NACD
National Advisory Committee on Drugs

Use of Lofexidine in the Management of Opiate Dependence Syndrome

Report to the National Advisory Committee on Drugs

on

"Use of Lofexidine in the Management of Opiate Dependence Syndrome"

From the working party
National Medicines Information Centre/St James's Hospital,
Dublin 8

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Designed by First Impression

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Minister of State's Foreword

I am delighted to welcome this new report from the NACD on the potential usefulness of Lofexidine as a treatment option in the management of opiate dependency.

Through its three-year research work programme, the NACD is seeking to address gaps in our knowledge of drug misuse in an Irish context. The results of this work, of which this report is an important part, will significantly increase the amount of available research, which will facilitate greater evidence-based policy making in this difficult and complex area.

Drug misuse, particularly opiate misuse, remains one of the major social problems facing Irish society today. The Government will continue to work in partnership with communities most affected by the problem. Implementing the 100 actions in the National Drugs Strategy 2001-2008 and initiatives such as the Local and Regional Drugs Task Forces remains a priority for Government.

The Strategy aims to broaden the range of treatment approaches available to drug misusers. In this context, it aims to have in place in each Health Board area a range of treatment and rehabilitation options as part of a planned programme of progression for each drug misuser. The study suggests that Lofexidine may be useful as an additional treatment for managed opiate withdrawal.

I welcome the report, therefore, and hope that it will help to aid the overall treatment of opiate users in this country.

Noel Ahern T.D.
Minister of State with responsibility for the National Drug Strategy

Preface

As part of its efforts to advise Government on the treatment and rehabilitation of problem drug users, the NACD has initiated several studies of different treatment approaches. Some of these approaches involve the use of medication to assist in achieving abstinence while some do not. Similarly some treatments involve substitute or maintenance prescribing while other treatment modalities are strictly drug and medication-free.

The NACD monitors developments in a whole range of treatment approaches and, as such, became aware of increased interest in the use of non-opiate based approaches to the management of withdrawal from opiates such as heroin and methadone.

It is our hope that this overview of the use of Lofexidine will provide useful and timely information to all those involved in service planning and delivery in the addictions area whether at national, regional or local level. Not surprisingly, the challenge will be to establish which clients presenting for treatment are likely to benefit from this particular medication. We are confident that the experience of using this aid to withdrawal, so excellently and professionally catalogued by Dr. Mary Teeling and her colleagues, will be of enormous benefit to those wishing to intervene with clients seeking to explore the drug-free treatment options available to them.

Dr. Desmond Corrigan
Chairperson
NACD

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Glossary

b.d.	Twice Daily
BP	Blood Pressure
Clon	Clonidine
db	double blind
EMCDDA	European Monitoring Centre for Drugs & Drug Addiction
EU	European Union
FDA	Food & Drugs Administration
IV	Intravenous
IM	Intramuscular
LAAM	Levo-alpha-acetyl-methadol
Lofex	Lofexidine
Meth	Methadone
Nal	Naloxone
Nalt	Naltrexone
NIDA	National Institute on Drug Abuse
ns	Not Significant
RCT	Randomised Controlled Trial
RD	Rapid opioid detoxification
SPC	Summary of Product Characteristics
SSRIs	Selective Serotonin Reuptake Inhibitors
URD	Ultra rapid opioid detoxification

Executive Summary

Opiate dependency continues to be a cause of morbidity and premature mortality among the inhabitants of the EU. Although many treatment modalities have been used, the pharmacotherapeutic approach, using methadone maintenance therapy, has proved most beneficial to date and is the mainstay of treatment in the Irish setting.

A systematic review was undertaken in order to evaluate the potential usefulness of lofexidine as a treatment option in the management of opiate dependency. All available data were retrieved by means of a comprehensive search of the published literature. Contact was made with experts in Ireland to evaluate the practical issues associated with use of lofexidine in a clinical setting.

Evaluation of clinical trials data for lofexidine showed that it appeared to be at least as effective as clonidine and reducing doses of methadone, the other treatment regimens currently used in the treatment of opiate withdrawal. It was not possible to define the optimal dosage regimen for this indication, because of the lack of data from controlled trials, but in general incremental dosing was used reaching a maximum of around 2.2mg/day by day 3-4, with gradual tapering of dose until zero by day 10.

Evaluation of its use in clinical practice showed that it was considered as effective as clonidine for managed withdrawal but had a better safety profile (i.e. less hypotension). Experts have suggested that lofexidine detoxification requires intensive input from all members of the drug treatment team and should be followed up by further treatment to prevent relapse. Although there were insufficient data to evaluate its use in specific subgroups, most workers have suggested that lofexidine is more effective in younger patients and those who have a shorter, less entrenched history of opiate use.

The review suggests that lofexidine may be useful as an additional treatment for managed opiate withdrawal.

Chapter 1

Introduction

Problem drug use, defined as injecting drug use of long-duration/regular use of opiates, cocaine and/or amphetamines, continues to be a problem throughout the European Union (EU). A recent capture recapture study of the prevalence of opiate use in Ireland 2000-2001 (Kelly et al, 2003) showed an overall prevalence of opiate use of 5.6/1,000 population. Males aged 25-34 years had a higher national prevalence (13.7 and 14.7/1,000 pop for 2000 and 2001) compared with the remaining males and females of all ages.

The current National Drugs Strategy 2001-2008, (entitled Building on Experience) which was approved by the Irish Government in April 2001, contains 4 "pillars" for tackling the drugs issue, namely supply reduction, prevention (including education and awareness), treatment (including rehabilitation and risk reduction) and research.

Methadone maintenance is still the major form of treatment in Ireland and this is provided to persons who fulfil specific criteria of admission (Sinclair et al, 2001). Buprenorphine has been used as a maintenance treatment in some EU countries since 1996 and was recently authorised for such use by the Irish Medicines Board in Ireland. The National Advisory Committee on Drugs (NACD) previously commissioned a review of the usefulness of buprenorphine (Teeling et al, 2002) and this showed that buprenorphine could be considered a useful treatment option in the management of opiate dependence in Ireland with an acceptable safety profile. It is reported that the Pharmaceutical Society of Ireland has proposed that the use of non-opioid alternatives to methadone (such as lofexidine) should be considered for use in the management of opioid dependence in the future (Sinclair et al, 2001).

Managed withdrawal, using a variety of medications including methadone, buprenorphine, as well as other (non-opioid) agents, has been evaluated infrequently as a type of treatment intervention in opiate dependency. Following on from the buprenorphine review, the NACD has commissioned this review of lofexidine, a non-opioid agent, which has been used in the management of opiate withdrawal in the UK for several years. The review was commissioned to evaluate the potential usefulness of lofexidine in the overall management of opiate dependence syndrome in the Irish setting.

Chapter 2

Aims and Objectives of the Review

The aim of this review was to evaluate the usefulness of lofexidine as a treatment option in the management of Opiate Dependence Syndrome.

The objectives of the review were to:

1. Retrieve all published information on the use of lofexidine in the management of opiate dependency, in particular, its use in managed opiate withdrawal.
2. Undertake a systematic review of the clinical studies retrieved, including a formal meta analysis if the data permitted.
3. Evaluate the practicalities of use of lofexidine in different treatment settings (inpatient clinics and outpatient clinics/primary care) including an assessment of safety issues such as need for regular medical supervision and patient acceptability.

Chapter 3

Research Methodology of the Review

Primary and review articles, abstracts and other published information on lofexidine were identified using the following sources –

- Medline, Pharmline, Micromedex, Iowa Drug Information Service, (computerised indexing and retrieval systems)

Review journals (such as Drugs) and reference textbooks (Martindale 32nd edition, "Pharmacological Basis of Therapeutics" Goodman and Gilman 10th Edition) were also searched for background pharmacology.

The National Documentation Centre's electronic library and specialist textbooks were searched for relevant articles and publications.

The search terms used were as follows – opiate, opioid, lofexidine, α_2-adrenergic agonist, addiction, therapeutic, withdrawal, detoxification, methadone and heroin. These were employed separately and in combination with one another. The reference lists of relevant articles and reviews were examined for further reports.

No time limit was put on the earliest date for acceptability of data and studies were evaluated from 1980 onwards. The data lock point for inclusion in the review was the 15th December, 2002. Articles that became available after that time were taken into account if they were judged to provide additional information, which might influence the outcome of the review. Once identified, all papers were evaluated for relevance to the review and were included in the assessment if considered relevant.

Data from randomised controlled clinical trials with lofexidine were pooled in order to determine whether it was appropriate to undertake a meta analysis to compare the efficacy of lofexidine with methadone and clonidine in the management of opiate withdrawal. A meta analysis is a statistical technique for combining the results of independent studies, to present an objective and quantitative measure of the effectiveness of an intervention. It reduces the chances of Type II errors by pooling the data across several smaller studies and therefore increases the confidence with which the efficacy of an intervention can be assessed (Sutton et al, 1999; Chalmers and Altman, 1995).

The data on lofexidine were systematically reviewed to determine the optimal dosing regimen and to see if it might be more effective for certain sub-groups of patients. Safety was assessed using published data on clinical usage.

Finally, in order to identify the practicalities of use, information on use of lofexidine in clinical practice was identified from the published literature. Where possible, Irish healthcare professionals who had experience of use of lofexidine in the management of opioid dependence were identified and contacted for further specific data on the advantages and disadvantages of such usage in clinical practice.

Chapter 4

Pharmacology

Lofexidine

4.1 Introduction

Many of the features of opiate withdrawal (e.g. sweating, hyperactivity, restlessness, irritability) are thought to be due to a hyperarousal of the locus coeruleus (Guthrie, 1990). The locus coeruleus possesses inhibitory α_2-adrenergic receptors as well as opioid receptors, therefore an α_2-adrenoreceptor agonist should be effective in treating withdrawal. Clonidine, a central and peripheral α_2-adrenoreceptor agonist has been shown to ameliorate these opiate withdrawal symptoms but its risk of hypotension has made it unsuitable for outpatient use (Cox and Alcorn, 1995).

4.2 Pharmacology

Lofexidine is a structural analogue of clonidine. It is an imidazoline with a high affinity for α_2-adrenergic receptor subtypes (SPC, 2003). This makes it less likely to cause hypotension than non-selective α_2-adrenergic agonists, while retaining potent in-vitro noradrenergic antagonist activity (Cox and Alcorn, 1995). Lofexidine has been reported to reduce withdrawal body shakes induced by discontinuation of chronic morphine infusion in rats, in a dose dependent manner. The activity of lofexidine was not prevented by naloxone (Shearman et al, 1980).

Although lofexidine has been used as a treatment for managed opioid withdrawal for many years, the number of published controlled studies remains small. An early clinical study with lofexidine (Gold et al, 1981) in chronic methadone users showed a significant reduction in opiate withdrawal symptoms from 2 hours after a dose of lofexidine of 0.2mg in 12/15 subjects. Subsequent studies have shown that lofexidine resolves withdrawal symptoms earlier than methadone.

Full details of published studies together with information of its effectiveness in clinical practice are found in Chapter 5.

4.3 Pharmacokinetics

Following oral administration lofexidine is rapidly and almost completely absorbed. Studies using ^{14}C -lofexidine hydrochloride in healthy male volunteers indicate an oral bioavailability > 90% (lofexidine company expert report). Peak plasma concentrations are obtained some 3 hours (range 2 to 5 hours) following oral administration. Plasma protein binding is estimated at 80 – 90% and is unlikely to be clinically relevant from the drug interaction standpoint. The terminal elimination half-life is approximately 11 hours following oral dosing (1.2mg and 2.0mg) in healthy volunteers. This indicates that steady state plasma concentrations will be achieved after 55 hours. Studies indicate linear pharmacokinetics over the dose range 0.4mg b.d. to 1.2 mg b.d. Detailed pharmacokinetics data are limited, however ^{14}C - lofexidine studies in healthy male volunteers indicate significant hepatic metabolism with four metabolites detected. The glucuronide metabolites accounted for 50% of those identified. Approximately 10% of the drug appears unchanged in the urine.

From the drug interaction aspect, caution should be used when combining lofexidine with other medications that undergo significant glucuronidation. Such compounds include analgesics (paracetamol, ketorolac, ketoprofen, naproxen), anticonvulsants (lamotrigine, valproic acid), anti-infectives (atoraquone, zidovudine), anti-hypertensive agents (labetalol), lipid lowering drugs (gemfibrozil), and the sedative/hypnotics (oxazepam, lorazepam, temazepam, propofol).

Pharmacodynamic interactions may also occur when lofexidine is given in combination with alcohol, sedatives, anti-hypertensive agents and tricyclic antidepressants. Particular care should be taken where pharmacokinetic and pharmacodynamic interactions may occur e.g. concurrent use of alcohol, sedatives and labetalol. There are few data available on formal drug interaction studies with lofexidine.

4.4 Summary

Lofexidine is an orally active α_2-adrenergic agonist which shows less anti-hypertensive activity than clonidine. It undergoes hepatic metabolism and may interact with other medications that undergo significant glucuronidation. Caution should be exercised in situations where pharmacokinetic and pharmacodynamic interactions may occur e.g. concomitant use of alcohol, sedatives and labetalol.

Chapter 5

Review of Clinical Usage with Lofexidine

5.1 Introduction

The availability of managed withdrawal is essential for the provision of an effective treatment system for opiate dependence (Gowing et al, 2001). It may be used either as a treatment entity in its own right, as a first step for other forms of treatment or at the end of maintenance treatment (Teeling et al, 2002).

5.2 Clinical Studies with Lofexidine

It has been known for some time that α_2-adrenergic agonists are effective in managing the symptoms of opioid withdrawal (see chapter 4). Although lofexidine has been used for the management of opioid withdrawal for several years, most of the published studies evaluating the use of α_2-adrenergic agonists have used clonidine. The Drugs and Alcohol Group of the Cochrane Collaboration have undertaken a series of systematic reviews evaluating the different modalities of treatment in the management of opioid withdrawal. These provide the biggest body of data which examines the role of lofexidine in this treatment setting.

5.2.1 Systematic Reviews

1) "α_2-adrenergic agonists for the management of opioid withdrawal" (Cochrane Library)

This review, undertaken by Gowing et al (2002a), provides a systematic review of α_2-adrenergic agonists in the management of opioid withdrawal. The focus of the review was to evaluate the effectiveness of these agents in this indication relative to other forms of treatment, placebo and each other. As with all Cochrane reviews an extensive search of electronic databases with subsequent retrieval of all relevant references was undertaken. Although the time limits on data collection were not specified, the retrieval identified papers from 1978-2000 and the systematic review included papers from 1981-1999.

A total of 68 studies were identified in the data retrieval process of which 24 were judged to fulfil the criteria for inclusion in the systematic review. Grounds for exclusion included no concurrent comparison treatment, insufficient data on either the treatment protocol, participant characteristics or study outcomes and variable treatment protocols.

Only 6 of the included studies evaluated the use of lofexidine (n = 200 subjects). Table 5.1 summarises the included studies. There was no consistency between the studies in terms of dosage regimens, duration of treatment or comparator used. In general, initial doses ranged from 0.6 – 1.8mg/day administered in 2 or 3 doses. All studies used incremental dosing up to a maximum of 2mg/day, usually achieved by the fifth day. Doses were subsequently tapered off to zero by day 10-18 (where stated). One study (Bearn et al, 1998) used an accelerated detoxification regimen which involved 1.8mg lofexidine/day on day 1, followed by 2mg for 3 days and then 1.2mg on day 5, all administered in divided doses. Only one study was in an "outpatient" setting - home treatment with regular house visits. Four were inpatient studies and the sixth study was undertaken in prison. This latter study undertaken by Howells et al, was unpublished at the time of the review but has since been published (Howells et al, 2002).

The results were presented as follows 1) withdrawal syndrome 2) duration of treatment 3) completion of withdrawal and 4) nature and incidence of adverse effects. It was not possible to undertake definitive quantitative meta-analysis on these criteria because of the heterogeneity of the protocols and conduct of the studies. Moreover, the reviewers had hoped to evaluate the effects of concurrent use of alcohol and other drugs via subgroup analysis but there were insufficient data to report on this.

Withdrawal Syndrome

The studies appeared to show that withdrawal signs and symptoms emerged more quickly in participants treated with lofexidine when compared with tapering doses of methadone. The main withdrawal symptoms reported were insomnia, drowsiness, anxiety, irritability, lethargy, aches/pains (including bone pain) and feeling of cold. Howells et al (2002) suggested that aches and pains and feeling cold were greater

problems for the lofexidine group whereas drowsiness scores were higher in the methadone treated group. Kahn (1997) showed that bone pain and insomnia were particular problems for both lofexidine and clonidine – treated patients.

Howells et al (2002) showed that withdrawal scores were consistently 5-10% higher in the lofexidine group compared with methadone. However, this study was conducted in a prison setting, with study entry occurring after 24-48 hours in custody and therefore the interval between the last opiate use and study entry, is uncertain. Therefore, the results may be confounded by time since last opiate use.

No significant difference in efficacy between clonidine and lofexidine was reported in any of the studies. Peak withdrawal scores were reported to occur on or about the second day of treatment (later if the participant was withdrawing from methadone).

It was noted by the reviewers that none of the treatments evaluated appeared to fully suppress the aches and pains, sleep disturbances, anergy, chills or anxiety associated with withdrawal.

Duration of Treatment

There was a marked difference in the duration of treatment between regimens used as reducing doses of methadone needed a much longer period of detoxification (minimum of 20 days) compared with the use of an α_2-adrenergic agonist (10 days usually). Therefore, it was difficult to compare apparent differences in absolute duration of treatment for the different treatment groups. It would appear that those treated with lofexidine were less likely to be retained in treatment for the scheduled period of treatment compared with tapering methadone treatment. However, this finding is subject to huge confounding which makes comparisons difficult to interpret. There was no difference in retention rates between lofexidine and clonidine.

Completion of Withdrawal

Definitive data on completion of withdrawal were not reported in all studies. Moreover, some of the data (Howells et al, 2002) had to be disregarded as 12 of the 23 participants who withdrew early did so for administrative rather than treatment related reasons. From the data available it would appear that the completion rates were similar for lofexidine and clonidine and similar (or slightly less) for lofexidine when compared with reducing doses of methadone. It was not possible to say if use of lofexidine was better in heroin withdrawal or methadone maintenance withdrawal.

Nature and Incidence of Side Effects

Hypotension was not reported to be a major problem with use of lofexidine when compared with reducing doses of methadone. No participants were withdrawn because of hypotension and only small numbers of subjects needed a reduction in dose. Of interest is the fact that the study from Bearn and workers (1998) which used two different lofexidine treatment regimens, (see Table 5.1) reported no significant difference in mean blood pressure between the two lofexidine groups.

Clonidine comparative studies reported consistently more hypotension with clonidine compared with lofexidine, resulting in significantly more omissions of, or reductions in, dose for the clonidine groups.

There is very little information on other adverse effects of treatment, as most of the studies focused on the possibility of hypotension. There are no data to suggest that the adverse effect profile of lofexidine is worse compared with clonidine or reducing doses of methadone for non-hypotension events.

Conclusions

The reviewers noted that α_2-adrenergic agonists could be used for the management of withdrawal. In comparison with reducing doses of methadone, such use was associated with shorter duration of treatment and similar or slightly lower rates of completion of withdrawal. The signs and symptoms occurred earlier and also resolved at an earlier stage with α_2-adrenergic agonists. Lofexidine appeared to cause less hypotension than clonidine. Because of this finding and the fact that clonidine and lofexidine are equally effective, the reviewers recommend that lofexidine should be the preferred option, particularly for withdrawal in an outpatient setting, if an α_2-adrenergic agonist is to be used.

Table 5.1

Lofexidine Studies included in Cochrane review "α_2-adrenergic agonists for the management of opioid withdrawal" (Gowing et al, 2002a)

Study	Type	Numbers	Doses **	Comparator	Results
Bearn et al, 1996	RCT db	42 Lofex; 44 Meth; on heroin +/- meth	Lofex: 0.6mg/d increasing by 0.4mg/d until day 4; max dose of 2mg/day x 3d + tapering x3d	Meth: variable start dose ↓ x10d	"Broadly equivalent" but more w/d symptoms with lofex early in treatment. No BP problems.
Bearn et al, 1998	RCT	22 Lofex (1); 20 Lofex (2); 19 Meth; on heroin +/- meth * (All subjects stabilised on meth prior to w/d treatment)	(1) Lofex 0.6mg/d ↑ to 2mg/d tapered to zero by d10 (2) Lofex 1.6mg/1d; 1mg/x3d; 0.6mg x 1d	Meth variable start dose ↓ x 10d	Overall similar rates of completion. (1) Lofex achieved earlier detoxification. No BP problems.
Carnwarth et al, 1998	RCT db	26 Lofex; 24 Clon; (+10 left trial before treatment) on heroin +/ meth	Lofex 0.6mg/d ↑ to 1.6mg/d then ↓ over 3d to zero at d12	Clon 0.2mg/d ↑ to 0.8mg/d then ↓ x 3d to zero at d12	17/26 +12/24 completed treatment (ns). More hypotension with Clon.
Howells et al, 2002 unpublished at time of Cochrane review	RCT db	32 Lofex; 36 Meth; (8 who were randomised not included); "opiate-dependent" non-specific	Lofex 0.6mg/d ↑ X 0.4mg/d to 2mg/d x3 ↓ 0.4mg/d x3 (10 days)	Meth 30mg x 1d ↓ x 5mg every second day to zero by d10	No significant difference in symptoms. (but see text)
Kahn et al 1997	RCT db	14 Lofex; 14 Clon; all stabilised on meth	Lofex 0.4mg/d ↑ to 1.8mg/d if necessary. Tapered to zero by d18	Clon 0.2mg/d ↑ to 0.9mg/d if necessary. Tapered to zero by d18	No significant difference in completion rates but lofex caused less hypotension.
Lin et al, 1997	RCT db	40 Lofex; 40 Clon; on heroin	Lofex 0.8mg x 1d ↑ to max of 1.6mg/x2d then tapered to zero	Clon 0.3mg x 1d ↑ to max of 0.8mg x 2d then tapered to zero	No significant difference in completion rates but lofex caused less hypotension.

Legend

** Lofexidine usually administered in divided daily doses.

Lofex	=	Lofexidine	db	=	double blind
Clon	=	Clonidine	w/d	=	withdrawal
Meth	=	Methadone	BP	=	blood pressure
RCT	=	Randomised controlled trial			

2) "Methadone at tapered doses for the management of opioid withdrawal" (Cochrane Library)

This review (Amato et al, 2002) compared the usefulness of reducing doses of methadone with α_2-adrenergic agonists, other opioids and placebo in the management of opiate withdrawal. Of 10 studies, which compared reducing doses of methadone with α_2-adrenergic agonist treatment, only 2 involved use of lofexidine (n = 42 lofexidine-treated subjects in each study). Details of these studies are given in table 5.1 (Bearn et al, 1996; Bearn et al, 1998). The review showed that lofexidine was comparable with methadone in terms of efficacy and safety. The reviewers commented on the wide variability of the data, which precluded quantitative meta analysis.

3) "Effectiveness of short-term use of buprenorphine in the management of opioid withdrawal" (Cochrane Library)

A full report of this review (Gowing et al, 2001) is contained elsewhere (Teeling et al, 2002). It is interesting to note that this review contains no comparison between lofexidine and buprenorphine, highlighting the lack of published data with lofexidine. A recently published open label study from the UK (White et al, 2001) compared the efficacy of lofexidine with buprenorphine in the management of withdrawal in 69 opiate-dependent subjects. A maximum of lofexidine 2.4mg/day using variable dosage regimens was used, compared with a maximum daily dose of 8mg buprenorphine. The treatment period allowable for detoxification was up to one month. Results showed that subjects were more likely to experience a severe withdrawal syndrome and less likely to complete treatment with lofexidine compared with buprenorphine. This study has many methodological flaws but is the only published comparative study evaluating lofexidine and buprenorphine in this treatment setting.

4) "Lofexidine for Detoxification: Review of recent randomised and open controlled trials" (Strang et al, 1999)

All of the studies in this review were included in the Cochrane review outlined above (Gowing et al, 2002a) and the conclusions drawn were similar. Lofexidine was found to have similar efficacy as clonidine and methadone regimens, but without the hypotensive problems of clonidine. These reviewers made the point that lofexidine may be particularly useful for managed withdrawal in situations where there is a problem using reducing doses of methadone, such as in the prison environment where there may be concerns about abuse or diversion, or in situations where methadone may not be available or acceptable for use by the treating clinician.

5.2.2 Other Studies with Lofexidine

Several published studies including small numbers of patients have evaluated the use of lofexidine in the management of withdrawal in an outpatient setting. Brown et al (1998) reported successful detoxification in 11/28 (39%) individuals, half of whom were taking heroin and the remainder were on methadone maintenance. Lofexidine was administered on a sliding scale for 14 days at a maximum of 1.6mg/day. The subjects were managed at home by community psychiatric nurses/community workers. The opiate was stopped 48 hours after initiation of lofexidine. Lofexidine was more likely to be successful in methadone-maintained subjects and those who had been taking heroin for less than one year. As the maximum dose of lofexidine used was 1.6mg/day, the authors suggested that this dose may have been insufficient for heroin detoxification.

In a study by Eveleigh (1995), detoxification was undertaken with lofexidine in an outpatient setting in 6 subjects, maintained on methadone. A maximum dose of lofexidine 1.6mg/day was allowed and the treatment duration was 16 days. Lofexidine was administered in incremental doses reaching maximum dosage from days 5-12 with subsequent tapering of dose. All subjects completed the withdrawal treatment satisfactorily although 4 had relapsed by 2 months (2 at 2 weeks). The remaining 2 remained drug-free at 6 months.

Subjects complained of sleeplessness, restlessness and bone aches during their period of withdrawal. The investigator noted that all subjects who relapsed stated that they had returned to drugs because they could not cope with their thoughts and/or emotions, thus highlighting the need to continue treatment (opiate antagonist and counselling) after the initial period of withdrawal has been successfully completed.

Washton and workers (1983) evaluated the use of lofexidine in 30 opiate dependent outpatients who were receiving substitution therapy with either methadone (10-45mg /day) or levo-alpha acetyl-methadol (LAAM) at doses of 28-43mg per week. Incremental lofexidine doses up to 2mg/day were used and success was defined as remaining opiate – free for at least 10 days after the last dose of methadone (14 days after LAAM). Subjects who had not successfully completed detoxification by 21 days were offered alternative treatment. Results showed 21/30 subjects (70%) completed detoxification. Only 2 of the 9 non-completers attributed their failure to unacceptable withdrawal symptoms. The remainder (n = 7) cited "opiate craving" or "not ready to detoxify" as reasons for returning to opiate use. Of interest, no relationship was found between the level of maintenance therapy prior to lofexidine and degree or severity of withdrawal symptoms. No hypotension was noted even at the maximum dose of 2mg lofexidine/day. However, this study did note that the withdrawal symptoms of insomnia and lethargy were not alleviated to any extent by lofexidine. Moreover, it also highlighted the need to ensure that lofexidine is used as part of a treatment programme (e.g. as a short-term treatment used to switch patients from opiate dependence to opioid antagonist therapy).

Summary

Lofexidine has been shown to be an effective treatment in the management of opioid withdrawal. It has been shown to be as effective as clonidine and reducing doses of methadone and has a better safety profile than clonidine in terms of hypotension. It does not appear to eliminate withdrawal symptoms completely (especially insomnia and lethargy) and ancillary treatments are usually necessary. Dosage regimens have varied between studies, but in general doses, should be titrated to the individual's symptoms. Doses up to a maximum of 2.2mg/day have been administered in divided doses, without significant hypotension. Treatment has generally lasted for approximately ten days although this has been extended in some subjects according to need. An accelerated regimen of five days has been shown to be as effective as the standard regimen in one study but this involved very small numbers (n = 22).

α_2-adrenergic agonists such as lofexidine have been judged to be particularly suited to those who are well motivated and who seek an earlier resolution of withdrawal symptoms. However, investigators (Gowing et al, 2002b) have stressed the need to use lofexidine within a treatment programme involving follow-up opioid antagonist treatment and counselling.

5.3 Lofexidine in Combination with Opiate Antagonists

The opioid withdrawal syndrome is rarely life-threatening but it makes completion of withdrawal without medication difficult for most people. In recent years, studies have been undertaken to investigate the value of an opioid antagonist in combination with medication, including α_2-adrenergic agonists, to ameliorate withdrawal symptoms, as a treatment option for managed withdrawal. Such regimens are used to shorten the period of detoxification (Merrill and Marshall, 1997). The rationale is that a more rapid transition from dependence to abstinence might increase rates of withdrawal (Gowing et al, 2002c).

Two published studies compared a lofexidine/opioid antagonist combination with conventional lofexidine therapy. Both of these studies were open label in design and patients were allowed to choose their treatment option. Treatment regimens differed between the two studies (Table 5.2) and were administered in specialist hospital units. Buntwal et al (2000) showed no significant difference in terms of the numbers of patients completing detoxification or the average length of stay between the two treatment groups (80% + 73%). It was noted that the withdrawal symptoms were significantly less severe with the combination whereas the adverse effect profile was similar. However numbers were small (n = 11 per group). Bearn et al (2001) showed no overall additional benefit with the lofexidine/naloxone combination in terms of rates of completion of detoxification or length of stay in treatment, although symptom severity was less during combination treatment. The authors postulated that the level of opioid receptor blockade with the treatment regimen used was inadequate to accelerate reversal of the dependence - associated neuroadaptatory changes. They suggested that the rate of antagonist occupancy

of opiate receptors may be a critical factor in determining the rate of resolution of opiate withdrawal. It is important to note that this study also involved small numbers (n = 49) and four patients changed treatment during the study (final numbers n = 26 for the combination; 23 for lofexidine only).

A double-blind randomised controlled study (Gerra et al, 2001) compared lofexidine/naloxone (n = 20) with a clonidine/naloxone regimen (n = 20) administered in an outpatient setting, over 3 days. All subjects were heroin dependent and had entered an outpatient recovery programme. All medications (including oxazepam, baclofen and ketoprofen) were administered in outpatient clinics for the three days of detoxification (Table 5.2). Patients were subsequently offered naltrexone maintenance along with counselling for a further three months. Results showed that the lofexidine-treated group suffered less withdrawal symptoms and mood changes compared with clonidine, although completion rates were similar (18 + 17 respectively). Approximately 75% of all those completing detoxification entered the naltrexone maintenance programme. Clonidine caused a significant decrease in mean systolic blood pressure compared to baseline but it is not clear from the report whether this resulted in dosage reduction in any patient. Lofexidine did not induce any significant change in blood pressure. Although this was undertaken in an "outpatient" setting, participants needed close monitoring during detoxification in a clinic and were closely monitored during the subsequent weeks. However, the authors conclude that these results suggest that lofexidine, in combination with opioid antagonist therapy, could be considered in an outpatient setting and future studies should evaluate this possibility.

Conclusions

Limited data are available evaluating the usefulness of lofexidine in combination with an opioid antagonist in managed opiate withdrawal. The available studies suggest that the combination is at least as effective as lofexidine alone and may also be associated with less severe withdrawal symptoms than lofexidine monotherapy. It also enables the period of detoxification to be shortened and this may help to improve rates of withdrawal and facilitate transfer to naltrexone maintenance programmes. Further studies are needed to determine the optimal treatment regimen. Finally, although some workers have suggested that the combination regimen of lofexidine and an opioid antagonist could be useful in an outpatient setting, more studies are needed to confirm this.

Table 5.2

Lofexidine/Opioid Antagonist Combination Studies

Study	Type	Numbers	Doses **	Comparator	Results
Buntwal et al, 2000	Open label	11 Lofex/ nalox/nalt; 11 Lofex; on heroin x/- meth	Lofex 1.8mg x 1d 2mg x 4-5d 1mg x 1d (7days)	Nalox 0.8mg 1/M Lofex 2mg Nalt 14mg } d1 Nalt dose ↑ To 50mg by d 4; Lofex dose ↑ to 1.8mg by d3 then ↓ to zero by d5	W/D symptoms less severe in combination group. No difference in rates of completion of detoxification.
Bearn et al, 2001	Open label	(1) 30 Lofex/ Nalox (2) 19 Lofex; (4 switched from (1) to (2) during study) all had poly-substance abuse	(1)* Lofex 2mg x 2d; Nalox 0.8mg 1/m +Lofex 1.6mg/x 4; * all were stabilised on meth x 3d prior to detoxification	(2)* Lofex 1.8mg x 1d; Lofex 2mg x 5d; Lofex 1.2mg x 1d	No significant difference between treatments.
Gerra et al, 2001	RCT db	(1) 20 Lofex/ nalox/nalt; (2) 20 Clon/ nalox/nalt; all on heroin	(1) Lofex 1.2mg x 1d; Lofex 1.6mg, Nalox 0.4mg IV + Nalt 5mg on d2; Lofex 1.2mg, Nalox 0.4mg IV + Nalt 50mg on d3	(2) Clon 0.9mg on d1; Clon 1.2mg, Nalox 0.4mg IV + Nalt 5mg on d2; Clon 0.9mg, Nalox 0.4mg IV + Nalt 50mg on d3	Lofex more useful in treating W/D symptoms and caused less hypotension than Clon.

Legend

** lofexidine and clonidine were given in divided daily doses

RCT	=	Randomised controlled trial	Nalox	=	Naloxone
db	=	double blind	Nalt	=	Naltrexone
Lofex	=	Lofexidine	Clon	=	Clonidine
Meth	=	Methadone	W/D	=	Withdrawal

5.4 Use of Lofexidine in Clinical Practice

5.4.1 United Kingdom

Lofexidine is authorised in the UK to "relieve symptoms in patients undergoing opiate detoxification" (SPC, 2003). Since its launch in 1992, usage has increased steadily and one report noted that more than 18,000 courses of lofexidine treatment were used in the UK in 1998 and this usage was estimated to increase to more than 21,000 in 1999 (Strang et al, 1999).

The results of a national survey on the efficacy and safety of lofexidine were recently published (Akhurst, 1999; Akhurst, 2000). The survey was conducted under the guidelines for company-sponsored safety assessment of marketed medicines (SAAM). A total of 1,074 questionnaires from 40 randomly chosen drug dependency units were completed and available for evaluation. The data set comprised 793 males and 270 females. Approximately 43% were taking heroin, 28% methadone and 20% both. The majority had been dependent on opiates for ≤ 5 years and almost three quarters had either never attempted a supervised detoxification before or had a maximum of 2 previous attempts.

Detoxification with lofexidine was undertaken in the community in 63% cases. The mean starting dose used was 0.8mg/day with the majority of patients achieving their maximum dose by day 3. Most patients were titrated to a mean maximum dose of 2.2mg/day although doses up to 5.6mg/day were recorded. The mean duration of treatment was 8.9 days (range 1-33 days) with a mean of 10 days for those who successfully completed treatment. Of interest, the duration of detoxification was significantly less for inpatients (mean 7.9 days) compared with outpatients (mean 9.5 days).

Information on efficacy was available on 686 detoxification episodes, of which 342 (49%) were rated as very successful, 261 (38%) as moderately successful and 83 (12%) as poor. Follow-up information was not available from all questionnaires but 333 patients were reported to be opiate-free for a period ranging from 3 days to 3 years and 327 patients were known to have relapsed. Of interest, 221 questionnaires recorded an improved lifestyle relating to relationships, employment and/or health status.

Adverse events were reported in 351/1074 (32.7%) detoxification episodes of which 239 were considered to be probably or possibly related to treatment (according to the WHO classification). Commonest events reported were dizziness (8.5%) sedation (6.6%) insomnia (4%) dry mouth (5%). Hypotension was recorded in 7.5% cases and this resulted in discontinuation of treatment in 16 cases and reduction in dosage in a further 47 cases. It is important to note that not all of the treatment units routinely monitored blood pressure and pulse rate, but from the data available it was noted that if hypotension and/or bradycardia were to occur, this usually happened within the first few days. Moreover, no record of hypotension, bradycardia or other adverse event was noted in the cases where doses of lofexidine in excess of 2.4mg/day were used.

This SAAM study involved a retrospective review of patient files and therefore data collection was incomplete for a number of the parameters. In addition the adverse events recorded in the files related primarily to symptoms as routine blood testing which might have picked up "concealed adverse events" (e.g. liver or renal dysfunction) was not undertaken. However, useful information on the general safety of lofexidine has been made available from this survey.

The use of lofexidine in 194 patients undergoing 214 opioid detoxifications over a 24 month period was reviewed by Sheridan et al (1999). All patients had been treated in the acute assessment unit at the Maudsley Hospital (UK) over a 24 month period (1994-1996). These patients had a significant drug-related problem and were resident in the catchment area of the hospital. The group included 151 males and 43 females with a mean age of 29.7 years (19-58 years), most of whom (n = 179) were unemployed. The majority of patients were dependent on heroin (by injection) and/or methadone. The mean duration of dependence was 95 months (range 4 - 372 months). Twenty patients had more than one detoxification episode during the period of review.

Lofexidine was administered to achieve maximum dosage (2.4mg) within 24 - 48 hours depending on blood pressure response. Adjunctive medicine was also allowable (for insomnia, pain etc). Detoxification was considered to have been completed if this was confirmed in the notes or if the patient still remained in the unit by day 14.

Results showed that 81 patients (37.9%) remained in treatment by day 8 and 52 (24.3%) were considered to have completed detoxification. Reasons for non-completion included failure of lofexidine to adequately control the withdrawal symptoms, psychosocial problems, or expulsion from the programme due to breaches of the treatment protocol (use of prohibited drugs or alcohol).

Blood pressure was recorded for the first 5 days of treatment. In general, hypotension, when present, occurred early in treatment and generally began to return to normal by the fourth day. Of 144 instances of hypotension recorded, only 23 resulted in a withholding or reduction of the dose. The remainder resolved spontaneously on continuing medication. Other adverse events were not recorded routinely but where they were, they consisted most commonly of dizziness, drowsiness, lethargy, nausea and vomiting.

Although the data represent a retrospective review they are still useful in highlighting the practical issues involved in the use of lofexidine. They confirm that lofexidine can be used safely, even at maximum doses. The authors argue that the low "completion rates" may reflect the definition of completion of treatment used – they suggest that many of those who had left the unit before day 14 might have actually achieved successful detoxification.

Finally, the practical issues of use of lofexidine at primary care level was discussed by 3 GPs in a published article (Smith et al, 1998). This report highlighted the need to ensure that lofexidine is used as part of an overall treatment plan (including counselling, self-help groups as well as other pharmacotherapy modalities such as naltrexone), in order to ensure long-term abstinence.

5.4.2 Ireland

Lofexidine is currently not authorised for use in the management of opiate withdrawal in Ireland, although an application is pending (Roberts, personal communication). Because it is not authorised, it has not been used in primary care (Delargy, personal communication) but it has been used by some inpatient units and outpatient clinics on a named-patient basis. The following information has been received from two treatment units in the Dublin area.

Darndale Clinic

This is a health board out-patient treatment centre with full time on-site nurse, pharmacist and counsellor. It also has the services of doctors on a sessional basis.

A pilot project evaluating the usefulness of lofexidine in the management of opiate withdrawal was begun in this centre in December 2000 (Dowdall, personal communication). Clients were selected as suitable for Lofexidine by counsellors involved. They were primarily heroin smokers or users with a relatively small heroin habit (1 to 2Q's per day) with a desire to become drug free. Also included were those on an existing methadone programme who had reduced down to low doses (less than 20 mls) and wished to become drug free.

A total of 98 addicts participated in this project between December 2000 and December 2002 and detailed information on these has been made available.

Lofexidine was prescribed using a 10 day regime as laid down in the SPC from the manufacturer. Symptomatic medications were also prescribed on "as required" basis. Successful detoxifixation was achieved if the patient's urine was free of opiates at the end of the programme. Lofexidine was administered in conjunction with full medical and counselling support and patients were seen on a daily basis (including weekends). Participants were usually helped by a non-drug using support person. The patient's GP was informed of the programme. After successful detoxification patients were offered Naltrexone therapy. Counselling was available during the follow-up period with emphasis on relapse prevention. Links were established with rehabilitation services (inpatient and outpatient) in an attempt at relapse prevention.

For the purpose of analysing results, patients were subdivided into the following groups.

1. Heroin smokers (only)
2. Those on methadone programmes, either

   (a) completely stable – no heroin use in 6 months or

   (b) continuing to dabble with heroin

3. Those users with a more complex history (i.e. poly-substance users, a history of IV heroin abuse etc.)

The overall success rate for patient attempts was 38% (37/98 attempts). The success rates for the separate groups were:

1. stable on methadone maintenance with no additional heroin use	80% (8/10)
2. pure heroin smokers	39% (13/33)
3. mixed use (including intra-venous use and polysubstance use)	34% (14/41)
4. unstable on methadone programme	14% (2/14)

The data were also examined to determine the number of patients that successfully completed detoxification. These results differed from those based on the number of successful attempts (above) because some patients tried more than once. The 98 attempts comprised 84 patients because:

- 8 patients tried twice and, of these, 4 were successful on the second attempt
- 2 people tried 3 times and, of these, 1 was successful on the third attempt and 1 was successful first time, relapsed and failed on the second attempt before succeeding again on the third attempt. This patient accounted for 2 of the 37 successes.

On this basis the success rate for patients was 43% (36/84). Serious problems with hypotension were not reported.

Follow-up information was available for 34 of the 36 successful patients. Of these, 26 reported that they were not using opiates and 8 had relapsed. Of the relapsed patients, 5 chose a methadone programme and 2 were planning repeat lofexidine detoxification attempts.

Dr. Dowdall has commented that the lofexidine programme offers patients an important choice in treatment options. The only other outpatient detoxification option hitherto available was a gradual methadone dose reduction. This type of detoxification option has a tendency to lead onto methadone maintenance.

Lofexidine is not suitable for all opiate users wishing to undergo managed withdrawal. Exclusion criteria include pregnancy or underlying cardiac or renal dysfunction and users with serious co-existing psychiatric morbidity. In addition, a history of polydrug use or high levels of alcohol consumption make successful detoxification less likely. It was felt that the best indicator of success was the patient's motivation to become drug-free.

In summary, lofexidine has been safe to use in this programme with only 3/98 patients (all slim females) displaying mild signs or symptoms of hypotension, which resolved with either omission of a dose or a reduction in the daily dose of lofexidine.

Fortune House/Trinity Court (outpatient clinics)/Cuan Dara (inpatient unit)

Dr. Eamon Keenan, consultant psychiatrist, has provided information on his experience of using lofexidine, both at inpatient and outpatient level. (Keenan, personal communication). Lofexidine is used as a 10-day programme using a maximum dosage of 2.2mg/day. Lesser doses may be needed as an inpatient. All doses are dispensed by the clinic pharmacy. Successful detoxification is defined as the patient reaching day 10 of treatment with negative urinalysis.

In general, lofexidine has been found to be suitable mainly for younger users with a short history of opiate dependence. It is less effective in those who have a long established use or a high dosage requirement of opiates. It may also play a role as adjunctive therapy at the end of reducing doses of methadone, used for detoxification.

Lofexidine is not used in pregnant women. Hypotension has been seen with lofexidine, which may necessitate discontinuation of treatment. In addition, lofexidine managed withdrawal requires intensive input from all clinic staff, (doctor, nurse, pharmacist and counsellor) because of its short duration. Dr. Keenan is of the opinion that lofexidine's place is in the outpatient management of opiate withdrawals for patients who are younger with less entrenched addiction.

5.5 Summary and Conclusions

Lofexidine, an α_2-adrenergic agonist has been shown to be effective in reducing the large adrenergic component of opioid withdrawal. Although few clinical studies, involving small numbers of patients and using diverse treatment regimens, have been published, the results suggest that lofexidine is at least as good as reducing doses of methadone and clonidine and causes less hypotension than clonidine. In studies where lofexidine was compared with methadone, it appeared that the symptoms of withdrawal occurred earlier with lofexidine and reached an earlier resolution. An escalating dose regimen (to a maximum of 2.2mg/day by day 3 or 4), administered in divided doses has been used in clinical practice. The duration of treatment has ranged from 10 - 14 days including dose tapering. It is important to note that most studies have also used additional medications such as tranquillisers, +/- antispasmodics +/- anti diarrhoeal agents to help relieve the symptoms of opioid withdrawal.

Lofexidine is a non-opiate treatment which brings about a quick detoxification. Although experts in this area have suggested that lofexidine is more effective for younger users or those with a brief history of opiate use, the data from controlled trials are not sufficient to support this. Lofexidine has also been shown to be more effective in those with a stable home situation but numbers are small here. Because the detoxification process with lofexidine is rapid (10 - 14 days) it requires close involvement of the entire drug treatment team with the patient during the withdrawal process and this may have resource implications. Furthermore, most workers recommend that lofexidine treatment is followed by a treatment programme including opioid antagonists and counselling to prevent relapse.

Chapter 6

Summary and Conclusions

Illicit opiate use has been a public health problem in Ireland since the early 1980's and drug-related deaths are an important cause of premature mortality. Methadone maintenance has been available since the 1990s and is the mainstay of treatment in Ireland. A review was previously undertaken on the effectiveness of buprenorphine as an intervention in the management of opiate dependence syndrome. The current review evaluated the effectiveness of lofexidine in the management of opiate dependence. A systematic review of all available data, retrieved from the published literature, was undertaken. Contact was made with experts in Ireland who have clinical experience in the use of lofexidine in order to evaluate the practical issues associated with their usage.

The results of the review may be summarised as follows:

1. Lofexidine has been evaluated for use in managed opioid withdrawal (detoxification) and has been seen to be at least as effective as clonidine and reducing doses of methadone, the currently used treatment modalities. It was not possible to identify the most appropriate treatment regimen (either in terms of dosage or treatment duration) because of the limited number of studies identified and the heterogeneity of the data contained therein.
2. Use of lofexidine was not associated with significant levels of hypotension, making it a suitable treatment for use in the outpatient setting.
3. It is not possible to make definitive statements about use of lofexidine in specific subgroups, but it has been suggested that response is better in younger opiate users or those with a shorter history of abuse. It is not recommended for use during pregnancy and there is no information on its use in this subgroup.
4. Reports from usage in clinical practice suggest that managed withdrawal using lofexidine requires the close involvement of all members of the drug treatment team with the patient during treatment and that lofexidine detoxification should be followed by further treatment (such as opioid antagonist therapy) and counselling to prevent relapse.

In conclusion, this review suggests that lofexidine may be regarded as a useful additional treatment option in the overall management of opiate dependence.

Questions on the Use of Lofexidine in the Pharmacological Management of Opiate Dependence

(1) Background Data on Clinic Protocol

Please give a brief description of the clinic set-up in terms of doctor/ pharmacist/ nurse/ counsellor input and whether patients have dispensing and supervised administration of withdrawal/ substitution drug at clinic or local pharmacy level (irrespective of drug type)

How often are patients seen (assuming a daily dosage regimen for all medications)? (tick for yes as appropriate)

- Daily ☐
- Alternate days ☐
- Weekly ☐
- > weekly ☐

Do patients get each dose on a daily basis (either at clinic or local pharmacy)?

Yes/No (please delete as appropriate)

If no, do they get majority of doses under daily supervision with "take-aways" according to their compliance?

Yes/No (please delete as appropriate)

If no, how are their supplies of medication controlled? (please specify)

How often are urines taken for analysis in induction phase? (tick for yes as appropriate)

- Daily ☐
- 2-3 per week ☐
- Weekly ☐
- > weekly ☐

How often are urines taken for analysis in maintenance phase? (tick for yes as appropriate)

- Daily ☐
- 2-3 per week ☐
- Weekly ☐
- > weekly ☐

(2) Practical Aspects of Lofexidine Usage

1. Do you use/have you used lofexidine in the management of opiate dependence?

   Yes/No (delete as appropriate)

2. If yes to 1. do you use it for (tick for yes as appropriate)
   - a. treatment of withdrawal only? ☐
   - b. other uses? (please specify) ☐

3. Do you use other therapies for the management of opiate withdrawal? (delete as appropriate)
   - a. clonidine **Yes/No**
   - b. methadone **Yes/No**
   - c. naltrexone **Yes/No**
   - d. naloxone **Yes/No**
   - e. dihydrocodeine **Yes/No**

f. other opiate substance (please specify)

g. other drug (please specify)

4. If lofexidine is used for treatment of withdrawal, what dosage regimen is used? (please specify)

5. How does lofexidine compare with other drug regimens in the treatment of withdrawal? (tick for yes as appropriate and assume optimal dosage of lofexidine)

a. Equal to comparator regimen(s) (please specify) ☐

b. More efficacious ☐

c. Less efficacious ☐

d. Less side effects ☐

e. Less withdrawal symptoms ☐

f. Other comment (please specify) ☐

6. Do you notice a linear dose-response for lofexidine?

Yes/No (delete as appropriate)

Any additional comments on this issue

7. Is lofexidine suitable for the following patient groups? (tick for yes as appropriate)

a. Males ☐

b. Females ☐

c. Pregnant females ☐

d. Patients on anti-HIV medication ☐

e. Pregnant females on anti-HIV medication ☐

f. Patients with liver disease ☐

g. Patients currently on methadone maintenance ☐

h. Patients with high opiate requirements ☐

i. Patients with longstanding dependence ☐

j. Patients with active/history of depression ☐

k. Patients with psychosocial problems ☐

l. Patients requiring treatment with psychotropics (please specify drugs) ☐

Any other group (please specify)

8. If lofexidine is not suitable for specific groups in question 7, please state the reasons

9. In your opinion, does lofexidine have an advantage in the management of withdrawal over other treatment modalities in any of the subgroups outlined in question 7?

   Yes/No (delete as appropriate)

   Please give reasons for your answer

(3) Practical/Clinical Issues with Lofexidine Usage

10. What are the common side effects encountered with lofexidine in the treatment of withdrawal?

11. Is hypotension a commonly occurring problem?

    Yes/No (delete as appropriate)

12. Are the side-effects transient/present for duration of treatment

    Yes/No (delete as appropriate)

    Would the occurrence of side-effects result in the discontinuation of use of lofexidine and change to another treatment?

    Yes/No (delete as appropriate)

    If yes, state circumstances

13. Does the use of lofexidine necessitate a change in the way opiate withdrawal is managed at clinic level, with respect to other treatment modalities (in terms of administration/medical supervision/other)

    Yes/No (delete as appropriate)

    Please give reasons for your answer

14. Is the issue of lofexidine-drug interactions (either with co-prescribed drugs/illicit drugs) a problem in clinical practice? (see also next question)

    Yes/No (delete as appropriate)

    If yes, would you describe the problem as **major/moderate/minor**? (delete as appropriate)

    Please give reasons for your answer

15. If Yes to 14, which drugs are most problematic? (please number 1 – 7 with 1 being the most problematic)

a. Benzodiazepines (please record specific drug(s) if difference between the class)

b. SSRIs/SRIs (please record specific drug(s) if difference between the class)

c. Other anti-depressants (please specify)

d. Neuroleptics (please specify)

e. Other opiates (please specify)

f. Alcohol (please specify details of amount if appropriate)

g. Other drugs (please specify)

16. Are there factors which contra-indicate the use of lofexidine in the management of withdrawal in clinical practice (medical/practical/other)

Yes/No (delete as appropriate)

Please outline the factors if present

17. Are there any other particular problems with use of lofexidine in practice (i.e. not seen with the other medications used)?

Yes/No (delete as appropriate)

Please give reasons for your answer

18. How do you rate lofexidine as a treatment for withdrawal in comparison to other treatment modalities?

(assume optimal dosage of lofexidine)

Clonidine:

a. Treatment not used in the clinic ☐
b. Equal to clonidine ☐
c. Better than clonidine ☐
d. Less efficacious than clonidine ☐
e. Less side effects ☐
f. More side effects ☐
g. Less abuse potential ☐
h. More abuse potential ☐
i. Better than clonidine for some subgroups (please specify) ☐

Methadone:

a. Treatment not used in clinic ☐
b. Equal to methadone ☐
c. Better than methadone ☐
d. Less efficacious than methadone ☐
e. Less side effects ☐
f. More side effects ☐
g. Better than methadone for some subgroups (please specify) ☐

Naltrexone:

a. Treatment not used in the clinic ☐
b. Equal to naltrexone ☐
c. Better than naltrexone ☐
d. Less efficacious than naltrexone ☐
e. Less side effects ☐
f. More side effects ☐
g. Less abuse potential ☐
h. More abuse potential ☐
i. Better than naltrexone for some subgroups (please specify) ☐

Buprenorphine:

a. Treatment not used in the clinic ☐
b. Equal to buprenorphine ☐
c. Better than buprenorphine ☐
d. Less efficacious than buprenorphine ☐
e. Less side effects ☐
f. More side effects ☐
g. Less abuse potential ☐
h. More abuse potential ☐
i. Better than buprenorphine for some subgroups (please specify) ☐

Other opiates/other treatment modalities
(please specify)

_____

_____

_____

a. Equal ☐

b. Better ☐

c. less efficacious ☐

d. less side effects ☐

e. more side effects ☐

f. Better than _____ for some subgroups (please specify groups and reasons) ☐

_____

_____

_____

19. Overall, what is your impression of the usefulness of lofexidine in the management of opiate dependence?

_____

_____

_____

(4) Any additional comments you may wish to make may be included here.

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Name of Respondent

_____

Practice Address

_____

End of questionnaire. *Thank you!*

Appendix II

Details on the Working Party Members

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References

Akhurst JS
The use of Lofexidine by Drug Dependency Units in the United Kingdom.
Eur Addict Res 1999; 5: 43-49

Akhurst JS
Lofexidine in opiate withdrawal:
A safety and usage survey.
Pharmacoepidemiology and Drug Safety 2000; 9: 43-47

Amato L, Davoli M
Methadone at tapered doses for the management of opioid withdrawal (Cochrane Review).
The Cochrane Library Issue 4, 2002 (Oxford: Update Software)

Bearn J, Bennet J, Martin T, Gossop M, Strang J
The impact of naloxone/lofexidine combination treatment of the opiate withdrawal syndrome.
Addiction Biology 2001; 6(2): 147-156

Bearn J, Gossop M, Strang J
Randomised double-blind comparison of lofexidine and methadone in the in-patient treatment of opiate withdrawal.
Drug and Alcohol Depend 1996; 43: 87-91

Bearn J, Gossop M, Strang J
Accelerated lofexidine treatment regimen compared with conventional lofexidine and methadone treatment for in-patient opiate detoxification.
Drug and Alcohol Depend 1998; 50: 227-232

Brown AS, Fleming PM
A naturalistic study of home detoxification from opiates using lofexidine.
Journal of Psychopharmacology 1998; 12(1): 93-96

Buntwal N, Bearn J, Gossop M, Strang J
Naltrexone and lofexidine combination treatment compared with conventional lofexidine treatment for in-patient opiate detoxification.
Drug and Alcohol Depend 2000; 59: 183-188

Carnwath T, Hardiman JA
Randomised double-blind comparison of lofexidine and clonidine in the out-patient treatment of opiate withdrawal.
Drug and Alcohol Depend 1998; 50: 251-254

Chalmers I, Altman D
Systematic Reviews.
BMJ Publishing Group, London 1995

Cox S, Alcorn R
Lofexidine and opioid withdrawal.
Lancet 1995; 345: 1385-6

European Monitoring Centre for Drugs & Drug Addiction (EMCDDA)
Annual Report on the state of the drugs problem in the European Union and Norway (2002).
Available online at **www.emcdda.org**

Eveleigh B
The use of lofexidine in an outpatient methadone detoxification programme.
The International Journal of Drug Policy 1995; 6(3): 2-3

Gerra G, Zaimovic A, Giusti F, Di Gennaro C, Zambelli U, Gardini S, Delsignore R
Lofexidine versus clonidine in rapid opiate detoxification.
Journal of Substance Abuse Treat 2001; 21: 11-17

Gold MS, Pottash AC, Sweeney DR, Extein I
Opiate detoxification with lofexidine.
Drug and Alcohol Depend 1981; 8: 307-315

Gowing L, Ali R, White J
Buprenorphine for the management of opioid withdrawal.
The Cochrane Library, Issue 2, 2001 Oxford.

Gowing L, Farrell M, Ali R, White J
α_2-adrenergic agonists for the management of opioid withdrawal (Cochrane Review).
The Cochrane Library, Issue 4, 2002 (Oxford: Update Software) (2002a)

Gowing LR, Farrell M, Ali R, White J
α_2-adrenergic agonists in opioid withdrawal.
Addiction 2002; 97: 49-58 (2002b)

Gowing L, Ali R, White J
Opioid antagonists with minimal sedation for opioid withdrawal (Cochrane Review).
The Cochrane Library, Issue 4, 2002 (Oxford: Update Software) (2002c)

Guthrie SK
Pharmacologic Interventions for the Treatment of Opioid Dependence and Withdrawal.
The Annals of Pharmacother 1990; 24: 721-34

Howells C, Allen S, Gupta J, Stillwell G, Marsden J, Farrell M
Prison based detoxification for opioid dependence: a randomised double blind controlled trial of lofexidine and methadone.
Drug and Alcohol Depend 2002; 67: 169-176

Kahn A, Mumford J.P, Ash Rogers G, Beckford H
Double-blind study of lofexidine and clonidine in the detoxification of opiate addicts in hospital.
Drug and Alcohol Depend 1997; 44: 57-61

Kelly A, Carvalho M, Teljeur C
A 3-source capture recapture study of the prevalence of opiate use in Ireland 2000 to 2001.
In press. Key findings summary tables available on **www.nacd.ie**

Lin SK, Strang J, Su LW, Tsai CJ, Hu WH
Double blind randomised controlled trial of lofexidine versus clonidine in the treatment of heroin withdrawal.
Drug & Alcohol Depend 1997; 48(2): 127-33

Lofexidine - Preclinical and Clinical Documentation.
Company Expert Report.
Britannia Pharmaceuticals Ltd., England

Merrill J, Marshall R
Opioid detoxification using naloxone.
Drug and Alcohol Review 1997; 16: 3-6.

Shearman GT, Lal H, Ursillo RC
Effectiveness of lofexidine in blocking morphine-withdrawal signs in the rat.
Pharmacology Biochemistry and Behaviour 1980; 12(4): 573-575

Sheridan J, Cook C, Strang J
Audit of the in-patient management of opioid withdrawal using lofexidine hydrochloride.
Journal of Substance Use 1999; 4: 29-34

Sinclair H, O'Brien M, Dillon L, Keane M, Pike B
Ireland National Report to EMCDDA (2001).
Drug Misuse Research Division, Health Research Board. Available at **www.emcdda.org**

Smith P, Gerada C, Kemp K
An addict who wants to detoxify.
Practitioner 1998; 242: 735-40

Strang J, Bearn J, Gossop M
Lofexidine for detoxification: Review of recent randomised and open controlled trials.
The American Journal on Addictions 1999; 8(4): 337-348 (1999)

Summary of Product Characteristics (SPC) for Britlofex (UK).
APBI Medicines Compendium, 2003.

Sutton A, Jones D, Abrams K, Sheldon T, Song F
Systematic reviews and meta-analysis: a structured review of the methodological literature.
Journal of Health Services Research & Policy
1999; 4(1): 49-55

Teeling M, Feely J, on behalf of the working party, NMIC/St James's Hospital
Use of buprenorphine in the management of opiate dependence syndrome – Report to the National Advisory Committee on Drugs.
Publishers: Stationery Office, Dublin, 2002. Available at **www.nacd.ie**

Washton AM, Resnick RB, Geyer G
Opiate withdrawal using lofexidine, A clonidine analogue with fewer side effects.
J Clin. Psychiatry 1983; 44: 335-337

White R, Alcorn R, Feinmann C
Two methods of community detoxification from opiates: an open-label comparison of lofexidine and buprenorphine.
Drug and Alcohol Depend 2001; 65: 77-83

Notes

Notes

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