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Introduction

People who use drugs of abuse (DOA) commonly have several comorbidities, which can be severe. Conditions such as chronic liver or heart failure, vascular disease and diabetes require medications. These medications can be taken unpredictably and even when taken predictably there is a high risk of both drug-drug and drug-DOA interactions. When ceasing a DOA, a variety of physiological changes occur affecting drug kinetics and activity. Specifically, factors such as improved control of underlying disease, better nutrition and altered lean body weight can variably affect pharmacokinetic processes such as absorption and clearance of some drugs. Further, when therapies to assist DOA cessation are initiated, they can interact with current therapies for chronic diseases causing additional drug interactions. Knowledge of the pharmacology of the drugs used and the changes in patient physiology that may affect drug clearance or drug concentrations can be used to guide physicians to likely clinical outcomes if dosing is unchanged. This Perspectives provides a brief pharmacological summary to guide clinicians of potential risks in this area.

Drugs of addiction and their interactions

Drugs may be metabolised through chemical modulation of their structure catalysed by cytochrome (CYP) P450 enzymes (Phase I metabolism) or via a conjugation reaction (e.g. glucuronidation or sulfation, Phase II metabolism) to promote
excretion.\textsuperscript{1}

Pharmacological properties of common drugs of addiction such as alcohol and smoking may impact the metabolism of other drugs. For example, cigarette smoking induces the activity of CYP1A2\textsuperscript{2} and CYP2B6,\textsuperscript{3} likely to be clinically relevant for medications such as clozapine which have a narrow therapeutic index anyway, and are metabolised by CYP1A2. Changes in the quantity of cigarettes smoked may require dose adjustments in other medications, particularly as several antidepressant medications are partially metabolised by CYP1A2.\textsuperscript{4}

CYP1A2 induction is rapidly reversed when smoking is ceased abruptly, with a new steady state reached after approximately one week.\textsuperscript{5} This results in reduced clearance of drugs metabolised by CYP1A2 (a mean increase of 72\% in plasma clozapine concentrations has been demonstrated\textsuperscript{6}) and increases the risk of adverse drug reactions. Patients on clozapine should thus (if possible) gradually reduce their smoking when attempting to stop, with close monitoring of clinical state, blood count and clozapine concentrations. Importantly also, compared to non smokers, smoking is associated with a lower body mass index, which alters the volume of distribution of fat soluble drugs, affecting drug concentrations; this may change when smoking ceases if body weight increases.

Alcohol is metabolised primarily in the liver via aldehyde dehydrogenase (ALDH), alcohol dehydrogenase (ADH), CYP2E1 and catalase. Chronic excessive use of alcohol (but not necessarily episodic drinking) leads to CYP2E1 induction, contributing to
metabolic tolerance for ethanol. CYP2E1 metabolises some medications commonly used in this population, including propranolol, diazepam and paracetamol, potentially making them less effective. This effect is reversed when alcohol is ceased and therefore doses of these medications should be reviewed when an alcohol dependent person ceases drinking, or if cirrhosis develops, reducing metabolism.

Accurate dose adjustment in liver impairment (both cirrhosis, alcoholic hepatitis or both) is difficult because unlike in renal failure, a reliable predictor of hepatic drug clearance is lacking. Although standard tools for assessing severity of liver disease have been suggested (Child-Pugh classification), they are not useful to guide dose adjustment in liver impairment. Rather, measures of clinical effects (desired e.g. pain relief and adverse e.g. sedation) or the concentration of drugs of interest, if available, can be measured to guide dosing.

Opioids are metabolised in the liver by glucuronidation and/or via the CYP system and then excreted by the kidneys. These are common metabolic systems for other medications patients may be taking. For example efficacy of oxycodone, a commonly abused opioid is affected by drugs that inhibit CYP3A4. Concomitant administration of antidepressants or medications such as most macrolides, azoles, verapamil or diltazem can potentially increase oxycodone concentrations and stopping these medications, or adding CYP3A4 inducer-drugs, has the opposite effect.

Benzodiazepines are a common DOA, but can also be helpfully prescribed in the
withdrawal setting, for example after ceasing alcohol. The main issues are tolerance, long half life for some compounds, and the fact that cirrhosis can result in liver ‘shunting’ of benzodiazepine parent drug and precipitation of hepatic encephalopathy.¹³

**Common comorbidities**

Comorbidities that occur in the patient population with addiction problems may impact drug pharmacology. Cirrhosis of the liver may be present in those with chronic alcohol abuse, or secondary to hepatitis C virus from intravenous drug use with contaminated injecting equipment.¹⁴ Chronic liver disease is associated with impaired drug metabolism due to reduced hepatic blood flow and impaired enzyme activity; this will have a larger impact on drugs which rely heavily on hepatic clearance including antidepressants and antipsychotics.¹⁵ Oedema and ascites in advanced liver disease cause an increased volume of distribution that may require dose adjustments of commonly used drugs; this may need to be revised once the precipitant for decompensation has been managed and vascular volume improved.

People with cirrhosis often have a marked reduction in metabolic function of the liver. Medications which rely on first pass metabolism can be impacted by portal-systemic venous shunting, causing increased drug concentrations in the systemic circulation.¹³ This can lead to significant pharmacodynamic interactions, causing sedation for example with other central nervous system (CNS) acting drugs such as opiates or benzodiazepines.¹⁵ In cases of continued alcohol ingestion, metabolism of some hepatically metabolised drugs may be augmented and pharmacokinetic drug
interactions may occur due to proliferation of the smooth endoplasmic reticulum, increase in microsomal protein content and cytochrome P450. The effects of chronic alcohol ingestion on drugs with low and high hepatic extraction, high and low binding, important tissue localisation and microsomal and non-microsomal metabolism are quite different however and not well studied from a clinical perspective, making predictions of overall effect difficult. Close monitoring and use of therapeutic drug monitoring where indicated can be helpful.

Active liver disease even without cirrhosis can also potentially both decrease clearance and/or alter oral bioavailability. This is particularly so if proton pump inhibitors are used as co-therapy for prevention of variceal bleeds; these change ionisation and reduce absorption of both nutrients (e.g. calcium and magnesium) and therapeutics across the small intestinal wall.

Unsafe injection practice can result in blood borne viral infections, including Human Immunodeficiency Virus (HIV) and hepatitis C. New, complex drug treatment regimens are often used in a population with significant comorbidity and/or on maintenance withdrawal therapies. Commonly used drugs in both populations are often potent CYP3A4 inhibitors such as azole antifungals, macrolides and non-dihydropyridine calcium channel blockers. This is relevant as many of the anti therapies are substrates for the CYP P450 system, as are several medications used to manage withdrawal of addictions.

Lastly, studies have shown a high prevalence of concomitant mental illness and
substance abuse. These conditions are commonly managed with drugs that are substrates, inhibitors or inducers of liver metabolic pathways, such as antidepressants and/or antipsychotic therapies. This makes knowledge of interactions between particular drugs of addiction, addiction treatment therapies and antipsychotics, antidepressants, antibiotics or antivirals particularly relevant.14

**Common interactions with drugs used to treat addiction**

The main therapies for treating nicotine addiction are nicotine replacement therapy (NRT), bupropion and varenicline. Varenicline, a partial agonist at neuronal nicotinic acetylcholine receptors, has no known clinically significant drug interactions.18

Bupropion, a selective catecholamine reuptake inhibitor and effective smoking cessation agent, is associated with a small but real dose-related risk of seizures. Use of other drugs that lower the seizure threshold or reducing benzodiazepines concurrently increase this risk. Bupropion is metabolised by CYP2B6 but inhibits the CYP2D6 pathway,19 a common metabolic pathway for many antidepressant and antipsychotic medications. Metoprolol, perhexiline and several other cardiovascular and analgesic medications are predominantly metabolised by CYP2D6 and dosages should be reduced to the lower end of the range if bupropion is used. Co-administration of drugs known to induce CYP2B6 metabolism (for example, carbamazepine and phenytoin19) or inhibit metabolism via a phase II process (for example, valproate20) may affect the activity of bupropion.
Alcohol dependence can be managed with disulfiram, acamprosate or naltrexone (an opioid antagonist). Disulfiram is a weak inhibitor of CYP2C9 metabolism and an inhibitor of ALDH, which converts acetaldehyde to acetate in alcohol metabolism. The increased concentration of acetaldehyde that occurs when alcohol is ingested with disulfiram causes the ‘aldehyde reaction’, an unpleasant combination of symptoms which acts as a deterrent to alcohol consumption. Disulfiram can enhance warfarin’s anticoagulant effect, potentially via inhibiting the hepatic synthesis of prothrombin. Hence, monitoring and adjustment of warfarin dosage may be necessary if disulfiram and warfarin are coadministered. There are several case reports of acute psychotic reaction and confusion when disulfiram is used with metronidazole. The effects of diazepam have been shown to be increased and prolonged by the concurrent use of disulfiram.

Acamprosate modulates the glutamate system through reduced calcium influx, and helps promotes abstinence by restoring the balance between the gamma-aminobutyric acid (GABA) and glutamate systems that is disrupted in alcohol use disorders. There is little evidence for significant drug interactions with acamprosate as it does not undergo metabolism, however coadministration with naltrexone can increase acamprosate peak concentrations by 33%. It has poor bioavailability, worsened by coadministration of food, and is renally excreted with a linear relationship between creatinine clearance and drug clearance. Patients with creatinine clearance less than 30 mL/min should not usually be prescribed acamprosate.
Although baclofen may be effective in reducing alcohol relapse, further research is required before it can be recommended routinely.23

Opioid dependence is routinely managed with controlled prescribing of either methadone or buprenorphine. Methadone is a synthetic opioid agonist which is predominantly metabolised via CYP3A4 and CYP2D6.30 Methadone has multiple potential pharmacodynamic and pharmacokinetic interactions. Pharmacodynamic interactions between methadone and other CNS depressants including benzodiazepines, alcohol, sedative antihistamines and tricyclic antidepressants can exacerbate respiratory depression and sedation.30 Subsequently, the risk of mortality or morbidity increases when a person on methadone takes other CNS depressants. Concurrent use of opioids and benzodiazepines has been demonstrated to increase rates of fatal overdose,31 emergency department presentations and inpatient admissions.32

A multitude of pharmacokinetic interactions between methadone and CYP3A4 inhibitors have been reported, resulting in a reduction in methadone clearance and potential opioid toxicity. CYP3A4 inducers such as carbamazepine, phenytoin, and phenobarbital may induce the metabolism of methadone and reduce methadone exposure, leading to opioid withdrawal.3 Methadone-induced prolongation of the QT interval is dose-dependent and may be worsened by concomitant use of CYP inhibitors.33

Buprenorphine, a mu opioid receptor partial agonist and kappa opioid receptor
antagonist, is co-formulated with naloxone, an opioid antagonist, to reduce the likelihood of abuse or diversion. Buprenorphine is oxidatively metabolised by CYP3A4 and has been found to have less clinically significant interactions than methadone, although the research is limited. The high affinity of buprenorphine for opioid receptors can cause issues with acute pain control, and may precipitate opioid withdrawal on commencing treatment in a dependent person. Concomitant use with benzodiazepines can result in adverse effects from respiratory depression. However, these toxicities are seen less commonly with buprenorphine than with methadone. Buprenorphine/naloxone treatment appears to be less likely than methadone to be associated with adverse drug effects in combination with antiretrovirals, which may be useful to clinicians who must treat both HIV and opioid dependence in the same patient.

**Common drug interactions with comorbidity**

Fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), is metabolised by CYP1A2 and therefore smokers may require higher doses than non smokers to achieve similar concentrations. The tricyclic antidepressants imipramine, amitriptyline, and clomipramine are partially metabolised by CYP1A2 and therefore smokers may require higher doses. Nortriptyline, also a tricyclic antidepressant, is predominantly a CYP2D6 substrate and unaffected by smoking. Warfarin’s less active enantiomer, R isomer is eliminated to a minor extent by CYP1A2. A meta-analysis has shown that smoking increases the warfarin dose requirement by 12%, potentially significant if liver synthetic function or diet is
changing. Consequently, a change in smoking status should prompt close monitoring of the international normalized ratio (INR). The induction of CYP1A2 is not related to the nicotine component of tobacco, and therefore use of NRT while ceasing smoking will not prevent these changes in drug metabolism.

The potential interactions between DOA and their therapies and antiretroviral medications for HIV are numerous. Atazanavir (a CYP3A4 inhibitor) has been associated with a lack of ALDH inhibition, indicating that disulfiram may be less effective at causing the aldehyde reaction if given with atazanavir. The clinical significance of these effects is not established. Coadministration of buprenorphine and atazanavir may cause sedation. Efavirenz and nevirapine are known to reduce plasma methadone concentrations, and their use may require an increase in methadone dose. Elvitegravir, atazanavir and darunavir have the potential to increase respiratory depression and sedation when used with benzodiazepines. Other drugs commonly used within this population, for example antidepressants, also have potential interactions with antiretrovirals and should be reviewed when changing prescriptions.

Currently available data on the newer agents available for hepatitis C treatment, including sofosbuvir, ombitasvir and paritaprevir-ritonavir, advises that dose adjustments of methadone or buprenorphine/naloxone are not necessary. A clinically significant drug interaction between sofosbuvir and amiodarone has been documented, with several patients having experienced serious bradycardia. Protein binding is one proposed mechanism of the drug-drug interaction. Amiodarone is
very rarely used in this population, the example is only to demonstrate that with newer drugs in this population, clinicians should be aware that drug interactions are likely, and that full knowledge of all interactions with the hepatitis C drugs will come once the products are used widely.

CONCLUSION

People with DOA issues commonly have difficulties with adherence to management plans, including complicated food, dose and timing regimens. This may be contributed to by the intoxicating effect of the DOA, or by common psychiatric comorbidities. Thus every opportunity should be taken to address as many coexisting health problems as possible, with consideration of likely drug and disease interactions, particularly when new therapies are added. A broad medical approach together with knowledge of the commonly encountered pharmacological problems will enable physicians to minimise potentially harmful medication problems, including those that lead to poor outcomes. This involves consideration that ongoing substance abuse may occur despite the medical advice given, management of comorbidities may not be optimal, or may be intermittent. Close clinical monitoring and use of therapeutic drug monitoring where possible may help to optimise health outcomes.

ETHICAL CONSIDERATIONS
• Practitioners should understand their obligation to utilise knowledge of pharmacological problems commonly encountered in the management of addiction and prevalent comorbidities.

• Practitioners should respect a patient’s right to self-determination and acknowledge that ongoing substance abuse may occur. The physician’s role is to empower the patient to make informed choices about their health care.

KEY PRACTICE POINTS

1. Smoking causes pharmacokinetic drug interactions and caution should be used when a person’s smoking status changes, in particular doses of antidepressants, antipsychotics and warfarin should be reviewed.

2. Opioids given with other CNS depressants cause increased respiratory depression and sedation.

3. Buprenorphine has fewer known drug interactions than methadone, and should be strongly considered in patients with co-morbidities requiring opioid stabilisation.

4. In patients who are dependent on drugs of abuse, it is not only the pharmacology of those drugs that causes adverse reactions, but other disease states including cirrhosis of the liver.
Figure 1. Pharmacology of drugs with common and significant interactions

<table>
<thead>
<tr>
<th>CYP P450</th>
<th>1A2</th>
<th>2E1</th>
<th>3A4</th>
<th>2D6</th>
<th>2C9</th>
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<td><strong>Inhibitors</strong></td>
<td>many fluoroquinolones</td>
<td>atazanavir</td>
<td>bupropion</td>
<td>disulfiram (weak inhibitor)</td>
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<td>warfarin (S-isomer)</td>
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<td>warfarin (R-isomer)</td>
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This table is not intended to be an exhaustive list

Adapted from

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table2-1 and

REFERENCES