feature

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Lofexidine: some questions answered

Lofexidine as a detox drug was first trialled in the early 1980s. But at the end of the decade the US manufacturer thought the drug had no future and withdrew it. Since then, and with a new manufacturer, support for the drug among clinicians has been growing, although some questions remain unanswered. So where are we at with Lofexidine?

Lofexidine has been available in the UK since 1992 and is licensed for the management of opioid withdrawal symptoms. It offers a non-opiate, rapid withdrawal treatment by reducing the release of noradrenaline, which occurs when the inhibitory effect of opiates is removed.[1] The noradrenaline-induced withdrawal symptoms, such as chills, abdominal cramps, diarrhoea, and pupil dilation are therefore suppressed. This article reports on the first large-scale, national survey on the current usage and safety of lofexidine.

The survey

The SCODA directory of drug services contains the names and addresses of approximately 215 drug dependency services in the United Kingdom.[2] Around one in five of these were found to be duplicates or had unavailable phone numbers; a further 17 projects were either needle exchanges or advisory services, and therefore did not offer detox; 19 could not be contacted in the time available and 14 refused to participate. This left 121 drug treatment agencies, 105 of which (87 per cent) were found to be using lofexidine.

We then divided these agencies into high, moderate and low users of lofexidine. High users were defined as those detoxifying eight or more patients each month with lofexidine; moderate users between four and seven patients, and low users between one and three patients.

All of the high users of lofexidine, three in four moderate users and one in four low users were selected for further study. This left us with a randomly stratified sample of 54 drug dependency units, 14 of which later withdrew (largely due to insufficient resources for completing the questionnaires).

The remaining 40 agencies were invited to complete a questionnaire for each patient who had recently embarked on a lofexidine detoxification, including those who had withdrawn from treatment ('failures'), as well as those who had completed detoxification ('successes'). Patient confidentiality was preserved by the use of a unique code for each questionnaire. A total of 1074 questionnaires were completed and returned for analysis.

Subsequently, eight of these agencies were randomly selected for auditing to validate the data.

The survey was conducted under the remit of the Safety Assessment of Marketed Medicines guidelines and, accordingly, the Medicines Control Agency was notified.[3] Since the survey was non-invasive, observational only and did not involve patients being approached for information, ethics review was not required by all but one drug dependency unit.

Who gets lofexidine?

Of the 1074 clients (aged 16 to 54), 74 per cent were male, in line with more general drug treatment data. Again, in line with most other data, nearly all the clients were 'White' (there were only 18 Afro-Caribbean, 17 Asian and three Oriental clients). Two thirds (776) were unemployed and a similar number lived with a spouse, family or friends.

Where it was recorded, most clients had been dependent on opiates for under five years, though a handful had taken opiates for over 20 (see Chart One). For over a third of clients, this was their first supervised detox, and two in five had only ever had one or two previous attempts. Moreover, over two-thirds (727) had never detoxified with lofexidine before (having used methadone reduction, clonidine or dihydrocodeine in the past). (See

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Chart One:
Length of opiate dependency (n=844)

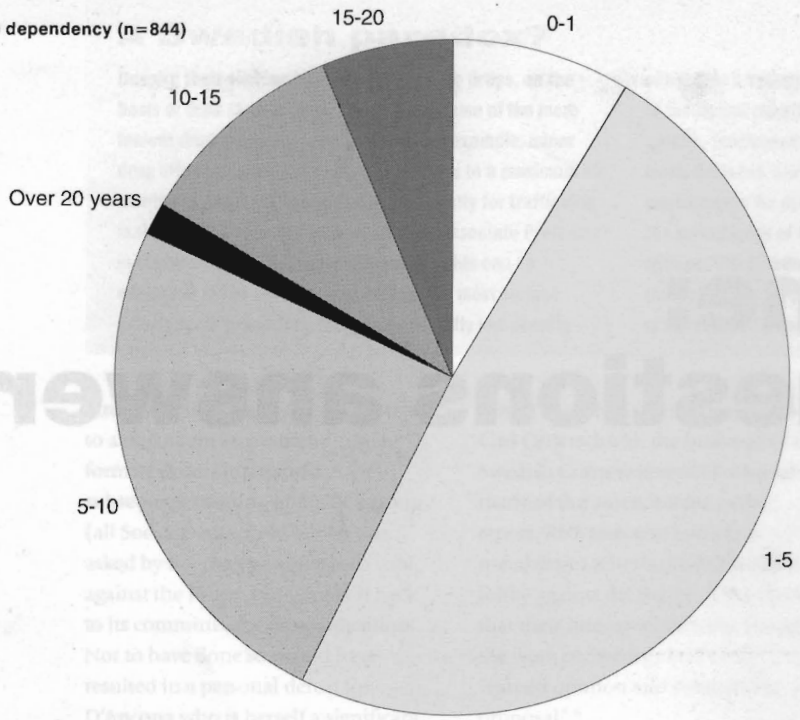
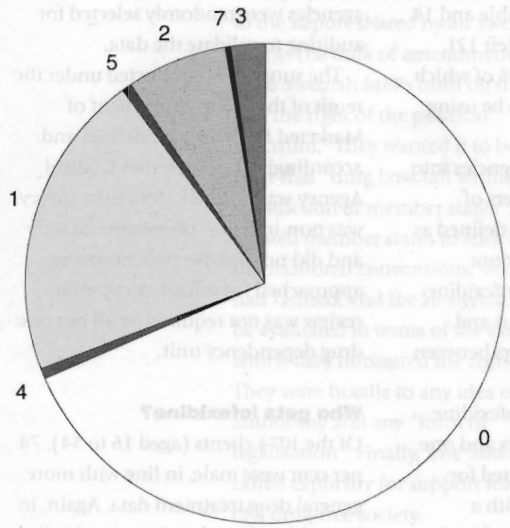


Chart Two:
Number of previous detox attempts with lofexidine (n=1058)



Graph One:
Starting dose of lofexidine

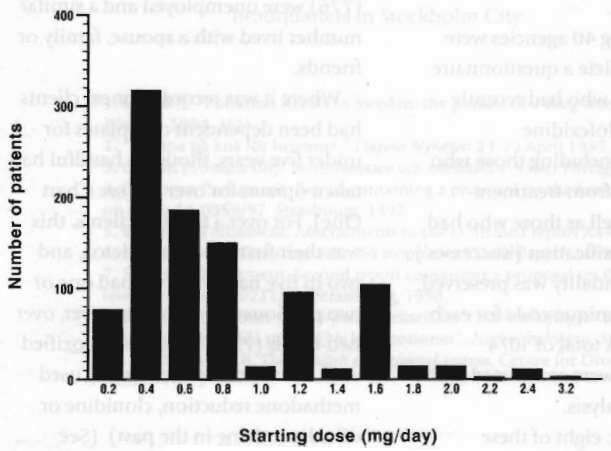


Chart Two). Finally, of the 1074 attempted detoxes, 671 (63 per cent) were carried out in the community, with the remainder undergoing inpatient detoxification.

Dosage

The mean starting dose of lofexidine was 0.8mg/day (see Graph One). More than half the clients reached their maximum dose by day three, and most clients who completed the detox titrated to a mean dose of 2.2mg/day.

Winners and losers

Outcomes were recorded for 1017 (626 outpatient and 391 inpatient) detoxifications. Of these, three in five successfully detoxed, with 60 per cent of outpatients and 62 per cent of inpatients successfully completing the detox programme. The main reasons cited for failing to complete were "craving for opiates" and "not ready to detoxify", emphasising the need to select clients committed to becoming opiate-free.

Nearly a third of clients (31 per cent) were subsequently known to be opiate-free for a period ranging from three days to three years, while 30 per cent were known to have relapsed. An improved lifestyle was recorded for a further one in five clients, which included improved relationships, employment prospects and state of health.

There was no significant difference between the completion rate for males and females, with 62 per cent of females successfully completing the course compared to 60 per cent of males. Employed clients, however, were more likely to succeed than unemployed clients, with 67 per cent and 59 per cent reaching completion respectively.

Clients who had tried to detoxify on two or fewer previous occasions were no more likely to succeed with lofexidine than those who had attempted two or more previous detoxes (59 per cent compared to 62 per cent respectively). Similarly, clients who had been dependent on opiates for two or fewer years were no more likely to succeed than those who had been dependent for two or more years (58 per cent compared to 61 per cent respectively).

Clients detoxifying from heroin were significantly less likely to succeed than those detoxifying from other opiates. Nevertheless, the completion rate associated with heroin withdrawal exceeded 50 per cent (239 out of 464 clients).

Clients had a variety of co-existing illnesses when they began detox. Consequently, a wide range of medications were also being prescribed as well as lofexidine (only 163 clients were not prescribed any other drugs).

An exploratory analysis revealed that the use of diazepam or naltrexone alongside lofexidine was associated with a raised completion rate compared to those receiving no additional medications, with a 65 per cent and 84 per cent completion rate respectively.

A comparison of starting doses of lofexidine between 'completers' and 'non-completers' found no evidence of an association between this and successful completion. Overall, the mean detox length was 8.9 days, ranging from one to 33. However, for those clients who successfully detoxified, the mean duration was 10 days. There was little difference between the dosage regime used for inpatients compared to outpatients, although the duration of the detoxification was significantly less for inpatients, who completed in a mean time of 7.9 days compared to 9.5 days for outpatients.

The best chances for successful detox went to employed clients withdrawing from opiates other than heroin, and taking diazepam and/or naltrexone as well as lofexidine

Effects and side-effects

Comments on the effectiveness of lofexidine was provided by drug agencies for 686 clients (nearly two-thirds of all attempted detoxes). In half these cases, lofexidine was rated as "very successful", as "moderately successful" in 38 per cent of cases and as "poor" for 12 per cent.

Adverse events (mostly attributable to underlying withdrawal symptoms) were recorded in a third of all cases, the most frequent being dizziness (nine per cent of all clients), hypotension (eight per cent), sedation (seven per cent) and dry mouth (five per cent). Of the 81 clients who experienced hypotension, 16 (20 per cent of this group or just over one per cent of the total sample) were withdrawn from treatment because of a fall in blood pressure and/or pulse rate. A further 47 clients (58 per cent of those who experienced hypotension or four per cent of the total sample) were able to continue with detoxification following a reduction in their daily dosage of lofexidine or dose of concomitant benzodiazepine.

There was no evidence that the starting dose influenced the likelihood of reduced blood pressure, although starting doses exceeding 1.6mg/day were associated with a slightly higher incidence of hypotension.

Three clients took lofexidine while pregnant. One patient, who took lofexidine during the first trimester, gave birth to healthy male twins (full term). The twins were still noted as healthy six months later. A premature male baby of a second patient, who also took lofexidine during the first trimester, required a chlorpromazine treatment programme, presumably as a result of the mother's opiate dependency during pregnancy. Follow-up enquiries revealed that the infant is now healthy. The third patient took lofexidine during the third trimester. Her baby was delivered full-term and also required chlorpromazine treatment.

A question of dosage

Retrospective data collection always carries with it a number of disadvantages, especially as in our case the recorded information on some clients was incomplete. However, this survey did allow rapid access to a large number of heterogeneous clients and – provided that the limitations are recognised – it is actually possible to begin sketching out the characteristics of a client most likely to succeed with lofexidine.

The best chances for successful detox went to employed clients withdrawing from opiates other than heroin, and taking diazepam and/or naltrexone as well as lofexidine. However, the success rate was nevertheless greater than 50 per cent for those withdrawing from heroin and for unemployed clients. Conversely, the starting dose of lofexidine, the number of previous detox attempts and the length of dependency appear not to influence outcome.

Continual monitoring of a drug after licensing is essential in order to detect adverse reactions and changes in prescribing. This survey has also helped to highlight how practice makes perfect.

Current uses of lofexidine clearly deviate from the manufacturer's prescribing information. The mean starting dose was found to be 0.8mg/day rather than the recommended 0.2-0.4mg/day, with some drug units starting clients on 2.4mg/day. This meant that most clients had reached their maximum dose by day three and completed the detoxification by day ten, with a sizeable number having completed by day seven. Current practice, then, clearly favours a higher starting dose, a more rapid titration to maximum dose and a shorter treatment duration. The manufacturer is currently reviewing the starting dose recommendations ■

1. Gold M. and Pottash A. "Endorphins, locus coeruleus, clonidine and lofexidine: a mechanism for opiate withdrawal and new non-opiate treatments." *Advances in Alcohol and Substance Abuse*: 1981, *1*(1), p.33-52.
2. *Drug Problems: Where to Get Help*. SCODA, 1992 (first edition).
3. *Guidelines for Company-Sponsored Safety Assessment of Marketed Medicines*. Association of the British Pharmaceutical Industry, 1993.

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