Pharmacological management of opiate withdrawal

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Opiate misuse is extremely prevalent in the UK. A high proportion of these individuals experience withdrawal symptoms. This article describes the clinical features and discusses the current literature on the pharmacological management of opiate withdrawal.

Opiates consist of a large number of naturally occurring and synthetic drugs, including heroin, opium, morphine, codeine and methadone. Heroin is the drug of choice for many drug misusers. In the UK there has been at least a ten-fold increase in heroin use in the last 20 years. A high proportion of these individuals experience severe withdrawal symptoms and may present to doctors for treatment. Doctors are often reluctant to manage opiate withdrawal, often because of a lack of knowledge. There is therefore a need for a review in this area.

Numerous terms have been used interchangeably to define opiate misuse, which has led to confusion in identifying individuals who may require pharmacological management of withdrawal. A common error is to presume that all individuals who misuse opiates require pharmacological treatment. Only individuals dependent on opiates require treatment for their withdrawal. Several classifications are available. The authors recommend the *Diagnostic and Statistical Manual of Mental Disorders*, which makes a useful distinction between opiate abuse and opiate dependence (American Psychiatric Association, 1994). The main features differentiating opiate dependence from abuse are evidence of tolerance, presence of characteristic withdrawal symptoms when opiate use has ceased or reduced and use of opiates to relieve withdrawal symptoms.

CLINICAL FEATURES OF OPIATE WITHDRAWAL

Withdrawal symptoms may be precipitated by reduction or complete cessation of opiate use. The symptoms are primarily the result of excess noradrenaline production and are mainly flu-like in nature (*Table 1*). Withdrawal intensity depends on the length of dependence, amount of drug used, reduction in dosage and the half-life of the opiate.

The onset of withdrawal symptoms from heroin is within 6–8 hours after the last dose. They tend to peak at 2–3 days, and last up to 14 days. In theory, as the half-life of methadone is longer, one would expect a longer withdrawal period. However, Gossop and Strang (1991) found no difference in the onset or duration of symptoms during opiate and methadone withdrawal. This study could be criticized as the symptoms were self-reported, 40% of subjects were dependent on both heroin and methadone, and the sample size was small.

During withdrawal one may find dilated pupils, tachycardia, hypertension and tachypnoea on examination. It is important to note that epileptic fits are not a feature of opiate withdrawal.

MANAGEMENT OF OPIATE WITHDRAWAL

Management consists of social, psychological and physical treatments. Social and psychological treatments are extremely important, but will not be discussed further here. Physical treatment includes the following:

TABLE 1.
Symptoms of opiate withdrawal

Running eyes
Running nose
Yawning
Disturbed sleep
Nausea
Abdominal cramps
Diarrhoea
Musculoskeletal aches
Nervousness
Feeling hot and cold
Sweating

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- Management of physical complications as a result of injecting habits, e.g. infections. This is outside the scope of this paper and will not be discussed further
- Specific management of opiate withdrawal.

TREATMENT SETTING

Conventional inpatient *vs* outpatient

There are surprisingly few studies in this area. Gossop et al (1986) compared the relative effectiveness of inpatient and outpatient withdrawal programmes among 60 opiate dependants. They concluded that the inpatient group were significantly more likely to complete successful withdrawal. However, there were a number of drawbacks in this study: subjects were not truly randomized, patient numbers were small, and the study periods were different, the outpatient group withdrawal being 5 weeks longer, thereby reducing the likelihood of success.

Strang et al (1997) investigated 186 opiate addicts randomized to either specialist units or general psychiatric wards. They concluded that those managed in drug dependency units were more likely to complete detoxification and remain opiate-free at 7-month follow-up. However, they compared only those subjects who had remained drug-free throughout the programme. Furthermore, if a comparison is made between all those who were drug-free at 7 months, then the results are not significant, and could well be the result of a type 1 error.

From these studies it may be concluded that there is no evidence of any difference in outcome between those detoxified in a specialist unit, general psychiatric ward or outpatient programmes. A commonly held perception is that inpatient wards offer a drug-free environment, but clinical experience shows that this is not the case. Inpatient wards are expensive, therefore routine admissions cannot be justified. However, for high-risk patients, e.g. those with concurrent physical or psychiatric disorders, high suicide risk patients, or in those without adequate support, inpatient admission may be justified.

Specialized inpatient treatment: rapid detoxification

In recent years there has been considerable controversy and debate regarding the efficacy and safety of this method of detoxification. The treatment regimens used in the studies are different, and hence difficult to compare.

Seoane et al (1997) concluded that rapid intravenous detoxification could be successfully achieved using relatively light sedation. Patients were withdrawn over 24 hours with intravenous naloxone and differing levels of sedation. They studied 300 heroin addicts, with only one severe complication. However, this was an open, non-randomized study with no long-term follow-up.

Scherbaum et al (1998) researched 22 patients who underwent ultra-rapid opiate detoxification. Their completion rates were high, but a large proportion of individuals suffered major and unexpected withdrawal symptoms. They concluded that because of the risks of general anaesthesia and the cost of treatment, this should be reserved for those patients unable to use conventional methods.

Pfab et al (1999) studied 12 opiate withdrawals using intravenous naloxone and general anaesthesia. Their study was terminated after one patient suffered pulmonary failure, and another renal failure. They concluded that there was no obvious benefit from this method, and the risks were high. At re-examination 18 months later, all patients reported recurrent use of illicit drugs.

Bearn et al (1998) studied opiate detoxification using three regimens: 5-day lofexidine, 10-day lofexidine or 10-day methadone. They found that the 5-day lofexidine regimen attenuated opiate withdrawal symptoms more rapidly, but there was no significant difference in outcome and length of stay. This study could be criticized for its design (non-random and open) and because small numbers were involved. No inferences could be made about long-term outcome in this study. The mean length of stay was 20 days.

There are no clear long-term advantages of rapid detoxification, and there are risks involved.

Day hospital

At present there are no data available in this area. However, clinical experience suggests that this is a useful setting, as it is more cost-effective and user friendly. There are risks that patients could relapse on return to their home environment in the evenings, but these should be no greater than those completing home detoxification. This area would benefit from further research.

PHARMACOLOGICAL MANAGEMENT

A regimen for the pharmacological management of opiate withdrawal is summarized in *Table 2*.

Alpha-2 adrenergic agonists

Clonidine was originally developed as a centrally acting antihypertensive agent. It has a variety of effects on the CNS, one being the ability to suppress symptoms of opiate withdrawal. Because of its hypotensive tendency, its use in this area has been limited. Lofexidine has the advantage of ameliorating opiate withdrawal symptoms without the hypotensive effects, as confirmed by

Kahn et al (1997) and Carnwath and Hardman (1998). Therefore, lofexidine should be used as a first-line treatment in opiate detoxification. A typical 10-day dosing schedule would begin with 200 μg twice daily, increasing by 400 μg daily up to a maximum of 2.4 mg, and then gradually reduced and stopped in 4 days (*Table 2*).

Buprenorphine

Buprenorphine resembles morphine and is a partial agonist at μ receptors. It has a low level of dependence compared to methadone, and is safer in overdose. The main disadvantage is the abuse potential, as it can produce a marked euphoria, particularly when taken with benzodiazepines. Cheskin et al (1994) compared buprenorphine with clonidine in 25 heroin dependant subjects during withdrawal. There was no significant difference in outcome between buprenorphine and clonidine. Buprenorphine could be useful in inpatient detoxification programmes, but should be used with care because of its abuse potential.

SYMPTOMATIC MANAGEMENT

Sedatives

Sedatives are a useful adjunct in acute withdrawal. Benzodiazepines can be divided into long acting (e.g. diazepam and chlordiazepoxide) and short acting (e.g. lorazepam). Long-acting preparations are preferable and a typical dose regimen would be diazepam 10 mg three times a day, reduced by around 25% every 2 days with a view to stopping within 10–14 days.

Hypnotics

During withdrawal, sleep is often difficult. Temazepam 10–20 mg at night is useful in the short term. It should be stopped within 14 days.

Antidiarrhoeal agents

Co-phenotrope or mixed kaolin to be used as needed. Drugs containing codeine should be avoided.

Analgesics

Paracetamol 1 g could again be used as required. Codeine or other opiate-based analgesics should be avoided.

Relapse prevention

Naltrexone is a long-acting competitive antagonist at opioid receptors which blocks the subjective and objective responses produced by opioid administration. It can be used as an adjunct in the maintenance of abstinence. It can be started 7–10 days after cessation of opiate use. The starting dose is 25 mg daily, increasing to 50 mg within 1 week.

CONCLUSIONS

Opiate withdrawal is common. Outpatient treatment is suitable in the majority of patients. Inpatient detoxification may be required in certain high-risk groups. Treatment is simple and effective, consisting of specific (lofexidine is the drug of choice) and symptomatic treatment. HM

Conflict of interest: none.

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TABLE 2.
Treatment regimen for the management of opiate withdrawal

Drug	Dosage schedule
Lofexidine	200 μg twice daily increasing by steps of 400 μg to a maximum of 2.4 mg per day. Reduce gradually over 2–4 days. Total duration of treatment 7–10 days
Diazepam	10 mg three times daily. Reduce by 25% every 2 days, with treatment duration not exceeding 14 days
Temazepam	10 mg nightly not exceeding 14 days
Paracetamol	Up to 1 g four times daily as required
Co-phenotrope	4 tablets followed by 2 tablets every 6 hours until diarrhoea controlled

KEY POINTS

- Opiate withdrawal is commonly encountered in clinical practice.
- Withdrawal symptoms are flu-like in nature.
- Opiate detoxification may be managed in inpatient and outpatient settings; patients with complex disorders should be treated as inpatients.
- Treatment consists of specific and symptomatic measures: specific treatment includes lofexidine, which is effective and safe, and symptomatic treatment may include benzodiazepines, antidiarrhoeals and analgesics.
- Naltrexone can be used post-withdrawal to aid relapse prevention.