

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 psychosis⁽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^{x(133)}.
 - An increase in sedation as a result of combinations of alcohol and benzodiazepines^x.

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 Bristol 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 **xxx**, fluoxetine **xx**, norfluoxetine **xx** and paroxetine **x** 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 **xxx**⁽¹⁵¹⁻¹⁵⁵⁾.
- Fluvoxamine is the most potent inhibitor of methadone and buprenorphine metabolism and is the most clinically relevant. Therefore, it should be avoided **xxx**⁽¹⁵⁰⁾.
- Fluoxetine and paroxetine should also be avoided **xx**.
- 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 **x**⁽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).

**Stimulants
(including
metham-
phetamine)**

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.