NACD
National Advisory Committee on Drugs

Use of Naloxone in the Management of Opiate Dependence Syndrome

Report to the National Advisory Committee on Drugs

on

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

From the working party

National Medicines Information Centre/St James's Hospital,

Dublin 8

Dublin
Published by the Stationery Office.

To be purchased directly from the
Government Publications Sales Office,
Sun Alliance House, Molesworth Street, Dublin 2,
or by mail order from
Government Publications, Postal Trade Section,
4 - 5 Harcourt Road, Dublin 2,
(Tel: 01-6476834/35/36/37; Fax: 01-4752760)
or through any bookseller.

Prn. 938
ISBN 0 7557 1785 6

€5

Baile Átha Cliath
Arna Fhoilsiú ag Oifig an tSoláthair

Le ceannach díreach ón
Oifig Dhíolta Foilseachán Rialtais,
Teach Sun Alliance, Sráid Theach Laighean, Baile Átha Cliath 2,
nó tríd an bpost ó
Foilseacháin Rialtais an Rannóg Post-Tráchta,
4 - 5 Bóthar Fhaearchair, Baile Átha Cliath 2,
(Teil: 01-6476834/35/36/37; Fax 01-4752760)
nó trí aon díoltóir leabhar.

Designed by First Impression

Table of Contents

Minister of State's Foreword

I am delighted to welcome this new report from the National Advisory Committee on Drugs (NACD) on the potential usefulness of Naloxone as a treatment option for opiate misuse.

The NACD was set up in 2000 to address gaps in our knowledge of drug use in an Irish context. A three-year research work programme was agreed by Government and the results of this work – and other studies that the NACD are carrying out – will significantly increase the amount of available research in this difficult and complex area.

Drug misuse, particularly opiate misuse, remains one of the major social problems facing Irish society today and 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. I hope that through greater understanding of the usefulness of Naloxone, this study 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

The NACD is required to advise Government about a number of aspects of the drugs phenomena in Ireland, notably the consequences of problem drug taking. The ultimate consequence with some drugs, for example heroin, is death, and problem drug users have mortality rates 20-30 times greater than normal. Surprisingly international experience indicates that most deaths occur, not in naïve experimenting drug users who cannot judge their dose of drug, but in experienced drug users in their late 20s and early 30s.

Methods to prevent such tragic premature deaths are urgently required. These measures can include advice to avoid using combinations of opiates (heroin or methadone) with tranquillisers ("benzos") and alcohol which are particularly lethal. Drug users who have become abstinent through a 'detox' also need to be counselled that if they slip back into drug use, their ability to tolerate high doses of a drug will have disappeared and that using such doses could now result in an overdose.

One medical response to opiate overdoses is the drug Naloxone which has been used for many years in casualty and A&E Departments to reverse the effects of opiate overdoses. As this review of the drug, ably put together by Dr. Mary Teeling and her team at St. James's Hospital, points out, speedier administration of Naloxone might have a role to play in reducing the death toll from drug overdoses. The NACD hopes that this report will help stimulate and inform discussions among those with responsibility for planning and delivery of emergency services about the proper role for Naloxone in such services. The report also describes the use of the drug in rapid opiate withdrawal and in combination with Buprenorphine as a maintenance treatment which was the subject of an NACD report in 2002.

All in all Naloxone is a drug which has much to offer within our overall response to problem drug taking and the NACD wishes, through this technical report to highlight its potential.

Dr. Desmond Corrigan
Chairperson
NACD

Acknowledgements

The members of the working party would like to thank the following for their assistance and expert advice during the review process.

Dr. Íde Delargy (Dublin)

Ms. Louise Farragher (Dublin)

Dr. Eamon Keenan (Dublin)

Mr. Laurence Kenna (Dublin)

Mr. Simon Lenton (Australia)

Ms. Mairéad Lyons (Dublin)

Dr. Paul Quartey (Schering Plough)

Mr. Tom McGuinn (Dublin)

Dr. Michael Ryan (Dublin)

Mrs. Bernie Maguire (Secretarial Support)

Mrs. Angela O'Flaherty (Secretarial Support)

Glossary

Clon	Clonidine
db	double blind
EMCDDA	European Monitoring Centre for Drugs & Drug Addiction
EU	European Union
FDA	Food & Drugs Administration
IV	Intravenous
IM	Intramuscular
Lofex	Lofexidine
Meth	Methadone
Nal	Naloxone
Nalt	Naltrexone
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 naloxone as a treatment option for opiate dependency. All available data were retrieved by means of a comprehensive search of the published literature. Contact was made with national and international experts to evaluate the practical issues associated with its use in the clinical setting.

Naloxone has been used in several treatment settings in the management of opiate dependency. It has been used for many years as an emergency room treatment for the management of opiate overdose. Evaluation of its use in this setting suggests that it is associated with a low rate of serious adverse effects but the data involved small numbers of patients. Its administration by trained ambulance staff in the pre-hospital setting resulted in less hospital admissions but follow-up data of the patients are lacking in many cases.

Although the availability of take-home naloxone for use by friends and relatives of an opiate user has been recommended by several workers, there are no controlled trials evaluating such usage. Furthermore records of use from pilot studies are insufficient to undertake a benefit/risk analysis of the use of naloxone in this setting. There are many logistical issues that would need to be dealt with before such a programme could be implemented in practice.

Naloxone has been used, with or without naltrexone, to effect rapid opiate withdrawal. Results of studies have shown that the withdrawal occurs earlier and is more severe with use of naloxone compared with α_2-adrenergic agents such as clonidine. However, it resolves more quickly leading to a quicker transition to maintenance antagonistic treatment. The long-term benefits of rapid withdrawal have not been compared with those from standard withdrawal regimens. Data are insufficient to identify the most appropriate dosage regimen.

A combination preparation of buprenorphine and naloxone (4:1 ratio) for sublingual use has recently been developed. It has been shown to be effective as a maintenance treatment for opiate dependence, while the presence of naloxone reduces the risk of misuse of the buprenorphine component. Data are insufficient to identify the optimal treatment regimen. The combination has been shown to be equipotent to buprenorphine alone. Subutex® is authorised for use in opiate dependence in Ireland, but there is no combination of buprenorphine and naloxone currently authorised.

This review has found data on the safety and efficacy of naloxone in its many potential uses in the management of opiate dependency are limited. However preliminary results suggest that it may be of use in these areas. Further information on the feasibility of use as an emergency treatment in the community setting would be needed before any such programme could be implemented.

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. Opiate-related deaths are a significant cause of premature death, especially in young adult males (Ward and Barry, 2001).

In April 2001, the Irish Government approved the National Drugs Strategy, 2001-2008 entitled "Building on Experience". This strategy has identified 7 overall aims including the accessibility of treatment for people with drug misuse problems, reduction of harm caused by such drug use to individuals, families and communities and reduction of risk behaviour associated with drug misuse (Sinclair et al, 2001).

Methadone maintenance is still the major form of substitution treatment in Ireland and this is provided to persons who fulfil specific criteria of admission. Although methadone maintenance treatment is associated with reduced mortality among opiate users (Caplehorn et al, 1994), methadone overdose is also dangerous – a recent study of opioid-related deaths in Dublin during 1999 (Ward and Barry, 2001) showed that 45/84 (53.6%) deaths were related to methadone. Diverted methadone accounted for the majority of deaths involving methadone.

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. A review of the usefulness of buprenorphine was undertaken previously (Teeling et al, 2002), on behalf of the NACD and this showed that buprenorphine could be considered a useful treatment option in the management of opiate dependence with an acceptable safety profile.

Following on from this review the NACD has commissioned a study evaluating the use of naloxone as another pharmacotherapeutic option. Naloxone is an opiate antagonist, which has been used as an emergency treatment for the management of opiate overdose in hospitals for several decades. The expansion of the use of naloxone to include its administration in the community has been suggested in recent years by many drug treatment workers in an effort to reduce or prevent fatal opiate-related overdoses. This review has been commissioned to evaluate the potential usefulness of naloxone 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 naloxone as an intervention in the management of Opiate Dependence Syndrome.

The objectives of the review were to:

1. Retrieve and systematically review all published literature relating to the use of naloxone in the management of opiate dependence syndrome, in particular its use as an emergency treatment for overdose in the emergency room and community setting.
2. Evaluate the practicalities of use of naloxone in these potential treatment settings.

Chapter 3

Research Methodology of the Review

Primary and review articles, abstracts and other published information on naloxone 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, naloxone, opioid antagonist, naltrexone addiction, therapeutic, withdrawal, detoxification, emergency treatment, overdose, 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.

The data on usage of naloxone in different areas of management of opiate dependence syndrome were reviewed, in particular, its use as an emergency treatment for opiate overdose, to determine its usefulness in each clinical situation. It was not possible to undertake formal meta analysis in any of the areas of use, due to lack of suitable data. A meta analysis is a statistical technique for combining the results of independent studies, to present an objective and quantitative measure of 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).

Finally, in order to identify the practicalities of use of naloxone in the various treatment settings, information on use in clinical practice was identified from the published literature. Where possible, healthcare professionals, experienced in its use were identified in Ireland and abroad and contacted for further specific data on the advantages and disadvantages of such usage in clinical practice. Contact was made with the Department of Health and Children to identify possible medico-legal issues involved in the use of naloxone as an emergency treatment.

Chapter 4

Pharmacology

Naloxone

4.1 Introduction

Opioid antagonists have been involved in the management of opiate dependent syndromes for many years. Opioid antagonists act by competitively binding at opiate receptors (Chamberlain and Klein, 1994) including mu, kappa and stereo-specific binding sites in the locus coeruleus of the brain. They are also thought to reverse opiate-induced respiratory depression by resensitising the respiratory centre to carbon dioxide (Rawal et al, 1986).

They have been used to reverse opioid overdose and more recently, they have been used in combination with other pharmacological agents, as part of managed withdrawal, abstinence and maintenance programmes in opiate dependence.

4.2 Pharmacology

Naloxone is an N-alkyl derivative of oxymorphine. Unlike other agents in the class, it has little or no agonist activity and therefore is a safe and effective treatment for opiate-induced respiratory depression (Chamberlain and Klein, 1994). It binds most strongly to mu receptors but displays antagonist activity at the other opioid receptors as well. It is highly lipophilic so that distribution to the brain is rapid.

Under ordinary circumstances, naloxone produces few effects unless opioids with agonistic actions have been administered previously – subcutaneous naloxone at doses of up to 12mg produced no discernible subjective effects in human volunteers and 24mg only caused slight drowsiness. (Gutstein and Akil, 2001). However, small doses (0.4 – 0.8mg) given intramuscularly (IM) or intravenously (IV) prevent or promptly reverse the effects of mu receptor agonists. In patients with respiratory depression, the respiratory rate increases within 1 or 2 minutes. Duration of the antagonistic effects depends on the dose and route of administration (SPC, 2002) with IM injection producing a more prolonged effect than IV doses. In general, clinical efficacy for opioid antagonism lasts for 45-70 minutes, although longer effects have been reported (Chamberlain and Klein, 1994). It has a half life of approximately 60 minutes in adults.

Antagonism of opioid effects by naloxone may be accompanied by "overshoot" phenomena. For example, respiratory rate, depressed by opioids, becomes higher than the rate prior to depression after naloxone administration. Rebound release of catecholamines may cause hypertension, tachycardia and arrhythmias. Pulmonary oedema has been reported with use of naloxone (Gutstein and Akil, 2001). These reactions have been reported rarely in clinical usage (see chapter 5).

4.3 Pharmacokinetics

Following oral administration it has poor bioavailability (2%) due to extensive first pass metabolism. Therefore, it is usually administered via the parenteral route although endotracheal and sublingual routes have also been used successfully (Trujillo et al, 1998). Less than 1% of the drug is excreted via the renal mechanism as unchanged drug. It is extensively metabolised i.e. over 90% with a short elimination half-life in the region of 60 minutes. The main metabolising enzyme is glucuronyl transferase with glucuronidation accounting for 60 – 70% of total metabolism.

Potential pharmacokinetic interactions may occur when co-administered with medications that are extensively metabolised by the same enzyme system. These medications are outlined above (see section 4.3). Case reports also suggest an interaction with the ACE inhibitor captopril, reducing the anti-hypertensive effect via an unknown mechanism.

4.4 Summary

Naloxone is an opioid antagonist, with little or no agonist activity. It is not active orally because of extensive first pass metabolism. Potential pharmacokinetic interactions may occur when co-administered with medications that are extensively metabolised via glucuronidation. Overall, the propensity for clinically relevant pharmacokinetic drug interactions is thought to be relatively low.

Chapter 5

Review of Clinical Usage with Naloxone

5.1 Introduction

The use of the opioid antagonist naloxone in the emergency management of overdose of heroin or other opioid agonists has been reported since the early 1960s (Osterwalder, 1996). It has been estimated that naloxone may be the most frequently prescribed specific antidote for human poisonings (Chamberlain and Klein, 1994). More recently its use for rapid detoxification has been reported and it has also been combined with buprenorphine, a partial opioid agonist, for use as maintenance treatment, as an alternative to methadone. This review focuses primarily on the use of naloxone in the emergency management of opiate overdose and refers briefly to its other uses.

5.2 The Management of Opiate Overdose

5.2.1 Emergency Room Usage

One of the most serious consequences of opiate use, in particular heroin use, is the risk of overdose (Dietze et al, 2000). Although variably defined, heroin overdose comprises a triad of depressed respiration with or without cyanosis, altered consciousness (up to and including death) and pinpoint pupils (Seidler et al, 1996).

Although naloxone has been used for the management of suspected opiate overdose for 4 decades very few clinical studies have been undertaken to evaluate its safety and efficacy in this indication, possibly for ethical and logistical reasons (Osterwalder, 1997). A prospective case series of 538 overdose episodes (involving 485 subjects who had overdosed with heroin alone or in combination with other substances) evaluated the complications attributable to naloxone administration in the emergency room setting (Osterwalder, 1996). As this was an observational study, the dosage regimens and routes of administration used varied (range 0.1 – 2.8mg administered either IV or IM or both). A total of 6/453 (1.3%) patients who received naloxone suffered a serious adverse event within 10 minutes of administration (doses of 0.2 – 0.8mg). These included pulmonary oedema (n = 1) generalised convulsions (n = 3) violent behaviour (n = 1) and asystole (n = 1). Although a causal association was not established conclusively, the author cited other cases of pulmonary oedema and cardiovascular adverse reactions from the literature and maintained that there was strong evidence to support a causal link with naloxone. He concluded that such a high incidence of serious adverse events was unacceptable and he recommended that naloxone be used cautiously in the emergency room. This study did not report on efficacy of treatment but it is interesting to note that 85/538 (15.8%) cases responded to assisted breathing using a bag-valve-mask device, without the need for naloxone.

The cases in Osterwalder's paper were confounded by the presence of co-existing disease – hyperthyroidism (n = 1), epilepsy (n = 1) – and/or use of other drugs such as benzodiazepines, alcohol, cocaine, all of which could have contributed to the reported adverse events (Hsu et al, 1997). However, the adverse event profile reported is in keeping with previous reports (see chapter 4).

A double blind randomised study (Kaplan et al, 1999) compared naloxone (2mg IV) with nalmefene a longer acting opiate antagonist (1mg or 2mg IV). The study involved 171 patients with suspected opiate overdose who were evaluated for 4 hours post administration of the test drug. Patients were divided equally among the 3 treatment groups. Results showed no differences between the groups, in terms of efficacy – all patients showed a rise in respiratory rate by 5 minutes post injection and improved scores on the neurobehavioral assessment scale (NAS) – and no serious adverse reactions were reported. The study had many methodological flaws which reduced its power to detect meaningful differences, however, the results supported the efficacy of naloxone as a treatment for suspected opiate overdose in the emergency room setting.

Summary

Naloxone has been used as an emergency room treatment for suspected opiate overdose for many years. However, there are few published controlled trials in this setting. Cases of convulsions, cardiovascular problems and

pulmonary oedema have been reported rarely with use. These may be due to occurrence of overshoot phenomena due to the antagonism of opioid effects by naloxone (see Chapter 4) or due to pre-existing disease and/or concomitant use of other drugs of abuse by the patient.

5.2.2 Use in the Community – Ambulance Staff

The rates of fatal opiate overdose in much of the developed world, including USA, Europe and Australia, have risen in recent years (Darke and Ross, 2000). It has been shown that death, due to heroin overdose, occurs up to 3 hours after the injection in up to 50% cases and the majority of overdoses, including fatal ones, take place in the company of others (Lenton and Hargreaves, 2000a). Therefore there is much interest in finding ways to reduce or prevent fatal overdoses in the community.

Data relating to use of naloxone prior to hospital admission consists of a series of observational studies as no controlled trials have been carried out in this area. Yealy et al (1990) presented a case series of 853 patients who had been treated by paramedics with naloxone in the pre-hospital situation for "blurred consciousness", thought to be due to opiate overdose. Five incidents (0.6%) occurred, including generalised convulsions (n = 1), vomiting (n = 2) and one serious case each of hypotonia and hypertonia. The authors concluded that naloxone was safe for use in the management of opiate overdose. However, since only 60 patients were definitively diagnosed as opiate overdose the significance of these results in terms of proving safety of use of naloxone in this indication has been called into question (Osterwalder, 1996).

A survey from Vienna (Seidler et al, 1996) reviewed the records of 77 subjects who were treated for 83 emergencies (suspected opiate overdose) in one of 4 hospitals over a 4-month period. Naloxone was administered by ambulance staff in 53/75 cases transported to hospital – 16 received 0.4mg ; 21 received 0.8mg and 16 received 3 or more ampoules of 0.4mg. Four of these patients became agitated after naloxone (thought to be due to withdrawal reaction). No further naloxone was given in hospital to 47 (63%) of subjects transported via ambulance and only 9 (12%) received naloxone for the first time in the emergency room.

A total of 47 patients discharged themselves after an average stay of 5.7 hours, of whom 20 left within the first 3 hours after admission. None of the subjects needed readmission, further pre-hospital treatment or died due to overdose within 48 hours after leaving hospital. The authors estimate that without pre-hospital administration of naloxone, the clinical condition of at least 40 of these subjects would have required intubation and admission to intensive care.

Sporer et al (1996) reviewed the use of naloxone by paramedics in a pre-hospital setting during 1993 in an area of Los Angeles known for a high prevalence of intravenous drug use. Administration occurred as part of the Advanced Life Support Emergency System and naloxone was administered to patients according to strict criteria. At least 3 of the following were required – respiratory rate < 6/minute, pinpoint pupils, evidence of intravenous drug use, Glasgow Coma Scale < 12, or cyanosis.

A total of 726 patients were identified with a diagnosis of suspected overdose, most of whom (609 or 85%) had an initial pulse and blood pressure. Most (94%) of this group responded to naloxone – 487 (80%) received naloxone IM and 122 (20%) received the drug IV with or without bag-valve-mask ventilation. Of the remainder, 101 (14%) had obvious signs of death and 16 (2.2%) were in cardiopulmonary arrest but did not survive. Of 443 patients transported to hospital, 12 were admitted – 4 with non-cardiogenic pulmonary oedema, 2 with pneumonia, 2 with other infections, 2 with persistent respiratory depression and 2 with persistent alteration in mental status. The authors noted that hypoxia was evident upon arrival to the emergency room in those with pulmonary oedema. The study concluded that use of naloxone in the pre hospital setting, together with assisted ventilation via the bag-valve-mask system was effective in this patient population and that serious adverse events were evident from early on after treatment.

Finally, a prospective observational study was undertaken by the ambulance service in British Columbia, Vancouver (Wanger et al, 1998) to evaluate whether naloxone (0.4mg) administered IV would have a more rapid therapeutic onset compared with subcutaneous administration of naloxone (0.8mg). Results showed no difference in interval from crew arrival to improvement of

respiratory rate to ≥ 10 breaths per minute (9.3+/-4.2min versus 9.6+/-4.58min respectively). Mean duration of bag-valve-mask ventilation was similar for both groups (approximately 8 + 9 minutes). The authors concluded that the slower rate of absorption from the subcutaneous route was offset by the delay in establishing IV access, thus resulting in equal efficacy for both routes.

Summary

Reports are available on the use of naloxone by ambulance personnel from various centres in Europe and North America for the management of suspected opiate overdose. It is important to note that the staff involved appeared to be trained in emergency procedures such as diagnosis and initial management of suspected opiate overdose (including administration of therapeutic agents using IV, IM and subcutaneous routes). Doses were titrated by these personnel to achieve adequate response. The average dose was <1mg (although doses up to 2mg were administered in some cases). Results showed that such usage was effective in terms of reversing the effects of opiate overdose and reducing the need for hospital admission. Adverse events occurred rarely and were usually evident from initial arrival in the emergency room.

The reports do not mention the occurrence of delayed onset problems as a result of patients opting not to travel to hospital post administration of naloxone although several patients in each study did not go to hospital for observation. However one report (Seidler et al, 1996) did mention that the hospital had a contingency plan in place in case a patient with a suspected overdose of methadone or oral ingestion of opiates chose not to stay for an optimal period of observation.

Available evidence suggests that pre-hospital administration of naloxone by paramedics/ ambulance personnel may be beneficial in patients with suspected opiate overdoses. Administration to patients with loss of consciousness not due to opiate overdose has shown no benefit. Therefore relevant personnel will require adequate paramedical training, both in diagnosis of suspected opiate overdose and in parenteral administration techniques.

The Prehospital Emergency Care Council was established in Ireland in 1999 and is currently working on protocols for training of ambulance staff as "advanced emergency technicians". Parenteral drugs are not administered by ambulance staff at present, although most ambulances carry emergency drugs. Naloxone is not on the advisory list but it may be carried in some ambulances (Kenna, personal communication).

5.2.3 Use in the Community – Peer Administration

Drug treatment workers in the UK and Australia have promoted the idea of take-home naloxone for heroin users for use by their family or friends (so called peer administration) in order to prevent or reduce fatal opiate overdoses. (Strang et al, 1999b; Lenton and Hargreaves, 2000a). No controlled trials have been carried out to evaluate the safety and efficacy of use of naloxone in this indication but reports of initial usage are available from the USA, UK, Germany and Jersey.

Dettmer et al, (2001) reported on 2 pilot projects. From January 1999, opiate users in Berlin were given naloxone to take home (2x 0.4mg ampoules plus needles and syringes) and were offered training in resuscitation . After 16 months, 124 users had received naloxone and resuscitation training. Of 40 who reported back, 22 had used naloxone for 29 overdoses. Dose and route of administration varied although the commonest dose administered was one ampoule. In 10 instances, naloxone provoked sudden withdrawal but no other side effects were reported. An ambulance was called for 9 cases but all 29 people were reported to have recovered. The report states that administration was judged appropriate in 26 (90%) cases, but it is not clear how this conclusion was reached. The same report referred to a similar project in Jersey, which began in October 1998, where users were provided with a prefilled injection pack of 0.8mg naloxone, along with instructions on its use and basic resuscitation techniques. Five instances of naloxone use (out of 101 distributions) were reported with no adverse events other than withdrawal symptoms being recorded.

This report has been severely criticised as "seriously flawed research" (Mountain, 2001) because of its poor response rate (<35%) leading to probable selection bias and because of the lack of methodological information supplied to support the validity of the results. Moreover, the coroner's figures for drug-related deaths in Jersey supplied by Blackwood (2001) showed no change

in the death rate during the period that the pilot study was taking place.

The experience of use of take-home naloxone in Chicago was outlined in a recently published letter (Bigg, 2002). To date over 550 active opiate injectors have been educated in the management of overdoses including administration of naloxone IM. Reports of 52 uses of naloxone have been received, all of which were said to have been "successful". (No further details given) This report noted, however, that the experience had been unpleasant for both the overdose individuals and the administrator resulting in a reluctance to repeat the incident. It is assumed that this was due to the development of withdrawal in the recipient but the report is sparse on details of the individuals' condition pre-naloxone administration, use of concomitant drugs, type of resuscitation used or whether an ambulance had been called. Strang (2001) reported that take-home naloxone has been made available in some of the addiction treatment services in South London since 2001, but there are no reports of the outcome of this availability to date.

In addition to these case reports it is understood that naloxone has been made available to heroin users as part of a training course on overdose management and prevention by the San Francisco Needle Exchange Unit (Darke and Hall, 1997). This is reported to be similar to the Chicago system but no results have been published. Italy made naloxone available over the counter in pharmacies for drug users in the 1990s but there are no published reports of how this has affected opiate overdose rates.

Summary

There is no information from controlled trials on the safety and efficacy of peer administration of naloxone in the prevention of opiate overdose. Anecdotal reports of use in various centres are available (involving <100 usages) but there is insufficient information from these to evaluate whether such usage has prevented fatalities from opioid overdose. It is noted that naloxone distribution to opiate users has only taken place in conjunction with first aid training in resuscitation, although the nature of the training given is not clear in all cases.

Opiate overdose is a major cause of mortality in young males – the average annual mortality rate among regular heroin injectors is 2%, a rate 6 – 20 times that for non-drug-using age peers, half of which is attributable to overdose (Sporer, 1999). Therefore any treatment or intervention, which could reduce these figures would have considerable benefits to society. Since data from controlled trials are not available to determine whether naloxone is safe and effective when administered by friends or relatives in the community, potential benefits and problems with such usage in clinical practice will now be considered.

5.2.4 Potential Benefits of Take-Home Naloxone

Opiate overdose is a common cause of premature death in heroin users (Strang et al, 1996). Naloxone has been shown to be an effective antidote and when used appropriately in conjunction with basic resuscitation intervention could prevent or reduce fatalities from overdose.

One of the main reasons put forward for the provision of take-home naloxone for peer administration is the fact that most overdoses occur in the presence of others in the community, thereby allowing for the possibility of peer administration of naloxone (McGregor et al, 1998). Moreover despite the fact that death, due to an opiate overdose may not occur for 1-3 hours post intake of the opiate, repeated studies have reported a reluctance on the part of witnesses to call an ambulance (McGregor et al, 1998; Darke et al, 1996a; Zador et al, 1996). Therefore, peer administration of naloxone in the early stages of overdose could reverse the effects of the opiate and reduce mortality.

Another potential benefit of take-home naloxone is that it would be provided in the context of a first aid training programme in resuscitation. This would make opiate users more aware of the risks of overdose and would enable them to give assistance if they witnessed an overdose. The training programme could include education regarding overdose risks, such as concomitant use of alcohol, polydrug use or the risks of solitary injecting (Darke et al, 1996b). Studies have consistently shown that a longer history of heroin use, greater heroin dependence and higher levels of alcohol consumption are all risk factors for overdose (Hall, 1999). All of these areas could be specifically covered in a training

programme. In addition, discharge from prison may be a risk factor for overdose. A review of HIV positive injecting drug users who had spent time in prison (n = 238) in Edinburgh showed an increased risk of overdose after release (Seaman et al, 1998). The risk of death from overdose for the group during the first 2 weeks after release from prison was 8 times higher than during the next 10 weeks after release, probably due to a decrease in tolerance to drugs as a result of less frequent/lower drug injecting in prison.

Retention in methadone maintenance programmes has been shown to reduce risk of overdose (Caplehorn et al, 1994) and therefore it might be argued that if naloxone is only administered as part of a training programme, then those most at risk might not be reached as they would not be in regular contact with a treatment centre. The San Francisco Needle Exchange has organised such training courses for injecting drug users in its area since mid 1999. This programme has used "underground" sources to reach users (Lenton and Hargreaves, 2000b). A similar system has been in place in Chicago for some time and it is reported that this programme has encouraged hard-to-reach users into making contact with the service (Lenton and Hargreaves 2000b). Unfortunately no published reports are available from the San Francisco project and to date only outline information on the Chicago project is available (Bigg, 2000; section 5.2.3 above).

Naloxone has no abuse potential and as a result should have no black market value. Therefore, its distribution to users for the purpose of peer administration should not worsen the illicit drugs trade. Some workers (Ashworth and Kidd, 2001) have suggested that opioid antagonists could be used as weapons against other drug users but there have been no formal reports of this happening.

5.2.5 Potential Problems with Take-Home Naloxone

Serious concerns have been raised by some workers (Osterwalder, 1996; section 5.2.1 above) about the safety of use of naloxone in this patient population in general. Moreover, there have been anecdotal reports (Gaddis and Watson, 1992) of violent behaviour after naloxone administration, requiring IV sedation. Naloxone has been used as an emergency treatment in hospital settings for many years, serious adverse events are predictable and have been reported rarely. However, the potential for serious adverse reactions would need to be included in a training programme.

There is concern that the availability of naloxone in the community might interfere with other harm reduction strategies, in particular the need to call an ambulance (Lenton and Hargreaves, 2000a). This could increase the risk of fatal overdose, especially if methadone or high doses of opiates have been taken as naloxone has a short half life (60-90 minutes). Also, in most cases of fatal overdose other drugs such as benzodiazepines, other CNS active drugs and alcohol will be found. Zador et al, (1996) reported that 2 or more drugs were detected in 71% of 152 fatal heroin overdoses and alcohol was detected in 45%. The short-acting nature of naloxone has recently been highlighted to prescribers by the UK Committee on the Safety of Medicines (CSM, 1997). The Committee issued a recommendation that naloxone IV infusion should be used in situations where a longer-acting opioid is known or suspected to be the cause of the symptoms. However, results from surveys undertaken in Australia (where naloxone is not currently available for peer administration) have shown that witnesses are slow to call an ambulance – in only 17% of overdose cases did the witness initially call an ambulance (Darke et al, 1996a). These findings have been repeated in other Australian studies (Zador et al, 1996; Mc Gregor et al, 1998). Most cited fear of police involvement as the impediment. Therefore the availability of naloxone may not result in less calls for ambulance help as it would only be made available in conjunction with a basic first aid training programme which would include the importance of calling the ambulance service.

Most recently, Strang et al, (2000) interviewed 115 patients attending a methadone clinic in South London about overdose experiences. Almost all had witnessed overdoses (on an average of 6 occasions each). Most reported taking some action and an ambulance had been called in 44% of cases. This group expressed a willingness to learn more about resuscitation techniques, including use of naloxone and stated that fear of police surveillance would not stop them from helping someone who had overdosed (including calling an ambulance). The differences in attitudes between

UK and Australian users may be due to different police policies in the different jurisdictions. However, the impact of the availability of naloxone on other harm reduction strategies can only be definitively answered by way of a controlled trial (Lenton and Hargreaves, 2000a).

Another concern which has been raised is that administration of naloxone to heroin users would encourage risky heroin and other drug use. This is thought unlikely to happen as heroin is still expensive in many jurisdictions and such usage would be regarded as wasteful (Darke and Hall, 1997). Furthermore naloxone causes acute withdrawal symptoms in many recipients which make the experience unpleasant (Bigg, 2002). Similar concerns were raised about the provision of clean needles and syringes to users in the past but these fears have not been borne out by the evidence (Lenton and Hargreaves, 2000b). Since naloxone would be provided in conjunction with first aid training, it is likely that this information would increase the recipients' awareness of the dangers of overdose rather than encourage use of naloxone in a risky manner (Darke and Hall, 1997). However, qualitative research carried out by Strang et al, (1999) showed that 19/142 (13%) injecting drug users considered the distribution of naloxone to be a "bad idea" and 9/142 (6%) felt that it might increase their heroin use. Once again, this question can only be definitively answered by a controlled trial.

Another potential obstacle to the provision of naloxone may be its cost and the short shelf life for some presentations. In order for the scheme to be effective all users attending the clinics would need to be supplied with naloxone. Results from the pilot projects (outlined above) to date have reported minimal usage therefore, it is presumed that most of the naloxone will not be used before its expiry date. This also raises logistical problems in that post-expired naloxone will need to be replaced. Some workers have suggested that users might be prepared to pay for a supply of naloxone (Darke and Hall, 1997). This aspect of provision of take-home naloxone would need to be dealt with before any scheme could take place.

A major obstacle to supply of take-home naloxone in many jurisdictions is its legal status. Naloxone is a prescription only medicine and therefore should only be prescribed by a physician for a specific patient. If an adverse event or fatality were to occur as a result of peer administration, this could result in legal action against the participants, including prescriber, the person and/or institution which dispensed the naloxone or the person who administered the dose (Lenton and Hargreaves, 2000b). A review of the legal aspects of providing naloxone to heroin users in the USA was recently undertaken (Burris et al, 2001). This concluded that since naloxone is the drug of choice for heroin overdose the physician's decision to prescribe would be seen as reasonable and not negligent, assuming that the patient was at risk of a fatal overdose and was properly instructed in the administration and risk of use of naloxone.

In Ireland, naloxone is a Schedule IA drug i.e. requiring prescription for dispensing. Distribution of naloxone to opiate users for peer administration may be covered by the "carer principle" i.e. where a lay person is taking care of a patient, he/she may administer a medicine, given to the patient, on the patient's behalf (McGuinn, personal communication). However, a formal legal opinion would be required to clarify the legal responsibilities of all participants involved in the implementation of take-home naloxone (See section 5.2.7).

A recent review of the strategies for preventing heroin overdose (Sporer, 2003) published after the data lock point, has discussed peer administration of naloxone and has reiterated many of the issues already highlighted in this section. This review recommended that any programme for take-home naloxone should involve education on a) the identification and management of overdose, including rescue breathing b) the importance of contacting emergency medical services and the need for hospital evaluation after an overdose in order to prevent/treat complications of both the drug(s) of overdose and also naloxone and c) the administration of naloxone and the need to use a sterile needle, if the naloxone is not in a prefilled syringe. Because of the short half-life of naloxone, it recommended that enough naloxone for at least 2 doses should be provided. It stated that evaluation of all potential problem areas should be incorporated into any programme established in this area.

5.2.6 Future Initiatives in Take-Home Naloxone

Although many experts from Australia and the UK have been campaigning for a controlled trial to evaluate the benefit/risk of take-home naloxone, no formal study has been undertaken to date. Moreover, review of clinical trials registers (**www.controlled-trials.com**; **www.clinicaltrials.gov**) has not identified ongoing studies in this area.

It is noted in a personal communication from Simon Lenton, National Drug Research Institute, Curtin University, Perth, Australia, that his research group has received approval in principle from the relevant state agency to undertake a multi-centre controlled trial (in several Australian jurisdictions). The aim of such a trial would be to identify whether the addition of naloxone to the best available alternative (comprehensive first aid training) would produce better or worse outcomes than the first aid training alone. It is unlikely that the trial will commence before mid 2003 as there are still many logistical problems to be addressed. Nevertheless, the undertaking of a properly designed controlled trial would be extremely useful in evaluating the benefit/risk of the availability of naloxone in the community setting for peer administration.

The 2002 Annual Report from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) noted that between 7000 and 8000 deaths, due to accidental or intentional overdose, were recorded during 2000 in the EU and Norway. Belgium, Germany, Finland, Norway and the UK are reported to have instituted programmes for the prevention of overdoses. These include training of drug users to protect against overdosing and to better manage overdoses they witness. In addition, programmes are said to include training in basic resuscitation techniques, use of naloxone and development of specific prevention information materials (EMCDDA, 2002). Although no further details on these initiatives are available, it is hoped that information on their outcome will be available in the near future.

Therefore, despite problems outlined above (see section 5.2.5) it appears that take-home naloxone is being supplied to opiate users in some countries. Additionally, it seems likely that a controlled trial will be undertaken in Australia within the next year. These initiatives should help define what role, if any, naloxone use has in a community setting for peer administration.

5.2.7 The Practicality of Take-Home Naloxone in the Irish Setting

Official Irish statistics of drug-related deaths from the General Mortality Register (GMR) are compiled routinely by the Central Statistics Office. Data from the GMR show that drug-related deaths increased from 43 in 1995 to 81 in 1997 (Sinclair et al, 2001). In 1998 an amendment was made to the information recorded in the case of a sudden death and the figure rose to 97. Provisional figures for 1999 and 2000 showed a levelling off at 85 and 89 respectively. The vast majority of deaths each year were in Dublin and it is known that intravenous heroin use in Ireland occurs primarily in the greater Dublin Area (Ward and Barry, 2001).

A retrospective review of coroners' files for Dublin City and County identified 84 Opiate-related deaths in the region during 1999 (Ward and Barry, 2001). Toxicological analysis had been performed on 82 victims of which 73 (87%) had identified use of 2 or more drugs. A total of 45 (53.6%) of the deaths were associated with methadone use. It is interesting to note that since methadone can only be dispensed to people on the Central Methadone Treatment List (since Oct. 1998), this finding implies diversion of methadone as not all of the cases who had taken methadone were on this treatment list.

The findings of this study are important for two reasons. Firstly, they suggest that the overall opiate-related death rate in Ireland is greater than the GMR figures would suggest. Since these deaths occurred in predominantly young males (mean age 30.3 years) this represents a major cause of premature death, most of which should be preventable. Secondly, they show that if a strategy is to be introduced to reduce opiate-related death from overdose, the possibility of polydrug use and use of methadone, a long acting opiate must be borne in mind. The findings underline the importance of ensuring that naloxone distribution should be only one aspect of a training programme, comprising 1) education on the risks of polydrug use, concomitant alcohol and solitary injection. 2) the need to call an ambulance and 3) basic resuscitation techniques.

If a decision were taken to establish a take-home naloxone programme, despite the availability of supporting data from clinical trials, several important areas would need to be clarified. Firstly, the legal basis and potential liabilities of the parties concerned must be satisfactorily addressed (see section 5.2.5) before a programme can be initiated.

Secondly, it must be decided where the programme will be based – should it be made available in all drug treatment centres/ GP surgeries involved in managed opiate dependence, or should it be run through other outlets. The Naloxone programmes in Chicago and San Francisco (see section 5.2.3 above) are run through needle exchange units and therefore aim to target those currently injecting opiates. There is a limited number of needle exchange units in Ireland at present, therefore, it is unlikely that they would have contact with all of the potential clients of such a scheme. The location of a programme would be important in determining whether or not it would be successful, therefore careful planning would need to be undertaken in this regard.

The capacity of drug treatment centres to implement take-home naloxone as part of a comprehensive training programme would also need to be evaluated. A recent survey of drug treatment centres in the UK (Winstock et al, 2000) reported that although 291/345 (84%) agencies had staff trained in resuscitation, only 20% had access to either oxygen or naloxone. Yet 21% of the agencies had experienced an overdose on-site at some time. The authors recommended that all agencies should provide basic resuscitation facilities and client training in the management of overdose.

Comprehensive information on the availability of naloxone or the training level of the drug workers in Irish treatment centres is not readily available. Most centres that dispense methadone have a doctor and nurse on site or on call (as at weekends) but the level of resuscitation facilities and the availability of naloxone are unknown. Most GP surgeries would have basic resuscitation equipment but would not hold naloxone supplies (Delargy, personal communication). If a training programme on resuscitation and take-home naloxone were to be made available at all treatment centres, the staff would need to be adequately trained to provide such training. This would have time and resource implications for these clinics.

The establishment of such a programme would also require ongoing evaluation, both in terms of outcome of the programme (usefulness of naloxone etc) and dispensing and monitoring of supplies to ensure that they are in-date. Once more, this would require input from the staff with resulting resource implications.

Finally, the feasibility of enrolling current IV users in a training programme must also be assessed. Although the reports outlined in section 5.2.3 (above) state that naloxone was administered in conjunction with training, details on how this was achieved were lacking. Results from a pilot study involving 9 opiate users in Glasgow (Graham et al, 2001) showed that all participants were able to perform basic resuscitation techniques after a training programme. Details on the type of training were not supplied. Although these results are encouraging it must be noted that all 9 participants volunteered to undertake training. It would be important to ensure that potential recipients (and/or their families) would only be allowed into the programme if they agreed to complete such training.

Dr. Michael Ryan is a Dublin-based doctor who is involved in the management of drug users. He has a particular interest in the use of naloxone in the emergency management of opiate overdose to prevent fatalities. He is involved with the DOORS (Dublin Opiate Overdose Reduction Strategy) group. This group (made up of professionals working in the area of drug dependence) would like a system for naloxone distribution for peer administration to be instituted in Ireland and has recently drawn up an outline proposal for such a scheme (Ryan, personal communication). In Dr. Ryan's opinion, such a system should only be implemented as part of a comprehensive training programme and initially it could be limited to users and their families.

Summary

Fatal opiate overdose is a major cause of premature mortality, especially in males. Naloxone has been used as an antidote for many years in the emergency room. Many workers have recommended that take-home naloxone should be given to users for peer administration in case

of opiate overdose. Although there are preliminary reports of such use from several areas in the UK and USA, there are no data from clinical trials to evaluate whether use of naloxone in this circumstance has any advantage over education and training in basic resuscitation techniques alone. It is noted that several EU countries appear to have implemented overdose reduction strategies in recent times, some of which may involve use of take-home naloxone and it is hoped that outcome information from these initiatives will be made available. Such information would be useful in determining whether take-home naloxone has resulted in a reduction in fatal overdoses in these countries. Furthermore, a controlled trial may be undertaken in Australia in the near future but the results may not be available for some time.

Apart from the lack of clinical trials data to support the safety and efficacy of naloxone in this indication there are many logistical issues that need to be evaluated before implementing a take-home naloxone programme. The legal consequences for all parties would need to be defined. A comprehensive training programme (including education on risky opiate use, the need to seek ambulance assistance, even with naloxone usage, as well as basic first aid training) would need to be provided in conjunction with the supply of naloxone. This would have major resource implications, especially if the programme were to be implemented nationally. Ongoing monitoring of the programme would be necessary to evaluate outcome and to ensure an adequate supply of in-date stock. This would also have major resource implications.

Finally, it is important that any programme would target those most at risk. Since retention in a methadone maintenance programme has been shown to reduce fatal opiate overdose (Caplehorn et al, 1994), it may be difficult to target at-risk groups i.e. those who don't attend clinics. An appropriate method of enrolling this group would need to be implemented.

5.3 Use in Managed Withdrawal

Traditionally, managed opiate withdrawal has involved the use of reducing doses of methadone or α_2-adrenergic agonists (O'Brien, 1997). More recently, techniques known as rapid opioid detoxification (RD) and ultra rapid opioid detoxification (URD) have been developed. These are designed to shorten detoxification by precipitating withdrawal, using opioid antagonists, including naloxone (O'Connor and Kosten, 1998). The rationale is that patients complete detoxification rapidly (1 – 5 days) enabling naltrexone maintenance (with counselling) to occur more quickly, thereby preventing relapse. RD usually involves administration of naloxone and/or naltrexone in association with other agents that will ameliorate the signs and symptoms of withdrawal (such as clonidine, lofexidine or buprenorphine) according to a protocol typically lasting 5 or more days. URD involves rapid IV administration of naloxone (minutes – few hours) to precipitate withdrawal using sedation or general anaesthesia, to help counteract the symptoms.

O'Connor and Kosten (1998) undertook a systematic review of RD and URD published trials. A total of 5 studies using naloxone for RD were identified but these involved only 118 patients whose clinical spectrum varied. Studies were generally not randomised or controlled. In addition, there was no consistency in 1) dosage regimen of naloxone used or whether it was used with or without naltrexone, 2) duration of treatment or 3) concomitant medications used. Although results generally recorded high completion rates, these were hard to interpret because most studies only commented on the period of detoxification, with no period of follow-up thereafter. Therefore it was not possible to evaluate the effectiveness of RD using naloxone or to identify the appropriate dosage regimen (including concomitant drugs) or duration of treatment.

Most of the URD studies (n = 9 in total) identified came from one centre and each had enrolled small numbers of patients. One large study was identified (Seoane et al, 1997) which administered IV naloxone 0.06-0.08mg/kg via rapid infusion (5-10 minutes) to 300 heroin users, followed by oral naltrexone 50mg/day. Patients were randomised to receive either light or heavy sedation. Results showed that all patients were successfully detoxified and 279 (93%) remained abstinent at the end of one month. However, details on the method of follow-up are sparse. In terms of safety, 4 in the heavy sedation group and 2 in the light sedation group required intubation and one patient developed aspiration pneumonia, which responded to antibiotic treatment.

The reviewers (O'Connor and Kosten 1998) suggest that data on the safety and efficacy of RD and URD are still limited, therefore further data from properly designed trials, with longer term outcome evaluation are needed to fully elucidate the place of RD and URD in the overall management of opiate dependence.

Gowing et al (2002) undertook a systematic review of opioid antagonists in the management of opiate withdrawal. They noted that there was great variability in the 10 studies that were included in the review in terms of

a. Use of naloxone or naltrexone or both in combination

b. Type of dosage regimens

c. Concomitant use of medications to ameliorate withdrawal (such as clonidine, lofexidine or buprenorphine)

d. Concomitant use of adjunctive medications.

As a result they were not able to identify a standard treatment regimen. They concluded that the use of an opioid antagonist, to induce withdrawal, in combination with an α_2-adrenergic agonist to manage the signs and symptoms of withdrawal appeared to be a feasible approach to the management of opiate withdrawal. The withdrawal syndrome tended to occur earlier and was more severe than that seen with clonidine or lofexidine alone. However, it resolved more quickly, which resulted in a higher number of patients entering an antagonist maintenance programme. The review was unable to evaluate the long-term benefit of this finding.

Summary

Naloxone has been used, either alone or in combination with naltrexone to bring about rapid opiate withdrawal. Different dosage regimens have been used and different concomitant medications have been administered to lessen the withdrawal symptoms. Data are too limited to evaluate the safety and effectiveness of any dosage schedule.

Use of naloxone and/or naltrexone, in combination with sedation or general anaesthesia has been reported. There is insufficient information regarding the efficacy and safety of this technique. Furthermore, since this requires sedation and rapid infusion of naloxone, this procedure may only be considered for inpatient usage. (Note: Further information on use of naloxone in managed withdrawal can be found in the report "Use of Lofexidine in the management of Opiate Dependence Syndrome" at **www.nacd.ie**)

5.4 Use in Combination with Buprenorphine

A combination of buprenorphine and naloxone (4:1 ratio) has been developed as a substitution treatment in opioid dependence and this was recently approved for use by the US Food and Drug Administration (FDA, 2002). Results of preliminary studies with this combination have previously been presented (Teeling et al, 2002). Among the pivotal studies that resulted in the US authorisation of this combination (Suboxone®) and the buprenorphine preparation (Subutex®) was a double blind randomised placebo-controlled trial which evaluated the safety and efficacy of 4 weeks' treatment with either Suboxone®, Subutex® or placebo in 323 opiate-dependent subjects (McClellan, 2002). Patients received daily doses of 16mg of either preparation or placebo (n = 105, 109, 109 respectively) for 4 weeks (Suboxone® company report, 2002). Results showed significant improvement in the treated groups compared to the placebo group, in terms of negative urines and opiate craving – the primary efficacy variables. In addition, the treated groups showed greater improvements in their self-reported and clinicians' global impression scores, compared with the placebo group.

The most frequently reported adverse events during the 4 weeks related to opiate withdrawal symptoms. There were no significant differences between the 3 groups in respect of liver or kidney function tests.

This study was carried into a 1-year open label safety study, which showed that, following 6 months of treatment, 50% of urine samples were negative for opiates. Safety profile with longer treatment revealed no unexpected toxicity. The commonest treatment-related effects were headache and constipation.

As Suboxone® has just recently been authorised for use in the US, there are no published studies available of use of this combination in clinical practice to date.

Subutex® and Suboxone® are the first opiate medications to be licensed for prescribing in an office setting in the USA, under the Drug Addiction Treatment Act, 2000 (FDA, 2002). This is because it is felt that they pose less risk of dependence. It also provides patients in the USA with greater access to treatment.

Subutex® is authorised for use in opiate dependence in Ireland, but there is no combination of buprenorphine and naloxone currently authorised.

Chapter 6

Summary and Conclusions

Illicit opiate use has been a public health problem in Ireland since the early 1980s 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 naloxone 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 who have experience in the use of naloxone in order to evaluate the practical issues associated with its usage.

The results of the review may be summarised as follows:

1. Naloxone has been used for many years as an emergency room treatment for suspected opiate overdose. However, few controlled studies, involving different dosage schedules, have been identified in this setting. Results showed that naloxone was effective in reversing the effects of opioid overdose but was associated with serious adverse events in a small number of treated patients.

2. Observational studies, evaluating the use of naloxone by trained ambulance personnel in the pre-hospital setting have shown that naloxone was effective in reversing the signs and symptoms of opiate overdose and in reducing the need for subsequent hospital admission. Different dosage regimens and routes of administration were used and long-term follow-up data are insufficient to determine the occurrence of long-term sequelae.

3. No controlled studies have been undertaken to evaluate the effectiveness of take-home naloxone (for peer administration) in prevention or reduction of fatal opiate overdose. Data from case reports (involving less than 100 usages) are insufficient data to judge whether the addition of naloxone has improved survival rates compared with use of basic first aid techniques (such as assisted breathing and calling for an ambulance) alone.

4. If a take-home naloxone programme were to be considered, in the absence of data from controlled trials, there are several key issues that need to be addressed before such a scheme could be initiated. These include 1) clarification of the legal responsibilities of all personnel involved, including prescriber, pharmacist, distributor, patient and administrator of the drug 2) identification of the proper location(s) of such a programme in order to reach users most at risk of overdose 3) provision of adequate training of the staff involved in running the programme 4) provision of adequate training for the drug users (and their peers) involved in the programme and 5) provision of adequate monitoring of the programme to record outcome data of use and to ensure that used/post-expired supplies are replaced.

5. Naloxone has been used in combination with other agents in the management of opiate withdrawal. Data are too heterogeneous to identify an optimal dosing regimen. It appears that the withdrawal syndrome occurs earlier, is more severe and resolves more quickly with naloxone. Long-term benefits of rapid opiate withdrawal have not been studied.

6. Naloxone has been combined with buprenorphine for sublingual use, with the aim of reducing the abuse potential of buprenorphine. Results from clinical trials show that this combination appears to be as effective as buprenorphine alone as a maintenance/substitution treatment for opiate dependence. There is no published experience of use of this combination in clinical practice to date.

In conclusion, this review suggests that naloxone may be regarded as a useful additional treatment option in the overall management of opiate dependence. However, several key issues would need to be addressed before a programme of take-home naloxone for emergency use could be implemented in practice.

Appendix

Questions on Naloxone Use in the Management of Opiate Overdose

I. General Questions

1. Have you experience of using naloxone in your practice/previous working experience for this indication?

   Yes/No (delete as appropriate)

2. If yes to 1, please outline

   a. The benefits of such a scheme to the patients involved

   b. The problems of such use (clinical, practical), excluding the medico-legal aspects

   c. The type of personnel who were involved in administering naloxone (e.g. community healthcare workers only/relative or friends/others)

3. What, in your opinion, is the biggest advantage of having naloxone available in the community for the management of opiate overdose

   For the patient?

   For the community?

4. What, in your opinion, are the disadvantages of making naloxone available in the community for the management of opiate overdose

   For the patient?

   For the community?

II. Clinical And Practical Issues

1. Because of its short duration of action, is naloxone rescue suitable for all situations – (tick for yes)

   a. Heroin alone ☐

   b. Methadone alone ☐

   c. Polydrug OD suspected ☐

   d. Overdose due to unknown drug/drugs ☐

   e. Other (please specify) ☐

2. If no to any listed in 1, please give reasons why

3. If no to any listed in 1, how do you think such use can be prevented in the community? (please specify)

4. What are the precautions that need to be taken when administering naloxone?

5. What are the basic requirements for instruction for correct use, before making naloxone available in the community for

   a. Patient (ultimate recipient)?

   b. Relative/friend who may be required to administer naloxone?

   c. Paramedic/healthcare worker who may be required to administer naloxone in the community (e.g. ambulance personnel)?

6. In your opinion, should naloxone use in the community be allowed to

   All who might come into contact with the patient?

   Yes/No (delete as appropriate)

   Paramedics/healthcare workers only, who have received basic training in the appropriate use of naloxone?

   Yes/No (delete as appropriate)

   Please give reasons for your answer

7. How could training for emergency use be implemented into the community, in your opinion?

   For paramedics

   For friends/relatives of heroin users

8. How could the practicalities of supply be handled at community level? (e.g. prescription, dispensing, storage precautions, expiry of naloxone supplies) – tick for yes as appropriate

   a. By setting up depots similar to needle exchange centres ☐

   b. Via the clinic/primary care setting for users, currently undergoing a treatment programme ☐

   c. By allowing dispensing without prescription, by community pharmacists ☐

   d. By allowing dispensing without prescription, by designated community pharmacists ☐

   e. Other means (please specify) ☐

9. Should such supply be monitored in the community by – tick for yes as appropriate

   a. The treatment clinic? ☐

   b. The provider of the supplies? ☐

   c. Community workers such as drug workers or public health nurses? ☐

   d. Community pharmacists? ☐

   e. No monitoring necessary ☐

   f. Monitoring not feasible ☐

Please add in any other points that you feel are important for naloxone use as a rescue medication in the community

Signature and date

End Of Questionnaire. *Thank you!*

Appendix II

Details on the Working Party Members

Co-ordinator of the Project

John Feely, MD, MA, BSc, FRCPE, FRCPI, FRCP, FFPHMI (Hon)
Professor (Head) Department of Pharmacology and Therapeutics, University of Dublin, Trinity College.

Project Leader and Contact Author

Mary Teeling, MD, BSc, MPH, FRCPI
Director of the Centre for Advanced Clinical Therapeutics, St. James's Hospital, Dublin 8.

Additional Personnel

Michael Barry, MB, PhD, BSc, FRCPI
Director of the National Centre for Pharmacoeconomics, St. James's Hospital, Dublin 8.

Kathleen Bennett BSc, PhD
Statistician, National Medicines Information Centre/National Centre for Pharmacoeconomics, St. James's Hospital, Dublin 8.

Mairin Ryan BSc, MPSI, Dip Clin Pharm, PhD
Chief Pharmacist National Medicines Information Centre/National Centre for Pharmacoeconomics, St. James's Hospital, Dublin 8.

References

Ashworth AJ, Kidd A
Apparent advantages may be balanced by hidden harms.
BMJ 2001; 323: 935

Bigg D
Data on take-home naloxone are unclear but not condemnatory.
BMJ 2002; 324: 678

Blackwood J
Figures in Jersey give no support to scheme's effectiveness.
BMJ 2001; 323: 934-935

Burris S, Norland N, Edlin BR
Legal Aspects of providing naloxone to heroin users in the United States.
International Journal of Drug Policy 2001; 12: 237-248

Caplehorn JR, Stella M, Dalton YN, Cluff MC, Petrenas AM
Retention in methadone maintenance and heroin addicts' risk of death.
Addiction 1994; 89: 203-209

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

Chamberlain JM, Klein K
A comprehensive Review of Naloxone for the Emergency Physician.
American Journal of Emergency Medicine November 1994 Vol 12 No. 6

Committee on Safety of Medicines (UK)
Naloxone – Use in opioid overdose: reminder
Current Problems in Pharmacovigilance 1997; 23: 7

Darke S and Hall W
The distribution of naloxone to heroin users
Addiction 1997; 92 (9): 1195-1199

Darke S and Ross J
Fatal heroin overdoses resulting from non-injecting routes of administration, NSW, Australia, 1992-1996.
Addiction 2000; 95(4): 569-573

Darke S, Ross J and Hall W
Overdose among heroin users in Sydney, Australia: 11. Responses to overdose.
Addiction 1996; 91(3): 413-417 (1996a)

Darke S, Ross J and Hall W
Overdose among heroin users in Sydney, Australia: 1. Prevalence and correlates of non-fatal overdose.
Addiction 1996; 91(3): 405-411 (1996b)

Dietze PM, Cvetkovski S, Rumbold G, Miller P
Ambulance attendance at heroin overdose in Melbourne: the establishment of a database of Ambulance Service records.
Drug and Alcohol Review 2000; 19: 27-33

Dettmer K, Saunders B, Strang J
Take-home naloxone and the prevention of deaths from opiate overdose: two pilot schemes.
BMJ 2001; 322: 895-896

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**

FDA Talk Paper
Subutex and Suboxone Approved to treat opiate dependence. Patient Information Leaflet & Product Label USA.
FDA, October 8, 2002, available at **www.fda.gov**

Gaddis GM and Watson WA
Naloxone-associated patient violence: An overlooked toxicity?
Ann Pharmacother 1992; 26: 196-198

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

Graham C, McNaughton G, Ireland A, Cassells K
Drug misusers may benefit from training in cardiopulmonary resuscitation.
BMJ 2001; 323: 934

Gutstein H and Akil H
Opioid analgesics in: The Pharmacological Basis of Therapeutics.
Goodman and Gilman's Eds: JG Hardman and LE Limbird, 10th Edition (2001): 569-620

Hall W
Reducing the toll of opioid overdose deaths in Australia.
Drug Alcohol Review 1999; 18: 213-220

Hsu W, Rao R, Nelson L
Naloxone Hazards Overstated.
Clinical Toxicology 1997; 35(2): 215-217

Kaplan JL, Marx JA et al
Double-blind Randomised Study of Nalmefene and Naloxone in Emergency Department Patients with Suspected Narcotic Overdose.
Annals of Emergency Medicine July 1999; 34(1): 42-50

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**

Lenton SR and Hargreaves KM
Should we conduct a trial of distributing naloxone to heroin users for peer administration to prevent fatal overdose?
MJA 2000; 173: 260-263 (2000a)

Lenton SR and Hargreaves KM
A trial of naloxone for peer administration has merit, but will the lawyers let it happen?
Drug and Alcohol Review 2000; 19: 365-369 (2000b)

Mc Clellan M
Two Drugs for Opioid Dependence.
JAMA 2002; 288(21): 2678

McGregor C, Darke S, Ali R, Christie P
Experience of non-fatal overdose among heroin users in Adelaide, Australia: circumstances and risk perceptions.
Addiction 1998; 93(5): 701-711

Mountain D
Big conclusions are drawn from little evidence.
BMJ 2001; 322: 248-9

O'Brien C
A range of research-based pharmacotherapies for addiction.
Science 1997; 278: 66-70

O'Connor PG, Kosten TR
Rapid and Ultra rapid Opioid Detoxification Techniques.
JAMA 1998; 279: 3

Osterwalder JJ
Naloxone – For intoxications with intravenous heroin and heroin mixtures- harmless or hazardous? A prospective clinical study.
Clinical Toxicology, 1996; 34(4): 409-416

Osterwalder JJ
Naloxone Hazards Overstated – Author's Reply.
Clinical Toxicology 1997; 35(2): 219-220

Rawal N, Schott U, Dahlstrom B, Inturrisi C, Tandon B, Sjostrand U, Wennhager M
Influence of Naloxone Infusion of Analgesia and Respiratory Depression Following Epidural Morphine.
Anesthesiology 1986; 64: 194-201

Seaman SR, Brettle RP, Gore SM
Mortality from overdose among injecting drug users recently released from prison: database linkage study.
BMJ 1998; 316: 426-428

Seidler D, Stuhlinger GH, Fischer G, Wolsetschlaeger C, Berzlanovich A, Schmid R, Hirsche H, Laggner A
After antagonization of acute opiate overdose: a survey at hospitals in Vienna.
Addiction 1996; 91(10): 1479-1487

Seoane A, Carrasco G, Cabre L
Efficacy and safety of two new methods of rapid intravenous detoxification in heroin addicts previously treated without success.
Br J Psychiatry 1997; 171: 340-45

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**

Sporer KA, Firestone J, Isaacs SM
Out-of-hospital treatment of opioid overdoses in an urban setting.
Acad Emerg Med 1996; 3(7): 660-7

Sporer KA
Acute Heroin Overdose.
Ann Intern Med. 1999; 130: 584-590

Sporer KA
Strategies for preventing heroin overdose.
BMJ 2003; 326: 442-444

Strang J
Take-home naloxone for opiate addicts: Author's reply.
BMJ 2001; 323: 935

Strang J, Powis B, Best D, Vinger L, Griffiths P, Taylor C, Welch S, Gossop M
Preventing opiate overdose fatalities with take-home naloxone: pre-launch study of possible impact and acceptability.
Addiction 1999; 94(2): 199-204

Strang J, Best D, Man LH, Noble A, Gossop M
Peer-initiated overdose resuscitation: fellow drug users could be mobilised to implement resuscitation.
International Journal of Drug Policy 2000; 11: 437-445

Strang J, Darke S, Farrell M, Ali R
Heroin overdose: the case for take-home naloxone.
BMJ 1996; 312: 1435

Suboxone (buprenorphine/naloxone sublingual tablets) Clinical Documentation Company Application Dossier, June 2002.
Schering Plough/Reckitt and Colman Products Ltd.

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**

Trujillo MH, Guerrero J, Fragachan C, Fernandez M
Pharmacologic antidotes in critical care medicine: A practical guide for drug administration.
Crit Care Med 1998; 26(2): 377-391

Wanger K, Brough L, Macmillan I, Goulding J, MacPhail I, Christenson JM
Intravenous versus subcutaneous naloxone for out-of-hospital management of presumed opioid overdose.
Acad Emerg Med 1998; 5(4): 283-5

Ward M, Barry J
Opiate-related deaths in Dublin
Irish Journal of Medical Science 2001; 170(1): 35-37

Winstock A, Sheridan J, Lovell S, Cummins M, Strang J
Availability of overdose resuscitation facilities: a survey of drug agencies in England and Wales.
Journal of Substance Use 2000; 5: 99-102

Yealy DM, Paris PM, Kaplan RM, Hellar MB, Marini SE
The safety of pre-hospital naloxone administration by paramedics.
Ann Emerg Med 1990; 19(8): 902-5

Zador D, Sunjic S, Darke S
Heroin-related deaths in New South Wales, 1992: toxicological findings and circumstances.
MJA 1996; 164: 204-207

Notes

NDP
NATIONAL DEVELOPMENT PLAN

Your Plan - Your Future

NACD
National Advisory
Committee on Drugs

3rd Floor
Shelbourne House
Shelbourne Road
Ballsbridge
Dublin 4

Tel: (01) 667 0760

Web: www.nacd.ie
email: info@nacd.ie