Guidance For The Use Of Lofexidine In The Symptomatic Management Of Opioid Withdrawal By Clinicians Working Within NHS Grampian

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1. Introduction

1.1. Objectives

This document provides guidance on the use of lofexidine for the prevention and alleviation of symptoms of opioid withdrawal experienced during opioid detoxification. It is intended for use by all clinicians involved in the management of opioid detoxification and applies equally to practice in primary and secondary care. It is recommended that clinicians possess specialist knowledge in the field of substance misuse before undertaking treatment with lofexidine or are acting on the recommendation of a specialist clinician in substance misuse.

1.2. Definitions

Nice Clinical Guidance 52 states that “Opioid detoxification refers to the process by which the effects of opioid drugs are eliminated from dependent opioid users in a safe and effective manner, such that withdrawal symptoms are minimised. This should be an active process carried out following the joint decision of the service user and healthcare professional, with continued treatment, support and monitoring. Detoxification should not be confused with stabilisation or gradual dose reduction” (NICE 2007).

1.3. Clinical Situations

Opioid detoxification is one of a range of interventions which may be offered to opioid dependent patients. Lofexidine allows the effective suppression of autonomic signs of withdrawal including; sweating, tremors, nausea, vomiting, diarrhoea, abdominal cramps, goose bumps, yawning, sneezing, pupil dilatation, lacrimation and rhinorrhoea. It is less effective at suppressing symptoms of subjective discomfort such as general muscle aches, insomnia and craving.

1.4. Patient Groups To Which This Document Applies

Patients should be provided with information on all of the available, appropriate treatment options and supported to make an informed decision based on these options. Methadone or buprenorphine products should be offered as the first-line treatment options for opioid dependent patients in community settings. However, lofexidine may be considered suitable for:

(i) Patients who have made an informed and clinically appropriate decision not to use methadone or buprenorphine and choose lofexidine to support detoxification.

(ii) Patients who have made an informed and clinically appropriate decision to detoxify within a short period of time.
(iii) Patients who describe a mild or uncertain dependence.

(iv) Patients currently prescribed methadone and strongly motivated to detoxify with lofexidine. It is recommended that patients have reduced to 30mg or less of methadone. (NB: The use of a buprenorphine containing product is preferable in this situation and should be discussed as a treatment option. In adequate doses patients should experience fewer symptoms of withdrawal and side effects than with lofexidine).

(v) Patients over 18 years of age. Younger patients should be referred to the specialist service and the clinical treatment plan agreed with a Consultant Addictions Psychiatrist. Lofexidine may be an appropriate treatment choice in these patients.

2. Evidence Base

Current guidance was accessed as per the reference section. Of note, the reason that neither of the NICE guidelines listed have been reviewed since the last update to this guidance was due to little emerging or changing evidence in the field. As such CG52 has been placed on the static list.

3. Process

3.1. Detoxification Regimen

(i) Pharmacological detoxification alone is unlikely to result in successful and sustained detoxification. Treatment should not rely solely on the prescription of medication but should be undertaken within a framework of medical, social and psychological treatment.

(ii) All detoxification regimens require close monitoring and support of the patient. It is the responsibility of the clinician to ensure that adequate facilities are in place before commencing detoxification.

(iii) For patients undergoing detoxification from illicit opioid drugs, a full assessment should be undertaken and opioid dependency confirmed. This should be supported by obtaining a minimum of 2 positive opioid urine or oral screens prior to commencing detoxification.

(iv) Due to the hypotensive effect of lofexidine, close monitoring of blood pressure and pulse is required. Baseline readings should be obtained prior to initiating treatment. Blood pressure and pulse should be monitored at least once a day over the first 2-3 days of lofexidine treatment until a stable dose is reached. Patients should be advised of this side effect.

(v) The initial dose should be 800 micrograms (4 tablets) daily in divided doses, increasing as necessary in steps of 400 to 800 micrograms (2 to 4 tablets) daily according to patient response. The dose should be titrated as necessary to control withdrawal symptoms, up to the maximum daily dose of 2400 micrograms (12 tablets), in divided doses at 6 hour intervals. The maximum single dose should not exceed 800 micrograms (4 tablets). The patient should be advised to take the final dose each day shortly before bedtime to help reduce symptoms of insomnia associated with withdrawal.
(vi) Lofexidine should be withdrawn in similar dosage decrements gradually over 2-4 days or longer to reduce the risk of rebound hypertension but will require tailoring in line with patient response. Time to complete the treatment course will generally be 7-10 days.

(vii) For community based detoxification it is recommended that the regimen should be dispensed in daily instalments and discussed with the patient’s community pharmacist prior to commencing.

(viii) Symptoms of the opioid withdrawal syndrome usually begin two to three half-lives after the last opioid dose. A patient withdrawing from methadone generally starts to experience withdrawal syndrome 24 to 48 hours after the last dose. Untreated methadone withdrawal typically reaches its peak around 4 to 6 days and symptoms may not subside substantially for 10 to 12 days.

In contrast, heroin withdrawal typically begins 6 to 8 hours after the patient’s last dose. The most severe withdrawal symptoms tend to be experienced around 48 to 72 hours after the last dose and last for an average of a week. This needs to be taken into consideration when devising a planned withdrawal using lofexidine. Lofexidine should be used on an increasing, then a decreasing sliding scale as suited to the needs of the individual.

To minimise the effects of withdrawal, the first doses of lofexidine may overlap the last few days use of opioid. In cases where no opioid use occurs during detoxification, duration of treatment of 7-10 days is recommended. In cases where opioid drugs continue to be used, a longer treatment period may be warranted.

See Appendix 1 for an example of a detoxification regimen.

3.2. Side Effects Of Lofexidine

A full list of side effects and cautions can be found in the Summary of Product Characteristics or the British National Formulary. http://www.emc.medicines.org.uk ; http://www.bnf.org/bnf/

The most common side effects of lofexidine include: dry mucous membranes (particularly mouth, throat and nose), hypotension, bradycardia, dizziness, rebound hypertension on withdrawal and drowsiness.

3.3. Cautions For The Use Of Lofexidine

(i) Lofexidine should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or chronic renal failure and in patients with known QT problems or those taking other drugs known to prolong the QT interval.

(ii) Lofexidine should not be discontinued abruptly, but withdrawn gradually over 2-4 days, or longer, to minimise any risk of rebound hypertension.

(iii) Lofexidine should be used with caution in patients with marked bradycardia and pulse rate should be monitored at each consultation.
3.4. Contra-Indications To The Use Of Lofexidine

Hypersensitivity to lofexidine and other imidazoline derivatives, e.g. clonidine and tizanidine.

3.5. Pregnancy And Breastfeeding

The safety of lofexidine in pregnancy and lactation has not been established. Lofexidine should be avoided in pregnancy and breastfeeding unless the benefits of use outweigh the potential risks to mother and baby. Stabilisation on methadone maintenance therapy is the preferred treatment option for opioid dependent, pregnant women.

3.6. Overdose

Overdose of lofexidine may cause hypotension, bradycardia and sedation. Gastric lavage should be carried out where appropriate. In most cases, all that is required are general supportive measures.

3.7. Drug Interactions

(i) Lofexidine may enhance the CNS depressive effects of alcohol and other sedatives, although concurrent medication to aid sleeping has frequently been used in withdrawal studies.

(ii) Concomitant use of tricyclic antidepressants may reduce the efficacy of lofexidine.

(iii) Lofexidine may enhance the effects of anti-hypertensive drug therapy.

(iv) Concomitant use of drugs which prolong the QT interval or cause electrolyte imbalance should be avoided.

3.8. General Advice For Patients

(i) There may be an immediate drop in tolerance to opioids, with a high risk of overdose in the case of relapse.

(ii) Once the maximum dose is reached, taking more tablets will only increase the side effects and will not further diminish the withdrawal symptoms.

(iii) If sedation is experienced, driving or operating machinery should be avoided.

(iv) Contact your clinician to reduce the dose of lofexidine if dizziness occurs.

3.9. Additional ‘Add-On’ Medications For Consideration When Undertaking Detoxification Using Lofexidine

Additional short-term medications may be needed to control other effects of opioid withdrawal. Prescribing symptomatically can reduce some of the physical effects of withdrawal. There is no systematic evidence that any of these medicines work to
improve outcome but they may be useful for the clinician in situations where it is not possible to prescribe effective opioid substitution. Prescribing should reflect current Grampian Joint Formulary recommendations. The BNF and summary of product characteristics should be used to check for full prescribing information.

When prescribing adjunctive medications during opioid detoxification using lofexidine, healthcare professionals should:

- Only use them when clinically indicated, such as when agitation, nausea, insomnia, pain and/or diarrhoea are present.
- Use the minimum effective dosage and number of drugs needed to manage symptoms.
- Be alert to the risks of adjunctive medications, as well as interactions between them.

**Diarrhoea**

Consider loperamide. Recommended dose is 2 capsules (4 mg) initially followed by 1 capsule (2 mg) after each loose stool. The maximum daily dose should not exceed 8 capsules (16 mg).

**Nausea and vomiting**

Consider metoclopramide or prochlorperazine.

Metoclopramide tablets 10mg: 1 tablet up to three times a day as required.

Prochlorperazine tablets 5mg

- Acute attack: Initial dose of 20 mg prochlorperazine followed by a further dose of 10mg after 2 hours if required. For severe symptoms consider an initial deep intramuscular dose of 12.5mg prochlorperazine followed if necessary after 6 hours by an oral dose.
- Prevention: 5-10mg prochlorperazine to be given 2 or 3 times a day as required.

**Stomach cramps**

Consider hyoscine butylbromide or mebeverine.

Hyoscine butylbromide tablets 10 mg: 2 tablets up to four times a day.
Mebeverine tablets 135mg: 1 tablet three times a day 20 minutes before meals and with plenty of water.

NB: Hyoscine remains an effective treatment for gastrointestinal spasm however there have been recent reports of hyoscine abuse. Prescribers should be aware of targeted or multiple requests for hyoscine. Further information can be found in the following link. [Public Health England Hyoscine Butylbromide alert](#)
Agitation, anxiety and insomnia

Any prescribing should be undertaken on a strictly short term basis and should be limited to the detoxification period. In severe cases of anxiety and agitation, obtain suitable psychiatric advice from a substance misuse psychiatrist or the on-call duty psychiatrist.

Agitation and anxiety: Consider prescribing diazepam (oral) 5 to 10 mg up to three times daily as required.

Insomnia: Zopiclone 7.5 mg at bedtime may be considered for insomnia.

Muscular pains and headaches

Consider paracetamol or a non-steroidal anti-inflammatory drug as appropriate.

4. References


5. Consultation List

Steve Beason Psychiatrist, NHSG Substance Misuse Service
Carol Buchanan GP with Special Interest in Substance Misuse
Helen Cheyne Nurse Manager, NHSG Substance Misuse Service
Bruce Davidson Consultant Psychiatrist and Clinical Lead NHS Grampian (NHSG) Substance Misuse Service
Richard Legg GP with Special Interest in Substance Misuse
Stephen Lynch GP Calsayseat, Cluster Clinical Lead Drug and Alcohol
6. Distribution List

Specialist substance misuse service teams
General Practitioners
Community Pharmacies
Lead CHP Pharmacists
Appendix 1: Example Of A Lofexidine Detoxification Regimen

The following is designed as an illustration only. The length of treatment will vary depending on when the patient becomes opioid free and their individual response to withdrawal. It will not always be necessary to reach the maximum daily dose of 2400 micrograms (12 tablets). Some patients will feel comfortable with the symptoms of withdrawal being controlled by a lower daily dose.

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<td>Max 800 micrograms in 24 hours</td>
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<td>(Induction phase)</td>
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<td>Max 1600 micrograms in 24 hours</td>
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<td>Max 2400 micrograms in 24 hours</td>
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<tr>
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<td>Max 2400 micrograms in 24 hours</td>
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