Standards & Guidelines Unit

Department of
Health, Social Services and Public Safety
An Roinn
Sláinte, Seirbhísí Sóisialta agus Sábháilteachta Poiblí
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[redacted]

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

Comments on ACD
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. 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 draft guidelines 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 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 byThe 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 Opiod 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.