



Anaesthetic implications of psychoactive drugs

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Key points

All of the commonly used psychoactive medications have the potential to cause dangerous interactions with drugs used commonly in anaesthesia.

There are very few evidence-based guidelines on the management of psychoactive drugs in the perioperative period.

Caution must be exercised if the psychoactive drug is stopped due to the risk of withdrawal symptoms and recurrence of the psychiatric illness.

Patients must have a plan in place for restarting their medications where appropriate.

Perioperative management should involve a multidisciplinary team.

Anaesthetic implications of psychoactive drugs

The management of patients on psychoactive medications in the perioperative period is largely based on the individual clinician's experience. Despite ~10% of the UK population having some form of mental health condition, there is surprisingly little by way of guidelines for the perioperative management of patients who may be on medications with significant anaesthetic implications.¹ Challenges for the anaesthetist may arise from the nature of the psychiatric condition itself, interactions of psychoactive and anaesthetic drugs, and the problems caused by the condition requiring surgery (e.g. electrolyte derangement and prolonged periods of fasting). Patients may also present for electroconvulsive therapy (ECT) under general anaesthesia.

This article aims to summarize the commonly used groups of psychoactive medications and outline their implications for the anaesthetist, which are summarized in Table 1. We have chosen not to discuss the benzodiazepines as all anaesthetists should already have a good working knowledge of this group of drugs. ECT will not be considered further as this is covered in an accompanying article.

Psychoactive drugs

Classically, psychiatric illnesses were thought to be due to biochemical imbalances within the central nervous system (CNS). This belief was based on the pharmacological actions of drugs known to be efficacious in the treatment of such illness. We now know that this is, at best, an overly simplistic view and that many of the psychoactive drugs affect several neurochemical pathways.

Psychoactive drugs can be classified as:

- (i) antidepressants,
- (ii) mood stabilizers,

- (iii) antipsychotics, and
- (iv) anxiolytics.

It is worth noting that there is a significant overlap between the groups, and drugs may be used to treat more than one type of disorder.

Antidepressants

Depression is thought to be due to a deficiency of norepinephrine, serotonin, or both within the CNS. Drugs which increase the concentration of these neurotransmitters although effective have a delay of up to 2 weeks before clinical improvements are appreciated. This may suggest that in addition to an increase in neurotransmitter levels, a change in receptor number or sensitivity is required before benefit is seen.

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) are used in the treatment of depression, chronic pain, and some forms of acute pain. Commonly encountered examples include amitriptyline, nortriptyline, and dosulepin. Their mode of action is by the prevention of presynaptic re-uptake of norepinephrine and serotonin (uptake 1). In addition, they also have anti-muscarinic, anti-histaminergic, and anti- α_1 -adrenergic effects. Metabolism occurs in the liver, via the cytochrome P450 pathway, and there is considerable inter-patient variation in the handling of these drugs.

In addition to the desired therapeutic effects, TCAs may cause sedation and reduce the seizure threshold. Anti-cholinergic side-effects may be problematic for the patient and may also be potentiated by the administration of other anti-cholinergic agents. The cardiovascular side-effects may be significant, particularly in overdose. These include widening of the QRS complexes and QT prolongation. Concerns regarding arrhythmias precipitated by halothane in patients on TCAs are probably

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Table 1 Summary of perioperative advice for patients taking psychotropic drugs

Drug group	Examples of drug	Perioperative concerns	Withdrawal symptoms	Preoperative discontinuation recommendations
TCAs	Amitriptyline, imipramine, dosulepin	Muscarinic, histaminergic, and α -adrenergic blocking effect	Yes	Discontinue
SSRIs	Venlafaxine, fluoxetine	Anti-cholinergic effect	Yes	Can continue
MAOIs	Phenelzine, moclobemide	Avoid serotonin crisis precipitants Avoid indirect-acting sympathomimetics	Yes	Irreversible MAOI—discontinue 2 weeks before surgery Reversible MAOI—discontinue on day of surgery
Mood stabilizers	Lithium	Avoid serotonin crisis precipitants Prolongation of NMB drugs Reduction in anaesthetic agent requirements Avoid NSAIDs	No	Discontinue 24 h before surgery
Typical antipsychotics	Carbamazepine	Inducer of cytochrome P450 system	No	Can continue
	Valproate	Interferes with platelet function	No	Can continue
Typical antipsychotics	Prochlorperazine, chlorpromazine	Cholinergic, α_1 -adrenergic, and histaminergic blocking effect Caution desflurane	Yes	Can continue
Atypical antipsychotics	Quetiapine, risperidone	α_1 -adrenergic blocking effect	Yes	Can continue
BDZs	Lorazepam, temazepam	Sedative	Yes	Can continue

less of a problem now that other inhalation agents are used more commonly. Postural hypotension may be significant in the elderly population and is due to α -receptor block. The combination of TCAs and tramadol can result in seizures and precipitate a serotonergic crisis.

One of the most significant interactions for the anaesthetist to be aware of is the potentiation of the effect of indirectly acting sympathomimetics (e.g. ephedrine and metaraminol) by TCAs. These should be avoided if possible and directly acting sympathomimetics used cautiously to prevent hypertensive crises.

Abrupt withdrawal of TCAs should be avoided because of the risk of mainly cholinergic symptoms.² In addition, withdrawing a TCA may precipitate a relapse of the condition for which it is being used. As is the case with all of the groups being discussed here, the risk to the patient of withdrawing a psychoactive medication on which they are stable may outweigh the benefits and each case must be considered individually.

Selective serotonin re-uptake inhibitors

The serotonin re-uptake inhibitors (SSRIs) have become the most commonly used drugs in the treatment of depression.³ This is because of their efficacy as antidepressants and preferable side-effect profile when compared with the other pharmacological treatment options.

The mechanism of action of these drugs is as the name would suggest presynaptic serotonin re-uptake inhibition.

There are a number of interactions with implications for the anaesthetist. Probably, the most important is the risk of precipitating a serotonin syndrome when tramadol or meperidine is given in conjunction with an SSRI. The serotonin syndrome features hyper-reflexia, agitation, and hyperthermia. SSRIs (particularly fluoxetine) may interfere with the metabolism of codeine to morphine by inhibiting CYP2D6. This means that patients given codeine may not receive adequate analgesia.¹ There is an increased risk of bleeding in patients taking non-steroidal anti-inflammatory drugs

(NSAIDs) or warfarin with an SSRI due to their interference with platelet function.

Withdrawal of SSRIs may cause dizziness, gastrointestinal upset, and a variety of psychiatric symptoms. Because of this and the fact that the risks associated with remaining on an SSRI are relatively low, it is generally considered acceptable to continue these drugs throughout the perioperative period.

Monoamine oxidase inhibitors

Although less frequently used these days, monoamine oxidase inhibitors (MAOIs) are worth consideration because of the severity of interaction with commonly used drugs in anaesthesia.⁴ Their use may also reflect psychiatric illness which has been refractory to other drug treatments and hence the risk of withdrawal may be greater.

Monoamine oxidases are enzymes involved in the breakdown of amine neurotransmitters (serotonin and norepinephrine). They are classified as MAO type A which has a preference for norepinephrine and serotonin, and MAO type B which deaminates tyramine and phenylethylamine. It is antagonism of MAO type A which is responsible for the antidepressant effect of these MAOIs.

MAOIs may be irreversible (phenelzine, tranylcypromine, and isocarboxazid inhibiting both MAO-A and -B) or reversible (moclobemide is specific for MAO-A, hence the term RIMA or reversible inhibitor of MAO-A). As one would imagine from the terminology, irreversible MAOIs have a longer duration of action (weeks), whereas moclobemide has a shorter duration and does not require a period of withdrawal before starting another antidepressant.

The most important anaesthetic consideration for patients taking MAOIs relate to the profound pressor effect that may be seen after administration of both indirectly and directly acting sympathomimetics. The metabolism of indirectly acting sympathomimetics is inhibited, resulting in the potentiation of their action. Where absolutely necessary, direct sympathomimetics are

preferable (by virtue of the fact that they are also metabolized by catechol-*O*-methyl-transferase so are not as dependent on MAO), but still require caution because there remains the risk of hypertensive crisis.

Meperidine can precipitate a serotonergic crisis in patients taking MAOI as it too interrupts presynaptic uptake of serotonin. It should therefore be avoided in patients known to be on an MAOI.

In the elective setting, there is some debate regarding the management of patients on MAOI. Although the risks associated with anaesthesia in those taking this group of drugs are significant, abrupt withdrawal may precipitate serious psychiatric relapse. Traditionally, irreversible MAOIs have been stopped 2 weeks before operation; however, omitting the dose of moclobemide on the day of surgery is acceptable. It has been suggested that in the elective situation, patients could be switched from an irreversible MAOI to moclobemide to avoid a prolonged period of discontinuation.²

When there is no time to consider withdrawal of MAOI, the anaesthetist must avoid meperidine and use only direct-acting sympathomimetics with extreme caution.

Mood stabilizers

Lithium

Lithium is used in the treatment of mania, bipolar disorders, and as an adjuvant for refractory depression and in some pain conditions, for example, cluster headaches. Its mechanism is poorly understood, although it is believed to mimic sodium *in vivo*, entering excitable cells during depolarization. This results in a reduction in the release of neurotransmitters both in the CNS and in the peripheral nervous system (PNS). More recent work suggests that it has a role as a neuroprotective factor via the inhibition of the *N*-methyl-D-aspartate receptor.⁵

Importantly, it has a narrow therapeutic ratio and is excreted solely by the kidneys. It has a myriad of side-effects ranging from interference of anti-diuretic hormone (ADH) action, cardiac dysrhythmias, gastrointestinal disturbances, and tremor. Features of lithium toxicity usually begin with lethargy or restlessness before progressing to ataxia, dysrhythmias, renal failure, and coma.

With the reduction in the release of neurotransmitters in the CNS and PNS, there is prolongation of depolarizing neuromuscular block and a reduction in the requirements of anaesthetic agents. NSAIDs, which reduce the excretion of lithium by the kidneys, can result in toxic plasma levels. Toxic symptoms tend to occur with plasma levels of >1.5 mmol litre⁻¹. Hence, it is prudent that lithium is stopped at least 24 h before surgery.

Carbamazepine and valproate

Although more commonly used in the treatment of epilepsy, carbamazepine and valproate can also be used as mood stabilizers and for pain management. They are however not the first-line therapy, and hence their use as such is indicative of more resistant illness

and hence an increased potential for recurrence of illness should the medication be stopped.

Valproate's anti-epileptic effect is related to inhibition of neuronal sodium channels and also calcium channels in the thalamus. Its side-effects can range from minor gastrointestinal disturbances and platelet dysfunction to life-threatening idiosyncratic reactions. There remains the potential for increased perioperative bleeding due to platelet dysfunction.

Carbamazepine besides being an anti-epileptic is also used for pain management. It stabilizes neuronal cells by blocking inactivated sodium channels. Side-effects include syndrome of inappropriate ADH, hepatitis, and life-threatening blood dyscrasias. Being an inducer of hepatic cytochrome P450, it can reduce the effects of other drugs metabolized by that system. In particular, the duration of effect of the non-depolarizing aminosteroid neuromuscular blockers, such as vecuronium, are shortened.

Antipsychotics

Psychotic disorders such as schizophrenia lead to an impairment in the patient's ability to comprehend reality. The precise underlying pathophysiology in psychotic disorders is poorly understood, although it is hypothesized to involve imbalances in dopaminergic pathways in the limbic system of the CNS. It is however undeniable that antipsychotic or neuroleptic drugs are efficacious. They are conventionally classified as being typical or atypical. Importantly, these patients have a high relapse rate when their medication is discontinued.

Typical antipsychotics

This class of medication includes prochlorperazine and chlorpromazine. In addition to blocking dopamine receptors in the limbic system, these drugs also block histamine, α_1 -adrenergic, and cholinergic receptors.

The large number of side-effects produced by antipsychotic agents is due to their ability to act as antagonists at the various other receptors. These are summarized in Table 2. Their most troubling side-effects are due to the blocking of dopamine receptors in

Table 2 Adverse effects of antipsychotic drugs

Anti-dopaminergic	Anti-emesis Extrapyramidal syndrome Akathisia Tardive dyskinesia Increased prolactin secretion
Anti-muscarinic	Dry mouth Constipation Urinary retention Blurred vision Precipitation of glaucoma
Anti- α_1 -adrenergic	Postural hypotension
Anti-histaminergic	Sedation

the basal ganglia. These so-called, extra-pyramidal syndromes include akathisia, Parkinsonian symptoms, and tardive dyskinesia.

A rare but significant side-effect of both the typical and the atypical antipsychotic drugs is the neuroleptic malignant syndrome. First described in the 1960s, it is characterized by hyperthermia, autonomic dysfunction, and muscle rigidity. Relevant to the anaesthetist is that the differential diagnosis includes malignant hyperthermia and can occur at any point of the patient's treatment. It carries a 20–30% chance of mortality. Treatment is supportive; however, dantrolene and non-depolarizing neuromuscular blocking drugs have been used to reduce rigidity.

There are no well-established interactions between anaesthetic agents and these drugs, although seizures have been reported during concomitant use with desflurane.⁶ Their anti-adrenergic and anti-cholinergic effects are unpredictable, and hence, other drugs with similar effects should be used with caution or avoided. It is also advisable to avoid drugs with an anti-dopaminergic effect as these could enhance the potential for side-effects attributable to this class of drugs.

Atypical antipsychotics

Atypical antipsychotics include drugs such as quetiapine and risperidone. Although dopaminergic block is still a feature, they differ from conventional antipsychotic agents, in that they may block subtypes of the dopaminergic receptor family, especially in the prefrontal cortex, and also affect the serotonin-2A receptor. This results in a significantly lower propensity to produce extra-pyramidal side-effects at clinically relevant doses. Owing to their more favourable side-effect profile, atypical antipsychotics have become the first-line drugs in the treatment of schizophrenia.

Important side-effects include the neuroleptic malignant syndrome, postural hypotension due to α_1 -adrenergic block, and weight gain.

Implications for the anaesthetists are as for typical antipsychotics.

Anxiolytics

Anxiety is a common emotion that becomes a clinical disorder when it is too severe, too protracted, or too pervasive for the patient. Although the benzodiazepines have been the mainstay of treatment, their use has to be balanced against the risk of dependence, tolerance, and overdose. Anaesthetists should be familiar with the actions and interactions of benzodiazepines already, but it is worth mentioning the need to monitor for signs of withdrawal, particularly in patients who remain fasted for prolonged periods.

Other anaesthetic implications of psychoactive drugs

Drug withdrawal

This review has outlined some of the most important interactions of psychoactive medications and their implications for the

anaesthetist. Although it is clear that several of these drugs in combination with those commonly used in the perioperative period have potential to cause dangerous effects, the decision to discontinue psychoactive medication should not be taken lightly. For patients with complex psychiatric illness, management should involve their usual mental health support team to ensure that the perioperative period is as smooth as possible. Where drugs have been discontinued to allow surgery, there should be a plan for these medications to be restarted after operation. Particular thought needs to go into the management of those who are unlikely to be able to take oral medication after operation as this could result in relapse.

Anaesthesia in the emergency situation does not allow for a period of withdrawal, and in this situation, it is particularly important to be aware of potential drug interactions.

Regional and local anaesthetics

We have concentrated on the interactions relevant to general anaesthesia in this article; however, it is important to remember potential interactions with local anaesthetic techniques. Of particular importance is the potential for local anaesthetic solutions containing epinephrine to cause hypertensive crises in patients receiving TCAs and MAOIs.

Valproate causes platelet dysfunction but there are no reports of adverse outcomes after neuroaxial block.

Consent

One final point to be considered relates to the issue of consent for anaesthesia by patients with mental health disorders. The process of consent requires that a person understands the information presented, is able to retain that information, use it to make an informed decision, and is able to communicate their decision.⁷ Where possible, efforts to reverse temporary incapacity must be made before any medical intervention.

Although mental illness may impair a person's ability to make an informed decision regarding treatment, it should not be assumed that this is the case (even if they are being treated under the terms of the Mental Health Act 1983). The Mental Capacity Act 2005 allows for patients who may predictably become incompetent to express a predetermined wish via an Advanced Decision or Lasting Power of Attorney (LPA). Where incapacity is irreversible and there is no Advanced Decision or LPA, then it is the anaesthetist's responsibility (as part of the multidisciplinary team) to treat the patient in their 'best interests'.

Conflict of interest

None declared.

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