

# Drug withdrawal

## — patient management

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This article describes the techniques used to withdraw routine drug therapy safely, focusing on the drugs that commonly cause withdrawal effects. It describes drug withdrawal in surgical patients and the treatment of neonatal abstinence syndrome



Surgical patients may need their regular medicines to be stopped temporarily

There are many situations in which routine drug therapy will need to be stopped, as described in the first part of this special feature (p363). This article describes the management of drug withdrawal and dependence.

### — Benzodiazepines

Once the decision has been made to stop a benzodiazepine the next step is to convert the patient from their current therapy to diazepam. Diazepam has a long half-life, as do its active metabolites desmethyldiazepam and nordiazepam. This long duration of action allows the drug to be eliminated more slowly from the body and thus reduces the likelihood of withdrawal symptoms developing compared with potent, short acting drugs such as lorazepam. In addition, diazepam is available in small dosage units and liquid preparations, enabling small dose alterations to be made. Conversion charts are available to help the process.<sup>1</sup>

Once converted to diazepam the dose should be tapered off by reductions of 5–10 per cent of the initial dose every one to two weeks. This should be done according to patient response and personal circumstances, and to some extent will depend on the initial starting dose. The percentage decrease may change if the patient is happy to take

larger steps or vice versa. The duration of withdrawal will vary, but withdrawal from a 40mg dose of diazepam may take anything between 30 and 60 weeks.

Patients maintained on nitrazepam and temazepam may consider attempting to stop these drugs without conversion to diazepam, but will be at higher risk of developing withdrawal symptoms.

**Pregnancy** Use of benzodiazepines in pregnancy can be problematic. Benzodiazepines are associated with floppy infant syndrome, neonatal respiratory depression and neonatal withdrawal symptoms when taken during pregnancy or after the first trimester. Pregnant patients maintained on benzodiazepines should be carefully considered for withdrawal treatment. This area is highly complex and advice should be sought from specialists.

### — Antidepressants

Due to the nature of antidepressant therapy it may be necessary to withdraw one drug before replacing it with another drug from a different class. This is often required when the patient has had a poor response or has developed intolerance to a certain drug.

The pharmacokinetics of the antidepressant to be discontinued need to be carefully considered in order to avoid adverse events during the “crossover” period. The aim is to avoid the occurrence of “serotonin syndrome”. This is caused by a build up of serotonin, caused by alteration of serotonin uptake. It causes a classic set of

symptoms, including tachycardia, hypertension, hyperthermia and over-responsive reflexes. It can lead to seizures, renal failure and other complications. Recommendations for switching between antidepressants are shown in Panel 1 (p368).

If an antidepressant is to be stopped and the patient is not switching to another drug, it is generally recommended to taper the dose over the about six months. The exception is fluoxetine which can be stopped abruptly at doses of 20mg per day due to its long half-life.

Patients receiving monoamine oxidase inhibitors and those considered to be at high risk of suffering withdrawal symptoms may require a longer withdrawal period.

General advice is as follows:

- After less than eight weeks treatment, withdraw over one to two weeks
- After six to eight months treatment, taper over six to eight weeks
- After long-term maintenance treatment, reduce dose by 25 per cent every four to six weeks

Severe withdrawal symptoms may require reintroduction of the original antidepressant until symptoms resolve and then smaller dose reductions over a longer period. This can be facilitated by using the liquid form of the antidepressant. Paroxetine is frequently reported to cause problems on withdrawal. The liquid formulation allows a very gradual discontinuation programme and has been shown to give good results despite being time consuming.<sup>2</sup>

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Pharmacists have a role in providing information and reassurance for patients who are stopping an antidepressant treatment (see Panel 2, p370).

**Pregnancy** Estimates suggest that about 10 per cent of women will have some kind of psychological problem during pregnancy. The recommendation is that this should be treated to avoid further complications. The majority of evidence suggests that the use of tricyclic antidepressants, particularly amitriptyline and imipramine, should be a first line consideration. Fluoxetine can be used second line if the patient has a suboptimal response or develops intolerance. Careful consideration should be given to reducing the dose of the antidepressant close to term to avoid neonatal complications. This is a specialist area and expert advice should be sought.

### — Antiepileptic drugs

Withdrawal of antiepileptic drug treatment should be carried out slowly over at least two to three months. One drug should be withdrawn at a time. One month should be left between completing withdrawal of one drug and beginning withdrawal of the next. Benzodiazepine and barbiturate withdrawal may take up to six months or longer and requires particular care because of the possibility of drug-related withdrawal symptoms or seizure recurrence.

Patients and their families or carers should be aware that if seizures recur, the last dose reduction should be reversed and medical advice should be sought.

## Panel 1: Switching between antidepressant drugs

### SSRI for SSRI

When replacing one selective serotonin reuptake inhibitor (SSRI) with another, the first should be withdrawn before the second is started. With drugs with a long half-life (eg, fluoxetine), the second drug should not be started until four to seven days after the first drug has been withdrawn.

### SSRI to TCA

When an SSRI is to be switched to a tricyclic antidepressant (TCA), cross-tapering is recommended (ie, reducing the dose of the SSRI and increasing the dose of the TCA at the same time). This does depend on the nature of the drug — for example, more serotonergic TCAs such as clomipramine should not be cross-tapered with SSRIs and fluoxetine should be stopped before starting a TCA. This is due to the fact that fluoxetine has active metabolites and a long half-life.

### SSRIs or TCAs to moclobemide

If an SSRI or a TCA is to be switched to moclobemide, the SSRI should be withdrawn with a period of two weeks (except for fluoxetine, in which case the patient should be given a five week “washout” period (no drug) before moclobemide is started. TCAs should be withdrawn at least one week before stopping moclobemide.

The Medical Research Council protocol for antiepileptic drug withdrawal suggests withdrawal in the following decrements every four weeks:<sup>3</sup>

- Phenobarbital, 30 mg
- Phenytoin, 50 mg
- Carbamazepine, 100 mg
- Sodium valproate, 200 mg
- Primidone, 125 mg

This approach may need to be modified in patients on low doses of antiepileptic drugs. For patients taking multiple drugs, the withdrawal should be sequential.

A serious adverse event experienced by one participant in a clinical trial may raise a new caution about the withdrawal of antiepileptic drugs when used for conditions other than epilepsy.<sup>4</sup> An elderly woman enrolled in a trial of pregabalin developed neurological symptoms, including headache, confusion and hallucinations, after abruptly discontinuing the drug. The study's authors suggest that all patients stopping antiepileptic drugs should do so gradually to avoid complications of withdrawal.

**Pregnancy** The management of epilepsy in pregnancy is complicated by the increased likelihood of seizures due to altered hormone balance, and possibly altered pharmacokinetics. Multiple drug regimens introduce further complications to both the mother and the fetus.

The management of epilepsy both before and after conception should be addressed by a neurologist and an obstetrician. If possible, multiple drug regimens should be reduced because they are associated with increased risk. Peak plasma levels of antiepileptic drugs can be reduced by increasing the dose frequency while carefully monitoring seizure frequency. Where possible doses should be decreased. In pregnant patients whose epilepsy is well controlled treatment should

be maintained and monitored. Intensive antenatal monitoring is required to ensure that the pregnancy is developing normally.

Antiepileptic drugs are teratogenic in general although data on newer agents are limited. Many problems have been recorded, including a number of malformations, premature delivery and feeding issues at and immediately after birth.

The deficiency of folic acid, which develops with chronic use of antiepileptic drugs, is thought to contribute to malformations associated with treatment. Supplementation with 5mg daily of folic acid both before and after conception is recommended in women who suffer from epilepsy. These women are classified as high risk in terms of the development of neural tube defects.

### — Surgical patients

Surgical patients are required to fast from midnight before the day of surgery, although they may have clear fluids up to two hours before surgery. This fast is imposed to lower the risk of the patient vomiting during anaesthesia and subsequent aspiration of the stomach contents. Fasting reduces gastric acidity as well as gastric volume. Patients who are given sips of water up to two hours before surgery show no increase in gastric volume or acidity compared with those who have fasted for a full nine hours before surgery.<sup>5</sup> In addition, patients given benzodiazepine pre-medication show no alteration in gastric volume. This would suggest that there should be no reason why patients should be denied their routine medicines while fasting. Indeed, omission of regular medication has been shown to be a significant risk factor in the development of postoperative complications.<sup>6</sup>

There are a number of reasons why drug therapy will need to be stopped. Drugs may interact with anaesthetics or affect the surgery itself. It can be a challenge to manage the routine medication of a patient in the peri-operative period, and a variety of protocols exist for the administration of therapy. The pharmacist has an important role in surgical pre-admission, helping to improve medicines management in the peri-operative period.

The various aspects of a surgical procedure are considered below along with agents which may cause problems.

**Anaesthesia** There is little evidence that anaesthetics interact with routine therapy with sufficient clinical significance to warrant temporary cessation of routine medicines, and the data that are available lack consensus.<sup>7</sup> Practice therefore varies. The more complex the drug treatment, the greater the risk of drug interactions.

Surgery and anaesthesia can cause a variety of complications. The stress response

experienced by patients post surgery involves increased levels of circulating catecholamines and may cause cardiac complications. Bronchospasm, which may occur as a result of airway instrumentation is another risk, as is the anaesthetic process itself. Any concurrent diseases should be managed optimally before and during surgery, to ensure that these potential complications are not exacerbated. Drugs such as serotonergic agents or monoamine oxidase inhibitors (MAOIs) have the potential to alter the response to or interact with a variety of drugs used in the anaesthetic period.

The withdrawal of selective serotonin re-uptake inhibitors (SSRIs) and MAOIs is difficult. It requires careful titration and there is a risk of withdrawal symptoms or acute exacerbation of depression. Serotonin syndrome is a risk when serotonergic anaesthetic agents such as pethidine, pentazocine, and tramadol are used. Current opinion is that patients should be maintained on their MAOI therapy and "MAOI safe" anaesthetic regimens should be used.

**Bleeding** Surgery involves tissue damage and there is the potential for bleeding. Avoidance of excessive haemorrhage is of paramount importance to patient safety, particularly in surgery involving delicate tissue such as retinal or intracranial surgery.<sup>8</sup> The decision to stop anticoagulants or antiplatelet treatment should be a balance between the risks of bleeding and the development of thromboembolic complications. These risks will vary for each patient depending on the surgery involved.

Anticoagulation and antiplatelet treatment should be stopped in sufficient time to restore normal blood coagulation or for monitoring parameters to reach accepted levels. An international normalised ratio (INR) of 1.5 is often considered to be the accepted safe level for surgery. Aspirin has a long duration of action and is a common drug for surgical patients to be taking because of its role in prevention of cerebrovascular events. Aspirin should be stopped seven to nine days before surgery to allow sufficient normal circulating platelets to be established.

Patients considered to be at high risk of thromboembolism may require treatment with low molecular weight heparin in the days before surgery, and treatment with heparin (shorter acting) immediately before and after surgery.

**Thromboembolism** The risk of thromboembolism varies according to the type of surgery a patient has undergone. High risk thromboembolic surgery includes abdominal surgery and orthopaedic surgery to the lower limbs. The risk can also be influenced by routine administration of

## Panel 2: Reassuring patients who stop needing antidepressants

Pharmacists should seek to reassure patients by providing the following information:

- Reassurance that antidepressants are not addictive, and that discontinuation symptoms may occur
- Common symptoms that the patient may experience
- The likely duration over which a dose will be reduced
- An indication of when symptoms are likely to occur, and how long they are likely to continue for

combined oral contraceptives and hormone replacement therapy. The risks of withdrawal of treatment should be balanced against risks of thromboembolism. In the case of elective surgery this should be considered before the patient is admitted.

Progesterone-only contraceptives do not pose a risk in terms of thromboembolism and are an option for patients taking combined oral contraceptives who do not wish to stop taking oral contraceptives. Recommendations suggest that combined oral contraceptives and hormone replacement therapy are continued and that patients are given thromboembolic prophylaxis in the peri-operative period, consisting of subcutaneous low molecular weight heparin and graduated elastic compression hosiery. However, not all authorities agree on this point and the opinions of individual surgical teams should be carefully considered when managing these patients.

**Blood pressure control** Before and during surgery control of blood pressure is paramount.

Beta-blockers should be continued in the perioperative period because abrupt cessation can cause rebound hypertension with a general increase in sympathetic activity. Operations may be cancelled at the last minute if, for example, a patient's blood pressure has become elevated due to the rebound effects of abrupt withdrawal of beta-blockers. This has resource implications for the health service, yet is relatively simple to avoid.

Prolonged administration of beta-blockers causes up-regulation of beta adrenoceptors. As a consequence of this up-regulation, increased sympathetic innervation occurs on cessation of treatment. This causes elevated blood pressure, tachycardia and the potential for serious cardiovascular morbidity. The effect of withdrawal will vary depending on which beta-blocker the patient is taking. It is less pronounced in those demonstrating intrinsic sympathomimetic activity. Diuretics should be used with care in surgical patients, particularly potassium-sparing drugs. Surgery causes a release of intracellular potassium as well as reducing renal perfusion, both of which may predispose the patient to hyperkalemia. The addition of potassium-sparing diuretics can further complicate treatment.

Routine use of drugs which cause vasodilation can augment the vasoactive effects of anaesthetic drugs and induce hypotension, possibly requiring increased administration of inotropes. This, combined with the likely hypovolaemic state of many surgical patients can be a challenge for the anaesthetist, and is best avoided.

Evidence for the discontinuation of ACE inhibitors before surgery is conflicting. ACE

inhibitors reduce the vascular responsiveness to noradrenaline and reduce systemic vascular resistance. This can contribute to patients developing hypotension during anaesthesia. ACE inhibitors being taken for uncomplicated hypertension should be stopped before surgery.<sup>6</sup>

## — Neonatal abstinence

A number of non-pharmacological treatments are available for the treatment of neonatal abstinence syndrome (NAS). Swaddling the child and frequent but small volume feeds with a hypercaloric milk formula may be all that is needed in the treatment of some infants.

Pharmacological management may consist of opiates or narcotics, barbiturates, diazepam or chlorpromazine.

**Morphine** The most common drug used in the UK for the management of NAS is morphine. A recent survey showed that two doses of morphine at 30–40µg/kg every four hours and a higher dose of 8–100µg/kg every four hours are commonly used. This range of doses may be explained in several guidelines that have adopted lower doses for Finnegan scores (see p365) of 8 to ten, and the higher dose for Finnegan scores of over 17.<sup>9</sup> Concerns about respiratory depression with morphine use in NAS have not been substantiated.

A commonly used preparation in the US is paregoric, a crude opiate mixture containing alcohol and morphine sulphate 0.4mg/ml. This is not recommended in the UK because of the alcohol content (44 to 46 per cent) of the product.

A maximal effect is seen with morphine at 48 to 72 hours after administration and subsequently doses are reduced by 10 per cent every 24 hours when Finnegan scores fall below 10.

**Phenobarbital** Phenobarbital is used in some neonatal units when treating NAS associated with seizures. Phenobarbital has an effect on irritability and insomnia, but has little effect on gastrointestinal symptoms. It impairs the sucking reflex and because it has a narrow therapeutic index careful blood monitoring is required to prevent toxicity. The normal dose of phenobarbital in NAS is 2–6mg/kg daily as a single dose.

**Diazepam** Diazepam is seldom used in the treatment of NAS. It interferes with the sucking reflex, causes sedation and its long half-life makes symptom monitoring difficult (it can take up to four weeks to be eliminated). Diazepam has been used in doses of 1–2 mg every eight hours, given as an oral solution that also contained alcohol and propylene glycol. In all head-to-head trials diazepam has been shown to be ineffective in the treatment of NAS.<sup>10</sup>

**Chlorpromazine** Chlorpromazine was previously used in NAS because it controls both central nervous system and gastrointestinal symptoms. It is still used in several neonatal departments where the usual dose is 0.55mg/kg, given orally or intramuscularly every six hours. However, chlorpromazine is contraindicated in children with elevated bilirubin and, like diazepam, elimination is prolonged (reported to be as long as 18 months). Thus it is currently rarely used in NAS.

**Other agents** In the past methadone and clonidine have been used to treat the symptoms of NAS. Initial doses of methadone of 0.5–1 mg/kg were used until symptoms were controlled, but its long half-life (26 hours) caused problems with its administration.

Clonidine specifically targets the adrenergic neurones, decreasing the amount of noradrenaline released and thus reducing the firing rate of these neurones. Doses of 3–5µg/kg per day controlled the symptoms, but poor sedation was achieved and acidosis occurred in several neonates. The use of clonidine with methadone is now discouraged in NAS.

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## Corrections — drug withdrawal feature

There were two errors in the special feature on drug withdrawal in December 2007's *Hospital Pharmacist*.

If an antidepressant is to be stopped and the patient is not switching to another drug, it is generally recommended to taper the dose over four to six weeks, not as stated in the article (p367).

Tricyclic antidepressants should be withdrawn at least one week before moclobemide is started, not one week before stopping moclobemide, as stated in the article (p368, Panel 1).