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.