabolised by CYP 450 enzymes which may result in the inhibition or induction of either drug group. Therefore, individuals should be monitored closely to ensure they are experiencing the appropriate therapeutic effect✖.
- Fluvoxamine will inhibit the metabolism of alprazolam, midazolam, triazolam and diazepam, causing increased plasma concentrations, sedation and potential toxicity✖.
- Citalopram and sertraline are the least likely SSRIs to have cytochrome mediated drug interactions✖.

### 6.7.3 Management approaches to comorbid anxiety disorders and benzodiazepine use

- Graded exposure is a highly effective component in the treatment of anxiety disorders. Patients taking benzodiazepines are unable to benefit from this approach if taking doses greater than 10mg diazepam equivalence and doses below this level may interfere with the person's ability to habituate to anxiety triggers.
- Benzodiazepine use should be discouraged and reduced, with cessation being a long-term goal and alternative management strategies introduced.
- If large quantities of benzodiazepines (e.g. 40mg diazepam daily equivalent or more) are being consumed then inpatient withdrawal to lower levels should be considered to avoid and manage seizure risk[194].
- If dependence has developed then graduated withdrawal through slow reduction of dosage should be commenced****[194-196], possibly after transferring the patient onto a long acting benzodiazepine.
- Lower levels of baseline anxiety at the time of benzodiazepine withdrawal are the best predictor of successful taper[196].
- If long-term benzodiazepine use is indicated, then:
  - This should be subject to a contract with the patient.
  - Authorities should be advised, including registration with the relevant local government health authority.
  - The seeking of additional benzodiazepines from other prescribers should be monitored (e.g. using the *Authority to release personal PBS claims information to a third party* form).
  - Daily or weekly dispensing of benzodiazepines should be considered and may assist with controlling use.
- CBT is effective in reducing symptoms of anxiety****[202] and will be more effective if there is minimal sedation and anxiolysis due to benzodiazepine use[196].
- CBT has been shown to improve the likelihood of patients successfully tapering and ceasing benzodiazepines when they also have an anxiety disorder***[203, 204].

- Antidepressant medication (SSRIs or other non-sedating antidepressants) can be commenced with the patient still taking benzodiazepines.
- Citalopram and sertraline are the least likely SSRIs to have cytochrome mediated drug interactions.

## 6.8 Major clinical issues with anxiety disorders and inhalant/solvent use

- Inhalant users have higher rates of anxiety disorders.
- The sedative effects of antidepressants and benzodiazepines may be exacerbated by inhalants and may possibly result in severe sedation and overdose.
- As with most other substances, inhalant users should be encouraged to reduce or cease use to observe whether anxiety symptoms resolve.

### *6.8.1 Effects of inhalants/solvents on anxiety disorders*

- Inhalant users have higher rates of anxiety disorders. Causal relationships are unclear[249, 250].

### *6.8.2 Interactions between inhalants/solvents and therapeutic agents for anxiety disorders*

- The sedative effects of antidepressants and benzodiazepines may be exacerbated by inhalants and may possibly result in severe sedation and overdose✖.
- Most antidepressants lower seizure threshold and tricyclic antidepressants can cause cardiac arrhythmias. Therefore, risks should be appraised prior to commencement✖.

### *6.8.3 Management approaches to comorbid anxiety disorders and inhalant/solvent use*

- There is no literature that sheds light on managing people with both anxiety and inhalant/solvent use related problems.
- As with most other substances, inhalant users should be encouraged to reduce or cease use to observe whether anxiety symptoms resolve.
- In general with respect to inhalant/solvent use[65]:
  - Outline the harms associated with inhalant/solvent use.
  - Investigate polysubstance use as this is common.
- Standard CBT approaches to both sets of issues should be used, with particular attention to the development of:
  - Assertiveness skills (refusal skills).
  - Coping skills for controlling and managing emotions such as anger and sadness.

Offer alternatives to inhalant use, for example, recreational activities.

- Community reinforcement approaches should be developed by mobilising the local health and welfare service system in individual care plans.
- Family interventions need to be considered, for example, increasing communication between the person and the family.
- Assertive outreach and follow-up may be required.

# 7 Psychosis (schizophrenia and bipolar disorder) and substance use

## 7.1 Psychosis

Psychosis is characterised by a loss of connectedness with reality. A person may develop false ideas or beliefs about reality (delusions) which in themselves may be based on false perceptions (hallucinations).

People experiencing psychosis also have characteristic flaws in the ways they think. These are termed 'thought disorders'. Examples are tangential thinking, loose associations between ideas, and incoherence.

Psychosis significantly impairs work, family and social functioning. People with psychoses often experience poorer physical health. The worse the psychotic symptoms are, the higher the associated level of impairment[251].

Psychotic symptoms can occur in response to physical conditions, e.g. acute delirium with septicaemia. Alternatively, psychoses can be functional. There are two broad classes of functional psychotic disorders: schizophrenia and bipolar disorder.

Generally, schizophrenia is a chronic condition with exacerbations, but always with some background symptoms. Bipolar disorder is generally an intermittent condition with the expectation of full recovery between episodes. There is considerable overlap between the two conditions and fluidity of diagnosis.

Symptoms of schizophrenia are sometimes grouped into two categories:

- Positive symptoms such as hallucinations and delusions.
- Negative symptoms such as social withdrawal and lack of energy and motivation that are similar to those found in depression.

While the clinician may realise that the psychosis could be drug-induced and is cautious in the prescription of neuroleptics or sedatives to control the symptoms, they may be under pressure to respond to the manifestation of bizarre or potentially destructive thinking or behaviour. On the other hand, alterations to the way the person behaves and thinks may be subtle in the early stages when early intervention may be most appropriate.

Shortening the period of untreated psychosis (whether this be substance induced or the early stages of psychotic disorders) has the potential to have a positive impact on treatment outcomes.

### *7.1.1 Management approaches to psychosis*

**Schizophrenia**

- Antipsychotics have shown their effectiveness in treating psychosis. The newer, so called atypical agents are effective at managing symptoms of psychosis****[252, 253], produce fewer extrapyramidal side effects****[252], are possibly associated with fewer relapses****[253], show possible improvements in cognitive deficits***[254-256] and have improved tolerability compared to typical antipsychotics[1, 2].
- Adjunctive benzodiazepines may be required for breakthrough anxiety and agitation and should be restricted to short-term use and gradual dose reduction[2].
- Antidepressants may also be useful for the treatment of associated depression[15].

**Bipolar disorder**

- Bipolar disorders are best managed with mood stabilising drugs such as lithium****[257-259], sodium valproate****[259], carbamazepine****[259, 260] and lamotrigine for depression****[257, 258, 261] with atypical antipsychotics such as olanzapine and risperidone being used in manic phases****[259, 262].
- Mood stabilisers such as sodium valproate, carbamazepine and lamotrigine are hepatically metabolised and liver function is particularly pertinent when prescribing these classes of medication.
- People with bipolar disorder and comorbid substance use are at a greater risk of contracting blood borne viruses due to increased risk taking, and are more likely to consume large quantities of alcohol. Therefore, liver function should be assessed in patients with bipolar and comorbid substance use disorders.

## 7.2 Comorbidity with psychosis

### *7.2.1 Schizophrenia*

- There are few differences in acute symptoms between schizophrenia with substance use and substance-induced psychosis. Distinction is primarily made on the basis of resolution of symptoms after withdrawal from the substance[2].
- Prodromal, or early non-specific symptoms of schizophrenia such as subtle personality changes, social withdrawal, reduced self-care and odd thinking, prior to the start of substance use and psychotic symptoms, may help make the distinction between a functional illness such as schizophrenia and substance-induced psychotic symptoms.
- Comorbid substance-use disorders are more common in people with psychosis than the general population[1, 2, 263].
- The number of injecting drug users is increasing in the general population. The rates of those with psychosis who are injecting drugs is increasing at a similar rate[2].
- Problematic substance use has been associated with earlier onset of psychosis [263].
- Even moderate use of substances can exacerbate psychotic symptoms which can make motivation for reduction of substance use difficult[1, 2, 263].
- Reasons for increased substance use in schizophrenia are dominated by self-medication hypotheses. The hypothesis is that people use substances in an effort to deal with their symptoms[15].
  - Those with substance-use disorders and schizophrenia report fewer negative symptoms[1, 264, 265].
  - Self medication does explain some but not all of the reasons for comorbid substance use and schizophrenia[266].
- Comorbid substance use and schizophrenia are associated with increased morbidity and poorer outcome[1, 2, 15, 263] and, in the past, people with this combination have generally not responded as well to treatment as those without substance-use disorders[265].
- Substance use is highly associated with treatment non-compliance[1, 15, 263] and longer duration of untreated schizophrenia[265].
- Decreases in substance use due to treatment retention is associated with reduced overall symptoms in people with psychosis[267].

### *7.2.2 Bipolar disorder*

- Large amounts of alcohol and other substance use frequently occur during the manic phase of bipolar illness.
- Manic symptoms are likely to be exacerbated by concurrent substance use, particularly stimulant and cannabis use.
- During the depressed phase of the illness period, there is also increased substance use with alcohol exacerbating depression, and the use of stimulants and cannabis having the risk of precipitating a manic swing or mixed symptoms.
- During periods of recovery, the person typically returns to limited use. Care is needed not to misdiagnose and attribute all problems to the substance intake.

### *7.2.3 General*

- Comorbidity with other mental disorders is common amongst those with psychosis, in particular anxiety and depression[15, 251, 268].
- Coexisting personality disorder[251, 263] can lead to poorer prognosis of substance use disorders in patients with schizophrenia[15, 263].
- Very little evidence is available to allow advice concerning safe levels of alcohol or substance use in patients with psychotic illnesses. The assumption can be made that any use during the active phase of illness will have a deleterious effect.
- Psychosis is associated with suicidal ideation and attempts which are exacerbated when comorbid substance use is involved[15, 251, 263, 268].

### *7.2.4 General management approaches to comorbidity*

**Assessment**

- The person experiencing psychosis who is using substances presents diagnostic and management challenges for the clinician.
- It is important to differentiate between three different phenomena with regard to psychosis and substance use:
  - People can experience an acute psychotic episode in response to substance intoxication, withdrawal and use due to the effects of the substance.
  - Substances can precipitate a psychotic disorder in predisposed individuals which can persist in the absence of the psychoactive substance.
  - Some people have an underlying psychotic disorder that is exacerbated by concurrent use of substances, in particular cannabis and amphetamines.
- The use of substances can exacerbate symptoms in people with a chronic psychotic disorder, exacerbating the condition and interfering with rehabilitation.

- Non-response to medication for psychosis may be indicative of substance use. This should be investigated before attempting to change the antipsychotic medication[2, 262].
- Comorbid substance use in people with psychosis has the potential to affect cognitive ability[269]. This may impact on treatment approaches and prolong the time it takes to observe a positive response to treatment.

**Treatment: Pharmacotherapy**

- Most research has occurred in relation to schizophrenia and substance use, rather than bipolar disorder.
- There is little difference between schizophrenia and substance-induced psychosis in the treatment of acute symptoms. However, substance-induced psychosis does not normally require long-term maintenance with antipsychotic medication[2].
- Despite a lack of controlled trials, it appears that people with comorbid substance use and schizophrenia fare better on newer atypical antipsychotics***[1, 2, 267, 270-274].
- Clozapine stands out as the most valuable treatment so far for comorbid substance use and schizophrenia***[1, 2, 267, 270, 272, 274, 275].
- Clozapine for schizophrenia appears to be as effective in people with substance use issues as it does in non-substance users**[276]. Additional substance use does not appear to interfere with the efficacy of clozapine for pyschosis[276].
- As well as controlling psychotic symptoms, clozapine also shows evidence of reducing substance use in those with psychosis***[1, 2, 267, 270, 272, 274, 275].

**Treatment: Psychotherapy**

- The efficacy of CBT as a single treatment for psychosis is not affected by substance use***[277].
- Integrated care for both disorders (including pharmacotherapy, motivational interviewing, CBT and caregiver interventions) significantly improves both psychotic positive symptoms and substance use***[1, 15, 267, 278].

## 7.3 Major clinical issues with psychosis and cannabis/hallucinogen use

- Cannabis can induce or cause a temporary psychotic state that clears within several days in individuals with no prior diagnosis of psychosis.
- Cannabis can trigger psychosis in individuals who are at risk of psychosis.
- Cannabis can worsen psychotic symptoms in those individuals who have a current diagnosis of psychosis.
- People with psychotic disorders should avoid cannabis and be counselled against its use. Brief interventions should be delivered for people with psychosis who may be using even small amounts of cannabis.
- In an acute psychotic episode caused by cannabis use, cessation of use will result in resolution of the episode.
- Psychoeducation and CBT orientated programs have shown promise in reducing cannabis use in first-episode psychosis patients.
- In the absence of other proven forms of treatment, CBT is, at present, the most widely employed form of treatment for cannabis use.

### *7.3.1 Effects of cannabis and other hallucinogens on psychotic disorders*

- One of the most commonly used substances in individuals with psychosis is cannabis, with individuals with schizophrenia and bipolar disorder quite often receiving an additional diagnosis of cannabis dependence[1, 2, 264, 265, 268, 279, 280].
- Duration of cannabis use in people with bipolar disorder is associated with the duration of mania[281].
- Cannabis increases the risk of tardive dyskinesia[2].
- There is growing evidence that cannabis use is a significant contributory factor in psychosis[126, 282-285]:
  - Cannabis can induce or cause a temporary psychotic state that clears within several days in individuals with no prior diagnosis of psychosis[2, 14, 15].
  - Cannabis can trigger psychosis in individuals who are at risk of psychosis [286, 287].
  - Cannabis can worsen psychotic symptoms in those individuals who have a current diagnosis of psychosis[15, 286-291].
  - Cannabis use is associated with an earlier onset of psychosis[264, 265, 279].
  - There is an association between cannabis and psychosis. However, when rates of cannabis use were increasing in Australia, no increase in the rates of schizophrenia was observed[286].
- People with psychosis generally do not use cannabis in a self-medicating manner to reduce psychotic symptoms. Reported reasons for use include social isolation, lack of emotion or feeling for others, lack of energy, difficulty sleeping, depression, anxiety, agitation, tremor or shaking and boredom. These symptoms may occur as part of the psychotic illness or may be due to additional anxiety or depressive illnesses or side effects of medication[15, 292, 293].

### 7.3.2 Interactions between cannabis and other hallucinogens and therapeutic agents for psychotic disorders

- It is unclear whether chronic cannabis consumption induces the metabolism of the antipsychotics and reduces plasma concentrations in a similar manner to tobacco [294].
- Cannabis can exacerbate the sedative effects of antipsychotics and mood stabilisers such as carbamazepine, lithium and sodium valproate✖.
- Cannabis will exacerbate the sedative effects of tricyclic antidepressants and benzodiazepines used to treat breakthrough depression[2] and anxiety in psychosis which increases the risk of overdose✖.

### 7.3.3 Management approaches to comorbid psychotic disorders and cannabis use

#### Prevention

- In general, people with psychotic disorders should avoid cannabis and be counselled against its use. Brief interventions should be delivered for people with psychosis who may be using even small amounts of cannabis.

#### Initial assessment

- Despite the common diagnosis of comorbid psychosis and cannabis dependence, there has been little research to define specific unique management approaches. It is generally thought that the best outcomes are achieved when treatment for both conditions is integrated.
- An attempt should be made to distinguish between people with:
  - An acute psychotic episode caused by cannabis use.
  - A first episode of a psychotic disorder.
  - An acute episode which has been precipitated by cannabis use in someone with an established chronic psychotic disorder.
- In an acute psychotic episode caused by cannabis use, cessation of use will result in resolution of the episode. The short-term use of an antipsychotic medication or benzodiazepines may be indicated, depending on the level of distress. The duration of use should be titrated against the symptoms.

#### Treatment

- Psychoeducation and CBT orientated programs have shown promise in reducing cannabis use in patients experiencing their first episode of psychosis***[295].
- Abstinence from cannabis is a difficult goal to achieve in cannabis dependent people[128]. This is particularly the case with people with psychosis due to the social isolation they often experience. This social isolation has been reported as a major motivator for continued use[15, 292, 293].
- In the absence of other proven forms of treatment, CBT is, at present, the most widely employed form of treatment for cannabis use****[128].
- Preliminary studies have shown clozapine to be more effective than risperidone in reducing cannabis use in people with psychotic disorders*[296].

- Early preliminary data in one trial also shows some benefit for olanzapine in cannabis induced psychotic disorder***[297].
- Benzodiazepine use for acute symptom control should be minimised as those with substance use disorders are at a greater risk of abusing benzodiazepines[196].

## 7.4 Major clinical issues with psychosis and alcohol use

- People with psychosis have high rates of alcohol use disorders.
- As alcohol has several negative effects on psychosis and interacts with medications used for the treatment of psychosis, its use should be minimised.
- There is evidence suggesting that clozapine is effective in reducing alcohol consumption as well as controlling psychosis in those with comorbid alcohol use and psychosis.
- Individuals with psychosis also respond well to adjunctive treatment for alcohol dependence.

### *7.4.1 Effects of alcohol on psychotic disorders*

- People with psychosis have high rates of alcohol use disorders. Alcohol is one of the most commonly used substances in people with psychosis[1, 2, 21, 251, 265, 268, 298].
- Alcohol may worsen or increase psychotic symptoms[15, 298, 299].
- The duration of alcohol use is associated with depression in people who have bipolar disorder[281].
- Disinhibition together with poorly controlled psychotic symptoms may lead to inappropriate or dangerous behaviours.
- There is increased general morbidity in those with psychosis and alcohol use disorders [267]:
  - Alcohol can increase the risk of tardive dyskinesia[2].
  - Alcohol impairs delayed recall, attention, working memory, and vigilance to a greater extent in those with psychosis compared to people without psychosis [299, 300].

### *7.4.2 Interactions between alcohol and therapeutic agents for psychotic disorders*

- Alcohol can exacerbate the sedative effects of antipsychotics✖[2].
- There do not appear to be any safety issues for the use of acamprosate in this population and, at present, there are no known interactions with antipsychotics[2].
- Disulfiram at high doses may trigger psychotic symptoms✖✖[301].
- Alcohol can exacerbate the sedative effects of any sedative agents (including tricyclic antidepressants and mirtazepine, and benzodiazepines) used to treat associated depression[2] and anxiety in psychosis✖.

- Alcohol toxicity may occur through:
  - The inhibition of CYPs by sedative antidepressant involved in the metabolism of alcohol✖[133].
  - An increase in sedation as a result of combinations of alcohol and benzodiazepines✖.

### *7.4.3 Management approaches to comorbid psychotic disorders and alcohol use*



- People with psychosis should be discouraged from using alcohol for the above mentioned reasons.
- There is evidence suggesting that clozapine is effective in reducing alcohol consumption as well as controlling psychosis in those with comorbid alcohol use and psychosis**[267, 270, 296].
- Individuals with psychosis also respond well to adjunctive treatment of alcohol dependence[302]:
  - Naltrexone as an adjunctive therapy has been shown to reduce drinking in individuals with psychosis and does not appear to have a negative impact on the actions of concurrently administered antipsychotics***[303].
    - As people with psychosis and comorbid substance use are at increased risk of morbidity and are more prone to risk taking, individuals need to be aware of the implications of using naltrexone for emergency pain management[2].
    - Patients on naltrexone therapy should be advised to carry a medical warning card or bracelet which states they will not respond to opioid analgesia (obtainable from Bristil Myers Squibb on 1800 067 567).
  - Preliminary studies suggest that disulfiram can result in decreasing alcohol consumption in those living with psychosis and may be an effective adjunctive therapy to concurrently administered antipsychotics*[2, 15, 304].
  - Naltrexone and disulfiram appear to be equally efficacious in reducing alcohol consumption when used as an adjunctive therapy to antipsychotics in people with psychosis***[302].
  - Acamprosate is yet to be studied in individuals with comorbid psychosis and alcohol dependence. However, there do not appear to be any safety issues for its use in this population and its use is worth considering[1, 2].
- Benzodiazepines used for acute alcohol withdrawal should be monitored closely and minimised for outpatient use[2]. Benzodiazepine use should be restricted to short-term symptomatic use only, as those with an existing substance use disorder are at a greater risk of misusing benzodiazepines[196].

## 7.5 Major clinical issues with psychosis and opioid use

- Concurrent opioid dependence and psychotic disorders are often associated with high levels of dysfunction.
- Opioids (including methadone and buprenorphine) will exacerbate the sedative effects of antipsychotics.
- Carbamazepine is a potent CYP inducer and will induce the metabolism of methadone and buprenorphine as well as reduce plasma concentrations.
- Early studies show olanzapine, in combination with opioid maintenance pharmacotherapies, to be effective in controlling illicit opioid use and symptoms of psychosis.
- Combined daily dispensing of psychotropic medication at the same time as daily dispensing of opioid maintenance pharmacotherapy may improve treatment compliance for the psychotic disorder.

### *7.5.1 Effects of opioids on psychotic disorders*

- The prevalence of comorbid psychosis and opioid use is generally low[263].
- However, comorbid psychosis and opioid use is associated with increased mortality[305].
- Concurrent opioid dependence and psychotic disorders are often associated with high levels of dysfunction.

### *7.5.2 Interactions between opioids and therapeutic agents for psychotic disorders*

- Opioids (including methadone and buprenorphine) will exacerbate the sedative effects of antipsychotics✖.
- Carbamazepine is a potent CYP inducer and will induce the metabolism of methadone and buprenorphine as well as reduce plasma concentrations✖✖[149, 157]. This has the potential to result in withdrawal and failure of retention in treatment✱✱✱✱[158-160].
- There do not appear to be any interactions between naltrexone and antipsychotics.
- Opioids can exacerbate the sedative effects of tricyclic antidepressants and benzodiazepines used to treat breakthrough depression[2] and anxiety in psychosis which increases the risk of overdose✖.
- Methadone itself has been shown to inhibit CYP3A4✖✖[240, 241] which also metabolises many benzodiazepines. This has the potential to increase both the plasma concentrations of benzodiazepines and their sedative effects✖[242, 243].
- Several deaths have been reported due to benzodiazepine use in conjunction with high dose buprenorphine and may be a result of similar metabolic interactions✖✖✖[244-246].

- Fluvoxamine ✖✖✖, fluoxetine✖✖, norfluoxetine✖✖ and paroxetine✖ can inhibit buprenorphine and methadone metabolism through inhibition of the CYPs involved in their metabolism[148-150]. This can result in an increase in plasma opioid pharmacotherapy concentrations and potential overdose. This can be a particular issue during induction onto methadone; however, the risk may persist even after stabilisation has occurred✖✖✖[151-155].
- Fluvoxamine is the most potent inhibitor of methadone and buprenorphine metabolism and is the most clinically relevant. Therefore, it should be avoided✖✖✖[150].
- Fluoxetine and paroxetine should also be avoided✖✖.
- Citalopram and sertraline are the least likely SSRIs to have cytochrome mediated drug interactions; however, due to the theoretical potential for an interaction, caution should still be used and individuals monitored closely✖[156].



### *7.5.3 Management approaches to comorbid psychotic disorders and opioid use*

- There is little research assessing the management of opioid use and psychosis. However, those with psychosis who participate in methadone treatment do not appear to experience any more side effects than those without comorbid psychosis and can benefit from opioid maintenance therapy[2, 306].
- Buprenorphine has yet to be studied in people with comorbid opioid dependence and schizophrenia[271].
- Early studies show olanzapine, in combination with opioid maintenance pharmacotherapies, to be effective in controlling illicit opioid use and symptoms of psychosis**[307].
- Close liaison between the prescriber and the pharmacist dispensing the opioid maintenance will assist with gaining insight into adherence to treatment, levels of self care and general stability.
- While there have been no studies to assess the impact on psychosis treatment compliance, combined daily dispensing of psychotropic medication at the same time as daily dispensing of opioid maintenance pharmacotherapy may improve treatment compliance for the psychotic disorder.
- Benzodiazepines prescribed for acute opioid withdrawal in individuals with psychosis should be monitored closely and minimised for outpatient use[2].
- The use of benzodiazepines should be restricted to short-term symptomatic use only, as those with substance-use disorders are at greater risk of abusing benzodiazepines[196].

## 7.6 Major clinical issues with psychosis and stimulant (including methamphetamine) use

- Psychostimulants can induce or precipitate psychotic states.
- Stimulant induced psychosis can often be indistinguishable from acute or chronic schizophrenia.
- Longer and heavier use of stimulants delays recovery and worsens the prognosis for stimulant induced psychosis.
- In an acute psychotic episode caused by a substance, treatment should involve efforts to encourage abstinence from stimulants which should result in the resolution of psychotic symptoms.
- Benzodiazepines (preferably oral but parenteral, if necessary) should be first-line agents in acute stimulant induced psychosis.
- Antipsychotics are useful second-line agents if benzodiazepines do not settle the agitation sufficiently.
- Limited ongoing antipsychotic use is justified if psychotic symptoms persist.

### *7.6.1 Effects of stimulants on psychotic disorders*

**Prevalence**

- Stimulants are amongst the most commonly used substances in individuals with psychosis[1, 2, 265].
- Stimulants may be used to reduce the apathy and lack of energy associated with schizophrenia[308].

**Stimulant induced disorders**

- Psychostimulants can induce or precipitate psychotic states[32-38].
- Stimulants can induce brief positive and negative psychotic symptoms even in a healthy control group [15] and, irrespective of an individual's mental state, a large enough dose of stimulant can produce a brief psychotic disorder[30].
- Stimulant-induced psychotic states develop during the chronic stage of intoxication and clear within days to a week of ceasing use[2, 32, 309].
- However, repetitive use of stimulants may involve prolonged psychotic states that can last up to several months after cessation of use[33, 37].
- Stimulant-induced psychosis involves both positive and negative symptoms including paranoid hallucinatory (auditory and visual) states, bizarre ideas as well as volitional disturbances and can often be indistinguishable from acute or chronic schizophrenia[32, 37].
- After complete recovery, acute reappearance of paranoid states or relapse of psychosis can be induced by a single use of stimulant in people with a history of stimulant-induced psychosis, years after the initial psychosis has resolved[35, 37].

- Spontaneous reoccurrence of stimulant-induced paranoid hallucinatory states (flashbacks) can also occur in response to stress (as well as continued use) in subjects with history of stimulant induced psychosis[36, 37]. This appears to be similar to how stress can induce a relapse in people with schizophrenia[34, 37].
- Longer and heavier use of stimulants delays recovery and worsens the prognosis for stimulant induced psychosis[35].
- The risk of stimulant-induced psychosis increases with increasing duration of stimulant use[35] and usually develops gradually with repeated episodes of stimulant use[310].
- Symptoms resembling both positive and negative symptoms of psychosis may continue after withdrawal and patients with persisting stimulant induced psychosis can develop long lasting residual symptoms resembling negative symptoms of schizophrenia[310].
- Acute stimulant-induced psychosis usually disappears shortly after the discontinuation of stimulant consumption and at the beginning of neuroleptic treatment[35].

**Stimulant use in people with chronic psychosis**

- People with an established psychotic disorder can experience an exacerbation of symptoms after acute exposure to psychostimulants, possibly due to an increase in monoamines[15, 30, 34].
- The presence of positive symptoms makes an individual more likely to experience a worsening of psychotic symptoms in response to a single administration of stimulant[30].
- There is debate as to whether compliance with antipsychotic medication will prevent relapse or worsening of symptoms if stimulants are used[30, 310].



### *7.6.2 Interactions between stimulants and therapeutic agents for psychotic disorders*

- As stimulants act in an antagonistic manner, their combinations with antipsychotics that act as antagonists, particularly at dopamine receptors, are unlikely to result in more pronounced pharmacodynamic outcomes than if they were taken alone✖.
- Stimulant drugs are likely to exacerbate the side-effects of SSRI and SNRI antidepressants (and vice versa) used in the treatment of breakthrough depression in psychosis[2] and may result in serotonin syndrome (Appendix 1)✖[127, 179, 180]. Patients should be warned of signs of serotonin syndrome and be monitored.
- MAO-Is (either irreversible or reversible) are contraindicated in people using amphetamines or MDMA. Deaths have been associated with concurrent use of moclobemide and MDMA✖✖✖[181, 182].
- Fluoxetine, paroxetine and norfluoxetine can inhibit the metabolism of MDMA through inhibition of the CYPs involved in its metabolism and may therefore cause toxicity✖.

### *7.6.3 Management approaches to comorbid psychotic disorders and stimulant use*

**Assessment**

- It is important to attempt to distinguish between people with an acute psychotic episode caused by substance use, a first episode of a psychotic disorder or an acute episode in someone with an established chronic psychotic disorder.

**Treatment**

*Acute psychotic episode*

- In an acute psychotic episode caused by a substance, treatment should involve efforts to encourage abstinence from stimulants[30] which should result in the resolution of psychotic symptoms.
- Benzodiazepines (preferably oral but parenteral if necessary) should be first-line agents in acute stimulant induced psychosis. Antipsychotics are useful second-line agents if benzodiazepines do not settle the agitation sufficiently.
- The use of benzodiazepines should be minimised for outpatient use as those with a history of substance use are at increased risk of benzodiazepine use[2, 196].
- Antipsychotics may be added if benzodiazepines are unsuccessful. However, for acute stimulant induced psychosis, their use is as an adjunctive tranquilliser.
- Limited ongoing use is justified if psychotic symptoms persist.

*Longer term psychotic episode*

- There are currently no pharmacotherapies for stimulant dependence[2].
- As soon as the person has recovered, they should be regularly reviewed in order to reduce and cease antipsychotic medication.
- In those who have experienced more than one episode of psychosis, regular low dose use of antipsychotics may be necessary[30].
- There is some evidence that clozapine is effective in individuals with psychosis and comorbid stimulant use[2, 267].
- Olanzapine has also shown promising results when used by people with psychosis and stimulant-use disorders[267]. It has been shown to reduce stimulant use and both positive and negative psychotic symptoms related to stimulant use, and improve overall functioning *[32].
- Follow up of the psychotic episode is important to ensure that the patient has not developed an underlying functional psychotic disorder.

For further information please consult:

*Guidelines for the medical management of patients with methamphetamine-induced psychosis:*

http://www.dassa.sa.gov.au/webdata/resources/files/Psychosis_guidelines.pdf

## 7.7 Major clinical issues with psychosis and benzodiazepine use

- Benzodiazepines may be required for breakthrough anxiety and agitation in psychosis.
- Benzodiazepines should be restricted to short-term use particularly in outpatient settings.
- If dependence has developed, then graduated withdrawal through slow reduction of dosage should be commenced, possibly after transferring the patient onto a long-acting benzodiazepine.
- If long-term benzodiazepine use is indicated, then this should be monitored closely.

### *7.7.1 Effects of benzodiazepines on psychotic disorders*

- Benzodiazepines may be required for breakthrough anxiety and agitation in psychosis[2].
- Benzodiazepine use should be restricted to short-term use particularly in outpatient settings as those with substance-use disorders are at a greater risk of abusing benzodiazepines[2, 196].
- Benzodiazepines may be used by patients to self-manage positive psychotic symptoms.
- Benzodiazepines will enhance the sedative effects of tricyclic antidepressants used to treat associated depression[2] with schizophrenia, which increases the risk of overdose.
- Benzodiazepines may exacerbate negative symptoms such as depression and psychomotor retardation as well as slowing of cognitions.

### *7.7.2 Interactions between benzodiazepines and therapeutic agents for psychotic disorders*

- Benzodiazepines will increase the sedative effects of antipsychotics✖.
- When used with clozapine✖, benzodiazepines may induce delirium, severe sedation and respiratory depression.

### *7.7.3 Management approaches to comorbid psychotic disorders and benzodiazepine use*

- Due to their sedative effects, benzodiazepines, in conjunction with major tranquilisers, e.g. lorazepam, clonazepam and diazepam, can be useful for the acute management of psychotic episodes.
- If large quantities of benzodiazepines (e.g. 40mg diazepam daily equivalent) are being consumed, then inpatient withdrawal to lower levels should be considered to avoid and manage seizure risk[194].
- If dependence has developed, then graduated withdrawal through slow reduction of dosage should be commenced ****[194-196], possibly after transferring the patient onto a long acting benzodiazepine.

- If long-term benzodiazepine use is indicated, then:
  - This should be subject to a contract with the patient.
  - Authorities should be advised, including registration with the relevant local government health authority.
  - The seeking of additional benzodiazepines from other prescribers should be monitored (e.g. using the *Authority to release personal PBS claims information to a third party* form).
  - Daily or weekly dispensing of benzodiazepines should be considered and may assist with controlling use.

## 7.8 Major clinical issues with psychosis and inhalant/solvent use

- Chronic inhalant use can produce persistent psychotic symptoms in susceptible individuals.
- Clozapine has been linked to cardiomyopathy and fatal myocarditis.
- As with most other substances, inhalant users should be encouraged to reduce or cease use to observe whether psychotic symptoms resolve.

### *7.8.1 Effects of inhalants/solvents on psychotic disorders*

- Chronic inhalant use can produce persistent psychotic symptoms in susceptible individuals[60, 62].
- Chronic inhalant use also has the potential to induce psychotic symptoms in those who are not susceptible to psychosis[61, 62].
- Inhalant use can induce a brief psychotic disorder that can last from a few hours up to a few weeks beyond the time of intoxication[61].

### *7.8.2 Interactions between inhalants/solvents and therapeutic agents for psychotic disorders*

- The sedative effects of antipsychotics may be exacerbated by inhalants and may possibly result in severe sedation and overdose✖.
- Clozapine has been linked to cardiomyopathy and fatal myocarditis✖✖[311]. Therefore, risks should be appraised prior to commencement.
- Inhalants will enhance the sedative effects of tricyclic antidepressants and benzodiazepines used to treat breakthrough depression[2] and anxiety with schizophrenia, which increases the risk of overdose✖.

### 7.8.3 *Management approaches to comorbid psychotic disorders and inhalants/solvent use*

- As with most other substances, inhalant users should be encouraged to try and reduce or cease use to observe whether psychotic symptomatology resolves.
- A case study reports the effectiveness of clozapine in reducing psychotic symptoms as well as glue sniffing[62].
- In general, with respect to inhalant/solvent use[65]:
  - Outline the harms associated with inhalant/solvent use.
  - Investigate polysubstance use as this is common.
- Standard CBT approaches to both sets of issues should be used, with particular attention to the development of:
  - Assertiveness skills (refusal skills).
  - Coping skills for controlling and managing emotions such as anger and sadness.
- Offer alternatives to inhalant use, for example, recreational activities.
- Community reinforcement approaches should be developed by mobilising the local health and welfare service system in individual care plans.
- Family interventions need to be considered, for example, increasing communication between the person and the family.
- Assertive outreach and follow-up may be required.

# 8 Personality disorders and substance use

## 8.1 Personality disorders

A personality disorder is an enduring pattern of inner experience, of seeing the world and relating to others in a manner that markedly deviates from cultural expectations, and includes, and results in, problematic and habitual behaviours that are pervasive and inflexible.

The onset of personality disorders occurs in adolescence or early adulthood, is stable over time, leads to impairment or distress and is not due to mental disorder or substance use.

Personality disorders are long-standing and maladaptive patterns of perceiving and responding to other people and to stressful circumstances.

Personality traits are conspicuous features of personality and are not necessarily pathological, although certain styles of personality traits may cause interpersonal problems. Personality disorders are not regarded as illnesses. However, some dominant personality traits and personality disorders can be modified and some managed on a systemic level.

### *8.1.1 Personality disorder subtypes*

**Cluster A personality disorder**

Includes paranoid, schizoid and schizotypal types. Individuals display odd and eccentric behaviour.

***Paranoid***

Person displays patterns of distrust and suspiciousness such that others' motives are interpreted as malevolent.

***Schizoid***

Person displays a pattern of detachment from social relationships and a restricted range of emotional expression.

***Schizotypal***

Person displays a pattern of acute discomfort in close relationships, cognitive or perceptual distortions, and eccentricities of behaviour.

**Cluster B personality disorder**

Includes antisocial, borderline, histrionic and narcissistic types. Individuals display dramatic, erratic and emotional behaviour.

***Antisocial***

Person displays a pattern of disregard for, and violation of, the rights of others.

***Borderline***

Person displays patterns of instability in interpersonal relationships, self image and effects as well as marked impulsivity.

***Histrionic***

Person displays patterns of excessive emotionality and attention-seeking behaviour.

***Narcissistic***

Person displays patterns of grandiosity, need for admiration and lack of empathy.

**Cluster C personality disorder**

Includes avoidant, dependent and obsessive compulsive types. Individuals display anxious and fearful behaviours.

***Avoidant***

Person displays patterns of social inhibition, feelings of inadequacy and hypersensitivity to negative evaluation.

***Dependent***

Person displays patterns of submissive and clinging behaviour relating to the excessive need to be taken care of.

***Obsessive compulsive***

Person displays patterns of preoccupation with orderliness, perfectionism and control.

**Personality disorders not otherwise specified**

Personality disorders not otherwise specified are those where:

- The individual's personality pattern meets the general criteria for a personality disorder and traits of several different personality disorders are present, but the criteria for any specific personality disorder are not met.
- The individual's personality pattern meets the general criteria for a personality disorder, but the individual is considered to have a personality disorder that is not included in the classification.

Of all the different types of personality disorders, Cluster B personality disorders (including narcissistic, histrionic, borderline and antisocial) come to the attention of health providers and authorities the most. People with antisocial personality disorders frequently end up in the criminal justice system[312, 313].

### *8.1.2 Management approaches*

- Limit setting and the use of therapeutic contracts are extremely important in this client group.
- It is important that clinicians remain vigilant when dealing with people who have personality disorders in order to avoid being manipulated.
- There is no specific pharmacological treatment for personality disorders. Personality disorders are not normally an indication for medication which adds to their management remaining controversial. A variety of medications have been reviewed for some types of behaviours associated with personality disorders such as impulsivity and aggression. However, good quality data relating to efficacy is limited.
- Antidepressants and mood-stabilising drugs such as carbamazepine, lithium, sodium valproate and other SSRIs are among those that have been studied. They do not provide a cure, but have assisted with some symptom control for some Cluster B personality traits****[314, 315].
- Scheduling of brief, structured and frequent visits to primary care providers is recommended. Restriction of access to emergency services and last minute appointments may be helpful in the management of personality disorders[316].
- A balance must be ensured between the fostering of dependency and providing the support and crisis intervention that is required.
- Early case management with other primary care providers (emergency department staff, locum services, after hours staff, emergency services and mental health staff) is indicated.

## 8.2 Comorbidity with personality disorders

People with personality disorders have:

- High rates of additional mental disorders[317].
- Higher rates of psychotic symptoms and psychotic disorders than controls and those with other mental disorders[316].
- Significant psychosocial impairment[312, 316].
- Higher rates of impulsivity compared with those who do not have a personality disorder[312, 316].
- Higher rates of suicidal ideation and suicidal behaviour than the general population[312, 316].

Substance use is common in people with personality disorders[120, 312, 317-319].

The term 'borderline' was first used to capture the features of the personality disorder that is borderline between psychosis and neurosis and characterised by extremes of mood and thinking.

Substance use is most common in those with Cluster B type personality disorder, in particular, borderline and antisocial personality disorder[120, 313, 318-320].

Conduct disorder in childhood (a necessary prerequisite to conclude that an adult has an antisocial personality disorder) is predictive of substance-use disorders between adolescence and early adulthood[320].

People with comorbid personality disorder and substance use:

- Have more problematic symptoms of substance use than those without a personality disorder[320].
- Are more likely to participate in risky substance-injecting practices that predispose them to blood borne viruses[312].
- Are more likely to engage in risky sexual practices[312] and other disinhibited behaviours.
- May have difficulty staying in treatment programs and complying with treatment plans[312, 316].

Treatment for substance use in people with personality disorders is associated with a reduction in substance use[313].

Treatment for substance use is also associated with a reduction in the likelihood of being arrested[313], suggesting a reduction in criminal activity.

### *8.2.1 General management approaches to comorbidity*

- People with personality disorders are difficult to manage. Often, the underlying disorders will only become apparent after previous attempts to treat comorbidities have failed.
- People with personality disorders should be counselled about substance use and the problems that arise from substance use, given their particular personalities.
- However, many clients have difficulty even recognising that their substance use is problematic.

## 8.3 Major clinical issues with personality disorders and cannabis/hallucinogen use

- People with personality disorders display more symptoms of cannabis use disorders than those who do not have a personality disorder.
- Advice regarding cannabis usage in these disorders depends on the degree of dysfunction associated with use.
- In the absence of other proven forms of treatment, CBT is, at present, the most widely-employed form of treatment for cannabis use.

### *8.3.1 Effects of cannabis and other hallucinogens on personality disorders*

- Conduct disorder in adolescence increases the risk of initiating marijuana use[320].
- Age of first use of cannabis is earlier in people with personality disorders compared to whose without personality disorders[320].

- People with personality disorders display more symptoms of cannabis dependence than those who do not have a personality disorder[320].
- Symptoms associated with cannabis dependence increase over time in those with personality disorders[320].

### 8.3.2 *Interactions between cannabis and other hallucinogens and therapeutic agents for personality disorders*

- Cannabis can exacerbate the sedative effects of carbamazepine, lithium and sodium valproate✖.
- Cannabis can exacerbate the sedative effects of antidepressants such as tricyclics✖.
- LSD may induce a serotonin syndrome (Appendix 1); therefore, caution should be exercised when prescribing SSRIs or MAO-I✖[127].
- Cannabis and antidepressants are metabolised by CYP 450 enzymes which may result in the inhibition or induction of either drug group. Therefore, individuals should be monitored closely to ensure outcomes are appropriate✖.

### 8.3.3 *Management approaches to comorbid personality disorders and cannabis use*

- Advice regarding cannabis use for people with these disorders depends on the degree of dysfunction associated with use.
- Overall approach depends on the person's readiness for change.
- Abstinence from cannabis is a difficult goal to achieve in cannabis dependent people[128].
- In the absence of other proven forms of treatment, CBT is, at present, the most widely-employed form of treatment for cannabis use✱✱✱✱[128].

## 8.4 Major clinical issues with personality disorders and alcohol use

- Personality disorders (in particular antisocial and borderline) and alcohol use disorders frequently co-exist.
- Alcohol can exacerbate the sedative effects of some antidepressants such as tricyclics and mirtazepine.
- Alcohol can exacerbate the sedative effects of carbamazepine, lithium, and sodium valproate.
- Acamprosate or naltrexone can be considered for long-term abstinence with naltrexone showing effectiveness in moderating drinking in those with antisocial personality traits.

### 8.4.1 *Effects of alcohol on personality disorders*

- Personality disorders (in particular antisocial and borderline) and alcohol use disorders frequently co-exist[16, 120, 317, 319-322].
- Personality disorders are associated with an earlier age of onset of alcohol use disorders[323].

- Symptom severity of alcohol dependence continues to increase over time in those with personality disorders[320].
- Personality disorders (in particular anti-social characteristics) are associated with[320, 324, 325]:
  - More severe alcohol disorders.
  - Poorer long-term drinking outcome.
  - Poorer outcomes for treatment of alcoholism.
- Personality disorders and alcohol use disorders are associated with:
  - More criminal convictions[321].
  - High levels of novelty-seeking behaviour and impulsivity[323, 326].
- Alcohol use also significantly complicates personality disorders[121].



### 8.4.2 Interactions between alcohol and therapeutic agents for personality disorders

- Alcohol can exacerbate the sedative effects of carbamazepine, lithium, and sodium valproate✖.
- Alcohol can exacerbate the sedative effects of some antidepressants such as tricyclics and mirtazepine. Alcohol toxicity and risk of overdose may occur through the inhibition of CYPs involved in the metabolism of alcohol✖[133].
- Interactions between antidepressants and acamprosate used to treat alcohol dependence are minimal, as are interactions between antidepressants and disulfiram and naltrexone also used to treat alcohol dependence✖✖[134].

### 8.4.3 Management approaches to comorbid personality disorders and alcohol use

- Carbamazepine***[327] and sodium valproate***[328, 329] can be used in alcohol withdrawal to reduce the risk of seizures.
- While studies are yet to confirm this, cabarmazepine has been discussed as being useful in the prevention of relapse to drinking[330, 331].
- Acamprosate or naltrexone can be considered for long-term abstinence****[141, 144, 235, 236], with naltrexone showing effectiveness in moderating drinking in those with antisocial personality traits**[332]. However, medication adherence may be problematic.
- As people with comorbid personality disorders and substance use are more prone to risk taking and subsequent injury, individuals prescribed with naltrexone need to be aware of its implications for emergency pain management.
- Patients prescribed with naltrexone should be advised to carry a medical warning card or bracelet which states they will not respond to opioid analgesia (obtainable from Orphan Australia).
- Disulfiram may be problematic as these patients may drink alcohol impulsively despite being warned of the risks.

## 8.5 Major clinical issues with personality disorders and opioid use

- A significant number of people with opioid dependence also have personality disorders.
- Particularly in the opioid dependent population, it is important to try to determine whether the behaviours are due to the opioid dependence or due to antisocial personality disorder.
- The presence of a personality disorder does not appear to impact on the effectiveness of opioid treatment.
- Methadone maintenance appears to be effective in people with personality disorders.
- Carbamazepine is a potent CYP inducer and will induce the metabolism of methadone and buprenorphine.
- Opioids can increase the sedative effects of carbamazepine, lithium and sodium valproate.

### *8.5.1 Effects of opioids on personality disorders*

- A significant number of people with opioid dependence also have personality disorders[312, 333]. Particularly in the opioid dependent population, it is important to try to determine whether the behaviours are due to the opioid dependence or the antisocial personality disorder.
- Opioid dependent people with personality disorders have more severe substance dependence as well as polydrug dependencies[312].
- Individuals with comorbid personality disorders and opioid dependence[312, 333]:
  - Participate in more criminal activities (likely related to procurement of drugs).
  - Participate in more risky injecting behaviour.
  - Have higher rates of suicidality and overdose.
  - Have more psychological distress compared to opioid dependent individuals without personality disorders.
- The presence of a personality disorder does not appear to impact on the effectiveness of opioid treatment; however, it may affect retention and result in continual switching between treatment regimes[312, 334]:
  - Treatment reduces participation in crime and improves injecting behaviour as well as risk of overdose and psychological distress. However, rates still remain above those without personality disorders[334].
  - Treatment improves risk of suicide to a level that is comparable to those without personality disorders[334].
- As with others who have initial legitimate needs for opioids to control pain, people with personality disorders may go on to develop dependence to opioids and feel a need to increase their dosage. This may be a contributor to the above-mentioned switching of treatment regimes or treatment providers in order to obtain subsequent increases in opioid dose.

### 8.5.2 Interactions between opioids and therapeutic agents for personality disorders

- Opioids can increase the sedative effects of carbamazepine, lithium and sodium valproate✖.
- Carbamazepine is a potent CYP inducer and will induce the metabolism of methadone and buprenorphine as well as reduce plasma concentrations✖✖[149, 157]. This has the potential to result in withdrawal and failure of retention in treatment✱✱✱✱[158-160].
- Opioids can exacerbate the sedative effects as well as increase the risk of overdose with tricyclic antidepressants✖✖[161].

### 8.5.3 Management approaches to comorbid personality disorders and opioid use

- Methadone maintenance appears to be effective in people with personality disorders✱✱[335, 336].
- Close liaison between the prescribing clinician and the pharmacist dispensing the opioid maintenance will assist with gaining insight into adherence to treatment, levels of self care and general stability.
- Considering the potential of personality disorders to impact on treatment retention, oral naltrexone is less likely to be effective in individuals with personality disorder.



## 8.6 Major clinical issues with personality disorders and stimulant (including methamphetamine) use

- Personality disorders are frequently observed in stimulant users.
- Use of stimulants may exacerbate impulsivity, mood disturbance and anger in people with Cluster B type personality disorders.
- MAO-Is (either irreversible or reversible) are contraindicated in people using amphetamines or MDMA. Deaths have been associated with concurrent use of moclobemide and MDMA.
- CBT can be used to address stimulant use and is effective.
- Assistance with coping skills may assist with impulsive use of stimulants.

### 8.6.1 Effects of stimulants on personality disorder

- Personality disorders are frequently observed in stimulant users, in particular cocaine and ecstasy users[41, 337].
- Use of stimulants may exacerbate impulsivity, mood disturbance and anger in people with Cluster B type personality disorders[338, 339].

### 8.6.2 Interactions between stimulants and therapeutic agents for personality disorders

- Stimulant drugs are likely to exacerbate the effects of SSRI and SNRI antidepressants (and vice versa) and may result in serotonin syndrome (Appendix 1)✖[127, 179, 180]. Patients should be warned of signs of serotonin syndrome and be monitored.

- MAO-Is (either irreversible or reversible) are contraindicated in people using amphetamines or MDMA. Deaths have been associated with concurrent use of moclobemide and MDMA✖✖✖[181, 182].
- Fluoxetine, paroxetine and norfluoxetine can inhibit the metabolism of MDMA through inhibition of the CYPs involved in its metabolism and may therefore cause toxicity✖.

### *8.6.3 Management approaches to comorbid personality disorders and stimulant use*

- The adverse behavioural, psychological and physical effects of stimulants should be discussed with the patient.
- CBT is effective at reducing stimulant use***[49, 183]. In particular, assistance with coping skills may assist with impulsive use of stimulants.

## 8.7 Major clinical issues with personality disorders and benzodiazepine use

- Benzodiazepines have been associated with reduced impulse control, disinhibition and increased levels of violence, particularly in people with Cluster B type personality disorders.
- There is an increased risk of sedation and overdose with the combination of benzodiazepines and sedative antidepressants.
- Benzodiazepines can increase the sedative effects of carbamazepine, lithium and sodium valproate.

### *8.7.1 Effects of benzodiazepines on personality disorders*

- Benzodiazepines are thought to have a negative effect on many of the problematic behaviours associated with these disorders.
- Benzodiazepines have been associated with reduced impulse control, disinhibition and increased levels of violence, particularly in people with Cluster B type personality disorders.

### *8.7.2 Interactions between benzodiazepines and therapeutic agents for personality disorders*

- Benzodiazepines can increase the sedative effects of carbamazepine, lithium and sodium valproate✖.
- There is an increased risk of sedation and overdose with the combination of benzodiazepines and sedative antidepressants such as tricyclics and mirtazepine✖.
- Benzodiazepines and antidepressants are both metabolised by CYP 450 enzymes which may result in the inhibition or induction of either drug group. Therefore, individuals should be monitored closely to ensure they are experiencing the appropriate therapeutic effect✖.
- Fluvoxamine will inhibit the metabolism of alprazolam, midazolam, triazolam and diazepam causing increased sedation and potential toxicity✖.
- Citalopram and sertraline are the least likely SSRIs to have cytochrome mediated drug interactions✖.

### 8.7.3 *Management approaches to comorbid personality disorders and benzodiazepine use*

- If benzodiazepine dependence has developed, then graduated withdrawal through slow reduction of dosage should be commenced****[194-196], possibly after transferring the patient onto a long acting benzodiazepine.
- If benzodiazepine use is indicated or to occur, then:
  - This should be subject to a contract with the patient.
  - Authorities should be advised, including registration with the relevant local government health authority.
  - The seeking of additional benzodiazepines from other prescribers should be monitored (e.g. using the *Authority to release personal PBS claims information to a third party* form).
  - A more direct liaison approach between clinicians who are dealing with individuals with suspected comorbid personality disorders and benzodiazepine use may help to minimise unnecessary prescribing.
  - Daily or weekly dispensing of benzodiazepines should be considered and may also assist with controlling use.
- If large quantities of benzodiazepines (e.g. 40mg diazepam daily equivalent) are being consumed, then inpatient withdrawal to lower levels should be considered to avoid seizures[194].

## 8.8 Major clinical issues with personality disorders and inhalant/solvent use

- Inhalant users have high rates of personality disorders with early-onset inhalant use in particular being strongly associated with personality disorders.
- Inhalants will exacerbate the sedative effects of carbamazepine, lithium, sodium valproate and antidepressants such as tricyclics.
- Inhalant users should be encouraged to try and reduce or cease use.



### 8.8.1 *Effects of inhalants/solvents on personality disorders*

- Inhalant users have high rates of personality disorders with early onset inhalant use, in particular, being strongly associated with personality disorders[250].

### 8.8.2 *Interactions between inhalants/solvents and therapeutic agents for personality disorders*

- Inhalants will exacerbate the sedative effects of carbamazepine, lithium, sodium valproate and antidepressants such as tricyclics×.

### 8.8.3 *Management approaches to comorbid personality disorders and inhalant/solvent use*

- As with most other substances, inhalant users should be encouraged to try and reduce or cease use.
- In general, with respect to inhalant/solvent use[65]:
  - Outline the harms associated with inhalant/solvent use.
  - Investigate polysubstance use as this is common.
- Standard CBT approaches to both sets of issues should be used, with particular attention to the development of:
  - Assertiveness skills (refusal skills).
  - Coping skills for controlling and managing emotions such as anger and sadness.
- Offer alternatives to inhalant use, for example, recreational activities.
- Community reinforcement approaches should be developed by mobilising the local health and welfare service system in individual care plans.
- Family interventions need to be considered, for example, increasing communication between the person and the family.
- Assertive outreach and follow-up may be required.

# 9 Eating disorders and substance use

## 9.1 Eating disorders

Eating disorders are more common in women than in men[119, 120]. However, it is important that these disorders are not overlooked in men[3].

Eating disorders are a group of disorders that include anorexia nervosa, bulimia nervosa and eating disorders not otherwise specified.

### *9.1.1 Anorexia nervosa*

Anorexia nervosa is characterised by a significant weight loss as a result of compromised eating, obsessive fears of being overweight and the voluntary pursuit of thinness. Anorexia is a chronic relapsing illness with one of the highest rates of mortality among psychiatric disorders.

Two main sub-types of anorexia nervosa include the:

- Restricting type where the individual restricts food intake.
- Binge eating/purging type where the individual alternates between binge eating and self induced vomiting, laxative or diuretic misuse[340, 341].

A 'binge' is defined as the consumption of an excessive amount of food in a short period of time, during which the person experiences loss of control of their behaviour.

**Management approaches**

Studies into the pharmacological treatment of anorexia are sparse and results for those that have assessed atypical antipsychotics and antidepressants are inconsistent.

In general, approaches to the management of people with anorexia nervosa involve[3, 342]:

- Restoring weight to a normal range and medical monitoring of physical status. Specialist input may be required in the resuscitation of low weight individuals.
- Reducing the distorted perception of body image and related consequences.
- Medications can be prescribed if indicated. However, there is good evidence for non-drug treatment of anorexia.

For further information please consult:

*Anorexia nervosa: A treatment guide for consumers and carers:*

http://www6.health.gov.au/internet/main/publishing.nsf/Content/mental-pubs-a-anorex

### *9.1.2 Bulimia*

Bulimia is characterised by episodes of binge eating followed by compensatory behaviours to rid the body of calories and an obsession with weight and shape.

There are two main types of bulimia (reflecting the compensatory behaviours)[342]:

- Purging type where the individual resorts to vomiting or uses laxatives, diuretics or enemas [340, 341].
- Non-purging type involving excessive exercising or fasting.

**Management approaches**

In general, approaches to the management of people with bulimia involve:

- Medical monitoring of medical status, particularly for electrolyte disturbance and the consequences of repeated purging behaviours.
- CBT which has been shown to be useful in the treatment of bulimia and is generally regarded as the first line of treatment****[343, 344].
- Different classes of antidepressants (TCAs, SSRIs, MAOIs) have shown good efficacy and tolerability in the treatment of bulimia[3, 342, 344]:
  - SSRIs (fluoxetine being the most widely studied) reduce bulimic symptoms by reducing the frequency of binge eating and purging as well as anxious and depressive symptoms****[344].
  - High doses may be required to be effective with inadequate dosing responsible for discontinuation of treatment****[344, 345].
- Preliminary evidence exists for the additional efficiency of combined CBT and medication management although further studies are required to confirm this****[344].

## 9.2 Comorbidity with eating disorders

### *9.2.1 Comorbidity with substance use*

- People with bulimia or bingeing/purging behaviours are more likely to use substances or have a substance use disorder than people with anorexia (in particular the restricting type) or the general population[346-351].
- Results from studies of bulimia and anorexia populations suggest that those people who use pharmacological methods of weight control (including laxatives, diet pills and diuretics) are more likely to use more traditional substances such as stimulants[352].
- A variant of eating disorders has been described where people have difficulty with 'multi-impulse control'[353]. These people are more prone to problems in a variety of areas of impulse control in the setting of their bulimic illness, including substance use. People with comorbid bulimia and substance use problems are more likely to attempt suicide, be impulsive and have personality disorders[350, 351, 354-356].
- The risk of substance use disorder in people with eating disorders continues over time and should be an ongoing part of assessment of these people[347, 354, 357, 358]. However, age-related tapering of substance use may decrease the incidence[347, 359] as does retention in treatment [347].

- Drug use may assist with weight control and may be a part of impulsiveness and loss of control[360]. It may also be a part of a risk taking or self harming pattern of behaviour[361].

### *9.2.2 Comorbidity with other mental disorders*

- People with eating disorders across all types have higher rates of mental disorders in general (reported up to 97% comorbidity)[346, 347], in particular, mood and anxiety disorders[346, 347, 354, 362]. These other mental disorders increase the severity and chronicity of the eating disorder as well as impact on the willingness to accept treatment[346, 363].
- People with bulimia or bingeing behaviours have high rates of other impulse control disorders (e.g. compulsive buying and pathological gambling) and, combined with personality disorders, show high rates of novelty seeking behaviour[364-367].
- In addition, consistent personality differences exist between people with anorexia and bulimia[351, 356]. It has been suggested that the less inhibited and more impulsive personality style associated with bulimia may predispose people to substance use[341, 346, 351, 363].
- People with anorexia (particularly the restricting type) have higher rates of obsessive compulsive disorders[346, 368].

### *9.2.3 General management approaches to comorbidity*

- Practitioners should always anticipate mental disorders and substance use comorbidity in people with eating disorders[346, 347], particularly those with binge/purging types.
- Treatment and prevention should be directed towards assisting individuals at risk in understanding the nature of their emotions and subsequently developing positive coping strategies to handle them[350].
- The disruptive symptoms of eating disorders can interfere with therapy for substance use disorders**[357] and vice versa.
- When assessing people with eating disorders, a detailed drug history should be elicited and should include specific inquiry about alcohol and stimulants as well as diuretics, laxatives and thyroxine.

## 9.3 Major clinical issues with eating disorders and cannabis/hallucinogen use

- Cannabis has been shown to be one of the most commonly used substances across eating disorders and its frequency of use has been correlated with the frequency of bulimia.
- Management of cannabis use should be determined by the level of impact associated with its use.
- In the absence of other proven forms of treatment, CBT is, at present, the most widely employed form of treatment for cannabis use.

### 9.3.1 *Effects of cannabis and other hallucinogens on eating disorders*

- Cannabis has been shown to be one of the most commonly-used substances across eating disorders and its frequency of use has been correlated with the frequency of bulimia[341, 351, 352, 360].
- As cannabis has been shown to cause appetite stimulation[369], its role in people with eating disorders is complex.
- Use of LSD in people with eating disorders has been shown to be of low frequency[347].

### 9.3.2 *Interactions between cannabis and other hallucinogens and therapeutic agents for eating disorders*

- Cannabis can exacerbate the sedative effects of antidepressants such as tricyclics✖.
- LSD may induce a serotonin syndrome (Appendix 1), therefore caution should be exercised when prescribing SSRIs or MAO-I✖[127].
- Cannabis and antidepressants are metabolised by CYP 450 enzymes which may result in the inhibition or induction of either drug group. Therefore, individuals should be monitored closely to ensure outcomes are appropriate✖.

### 9.3.3 *Management approaches to comorbid eating disorders and cannabis or other hallucinogen use*

- Management of cannabis use should be determined by the level of impact associated with its use.
- Abstinence from cannabis is a difficult goal to achieve in cannabis dependent people[128].
- In the absence of other proven forms of treatment, CBT is, at present, the most widely employed form of treatment for cannabis use****[128].

## 9.4 Major clinical issues with eating disorders and alcohol use

- Alcohol is one of the most commonly used substances amongst people with eating disorders, in particular, those with purging behaviours.
- Alcohol can exacerbate the sedative effects of some antidepressants such as tricyclics and mirtazepine, which may be used in the management of some eating disorders.
- Alcohol dependence and the eating disorders need to be addressed in an integrated manner.
- CBT is effective for treatment of eating disorders (in particular bulimia) and there is no evidence that alcohol dependence affects the efficacy of CBT negatively.
- Assistance with stress management (structured problem solving, coping skills therapy) has been found to be effective in the treatment of alcohol use and is useful for people with eating disorders.

### 9.4.1 Effects of alcohol on eating disorders

- Alcohol is one of the most commonly used substances amongst people with eating disorders, in particular, those with the purging behaviours[341, 351, 352].
- People with bulimia or bingeing/purging behaviours have higher rates of alcohol use than people with anorexia (up to twice as likely in people with the restrictive type of anorexia) and control groups without eating disorders[341, 346, 349-351, 354, 355, 362, 363, 370, 371].
- People with anorexia have reported avoiding alcohol to prevent weight gain from the calories it contains[341].
- The majority of people affected by eating disorders and alcohol-use disorders report that the eating disorder developed first[363]. This may explain the fact that eating disorder symptoms (vomiting and exercise) seem to be predictive of the course of alcohol-related problems in people with comorbid alcohol use and eating disorders[357].
- People with both bulimia and alcohol dependency have higher rates of self-harm, and borderline personality disorders, and poorer outcomes than those without alcohol-related problems[370, 371].

### 9.4.2 Interactions between alcohol and therapeutic agents for eating disorders

- Alcohol can exacerbate the sedative effects of some antidepressants such as tricyclics and mirtazepine which may be used in the management of some eating disorders. Alcohol toxicity and risk of overdose may occur through the inhibition of CYPs involved in the metabolism of alcohol✖[133].
- Interactions between antidepressants and acamprosate used to treat alcohol dependence are minimal as are interactions between antidepressants and disulfiram and naltrexone also used to treat alcohol dependence✖[134].

### 9.4.3 Management approaches to comorbid eating disorders and alcohol use

- Alcohol dependence and the eating disorder need to be addressed in an integrated manner[3, 372].
- Antidepressants have been shown to reduce depressive symptoms and alcohol consumption in depressed people with alcohol dependence***[130]. However, there have been no specific studies of the role of SSRIs in people with eating disorders and alcohol dependence.
- CBT is effective for treatment of eating disorders (in particular bulimia)****[343, 344]. There is no evidence that alcohol dependence affects the efficacy of CBT negatively. However, no available studies have reported effectiveness of CBT in managing alcohol use and eating disorders[3, 372].
- Naltrexone has been shown to be effective in the treatment of alcohol dependence ****[141, 235, 236] and in early studies shows some efficacy in reducing bingeing/purging behaviours[3, 372]. However, it has not been rigorously tested for the combination of eating disorders and alcohol use[372, 373].
- Assistance with stress management (structured problem solving, coping skills therapy) has been found to be effective in the treatment of alcohol use, is useful for people with eating disorders and can be easily integrated with pharmacological approaches[3].

## 9.5 Major clinical issues with eating disorders and opioid use

- People with eating disorders do not commonly use opioids.
- Fluvoxamine×××, fluoxetine××, norfluoxetine×× and paroxetine× can inhibit buprenorphine and methadone metabolism through inhibition of the CYPs involved in their metabolism.
- If the person is opioid dependent, stabilise the use of opioids preferably using opioid pharmacotherapy such as buprenorphine or methadone.
- Where possible, it is important to avoid the use of opioid antagonists due to their appetite suppressing effects.

### *9.5.1 Effects of opioids on eating disorders*

- People with eating disorders do not commonly use opioids.
- Endogenous opioid peptides have been shown to play a role in food intake. The use of opioid agonists on a regular basis (in contrast with the acute setting) generally results in an increase in food intake, whereas opioid antagonists decrease food intake[374, 375].

### *9.5.2 Interactions between opioids and therapeutic agents for eating disorders*

- Fluvoxamine×××, fluoxetine××, norfluoxetine×× and paroxetine× can inhibit buprenorphine and methadone metabolism through inhibition of the CYPs involved in their metabolism[148-150]. This can result in an increase in plasma opioid pharmacotherapy concentrations and potential overdose. This can be a particular issue during induction onto methadone; however, the risk may persist even after stabilisation has occurred×××[151-155].
- Fluvoxamine is the most potent inhibitor of methadone and buprenorphine metabolism and is the most clinically relevant. Therefore, it should be avoided ×××[150].
- Fluoxetine and paroxetine should also be avoided××.
- Citalopram and sertraline are the least likely SSRIs to have cytochrome mediated drug interactions, however, due to the theoretical potential for an interaction, caution should still be used and individuals monitored closely×[156].
- There is an increase in sedation as well as risk of fatal overdose with opioid use and tricyclic antidepressants××[161].

### *9.5.3 Management approaches to comorbid eating disorders and opioid use*

- If the person is opioid dependent, stabilise the use of opioids, preferably using opioid pharmacotherapy such as buprenorphine or methadone which may inadvertently also help to stimulate appetite.
- Counselling for the opioid dependence should be integrated with standard approaches to the eating disorder.
- Where possible, it is important to avoid the use of opioid antagonists due to their appetite suppressing effects when treating opioid dependence in people with eating disorders[374, 375].

## 9.6 Major clinical issues with eating disorders and stimulant (including methamphetamine) use

- People with eating disorders may use stimulants to control appetite and to provide energy for exercise.
- MAO-Is (either irreversible or reversible) are contraindicated in people using amphetamines or MDMA. Deaths have been associated with concurrent use of moclobemide and MDMA.
- The use of stimulants at any level should be discouraged.
- CBT can be used to address stimulant use and the eating disorder.
- In particular, assistance with coping skills may assist with impulsive use of stimulants and bingeing behaviours.



### 9.6.1 Effects of stimulants on eating disorders

- People with eating disorders may use stimulants to control appetite and to provide energy for exercise[360]. Consequently, dependence can develop.
- High rates of cocaine and amphetamine use have been observed in people with eating disorders[347].
- Appetite suppression and weight loss have been reported to be the reason for the commencement and continuation of cocaine[340].
- Severity of bulimia has been shown to correlate with the frequency of MDMA and amphetamine use, with users reporting that ecstasy aids in weight loss[360].

### 9.6.2 Interactions between stimulants and therapeutic agents for eating disorders

- Stimulant drugs are likely to exacerbate the effects of SSRI and SNRI antidepressants in particular (and vice versa) and may result in serotonin syndrome (Appendix 1)✖[127, 179, 180]. Patients should be warned of signs of serotonin syndrome and be monitored.
- MAO-Is (either irreversible or reversible) are contraindicated in people using amphetamines or MDMA. Deaths have been associated with concurrent use of moclobemide and MDMA✖✖✖[181, 182].
- Fluoxetine, paroxetine and norfluoxetine can inhibit the metabolism of MDMA through inhibition of the CYPs involved in its metabolism and may therefore cause toxicity✖.

### 9.6.3 Management approaches to comorbid eating disorders and stimulant use

- The use of stimulants at any level should be discouraged due to the risk of dependence and, most importantly, the possibility of increased chances of toxicity.
- CBT can be used to address stimulant use***[49, 183] and the eating disorder****[343, 344]. In particular, assistance with coping skills may assist with impulsive use of stimulants and bingeing behaviours.

## 9.7 Major clinical issues with eating disorders and benzodiazepine use

- People with eating disorders do not commonly use benzodiazepines.
- Benzodiazepine use should be discouraged.
- If dependence has developed, then graduated withdrawal through slow reduction of dosage should be commenced.
- If long-term benzodiazepine use is indicated, then this should be monitored closely.

### *9.7.1 Effects of benzodiazepines on eating disorders*

- People with eating disorders do not commonly use benzodiazepines[349].
- Benzodiazepines have been shown to increase the palatability of food and often result in the increased consumption of food[376].

### *9.7.2 Interactions between benzodiazepines and therapeutic agents for eating disorders*

- There is an increased risk of sedation and overdose with the combination of benzodiazepines and sedative antidepressants such as tricyclics and mirtazepine✖.
- Benzodiazepines and antidepressants are both metabolised by CYP 450 enzymes which may result in the inhibition or induction of either drug group. Therefore, individuals should be monitored closely to ensure they are experiencing the appropriate therapeutic effect✖.
- Fluvoxamine will inhibit the metabolism of alprazolam, midazolam, triazolam and diazepam causing increased sedation and potential toxicity✖.
- Citalopram and sertraline are the least likely SSRIs to have cytochrome mediated drug interactions✖.

### *9.7.3 Management approaches to comorbid eating disorders and benzodiazepines use*

- Benzodiazepine use should be discouraged.
- If large quantities of benzodiazepines (e.g. 40mg diazepam daily equivalent or more) are being consumed, then inpatient withdrawal to lower levels should be considered to avoid and manage seizure risk[194].
- If dependence has developed, then graduated withdrawal through slow reduction of dosage should be commenced****[194-196], possibly after transferring the patient onto a long acting benzodiazepine.
- If long-term benzodiazepine use is indicated, then:
  - This should be subject to a contract with the patient.
  - Authorities should be advised, including registration with the relevant local government health authority.

  - The seeking of additional benzodiazepines from other prescribers should be monitored (e.g. using the *Authority to release personal PBS claims information to a third party* form).
  - Daily or weekly dispensing of benzodiazepines should be considered and may assist with controlling use.
- Standard management of the eating disorder should commence if the patient is willing and engaged.

## 9.8 Major clinical issues with eating disorders and inhalant/solvent use

- People with eating disorders do not commonly use inhalants or solvents.
- There is no literature that sheds light on managing people with comorbid eating disorders and problems relating to inhalant/solvent use.

### *9.8.1 Effects of inhalant/solvents on eating disorders*

- People with eating disorders do not commonly use inhalants or solvents[347].

### *9.8.2 Interactions between inhalants/solvents and therapeutic agents for eating disorders*

- Inhalants can exacerbate the sedative effects of some antidepressants including tricyclic antidepressants and mirtazepine✖.
- Most antidepressants reduce seizure threshold and tricyclic antidepressants can cause cardiac arrhythmias. Therefore, risks should be appraised prior to commencement✖.

### *9.8.3 Management approaches to comorbid eating disorders and inhalant/solvent use*

- There appears to be no literature that sheds light on managing people with comorbid eating disorders and problems relating to inhalant/solvent use.
- As with most other substances, inhalant users should be encouraged to try and reduce or cease use.
- In general with respect to inhalant/solvent use[65]:
  - Outline the harms associated with inhalant/solvent use.
  - Investigate polysubstance use as this is common.

- Standard CBT approaches to both sets of issues should be used, with particular attention to the development of:
  - Assertiveness skills (refusal skills).
  - Coping skills for controlling and managing emotions such as anger and sadness.
- Offer alternatives to inhalant use, for example, recreational activities.
- Community reinforcement approaches should be developed by mobilising the local health and welfare service system in individual care plans.
- Family interventions need to be considered, for example, increasing communication between the person and the family.
- Assertive outreach and follow-up may be required.

# 10 Somatoform disorders and substance use

## 10.1 Somatoform disorders

The common feature of somatoform disorders is the presence of physical symptoms that suggest a general medical condition. However, these symptoms are not adequately explained by a general medical condition by the direct effects of a substance, or by another mental disorder (such as anxiety producing palpitations or breathlessness, depression causing lack of energy).

Symptoms cause significant distress or impairment in social, occupational or other areas of functioning. There is no diagnosable medical condition that can fully account for the physical symptoms. People with somatoform disorders are reluctant to accept that psychological factors may be contributing to their physical symptoms.

This expression of physical symptoms is *not a conscious* deception by the patient.

There are a number of diagnostic subtypes of somatoform disorders.

In addition, unexplainable physical symptoms can be seen in situations where the symptoms are *intentionally* expressed. If the motivator behind this is the adoption of the sick role, then the condition is termed a 'factitious disorder'; if the intent is some external gain, then the condition is termed 'malingering'.

It is important to note that while unexplained physical symptoms are extremely common, most people with such symptoms do not have a somatoform disorder – most of the 'somatizing' presentations to general practice settings would not meet the criteria for one of these disorders.

Similarly, most people presenting with pain do not have a 'pain disorder' or form a somatoform disorder, but rather, have pain of organic origin that may be expressed in a range of ways.

### *10.1.1 Somatization disorder*

This disorder is a polysymptomatic disorder commencing before the age of 30 and extending over a period of years. It is characterised by multiple somatic symptoms in a combination of pain, gastrointestinal, sexual and pseudoneurological symptom areas.

### *10.1.2 Undifferentiated somatoform disorder*

This disorder is characterised by unexplained physical complaints that last for at least six months and are below the threshold for a diagnosis of somatization disorder.

### *10.1.3 Conversion disorder*

This disorder involves unexplained symptoms or deficits affecting voluntary motor or sensory function that suggests a neurological or other general medical condition. Psychological factors are judged as being associated with the symptoms or deficits.

### *10.1.4 Pain disorder*

Pain is the predominant focus of clinical attention in this disorder. Additionally, psychological factors are judged to play an important role in the onset, severity, exacerbation and maintenance of the disorder.

### *10.1.5 Hypochondriasis*

This disorder involves a preoccupation with the fear of having, or the idea that a person has, a serious disease based on the individuals misinterpretation of bodily symptoms or functions.

### *10.1.6 Body dysmorphic disorder*

This disorder involves a preoccupation with an imagined or exaggerated defect in physical appearance.

The following disorders are not within the group known of somatoform disorders, but may present with physical symptoms for which there is no adequate physical cause.

### *10.1.7 Chronic fatigue syndrome*

This syndrome refers to a symptom complex of marked and prolonged fatigue for which no identifiable physical cause can be found.

### *10.1.8 Factitious disorder*

This disorder is characterised by physical or psychological symptoms that are intentionally produced in order to assume the sick role (psychological reasons assumed).

### *10.1.9 Malingering*

- This involves intentional production of false or grossly exaggerated physical or psychological symptoms motivated by external incentives such as financial compensation, avoidance of work or obtaining drugs.
- Malingering disorders differ from factitious disorders in that external incentives are absent in factitious disorders.

**Management approaches to somatoform disorders**

- Patients with somatoform disorders present considerable diagnostic difficulty and treatment can be challenging. Somatisation should be best viewed as a process rather than a diagnosis[377]. Many GPs report difficulties in dealing with somatising patients[377, 378].
- Referral times for clients to attend pain clinics, psychologists and psychiatrists equipped to manage clients with somatoform disorders are often long or unavailable[377]. Frequently, patients fail to attend.
- It is important to develop a good working relationship with the patient. However, the major challenge is developing a common understanding of the problem[379].
- Somatoform disorders are best managed behaviourally and with cognitive therapy which has shown reductions in somatic symptoms and improved functioning ***[380-386].

- Emphasis should always be placed on non-medication management of the somatoform or chronic pain disorder as a first line of treatment[377]. While non-medication management can be extremely challenging at times, if the resources are available in the general practice setting and the client is willing to engage in behavioural therapy, then this should be offered.
- To engage in treatment, the patient needs to have some insight into the problem and be willing to try to approach the problem differently. If this insight cannot be achieved, then a health-system based containment strategy is required.

For further information please refer to:

*Understanding somatisation and somatisation disorders: A handbook for health care workers*[387].

## 10.2 Comorbidity with somatoform disorders

- Somatic presentations of underlying mental disorder or distress are extremely common in general practice with somatisation frequently being a way of presenting anxiety and depression[388]. Many of these presentations are easy to sort out for the clinician, with the underlying stressor or disorder quickly coming to the fore and the patient willing to attribute the physical symptoms to the underlying problem.
- There is a linear relationship between the severity of anxiety and depression and frequency and severity of somatic symptoms[389-392].
- There is a high degree of comorbidity with depression and anxiety amongst people with somatoform disorders[389, 392-398]. A combination of anxiety and depression and a somatoform disorder results in more somatic symptoms than if anxiety or depression alone occurs with the somatoform disorder[392, 396, 398]. Individuals with somatoform disorders and comorbid depression may use both organic and psychological explanations for their symptoms[399].
- Overlap of symptoms of diagnostic criteria for somatoform disorders and anxiety and depression may explain the high prevalence of somatic symptoms in those with anxiety and depression[392, 400].
- Anxiety and depression are more likely than somatoform disorders to be the source of medically unexplained symptoms[401]. Regardless, depression and anxiety make pain feel worse and individuals present with a higher level of functional somatic symptoms[392, 402].
- There is obvious scope for inappropriate substance use in these individuals as the medical practitioner attempts to deal with some of the symptomatology before the correct diagnosis is recognised[377, 403].
- There are strong correlations between pain disorders and opioid dependence and misuse. However, this does not suggest that all people with pain and opioid dependence have a somatoform disorder.
- Somatoform disorders also correlate with alcohol and benzodiazepine dependence and misuse[379, 404].
- Delay in diagnosing these disorders may result in the individuals being prescribed opioids or benzodiazepines with subsequent increased risk of dependence[404].

### *10.2.1 General management approaches to comorbidity*

- The challenge is to recognise the diagnosis of somatoform disorder early.
- Psychosocial assessment should be performed prior to treatment with any form of pharmacological treatment[405].
- Clinicians need to be aware of comorbid anxiety and depression in those with somatoform disorders and manage them accordingly[392, 398].
- In determining whether the depression is a cause or an effect of chronic pain or somatoform disorders, it should be considered at least a comorbid condition that requires concurrent treatment[402]. Use of antidepressants has been shown to be effective in reducing somatic symptoms in those with depression and anxiety[406, 407].
- Use of antidepressants may be required for comorbid depression and anxiety***[406, 407], with tricyclics being useful[377] in aiding chronic tension headaches and fibromyalgia.
- Understanding the impact of fear, expectations and attention can help physicians deal more effectively with acute pain[402].
- There is evidence that pain perception seems to be responsive to changes in patient mood, even in people with concomitant substance use**[408]. This supports cognitive approaches to pain management even in substance dependent individuals.
- Cognitive approaches may result in improved quality of life in patients with long-term somatoform disorders[398].

## 10.3 Major clinical issues with somatoform disorders and cannabis/hallucinogen use

- There is currently little rigorous evidence to indicate what the role of cannabis might be in managing pain.
- In the absence of other proven forms of treatment, CBT is, at present, the most widely employed form of treatment for cannabis use.
- Somatoform disorders are best managed behaviourally and with cognitive therapy.

### *10.3.1 Effects of cannabis and other hallucinogens on somatoform disorders*

- Cannabis may have a beneficial effect on pain[409]. However, there is currently little rigorous evidence (by way of randomised controlled trials) to indicate what the role of cannabis might be in managing pain[410-414].
- Despite this, cannabis is one of the most commonly used substances among individuals with somatoform disorders[415]. It may be used by individuals with somatoform or pain disorders in an attempt to alleviate pain or as an antiemetic to relieve nausea associated with opioid use[409, 412, 416].

### 10.3.2 Interactions between cannabis and therapeutic agents for somatoform disorders

- Cannabis can exacerbate the sedative effects of tricyclic antidepressants and benzodiazepines which increase the risk of impaired driving and injury as well as overdose✖.
- Cannabis, benzodiazepines, opioids and antidepressants are metabolised by CYP 450 enzymes which may result in the inhibition or induction of each drug group. Therefore, individuals should be monitored closely to ensure outcomes are appropriate and people are not experiencing increased sedation✖.

### 10.3.3 Management approaches for comorbid somatoform disorders and cannabis and other hallucinogen use

- Abstinence from cannabis is a difficult goal to achieve in cannabis dependent people[128].
- In the absence of other proven forms of treatment, CBT is, at present, the most widely employed form of treatment for cannabis use****[128].
- Somatoform disorders are best managed behaviourally and with cognitive therapy****[380-386].
- There is currently no research that reports the effect of CBT on both cannabis use and somatoform disorders.
- Use of antidepressants may be required for comorbid depression and anxiety***[406, 407], with tricyclics being useful[377] in aiding chronic tension headaches and fibromyalgia.

## 10.4 Major clinical issues with somatoform disorders and alcohol use

- Alcohol is one of the most commonly used substances by people with somatoform disorders.
- If alcohol consumption is hazardous or harmful, then the person should be counselled accordingly.
- Look for links between the patient's symptomatology and alcohol use so that insight can be raised.
- Acamprosate and naltrexone are both effective in the management of alcohol dependence and maintaining abstinence.

### 10.4.1 Effects of alcohol on somatoform disorders

- Alcohol is one of the most commonly used substances by people with somatoform disorders[404, 415].
- People with somatoform disorders may self medicate with alcohol to mask pain or to reduce anxiety symptoms[379], as do people with organic physical pain and primary anxiety disorders.
- Alcohol use and intermittent withdrawal may result in exacerbation of a variety of physical symptoms particularly associated with anxiety[10, 18-23, 404].

### 10.4.2 Interactions between alcohol and therapeutic agents for somatoform disorders

- Benzodiazepines, opioids and antidepressants are metabolised by CYP 450 enzymes which may result in the inhibition or induction of each drug group. Therefore, individuals should be monitored closely to ensure they are receiving the appropriate therapeutic effect and not experiencing increased sedation✖.
- Alcohol can exacerbate the sedative effects of any sedative agents (including tricyclic antidepressants and mirtazepine, benzodiazepines and opioids) used in the treatment of somatoform disorders. Alcohol toxicity and risk of overdose may occur through the inhibition of CYPs by sedative antidepressant involved in the metabolism of alcohol[133] or increase in sedation as a result of combinations of alcohol and benzodiazepines or opioids✖.
- Disulfiram and acamprosate used to treat alcohol dependence are unlikely to interact with antidepressants or with opioids if these are being used✖[229].
- Acamprosate and benzodiazepines do not appear to interact with one another✖[230].

### 10.4.3 Management approaches to comorbid somatoform disorders and alcohol use

- Individuals with pain disorders may be taking benzodiazepines or opioids[377, 404].
- If alcohol consumption is hazardous or harmful, then the person should be counselled accordingly.
- Try to raise patient awareness of any links between their symptoms and their alcohol use.
- Somatoform disorders are best managed behaviourally and with cognitive therapy****[380-386].
- Alcohol intoxication will interfere with CBT and any structured problem solving or motivational therapy.
- Acamprosate and naltrexone are both effective in the management of alcohol dependence and maintaining abstinence****[141, 144, 235, 236].
- If the patient is taking opioid agonists for pain relief, the use of nalrexone to control alcohol consumption will block the therapeutic effect of opioid antagonists✖✖✖.
- Antidepressants may be required for comorbid depression and anxiety***[406, 407], with tricyclics being useful[377] for aiding chronic tension headaches and fibromyalgia.

## 10.5 Major clinical issues with somatoform disorders and opioid use

- Emphasis should always be placed on non-medication management of the somatoform disorder as a first line of treatment.
- CBT has shown reductions in somatic symptoms and improved functioning in people with somatoform disorders.
- The patient should be managed with the assistance of a clinical psychologist with experience in the management of pain.
- If exercise and rehabilitation avoidance behaviours are present, then the help of a physiotherapist with experience in the area will be required.
- People with somatoform and pain disorders frequently use opioids. Due to the chronic nature of the pain and subsequent opioid use, dependence is common.
- However, long-term opioid use can result not only in tolerance but can actually cause pain hypersensitivity, potentially exacerbating somatic symptoms.
- Methadone itself has the potential to increase plasma concentrations of benzodiazepines and increase their sedative effects.
- Several deaths have been reported due to benzodiazepine use in conjunction with high dose buprenorphine and may be a result of similar metabolic interactions.
- Fluvoxamine×××, fluoxetine××, norfluoxetine×× and paroxetine× can inhibit buprenorphine and methadone metabolism through inhibition of the CYPs involved in their metabolism.



### 10.5.1 Effects of opioids on somatoform disorders

- People with somatoform and pain disorders frequently use opioids. Opioids have analgesic, hypnotic and sedative effects – characteristics that are often sought after or are rewarding for patients with somatoform disorders (particularly pain). There is also evidence that opioids are more likely to be prescribed to people with pain who demonstrate anxiety or depression during an interview[417, 418].
- Due to the chronic nature of the pain and subsequent opioid use, dependence is common[377, 403, 404].
- However, long-term opioid use can result not only in tolerance but can actually cause pain hypersensitivity[419], potentially exacerbating somatic symptoms.

### 10.5.2 Interactions between opioids and therapeutic agents for somatoform disorders

- Opioids, benzodiazepines and antidepressants are metabolised by CYP 450 enzymes which may result in the inhibition or induction of each drug group. Therefore, individuals should be monitored closely to ensure they are receiving the appropriate therapeutic effect and not experiencing increased sedation which may result in impaired driving, injury and, in extreme cases, overdose.
- Combinations of sedative antidepressants such as tricyclics, opioids and benzodiazepines will increase the risk of sedation, overdose, impaired driving and injury.

- Methadone itself has been shown to inhibit CYP3A4✖✖[240, 241], which also metabolises many benzodiazepines. This has the potential to increase plasma concentrations of benzodiazepines and increase their sedative effects✖[242, 243].
- Several deaths have been reported due to benzodiazepine use in conjunction with high dose buprenorphine and may be a result of similar metabolic interactions✖✖✖[244-246].
- Fluvoxamine✖✖✖, fluoxetine✖✖, norfluoxetine✖✖ and paroxetine✖ can inhibit buprenorphine and methadone metabolism through inhibition of the CYPs involved in their metabolism[148-150]. This can result in an increase in plasma opioid pharmacotherapy concentrations and potential overdose. This can be a particular issue during induction onto methadone; however, the risk may persist even after stabilisation has occurred✖✖✖[151-155].
- Fluvoxamine is the most potent inhibitor of methadone and buprenorphine metabolism and is the most clinically relevant. Therefore, it should be avoided✖✖✖[150].
- Fluoxetine and paroxetine should also be avoided✖✖.
- Citalopram and sertraline are the least likely SSRIs to have cytochrome mediated drug interactions; however, due to the theoretical potential for an interaction, caution should still be used and individuals monitored closely✖[156].

### *10.5.3 Management approaches to comorbid somatoform disorders and opioid use*

- Emphasis should always be placed on non-medication management of the somatoform disorder as a first line of treatment[377] when the resources are available and the client is willing to engage.
- CBT has shown reductions in somatic symptoms and improved functioning in people with somatoform disorders[380-386].
- The risk of dependence should be assessed if opioids are to be used. Risk factors for dependence include[420]:
  - A personal history of substance dependence.
  - A family history of substance dependence.
  - Age less than 45 years.
  - History of pre-adolescent sexual abuse.
  - Current psychological problems.
- The advice of a specialist pain clinic while optimal, is not always readily available. However, this type of clinic will provide a multi-disciplinary approach to the management of the patient's pain that is not readily available in general practice.
- If opioid dependence is identified, then this needs to be discussed with the patient and their readiness for change identified.
- The patient should be managed with the assistance of a clinical psychologist with experience in the management of pain.

- If exercise and rehabilitation avoidance behaviours are present, then the help of a physiotherapist with experience in the area will be required.
- If opioid analgesics are used, then:
  - Long-acting opioids are preferable.
  - Daily or weekly dispensing of opioids may assist with controlling use (observed single daily dosing may be required).
  - Use of methadone as part of a formalised program will allow probable control of the pain and the drug-seeking lifestyle.
- Use of antidepressants may be required for comorbid depression and anxiety***[406, 407] with tricyclics being useful[377], for aiding with chronic tension headaches and fibromyalgia.

## 10.6 Major clinical issues with somatoform disorders and stimulant (including methamphetamine) use

- If stimulants are used to treat symptoms of chronic fatigue, tolerance frequently develops with continued use, and there is a significant risk of developing dependence.
- MAO-Is (either irreversible or reversible) are contraindicated in people using amphetamines or MDMA due to risk of serotonin syndrome. Deaths have been associated with concurrent use of moclobemide and MDMA.
- Brief interventions and motivational interviewing for stimulant use are recommended.
- CBT can be used to address both the stimulant use and the somatoform disorder.
- Antidepressants may be required for comorbid depression and anxiety.



### *10.6.1 Effects of stimulants on somatoform disorders*

- Stimulants may cause a variety of sympathetic nervous system related symptoms[421, 422] that may be confused with symptoms of somatoform disorders. However, these are generally short lived, are related to drug intoxication and resolve as drug concentrations decline.
- Evidence regarding the effect of stimulants on fatigue in patients with chronic fatigue syndrome is inconsistent[423-425]. However, as symptoms are generally long lived, and tolerance to stimulants frequently develops with continued use, there is a significant risk of developing dependence.

### *10.6.2 Interactions between stimulants and therapeutic agents for somatoform disorders*

- MAO-Is (either irreversible or reversible) are contraindicated in people using amphetamines or MDMA due to risk of serotonin syndrome (Appendix 1). Deaths have been associated with concurrent use of moclobemide and MDMA✖✖✖[181, 182].

- Stimulant drugs are likely to exacerbate the effects of SSRI and SNRI antidepressants (and vice versa) and may result in serotonin syndrome (Appendix 1)✖[127, 179, 180]. Patients should be warned of signs of serotonin syndrome and be monitored.
- Fluoxetine, norfluoxetine, paroxetine and sertraline are potential inhibitors of CYP 2D6 which metabolises MDMA and methamphetamine. This may result in elevated plasma concentrations leading to toxicity✖.

### *10.6.3Management approaches to comorbid somatoform disorders and stimulant use*

- The use of stimulants at any level should be discouraged due to the risk of dependence and most importantly the possibility of increased chances of toxicity. The patient needs to be guided towards this realisation and readiness for change determined.
- Brief interventions and motivational interviewing for stimulant use are recommended.
- CBT can be used to address both the stimulant use***[49, 183] and the somatoform disorder****[380-386].
- There are no available studies that have reported the effectiveness of CBT in managing both stimulant use and somatoform disorders.
- Use of antidepressants may be required for comorbid depression and anxiety***[406, 407] with tricyclics being useful[377], for aiding with chronic tension headaches and fibromyalgia.
- Links between the stimulant use and the particular somatoform disorder should be sought.

## 10.7 Major clinical issues with somatoform disorders and benzodiazepine use

- People with somatoform disorders often use benzodiazepines to alleviate anxiety symptoms or to moderate pain, frequently resulting in benzodiazepine dependence.
- Emphasis should always be placed on non-medication management of the somatoform disorder as a first line of treatment.
- CBT has shown reductions in somatic symptoms and improved functioning in people with somatoform disorders.
- In general, use of benzodiazepines should be discouraged due to its dependence potential and psychomotor effects.

### *10.7.1 Effects of benzodiazepines on somatoform disorders*

- People with somatoform disorders often use benzodiazepines to alleviate anxiety symptoms or to moderate pain, frequently resulting in benzodiazepine dependence[377, 404].
- Short-acting benzodiazepines, in particular, may result in fluctuating plasma concentrations. These may result in exacerbation of anxiety symptoms when levels are low resulting in frequent attendances at health services.

### 10.7.2 Interactions between benzodiazepines and therapeutic agents for somatoform disorders

- Benzodiazepines, opioids and antidepressants are metabolised by CYP 450 enzymes which may result in the inhibition or induction of each drug group. Therefore, individuals should be monitored closely to ensure they are receiving the appropriate therapeutic effect and not experiencing increased sedation which may result in impaired driving, injury and, in extreme cases, overdose✖.
- Methadone itself has been shown to inhibit CYP3A4✖✖(240, 241) which also metabolises many benzodiazepines. This has the potential to increase plasma concentrations of benzodiazepines and increase their sedative effects✖(242, 243).
- Several deaths have been reported due to benzodiazepine use in conjunction with high dose buprenorphine and may be a result of similar metabolic interactions✖✖✖(244-246).
- Fluvoxamine✖✖✖, fluoxetine✖✖, norfluoxetine✖✖ and paroxetine✖ can inhibit buprenorphine and methadone metabolism through inhibition of the CYPs involved in their metabolism(148-150). This can result in an increase in plasma opioid pharmacotherapy concentrations and potential overdose. This can be a particular issue during induction onto methadone; however, the risk may persist even after stabilisation has occurred✖✖✖(151-155).
- Fluvoxamine is the most potent inhibitor of methadone and buprenorphine metabolism and is the most clinically relevant, therefore, it should be avoided✖✖✖(150).
- Fluoxetine and paroxetine should also be avoided✖✖.
- Citalopram and sertraline are the least likely SSRIs to have cytochrome mediated drug interactions; however, due to the theoretical potential for an interaction, caution should still be used and individuals monitored closely✖(156).

### 10.7.3 Management approaches to comorbid somatoform disorders and benzodiazepine use

- Emphasis should always be placed on non-medication management of the somatoform disorder as a first line of treatment when the resources are available and the client is willing to engage.
- CBT has shown reductions in somatic symptoms and improved functioning in people with somatoform disorders ****(380-386).
- In general, use of benzodiazepines should be discouraged due to its dependence potential and psychomotor effects.
- If large quantities of benzodiazepines (e.g. 40mg diazepam daily equivalent) are being consumed, then inpatient withdrawal to lower levels should be considered to avoid and manage seizure risk(194).
- If dependence has developed, then graduated withdrawal through slow reduction of dosage should be commenced ****(194-196), possibly after transferring the patient onto a long acting benzodiazepine.
- If long-term benzodiazepine use is indicated, then:
  - This should be subject to a contract with the patient.
  - Authorities should be advised, including registration with the relevant local government health authority.

  - The seeking of additional benzodiazepines from other prescribers should be monitored (e.g. using the *Authority to release personal PBS claims information to a third party* form).
  - Daily or weekly dispensing of benzodiazepines should be considered and may assist with controlling use.

- If the person is ready for change and willing to engage in CBT specifically for their somatoform disorder, then minimisation of benzodiazepine dosage is required so that the CBT can have greater effectiveness.
- Benzodiazepines are frequently prescribed to induce 'muscle relaxation'. However, large doses are often required (up to 40mg diazepam equivalents per day) which will not be conducive to rehabilitation.
- Use of antidepressants may be required for comorbid depression and anxiety***[406, 407], with tricyclics being useful[377] for aiding chronic tension headaches and fibromyalgia.

## 10.8 Major clinical issues with somatoform disorders and inhalant/solvent use

### *10.8.1 Effects of inhalants/solvents on somatoform disorders*

- There is a dearth of information concerning reports of comorbid inhalant use and somatoform disorders.
- It is likely that the two conditions do not often co-exist because inhalant and solvent use occurs more commonly in younger people and somatoform disorders more frequently occur in older people.

### *10.8.2 Interactions between inhalants/solvents and therapeutic agents for somatoform disorders*

- The sedative effects of antidepressants, opioids and benzodiazepines may be exacerbated by inhalants and may possibly result in severe sedation and overdose✖.

### *10.8.3 Management approaches to comorbid somatoform disorders and inhalant/solvent use*

- There appears to be no literature that sheds light on managing people with both somatoform disorders and problems relating to inhalant/solvent use.
- As with most other substances, inhalant users should be encouraged to try and reduce or cease use.
- In general, with respect to inhalant/solvent use[65]:
  - Outline the harms associated with inhalant/solvent use.
  - Investigate polysubstance use as this is common.

- Standard CBT approaches to both sets of issues should be used, with particular attention to the development of:
  - Assertiveness skills (refusal skills).
  - Coping skills for controlling and managing emotions such as anger and sadness.
- Offer alternatives to inhalant use, for example, recreational activities.
- Community reinforcement approaches should be developed by mobilising the local health and welfare service system in individual care plans.
- Family interventions need to be considered, for example, increasing communication between the person and the family.
- Assertive outreach and follow-up may be required.

# 11 Gambling and substance use

## 11.1 Gambling

Problem gambling affects a large proportion of the population[426-429]. Pathological gambling is listed in the DSM-IV as an impulse control disorder. These disorders are initially driven by pleasure, arousal and gratification.

Recurrent gambling behaviour causes significant disruptions in personal, family, social and vocational pursuits[426-429]. People preoccupied with gambling may report that they are seeking action or an aroused, euphoric state, more so than the money itself[426, 428].

The features of pathological gambling are persistent. Over time, patients develop unpleasant feelings, physiological activation and dysphoria which are relieved when the compulsive behaviour is undertaken.

In a manner similar to substance use disorders, as the opportunities for gambling increase (e.g. easily accessible internet gambling can be likened to an increase in the 'supply' of a substance of misuse), so does the proportion of the population that develops gambling associated problems. Hence, gambling disorders and problem gambling continue to rise[426, 428-430].

Gambling addictions typically begin in early adolescence in males and later in life for females[428, 431]. Males are significantly more likely to experience gambling-related problems than females[431-436].

Gambling is a complex phenomenon and may also be viewed as:

- An addiction:
  - Tolerance can develop as people feel the need to spend increasing amounts of time and money in order to achieve the same level of excitement[426, 428].
  - Withdrawal symptoms can occur on cessation of gambling and can resolve on recommencement of gambling[426, 428].
  - Self medication theories of other mental disorders are also applied to gambling as they can be to chemical substances of addiction[426, 428].

There is evidence, however, that gambling behaviours persist over time in contrast to substance use related problems which become less prevalent as people age[68, 432, 437].

- An affective disorder.
- A specific type of obsessive compulsive disorder.

The above theories have provided the theoretical rationale for the use of certain pharmacological agents to treat people affected by problem gambling[427, 438].

The clinical course of gambling can be separated into three phases[428].

- **Winning:** Wins are greatly dramatised and losses are often forgotten about and even denied.
- **Losing:** The individual begins to gamble less cautiously in an attempt to win back lost finances and impending losses mount.

- **Desperation:** Gambling is frequently associated with criminality and legal problems in an attempt to gain more money to gamble[428, 439, 440]. Debts grow, individuals may be prosecuted and guilt and depression set in leading to suicide.

### *Management approaches*

- Treatment of problem gambling is often delayed due to cognitive distortions and denial[428].
- Few clinicians are skilled in the area of treatment of problem gambling[430].
- CBT, in particular, exposure therapy is effective at reducing problem gambling ****[441-443].
- Motivational approaches are also effective when used in the treatment of problem gambling ***[444].
- Pharmacological treatments for gambling are more effective than no treatment or placebo ****[445].
- There are three broad classes of pharmacological agents used in an attempt to treat and manage problem gambling. These are antidepressants, opioid antagonists and mood stabilisers[438, 445, 446].
- There appears to be no significant difference in outcome between the three main classes of pharmacological interventions used ****. However, it may be that some people with problem gambling with specific comorbidities may benefit more from certain drug interventions than others[445].

#### Antidepressants

##### *SSRIs*

- SSRIs have been used when problem gambling is viewed as an OCD or an affective disorder[427].
- If there is any benefit, doses of SSRIs used in the treatment of gambling may need to be higher and require administration for longer periods of time before a response is observed[428, 447].
- The effect of SSRIs appear to be independent of underlying depressive symptoms ***[447-450].
- Fluvoxamine ***[448, 451] and citalopram *[450] have been shown to significantly improve overall gambling severity [reduced urge to gamble, reduced number of days gambled, reduced amount of money lost]. Results for paroxetine are mixed[449, 452].
- SSRIs are well tolerated when used for these indications[448, 453].

##### *Other antidepressants*

- Bupropion is also effective in reducing gambling scale scores as well as global functioning scale scores and is as effective as naltrexone in producing full responders to gambling treatment ***[454].
- Note: Bupropion is not currently indicated for problem gambling in Australia.

#### Opioid antagonists

The mechanism by which naltrexone may be effective in reducing problem gambling is by reducing the urge to gamble ****[454-456].

**Mood stabilisers and anticonvulsants**

- A study of small numbers of people using mood stabilisers for the treatment of gambling alone (valproate and lithium) has shown promise in reducing gambling. However, few conclusions are able to be drawn from this single study**[457].
- Topiramate is as effective in reducing gambling as fluvoxamine with even more individuals in full remission following topirimate than fluoxetine, as well as higher treatment compliance following topiramate***[458].
- Note: Topiramate is not currently indicated for problem gambling in Australia.

## 11.2 Comorbidity with gambling

### *11.2.1 Gambling and substance use*

- There is a high prevalence of current and lifetime substance use amongst people who are affected by problem gambling, exceeding that of the general population[426, 428, 431, 432, 435-437, 443, 459-462].
- There is also a strong correlation between the severity of substance use and the severity of problem gambling, with higher rates and severity of substance use being predictive of more severe gambling problems and vice versa[23, 365, 367, 428, 429, 433, 463].
- Substance use can be a significant discriminator between people with problematic versus non-problematic gambling. The greater the number of substances used the more severe the gambling problems experienced[367, 463, 464].
- Problem gambling is often associated with increased impulsivity, antisocial tendencies as well as the inability to control anger[426, 465-468].
- Gambling at an earlier age increases the risk of multiple addictions and risky behaviour[437].
- People with comorbid substance use and gambling problems experience increased impulsivity which leads to further poor decision making[428].
- Impaired impulse control and poor risk assessment occurs with both gambling and substance use disorders[365, 428].
- Failure to treat comorbid substance use disorders in gambling may lead to higher gambling relapse rates[428].
- People with comorbid substance use and gambling problems are more likely to report other psychiatric histories[433].

### *11.2.2 Gambling and mental disorders*

- Increased gambling is associated with reduced mental health status[469]. The majority of people with problem gambling have more than one psychiatric disorder[459].
- The causative relationship between comorbid problem gambling and other mental disorders has not been clearly established:
  - Gambling may be pursued to relieve anxiety[428] and depression[429].
  - Early onset problematic gambling is associated with pre-existing depression[470].
  - Mental disorders such as depression and anxiety may develop or be exacerbated by gambling[428].
  - People most at risk for problem gambling are those with major mental disorders who often experience significant social isolation and separation[429].
  - Use of psychiatric medication has shown a decline following behavioural and motivational treatment of problem gambling[464]. This suggests that anxiety and depression may be secondary to gambling, at least in some people.
- Women are more likely than men to have additional mood or anxiety disorders and use gambling to escape depressed moods[428, 431, 471]. Women with problem gambling are also significantly more likely to seek treatment for their mood or anxiety disorder[431].
- Affective disorders are more common amongst people who are affected by problem gambling compared to the general population[428, 429, 432, 434, 437, 440, 459, 462, 465, 466, 469, 471-478].
- Gambling is more common amongst people with bipolar disorder than the general population[462, 479].
- Higher rates of anxiety are also correlated with more severe gambling problems[23, 480].
- There are also increased rates of obsessive compulsive disorders in people with problem gambling[427, 428, 438, 459, 460, 481].
- As mentioned above, problem gambling is also highly correlated with personality disorders, particularly antisocial, borderline and obsessive compulsive personality disorders[428, 435, 437, 465, 470, 471, 482, 483].
- Problem gambling is associated with high comorbidity of other impulse control disorders (including kleptomania, impulsive shopping and impulsive sexual behaviour), as well as purging type eating disorders[364-367, 432, 462, 484].

### *11.2.3 Gambling and suicide*

- Problem gambling is often associated with increased suicidal ideation and attempts compared to the general population[427-429, 432, 437, 472, 476, 477, 485].
- Early onset problem gambling increases lifetime risk of suicide[470].
- However, gambling-related suicide attempts are usually made by older people with problem gambling[485].
- Both comorbid substance use[432, 433] and comorbid mental disorders increase the risk of suicide in people with problem gambling[485].

### 11.2.4 General management approaches to comorbidity

- A history of past substance use and mental disorders does not lessen the effectiveness of current treatment for gambling[464].
- People with current substance use as well as problem gambling must avoid replacing one addiction with the other[436].
- People with problem gambling and bipolar spectrum disorder show significant improvement on gambling thoughts, urges and behaviour as well as in manic behaviour while taking lithium***[486].
- SSRIs as a combined treatment may be effective in treating co-occurring anxiety and gambling*[487] as well as depression.

## 11.3 Major clinical issues with gambling and cannabis/hallucinogen use

- There is a significant association between cannabis use and problem gambling, with more severe problem gambling being associated with greater intensity of cannabis use and vice versa.
- CBT approaches that target both gambling and cannabis use may be effective in people with comorbid cannabis use disorders and problem gambling.

### 11.3.1 Effects of cannabis and other hallucinogens on problem gambling

- As is the case with the general population, cannabis is the most commonly used illicit substance amongst people with problem gambling[432, 464, 488].
- There is a significant association between cannabis use and problem gambling with more severe problem gambling being associated with greater intensity of cannabis use and vice versa[365, 436, 440, 443, 464, 468, 470].
- Additional hallucinogen use is also reported by people with problem gambling although not to the same extent as cannabis[432, 464].

### 11.3.2 Interactions between cannabis and other hallucinogens and therapeutic agents for problem gambling

- Cannabis can exacerbate the sedative effects of tricyclic antidepressants and mood stabilisers (lithium and sodium valproate). This increases the risk of impaired driving and injury as well as overdose✖.
- LSD may induce a serotonin syndrome (Appendix 1), therefore caution should be exercised when prescribing SSRIs or MAO-I✖[127].
- Cannabis and antidepressants are metabolised by CYP 450 enzymes which may result in the inhibition or induction of either drug group. Therefore, individuals should be monitored closely to ensure responses are within the therapeutic range✖.

### 11.3.3 Management approaches to comorbid problem gambling and cannabis use

- Abstinence from cannabis is a difficult goal to achieve in cannabis dependent people[128].
- In the absence of other proven forms of treatment, CBT is, at present, the most widely employed form of treatment for cannabis use****[128].
- CBT, in particular, exposure therapy is effective at reducing problem gambling****[441-443].
- CBT approaches that target both gambling and cannabis use may be effective in people with comorbid cannabis use disorders and problem gambling. However, studies are yet to confirm this.

## 11.4 Major clinical issues with gambling and alcohol use

- Problem gambling and alcohol use frequently co-occur.
- Comorbid gambling and alcohol use increase the risk of suicide.
- Alcohol can exacerbate the sedative effects of tricyclic antidepressants and mood stabilisers (lithium and sodium valproate).
- Alcohol consumption will interfere with the effectiveness of exposure based treatments for gambling.
- As naltrexone has been shown to improve problem gambling, it may be an effective treatment to manage both problem gambling and alcohol consumption.
- CBT that addresses both gambling behaviour and alcohol use may also be an effective treatment for comorbid problem gambling and alcohol consumption.

### 11.4.1 Effects of alcohol on problem gambling

- Problem gambling and alcohol use frequently co-occur, with alcohol use being the most common substance used in people with problem gambling[432, 433, 435, 460, 462, 464, 468, 478, 483, 488, 489].
- Increased severity of problem gambling is associated with heavy drinking[23, 365, 431, 434, 440, 466, 467, 469, 470, 490].
- Alcohol consumption results in increased rates of play in gambling and prolongs gambling episodes[491, 492].
- Comorbid gambling and alcohol use increase the risk of suicide[493].

### 11.4.2 Interactions between alcohol and therapeutic agents for problem gambling

- Alcohol can exacerbate the sedative effects of tricyclic antidepressants and mood stabilisers (lithium and sodium valproate). This increases the risk of impaired driving and injury as well as overdose✖.
- Alcohol can exacerbate the sedative effects of some antidepressants including tricyclic antidepressants and mirtazepine. Alcohol toxicity and risk of overdose may occur through the inhibition of CYPs by sedative antidepressants involved in the metabolism of alcohol✖[133].
- Interactions between antidepressants and acamprosate used to treat alcohol dependence are minimal as are interactions between antidepressants and disulfiram and naltrexone also used to treat alcohol dependence[134].

### 11.4.3 Management approaches to comorbid problem gambling and alcohol use

- Alcohol consumption will interfere with the effectiveness of exposure based treatments for gambling.
- If large quantities of alcohol are being consumed, then inpatient withdrawal or detoxification should always be considered to avoid and manage seizure risk. Concerns about benzodiazepine dependence should not prevent controlled prescribing for withdrawal states.
- Benzodiazepine use should be monitored and minimised as those with substance use disorders are at a greater risk of abusing benzodiazepines[196].
- Acamprosate and naltrexone are both effective in the management of alcohol dependence and maintaining abstinence****[141, 144, 235, 236].
- As naltrexone has been shown to improve problem gambling****[454-456], it may be an effective treatment to manage both problem gambling and alcohol consumption****[235, 236, 494]. However, large scale trials are yet to confirm this.
- SSRIs may be effective in managing problem gambling***[448, 450, 451], particularly in those people with comorbid alcohol use and depression***[130, 135-137]. However, large scale trials are yet to confirm this.
- CBT, in particular exposure therapy, is effective at reducing problem gambling****[441-443].
- CBT that addresses both gambling behaviour and alcohol use may also be an effective treatment for comorbid problem gambling and alcohol consumption.

## 11.5 Major clinical issues with gambling and opioid use

- Heroin use is relatively rare among people with problem gambling. The use of prescription opioids is more common.
- However, problem gambling is prevalent among people on methadone maintenance.
- Buprenorphine impairs decision-making less than methadone maintenance in opioid dependent individuals and may therefore be more beneficial when used to manage people with opioid dependence and problem gambling.

### 11.5.1 Effects of opioids on problem gambling

- Heroin use is relatively rare among people with problem gambling[464]. The use of prescription opioids is more common[432, 464].
- However, amongst people on methadone maintenance:
  - Problem gambling is prevalent[495, 496].
  - People with problem gambling are more likely to use other substances when compared with people whose gambling is non-problematic[495].
  - Problem gambling negatively impacts program retention rates[495].
  - People with problem gambling report poorer mental health status than people whose gambling is not problematic[496].

### 11.5.2 Interactions between opioids and therapeutic agents for problem gambling

- Opioids can exacerbate the sedative effects of tricyclic antidepressants and mood stabilisers (lithium and sodium valproate). This increases the risk of impaired driving and injury as well as overdose✖.
- Fluvoxamine✖✖✖, fluoxetine✖✖, norfluoxetine✖✖ and paroxetine✖ can inhibit buprenorphine and methadone metabolism through inhibition of the CYPs involved in their metabolism[148-150]. This can result in an increase in plasma opioid pharmacotherapy concentrations and potential overdose. This can be a particular issue during induction onto methadone; however, the risk may persist even after stabilisation has occurred✖✖✖[151-155].
- Fluvoxamine is the most potent inhibitor of methadone and buprenorphine metabolism and is the most clinically relevant, therefore, it should be avoided✖✖✖[150].
- Fluoxetine and paroxetine should also be avoided✖✖.
- Citalopram and sertraline are the least likely SSRIs to have cytochrome mediated drug interactions. However, due to the theoretical potential for an interaction, caution should still be used and individuals monitored closely✖[156].

### 11.5.3 Management approaches to comorbid problem gambling and opioid use

- As naltrexone has been shown to improve problem gambling****[454-456] and be effective in the management of opioid dependence***[497], it may be useful in the treatment of comorbid problem gambling and opioid dependence. However, there have been no studies to confirm this and compliance is likely to be an issue.
- Buprenorphine improves decision making compared to methadone maintenance in opioid dependent individuals**[498]and may therefore be more beneficial when used to manage people with opioid dependence and problem gambling.

## 11.6 Major clinical issues with gambling and stimulant (including methamphetamine) use

- Stimulant users are frequently affected by problem gambling.
- MAO-Is (either irreversible or reversible) are contraindicated in people using amphetamines or MDMA. Deaths have been associated with concurrent use of moclobemide and MDMA.

### *11.6.1 Effects of stimulants on problem gambling*

- Rates of stimulant use are higher in people with problem gambling than the general population[488]. Stimulant users are frequently affected by problem gambling[439].
- Stimulants may increase risk taking and impulsivity[338, 339] and are therefore likely to adversely affect people with problem gambling.
- Stimulants are amongst the most commonly used illicit substances by people with problem gambling[432, 464].

### *11.6.2 Interactions between stimulants and therapeutic agents for problem gambling*

- Stimulant drugs are likely to exacerbate the effects of SSRI and SNRI antidepressants, in particular (and vice versa), and may result in serotonin syndrome (Appendix 1)✖[127, 179, 180]. Patients should be warned of signs of serotonin syndrome and be monitored.
- MAO-Is (either irreversible or reversible) are contraindicated in people using amphetamines or MDMA. Deaths have been associated with concurrent use of moclobemide and MDMA✖✖✖[181, 182].
- Fluoxetine, norfluoxetine, paroxetine and sertraline are potential inhibitors of CYP 2D6 which metabolises MDMA and methamphetamine. This may result in elevated plasma concentrations leading to toxicity✖.

### *11.6.3 Management approaches to comorbid problem gambling and stimulants use*

- Formal drug detoxification should be considered if the person is dependent on stimulants.
- CBT is effective in reducing stimulant use***[49, 183] as well as problem gambling****[441-443] and an approach that integrates treatments for both conditions may be more effective in managing comorbid stimulant use and problem gambling. This is yet to be investigated.

## 11.7 Major clinical issues with gambling and benzodiazepine use

- Benzodiazepines will interfere with response to psychological treatments in a dose-related manner.
- Benzodiazepine use should be discouraged and reduced. Cessation should be a long-term goal with the introduction of alternative management strategies.

### *11.7.1 Effects of benzodiazepines on problem gambling*

- Comorbid benzodiazepine use and gambling is not commonly reported.
- High doses of benzodiazepines (or low doses combined with alcohol) can increase risk taking, impulsive behaviours[499] and cognitive impairment, all of which are likely to result in adverse consequences in people with problem gambling.

### *11.7.2 Interactions between benzodiazepines and therapeutic agents for problem gambling*

- Benzodiazepines can exacerbate the sedative effects of tricyclic antidepressants, and mood stabilisers (lithium and sodium valproate). This increases the risk of impaired driving and injury as well as overdose✖.
- Benzodiazepines and antidepressants are both metabolised by CYP 450 enzymes which may result in the inhibition or induction of either drug group. Therefore, individuals should be monitored closely to ensure they are experiencing the appropriate therapeutic effect✖.
- Fluvoxamine will inhibit the metabolism of alprazolam, midazolam, triazolam and diazepam causing increased sedation and potential toxicity✖.
- Citalopram and sertraline are the least likely SSRIs to have cytochrome mediated drug interactions✖.

### *11.7.3 Management approaches to comorbid problem gambling and benzodiazepine use*

- Benzodiazepines will interfere with response to psychological treatments in a dose-related manner[196].
- Benzodiazepine use should be discouraged and reduced. Cessation should be a long-term goal with the introduction of alternative management strategies.
- If large quantities of benzodiazepines (e.g. 40mg diazepam daily equivalent or more) are being consumed, then inpatient withdrawal to lower levels should be considered to avoid and manage seizure risk[194].
- If dependence has developed, then graduated withdrawal through slow reduction of dosage should be commenced****[194-196], possibly after transferring the patient onto a long acting benzodiazepine.

- If long-term benzodiazepine use is indicated, then:
  - This should be subject to a contract with the patient.
  - Authorities should be advised, including registration with the relevant local government health authority.
  - The seeking of additional benzodiazepines from other prescribers should be monitored (e.g. using the *Authority to release personal PBS claims information to a third party* form).
  - Daily or weekly dispensing of benzodiazepines should be considered and may assist with controlling use.

## 11.8 Major clinical issues with gambling and inhalant/solvent use

### *11.8.1 Effects of solvents/inhalants on problem gambling*

Inhalant use is relatively rare among people with problem gambling[464] and appears to be one of the least misused classes of substances reported by people with problem gambling[432, 485].

### *11.8.2 Interactions between solvents/inhalants and therapeutic agents for problem gambling*

- Inhalants can exacerbate the sedative effects of tricyclic antidepressants, and mood stabilisers (lithium and sodium valproate). This increases the risk of impaired driving and injury as well as overdose✖.
- Most antidepressants reduce seizure threshold. Therefore, risks should be appraised prior to commencement✖.

### *11.8.3 Management approaches to comorbid problem gambling and inhalant/solvent use*

- As with most other substances, inhalant users should be encouraged to try and reduce or cease use.
- In general, with respect to inhalant/solvent use[65]:
  - Outline the harms associated with inhalant/solvent use.
  - Investigate polysubstance use as this is common.
- Standard CBT approaches to both sets of issues should be used, with particular attention to the development of:
  - Assertiveness skills (refusal skills).
  - Coping skills for controlling and managing emotions such as anger and sadness.
- Offer alternatives to inhalant use, for example, recreational activities.
- Community reinforcement approaches should be developed by mobilising the local health and welfare service system in individual care plans.
- Family interventions need to be considered, for example, increasing communication between the person and the family.
- Assertive outreach and follow-up may be required.

# 12 Brain injury, mental disorders and substance use

## 12.1 Brain injury

Brain injury can occur as a result of head trauma or through a variety of other physiological and biochemical mechanisms:

- Head trauma can result in both open and closed head injuries.
- Acceleration/ deceleration forces on the brain can result in both macroscopic and microscopic lesions such as diffuse axonal injury.
- The brain's response to trauma can result in local metabolic changes that seem to worsen the initial trauma-related injury.
- Other physiological or biochemical changes to the brain that cause injury include direct toxicity from substances such as alcohol and volatile solvents, hypoxia and hypoglycaemia.

It is important to consider the impact of brain injury on each individual. Those who experience brain injury may be less resilient pre-injury and are frequently those who have the least ability to cope with the associated lifestyle changes following brain injury.

- Certain personality traits or disorders (e.g. those characterised by impulsivity or violence) can result in a higher risk of brain injury.
- Brain injury may occur as a result of attempted suicide related to psychosis or depression.
- There is a strong relationship between substance use and brain injury, but the order of causality remains unclear.
- Emotional and psychiatric disturbances, especially depression, are common after brain injury among those who have a past history of brain injury.
- People who have experienced traumatic brain injury have been shown to have increased rates of suicide, suicidal ideation, suicide attempts and completed suicide.
- There is some evidence that rates of post-brain injury substance use does not actually increase over the longer term and, in fact, may even decline.



## 12.2 Do mental disorders predispose individuals to brain injury?

Mental disorders have been associated with an increased risk of brain injury[500].

Certain personality traits or disorders can result in a higher risk of brain injury. For example[501]:

- Impulsivity and risk taking or novelty seeking combined with low harm-avoidance behaviour may result in head trauma from falls or road traffic accidents.
- Impulsivity may result in unintentional overdose in inexperienced substance users[354].
- Tendency towards violence as a means of resolving conflict will result in a greater likelihood of head trauma.

Brain injury may occur as a result of attempted suicide[502] related to psychosis or depression. Such suicide attempts may result in both head trauma from jumping from heights or intentional road crashes, through to drug overdose or poisoning-related direct toxicity[351, 354].

## 12.3 Does substance use predispose individuals to brain injury?

Substance use (including alcohol, cannabis and other illicit substances) has been associated with brain injury. Up to 40% of individuals with a brain injury have been found to meet DSM-IV criteria for substance use disorders prior to the injury. Conversely, 68% of people with a substance use disorder have also been found to have had some sort of previous head injury[503, 504].

While there is a strong relationship between substance use and brain injury, the order of causality remains unclear[504-506]. Some debate also remains as to whether substance use or its severity is an actual predictor of brain injury[507, 508].

The risk of brain injury as a result of increased impulsivity and risk taking or novelty seeking behaviour associated with underlying personality traits may be exacerbated by substance use. Combined with low harm avoidance, this increased impulsivity can result in head trauma from falls or accidents or unintentional overdose[2, 501].

Substance dependence may result in attempted suicide due to the inability to cope with the negative consequences of such dependence[351, 501, 507, 509].

Brain injury can also result from:

- The direct effects of substances on the brain (e.g. frontal lobe dysfunction, cerebellar dysfunction).
- Indirect effects such as hypertension resulting in stroke.
- Secondary nutritional deficiencies such as thiamine deficiency resulting in Wernicke-Korsakoff syndrome.

Patients with brain injury and alcohol use disorders have been shown to have significantly reduced grey matter volumes compared with brain injured patients without alcohol use disorders[508]. The question is whether an initial brain injury predisposes people to an increased risk of subsequent alcohol or other substance-induced brain injury.

## 12.4 Does brain injury predispose individuals to mental disorders or to suicide?

### *12.4.1 Brain injury and mental disorders*

- Emotional and psychiatric disturbances are common following brain injury, with those who have a past history of brain injury being diagnosed with a significantly greater number of psychiatric disorders. This association seems to apply to those within the general population who have been identified as having had a head injury, as well as specific patient populations attending brain injury rehabilitation services[503, 506, 510, 511].
- There is controversy as to whether pre-brain injury psychiatric morbidity is predictive of post-psychiatric morbidity[503, 504, 506, 511, 512]. Some authors have postulated that individuals with no pre-brain-injury psychiatric history may actually be more likely to develop post-brain injury psychiatric morbidity as they are likely to experience greater lifestyle changes[504].

- The most frequently reported psychological challenge following brain injury is depression, with increased rates observed in individuals with a history of brain injury[503-505, 507, 512-516].
- Occurrence of depression appears to be unrelated to severity of brain injury[504, 505, 512, 514, 516, 517].
- Emotional disturbances following brain injury are disruptive both socially and occupationally and greatly affect daily functioning. Individuals who experience brain injury and depression have been observed to have generally poorer health outcomes (both physically and emotionally). They report higher levels of psychosocial dysfunction, psychological distress, neurobehavioural and cognitive dysfunction, including memory problems, and also have diminished life satisfaction[503, 506, 512, 516-518].
- There is significant debate as to whether depression following brain injury is an episodic event and perhaps a normal phase in the overall initial adjustment to brain injury, or whether depression following brain injury is a long-term disorder. There appears to be a lack of correlation between the time after injury and the onset of depression. It is suggested that depression may occur at any time following brain injury with no clearly defined time line for resolution[504, 505, 512-516].
- Resolution of depression following brain injury is accompanied by improvement in psychosocial functioning and perceived enhancement of one's health[512].
- Increased rates of anxiety following brain injury have also been observed, most commonly in people with PTSD, panic and OCD (e.g. writing and checking lists to compensate for cognitive disabilities)[503-506, 514].
- Anxiety disorders are more likely to present as comorbidity with other Axis 1 diagnoses[503, 504, 512].
- Comorbidity with mental disorders following brain injury is common, with more than one psychiatric disorder being identifiable in many individuals[503, 504, 512, 514].
- The incidence of psychiatric disorders such as bipolar disorder and schizophrenia following brain injury more closely resembles that of the general population and is much less prevalent than depression and anxiety following brain injury[503, 504, 506, 514].

**Implications for management**

- Considering that mental disorders are common following brain injury, post-brain injury management should routinely include a psychological assessment.
- Assessments should be undertaken at regular intervals following brain injury. It is important to try to establish what the mental health of the patient was prior to the injury and, particularly, to assess for the presence of anxiety and depression on an ongoing basis after the injury[504, 512, 514-516].
- People who have experienced brain injury, as well as their families, should be made aware of the risk of experiencing a mental disorder in the future. This should be done whether or not the patient had mental health problems prior to the injury[504].
- Individuals may present with hidden brain injury where the patient does not associate a connection between current problems and a previous brain injury. Brain injury-related symptoms such as problems with memory, attention, fatigue, the processing of multiple stimuli and impulse control may not be managed appropriately[506]. Therefore, the possibility of brain injury in people presenting with non-specific cognitive type problems should be considered by the clinician.

- Early identification and treatment of depression following a brain injury may directly improve outcome and quality of life. Considering the effects of depression on cognitive impairment in those with brain injury[512, 516, 517], detection and appropriate management of depression may allow cognitive therapy approaches for brain injury to be more effective.
- A number of motor, sensory and cognitive deficits overlap with the vegetative features of depression and may lead to over-diagnosis of depression. Similarly, there is significant symptom overlap with post-concussive syndrome[505]. Feelings of hopelessness, worthlessness and anhedonia which are more specific features of depression that should be looked for by the clinician[516, 519].

### *12.4.2 Brain injury and suicide*

- People who have experienced traumatic brain injury have been shown to have increased rates of suicidal ideation, suicide attempts and completed suicide. This increased risk has been attributed to both the presence of a mental disorder and to the problems associated with adjustment to living with a brain injury[501, 505, 506, 510].
- Individuals with brain injury employ a wide range of diverse methods to commit suicide[520].
- Suicide following brain injury may be the result of multiple factors: the suddenness of onset of disability in previously healthy individuals, the global effects of disability, grief over the loss of a pre-injury lifestyle, the growing realisation of the effort involved in maintaining a similar level of functioning to that prior to brain injury, as well as a reduced level of neuropsychological coping mechanisms[510, 520].
- Emotional and psychiatric disturbances and suicide ideation following brain injury have been shown to be significant predictors of suicide attempts[510].
- Thoughts of hopelessness may be a stronger predictor of suicide ideation than the presence of depression alone[505, 510].
- There is uncertainty about whether suicidal ideation is related to the severity of brain injury *per se* or whether it is related to the person's assessment of the effects of the injury.
- Pre-injury history of suicide attempts does not seem to confer additional increased risk post-injury[501, 510].
- In parallel with the observations of the timing of depression following brain injury, the risk of suicide does not diminish but may fluctuate over time following brain injury[501, 505, 510]. Years of disappointment can set in and the individual may have to face the confronting fact that they will not return to full pre-morbid functioning [501].

**Implications for management**

- The main clinical concern is the prevention of suicide[520].
- There are increased numbers of individuals accessing GP services following brain injury; therefore, the GP is in an ideal position to monitor the patient's mental state and suicide risk[519].
- Individuals with brain injury may present for medical reasons and may not reveal suicidal ideation[519].

- Assessment needs to involve seeking a history of pre-brain injury:
  - Suicidal behaviour.
  - Substance use.
  - Psychological disorders.
- Assessment needs to include a history of post-brain injury suicide attempts as these are far more predictive of suicide risk following brain injury.
- Post-brain injury management needs to include continuous and extended monitoring of warning signs for risk of suicide, including:
  - Symptoms of hopelessness and suicidal ideation[510, 519].
  - Signs that the individual is not adjusting to life following brain injury.
- To prevent isolation, there is a need to continuously monitor the individual's support networks, including social and familial. There is also a need to provide education to individual and support networks in relation to difficulties that may be encountered following brain injury[519, 520].
- As individuals with brain injury may attempt suicide using a range of methods. It is important to reduce lethality where possible by:
  - Identifying the safest approach for prescribing, dispensing and administering medications[519].
  - Ensuring that people at risk have minimal access to weapons such as firearms[519].

## 12.5 Does brain injury predispose individuals to substance use?

The relationship between brain injury and post-brain injury substance use (including alcohol, cannabis and other illicit substances) is still unclear and, as mentioned, causality remains uncertain. Those with a brain injury have been shown to have higher lifetime rates of substance use than those without[506].

On the other hand, there is some evidence that rates of post-brain injury substance use does not increase[508, 514] and, in fact, may even decline[504]. However, post-brain injury mood disorders are closely linked to post-brain injury alcohol use disorders and people with both have a poorer prognosis[508].

Interestingly, several studies have shown increased rates of substance use within a year of brain injury that resolve in later years. It has been suggested that substance use may be used as an initial coping mechanism and may resolve itself as coping mechanisms improve over time[511, 514].

There is also controversy as to whether the severity of brain injury is a predictor of post-brain injury substance use. Some patients who have relapsed back into substance use following brain injury have been observed to have significantly more frequent and more severe brain injuries than those who remained abstinent[504, 508].

Substance dependent individuals with brain injury have more clinically-rated depressive symptoms and self-reported somatic symptoms and are more likely to attempt suicide[501, 507]. Therefore, it is important to ensure that substance use is managed following brain injury.

**Implications for management**

- In parallel to mental disorders after brain injury, there is a need for consumer-based education regarding long-term substance use risk after brain injury, regardless of the individual's previous substance use history[504].
- Substance use should be monitored along with indicators of mental disorders and suicide risk. The clinician should intervene if the substance use becomes problematic.

## 12.6 Does brain injury impact on treatment approaches to mental disorders and substance use?

- The treatment of mental disorders following brain injury is not well understood.
- It is vital to actively manage mental disorders following brain injury as individuals with post-brain injury history of emotional distress and substance use are the most likely to attempt suicide.
- Sertraline has been shown to be effective in treating depression following brain injury.
- It is important to minimise side effects as brain-injured clients may not have the coping mechanisms to deal with the side effects of psychotropic medications.
- CBT has been shown to be effective in managing acute stress disorder following mild brain injury.
- A level of substance use that may be regarded as 'low risk' in the general population may carry a significantly higher risk for a person who has experienced a brain injury.
- Pharmacotherapy treatments for substance use may also have a variable effect on individuals who have experienced brain injury.

### *12.6.1 Approaches to substance use*

Every brain injury affects individuals in different ways. It is difficult to predict the full extent of the injury and the effects it may have on different neurotransmitter and metabolic systems. The effect of continued substance use following brain injury is also difficult to predict. However, there is evidence that levels of dysfunction are worse in those who have had a history of pre-brain injury substance-use disorders, (for instance alcohol), who relapse following brain injury[508].

In addition, a level of substance use that may be regarded as 'low risk' in the general population may carry a significantly higher risk for a person who has experienced a brain injury:

- Individuals need to be counselled on the possible increased risk associated with substance use post-injury.
- It is important to consider the variable cognitive abilities, insight and degree of impulse control when counselling the person who has experienced brain injury[512, 514, 516]. These variables will influence the choice of psychological approaches to the person following brain injury.

- Similarly, pharmacotherapy treatments for substance use may also have a variable effect on individuals who have experienced brain injury due to altered metabolic or neurotransmitter pathways[521]. Pharmacotherapies that may be effective in one individual may not be effective in another who has experienced brain injury.
- As the brain recovers following injury, the effectiveness of pharmacotherapies for substance use and the severity of side effects may change over time within the one individual.
- The sedative effects of benzodiazepines used for acute symptomatic relief during substance withdrawal and opioids such as methadone may be exacerbated in people with brain injury. Therefore, they may increase the risk of overdose✖.

### *12.6.2 Approaches to mental disorders*

Available evidence on the treatment of mental disorders following brain injury is scarce. Studies are generally uncontrolled and have mixed results. An overlap between brain injury sequelae and the features of mental disorder will inevitably have implications for diagnosis and treatment planning.

Treatment is usually based on what works best from clinical experience[522].

- Clinicians need to carefully assess individuals with mental disorders for past history of brain injury[506]. Comorbid brain injury is a frequent problem for people with a mental disorder. Their risk of self harm is higher than for those people without comorbid brain injury.
- People with both a mental disorder and a brain injury may need additional cognitive and psychotherapeutic interventions that are not usually available to people who only have psychiatric diagnoses.
- In a similar fashion to management of individuals with substance use issues following brain injury, pharmacotherapy-based treatments for individuals with mental disorders and brain injury need to be assessed on an individual basis. The risk–benefit balance of drug-based treatments may be quite different in those with brain injury. There may be significant variation from one person to another due to altered metabolic or neurotransmitter pathways[521].
- In addition, the risk–benefit balance may, in fact, change over time within the individual as the healing process continues and the brain recovers from injury. Therefore, a medication that may have been effective in relieving depressive symptoms immediately following brain injury may not be effective after an extended period of time, or vice versa. This would account for the overall inconsistencies observed in the treatment effectiveness of psychopharmacological drugs following brain injury[523].
- There is also evidence that medications administered to control mental disorders following brain injury may, depending on their mechanisms of action and timing of administration, have a neuroprotective effect. However, they may also slow the recovery process[524].
- It is important to minimise side effects as brain-injured clients may not have the coping mechanisms to deal with the side effects of psychotropic medications.
- It is vital to actively manage mental disorders following brain injury as individuals with post-brain injury history of emotional distress and substance use are the most likely to attempt suicide[519]. Resolution of depression (whether spontaneous or in response to treatment) following brain injury is accompanied by improvement in psychosocial functioning and perceived enhancement of one's

health[512]. Active treatment of depression following brain injury significantly improves emotional functioning and general mental health, physical functioning, sleep and vitality, and social, work and family functioning. Such treatment may also reduce unexplained somatic symptoms, perception of illness severity and disability, and subsequent illness behaviour[500].

- With doses similar to those used in the general population, sertraline (SSRI) has been shown to be effective in treating depression following brain injury***[523, 525, 526]:
  - Decreases in overall psychological distress have been observed along with minimal side effects***[523, 525]. This is promising, as individuals with brain injury do not usually present with symptoms that fall into strict DSM-IV criteria but with an array of symptoms such as depression and anxiety [519, 525].
  - Similarly, sertraline has been shown to significantly decrease the burden of post-concussive symptoms*[500].
  - If sertraline decreases psychological distress across many domains and minimises the impact of post-concussive syndrome, then it may not be as important to make a strict diagnosis (which may not be possible anyway) following brain injury. In addition, screening for and treating depression in patients with persistent post-concussive symptoms may be an effective way to decrease unnecessary suffering and reduce excess disability[500].
- The sedative effects of antipsychotics, mood stabilisers, benzodiazepines and sedative antidepressants such as tricyclics may be exacerbated in people with brain injury. Therefore, they may increase the risk of overdose✖.
- CBT has been shown to be effective in managing acute stress disorder following mild brain injury****[527]. However, the cognitive capacities of the individual need to be considered before undertaking this line of treatment.

For further information please consult:

*Alcohol related brain injury: A guide for general practitioners and other health workers*[528]

*Clinical practice guidelines for the care of people living with traumatic brain injury in the community*[529]:

http://www.lifetimecare.nsw.gov.au/default.aspx?MenuID=49

Brain Injury Australia:

http://www.braininjuryaustralia.org.au/

# 13 Bibliography


1. Green, A. I. (2006) Treatment of schizophrenia and comorbid substance abuse: pharmacologic approaches. *Journal of Clinical Psychiatry*, 67 Suppl 7, 31-5; quiz 6-7.
2. Kavanagh, D. J., McGrath J., Saunders J. B., Dore G., Clark D. (2002) Substance misuse in patients with schizophrenia: epidemiology and management. *Drugs*, 62, 743-55.
3. Grilo, C. M., Sinha R., O'Malley S S. Eating disorders and alcohol use disorders. In: Health, ed. 2002:151-60.
4. Degenhardt, L., Hall W., Lynskey M. (2003) Exploring the association between cannabis use and depression. *Addiction*, 98, 1493-504.
5. Harder, V. S., Morral A. R., Arkes J. (2006) Marijuana use and depression among adults: Testing for causal associations. *Addiction*, 101, 1463-72.
6. Patton, G. C., Coffey C., Carlin J. B., Degenhardt L., Lynskey M., Hall W. (2002) Cannabis use and mental health in young people: cohort study. *British Medical Journal*, 325, 1195-8.
7. Buckner, J. D., Bonn-Miller M. O., Zvolensky M. J., Schmidt N. B. (2007) Marijuana use motives and social anxiety among marijuana-using young adults. *Addictive Behaviors*, 32, 2238-52.
8. Buckner, J. D., Mallott M. A., Schmidt N. B., Taylor J. (2006) Peer influence and gender differences in problematic cannabis use among individuals with social anxiety. *Journal of Anxiety Disorders*, 20, 1087-102.
9. Hayatbakhsh, M. R., Najman J. M., Jamrozik K., Mamun A. A., Alati R., Bor W. (2007) Cannabis and anxiety and depression in young adults: a large prospective study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 46, 408-17.
10. Lipschitz, D. S., Rasmusson A. M., Anyan W., Gueorguieva R., Billingslea E. M., Cromwell P. F. *et al.* (2003) Posttraumatic stress disorder and substance use in inner-city adolescent girls. *The Journal of Nervous and Mental Disease*, 191, 714-21.
11. Sareen, J., Chartier M., Paulus M. P., Stein M. B. (2006) Illicit drug use and anxiety disorders: findings from two community surveys. *Psychiatry Research*, 142, 11-7.
12. Zvolensky, M. J., Bernstein A., Sachs-Ericsson N., Schmidt N. B., Buckner J. D., Bonn-Miller M. O. (2006) Lifetime associations between cannabis, use, abuse, and dependence and panic attacks in a representative sample. *Journal of Psychiatric Research*, 40, 477-86.
13. Zvolensky, M. J., Bonn-Miller M. O., Bernstein A., McLeish A. C., Feldner M. T., Leen-Feldner E. W. (2006) Anxiety sensitivity interacts with marijuana use in the prediction of anxiety symptoms and panic-related catastrophic thinking among daily tobacco users. *Behaviour Research and Therapy*, 44, 907-24.
14. D'Souza, D. C., Perry E., MacDougall L., Ammerman Y., Cooper T., Wu Y. T. *et al.* (2004) The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology*, 29, 1558-72.
15. Krystal, J. H., D'Souza D. C., Madonick S., Petrakis I. L. (1999) Toward a rational pharmacotherapy of comorbid substance abuse in schizophrenic patients. *Schizophrenia Research*, 35 Suppl, S35-S49.
16. Haw, C., Houston K., Townsend E., Hawton K. (2001) Deliberate self-harm patients with alcohol disorders: characteristics, treatment, and outcome. *Crisis*, 22, 93-101.
17. Manwell, L. B., Czabala J. C., Ignaczak M., Mundt M. P. (2004) Correlates of depression among heavy drinkers in Polish primary care clinics. *International Journal of Psychiatry in Medicine*, 34, 165-78.

18. Abrams, K., Kushner M., Medina K. L., Voight A. (2001) The pharmacologic and expectancy effects of alcohol on social anxiety in individuals with social phobia. *Drug and Alcohol Dependence*, 64, 219-31.

19. Liappas, J., Paparrigopoulos T., Tzavellas E., Christodoulou G. (2003) Alcohol detoxification and social anxiety symptoms: a preliminary study of the impact of mirtazapine administration. *Journal of Affective Disorders*, 76, 279-84.

20. Schuckit, M. A., Tipp J. E., Bergman M., Reich W., Hesselbrock V. M., Smith T. L. (1997) Comparison of induced and independent major depressive disorders in 2,945 alcoholics. *The American Journal of Psychiatry*, 154, 948-57.

21. Schuckit, M. A., Tipp J. E., Bucholz K. K., Nurnberger J. I., Jr., Hesselbrock V. M., Crowe R. R. *et al.* (1997) The life-time rates of three major mood disorders and four major anxiety disorders in alcoholics and controls. Addiction, 92, 1289-304.

22. Sinha, R., Robinson J., O'Malley S. (1998) Stress response dampening: effects of gender and family history of alcoholism and anxiety disorders. *Psychopharmacology (Berl)*, 137, 311-20.

23. Ste-Marie, C., Gupta R., Derevensky J. L. (2006) Anxiety and social stress related to adolescent gambling behavior and substance use. *Journal of Child and Adolescent Substance Use*, 15, 55-74.

24. Ahmadi, J., Farrashbandi H., Majdi B., Mahdavi S., Babaee M. A., Menzies P. *et al.* (2005) Prevalence of Mood and Anxiety Diorders in a Sample of Iranian Outpatient Opioid Addicts. *German Journal of Psychiatry*, 5-7.

25. Ahmadi, M., Ahmadi J. (2005) Substance-Induced Anxiety Disorder In Opioid Dependents. *Addictive Disorders and Their Treatment*, 4, 157-9.

26. Darke, S., Ross J., Williamson A., Mills K. L., Havard A., Teesson M. (2007) Patterns and correlates of attempted suicideby heroin users over a 3-year period: findings from the Australian treatment outcome study. *Drug and Alcohol Dependence*, 87, 146-52.

27. Wild, T. C., el-Guebaly N., Fischer B., Brissette S., Brochu S., Bruneau J. *et al.* (2005) Comorbid depression among untreated illicit opiate users: results from a multisite Canadian study. *Canadian Journal of Psychiatry*, 50, 512-8.

28. Clark, H. W., Masson C. L., Delucchi K. L., Hall S. M., Sees K. L. (2001) Violent traumatic events and drug abuse severity. *Journal of Substance Abuse Treatment*, 20, 121-7.

29. Valentiner, D. P., Mounts N. S., Deacon B. J. (2004) Panic attacks, depression and anxiety symptoms, and substance use behaviors during late adolescence. *Journal of Anxiety Disorders*, 18, 573-85.

30. Curran, C., Byrappa N., McBride A. (2004) Stimulant psychosis: systematic review. *The British Journal of Psychiatry*, 185, 196-204.

31. Krystal, J. H., Perry E. B., Jr., Gueorguieva R., Belger A., Madonick S. H., Abi-Dargham A. *et al.* (2005) Comparative and interactive human psychopharmacologic effects of ketamine and amphetamine: implications for glutamatergic and dopaminergic model psychoses and cognitive function. *Archives of General Psychiatry*, 62, 985-94.

32. Landabaso, M. A., Iraurgi I., Jimenez-Lerma J. M., Calle R., Sanz J., Gutierrez-Fraile M. (2002) Ecstasy-induced psychotic disorder: six-month follow-up study. *European Addiction Research*, 8, 133-40.

33. Lin, S. K., Ball D., Hsiao C. C., Chiang Y. L., Ree S. C., Chen C. K. (2004) Psychiatric comorbidity and gender differences of persons incarcerated for methamphetamine abuse in Taiwan. *Psychiatry and Clinical Neurosciences*, 58, 206-12.

34. Ujike, H. (2002) Stimulant-induced psychosis and schizophrenia: the role of sensitization. *Current Psychiatry Reports*, 4, 177-84.

35. Ujike, H., Sato M. (2004) Clinical features of sensitization to methamphetamine observed in patients with methamphetamine dependence and psychosis. *Annals of the New York Academy of Sciences*, 1025, 279-87.

36. Yui, K., Ikemoto S., Goto K., Nishijima K., Yoshino T., Ishiguro T. (2002) Spontaneous recurrence of methamphetamine-induced paranoid-hallucinatory states in female subjects: susceptibility to psychotic states and implications for relapse of schizophrenia. *Pharmacopsychiatry*, 35, 62-71.

37. Yui, K., Ikemoto S., Ishiguro T., Goto K. (2000) Studies of amphetamine or methamphetamine psychosis in Japan: relation of methamphetamine psychosis to schizophrenia. *Annals of the New York Academy of Sciences*, 914, 1-12.

38. Yui, K., Ishiguro T., Goto K., Ikemoto S., Kamata Y. (1999) Spontaneous recurrence of methampetamine psychosis: increased sensitivity to stress associated with noradrenergic hyperactivity and dopaminergic change. *European Archives of Psychiatry and Clinical Neuroscience*, 249, 103-11.

39. Curran, H. V., Travill R. A. (1997) Mood and cognitive effects of +/-3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'): week-end 'high' followed by mid-week low. *Addiction*, 92, 821-31.

40. Falck, R. S., Carlson R. G., Wang J., Siegal H. A. (2006) Psychiatric disorders and their correlates among young adult MDMA users in Ohio. *Journal of Psychoactive Drugs*, 38, 19-29.

41. Falck, R. S., Wang J., Carlson R. G., Siegal H. A. (2006) Prevalence and correlates of current depressive symptomatology among a community sample of MDMA users in Ohio. *Addictive Behaviors*, 31, 90-101.

42. Gerra, G., Zaimovic A., Giucastro G., Maestri D., Monica C., Sartori R. *et al.* (1998) Serotonergic function after (+/-)3,4-methylene-dioxymethamphetamine ('Ecstasy') in humans. *International Clinical Psychopharmacology*, 13, 1-9.

43. Lamers, C. T., Bechara A., Rizzo M., Ramaekers J. G. (2006) Cognitive function and mood in MDMA/THC users, THC users and non-drug using controls. *Journal of Psychopharmacology*, 20, 302-11.

44. MacInnes, N., Handley S. L., Harding G. F. (2001) Former chronic methylenedioxymethamphetamine (MDMA or ecstasy) users report mild depressive symptoms. *Journal of Psychopharmacology*, 15, 181-6.

45. McCardle, K., Luebbers S., Carter J. D., Croft R. J., Stough C. (2004) Chronic MDMA (ecstasy) use, cognition and mood. *Psychopharmacology (Berl)*, 173, 434-9.

46. McGregor, C., Srisurapanont M., Jittiwutikarn J., Laobhripatr S., Wongtan T., White J. M. (2005) The nature, time course and severity of methamphetamine withdrawal. *Addiction*, 100, 1320-9.

47. Parrott, A. C. (2001) Human psychopharmacology of Ecstasy (MDMA): a review of 15 years of empirical research. *Human Psychopharmacology*, 16, 557-77.

48. Parrott, A. C., Lasky J. (1998) Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. *Psychopharmacology (Berl)*, 139, 261-8.

49. Peck, J. A., Reback C. J., Yang X., Rotheram-Fuller E., Shoptaw S. (2005) Sustained reductions in drug use and depression symptoms from treatment for drug abuse in methamphetamine-dependent gay and bisexual men. *Journal of Urban Health*, 82, i100-i8.

50. Soar, K., Turner J. J., Parrott A. C. (2006) Problematic versus non-problematic ecstasy/MDMA use: the influence of drug usage patterns and pre-existing psychiatric factors. *Journal of Psychopharmacology*, 20, 417-24.

51. Sumnall, H. R., Cole J. C. (2005) Self-reported depressive symptomatology in community samples of polysubstance misusers who report Ecstasy use: a meta-analysis. *Journal of Psychopharmacology*, 19, 84-92.

52. Verheyden, S. L., Hadfield J., Calin T., Curran H. V. (2002) Sub-acute effects of MDMA (+/-3,4-methylenedioxymethamphetamine, "ecstasy") on mood: evidence of gender differences. *Psychopharmacology (Berl)*, 161, 23-31.

53. Vincent, N., Schoobridge J., Ask A., Allsop S., Ali R. (1998) Physical and mental health problems in amphetamine users from metropolitan Adelaide, Australia. *Drug and Alcohol Review*, 17, 187-95.

54. Williamson, S., Gossop M., Powis B., Griffiths P., Fountain J., Strang J. (1997) Adverse effects of stimulant drugs in a community sample of drug users. *Drug and Alcohol Dependence*, 44, 87-94.

55. Huizink, A. C., Ferdinand R. F., van der Ende J., Verhulst F. C. (2006) Symptoms of anxiety and depression in childhood and use of MDMA: prospective, population based study. *British Medical Journal*, 332, 825-8.

56. Parrott, A. C., Buchanan T., Scholey A. B., Heffernan T., Ling J., Rodgers J. (2002) Ecstasy/MDMA attributed problems reported by novice, moderate and heavy recreational users. *Human Psychopharmacology*, 17, 309-12.

57. Helmus, T. C., Tancer M., Johanson C. E. (2005) Reinforcing effects of diazepam under anxiogenic conditions in individuals with social anxiety. *Experimental and Clinical Psychopharmacology*, 13, 348-56.

58. Kasper, S., Resinger E. (2001) Panic disorder: the place of benzodiazepines and selective serotonin reuptake inhibitors. *European Neuropsychopharmacology*, 11, 307-21.

59. Nelson, J., Chouinard G. (1999) Guidelines for the clinical use of benzodiazepines: pharmacokinetics, dependency, rebound and withdrawal. Canadian Society for Clinical Pharmacology. *The Canadian Journal of Clinical Pharmacology*, 6, 69-83.

60. Duggal, H. S., Sinha B. N., Nizamie S. H. (2000) Gasoline inhalation dependence and bipolar disorder. *The Australian and New Zealand Journal of Psychiatry,* 34, 531-2.

61. Jung, I. K., Lee H. J., Cho B. H. (2004) Persistent psychotic disorder in an adolescent with a past history of butane gas dependence. *European Psychiatry*, 19, 519-20.

62. Shu, L. R., Tsai S. J. (2003) Long-term glue sniffing: report of six cases. *International Journal of Psychiatry in Medicine*, 33, 163-8.

63. Kubik, M. Y., Lytle L. A., Birnbaum A. S., Murray D. M., Perry C. L. (2003) Prevalence and correlates of depressive symptoms in young adolescents. *American Journal of Health Behavior*, 27, 546-53.

64. Ridenour, T. A. (2005) Inhalants: not to be taken lightly anymore. *Current Opinion in Psychiatry*, 18, 243-7.

65. National Inhalant Abuse Taskforce, D. P. a. S. B., Victorian Department of Human Services. National Directions On Inhalant Abuse Final report. In: Ageing Ha, ed. Melbourne: Victorian Government Department of Human Services 2006.

66. Zwar, N., Richmond R., Borland R., Stillman S., Cunningham M., Litt J. Smoking Cessation Guidleines for Australian General Practice. In: Ageing Ha, ed. 2004.

67. Jablensky, A., McGrath J., Herrman H., Castle D., Gureje O., Morgan V. *et al.* People with psychotic illness: An Australian study 1997-98. An overveiw, National Mental Health Strategy. 1999.

68. McLennan, W. Mental Health and Wellbeing: Profile of Adults, Australia. In: Statistics ABo, ed. Canberra: Australian Government Publishing Service 1997.

69. Jorm, A. F. (1999) Association between smoking and mental disorders: results from an Australian National Prevalence Survey. *Australian and New Zealand Journal of Public Health*, 23, 245-8.

70. Ragg, M., Ahmed T. (2007) Smoking and Mental Health: A review of the literature.

71. Adler, L. E., Hoffer L. D., Wiser A., Freedman R. (1993) Normalization of auditory physiology by cigarette smoking in schizophrenic patients. *The American Journal of Psychiatry,* 150, 1856-61.

72. Buckley, T. C., Holohan D. R., Mozley S. L., Walsh K., Kassel J. (2007) The effect of nicotine and attention allocation on physiological and self-report measures of induced anxiety in PTSD: a double-blind placebo-controlled trial. *Experimental and Clinical Psychopharmacology*, 15, 154-64.

73. Feldner, M. T., Babson K. A., Zvolensky M. J. (2007) Smoking, traumatic event exposure, and post-traumatic stress: a critical review of the empirical literature. *Clinical Psychology Review*, 27, 14-45.

74. Feldner, M. T., Babson K. A., Zvolensky M. J., Vujanovic A. A., Lewis S. F., Gibson L. E. *et al.* (2007) Posttraumatic stress symptoms and smoking to reduce negative affect: an investigation of trauma-exposed daily smokers. Addictive Behaviors, 32, 214-27.

75. Lyon, E. R. (1999) A review of the effects of nicotine on schizophrenia and antipsychotic medications. *Psychiatric Services*, 50, 1346-50.

76. McNeill, A. (2001) Smoking and metnal health: A review of the literature. Smoke Free London and Action on Smoking and Health.

77. Barnes, M., Lawford B. R., Burton S. C., Heslop K. R., Noble E. P., Hausdorf K. *et al.* (2006) Smoking and schizophrenia: is symptom profile related to smoking and which antipsychotic medication is of benefit in reducing cigarette use? The Australian and New Zealand Journal of Psychiatry, 40, 575-80.

78. Anzengruber, D., Klump K. L., Thornton L., Brandt H., Crawford S., Fichter M. M. *et al.* (2006) Smoking in eating disorders. Eating Behaviors, 7, 291-9.

79. George, A., Waller G. (2005) Motivators for Smoking in Women with Eating Disorders. *European Eating Disorders Review*, 13, 417-23.

80. Maldonado-Molina, M. M., Komro K. A., Prado G. (2007) Prospective association between dieting and smoking initiation among adolescents. *American Journal of Health Promotion*, 22, 25-32.

81. White, M. A., McKee S. A., O'Malley S S. (2007) Smoke and mirrors: magnified beliefs that cigarette smoking suppresses weight. *Addictive Behaviors*, 32, 2200-10.

82. Benowitz, N. L. Nicotine Safety and Toxicity: Oxford University Press 1998.

83. Lubman, D. I., Sundram S. (2003) Substance misuse in patients with schizophrenia: a primary care guide. *Medical Journal of Australia*, 178 Suppl, S71-5.

84. NSW Health Department, N. S. W. H. D. Guide for the management of nicotine dependent inpatients: summary of evidence. 2002.

85. Ashton, M. E., Weston M. K. A Smoking Cessation Program for People with Mental Illness. *The Australian and New Zealand Mental Health Services Conference.* Sydney, Australia 2002.

86. Ashton, M. E., Weston M. K., Condon S. Tobacco and mental illness project. Adelaide: The Queen Elizabeth Hospital 1998-1999.

87. Lawn, S. J. Systemic barriers to quitting smoking among institutionalised public mental health service populations. Adelaide: Flinders University of South Australia; 2001.

88. Lucksted, A., Dixon L. B., Sembly J. B. (2000) A Focus Group Pilot Study of Tobacco Smoking Among Psychosocial Rehabilitation Clients. *Psychiatric Services*, 51, 1544-8.

89. Lawn, S. J. (2001) Australians with mental illness who smoke. *The British Journal of Psychiatry*, 178, 85.

90. Lawn, S. J., Pols R. G., Barber J. G. (2002) Smoking and Quitting: A Qualitative Study with Community-Living Psychiatric Clients. *Social Science and Medicine*, 1, 93-104.

91. Prochaska, J. J., Rossi J. S., Redding C. A., Rosen A. B., Tsoh J. Y., Humfleet G. L. *et al.* (2004) Depressed smokers and stage of change: implications for treatment interventions. *Drug and Alcohol Dependence*, 76, 143-51.

92. Brown, R. A., Kahler C. W., Niaura R., Abrams D. B., Sales S. D., Ramsey S. E. *et al.* (2001) Cognitive-behavioral treatment for depression in smoking cessation. *Journal of Consulting and Clinical Psychology*, 69, 471-80.

93. Chou, K. R., Chen R., Lee J. F., Ku C. H., Lu R. B. (2004) The effectiveness of nicotine-patch therapy for smoking cessation in patients with schizophrenia. *International Journal of Nursing Studies*, 41, 321-30.

94. Cox, L. S., Patten C. A., Niaura R. S., Decker P. A., Rigotti N., Sachs D. P. *et al.* (2004) Efficacy of bupropion for relapse prevention in smokers with and without a past history of major depression. *Journal of General Internal Medicine*, 19, 828-34.

95. Evins, A. E., Cather C., Rigotti N. A., Freudenreich O., Henderson D. C., Olm-Shipman C. M. *et al.* (2004) Two-year follow-up of a smoking cessation trial in patients with schizophrenia: increased rates of smoking cessation and reduction. *Journal of Clinical Psychiatry*, 65, 307-11; quiz 452-3.

96. George, T. P., Vessicchio J. C., Sacco K. A., Weinberger A. H., Dudas M. M., Allen T. M. *et al.* (2007) A Placebo-Controlled Trial of Bupropion Combined with Nicotine Patch for Smoking Cessation in Schizophrenia. *Biological Psychiatry*.

97. George, T. P., Vessicchio J. C., Termine A., Bregartner T. A., Feingold A., Rounsaville B. J. *et al.* (2002) A placebo controlled trial of bupropion for smoking cessation in schizophrenia. *Biological Psychiatry*, 52, 53-61.

98. Hall, S. M., Tsoh J. Y., Prochaska J. J., Eisendrath S., Rossi J. S., Redding C. A. *et al.* (2006) Treatment for cigarette smoking among depressed mental health outpatients: a randomized clinical trial. *American Journal of Public Health,* 96, 1808-14.

99. Hertzberg, M. A., Moore S. D., Feldman M. E., Beckham J. C. (2001) A preliminary study of bupropion sustained-release for smoking cessation in patients with chronic posttraumatic stress disorder. *Journal of Clinical Psychopharmacology*, 21, 94-8.

100. Horn, K., Dino G., Kalsekar I., Massey C. J., Manzo-Tennant K., McGloin T. (2004) Exploring the relationship between mental health and smoking cessation: a study of rural teens. *Prevention Science*, 5, 113-26.

101. Kisely, S., Campbell L. A. (2008) Use of smoking cessation therapies in individuals with psychiatric illness : an update for prescribers. *CNS Drugs*, 22, 263-73.

102. Bobo, J. K., McIlvain H. E., Lando H. A., Walker R. D., Leed-Kelly A. (1998) Effect of smoking cessation counseling on recovery from alcoholism: findings from a randomized community intervention trial. *Addiction*, 93, 877-87.

103. Hitsman, B., Abrams D. B., Shadel W. G., Niaura R., Borrelli B., Emmons K. M. *et al.* (2002) Depressive symptoms and readiness to quit smoking among cigarette smokers in outpatient alcohol treatment. *Psychology of Addictive Behaviors*, 16, 264-8.

104. Begg, S., Vos T., Barker B., Stevenson C., Stanley L., Lopez A. D. The burden of disease and injury in Australia 2003. In: Welfare AIoHa, ed. Canberra 2007.

105. Prochaska, J. J., Delucchi K., Hall S. M. (2004) A meta-analysis of smoking cessation interventions with individuals in substance abuse treatment or recovery. *Journal of Consulting and Clinical Psychology*, 72, 1144-56.

106. Reid, M. S., Fallon B., Sonne S., Flammino F., Nunes E. V., Jiang H. *et al.* (2007) Smoking cessation treatment in community-based substance abuse rehabilitation programs. *Journal of Substance Abuse Treatment*.

107. El-Guebaly, N., Cathcart J., Currie S., Brown D., Gloster S. (2002) Smoking cessation approaches for persons with mental illness or addictive disorders. *Psychiatric Services*, 53, 1166-70.

108. Lee, N., Coonan D., Dunlop A., Stephens R., Ritter A. Clinical Treatment Guidelines for Alcohol and Drug Clinicians. No 12: Smoking cessation - working with clients to quit. In: Inc TPAaDC, ed. Fitzroy, Victoria: Turning Point Alcohol and Drug Centre Inc 2005.

109. Bozikas, V. P., Papakosta M., Niopas I., Karavatos A., Mirtsou-Fidani V. (2004) Smoking impact on CYP1A2 activity in a group of patients with schizophrenia. *European Neuropsychopharmacology*, 14, 39-44.

110. Ozdemir, V., Kalow W., Posner P., Collins E. J., Kennedy J. L., Tang B. K. *et al.* (2001) CYP1A2 activity as measured by a caffeine test predicts clozapine and active metabolite steady-state concentrationin patients with schizophrenia. *Journal of Clinical Psychopharmacology*, 21, 398-407.

111. Taylor, D. (1997) Pharmacokinetic interactions involving clozapine. *The British Journal of Psychiatry*, 171, 109-12.

112. Callaghan, J. T., Bergstrom R. F., Ptak L. R., Beasley C. M. (1999) Olanzapine. Pharmacokinetic and pharmacodynamic profile. *Clinical Pharmacokinetics*, 37, 177-93.

113. Carrillo, J. A., Herraiz A. G., Ramos S. I., Gervasini G., Vizcaino S., Benitez J. (2003) Role of the smoking-induced cytochrome P450 (CYP)1A2 and polymorphic CYP2D6 in steady-state concentration of olanzapine. *Journal of Clinical Psychopharmacology*, 23, 119-27.

114. Addington, J. (1998) Group treatment for smoking cessation among persons with schizophrenia. *Psychiatric Services*, 49, 925-8.

115. Association, A. P. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition Text Revision ed. Washington: American Psychiatric Association 2000.

116. Practitioners, T. R. A. C. o. G. (2006) Putting Prevention into practice: Guidelines for the implantation of prevention in the general practice setting. South Melbourne: The Royal Australian College of General Practitioners.

117. Silagy, C., Lancaster T., Stead L., Mant D., Fowler G. (2001) Nicotine replacement Therapy for Smoking Cessation. *Cochrane Database of Systematic Reviews*.

118. Jorenby, D. E., Hays J. T., Rigotti N. A., Azoulay S., Watsky E. J., Williams K. E. *et al.* (2006) Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *The Journal of the American Medical Association*, 296, 56-63.

119. Aalto-Setala, T., Marttunen M., Tuulio-Henriksson A., Poikolainen K., Lonnqvist J. (2001) One-month prevalence of depression and other DSM-IV disorders among young adults. *Psychological Medicine*, 31, 791-801.

120. Landheim, A. S., Bakken K., Vaglum P. (2003) Gender differences in the prevalence of symptom disorders and personality disorders among poly-substance abusers and pure alcoholics. Substance abusers treated in two counties in Norway. *European Addiction Research*, 9, 8-17.

121. Melartin, T. K., Rytsala H. J., Leskela U. S., Lestela-Mielonen P. S., Sokero T. P., Isometsa E. T. (2002) Current comorbidity of psychiatric disorders among DSM-IV major depressive disorder patients in psychiatric care in the Vantaa Depression Study. *Journal of Clinical Psychiatry*, 63, 126-34.

122. Vuorilehto, M., Melartin T., Isometsa E. (2005) Depressive disorders in primary care: recurrent, chronic, and co-morbid. *Psychological Medicine*, 35, 673-82.

123. Carey, P. D., Stein D. J., Zungu-Dirwayi N., Seedat S. (2003) Trauma and posttraumatic stress disorder in an urban Xhosa primary care population: prevalence, comorbidity, and service use patterns. *The Journal of Nervous and Mental Disease*, 191, 230-6.

124. Zimmerman, M., Chelminski I. (2003) Generalized anxiety disorder in patients with major depression: is DSM-IV's hierarchy correct? *The American Journal of Psychiatry*, 160, 504-12.

125. Nunes, E. V., Levin F. R. (2004) Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis. *The Journal of the American Medical Association*, 291, 1887-96.

126. van Laar, M., van Dorsselaer S., Monshouwer K., de Graaf R. (2007) Does cannabis use predict the first incidence of mood and anxiety disorders in the adult population? *Addiction*, 102, 1251-60.

127. Hall, M., Buckley N. (2003) Serotonin Syndrome. *Australian Prescriber*, 26, 62-3.

128. Denis, C., Lavie E., Fatseas M., Auriacombe M. (2006) Psychotherapeutic interventions for cannabis abuse and/or dependence in outpatient settings. *Cochrane Database of Systematic Reviews*, 3, CD005336.

129. Preuss, U. W., Schuckit M. A., Smith T. L., Danko G. R., Dasher A. C., Hesselbrock M. N. *et al.* (2002) A comparison of alcohol-induced and independent depression in alcoholics with histories of suicide attempts. *Journal of Studies on Alcohol*, 63, 498-502.

130. Cornelius, J. R., Salloum I. M., Ehler J. G., Jarrett P. J., Cornelius M. D., Perel J. M. *et al.* (1997) Fluoxetine in depressed alcoholics. A double-blind, placebo-controlled trial. *Archives of General Psychiatry*, 54, 700-5.

131. Sher, L. (2006) Alcoholism and suicidal behavior: a clinical overview. *Acta Psychiatrica Scandinavica*, 113, 13-22.

132. McKeon, A., Frye M. A., Delanty N. (2007) The Alcohol Withdrawal Syndrome. *Journal of Neurology, Neurosurgery, and Psychiatry.*

133. Tassaneeyakul, W., Birkett D. J., Miners J. O. (1998) Inhibition of human hepatic cytochrome P4502E1 by azole antifungals, CNS-active drugs and non-steroidal anti-inflammatory agents. *Xenobiotica*, 28, 293-301.

134. Salloum, I. M., Cornelius J. R., Thase M. E., Daley D. C., Kirisci L., Spotts C. (1998) Naltrexone utility in depressed alcoholics. *Psychopharmacology Bulletin*, 34, 111-5.

135. Roy, A. (1998) Placebo-controlled study of sertraline in depressed recently abstinent alcoholics. *Biological Psychiatry*, 44, 633-7.

136. Cornelius, J. R., Bukstein O. G., Birmaher B., Salloum I. M., Lynch K., Pollock N. K. *et al.* (2001) Fluoxetine in adolescents with major depression and an alcohol use disorder: an open-label trial. *Addictive Behaviors*, 26, 735-9.

137. Yoon, S. J., Pae C. U., Kim D. J., Namkoong K., Lee E., Oh D. Y. *et al.* (2006) Mirtazapine for patients with alcohol dependence and comorbid depressive disorders: a multicentre, open label study. *Progress in Neuropsychopharmacology and Biological Psychiatry*, 30, 1196-201.

138. Chick, J., Aschauer H., Hornik K. (2004) Efficacy of fluvoxamine in preventing relapse in alcohol dependence: a one-year, double-blind, placebo-controlled multicentre study with analysis by typology. *Drug and Alcohol Dependence*, 74, 61-70.

139. Pettinati, H. M., Volpicelli J. R., Kranzler H. R., Luck G., Rukstalis M. R., Cnaan A. (2000) Sertraline treatment for alcohol dependence: interactive effects of medication and alcoholic subtype. *Alcoholism: Clinical and Experimental Research*, 24, 1041-9.

140. Ramsey, S. E., Brown R. A., Stuart G. L., Burgess E. S., Miller I. W. (2002) Cognitive variables in alcohol dependent patients with elevated depressive symptoms: changes and predictive utility as a function of treatment modality. *Substance Abuse*, 23, 171-82.

141. Kranzler, H. R., Van Kirk J. (2001) Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis. *Alcoholism: Clinical and Experimental Research*, 25, 1335-41.

142. Miotto, K., McCann M., Basch J., Rawson R., Ling W. (2002) Naltrexone and dysphoria: fact or myth? *The American Journal on Addictions*, 11, 151-60.

143. Oslin, D. W. (2005) Treatment of late-life depression complicated by alcohol dependence. *The American Journal of Geriatric Psychiatry*, 13, 491-500.

144. Kiefer, F., Helwig H., Tarnaske T., Otte C., Jahn H., Wiedemann K. (2005) Pharmacological relapse prevention of alcoholism: clinical predictors of outcome. *European Addiction Research*, 11, 83-91.

145. Krystal, J. H., Gueorguieva R., Cramer J., Collins J., Rosenheck R. (2008) Naltrexone is associated with reduced drinking by alcohol dependent patients receiving antidepressants for mood and anxiety symptoms: results from VA Cooperative Study No. 425, "Naltrexone in the treatment of alcoholism". *Alcoholism: Clinical and Experimental Research*, 32, 85-91.

146. Dean, A. J., Bell J., Christie M. J., Mattick R. P. (2004) Depressive symptoms during buprenorphine vs. methadone maintenance: findings from a randomised, controlled trial in opioid dependence. *European Psychiatry*, 19, 510-3.

147. Stein, M. D., Herman D. S., Solomon D. A., Anthony J. L., Anderson B. J., Ramsey S. E. *et al.* (2004) Adherence to treatment of depression in active injection drug users: the minerva study. *Journal of Substance Abuse Treatment*, 26, 87-93.

148. Eap, C. B., Bertschy G., Powell K., Baumann P. (1997) Fluvoxamine and fluoxetine do not interact in the same way with the metabolism of the enantiomers of methadone. *Journal of Clinical Psychopharmacology*, 17, 113-7.

149. Eap, C. B., Buclin T., Baumann P. (2002) Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. *Clinical Pharmacokinetics*, 41, 1153-93.

150. Iribarne, C., Picart D., Dreano Y., Berthou F. (1998) In vitro interactions between fluoxetine or fluvoxamine and methadone or buprenorphine. *Fundamental and Clinical Pharmacology,* 12, 194-9.

151. Ballesteros, M. F., Budnitz D. S., Sanford C. P., Gilchrist J., Agyekum G. A., Butts J. (2003) Increase in deaths due to methadone in North Carolina. *The Journal of the American Medical Association*, 290, 40.

152. Buster, M. C., van Brussel G. H., van den Brink W. (2002) An increase in overdose mortality during the first 2 weeks after entering or re-entering methadone treatment in Amsterdam. *Addiction*, 97, 993-1001.

153. Caplehorn, J. R., Drummer O. H. (1999) Mortality associated with New South Wales methadone programs in 1994: lives lost and saved. *Medical Journal of Australia*, 170, 104-9.

154. Williamson, P. A., Foreman K. J., White J. M., Anderson G. (1997) Methadone-related overdose deaths in South Australia, 1984-1994. How safe is methadone prescribing? *Medical Journal of Australia*, 166, 302-5.

155. Zador, D., Sunjic S. (2000) Deaths in methadone maintenance treatment in New South Wales, Australia 1990-1995. *Addiction*, 95, 77-84.

156. Hamilton, S. P., Nunes E. V., Janal M., Weber L. (2000) The effect of sertraline on methadone plasma levels in methadone-maintenance patients. *The American Journal on Addictions*, 9, 63-9.

157. Benitez-Rosario, M. A., Salinas Martin A., Gomez-Ontanon E., Feria M. (2006) Methadone-induced respiratory depression after discontinuing carbamazepine administration. *Journal of Pain and Symptom Management*, 32, 99-100.

158. Farre, M., Mas A., Torrens M., Moreno V., Cami J. (2002) Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis. *Drug and Alcohol Dependence*, 65, 283-90.

159. Joseph, H., Stancliff S., Langrod J. (2000) Methadone maintenance treatment (MMT): a review of historical and clinical issues. *The Mount Sinai Journal of Medicine*, 67, 347-64.

160. Ward, J., Hall W., Mattick R. P. (1999) Role of maintenance treatment in opioid dependence. *Lancet*, 353, 221-6.

161. Burns, J. M., Martyres R. F., Clode D., Boldero J. M. (2004) Overdose in young people using heroin: associations with mental health, prescription drug use and personal circumstances. *Medical Journal of Australia*, 181, S25-8.

162. Carpenter, K. M., Brooks A. C., Vosburg S. K., Nunes E. V. (2004) The effect of sertraline and environmental context on treating depression and illicit substance use among methadone maintained opiate dependent patients: a controlled clinical trial. *Drug and Alcohol Dependence*, 74, 123-34.

163. Dean, A. J., Bell J., Mascord D. J., Parker G., Christie M. J. (2002) A randomised, controlled trial of fluoxetine in methadone maintenance patients with depressive symptoms. *Journal of Affecticve Disorders*, 72, 85-90.

164. Dean, A. J., Saunders J. B., Jones R. T., Young R. M., Connor J. P., Lawford B. R. (2006) Does naltrexone treatment lead to depression? Findings from a randomized controlled trial in subjects with opioid dependence. *Journal of Psychiatry and Neuroscience*, 31, 38-45.

165. Petrakis, I., Carroll K. M., Nich C., Gordon L., Kosten T., Rounsaville B. (1998) Fluoxetine treatment of depressive disorders in methadone-maintained opioid addicts. *Drug and Alcohol Dependence*, 50, 221-6.

166. Modesto-Lowe, V., Van Kirk J. (2002) Clinical uses of naltrexone: a review of the evidence. *Experimental and Clinical Psychopharmacology*, 10, 213-27.

167. de Win, M. M., Reneman L., Reitsma J. B., den Heeten G. J., Booij J., van den Brink W. (2004) Mood disorders and serotonin transporter density in ecstasy users--the influence of long-term abstention, dose, and gender. *Psychopharmacology (Berl)*, 173, 376-82.

168. Falck, R. S., Jichuan W., Carlson R. G. (2008) Depressive symptomatology in young adults with a history of MDMA use: a longitudinal analysis. *Journal of Psychopharmacology*, 22, 47-54.

169. Abraham, H. D., Fava M. (1999) Order of onset of substance abuse and depression in a sample of depressed outpatients. *Comprehensive Psychiatry*, 40, 44-50.

170. Guillot, C., Greenway D. (2006) Recreational ecstasy use and depression. *Journal of Psychopharmacology*, 20, 411-6.

171. Parrott, A. C. (2006) MDMA in humans: factors which affect the neuropsychobiological profiles of recreational ecstasy users, the integrative role of bioenergetic stress. *Journal of Psychopharmacology*, 20, 147-63.

172. Baumann, M. H., Wang X., Rothman R. B. (2007) 3,4-Methylenedioxymethamphetamine (MDMA) neurotoxicity in rats: a reappraisal of past and present findings. *Psychopharmacology (Berl)*, 189, 407-24.

173. Cowan, R. L. (2007) Neuroimaging research in human MDMA users: a review. *Psychopharmacology (Berl)*, 189, 539-56.

174. McCann, U. D., Szabo Z., Seckin E., Rosenblatt P., Mathews W. B., Ravert H. T. *et al.* (2005) Quantitative PET studies of the serotonin transporter in MDMA users and controls using [11C]McN5652 and [11C]DASB. *Neuropsychopharmacology*, 30, 1741-50.

175. Parrott, A. C. (2002) Recreational Ecstasy/MDMA, the serotonin syndrome, and serotonergic neurotoxicity. *Pharmacology Biochemisty and Behavior*, 71, 837-44.

176. Parrott, A. C., Rodgers J., Buchanan T., Ling J., Heffernan T., Scholey A. B. (2006) Dancing hot on Ecstasy: physical activity and thermal comfort ratings are associated with the memory and other psychobiological problems reported by recreational MDMA users. *Human Psychopharmacology*, 21, 285-98.

177. Reneman, L., de Win M. M., van den Brink W., Booij J., den Heeten G. J. (2006) Neuroimaging findings with MDMA/ecstasy: technical aspects, conceptual issues and future prospects. *Journal of Psychopharmacology*, 20, 164-75.

178. Parrott, A. C. (2005) Chronic tolerance to recreational MDMA (3,4-methylenedioxymethamphetamine) or Ecstasy. *Journal of Psychopharmacology*, 19, 71-83.

179. Freezer, A., Salem A., Irvine R. J. (2005) Effects of 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy') and para-methoxyamphetamine on striatal 5-HT when co-administered with moclobemide. *Brain Research*, 11041, 48-55.

180. Hewton, R., Salem A., Irvine R. J. (2007) Potentiation of 3,4-methylenedioxymethamphetamine-induced 5-HT release in the rat substantia nigra by clorgyline, a monoamine oxidase A inhibitor. *Clinical and Experimental Pharmacology and Physiology*, 34, 1051-7.

181. NCIS, N. C. I. S. Interactions between amphatamines, ecstasy and anti-depressants. In: Medicine VIoF, ed. Melbourne 2007.

182. Vuori, E., Henry J. A., Ojanpera I., Nieminen R., Savolainen T., Wahlsten P. *et al.* (2003) Death following ingestion of MDMA (ecstasy) and moclobemide. *Addiction*, 98, 365-8.

183. Jaffe, A., Shoptaw S., Stein J., Reback C. J., Rotheram-Fuller E. (2007) Depression ratings, reported sexual risk behaviors, and methamphetamine use: latent growth curve models of positive change among gay and bisexual men in an outpatient treatment program. *Experimental and Clinical Psychopharmacology*, 15, 301-7.

184. Baicy, K., Bearden C. E., Monterosso J., Brody A. L., Isaacson A. J., London E. D. (2005) Common substrates of dysphoria in stimulant drug abuse and primary depression: therapeutic targets. *International Review of Neurobiology*, 65, 117-45.

185. Thase, M. E. (2006) Depression and sleep: pathophysiology and treatment. *Dialogues in Clinical Neuroscience*, 8, 217-26.

186. Pagel, J. F., Parnes B. L. (2001) Medications for the Treatment of Sleep Disorders: An Overview. *Primary Care Companion to the Journal of Clinical Psychiatry*, 3, 118-25.

187. Rijnbeek, B., de Visser S. J., Franson K. L., Cohen A. F., van Gerven J. M. (2003) REM sleep effects as a biomarker for the effects of antidepressants in healthy volunteers. *Journal of Psychopharmacology*, 17, 196-203.

188. Rosenberg, R. P. (2006) Sleep maintenance insomnia: strengths and weaknesses of current pharmacologic therapies. *Annals of Clinical Psychiatry*, 18, 49-56.

189. Chouinard, G. (2004) Issues in the clinical use of benzodiazepines: potency, withdrawal, and rebound. *Journal of Clinical Psychiatry*, 65 7-12.

190. Jacobs, G. D., Pace-Schott E. F., Stickgold R., Otto M. W. (2004) Cognitive behavior therapy and pharmacotherapy for insomnia: a randomized controlled trial and direct comparison. *Archives of nternal Medicine*, 164, 1888-96.

191. Roth, T., Krystal A. D., Lieberman J. A. r. (2007) Long-term issues in the treatment of sleep disorders. *CNS Spectrums*, 12, 1-13.

192. Winkelman, J., Pies R. (2005) Current patterns and future directions in the treatment of insomnia. *Annals of Clinical Psychiatry*, 17, 31-40.

193. Morin, C. M., Bootzin R. R., Buysse D. J., Edinger J. D., Espie C. A., Lichstein K. L. (2006) Psychological and behavioral treatment of insomnia:update of the recent evidence (1998-2004). *Sleep*, 29, 1398-414.

194. Riddle, M. A., Bernstein G. A., Cook E. H., Leonard H. L., March J. S., Swanson J. M. (1999) Anxiolytics, adrenergic agents, and naltrexone. *Journal of the American Academy of Child and Adolescent Psychiatry*, 38, 546-56.

195. Denis, C., Fatseas M., Lavie E., Auriacombe M. (2006) Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings. *Cochrane Database of Systematic Reviews*, 3, CD005194.

196. Posternak, M. A., Mueller T. I. (2001) Assessing the risks and benefits of benzodiazepines for anxiety disorders in patients with a history of substance abuse or dependence. *The American Journal on Addictions*, 10, 48-68.

197. Boothroyd, L. J., Kirmayer L. J., Spreng S., Malus M., Hodgins S. (2001) Completed suicides among the Inuit of northern Quebec, 1982-1996: a case-control study. *Canadian Medical Association Journal*, 165, 749-55.

198. Kelly, T. M., Cornelius J. R., Lynch K. G. (2002) Psychiatric and substance use disorders as risk factors for attempted suicide among adolescents: a case control study. *Suicide and Life-Threatening Behavior*, 32, 301-12.

199. Sakai, J. T., Hall S. K., Mikulich-Gilbertson S. K., Crowley T. J. (2004) Inhalant use, abuse, and dependence among adolescent patients: commonly comorbid problems. *Journal of the American Academy of Child and Adolescent Psychiatry*, 43, 1080-8.

200. Wilcox, H. C., Anthony J. C. (2004) The development of suicide ideation and attempts: an epidemiologic study of first graders followed into young adulthood. *Drug and Alcohol Dependence*, 76 Suppl, S53-S67.

201. Birchall, H., Brandon S., Taub N. (2000) Panic in a general practice population: prevalence, psychiatric comorbidity and associated disability. *Social Psychiatry and Psychiatric Epidemiology*, 35, 235-41.

202. Hofmann, S. G., Smits J. A. (2008) Cognitive-Behavioral Therapy for Adult Anxiety Disorders: A Meta-Analysis of Randomized Placebo-Controlled Trials. *Journal of Clinical Psychiatry*, e1-e12.

203. Gorenstein, E. E., Kleber M. S., Mohlman J., Dejesus M., Gorman J. M., Papp L. A. (2005) Cognitive-behavioral therapy for management of anxiety and medication taper in older adults. *The American Journal of Geriatric Psychiatry*, 13, 901-9.

204. Gosselin, P., Ladouceur R., Morin C. M., Dugas M. J., Baillargeon L. (2006) Benzodiazepine discontinuation among adults with GAD: A randomized trial of cognitive-behavioral therapy. *Journal of Consulting and Clinical Psychology*, 74, 908-19.

205. Blomhoff, S., Haug T. T., Hellstrom K., Holme I., Humble M., Madsbu H. P. *et al.* (2001) Randomised controlled general practice trial of sertraline, exposure therapy and combined treatment in generalised social phobia. *The British Journal of Psychiatry*, 179, 23-30.

206. Davidson, J. R., Foa E. B., Huppert J. D., Keefe F. J., Franklin M. E., Compton J. S. *et al.* (2004) Fluoxetine, comprehensive cognitive behavioral therapy, and placebo in generalized social phobia. *Archives of General Psychiatry*, 61, 1005-13.

207. Fedoroff, I. C., Taylor S. (2001) Psychological and pharmacological treatments of social phobia: a meta-analysis. *Journal of Clinical Psychopharmacology*, 21, 311-24.

208. Lader, M., Stender K., Burger V., Nil R. (2004) Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: randomised, double-blind, placebo-controlled, fixed-dose study. *Depression and Anxiety*, 19, 241-8.

209. Lepola, U., Bergtholdt B., St Lambert J., Davy K. L., Ruggiero L. (2004) Controlled-release paroxetine in the treatment of patients with social anxiety disorder. *Journal of Clinical Psychiatry*, 65, 222-9.

210. Liebowitz, M. R., DeMartinis N. A., Weihs K., Londborg P. D., Smith W. T., Chung H. *et al.* (2003) Efficacy of sertraline in severe generalized social anxiety disorder: results of a double-blind, placebo-controlled study. *Journal of Clinical Psychiatry*, 64, 785-92.

211. Stein, M. B., Fyer A. J., Davidson J. R., Pollack M. H., Wiita B. (1999) Fluvoxamine treatment of social phobia (social anxiety disorder): a double-blind, placebo-controlled study. *The American Journal of Psychiatry*, 156, 756-60.

212. Stein, M. B., Liebowitz M. R., Lydiard R. B., Pitts C. D., Bushnell W., Gergel I. (1998) Paroxetine treatment of generalized social phobia (social anxiety disorder): a randomized controlled trial. *The Journal of the American Medical Association*, 280, 708-13.

213. Van Ameringen, M. A., Lane R. M., Walker J. R., Bowen R. C., Chokka P. R., Goldner E. M. *et al.* (2001) Sertraline treatment of generalized social phobia: a 20-week, double-blind, placebo-controlled study. *The American Journal of Psychiatry*, 158, 275-81.

214. Chouinard, G., Goodman W., Greist J., Jenike M., Rasmussen S., White K. *et al.* (1990) Results of a double-blind placebo controlled trial of a new serotonin uptake inhibitor, sertraline, in the treatment of obsessive-compulsive disorder. *Psychopharmacology Bulletin*, 26, 279-84.

215. Greist, J., Chouinard G., DuBoff E., Halaris A., Kim S. W., Koran L. *et al.* (1995) Double-blind parallel comparison of three dosages of sertraline and placebo in outpatients with obsessive-compulsive disorder. *Archives of General Psychiatry*, 52, 289-95.

216. Montgomery, S. A., McIntyre A., Osterheider M., Sarteschi P., Zitterl W., Zohar J. *et al.* (1993) A double-blind, placebo-controlled study of fluoxetine in patients with DSM-III-R obsessive-compulsive disorder. The Lilly European OCD Study Group. *European Neuropsychopharmacology*, 3, 143-52.

217. Pigott, T. A., Pato M. T., Bernstein S. E., Grover G. N., Hill J. L., Tolliver T. J. *et al.* (1990) Controlled comparisons of clomipramine and fluoxetine in the treatment of obsessive-compulsive disorder. Behavioral and biological results. *Archives of General Psychiatry*, 47, 926-32.

218. Tollefson, G. D., Rampey A. H., Jr., Potvin J. H., Jenike M. A., Rush A. J., kominguez R. A. *et al.* (1994) A multicenter investigation of fixed-dose fluoxetine in the treatment of obsessive-compulsive disorder. *Archives of General Psychiatry*, 51, 559-67.

219. Grubaugh, A. L., Magruder K. M., Waldrop A. E., Elhai J. D., Knapp R. G., Frueh B. C. (2005) Subthreshold PTSD in primary care: prevalence, psychiatric disorders, healthcare use, and functional status. *The Journal of Nervous and Mental Disease*, 193, 658-64.

220. Labbate, L. A., Sonne S. C., Randal C. L., Anton R. F., Brady K. T. (2004) Does comorbid anxiety or depression affect clinical outcomes in patients with post-traumatic stress disorder and alcohol use disorders? *Comprehensive Psychiatry*, 45, 304-10.

221. Magruder, K. M., Frueh B. C., Knapp R. G., Davis L., Hamner M. B., Martin R. H. *et al.* (2005) Prevalence of posttraumatic stress disorder in Veterans Affairs primary care clinics. *General Hospital Psychiatry*, 27, 169-79.

222. Roy-Byrne, P. P., Stein M. B., Russo J., Mercier E., Thomas R., McQuaid J. *et al.* (1999) Panic disorder in the primary care setting: comorbidity, disability, service utilization, and treatment. *Journal of Clinical Psychiatry*, 60, 492-9; quiz 500.

223. Sareen, L., Stein M. (2000) A review of the epidemiology and approaches to the treatment of social anxiety disorder. *Drugs*, 59, 497-509.

224. Stein, M. B., McQuaid J. R., Pedrelli P., Lenox R., McCahill M. E. (2000) Posttraumatic stress disorder in the primary care medical setting. *General Hospital Psychiatry*, 22, 261-9.

225. Bonn-Miller, M. O., Zvolensky M. J., Leen-Feldner E. W., Feldner M. T., Yartz A. R. (2005) Marijuana Use Among Daily Tobacco Smokers: Relationship to Anxiety-Related Factors. *Journal of Psychopathology and Behavioral Assessment*, 27, 279-89.

226. Brady, K. T., Tolliver B. K., Verduin M. L. (2007) Alcohol use and anxiety: diagnostic and management issues. *The American Journal of Psychiatry*, 164, 217-21; quiz 372.

227. Schmidt, N. B., Buckner J. D., Keough M. E. (2007) Anxiety sensitivity as a prospective predictor of alcohol use disorders. *Behavior Modification*, 31, 202-19.

228. Willinger, U., Lenzinger E., Hornik K., Fischer G., Schönbeck G., Aschauer H. N. *et al.* (2002) Anxiety as a Predictor of Relapse in Detoxified Alchol-Dependent Patients. *Alcohol and Alcoholism*, 37, 609-12.

229. AMH, A. M. H. Australian Medicines Handbook. Adelaide 2007.

230. Saivin, S., Hulot T., Chabac S., Potgieter A., Durbin P., Houin G. (1998) Clinical pharmacokinetics of acamprosate. *Clinical Pharmacokinetics*, 35, 331-45.

231. Schade, A., Marquenie L. A., van Balkom A. J., Koeter M. W., de Beurs E., van den Brink W. *et al.* (2005) The effectiveness of anxiety treatment on alcohol-dependent patients with a comorbid phobic disorder: a randomized controlled trial. *Alcoholism: Clinical and Experimental Research*, 29, 794-800.

232. Thevos, A. K., Roberts J. S., Thomas S. E., Randall C. L. (2000) Cognitive behavioral therapy delays relapse in female socially phobic alcoholics. *Addictive Behaviors*, 25, 333-45.

233. Randall, C. L., Johnson M. R., Thevos A. K., Sonne S. C., Thomas S. E., Willard S. L. *et al.* (2001) Paroxetine for social anxiety and alcohol use in dual-diagnosed patients. *Depression and Anxiety*, 14, 255-62.

234. Brady, K. T., Sonne S., Anton R. F., Randall C. L., Back S. E., Simpson K. (2005) Sertraline in the treatment of co-occurring alcohol dependence and posttraumatic stress disorder. *Alcoholism: Clinical and Experimental Research*, 29, 395-401.

235. Garbutt, J. C., Kranzler H. R., O'Malley S. S., Gastfriend D. R., Pettinati H. M., Silverman B. L. *et al.* (2005) Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *The Journal of the American Medical Association*, 293, 1617-25.

236. Kranzler, H. R., Wesson D. R., Billot L. (2004) Naltrexone depot for treatment of alcohol dependence: a multicenter, randomized, placebo-controlled clinical trial. *Alcoholism: Clinical and Experimental Research*, 28, 1051-9.

237. Petrakis, I. L., Poling J., Levinson C., Nich C., Carroll K., Ralevski E. *et al.* (2006) Naltrexone and disulfiram in patients with alcohol dependence and comorbid post-traumatic stress disorder. *Biological Psychiatry*, 60, 777-83.

238. Hien, D. A., Nunes E., Levin F. R., Fraser D. (2000) Posttraumatic stress disorder and short-term outcome in early methadone treatment. *Journal of Substance Abuse Treatment*, 19, 31-7.

239. Trafton, J. A., Minkel J., Humphreys K. (2006) Opioid substitution treatment reduces substance use equivalently in patients with and without posttraumatic stress disorder. *Journal of Studies on Alcohol*, 67, 228-35.

240. Boulton, D. W., Arnaud P., DeVane C. L. (2001) A single dose of methadone inhibits cytochrome P-4503A activity in healthy volunteers as assessed by the urinary cortisol ratio. *British Journal of Clinical Pharmacology*, 51, 350-4.

241. Totah, R. A., Allen K. E., Sheffels P., Whittington D., Kharasch E. D. (2007) Enantiomeric metabolic interactions and stereoselective human methadone metabolism. *The Journal of Pharmacology and Experimental Therapeutics*, 321, 389-99.

242. Thummel, K. E., Wilkinson G. R. (1998) In vitro and in vivo drug interactions involving human CYP3A. *Annual Review of Pharmacology and Toxicology*, 38, 389-430.

243. Zhang, W., Ramamoorthy Y., Tyndale R. F., Sellers E. M. (2003) Interaction of buprenorphine and its metabolite norbuprenorphine with cytochromes p450 in vitro. *Drug Metabolism and Disposition*, 31, 768-72.

244. Kintz, P. (2002) A new series of 13 buprenorphine-related deaths. *Clin Biochem*, 35, 513-6.

245. Lai, S. H., Yao Y. J., Lo D. S. (2006) A survey of buprenorphine related deaths in Singapore. *Forensic Science International*, 162, 80-6.

246. Reynaud, M., Petit G., Potard D., Courty P. (1998) Six deaths linked to concomitant use of buprenorphine and benzodiazepines. *Addiction*, 93, 1385-92.

247. Dyer, K. R., White J. M., Foster D. J., Bochner F., Menelaou A., Somogyi A. A. (2001) The relationship between mood state and plasma methadone concentration in maintenance patients. *Journal of Clinical Psychopharmacology*, 21, 78-84.

248. Gowing, L., Ali R., White J. (2006) Buprenorphine for the management of opioid withdrawal. *Cochrane Database of Systematic Reviews*, CD002025.

249. Evren, C., Barut T., Saatcioglu O., Cakmak D. (2006) Axis I psychiatric comorbidity among adult inhalant dependents seeking treatment. *Journal of Psychoactive Drugs*, 38, 57-64.

250. Wu, L. T., Howard M. O. (2007) Psychiatric disorders in inhalant users: results from The National Epidemiologic Survey on Alcohol and Related Conditions. *Drug and Alcohol Dependence*, 88, 146-55.

251. Olfson, M., Lewis-Fernandez R., Weissman M. M., Feder A., Gameroff M. J., Pilowsky D. *et al.* (2002) Psychotic symptoms in an urban general medicine practice. *The American Journal of Psychiatry*, 159, 1412-9.

252. Leucht, S., Pitschel-Walz G., Abraham D., Kissling W. (1999) Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. *Schizophrenia Research*, 35, 51-68.

253. Wahlbeck, K., Cheine M., Essali A., Adams C. (1999) Evidence of clozapine's effectiveness in schizophrenia: a systematic review and meta-analysis of randomized trials. *The American Journal of Psychiatry*, 156, 990-9.

254. Bilder, R. M., Goldman R. S., Volavka J., Czobor P., Hoptman M., Sheitman B. *et al.* (2002) Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. *The American Journal of Psychiatry*, 159, 1018-28.

255. Green, M. F., Marshall B. D., Jr., Wirshing W. C., Ames D., Marder S. R., McGurk S. *et al.* (1997) Does risperidone improve verbal working memory in treatment-resistant schizophrenia? *The American Journal of Psychiatry*, 154, 799-804.

256. Meltzer, H. Y., McGurk S. R. (1999) The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. *Schizophrenia Bulletin*, 25, 233-55.

257. Bowden, C. L., Calabrese J. R., Sachs G., Yatham L. N., Asghar S. A., Hompland M. *et al.* (2003) A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Archives of General Psychiatry*, 60, 392-400.

258. Calabrese, J. R., Bowden C. L., Sachs G., Yatham L. N., Behnke K., Mehtonen O. P. *et al.* (2003) A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *Journal of Clinical Psychiatry*, 64, 1013-24.

259. Smith, L. A., Cornelius V., Warnock A., Tacchi M. J., Taylor D. (2007) Pharmacological interventions for acute bipolar mania: a systematic review of randomized placebo-controlled trials. *Bipolar Disorders*, 9, 551-60.

260. El-Mallakh, R. S., Ketter T. A., Weisler R. H., Hirschfeld R., Cutler A. J., Gazda T. *et al.* (2008) Switching from other agents to extended-release carbamazepine in acute mania. *Psychopharmacology Bulletin*, 41, 52-8.

261. Calabrese, J. R., Huffman R. F., White R. L., Edwards S., Thompson T. R., Ascher J. A. *et al.* (2008) Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. *Bipolar Disorders*, 10, 323-33.

262. Buckley, P. F. (2008) Update on the treatment and management of schizophrenia and bipolar disorder. *CNS Spectrums*, 13, 1-10; quiz 1-2.

263. Gregg, L., Barrowclough C., Haddock G. (2007) Reasons for increased substance use in psychosis. *Clinical Psychology Review*, 27, 494-510.

264. Dubertret, C., Bidard I., Ades J., Gorwood P. (2006) Lifetime positive symptoms in patients with schizophrenia and cannabis abuse are partially explained by co-morbid addiction. *Schizophrenia Research*, 86, 284-90.

265. Green, A. I., Tohen M. F., Hamer R. M., Strakowski S. M., Lieberman J. A., Glick I. *et al.* (2004) First episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. *Schizophrenia Research*, 66, 125-35.

266. Goswami, S., Mattoo S. K., Basu D., Singh G. (2004) Substance-abusing schizophrenics: do they self-medicate? *The American Journal on Addictions*, 13, 139-50.

267. San, L., Arranz B., Martinez-Raga J. (2007) Antipsychotic drug treatment of schizophrenic patients with substance abuse disorders. *European Addiction Research*, 13, 230-43.

268. Kawa, I., Carter J. D., Joyce P. R., Doughty C. J., Frampton C. M., Wells J. E. *et al.* (2005) Gender differences in bipolar disorder: age of onset, course, comorbidity, and symptom presentation. *Bipolar Disorders*, 7, 119-25.

269. Wobrock, T., Sittinger H., Behrendt B., D'Amelio R., Falkai P., Caspari D. (2007) Comorbid substance abuse and neurocognitive function in recent-onset schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*, 257, 203-10.

270. Drake, R. E., Xie H., McHugo G. J., Green A. I. (2000) The effects of clozapine on alcohol and drug use disorders among patients with schizophrenia. *Schizophrenia Bulletin*, 26, 441-9.

271. Green, A. I., Noordsy D. L., Brunette M. F., O'Keefe C. (2008) Substance abuse and schizophrenia: pharmacotherapeutic intervention. *Journal of Substance Abuse Treatment*, 34, 61-71.

272. McEvoy, J. P., Freudenreich O., Wilson W. H. (1999) Smoking and therapeutic response to clozapine in patients with schizophrenia. *Biological Psychiatry*, 46, 125-9.

273. Stuyt, E. B., Sajbel T. A., Allen M. H. (2006) Differing effects of antipsychotic medications on substance abuse treatment patients with co-occurring psychotic and substance abuse disorders. *The American Journal on Addictions*, 15, 166-73.

274. Zimmet, S. V., Strous R. D., Burgess E. S., Kohnstamm S., Green A. I. (2000) Effects of clozapine on substance use in patients with schizophrenia and schizoaffective disorder: a retrospective survey. *Journal of Clinical Psychopharmacology*, 20, 94-8.

275. McEvoy, J. P., Lieberman J. A., Stroup T. S., Davis S. M., Meltzer H. Y., Rosenheck R. A. *et al.* (2006) Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *The American Journal of Psychiatry*, 163, 600-10.

276. Buckley, P., Thompson P., Way L., Meltzer H. Y. (1994) Substance abuse among patients with treatment-resistant schizophrenia: characteristics and implications for clozapine therapy. *The American Journal of Psychiatry*, 151, 385-9.

277. Naeem, F., Kingdon D., Turkington D. (2005) Cognitive behavior therapy for schizophrenia in patients with mild to moderate substance misuse problems. *Cognitive Behaviour Therapy*, 34, 207-15.

278. Barrowclough, C., Haddock G., Tarrier N., Lewis S. W., Moring J., O'Brien R. *et al.* (2001) Randomized controlled trial of motivational interviewing, cognitive behavior therapy, and family intervention for patients with comorbid schizophrenia and substance use disorders. *The American Journal of Psychiatry*, 158, 1706-13.

279. Grace, R. F., Shenfield G., Tennant C. (2000) Cannabis and psychosis in acute psychiatric admissions. *Drug and Alcohol Review*, 19, 287-90.

280. Wittchen, H. U., Frohlich C., Behrendt S., Gunther A., Rehm J., Zimmermann P. *et al.* (2007) Cannabis use and cannabis use disorders and their relationship to mental disorders: a 10-year prospective-longitudinal community study in adolescents. *Drug and Alcohol Dependence*, 88 Suppl 1, S60-S70.

281. Strakowski, S. M., DelBello M. P., Fleck D. E., Arndt S. (2000) The impact of substance abuse on the course of bipolar disorder. *Biological Psychiatry*, 48, 477-85.

282. Boydell, J., van Os J., Caspi A., Kennedy N., Giouroukou E., Fearon P. *et al.* (2006) Trends in cannabis use prior to first presentation with schizophrenia, in South-East London between 1965 and 1999. *Psychological Medicine*, 36, 1441-6.

283. de Irala, J., Ruiz-Canela M., Martinez-Gonzalez M. A. (2005) Causal relationship between cannabis use and psychotic symptoms or depression. Should we wait and see? A public health perspective. *Medical Science Monitor*, 11, RA355-RA8.

284. Fergusson, D. M., Horwood L. J., Ridder E. M. (2005) Tests of causal linkages between cannabis use and psychotic symptoms. *Addiction*, 100, 354-66.

285. Semple, D. M., McIntosh A. M., Lawrie S. M. (2005) Cannabis as a risk factor for psychosis: systematic review. *Journal of Psychopharmacology*, 19, 187-94.

286. Degenhardt, L., Hall W., Lynskey M. (2003) Testing hypotheses about the relationship between cannabis use and psychosis. *Drug and Alcohol Dependence*, 71, 37-48.

287. Miller, P. M., Johnstone E. C., Lawrie S. M., Owens D. G. C. (2006) Substance use, psychiatric symptoms and the onset of schizophrenia illness. *Journal of Substance Use*, 11, 101-13.

288. Degenhardt, L., Tennant C., Gilmour S., Schofield D., Nash L., Hall W. *et al.* (2007) The temporal dynamics of relationships between cannabis, psychosis and depression among young adults with psychotic disorders: findings from a 10-month prospective study. *Psychological Medicine*, 37, 927-34.

289. D'Souza, D. C., Abi-Saab W. M., Madonick S., Forselius-Bielen K., Doersch A., Braley G. *et al.* (2005) Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biological Psychiatry*, 57, 594-608.

290. Hall, W., Degenhardt L., Teesson M. (2004) Cannabis use and psychotic disorders: an update. *Drug and Alcohol Review*, 23, 433-43.

291. Isaac, M., Holloway F. (2005) Is cannabis an anti-antipsychotic? The experience in psychiatric intensive care. *Human Psychopharmacology*, 20, 207-10.

292. Green, B., Kavanagh D. J., Young R. M. (2004) Reasons for cannabis use in men with and without psychosis. *Drug and Alcohol Review*, 23, 445-53.

293. Schofield, D., Tennant C., Nash L., Degenhardt L., Cornish A., Hobbs C. *et al.* (2006) Reasons for cannabis use in psychosis. The Australian and New Zealand Journal of Psychiatry, 40, 570-4.

294. Zullino, D. F., Delessert D., Eap C. B., Preisig M., Baumann P. (2002) Tobacco and cannabis smoking cessation can lead to intoxication with clozapine or olanzapine. *International Clinical Psychopharmacology*, 17, 141-3.

295. Edwards, J., Elkins K., Hinton M., Harrigan S. M., Donovan K., Athanasopoulos O. *et al.* (2006) Randomized controlled trial of a cannabis-focused intervention for young people with first-episode psychosis. *Acta Psychiatrica Scandinavica*, 114, 109-17.

296. Green, A. I., Burgess E. S., Dawson R., Zimmet S. V., Strous R. D. (2003) Alcohol and cannabis use in schizophrenia: effects of clozapine vs. risperidone. *Schizophrenia Research*, 60, 81-5.

297. Berk, M., Brook S., Trandafir A. I. (1999) A comparison of olanzapine with haloperidol in cannabis-induced psychotic disorder: a double-blind randomized controlled trial. *International Clinical Psychopharmacology*, 14, 177-80.

298. Frye, M. A., Salloum I. M. (2006) Bipolar disorder and comorbid alcoholism: prevalence rate and treatment considerations. *Bipolar Disorders*, 8, 677-85.

299. D'Souza, D. C., Gil R. B., Madonick S., Perry E. B., Forselius-Bielen K., Braley G. *et al.* (2006) Enhanced sensitivity to the euphoric effects of alcohol in schizophrenia. *Neuropsychopharmacology*, 31, 2767-75.

300. Thoma, R. J., Hanlon F. M., Miller G. A., Huang M., Weisend M. P., Sanchez F. P. *et al.* (2006) Neuropsychological and sensory gating deficits related to remote alcohol abuse history in schizophrenia. *Journal of the International Neuropsychological Society*, 12, 34-44.

301. Murthy, K. K. (1997) Psychosis during disulfiram therapy for alcoholism. *Journal of the Indian Medical Association*, 95, 80-1.

302. Petrakis, I. L., Nich C., Ralevski E. (2006) Psychotic spectrum disorders and alcohol abuse: a review of pharmacotherapeutic strategies and a report on the effectiveness of naltrexone and disulfiram. *Schizophrenia Bulletin*, 32, 644-54.

303. Petrakis, I. L., O'Malley S., Rounsaville B., Poling J., McHugh-Strong C., Krystal J. H. (2004) Naltrexone augmentation of neuroleptic treatment in alcohol abusing patients with schizophrenia. *Psychopharmacology (Berl)*, 172, 291-7.

304. Mueser, K. T., Noordsy D. L., Fox L., Wolfe R. (2003) Disulfiram treatment for alcoholism in severe mental illness. *The American Journal on Addictions*, 12, 242-52.

305. Sorensen, H. J., Jepsen P. W., Haastrup S., Juel K. (2005) Drug-use pattern, comorbid psychosis and mortality in people with a history of opioid addiction. *Acta Psychiatrica Scandinavica*, 111, 244-9.

306. Miotto, P., Preti A., Frezza M. (2001) Heroin and schizophrenia: subjective responses to abused drugs in dually diagnosed patients. *Journal of Clinical Psychopharmacology*, 21, 111-3.

307. Gerra, G., Di Petta G., D'Amore A., Iannotta P., Bardicchia F., Falorni F. *et al.* (2007) Combination of olanzapine with opioid-agonists in the treatment of heroin-addicted patients affected by comorbid schizophrenia spectrum disorders. *Clinical Neuropharmacology*, 30, 127-35.

308. Nolte, S., Wong D., Latchford G. (2007) Amphetamines for schizophrenia. *Cochrane Database of Systematic Reviews*.

309. Chen, C. K., Lin S. K., Sham P. C., Ball D., Loh E. W., Hsiao C. C. *et al.* (2003) Pre-morbid characteristics and co-morbidity of methamphetamine users with and without psychosis. *Psychological Medicine*, 33, 1407-14.

310. Sweeting, M., Farrell M. (2005) Methamphetamine Psychosis: How is it Related to Schizophrenia? A Review of the Literature. *Current Psychiatry Reviews*, 1, 115-22.

311. Degner, D., Bleich S., Grohmann R., Bandelow B., Ruther E. (2000) Myocarditis associated with clozapine treatment. *Australian and New Zealand Journal of Psychiatry*, 34, 880.

312. Havens, J. R., Strathdee S. A. (2005) Antisocial Personality Disorder and Opioid Treatment Outcomes: A Review. *Addictive Disorders and Their Treatment*, 4, 85-97.

313. Messina, N. P., Wish E. D., Hoffman J. A., Nemes S. (2002) Antisocial personality disorder and TC treatment outcomes. *The American Journal of Drug and Alcohol Abuse*, 28, 197-212.

314. Benedetti, F., Sforzini L., Colombo C., Maffei C., Smeraldi E. (1998) Low-dose clozapine in acute and continuation treatment of severe borderline personality disorder. *Journal of Clinical Psychiatry*, 59, 103-7.

315. Hori, A. (1998) Pharmacotherapy for personality disorders. *iPsychiatry and Clinical Neurosciences*, 52, 13-9.

316. Gross, R., Olfson M., Gameroff M., Shea S., Feder A., Fuentes M. *et al.* (2002) Borderline personality disorder in primary care. *Archives of Internal Medicine*, 162, 53-60.

317. Tomasson, K., Vaglum P. (2000) Antisocial addicts: the importance of additional axis I disorders for the 28-month outcome. *European Psychiatry*, 15, 443-9.

318. Goldstein, R. B., Compton W. M., Pulay A. J., Ruan W. J., Pickering R. P., Stinson F. S. *et al.* (2007) Antisocial behavioral syndromes and DSM-IV drug use disorders in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Drug and Alcohol Dependence*, 90, 145-58.

319. Grant, B. F., Stinson F. S., Dawson D. A., Chou S. P., Ruan W. J., Pickering R. P. (2004) Co-occurrence of 12-month alcohol and drug use disorders and personality disorders in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Archives of General Psychiatry*, 61, 361-8.

320. Cohen, P., Chen H., Crawford T. N., Brook J. S., Gordon K. (2007) Personality disorders in early adolescence and the development of later substance use disorders in the general population. *Drug and Alcohol Dependence*, 88 Suppl 1, S71-S84.

321. Huang, D. B., Kamat P. P., Wang J. (2006) Demographic characteristics and antisocial personality disorder of early and late onset alcoholics identified in a primary care clinic. *The American Journal on Addictions*, 15, 478-82.

322. Kovac, I., Merette C., Legault L., Dongier M., Palmour R. M. (2002) Evidence in an international sample of alcohol-dependent subjects of subgroups with specific symptom patterns of antisocial personality disorder. *Alcoholism: Clinical and Experimental Research*, 26, 1088-96.

323. Ducci, F., Enoch M. A., Funt S., Virkkunen M., Albaugh B., Goldman D. (2007) Increased anxiety and other similarities in temperament of alcoholics with and without antisocial personality disorder across three diverse populations. *Alcohol*, 41, 3-12.

324. Hunter, E. E., Powell B. J., Penick E. C., Nickel E. J., Liskow B. I., Cantrell P. J. *et al.* (2000) Comorbid psychiatric diagnosis and long-term drinking outcome. *Comprehensive Psychiatry*, 41, 334-8.

325. Krampe, H., Wagner T., Stawicki S., Bartels C., Aust C., Kroener-Herwig B. *et al.* (2006) Personality disorder and chronicity of addiction as independent outcome predictors in alcoholism treatment. *Psychiatric Services*, 57, 708-12.

326. Whiteside, S. P., Lynam D. R. (2003) Understanding the role of impulsivity and externalizing psychopathology in alcohol abuse: application of the UPPS impulsive behavior scale. *Experimental and Clinical Psychopharmacology*, 11, 210-7.

327. Malcolm, R., Ballenger J. C., Sturgis E. T., Anton R. (1989) Double-blind controlled trial comparing carbamazepine to oxazepam treatment of alcohol withdrawal. *The American Journal of Psychiatry*, 146, 617-21.

328. Myrick, H., Brady K. T., Malcolm R. (2000) Divalproex in the treatment of alcohol withdrawal. *The American Journal of Drug and Alcohol Abuse*, 26, 155-60.

329. Reoux, J. P., Saxon A. J., Malte C. A., Baer J. S., Sloan K. L. (2001) Divalproex sodium in alcohol withdrawal: a randomized double-blind placebo-controlled clinical trial. *Alcoholism: Clinical and Experimental Research*, 25, 1324-9.

330. Book, S. W., Myrick H. (2005) Novel anticonvulsants in the treatment of alcoholism. *Expert Opinion on Investigational Drugs*, 14, 371-6.

331. Soyka, M., Roesner S. (2006) New pharmacological approaches for the treatment of alcoholism. *Expert Opinion on Pharmacotherapy*, 7, 2341-53.

332. Rohsenow, D. J., Miranda R., Jr., McGeary J. E., Monti P. M. (2007) Family history and antisocial traits moderate naltrexone's effects on heavy drinking in alcoholics. *Experimental and Clinical Psychopharmacology*, 15, 272-81.

333. Darke, S., Williamson A., Ross J., Teesson M., Lynskey M. (2004) Borderline personality disorder, antisocial personality disorder and risk-taking among heroin users: findings from the Australian Treatment Outcome Study (ATOS). *Drug and Alcohol Dependence*, 74, 77-83.

334. Darke, S., Ross J., Williamson A., Mills K. L., Havard A., Teesson M. (2007) Borderline personality disorder and persistently elevated levels of risk in 36-month outcomes for the treatment of heroin dependence. *Addiction*, 102, 1140-6.

335. Broome, K. M., Joe G. W., Simpson D. D. (1999) HIV risk reduction in outpatient drug abuse treatment: individual and geographic differences. *AIDS Education and Prevention*, 11, 293-306.

336. King, V. L., Kidorf M. S., Stoller K. B., Carter J. A., Brooner R. K. (2001) Influence of antisocial personality subtypes on drug abuse treatment response. *The Journal of Nervous and Mental Disease*, 189, 593-601.

337. Falck, R. S., Wang J., Siegal H. A., Carlson R. G. (2004) The prevalence of psychiatric disorder among a community sample of crack cocaine users: an exploratory study with practical implications. *The Journal of Nervous and Mental Disease*, 192, 503-7.

338. de Win, M. M., Schilt T., Reneman L., Vervaeke H., Jager G., Dijkink S. *et al.* (2006) Ecstasy use and self-reported depression, impulsivity, and sensation seeking: a prospective cohort study. *Journal of Psychopharmacology*, 20, 226-35.

339. Hoffman, W. F., Moore M., Templin R., McFarland B., Hitzemann R. J., Mitchell S. H. (2006) Neuropsychological function and delay discounting in methamphetamine-dependent individuals. *Psychopharmacology (Berl)*, 188, 162-70.

340. Cochrane, C., Malcolm R., Brewerton T. (1998) The role of weight control as a motivation for cocaine abuse. *Addictive Behaviors*, 23, 201-7.

341. Stock, S. L., Goldberg E., Corbett S., Katzman D. K. (2002) Substance use in female adolescents with eating disorders. *Journal of Adolescent Health*, 31, 176-82.

342. Ramoz, N., Versini A., Gorwood P. (2007) Eating disorders: an overview of treatment responses and the potential impact of vulnerability genes and endophenotypes. *Expert Opinion on Pharmacotherapy*, 8, 2029-44.

343. Hay, P. J., Bacaltchuk J., Stefano S. (2004) Psychotherapy for bulimia nervosa and binging. *Cochrane Database of Systematic Reviews*, CD000562.

344. Shapiro, J. R., Berkman N. D., Brownley K. A., Sedway J. A., Lohr K. N., Bulik C. M. (2007) Bulimia nervosa treatment: a systematic review of randomized controlled trials. *The International Journal of Eating Disorders*, 40, 321-36.

345. Crow, S., Mussell M. P., Peterson C., Knopke A., Mitchell J. (1999) Prior treatment received by patients with bulimia nervosa. *The International Journal of Eating Disorders*, 25, 39-44.

346. Blinder, B. J., Cumella E. J., Sanathara V. A. (2006) Psychiatric comorbidities of female inpatients with eating disorders. *Psychosomatic Medicine*, 68, 454-62.

347. Herzog, D. B., Franko D. L., Dorer D. J., Keel P. K., Jackson S., Manzo M. P. (2006) Drug abuse in women with eating disorders. *International Journal of Eating Disorders*, 39, 364-8.

348. Patton, G. C., Coffey C., Carlin J. B., Sanci L., Sawyer S. (2008) Prognosis of adolescent partial syndromes of eating disorder. *The British Journal of Psychiatry*, 192, 294-9.

349. Piran, N., Robinson S. (2006) The association between disordered eating and substance use and abuse in women: a community-based investigation. *Women and Health*, 44, 1-20.

350. Wiederman, M. W. (1997) Adolescent Substance Use and Eating Disorders. *The Prevention Researcher*, 4, 10-1.

351. Wiederman, M. W., Pryor T. (1996) Substance use and impulsive behaviors among adolescents with eating disorders. *Addictive Behaviors*, 21, 269-72.

352. Corte, C., Stein K. F. (2000) Eating disorders and substance use; An examination of behavioral associations. *Eating Behaviors*, 1, 173-89.

353. Lacey, J. H., Evans C. D. (1986) The impulsivist: a multi-impulsive personality disorder. *British Journal of Addiction*, 81, 641-9.

354. Fischer, S., Grange D. (2007) Comorbidity and high-risk behaviors in treatment-seeking adolescents with bulimia nervosa. *The International Journal of Eating Disorders*, 40, 751-3.

355. Haug, N. A., Heinberg L. J., Guarda A. S. (2001) Cigarette smoking and its relationship to other substance use among eating disordered inpatients. *Eating and Weight Disorders*, 6, 130-9.

356. Sansone, R. A., Levitt J. L. (2002) Self-harm behaviors among those with eating disorders: an overview. *Eating Disorders*, 10, 205-13.

357. Franko, D. L., Dorer D. J., Keel P. K., Jackson S., Manzo M. P., Herzog D. B. (2005) How do eating disorders and alcohol use disorder influence each other? *The International Journal of Eating Disorders*, 38, 200-7.

358. Piran, N., Gadalla T. (2006) Eating disorders and substance abuse in Canadian women: a national study. *Addiction*, 102, 105-13.

359. Pelchat, M. L. (2002) Of human bondage: food craving, obsession, compulsion, and addiction. *Physiology and Behavior*, 76, 347-52.

360. Curran, H. V., Robjant K. (2006) Eating attitudes, weight concerns and beliefs about drug effects in women who use ecstasy. *Journal of Psychopharmacology*, 20, 425-31.

361. Nagata, T., Oshima J., Wada A., Yamada H., Kiriike N. (2003) Repetitive self-mutilation among Japanese eating disorder patients with drug use disorder: comparison with patients with methamphetamine use disorder. *The Journal of Nervous and Mental Disease*, 191, 319-23.

362. Patton, G. C., Coffey C., Sawyer S. M. (2003) The outcome of adolescent eating disorders: findings from the Victorian Adolescent Health Cohort Study. *European Child and Adolescent Psychiatry*, 12 Suppl 1, I25-129.

363. Bulik, C. M., Klump K. L., Thornton L., Kaplan A. S., Devlin B., Fichter M. M. *et al.* (2004) Alcohol use disorder comorbidity in eating disorders: a multicenter study. *Journal of Clinical Psychiatry*, 65, 1000-6.

364. Alvarez-Moya, E. M., Jimenez-Murcia S., Granero R., Vallejo J., Krug I., Bulik C. M. *et al.* (2007) Comparison of personality risk factors in bulimia nervosa and pathological gambling. *Comprehensive Psychiatry*, 48, 452-7.

365. Engwall, D., Hunter R., Steinberg M. (2004) Gambling and other risk behaviors on university campuses. *Journal of American College Health*, 52, 245-55.

366. Fernandez-Aranda, F., Jimenez-Murcia S., Alvarez-Moya E. M., Granero R., Vallejo J., Bulik C. M. (2006) Impulse control disorders in eating disorders: clinical and therapeutic implications. *Comprehensive Psychiatry*, 47, 482-8.

367. Huang, J. H., Jacobs D. F., Derevensky J. L., Gupta R., Paskus T. S. (2007) Gambling and health risk behaviors among U.S. college student-athletes: findings from a national study. *Journal of Adolescent Health*, 40, 390-7.

368. Davis, C., Claridge G. (1998) The eating disorders as addiction: a psychobiological perspective. *Addictive Behaviors*, 23, 463-75.

369. Cooper, S. J. (2004) Endocannabinoids and food consumption: comparisons with benzodiazepine and opioid palatability-dependent appetite. *European Journal of Pharmacology*, 500, 37-49.

370. Adams, T. B., Araas T. E. (2006) Purging and alcohol-related effects in college women. *The International Journal of Eating Disorders*, 39, 240-4.

371. Neumark-Sztainer, D., Story M., Dixon L. B., Murray D. M. (1998) Adolescents engaging in unhealthy weight control behaviors: are they at risk for other health-compromising behaviors? *American Journal of Public Health*, 88, 952-5.

372. Conason, A. H., Sher L. (2006) Alcohol use in adolescents with eating disorders. *International Journal of Adolescent Medicine and Health*, 18, 31-6.

373. O'Malley, S. S., Sinha R., Grilo C. M., Capone C., Farren C. K., McKee S. A. *et al.* (2007) Naltrexone and cognitive behavioral coping skills therapy for the treatment of alcohol drinking and eating disorder features in alcohol-dependent women: a randomized controlled trial. *Alcoholism: Clinical and Experimental Research*, 31, 625-34.

374. Glass, M. J., Billington C. J., Levine A. S. (1999) Opioids and food intake: distributed functional neural pathways. *Neuropeptides*, 33, 360-8.

375. Mercer, M. E., Holder M. D. (1997) Food cravings, endogenous opioid peptides, and food intake: a review. *Appetite*, 29, 325-52.

376. Cooper, S. J. (2005) Palatability-dependent appetite and benzodiazepines: new directions from the pharmacology of GABA(A) receptor subtypes. *Appetite*, 44, 133-50.

377. Singh, B. S. (1998) Managing somatoform disorders. *Medical Journal of Australia*, 168, 572-7.

378. Rosendal, M., Bro F., Sokolowski I., Fink P., Toft T., Olesen F. (2005) A randomised controlled trial of brief training in assessment and treatment of somatisation: effects on GPs' attitudes. *Family Practice*, 22, 419-27.

379. Escobar, J. I. (1995) Transcultural aspects of dissociative and somatoform disorders. *Psychiatric Clinics of North America*, 18, 555-69.

380. Allen, L. A., Woolfolk R. L., Escobar J. I., Gara M. A., Hamer R. M. (2006) Cognitive-behavioral therapy for somatization disorder: a randomized controlled trial. *Archives of Internal Medicine*, 166, 1512-8.

381. Barsky, A. J., Ahern D. K. (2004) Cognitive behavior therapy for hypochondriasis: a randomized controlled trial. *The Journal of the American Medical Association*, 291, 1464-70.

382. Buwalda, F. M., Bouman T. K., van Duijn M. A. (2007) Psychoeducation for hypochondriasis: a comparison of a cognitive-behavioural approach and a problem-solving approach. *Behaviour Research and Therapy*, 45, 887-99.

383. Clark, D. M., Salkovskis P. M., Hackmann A., Wells A., Fennell M., Ludgate J. *et al.* (1998) Two psychological treatments for hypochondriasis. A randomised controlled trial. *The British Journal of Psychiatry*, 173, 218-25.

384. Escobar, J. I., Gara M. A., Diaz-Martinez A. M., Interian A., Warman M., Allen L. A. *et al.* (2007) Effectiveness of a time-limited cognitive behavior therapy type intervention among primary care patients with medically unexplained symptoms. *Annals of Family Medicine*, 5, 328-35.

385. Magarinos, M., Zafar U., Nissenson K., Blanco C. (2002) Epidemiology and treatment of hypochondriasis. *CNS Drugs*, 16, 9-22.

386. Visser, S., Bouman T. K. (2001) The treatment of hypochondriasis: exposure plus response prevention vs cognitive therapy. *Behaviour Research and Therapy*, 39, 423-42.

387. Pols, R. G., Holmwood C., Battersby M. (1999) Understanding somatisation and somatisation disorders: A handbook for healthcare workers.

388. Aragones, E., Labad A., Pinol J. L., Lucena C., Alonso Y. (2005) Somatized depression in primary care attenders. *Journal of Psychosomatic Research*, 58, 145-51.

389. Allen, L. A., Gara M. A., Escobar J. I., Waitzkin H., Silver R. C. (2001) Somatization: a debilitating syndrome in primary care. *Psychosomatics*, 42, 63-7.

390. Creed, F., Barsky A. (2004) A systematic review of the epidemiology of somatisation disorder and hypochondriasis. *Journal of Psychosomatic Research*, 56, 391-408.

391. Gureje, O., Von Korff M., Kola L., Demyttenaere K., He Y., Posada-Villa J. *et al.* (2008) The relation between multiple pains and mental disorders: results from the World Mental Health Surveys. *Pain*, 135, 82-91.

392. Haug, T. T., Mykletun A., Dahl A. A. (2004) The association between anxiety, depression, and somatic symptoms in a large population: the HUNT-II study. *Psychological Medicine*, 66, 845-51.

393. Escobar, J. I., Gara M., Silver R. C., Waitzkin H., Holman A., Compton W. (1998) Somatisation disorder in primary care. *The British Journal of Psychiatry*, 173, 262-6.

394. Escobar, J. I., Gara M., Waitzkin H., Silver R. C., Holman A., Compton W. (1998) DSM-IV hypochondriasis in primary care. *General Hospital Psychiatry*, 20, 155-9.

395. Gureje, O., Simon G. E., Von Korff M. (2001) A cross-national study of the course of persistent pain in primary care. *Pain*, 92, 195-200.

396. Leiknes, K. A., Finset A., Moum T., Sandanger I. (2007) Current somatoform disorders in Norway: prevalence, risk factors and comorbidity with anxiety, depression and musculoskeletal disorders. *Social Psychiatry and Psychiatric Epidemiology*, 42, 698-710.

397. Mergl, R., Seidscheck I., Allgaier A., Moller H., Hegerl U., Henkel V. (2007) Depressive, anxiety, and somatoform disorders in primary care: prevalence and recognition. *Depression and Anxiety*, 24, 185-95.

398. Stordal, E., Bjelland I., Dahl A. A., Mykletun A. (2003) Anxiety and depression in individuals with somatic health problems. The Nord-Trondelag Health Study (HUNT). *Scandanavian Journal of Primary Health Care*, 21, 136-41.

399. Rief, W., Nanke A., Emmerich J., Bender A., Zech T. (2004) Causal illness attributions in somatoform disorders: associations with comorbidity and illness behavior. *Journal of Psychosomatic Research*, 57, 367-71.

400. Henningsen, P., Jakobsen T., Schiltenwolf M., Weiss M. G. (2005) Somatization revisited: diagnosis and perceived causes of common mental disorders. *The Journal of Nervous and Mental Disease*, 193, 85-92.

401. Smith, R. C., Gardiner J. C., Lyles J. S., Sirbu C., Dwamena F. C., Hodges A. *et al.* (2005) Exploration of DSM-IV criteria in primary care patients with medically unexplained symptoms. *Psychosomatic Medicine*, 67, 123-9.

402. Hansen, G. R., Streltzer J. (2005) The psychology of pain. *Emergency Medicine Clinics of North America*, 23, 339-48.

403. Ballantyne, J. C., LaForge K. S. (2007) Opioid dependence and addiction during opioid treatment of chronic pain. *Pain*, 129, 235-55.

404. Hasin, D., Katz H. (2007) Somatoform and substance use disorders. *Psychological Medicine*, 69, 870-5.

405. Molloy, A. R., Nicholas M. K., Asghari A., Beeston L. R., Dehghani M., Cousins M. J. *et al.* (2006) Does a combination of intensive cognitive-behavioral pain management and a spinal implantable device confer any advantage? A preliminary examination. *Pain Practice*, 6, 96-103.

406. Kroenke, K., Messina N., 3rd, Benattia I., Graepel J., Musgnung J. (2006) Venlafaxine extended release in the short-term treatment of depressed and anxious primary care patients with multisomatoform disorder. *Journal of Clinical Psychiatry*, 67, 72-80.

407. Voon, V., Lang A. E. (2005) Antidepressant treatment outcomes of psychogenic movement disorder. *Journal of Clinical Psychiatry*, 66, 1529-34.

408. Rhudy, J. L., Dubbert P. M., Parker J. D., Burke R. S., Williams A. E. (2006) Affective modulation of pain in substance-dependent veterans. *Pain Medicine*, 7, 483-500.

409. Warms, C. A., Turner J. A., Marshall H. M., Cardenas D. D. (2002) Treatments for chronic pain associated with spinal cord injuries: many are tried, few are helpful. *The Clinical Journal of Pain*, 18, 154-63.

410. Campbell, F. A., Tramer M. R., Carroll D., Reynolds D. J., Moore R. A., McQuay H. J. (2001) Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. *British Medical Journal*, 323, 13-6.

411. Corey, S. (2005) Recent developments in the therapeutic potential of cannabinoids. *Puerto Rico Health Sciences Journal*, 24, 19-26.

412. Hall, W., Degenhardt L., Lynskey M. The health and psychological effects of cannabis use. In: Ageing Ha, ed. 2nd ed. Canberra 2001.

413. Robson, P. (2005) Human studies of cannabinoids and medicinal cannabis. *Handbook of Experimentqal Pharmacology*, 719-56.

414. Williamson, E. M., Evans F. J. (2000) Cannabinoids in clinical practice. *Drugs*, 60, 1303-14.

415. Grant, J. E., Menard W., Pagano M. E., Fay C., Phillips K. A. (2005) Substance use disorders in individuals with body dysmorphic disorder. *Journal of Clinical Psychiatry*, 66, 309-16; quiz 404-5.

416. Ware, M. A., Doyle C. R., Woods R., Lynch M. E., Clark A. J. (2003) Cannabis use for chronic non-cancer pain: results of a prospective survey. *Pain*, 102, 211-6.

417. Breckenridge, J., Clarke J. D. (2003) Patient characteristics associated with opioid versus nonsteroidal anti-inflammatory drug management of chronic low back pain. *The Journal of Pain*, 4, 344-50.

418. Edlund, M. J., Sullivan M., Steffick D., Harris K. M., Wells K. B. (2007) Do users of regularly prescribed opioids have higher rates of substance use problems than nonusers? *Pain Medicine*, 8, 647-56.

419. Doverty, M., White J. M., Somogyi A. A., Bochner F., Ali R., Ling W. (2001) Hyperalgesic responses in methadone maintenace patients. *Pain*, 90, 91-6.

420. Webster, L. R., Webster R. M. (2005) Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the opioid risk tool. *Pain Medicine*, 6, 432-42.

421. Brauer, L. H., De Wit H. (1997) High dose pimozide does not block amphetamine-induced euphoria in normal volunteers. *Pharmacology Biochemisty and Behavior*, 56, 265-72.

422. Degenhardt, L., Topp L. (2003) 'Crystal meth' use amongst polydrug users in Sydney's dance party subculture: characteristics, use patterns and associated harms. *International Journal of Drug Policy*, 14, 17-24.

423. Blockmans, D., Persoons P., Van Houdenhove B., Bobbaers H. (2006) Does methylphenidate reduce the symptoms of chronic fatigue syndrome? *The American Journal of Medicine*, 119, 167 e23-30.

424. Olson, L. G., Ambrogetti A., Sutherland D. C. (2003) A pilot randomized controlled trial of dexamphetamine in patients with chronic fatigue syndrome. *Psychosomatics*, 44, 38-43.

425. Randall, D. C., Cafferty F. H., Shneerson J. M., Smith I. E., Llewelyn M. B., File S. E. (2005) Chronic treatment with modafinil may not be beneficial in patients with chronic fatigue syndrome. *Journal of Psychopharmacology*, 19, 647-60.

426. Martin, P. R., Weinberg B. A., Bealer B. K. Pathological Gambling. *Healing Addiction: An integrated pharmacopsychosocial approach to treatment*. Hoboken: John Wiley & Sons Inc 2007:149-59.

427. Moreyra, P., Ibanez A., Saiz-Ruiz J., Nissenson K., Blanco C. (2000) Review of the phenomenology, etiology and treatment of pathological gambling. *German Journal of Psychiatry*, 3, 37-52.

428. Pallanti, S. Pathological Gambling. *Clinical Manual of Impulse-Control Disorders* 2006:251-89.

429. Volberg, R. A. (2002) The epidemiology of pathological gambling. *Psychiatric Annals*, 32, 171-8.

430. Petry, N. M. Introduction. *Pathological Gambling:Etiology, comorbidity, and treatment*. Washington: American Psychological Association 2005:3-8.

431. Blanco, C., Hasin D. S., Petry N., Stinson F. S., Grant B. F. (2006) Sex differences in subclinical and DSM-IV pathological gambling: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychological Medicine*, 36, 943-53.

432. Kausch, O. (2003) Patterns of substance abuse among treatment-seeking pathological gamblers. *Journal of Substance Abuse Treatment*, 25, 263-70.

433. Ladd, G. T., Petry N. M. (2003) A comparison of pathological gamblers with and without substance abuse treatment histories. *Experimental and Clinical Psychopharmacology*, 11, 202-9.

434. Pasternak, A. V. t., Fleming M. F. (1999) Prevalence of gambling disorders in a primary care setting. *Archives of Family Medicine*, 8, 515-20.

435. Petry, N. M., Stinson F. S., Grant B. F. (2005) Comorbidity of DSM-IV pathological gambling and other psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of Clinical Psychiatry*, 66, 564-74.

436. Toneatto, T., Brennan J. (2002) Pathological gambling in treatment-seeking substance abusers. *Addictive Behaviors*, 27, 465-9.

437. Magoon, M. E., Gupta R., Derevensky J. L. (2005) Juvenile delinquency and adolescent gambling. *Criminal Justice and Behavior*, 32, 690-712.

438. Dell'Osso, B., Altamura A. C., Allen A., Marazziti D., Hollander E. (2006) Epidemiologic and clinical updates on impulse control disorders: a critical review. *European Archives of Psychiatry and Clinical Neuroscience*, 256, 464-75.

439. Hall, G. W., Carriero N. J., Takushi R. Y., Montoya I. D., Preston K. L., Gorelick D. A. (2000) Pathological gambling among cocaine-dependent outpatients. *The American Journal of Psychiatry*, 157, 1127-33.

440. Petry, N. M., Tawfik Z. (2001) Comparison of problem-gambling and non-problem-gambling youths seeking treatment for marijuana abuse. *Journal of the American Academy of Child and Adolescent Psychiatry*, 40, 1324-31.

441. Ladouceur, R., Sylvain C., Boutin C., Lachance S., Doucet C., Leblond J. *et al.* (2001) Cognitive treatment of pathological gambling. *The Journal of Nervous and Mental Disease*, 189, 774-80.

442. Sylvain, C., Ladouceur R., Boisvert J. M. (1997) Cognitive and behavioral treatment of pathological gambling: a controlled study. *Journal of Consulting and Clinical Psychology*, 65, 727-32.

443. Toneatto, T., Ladoceur R. (2003) Treatment of pathological gambling: a critical review of the literature. *Psychology of Addictive Behaviors*, 17, 284-92.

444. Hodgins, D. C., Currie S. R., el-Guebaly N. (2001) Motivational enhancement and self-help treatments for problem gambling. *Journal of Consulting and Clinical Psychology*, 69, 50-7.

445. Pallesen, S., Molde H., Arnestad H. M., Laberg J. C., Skutle A., Iversen E. *et al.* (2007) Outcome of pharmacological treatments of pathological gambling: a review and meta-analysis. *Journal of Clinical Psychopharmacology*, 27, 357-64.

446. Hollander, E., Buchalter A. J., DeCaria C. M. (2000) Pathological gambling. *Psychiatric Clinics of North America*, 23, 629-42.

447. Kim, S. W., Grant J. E., Eckert E. D., Faris P. L., Hartman B. K. (2006) Pathological gambling and mood disorders: clinical associations and treatment implications. *Journal of Affecticve Disorders*, 92, 109-16.

448. Hollander, E., DeCaria C. M., Finkell J. N., Begaz T., Wong C. M., Cartwright C. (2000) A randomized double-blind fluvoxamine/placebo crossover trial in pathologic gambling. *Biological Psychiatry*, 47, 813-7.

449. Kim, S. W. (2002) Review of published studies on drug treatments for PGD. *Minnesota Medicine*, 85, 51-2.

450. Zimmerman, M., Breen R. B., Posternak M. A. (2002) An open-label study of citalopram in the treatment of pathological gambling. *Journal of Clinical Psychiatry*, 63, 44-8.

451. Hollander, E., DeCaria C. M., Mari E., Wong C. M., Mosovich S., Grossman R. *et al.* (1998) Short-term single-blind fluvoxamine treatment of pathological gambling. *The American Journal of Psychiatry*, 155, 1781-3.

452. Grant, J. E., Kim S. W., Potenza M. N. (2003) Advances in the pharmacological treatment of pathological gambling. *Journal of Gambling Studies*, 19, 85-109.

453. Kim, S. W., Grant J. E. (2001) The psychopharmacology of pathological gambling. *Seminars in Clinical Neuropsychiatry*, 6, 184-94.

454. Dannon, P. N., Lowengrub K., Musin E., Gonopolski Y., Kotler M. (2005) Sustained-release bupropion versus naltrexone in the treatment of pathological gambling: a preliminary blind-rater study. *Journal of Psychopharmacology*, 25, 593-6.

455. Kim, S. W. (1998) Opioid antagonists in the treatment of impulse-control disorders. *Journal of Clinical Psychiatry*, 59, 159-64.

456. Kim, S. W., Grant J. E., Adson D. E., Shin Y. C. (2001) Double-blind naltrexone and placebo comparison study in the treatment of pathological gambling. *Biological Psychiatry*, 49, 914-21.

457. Pallanti, S., Quercioli L., Sood E., Hollander E. (2002) Lithium and valproate treatment of pathological gambling: a randomized single-blind study. *Journal of Clinical Psychiatry*, 63, 559-64.

458. Dannon, P. N., Lowengrub K., Gonopolski Y., Musin E., Kotler M. (2005) Topiramate versus fluvoxamine in the treatment of pathological gambling: a randomized, blind-rater comparison study. *Clinical Neuropharmacology*, 28, 6-10.

459. Dannon, P. N., Lowengrub K., Aizer A., Kotler M. (2006) Pathological gambling: comorbid psychiatric diagnoses in patients and their families. *The Israel Journal of Psychiatry and Related Science*, 43, 88-92.

460. Dannon, P. N., Lowengrub K., Shalgi B., Sasson M., Tuson L., Saphir Y. *et al.* (2006) Dual psychiatric diagnosis and substance abuse in pathological gamblers: a preliminary gender comparison study. *Journal of Addictive Diseases*, 25, 49-54.

461. Martins, S. S., Storr C. L., Ialongo N. S., Chilcoat H. D. (2007) Mental health and gambling in urban female adolescents. *Journal of Adolescent Health*, 40, 463-5.

462. Zimmerman, M., Chelminski I., Young D. (2006) Prevalence and Diagnostic Correlates of DSM-IV Pathological Gambling in Psychiatric Outpatients. *Journal of Gambling Studies*, 22, 255-62.

463. Clarke, D. (2003) Gambling and the trait of addiction in a sample of New Zealand university students. *New Zealand Journal of Psychology*, 32, 39-48.

464. Toneatto, T., Skinner W., Dragonetti R. (2002) Patterns of substance use in treatment-seeking problem gamblers: impact on treatment outcomes. *Journal of Clinical Psychology*, 58, 853-9.

465. Fernandez-Montalvo, J., Echeburua E. (2004) Pathological gambling and personality disorders: an exploratory study with the IPDE. *Journal of Personality Disorders*, 18, 500-5.

466. Gerdner, R., Svensson K. (2003) Predictors of gambling problems among male adolescents. *International Journal of Social Welfare*, 12, 182-92.

467. Langenbucher, J., Bavly L., Labouvie E., Sanjuan P. M., Martin C. S. (2001) Clinical features of pathological gambling in an addictions treatment cohort. *Psychology of Addictive Behaviors*, 15, 77-9.

468. Slutske, W. S., Caspi A., Moffitt T. E., Poulton R. (2005) Personality and problem gambling: a prospective study of a birth cohort of young adults. *Archives of General Psychiatry*, 62, 769-75.

469. Morasco, B. J., Pietrzak R. H., Blanco C., Grant B. F., Hasin D., Petry N. M. (2006) Health problems and medical utilization associated with gambling disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychosomatic Medicine*, 68, 976-84.

470. Kaminer, Y., Burleson J. A., Jadamec A. (2002) Gambling behavior in adolescent substance abuse. *Substance Abuse*, 23, 191-8.

471. McNeilly, D. P., Burke W. J. (2002) Disposable time and dispossable income: Problem casino gambling behavior in older adults. *Journal of Clinical Geropsychology*, 8, 75-85.

472. Battersby, M., Tolchard B., Scurrah M., Thomas L. (2006) Suicide ideation and behaviour in people with pathological gambling attending a treatment service. *International Journal of Mental Health Addiction*, 4, 233-46.

473. Biddle, D., Hawthorne G., Forbes D., Coman G. (2005) Problem gambling in Australian PTSD treatment-seeking veterans. *Journal of Traumatic Stress*, 18, 759-67.

474. Dannon, P. N., Lowengrub K., Sasson M., Shalgi B., Tuson L., Saphir Y. *et al.* (2004) Comorbid psychiatric diagnoses in kleptomania and pathological gambling: a preliminary comparison study. *European Psychiatry*, 19, 299-302.

475. Feigelman, W., Gorman B. S., Lesieur H. (2006) Examining the relationship between at-risk gambling and suicidality in a national representative sample of young adults. *Suicide and Life-Threatening Behavior*, 36, 396-408.

476. Maccallum, F., Blaszczynski A. (2003) Pathological gambling and suicidality: an analysis of severity and lethality. *Suicide and Life-Threatening Behavior*, 33, 88-98.

477. Martins, S. S., Tavares H., da Silva Lobo D. S., Galetti A. M., Gentil V. (2004) Pathological gambling, gender, and risk-taking behaviors. *Addictive Behaviors*, 29, 1231-5.

478. Shaffer, H. J., Vander Bilt J., Hall M. N. (1999) Gambling, drinking, smoking and other health risk activities among casino employees. *American Journal of Industrail Medicine*, 36, 365-78.

479. McIntyre, R. S., McElroy S. L., Konarski J. Z., Soczynska J. K., Wilkins K., Kennedy S. H. (2007) Problem gambling in bipolar disorder: results from the Canadian Community Health Survey. *Journal of Affecticve Disorders*, 102, 27-34.

480. Ledgerwood, D. M., Petry N. M. (2006) Posttraumatic stress disorder symptoms in treatment-seeking pathological gamblers. *Journal of Traumatic Stress*, 19, 411-6.

481. Frost, R. O., Meagher B. M., Riskind J. H. (2001) Obsessive-compulsive features in pathological lottery and scratch-ticket gamblers. *Journal of Gambling Studies*, 17, 5-19.

482. Cunningham-Williams, R. M., Abdallah A. B., Callahan C., Cottler L. (2007) Problem gambling and violence among community-recruited female substance abusers. *Psychology of Addictive Behaviors*, 21, 239-43.

483. Ibanez, A., Blanco C., Donahue E., Lesieur H. R., Perez de Castro I., Fernandez-Piqueras J. *et al.* (2001) Psychiatric comorbidity in pathological gamblers seeking treatment. *The American Journal of Psychiatry*, 158, 1733-5.

484. Grant, J. E., Kim S. W. (2003) Comorbidity of impulse control disorders in pathological gamblers. *Acta Psychiatrica Scandinavica*, 108, 203-7.

485. Kausch, O. (2003) Suicide attempts among veterans seeking treatment for pathological gambling. *Journal of Clinical Psychiatry*, 64, 1031-8.

486. Hollander, E., Pallanti S., Allen A., Sood E., Baldini Rossi N. (2005) Does sustained-release lithium reduce impulsive gambling and affective instability versus placebo in pathological gamblers with bipolar spectrum disorders? *The American Journal of Psychiatry*, 162, 137-45.

487. Grant, J. E., Potenza M. N. (2006) Escitalopram treatment of pathological gambling with co-occurring anxiety: an open-label pilot study with double-blind discontinuation. *International Clinical Psychopharmacology*, 21, 203-9.

488. Maccallum, F., Blaszczynski A. (2001) Pathological gambling and comorbid substance use. *Australian and New Zealand Journal of Psychiatry*, 36, 411-5.

489. Sellman, J. D., Adamson S., Robertson P., Sullivan S., Coverdale J. (2002) Gambling in mild-moderate alcohol-dependent outpatients. *Substance Use and Misuse*, 37, 199-213.

490. Lejoyeux, M., Feuche N., Loi S., Solomon J., Ades J. (1999) Study of impulse-control disorders among alcohol-dependent patients. *Journal of Clinical Psychiatry*, 60, 302-5.

491. Kyngdon, A., Dickerson M. (1999) An experimental study of the effect of prior alcohol consumption on a simulated gambling activity. *Addiction*, 94, 697-707.

492. Phillips, J. G., Ogeil R. P. (2007) Alcohol consumption and computer blackjack. *The Journal of General Psychology*, 134, 333-53.

493. Potenza, M. N., Steinberg M. A., Wu R. (2005) Characteristics of gambling helpline callers with self-reported gambling and alcohol use problems. *Journal of Gambling Studies*, 21, 233-54.

494. Crockford, D. N. (1998) Naltrexone in the treatment of pathological gambling. *Canadian Journal of Psychiatry*, 43, 86.

495. Ledgerwood, D. M., Downey K. K. (2002) Relationship between problem gambling and substance use in a methadone maintenance population. *Addictive Behaviors*, 27, 483-91.

496. Weinstock, J., Blanco C., Petry N. M. (2006) Health correlates of pathological gambling in a methadone maintenance clinic. *Experimental and Clinical Psychopharmacology*, 14, 87-93.

497. Comer, S. D., Sullivan M. A., Yu E., Rothenberg J. L., Kleber H. D., Kampman K. *et al.* (2006) Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Archives of General Psychiatry*, 63, 210-8.

498. Pirastu, R., Fais R., Messina M., Bini V., Spiga S., Falconieri D. *et al.* (2006) Impaired decision-making in opiate-dependent subjects: effect of pharmacological therapies. *Drug and Alcohol Dependence*, 83, 163-8.

499. Deakin, J. B., Aitken M. R., Dowson J. H., Robbins T. W., Sahakian B. J. (2004) Diazepam produces disinhibitory cognitive effects in male volunteers. *Psychopharmacology (Berl)*, 173, 88-97.

500. Fann, J. R., Leonetti A., Jaffe K., Katon W. J., Cummings P., Thompson R. S. (2002) Psychiatric illness and subsequent traumatic brain injury: a case control study. *Journal of Neurology, Neurosurgery, and Psychiatry*, 72, 615-20.

501. Teasdale, T. W., Engberg A. W. (2001) Suicide after traumatic brain injury: a population study. *Journal of Neurology, Neurosurgery, and Psychiatry*, 71, 436-40.

502. Mann, J. J., Waternaux C., Haas G. L., Malone K. M. (1999) Toward a clinical model of suicidal behavior in psychiatric patients. *The American Journal of Psychiatry*, 156, 181-9.

503. Deb, S., Lyons I., Koutzoukis C., Ali I., McCarthy G. (1999) Rate of psychiatric illness 1 year after traumatic brain injury. *The American Journal of Psychiatry*, 156, 374-8.

504. Hibbard, M. R., Uysal S., Kepler K., Bogdany J., Silver J. (1998) Axis I psychopathology in individuals with traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, 13, 24-39.

505. Anstey, K. J., Butterworth P., Jorm A. F., Christensen H., Rodgers B., Windsor T. D. (2004) A population survey found an association between self-reports of taumatic brain injury and increased psychiatric symptoms. *Journal of Clinical Epidemiology*, 57, 1202-9.

506. Silver, J. M., Kramer R., Greenwald S., Weissman M. (2001) The association between head injuries and psychiatric disorders: findings from the New Haven NIMH Epidemiologic Catchment Area Study. *Brain Injury*, 15, 935-45.

507. Felde, A. B., Westermeyer J., Thuras P. (2006) Co-morbid traumatic brain injury and substance use disorder: childhood predictors and adult correlates. *Brain Injury*, 20, 41-9.

508. Jorge, R. E., Starkstein S. E., Arndt S., Moser D., Crespo-Facorro B., Robinson R. G. (2005) Alcohol misuse and mood disorders following traumatic brain injury. *Archives of General Psychiatry*, 62, 742-9.

509. Ries, R. K., Yuodelis-Flores C., Comtois K. A., Roy-Byrne P. P., Russo J. E. (2008) Substance-induced suicidal admissions to an acute psychiatric service: characteristics and outcomes. *Journal of Substance Abuse Treatment*, 34, 72-9.

510. Simpson, G., Tate R. (2002) Suicidality after traumatic brain injury: demographic, injury and clinical correlates. *Psychological Medicine*, 32, 687-97.

511. Timonen, M., Miettunen J., Hakko H., Zitting P., Veijola J., von Wendt L. *et al.* (2002) The association of preceding traumatic brain injury with mental disorders, alcoholism and criminality: the Northern Finland 1966 Birth Cohort Study. *Psychiatry Research*, 113, 217-26.

512. Hibbard, M. R., Ashman T. A., Spielman L. A., Chun D., Charatz H. J., Melvin S. (2004) Relationship between depression and psychosocial functioning after traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, 85, S43-S53.

513. Holsinger, T., Steffens D. C., Phillips C., Helms M. J., Havlik R. J., Breitner J. C. *et al.* (2002) Head injury in early adulthood and the lifetime risk of depression. *Archives of General Psychiatry*, 59, 17-22.

514. Koponen, S., Taiminen T., Portin R., Himanen L., Isoniemi H., Heinonen H. *et al.* (2002) Axis I and II psychiatric disorders after traumatic brain injury: a 30-year follow-up study. *The American Journal of Psychiatry*, 159, 1315-21.

515. Seel, R. T., Kreutzer J. S. (2003) Depression assessment after traumatic brain injury: an empirically based classification method. *Archives of Physical Medicine and Rehabilitation*, 84, 1621-8.

516. Seel, R. T., Kreutzer J. S., Rosenthal M., Hammond F. M., Corrigan J. D., Black K. (2003) Depression after traumatic brain injury: a National Institute on Disability and Rehabilitation Research Model Systems multicenter investigation. *Archives of Physical Medicine and Rehabilitation*, 84, 177-84.

517. Rapoport, M. J., McCullagh S., Streiner D., Feinstein A. (2003) The clinical significance of major depression following mild traumatic brain injury. *Psychosomatics*, 44, 31-7.

518. Underhill, A. T., Lobello S. G., Stroud T. P., Terry K. S., Devivo M. J., Fine P. R. (2003) Depression and life satisfaction in patients with traumatic brain injury: a longitudinal study. *Brain Injury*, 17, 973-82.

519. Simpson, G. K., Tate R. L. (2007) Preventing suicide after traumatic brain injury: implications for general practice. *Medical Journal of Australia*, 187, 229-32.

520. Tate, R., Simpson G., Flanagan S., Coffey M. (1997) Completed suicide after traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, 12, 16-28.

521. Kalsotra, A., Turman C. M., Dash P. K., Strobel H. W. (2003) Differential effects of traumatic brain injury on the cytochrome p450 system: a perspective into hepatic and renal drug metabolism. *Journal of Neurotrauma*, 20, 1339-50.

522. Wroblewski, B. A., Joseph A. B., Cornblatt R. R. (1996) Antidepressant pharmacotherapy and the treatment of depression in patients with severe traumatic brain injury: a controlled, prospective study. *Journal of Clinical Psychiatry*, 57, 582-7.

523. Lee, H., Kim S. W., Kim J. M., Shin I. S., Yang S. J., Yoon J. S. (2005) Comparing effects of methylphenidate, sertraline and placebo on neuropsychiatric sequelae in patients with traumatic brain injury. *Human Psychopharmacology*, 20, 97-104.

524. Perna, R. (2006) Brain injury: benzodiazepines, antipsychotics, and functional recovery. *The Journal of Head Trauma Rehabilitation*, 21, 82-4.

525. Fann, J. R., Uomoto J. M., Katon W. J. (2000) Sertraline in the treatment of major depression following mild traumatic brain injury. *Journal of Neuropsychiatry and Clinical Neurosciences*, 12, 226-32.

526. Turner-Stokes, L., Hassan N., Pierce K., Clegg F. (2002) Managing depression in brain injury rehabilitation: the use of an integrated care pathway and preliminary report of response to sertraline. *Clinical Rehabilitation*, 16, 261-8.

527. Soo, C., Tate R. (2007) Psychological treatment for anxiety in people with traumatic brain injury. *Cochrane Database of Systematic Reviews*, CD005239.

528. DASSA, D. a. A. S. S. A. (2005) Alcohol Related Brain Injury: A Guide for General Practitioners and Other Health Workers. Adelaide: Drug and Alcohol Services South Australia.

529. Trevena, L., Cameron I., Porwal M. (2004) Clinical Practice Guidelines for the Care of People Living with Traumatic Brain Injury in the Community. Sydney: The University of Sydney.

530. Isbister, G. K., Buckley N. A., Whyte I. M. (2007) Serotonin toxicity: a practical approach to diagnosis and treatment. *Medical Journal of Australia*, 187, 361-5.

# 14 Appendices

## 14.1 Serotonin toxicity

An overdose of some medications or some medication combinations can cause the build up of too much serotonin in the nervous system and the rest of the body. The syndrome is potentially fatal.

**Common features are as follows:**

- Severe restlessness.
- Over-excitability and hyperactivity (hypomania).
- Sweating and shivering.
- Diarrhoea.
- Fever.
- Lack of coordination.
- Confusion and altered consciousness.
- Tremor.
- Jerking limb movements (termed myoclonus).

**It is important to let your doctor know or attend an emergency department should you develop these symptoms.**

The syndrome can be treated with withdrawal of the medications that caused it in the first place. Sedative medications such as diazepam or lorazepam are sometimes needed. If more severe then intensive care is required.

Derived from Isbister, 2007(530).

## 14.2 NRT management

| | For those who smoke: | Dose | Duration |
|---|---|---|---|
| Patch | >10 cigarettes per day and weight > 45 kg | 21mg/24 hour or 15mg/16 hour patch | >8 weeks |
| | <10 cigarettes/day or weight <45 kg or cardiovascular disease | 14mg/24 hour or 10mg/16 hour patch | >8 weeks |
| | | | |
| Gum | > 20 cigarettes/day | 4 mg and 6–10 per day | >8 weeks |
| | > 10 and <20 cigarettes/day | 2mg and 8–12 per day | >8 weeks |
| | | | |
| Inhaler | >10 cigarettes/day | 6-12 cartridges per day | >8 weeks |
| | | | |
| Lozenge | First cigarette >30 minutes after waking | 2mg and 1 every 1–3 hours | >8 weeks |
| | First cigarette <30 minutes after waking | 4 mg and 1 every 1–2 hours | >8 weeks |

| | How to use: |
|---|---|
| Patch | Place the patch on a clean, non-hairy part of the body upon waking, place on a different site each day. |
| Gum | Chew the gum until a peppery/tingling feeling, flatten and 'park' it between the gum and the cheek. Chew and 'park' several times for each piece of gum.<br>Avoid coffee and drinks for 15 minutes before and while using the gum. |
| Inhaler | Inhale air through the cartridge for 20 minutes. |
| Lozenge | Suck the lozenge and then 'park' it between the gum and the cheek. Suck and 'park' several times for each lozenge.<br>Avoid coffee and drinks for 15 minutes before and while using the lozenge. |

Derived from NSW Department of Health[84].