Illicit drugs and drug interactions

by Angela Dean

Almost half the population of Australian adults reports use of an illicit substance at least once. Therefore it is likely that some of our patients may be using illicit drugs in combination with other medications. Illicit substance use may contribute to adverse effects, interfere with treatment efficacy, or even augment treatment effects. Additionally, regular users of illicit substances may exhibit poor medication adherence or impaired ability to engage in behaviours such as blood glucose testing in diabetes.

Systematic research on drug interactions with illicit drugs is not routinely conducted – most evidence comes from case reports. However, drug interactions are important. Many deaths that are attributed to illicit drug toxicity alone are often actually the result of drug interactions. This article reviews potential drug interactions with illicit drugs, with an emphasis on the two most popular illicit drugs in Australia – cannabis and methamphetamine.

Cannabis

Cannabis *(Cannabis sativa)* is the most widely used illicit drug. Drug effects include well-being, relaxation and altered sensory perception. Acute adverse effects include psychomotor impairment, dysphoria, anxiety, paranoia, tachycardia, flushing and nausea.[1] There are no reports of fatalities occurring due to cannabis toxicity.[2] Cannabis is generally perceived to have low dependence liability than many other drugs of abuse. However, there is increasing awareness that some users (about 10%) find it difficult to stop – this is more common in regular heavy users.[2]

There are more than 60 psychoactive constituents of cannabis that contribute to its effects; these are called cannabinoids, the most important of which is delta-9-tetrahydrocannabinol (THC). Synthetic THC (dronabinol, *Marinol*) is US FDA-approved for treatment of chemotherapy-related nausea and vomiting, and appetite and weight loss associated with HIV/AIDS.[3] More recently, a buccal spray formulated from the whole cannabis plant *(Sativex)*, has been developed in Canada for treatment of neuropathic pain associated with multiple sclerosis.[4]

Drug interactions

General considerations

A sedative medication may display added sedative effects when used in combination with cannabis. Similarly, cannabis use may augment the adverse effects of drugs with a similar side effect profile.[1] It remains to be established whether some drugs interact with cannabis via their influence on the endogenous cannabinoid systems.

Pharmacokinetic interactions may also occur. Cannabinoids are highly protein bound, raising the potential for interactions with other highly protein bound drugs such as warfarin. Clearance from the body is slow – THC distributes into adipose tissue from where it is slowly released.[1] In heavy users, it can take more than one month for cannabis to be completely eliminated from the body and for clean urine tests. It is unclear whether the delayed clearance in regular heavy users is associated with any subtle biological effects.

Cannabinoids are also metabolised by a range of enzymes, including CYP2C9 and CYP3A4. Any form of smoking can induce CYP1A2. This effect may be enhanced when cannabis is smoked with tobacco. CYP1A2 substrates include clozapine, olanzapine, theophylline, some tricyclic antidepressants and mirtazapine. Cannabinoids may also influence CYP3A4 – although existing reports suggest both inhibition and induction.[3] Ceasing cannabis use may also lead to altered serum concentrations of existing therapy.

Tricyclic antidepressants and anticholinergics

Case reports suggest that concurrent use of cannabis with TCAs or anticholingergic drugs can produce significant tachycardia. This may be due to beta-adrenergic effects of cannabis coupled with the anticholinergic effect of tricyclic antidepressants.[1,3] Increases in heart rate may be considered alarming (100-160 beats/minute). In one case, heart rate was 300 beats/minute and failed to respond to IV verapamil.[1] Onset is variable, but typically occurs within one hour of administration. Patients receiving treatment with anticholinergic medication and who use cannabis should be advised to monitor their heart rate.[1,3]

Other antidepressants

A single case report describes mania occurring following use of cannabis after four weeks of fluoxetine treatment. It is unclear whether this was a specific interaction, or caused by fluoxetine alone.[1,3] In clinical practice, cannabis and SSRIs are frequently used together with neglible adverse effects, suggesting that this proposed interaction is rare. *(For more on interactions between antidepressants and illicit drugs see Clinical update on page 714.)*

Antipsychotics

Smoking both cannabis and tobacco may increase chlorpromazine clearance.[1] A case report describes a patient who displayed confusion and raised serum concentrations of clozapine after ceasing cannabis and tobacco smoking.[5] These interactions are probably mediated by pharmacokinetic effects.

Research suggests cannabis use is a risk factor for a later diagnosis of schizophrenia, but is not considered a true causative factor alone.[2] For patients with established schizophrenia, cannabis use is associated with a range of poor outcomes, including increased risk of relapse, and poorer adherence with antipsychotic treatment.[2] Emerging research suggests that antipsychotic treatment may influence the endogenous cannabinoid system – the clinical relevance of this is unclear.[6]

Protease inhibitors

One study reports that cannabis use was associated with reduced area under the curves and serum concentrations for both indinavir and nelfinavir (10-17%),[1] although some participants exhibited an increase in drug serum concentrations, making it difficult to determine the clinical significance of these results. Nonetheless, patients receiving treatment with protease inhibitors who also use cannabis should receive regular monitoring of viral indicators to confirm effectiveness of antiviral treatment.[3]

Cocaine

Using cannabis with cocaine may enhance onset of action and bioavailability of cocaine, leading to increased subjective effects of cocaine, and increased heart rate.[7,8] It is possible that cannabis-induced vasodilation of the nasal mucosa leads to increased cocaine absorption, although these effects have also been demonstrated using intravenous cocaine.[8] Many drug takers use cannabis in combination with other drugs to enhance their effects – it is likely that they intentionally use this combination together to get better cocaine effects.

Disulfiram

Concurrent use of cannabis and disulfiram was associated with emergence of hypomania in a man who had prior exposure to both drugs alone, without ill effect. However, others have used this combination without adverse effects, and it has been suggested that the cannabis involved in this case may have been adulterated.[1,3]

Lithium

One case report claims that cannabis may interact with lithium, causing an increase in lithium concentrations. However, the actual significance of this report is uncertain, as the patient involved had fluctuating lithium levels prior to cannabis use, and no potential mechanism was proposed.[1]

Sildenafil

Ones report claims that the combined use of sildenafil and cannabis contributed to myocardial infarction in a 41-year-old man. However, available information was insufficient to confirm the interaction, and both drugs have been independently linked to myocardial infarction.[1,3]

Theophylline

A number of studies report that regular cannabis use (at least twice-weekly) can increase theophylline clearance and reduce efficacy via induction of CYP1A2. Smoking both tobacco and cannabis is likely to produce a greater effect than use of either drug alone. Regular cannabis users may require higher theophylline doses. Although cannabis may exert bronchodilatory effects, regular smoking contributes to poorer respiratory function. Cessation of cannabis use may increase theophylline clearance.[1,3]

Rimonabant

Rimonabant is a selective antagonist at the central cannabinoid receptor (CB1). It is not yet routinely available, but is being investigated for indications such as smoking cessation and obesity.[9] As cannabis exerts its primary effects via CB1, concurrent use of rimonabant may reduce the effects of either drug.

Immunosuppressants

The cannabinoid receptor CB2 mediates immunosuppressant effects and is currently the target of development of novel immunosuppressants. It is unclear whether using cannabis produces clinically relevant immunosuppression – studies of HIV patients have not supported a link between cannabis use and progression of HIV.[1] It is also unclear whether cannabis may interfere with the actions of purported immune stimulants, such as *Echinacea*.

Amphetamines

In Australia, methamphetamine is the second most commonly used illicit drug after cannabis, with almost 10% of the population having tried it.[10,11] Methamphetamine produces similar effects to amphetamine, but at smaller doses, it produces prominent CNS stimulation with fewer peripheral effects. Amphetamines are weakly basic and are available in various forms:

- Salt form, e.g. methamphetamine sulphate, commonly called 'speed'
- Free base form, which looks like a damp or oily paste, referred to as 'base'
- Crystallised form, generally more pure, referred to as 'ice' or 'crystal meth'.

The quality of methamphetamine varies widely.[11] Amphetamines may be taken orally, intranasally ('snorting') or injected intravenously.

The primary mode of amphetamine action is increased release of dopamine. Amphetamine is also able to inhibit dopamine metabolism and its re-uptake, and increase release of noradrenaline and serotonin.[12] Amphetamines produce euphoria, mood elevation, increased energy and a reduction in fatigue.[12] As sympathomimetic agents, they produce a range of cardiovascular effects, including hypertension and increased cardiac output. Adverse effects typically predominate at higher doses, and include restlessness, tremor, anxiety, irritability, insomnia, psychosis, aggression, sweating, palpitations, chest pain, shortness of breath, and headache.[13] Injecting methamphetamine is common practice – many drug users accessing needle exchange facilities are often using amphetamine rather than heroin.

Policies restricting pseudoephedrine availability have intended to prevent its use as a precursor for amphetamine manufacture. It is difficult to determine the actual impact of pseudoephedrine restriction on amphetamine use in Australia. There are numerous techniques for manufacturing amphetamines – each requiring a different range of precursors. As some precursors become restricted, new 'recipes' are developed that utilise different precursors. Additionally, large scale importation of pseudoephedrine and ephedrine for illicit drug manufacture has occurred recently[14] and recent reports indicate that most methamphetamine users still find it easy to obtain.[11]

General considerations

Pharmacodynamic interactions may occur with a range of drug types, primarily cardiovascular and psychotropic medications. Amphetamines are metabolised by a range of liver enzymes, primarily CYP2D6.[15] Inhibitors of CYP2D6 (e.g. paroxetine, fluoxetine, ritonavir, quinidine) may increase serum concentrations of amphetamines and increase risk of adverse effects. (Drug interactions with psychostimulants are described in Table 1, opposite page.)

Antidepressant interactions

Interactions between amphetamines and antidepressants may occur secondary to serotonergic, noradrenergic or pharmacokinetic effects. One case describes a patient maintained on dexamphetamine who developed signs of serotonin toxicity after initiating venlafaxine. After venlafaxine was discontinued and symptoms abated, he was initiated on citalopram, which lead to reemergence of serotonergic symptoms.[16] Concurrent use of amphetamine-related substances and non-selective MAOIs results in severe hypertensive crisis.[3] Acute elevations in blood pressure have also been noted after co-ingestion of methylphenidate and tricyclic antidepressants.[17] This interaction has the potential to occur with other antidepressants that enhance noradrenergic activity, including moclobemide, tricyclic

Table 1: Drug interactions with psychostimulants: methamphetamine, MDMA and cocaine

Antidepressants: All psychostimulants have the potential to interact adversely with antidepressants based on serotonergic, noradrenergic and pharmacokinetic mechanisms. (See the text for more detail.)

Serotonergic drugs: A range of serotonergic drugs have the potential to interact with psychostimulants, especially MDMA, to produce symptoms of serotonin toxicity. No case reports describe such interactions, but they may potentially with a range of agents, such as St John's wort, tramadol, pethidine or triptans.

Antipsychotics: All antipsychotics antagonise the effects of dopamine at the D2 receptor. Concurrent use of psychostimulants and antipsychotics may reduce the efficacy of either agent. The actual clinical outcome will vary with the doses of each agent. It is likely that this effect is more pronounced with methamphetamine.

High doses of amphetamines and other psychostimulants may produce a drug-induced psychosis or psychotic symptoms.[1,3]

Small studies suggest that cocaine users experience greater incidence of antipsychotic-induced acute dystonias than non-cocaine users. One report described concurrent use of cocaine and clozapine leading to increased cocaine serum concentrations, but reduced psychoactive and pressor effects.[1]

Antihypertensives: All psychostimulants can increase blood pressure and may counteract therapeutic effect of antihypertensives.[1] Patients with hypertension who also use psychostimulants may find it more difficult to achieve adequate control.

Use of propranolol in combination with cocaine leads to greater coronary vasoconstriction compared to cocaine alone. Research and clinical opinion is divided on whether cocaine should be avoided in patients who have recently used cocaine or other stimulants. It has been suggested that use in combination with a vasodilating agent may reduce risks related to excessive vasoconstriction.[1]

Urinary alkalinisers: Alkaline urine increases amounts of un-ionised amphetamine, which then permits increased tubular reabsorption. This effect may increase the half-life from 7-12 hours to 18-34 hours for methamphetamine or from seven to 16-31 hours for MDMA.[12,26] Depending on the situation, some amphetamine users may find this a beneficial effect, whereas others may find it problematic.

Anticonvulsants: Methamphetamine, MDMA and cocaine lower the seizure threshold, and may cause seizures. They should be avoided in individuals with seizure disorders.[1] Of these drugs, cocaine poses the greatest risk for drug-induced seizures. Concurrent use of cocaine and carbamazepine may lead to large elevations in blood pressure and heart rate, although this effect is not consistently reported.[1]

Protease inhibitors: One case report describes an individual receiving ritonavir and other antiretroviral therapy who died after using methamphetamine and amyl nitrate. Although it is unclear whether the drug combination or methamphetamine alone contributed to the death, the authors suggest that ritonavir may have inhibited CYP2D6 mediated methamphetamine metabolism, increasing risk of toxicity.[27]

Several cases are reported where concurrent use of MDMA and ritonavir produced serious, sometimes fatal interactions. In one case, serum concentrations of MDMA were 10-times higher than what was expected given the dose ingested. It is thought that this interaction is mediated via ritonavir inhibition of CYP2D6 and CYP3A4.[1,18]

Hepatotoxic drugs: Growing evidence suggests that MDMA may be hepatotoxic.[1,12] Concurrent use of MDMA and hepatotoxic medication such as methotrexate may theoretically increase risk of adverse hepatic effects. The risk of hepatotoxicity from other psychostimulants has not been determined.

Tobacco/nicotine: Smoking methamphetamine in combination with tobacco creates the pyrolysis product cyanomethylmethamphetamine, which may possess stimulant properties.[12] The potential toxicity of this product has not been established. Smoking is not a predominant route of amphetamine administration in Australia.

Psychostimulants may act as behavioural stimulants, increasing rate of learned behaviour. This may lead to increases in number of cigarettes smoked and total amount of tobacco consumed.[12]

Cocaine and nicotine produce a synergistic effect on dopamine release in the reward areas of the brain. Cocaine and nicotine may also exert synergistic effects on myocardial oxygen supply, arterial pressure and cardiac contractility. Since nicotine, like cocaine, is a risk factor for cardiac disease, it is thought that smoking may increase the incidence of cardiac complications arising from cocaine use.[12]

Ethanol: Concurrent use of ethanol and psychostimulants may reduce the subjective effects of ethanol, and produce greater increases in blood pressure than when either drug is taken alone.[1,12,28] Stimulants do not reverse ethanol-related performance deficits.[12] Alcohol may slow methamphetamine metabolism and may increase serum concentrations of MDMA by 9-15%; the mechanism of these changes is unclear.[12,18]

Concurrent use of alcohol and cocaine use may increase risk of cardiovascular toxicity which may result from the formation of an active, ethanol-induced metabolite, cocaethylene, which is more reinforcing than cocaine, and potentially more toxic.[3,12]

antidepressants and venlafaxine.[1] Most antidepressants (SSRIs, TCAs, venlafaxine) inhibit CYP2D6 and may increase adverse effects of amphetamines; the strongest inhibitors are paroxetine and fluoxetine. False positive urine tests for amphetamine may also occur during TCA treatment.[3] The frequency of these interactions is difficult to determine, as many amphetamine users receive antidepressants in practice. Apart from MAOIs, such combinations are not contraindicated, but patients should be monitored for relevant adverse effects such as serotonin toxicity or hypertension. The antidepressant of choice for patients who use amphetamines has not been established.

Methylene dioxymethamphetamine ('ecstasy')

Methylene dioxymethamphetamine (MDMA) is structurally related to both amphetamine and the hallucinogen mescaline. It is usually administered orally, and it is typically available as a tablet with an embossed logo or pictures on it.[18]

MDMA produces large increases in serotonin release via its actions on the serotonin transporter.[19] MDMA exerts a variety of other monoamine effects including enhancing release, inhibiting reuptake and direct receptor interactions.[12] Desired effects of MDMA relate to mood elevation, feeling a sense of closeness to others, greater sociability, sharpened sensory perception, and extraversion. Adverse effects are similar to those of amphetamines related to excessive CNS and cardiovascular stimulation.[12,18] Additional effects related to serotonergic excess include jaw clenching and tooth grinding.

General considerations

Similar to amphetamines, MDMA can interact with a range of drugs based its serotonergic effects. MDMA is metabolised by a range of CYP enzymes, primarily CYP2D6. MDMA exhibits non-linear kinetics. Drugs which inhibit CYP2D6 and other CYP enzymes may increase the risk of MDMA toxicity.[18] (See Table 1.)

Antidepressant interactions

MDMA and most antidepressants enhance activity of serotonin; concurrent use may increase the risk of serotonergic side effects. Four deaths have been reported following ingestion of MDMA and moclobemide.[20] The mode of death in each case was consistent with a serotonin syndrome. Another report describes a fatality occurring after ingestion of MDMA and phenelzine.[21]

Most antidepressants used in Australia act by inhibiting reuptake of serotonin via interaction with the serotonin transporter (e.g. SSRIs). Via this transporter, MDMA produces serotonin release, and SSRIs remove serotonin from the synapse. The drug interaction arising from concomitant administration of MDMA and SSRIs depends on the temporal ordering of drug use. Initial use of an SSRI will inhibit serotonin transporter function, impairing the activity of any subsequently used MDMA. The ability of pretreatment with an SSRI to block effects of MDMA has been demonstrated in animal studies.[22] However, in the reverse scenario, if SSRIs are used after MDMA, the opposite interaction may occur. Initial use of MDMA increases release of serotonin; use of an SSRI after this release may prevent its removal from the synapse, leading to potentiation of serotonergic effects and possible toxicity. The actual clinical outcome produced in real situations is difficult to predict. One report[23,24] describes a case where ingestion of citalopram and MDMA led to symptoms resembling serotonin syndrome which improved after cessation of the citalopram.

Both MDMA and antidepressants are able to cause hyponatraemia. There is a theoretical risk of additive effects, especially when used in situations where dehydration may occur, such as long periods of dancing.[1]

Cocaine

Cocaine is the only naturally occurring local anaesthetic. Generally, the market for cocaine in Australia is smaller than for methamphetamine or heroin.[11] Cocaine blocks reuptake of dopamine and other monoamines. Like other local anaesthetics, cocaine produces direct effects on cell membranes blocking sodium channel activity.[12,25] Cocaine produces euphoria, mood elevation, and energy. Adverse effects include tremors, chest pain, agitation, aggression, paranoia and convulsions. Cocaine may increase heart rate, blood pressure and cardiac output, and enhance platelet aggregation.[12,25] (See Table 1.)

Antidepressant interactions

Use of cocaine and MAOIs may lead to hypertensive crisis.[3] No clear interactions have been documented for other antidepressants. One report suggests that fluoxetine can reduce the euphoric effects of cocaine.[1]

Other drugs

Table 2 (opposite page) describes potential interactions from other drugs.

Talking to patients about illicit drug use

For many patients, illicit drug use is a sensitive area. Many people will avoid mentioning their drug use. When discussing these issues, it is important to maintain a confidential, private and non-judgemental environment. In some cases, clinical information and advice can be provided without requiring the patient to disclose any drug use, using statements such as 'some people who use this medication also use cannabis from time to time – this may interfere with the beneficial effects of this drug'.

With some treatments, it may be optimal for patients to avoid illicit drugs. However, encouraging substance users to avoid drug use is commonly ineffective. Patients should always be informed about interactions which are well documented with the potential to be fatal, such as that between amphetamines and MAOIs. In most cases, harm reduction approaches and language are appropriate, e.g. 'It is best for your safety to avoid this combination of drugs. However, if that is not an option for you, we recommend that that you use smaller amounts of drug, and have non-drug using friends with you to look after you or call an ambulance if required'.

Drug users are a heterogenous group. Some will feel uncomfortable discussing their drug use, some will not. Some are concerned about their health, some are not. Some will appreciate your advice, others may not. Nonetheless, being aware of drug interactions with illicit drugs can facilitate our roles as pharmacists, and improve outcomes for a diverse patient group.

Table 2: Potential drug interactions with other drug groups[1,3]

***Drug* – Heroin**

***Interactions* – Benzodiazepines, alcohol, other opioids and other sedatives:** alcohol and sedatives interact with heroin synergistically to produce greater respiratory depression. Hypotension, profound sedation or coma may occur. Research indicates that heroin used in combination with benzodiazepines, alcohol or sedative mediation is more likely to trigger a fatal heroin overdose compared to heroin use alone.[3,29] If such combinations are unable to be avoided, heroin users should be advised to use smaller doses of heroin in the presence of other individuals who are able to monitor for, and respond to, signs of overdose. It is unclear whether less potent sedatives such as antihistamines or valerian are able to increase risk of overdose.

Naltrexone: naltrexone competitively antagonises the mu opioid receptor which is the primary site of action for heroin and other opioids. Use of naltrexone during regular or dependent heroin use may trigger a severe opioid withdrawal syndrome. Patients should be heroin-free for at least seven days before initiating naltrexone.[3]

Panax ginseng: animal studies suggest that Panax ginseng is able to counteract the analgesics and other effects of opiates.[3]

MAOIs: It has been suggested that use of MAOIs with central nervous system (CNS) depressants, including opiates, may result in hypotension and exaggeration of the CNS and respiratory depressant effects.[3] No case reports confirming this interaction were identified.

***Drug* – Hallucinogens:** Includes a wide range of synthetic and plant based substances, e.g. Lysergic acid diethylamide –LSD or 'acid', Psilocybin – 'magic mushrooms', mescaline (Peyote cactus, *Lophophora williamsii*)

***Interactions* – Antidepressants:** small studies in LSD users suggest that chronic use of TCAs and lithium may *increase* subjective effects of LSD, whereas chronic use of SSRIs and MAOIs may *reduce* the subjective effects of LSD.[1]

Most hallucinogens act on serotonergic systems, so caution should be exercised with other serotonergic drugs.

***Drug* – Gamma hydroxybutyrate – GHB** (Also called fantasy or liquid ecstasy)

***Interactions* – Sedative drugs:** pronounced sedative effects of GHB likely to be increased by concurrent use of other CNS depressants. Some deaths reported implicate alcohol.[1]

Ritonavir and enzyme inhibitors: one case report describes near fatal CNS depression occurring in a man using GHB in combination with ritonavir and saquinavir. He had used similar and higher doses of GHB in the past without other meds and no ill effects.[1]

***Drug* – Amyl nitrite**

***Interactions* – Sildenafil:** concurrent use of nitrates with sildenafil can lead to potentially fatal hypotension.

***Drug* – Volatile substances**

Includes: petrol, fuels, glue, aerosol propellants, paint thinners, other solvents

Interactions – No particular drug interactions were identified. Specific toxicity profiles vary substantially between agents.

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