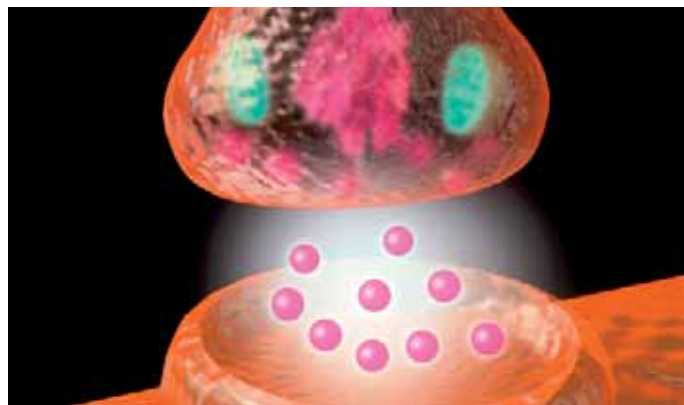


Drug withdrawal

— the most common problems

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Withdrawal effects can occur when drugs acting on the central nervous system are discontinued, and may be mistaken for other diseases. This article describes the most common withdrawal effects seen in both secondary and primary care



Psychological dependence results from increased dopamine-mediated synaptic transmission throughout the “reward pathways” of the brain

When a drug that acts on the central nervous system needs to be withdrawn it should be done carefully. Patients may wish to stop using illicit drugs or may need to withdraw from prescribed therapy upon which they have become dependant. Other situations in which drugs may need to be withdrawn include changing treatment after a suboptimal response (eg, switching between antidepressant drugs) or after the patient has experienced an adverse drug reaction. There are also numerous situations in which routine therapy needs to be changed due to factors such as pregnancy or the need to undergo elective surgery.

Withdrawing medicines can be complex and the method used is influenced by the reason for withdrawal. For example, the decision of whether to continue routine drug therapy in patients undergoing surgery is influenced by the indication for treatment, the type of anaesthesia to be used and the nature of the surgery (see p370). The increasing age of the population and the prevalence of chronic disease states means that pharmacological management of surgical patients is becoming an increasingly complex problem.

Appropriate management of drug withdrawal is essential to ensure that the

therapy is optimal and safe. Pharmacists' input is an essential part of the treatment decision.

This article will describe the psychological and physiological mechanisms that cause problems in drug withdrawal. The second part of this feature (p367) will describe the techniques used to withdraw drugs that commonly cause problems, and the management of drug withdrawal in special patient groups.

Dependence

Withdrawal effects can occur after abrupt cessation of a drug because a patient has become physically and psychologically dependant on the drug, or because of physiological stimulation of a receptor that is no longer being counteracted by the discontinued drug. Drug dependence comprises social and psychological issues as well as pharmacodynamic effects. The concept of drug withdrawal or, more specifically, drug dependence, is mainly associated with drugs of abuse or those with significant central nervous system effects.

Drugs that are regularly associated with dependence all have an effect on the central nervous system and produce pleasurable sensations that patients desire to repeat. The strength of this desire, along with genetic and psychosocial factors, dictates the likelihood of a person becoming dependent on a drug. This has a major influence on patients' lives in terms of the cost to themselves and their social circle, often

resulting in them resorting to crime to fund the addiction. If intravenous drug abuse is involved, patients may be exposed to infectious diseases such as hepatitis and HIV.

Drug dependence is usually accompanied by tolerance, where repeated administration of a drug results in a decreased pharmacological effect.

Psychological dependence Certain areas of the brain increase dopamine-mediated synaptic transmission in response to natural rewards such as food, water and commonly abused drugs. These areas include the ventral tegmental area, the nucleus accumbens, the shell region and the prefrontal cortex. Stimulating this “reward” pathway appears central to the pleasurable effects of some drugs — unrelated to any other pharmacodynamic effect.

Chronic stimulation of these pathways is thought to result in dysfunction of the pathways. One theory suggests that the initial feeling of euphoria is replaced by negative symptoms such as dysphoria and depression. Cocaine and amphetamine-related transcript (CART) peptide, contained within the neurones of the mesolimbic dopamine system, is also believed to be closely involved with the rewarding and reinforcing properties of drug abuse.¹

Physiological dependence Long-term administration of receptor-blocking drugs can cause up-regulation of the receptors. If the receptor blocker is suddenly withdrawn,

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Panel 1: Symptoms of benzodiazepine withdrawal

Symptoms of benzodiazepine withdrawal can be classified as mild or severe.

Severe symptoms include:

- Muscle twitches
- Seizures
- Tachycardia
- Confusion
- Panic attacks.

Mild symptoms include:

- Insomnia
- Dizziness
- Headache
- Anxiety
- Hypersensitivity to light or sound

physiological over-stimulation occurs. For example, abruptly stopping beta-blockers causes rebound hypertension which can be fatal.

Discontinuation symptoms are often mistaken for diseases in clinical practice. It is important that clinicians are aware of these symptoms, and that psychological dependence is distinguished from physiological withdrawal. This can be difficult, since many drugs only have a small number of reported cases of withdrawal effects.

Common offenders

The following drugs or groups of drugs commonly cause problems on withdrawal, or cause particularly severe symptoms.

Antipsychotics Abrupt cessation of oral antipsychotics is associated with discontinuation effects within one to four days that can continue for two weeks. The most prominent symptoms are caused by cholinergic rebound syndrome. This is a flu-like illness which comprises symptoms of abdominal cramping, runny nose, excessive lacrimation, hypersalivation and dyspepsia. Withdrawal dyskinesias can also occur, including extrapyramidal symptoms, akathisia (motor restlessness) and worsening of tardive dyskinesia (involuntary chewing or grimacing).²

Benzodiazepines The typical symptoms following abrupt discontinuation of benzodiazepines are shown in Panel 1. These symptoms usually start within one to two days of stopping the drug³ and last for about four weeks.

Benzodiazepines act by binding to a site on the GABA_A (gamma-aminobutyric acid) receptor and mimicking the action of endogenous GABA. One unconfirmed

theory for the mechanism of tolerance and withdrawal effects is down-regulation of the GABA receptor. Dependence results from genetic alteration that modifies receptor expression and turnover.⁴ The altered receptor behaves differently after the benzodiazepine has been discontinued.

Patients are at greater risk of suffering withdrawal symptoms when the prescribed benzodiazepine:

- Has a short half-life
- Has a high receptor affinity
- Is used at high doses
- Is used for prolonged periods⁵

Antidepressants The symptoms that occur when an antidepressant is discontinued can often be explained by receptor rebound. Discontinuing an antidepressant with potent anticholinergic side effects may cause cholinergic rebound symptoms. Such symptoms are experienced by at least a third of patients and may be new or similar to the original presentation of illness.

Symptoms typically start within 24–72 hours of stopping the antidepressant. If the antidepressant has a short half-life (eg, paroxetine, venlafaxine), symptoms can present when tapering a dose, or after a single missed dose. These effects are usually mild and self-limiting, lasting for seven to 14 days, but can be prolonged and severe.

Clarification of withdrawal effects is essential in terms of patient management. If discontinuation symptoms are mistaken for relapse or new physical illness, they may result in unnecessary tests and treatments, or interference with daily functioning. Patients

may misinterpret these symptoms to mean they are “addicted” to antidepressants and refuse further treatment.

An antidepressant is more likely to cause discontinuation symptoms if:

- The drug has a short half-life
- The patient regularly misses doses
- The patient developed marked anxiety symptoms when the treatment was started
- The patient takes other centrally acting drugs (eg, antihypertensives, antihistamines, antipsychotics)
- The patient is a child or an adolescent
- The patient has suffered discontinuation symptoms with previous treatment

A summary of the likely symptoms experienced with individual groups of antidepressants appears in Panel 2.

Antiepileptic drugs Withdrawal of antiepileptic drugs (AEDs) is usually considered once the patient has been seizure-free for at least two years. It requires the guidance of a specialist.

Paediatricians are more likely to attempt AED withdrawal than neurologists, partly because there is a better outlook for childhood seizure disorders (about 75 per cent of childhood seizure disorders diminish by adulthood and AEDs can be successfully discontinued). Also, AEDs can affect cognitive function, learning and behaviour, so consideration of withdrawal of AEDs in appropriate cases is vital in children.

Unsuccessful withdrawal is more likely if the patient:

Panel 2: Typical symptoms of antidepressant withdrawal

Class of antidepressant	Common symptoms	Rare symptoms	Most reported drug
Monoamine oxidase inhibitors	Agitation, irritability, ataxia, movement disorders, insomnia, somnolence, vivid dreams, cognitive impairment	Hallucinations, paranoid delusions	Tranylcypamine
Tricyclic antidepressants	Flu-like symptoms, headache, restlessness, diarrhoea, vomiting, sleep disturbance, lethargy	Movement disorders, mania, cardiac arrhythmias	Amitriptyline, imipramine
Selective serotonin reuptake inhibitors and venlafaxine	Flu-like symptoms, electric shock-like sensations in the head, abdominal cramps, dizziness, vertigo, crying spells, sleep disturbance, fatigue, sensory disturbance	Movement disorders, poor concentration and memory	Paroxetine, venlafaxine

- Has had an abnormal electroencephalogram in the previous 12 months
- Takes more than one AED
- Has learning difficulties
- Was over 16 years old when seizures began
- Has suffered seizures since starting AED therapy
- Has a history of myoclonic or generalised tonic-clonic seizures

A joint decision on whether to withdraw therapy should be made after the clinician has discussed the risks and benefits with the patient and his or her family or carer.

— Neonatal withdrawal

Newborn babies who have been exposed to drugs *in utero* often suffer withdrawal symptoms after birth. This is known as neonatal abstinence syndrome (NAS). It is most commonly seen in relation to drugs of abuse, but there are reports of it occurring in after exposure to fluoxetine, paroxetine, citalopram, venlafaxine, tricyclic antidepressants, hydroxyzine and baclofen.

US studies in the 1980s demonstrated that about 90,000 women were discharged each year from maternity services across the US with a diagnosis of drug abuse.⁶ This equates to 2.2 per cent of all women giving birth in the US. Despite data demonstrating a reduction in drug use during pregnancy from 15 per cent in 1986 to 8 per cent in 1990, it is widely agreed that the issue is still a problem.⁶ The most common illicit drugs used in pregnancy are alcohol and cannabis, although narcotic drugs such as heroin, cocaine and amphetamines are also used.

Symptoms The symptoms of NAS are generally categorised as follows:

- Central nervous system disturbances — tremors, seizures, increased muscle tone, myoclonic jerks and increased moro reflex (a “startling” reflex in response to noise etc)
- Metabolic, vasomotor and respiratory disturbances — sneezing, nasal stuffiness, rapid breathing, frequent yawning, fever and sweating
- Gastrointestinal dysfunction — excessive sucking, poor feeding (due to lack of co-ordination), regurgitation, vomiting, watery stools

The symptoms will depend on the drug used by the expectant mother, and will usually occur within 24 hours of birth.

The severity of NAS is often assessed using the Finnegan scale.⁷ Points are allocated to each symptom experienced, with severe symptoms being given higher scores (eg, four points for severe tremors, three points for watery stools). A total score

(out of 45) is usually recorded over four hours. Scores are assessed over 24 hours to establish a pattern of improvement or deterioration.

The Finnegan scale should be used to make an informed clinical decision of diagnosis of NAS and subsequent treatment, but is not itself an indication for whether treatment should be initiated or stopped.

The severity of symptoms appears not to be influenced by gestational age, maternal age, APGAR score (a measure of physical status at birth) or the race or sex of the neonate.

Cannabis Cannabis is associated with a reduced gestation period and a reduction in birth weight, although this may be due to exposure to tobacco (which is commonly mixed with cannabis when smoked).

An average birth weight reduction of approximately 150–250g has been suggested by meta-analyses of the studies examining intrauterine cannabis exposure. Small studies have suggested that pre-natal exposure to cannabis reduces the child’s ability in later life to perform tasks that require visual memory, analysis and integration of data.⁸

Opiates Exposing a developing fetus to heroin, methadone and codeine has been shown to cause symptoms of NAS.⁹ Studies show that opiate exposure occurs in 6–7.5 pregnancies per 1,000,¹⁰ and 79 per cent of the exposed infants suffered from NAS. Of these, a half to three quarters will require treatment.¹¹ Seizures may occur in as many as 2–11 per cent of neonates exposed to opiates.

The symptoms of NAS differ depending on the opiate to which the fetus is exposed. For example, neonates exposed to morphine tend to experience NAS earlier than those exposed to methadone. Also, the maternal blood level of morphine does not influence the severity of symptoms, whereas the level of methadone does. Treatment depends on the severity of symptoms.

Cocaine Exposing a developing fetus to cocaine has not been shown to increase the incidence of NAS. Recent studies have shown that neonates exposed to cocaine during pregnancy have a lower birth weight, but physical and mental development are not affected. If NAS does occur, treatment is the same as for other drug-exposed neonates (see p372).

Amphetamines Studies have demonstrated that fetal exposure to amphetamine and methamphetamine is associated with reduced birth weight and slower infant growth. A recent study showed that pharmacological intervention was required in 4 per cent of methamphetamine exposed infants¹² because of the development of NAS.

— Pregnancy

Managing a pregnant patient with chronic conditions is challenging, since drug treatments that control the condition may have an adverse effect on the developing foetus. Patients taking regular medicines are not always aware that they are pregnant, since the confirmation of pregnancy may occur late in the first trimester. This can be problematic, since the potential damage to fetal development caused by many drugs occurs due to first trimester exposure.

However, the risk to the fetus of exposure to these regular medicines needs to be balanced against the risk of worsening maternal health as a result of not receiving the medicines, which may also affect the health of the fetus. Some of these issues are discussed on p370.

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