Standards & Guidelines Unit

Department of
Health, Social Services and Public Safety
An Roinn
Sláinte, Seirbhísí Sóisialta agus Sábháilteachta Poiblí
www.dhsspsni.gov.uk

Our Ref: NICE/ACD/Drug misuse
Date: 5 July 2006

Dear colleague

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE (NICE)

Drug misuse – naltrexone
Drug misuse – methadone and buprenorphine

Thank you for agreeing to comment on the above NICE technology appraisals. I now attach a hyperlink to the Appraisal Consultation Documents (ACD).

http://www.nice.org.uk/page.aspx?o=337197.

http://www.nice.org.uk/page.aspx?o=337219

As we are in the initial stages of sting up the process, this will not be the usual format in which you will receive the ACD. At this stage **DO NOT** send your comments directly to NICE but use the pro forma to send your comments to the Department.

To adhere to strict deadlines imposed by NICE, the attached pro forma should be completed and returned to sgu-niceguidance@dhsspsni.gov.uk no later than 20 July 2006.

I would be grateful if you would liaise with colleagues in your field of expertise to gain consensus on the recommendations you provide.

What to look for at this stage

- Do you agree with the provisional recommendations shown in Section 1 of the ACD?

- If you do not agree, take a look at Section 4, the Consideration of the Evidence, which explains how the Committee reached its decision. Let us know why you think the Committee has reached an inappropriate or incorrect decision.

- Are there any inaccuracies in the document?

- If you think the Committee has failed to take account of evidence in the Evaluation Report, let us know what the evidence is.

Thank you for your co-operation.

NICE Technology Appraisal - Drug misuse methadone, buprenorphine and naltrexone

Dr CE Cassidy on behalf on the Department of Health, Social Services and public Safety, Northern Ireland.

Comments on ACD
Comments on NICE Methadone and Buprenorphine preliminary technology Appraisal recommendations; The preliminary recommendations and document provide an excellent guidance on the management of Opiate Substitution. However, I have **very significant concerns about the preliminary recommendation 1.2 particularly the statement that Methadone should be prescribed as first choice**. This statement in an era of major pre-occupation with safety and serious adverse incidents and fatalities does not take account of the very significant and major intrinsic safety features and differences between Methadone and Buprenorphine. There is a particular duty to take this into account when introducing Opiate Substitutes into new populations and new services as in the Northern Ireland context. I disagree due to the major differential regarding safety between the two drugs. I disagree with the committee recommending that Methadone should be prescribed as first choice as this prejudices and discriminates against establishing the equally effective and much safer medication. This statement is contrary to many ethical and philosophical considerations in the clinical practice of medicine. I also wish to draw the committees attention to the concern that in making this statement they have not given sufficient consideration to the risk to more chaotic high risk individuals, children of addicts, and the wider community from diversion of Methadone in particular. Regarding recommendation 1.3, I disagree with the wording, in that it fails to emphasise the greater risk and greater need for adequate supervision of Methadone due to its greater toxicity. The consequences of these recommendations is that the progressively increasing number of individuals on opiate substitution will inevitably lead to increasing numbers unsupervised due to capacity limitations. While services strive to implement the ideal of "adequate supervision" the limits of capacity results in more and more unsupervised prescribing. The safety of buprenorphine in these situations is increasingly important and should influence choice. The following facts regarding the two medications is crucial and pivotal when considering recommending choice in prescribing. These facts have been insufficiently highlighted in the draft document: 1. The **intrinsic dangerousness of Methadone** as illustrated by the fact that in England and Wales during the mid 1990's (1994-97) the Office for National Statistics ONS recorded twice the number of drug related deaths due to Methadone compared to heroin. The "Reducing Drug Related Deaths Report" notes there were 674 Methadone related deaths in 1997. This dangerousness is heightened in those addicts in poor physical health, engaging in polydrug

abuse and with other diseases. This intrinsic dangerousness is also well illustrated in the Australian literature by Caplehorn and Drummer MJA 1999 . This Australian literature especially highlights the dangerousness of Methadone in new, inexperienced or rapidly expanding services.

2. The **inherent safety of Buprenorphine** even in overdose or when diverted to others is a marked contrast to the dangerousness of Methadone. This is illustrated by the French field experience Auriacombe M. et al. It is also evidenced at the conclusion of Ling's Review. The contrast in safety profile between the two medications is striking.

The rationale for prescribing Buprenorphine as a first choice treatment especially in a new service and in a new population is as follows:

The rationale in a new service for using buprenorphine as the first line opiate substitute treatment, is safety, for the individuals, for any young children they may have and the community they reside in. This safety benefit is most realised in the event of overdose on opiates, or diversion to individuals not on opiate substitution. This enhanced safety is based on the following;

- The intrinsic safety of buprenorphine in overdose compared to the inherent dangerousness of methadone. This is increasingly acknowledged by all the literature.
- If buprenorphine is diverted, its risks to the community are significantly less than methadone due to its relative inherent safety.
- The opiate receptor blocking effect of buprenorphine reduces the motivation and impulse to use other opiates "on top" as euphoria is not experienced. This reduces the associated risks of additional intravenous or oral consumption.
- The less addictive quality of buprenorphine compared to methadone with consequent ease of detoxification of patients who decide eventually to abstain. It is therefore less likely to promote an ever increasing cohort of individuals with little realistic option but to be retained in opiate substitution.
- The 'clearer consciousness' afforded by buprenorphine thereby increasing likelihood of normalising social and occupational functioning.

In contrast the risk to the community of using methadone first line is the accumulation of an increasing cohort of patients on methadone substitution who will only with considerable motivation and determination be able to detoxify and rehabilitate themselves, even if they wish to. This accumulating cohort is also a potential source of diversion, of the inherently dangerous and marketable methadone to the rest of the community. This negative potential is illustrated by the widespread availability of Methadone throughout all centres in the UK where it is used for Opiate Substitution.
The mortality figures for Methadone related deaths in these areas highlight this concern.
Even with active supervised consumption of Methadone, more and more patients progress to weekly or fortnightly take home Methadone.

The choice of buprenorphine first line may be a departure from current practice in

most of the UK, however in addition to its pharmacological benefits there are clear justifications for adopting this first line choice in the context of developing new services, as is the experience in N.I. These are as follows:

- New services are establishing, fortunately at a time when an equally effective and much safer medication is available.
- A new service where methadone use is not widespread or entrenched does not have to overcome resistance to change among large numbers of current patients.
- The duty to avoid the introduction of a potentially lethal opiate, to a methadone naïve population, when a much safer one is now available.
- Realising the safety advantages of a safer medication while developing and training a new opiate substitution team and service.
- In practice, the first line choice of buprenorphine is a reality in three of the five new services in Northern Ireland, where a historical reliance on methadone prescribing is not established. The other two services are prescribing in excess of 40% buprenorphine. In France buprenorphine is also first line for opiate substitution with well recognised mortality benefits. In other parts of the UK where there are new services the prescription of buprenorphine is rapidly rising despite the traditional reliance and enthusiasm for methadone. This is illustrated in the research report "The Rise of Buprenorphine Prescribing in England: Analysis of NHS Regional Data, 2001-03 (Addiction 100, 495-499)".

The preliminary recommendations do not sufficiently highlight and illustrate some of the characteristics of buprenorphine which significantly influences its appeal as a first line treatment for opiate substitution. These were usefully articulated in the research report "The Rise of Buprenorphine in England: Analysis of NHS Regional Data, 2001-2003". Cornelis J. de Wet (Addiction 100, 495 – 499. 2005)

> *"It is safer in overdose, and as such is more suitable for prescription outside specialist drug treatment centres, particularly in primary care. Preliminary studies suggest that Buprenorphine has fewer side effects than Methadone at therapeutic doses, and adverse reactions are rare. Owing to its long half life patients can be maintained on alternate day dosing, and following tapered withdrawal treatment patients can be transferred to Naltrexone almost immediately. Like Methadone, Buprenorphine can be diverted but its slow onset and propensity to precipitate withdrawal make it a less attractive drug of misuse to use out of treatment. When it has been implicated in overdose deaths, it is usually in the context of polysubstance misuse. It is relatively safe during pregnancy and breastfeeding, and neonatal withdrawal may be less frequent, less severe and of shorter duration. Buprenorphine may also have a more positive reputation among drug users and attract more into treatment than traditional Methadone treatment."*

Additional characteristics of note are that buprenorphine is less addictive with a lower addictive potential compared to methadone. There is greater ease and speed of detoxification from buprenorphine compared to methadone which is highly addictive and requires a prolonged and highly motivated process for detoxification and withdrawal. The incentive to use other opiates "on top" of buprenorphine is lower as it blocks the opiate receptors and prevents euphoria. Methadone by contrast

particularly in low or moderate dosage allows the addict to experience euphoria when other opiates are used "on top" of the methadone. This characteristic of methadone increases the possibility of the continued or intermittent abuse of **heroin**.

The draft guidelines also fail to make explicit the high risk associated with fatalities from the combined misuse of methadone, illicit opiates, high dose benzodiazepines and alcohol. The high risk of overdose and drug related mortality associated with this pattern of drug misuse is singled out for special concern and advice in the ACMD "Reducing Drug Related Death" 2000 publication. There is no acknowledgement, that in chaotic individuals the risk of death by overdose will be reduced by the choice of the safer buprenorphine. The pharmacological basis of this is the inherent safety of buprenorphine and the opiate receptor blocking effect it has. This will be protective if other illicit opiates are consumed. In addition this opiate receptor blocking effect and the lack of euphoria will discourage continued use of other opiates "on top" of the buprenorphine. The problem and the dangers of continued use of illicit opiates "on top" of opiate substitution is illustrated in the South London studies where the problem of continued daily use of heroin occurs in 31% of patients on methadone maintenance. This continued daily or monthly use of heroin while on methadone is one of the most salient reasons for choice of buprenorphine rather than methadone. Safety is a major consideration, especially in the more chaotic individuals engaging in multiple and combined drug and alcohol misuse.

The recommendation that methadone rather than buprenorphine should be prescribed first choice is contrary to the natural history and progression of medicine, in that medicines with more risk and side effects are gradually superseded, when equally effective and safer ones become available. A recent example of this is the withdrawal of the analgesic Co-proxamol by The Chairman of the Committee on Safety of Medicines. This widely used analgesic has been recently withdrawn from use due to its unacceptable toxicity in overdose and especially in combination with alcohol (Ref CEM/CMO/2005/2).

Although patient preference has an important place in prescribing decisions, considerations of risk should be the paramount factor. In the draft document there appears to be very little emphasis placed on individual assessment of risk, as is considered an urgent duty by the ACMD report (para 8.23 – 8.27 Para 10.8 and 10.11)

Paragraphs 10.8 and 10.11 call for a change in culture of services, with complacency unacceptable The report condemns as deeply unsatisfactory the lax system which permits the prescribing and dispensing of methadone so that it spills to the illicit market, and the too generous prescribing of benzodiazepines. Deaths due to methadone may fairly be described as a cause for national reproach. Prescribers must acknowledge a responsibility towards their communities as well as toward the individual drug user.

Actively motivating and educating patients to accept the safest and least addictive medication should be a priority. The avoidance and prevention of methadone deaths in the community, is the motivation for the adoption of buprenorphine as first line opiate substitute and not explicitly stating as in this draft, that methadone should be prescribed first choice.

The risk of methadone and buprenorphine to children is another important consideration. Again the marked contrast in the literature and incident reports regarding these two medications and risk of children, needs to be taken into account.

All the key policy documents draw attention to the annual occurrence of accidental poisoning of children who swallow methadone prescribed for their parents or carers.

- *ACMD para 7.12*
- *NTA Guidance or treatment providers*
- *NTA Guidance for Commissioners para 3.1*

By contrast Gaulier in a case report to Clinical Toxicology Vol 42, No. 7, 2004 concludes that a 4 year old child's accidental swallowing 4 mg of buprenorphine, suffered only mild consequences.

Eastwood, (London England 1998); gives a description of 13 children poisoned with methadone syrup prescribed to a parent, 5 died. Methadone serum concentrations in children who died overlapped that in children who survived.

Although this draft report recommends that methadone should be prescribed as first choice, alternative and contrary opinions are being clearly and urgently expressed in the leading UK medical literature.

BMJ editorial 10th December 2005 **Is methadone too dangerous for opiate addiction? The case for using a safer alternative, buprenorphine, is strong.**
This editorial concludes "*Nevertheless, the safety of buprenorphine in overdose is a significant advantage over methadone, especially considering the continued failure to prevent diversion of these agents on to the black market.*"

Ref . de Wet, Reed and Bearn (2005) Addiction 100 **The rise of buprenorphine prescribing in England: analysis of NHS regional data, 2001-03.** This research paper concludes:

"Buprenorphine prescribing has increased dramatically and represents a disproportionately large fraction of community opiate prescribing costs. The marked regional variation suggests the need for further research and the development of national guidelines to support rational prescribing and equitable access to treatment."

It seems rational and logical that buprenorphine should be the mainstay of opiate substitution especially in new services for very sound reasons of safety and avoidance of any methadone related mortality.

Outside the UK, in the USA, the US Department of Health and Human Services has published a detailed Treatment Improvement Protocol "Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (Ref www.samhsa.gov).

The rise of buprenorphine prescribing is clearly evident in the new services in Northern Ireland. It is also evident in the newer services in England and especially where problems with Methadone mortality are encountered. This rise is set to continue with the increasing realisation of its safety benefits. Recommending methadone first choice is contrary to the growing concerns re safety.

Responses to Specific Paragraphs

2.3 The phrase "opioid use quickly escalates to misuse" may give the misleading impression the illicit opioid use in the initial stages is not perceived to be 'misuse'.
2.7 The ease of eventual progression to abstinence therapy is an important factor in the initial choice of opiate substitute. The flexibility, shorter time scale for withdrawal, and reduced withdrawal effects of buprenorphine are all clinically crucial factors for choice of buprenorphine in patients who eventually wish to progress to abstinence. These factors in the midterm and long-term will also have economic cost effective benefits.

2.9 The recommendation regarding supervision of the first three months only, acknowledges that many or most patients rapidly progress to being unsupervised. This practice is an important reason for the choice of the much safer substitute buprenorphine, especially in community and primary care settings.

2.11 The approximate 5:1 ratio of Methadone to buprenorphine use relates to historical factors such as the timing of licensing of the opiates substitutes and established clinical habits and practice, rather than the effectiveness of the respective medication. The rapidly growing use of buprenorphine is related to the increasing recognition of its superior safety profile and ease of clinical manourverability.

3.2 The statement that the usual maintenance dose range is 60-120mg daily is not consistent with the assumption of an average dose of 50mg per day in paragraph 2.11 above.

3.3-3.9 The content of these paragraphs illustrate the striking contrast between the inherent dangerousness of Methadone and the intrinsic safety of buprenorphine especially in unsupervised consumption which most individuals progress to eventually. On consideration of safety the recommendation in 1.2 that Methadone should be prescribed as first choice seems perverse and contrary to patient, child and community safety obligations.

Regarding economic considerations the apparently greater cost of buprenorphine will be offset in the middle and long-term by the need for less frequent consumption (3 days per week) and less safety concerned about unsupervised consumption. These middle and longer term economic considerations appear not to have been built into the cost effectiveness assessment.

4.0-4.1.24 Regarding the interpretation of Methadone and buprenorphine maintenance outcome research it is important to appreciate that outcome studies and reviews report on the **proxy** measure of the ability of Methadone to **retain patients in Methadone maintenance**. They provide very limited evidence of reduction in mortality and no evidence regarding mortality from Methadone in the overall population or in chaotic high-risk sub groups. This overall mortality from Methadone, and other drugs and alcohol combined with Methadone, was the central concern of the ACMD "Reducing Drug Related Deaths" report in 2000. The over-reliance on the proxy measure of retention in Methadone maintenance is obscuring the overall mortality figures for Methadone relative to buprenorphine. This has heightened significance especially in

chaotic high-risk subgroups and particularly in those not retained in treatment or never involved in treatment.
It must be considered that the ability of Methadone to retain individuals in treatment partly relates to its more highly addictive properties and the major difficulty and lengthy effort involved if one decides to detoxify or abstain.
To summarise with a familiar metaphor; the trees of the proxy measure (retention in Methadone maintenance) is obscuring the wood of mortality risk from Methadone.
The relevance of the good safety profile of buprenorphine briefly mentioned in paragraph 3.8 needs more detailed consideration especially in relation to realising its benefits in reducing risk to individual addicts (either in or out of treatment), children and the wider community. When these safety benefits are given due consideration it is very difficult to justify recommending the more toxic and dangerous Methadone as 1st choice as in paragraph 1.2. The French field experience with buprenorphine is particularly relevant to this issue of mortality.

4.2 **Cost Effectiveness**:
Given the committee's comments in 4.3.2, about the uncertainty around the risk of mortality and the potential increased risk of death for people using Methadone compared with buprenorphine, and the comments in 4.3.7 that Methadone yields only marginally more QALYs, it is contrary to the usual quality and safety standards, and also to good sense, that the committee would seek to reinforce the dominance of Methadone prescribing by stating that it should be 1st choice in paragraphs 4.3.9 and 1.2.
The main justification for this expressed choice appears to be "cheapness". The human and economic costs of accumulating large cohorts of patients on highly addictive and potentially lethal Methadone (mostly, realistically unsupervised in practice) has not been given insufficient and appropriate weight.
In 4.3.10, it has not been sufficiently highlighted that with buprenorphine there is much less potential risk of death due to diversion or inadequate supervision.

5.0 **Implementation**
It is alarming and inappropriate, given the uncertainties regarding mortality that the committee has stated that Methadone should be prescribed 1st choice. Given core standard C5 it is alarming that health care organisations may well interpret this as a duty to ensure the dominance of Methadone, the more toxic, addictive and lethal substitute.
The prospect in particular of new opiate substitute services being obliged to ensure that they conform to the recommendation that Methadone should be the treatment of choice raises many ethical, philosophical and legal issues.
In setting up new services the justifications for preferring the equally effective and much safer buprenorphine are responsible, prudent and informed by the perspective of hindsight of established services, with high Methadone use and high drug related mortality in various regions of the UK. These justifications include;

- The inherent dangerousness of Methadone compared to the intrinsic safety of buprenorphine regardless of what system of supervision is adopted.
- The overall recognition in the literature review is that there is very little difference between the effectiveness of buprenorphine and Methadone in treatment.
- The recognition from the French field experience and the clinical pharmacology of buprenorphine, that it is much safer for high-risk subgroups and especially safer in the event of overdose of opiates.

- The public health benefit of avoiding the introduction of the problem of diverted Methadone into a Methadone naïve community.
- The public health and community benefit of avoiding risk to young families with Methadone especially where both parents or young mothers require opiate substitution.
- The inalienable responsibility which lies with the individual prescribing doctor to give all medications responsibly. This is especially pertinent when a safer equally effective medication is now available. This applies to every other branch of medicine where safer treatments supersede and gradually replace more dangerous existing ones.
- The observation in the New South Wales Methadone mortality studies (Caplehorn and Drummer), of the increased Methadone related mortality in new, inexperienced or rapidly expanding drug treatment services.

There are **philosophical and ethical considerations** that influence clinical choice of opiate substitute which are contrary to the preliminary recommendation to prescribe Methadone 1st choice. They include the following;

Primum non nocere, "first do no harm" is an important dictum in medicine. The recommendation that a clinician should as 1st choice prescribe the more toxic and lethal Methadone when an equally effective and much safer one is available in buprenorphine is contrary to this ethical principle. This principle has been brought to bear on other prescribing decisions in medicine e.g. the use of the analgesic Co-Proxamal and the prescription of the newer more expensive atypical anti-psychotic.

The issues and dilemmas associated with **patient autonomy and choice** are most concisely expressed in John Stuart Mills utilitarian concept of Liberty. The famous principle he enunciates in his work "On Liberty".

"The only purpose for which power can be rightfully exercised over any member of a civilised community against his will, is to prevent harm to others. His own good, either physical or moral, is not a sufficient warrant."

In the application of this principle, although Doctors also must be accorded the right of autonomy and choice in the context of prescribing, ultimately it is the prevention of harm to others (children and the community) which must apply some check and balance to unfettered patient choice.

There is the additional consideration of harm to the professions which inevitably accrues in a context where policy is promoting the choice of prescribing large amounts of the most toxic, addictive and lethal opiate substitute. This is frequently the subject of public concern, political concern and GMC inquiries.

When considering the **clinical responsibility for prescribing choice**, the philosophical classification of **responsibility** includes **causal**, **legal** and **moral** responsibility.

In the matter of prescribing choice, in the event of death by overdose, the prescribing Doctor will be directly causally responsible if he has prescribed a more dangerous drug, while knowing that a much safer one is available, especially in high-risk cases. Legal responsibility, in the event of death by opiate overdose, is likely to be influenced by whether the clinician is judged under the law to have been responsible and accountable for safe prescribing. This would apply to the choice of opiate substitute.

Moral responsibility;

A Doctor can be held morally responsible for deliberately failing to act. The knowing failure to recommend the significantly safer buprenorphine, in the context of high risk, incurs a moral responsibility in the event of death by overdose. This will particularly be an issue currently, particularly when introducing new patients and new populations to opiate substitution.