NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Naltrexone for the management of opioid misuse

Response to consultee and commentator comments on the ACD

CONSULTEE	COMMENTS	RESPONSE
BAPS	1.1 The statement recommending naltrexone 'as treatment option in detoxified formerly opioid people who are highly motivated to remain on treatment' is ambiguous. There are other ways that highly motivated people can remain 'on treatment' other than taking Naltrexone such as various psychosocial interventions. The term 'on treatment' is also not clear. Who are the patients the recommendations are aimed at? Whilst the evidence is clear that those who are highly motivated to remain abstinent do better on naltrexone than those who are not so highly motivated, this is not what this recommendation states. Does 'remain on treatment' mean helps support abstinence or whether they are suggesting that Naltrexone is a way of continuing to engage people in treatment and therefore have more contact with them. If this is the case then psychosocial treatment can offer the same benefits.	FAD has been amended to state that naltrexone is recommended as a treatment option in detoxified formerly opioid-dependent people who are highly motivated to remain in an abstinence programme (see Section 1.1).
BAPS	2.7. The definition here of abstinence, our comment is the same as in our appraisal of the methadone and buprenorphine HTA section 2.7 and is stated here again: Abstinence is not also known as detoxification and withdrawal. In order to become abstinent an individual usually undergoes a process of detoxification and withdrawal. In addition for opiate dependence, we suggest separating abstinence from detoxification since they are different stages of treatment / addiction. Interventions can be	Section 2.7 has been amended.to include the following: "Pharmacological treatments are broadly categorised as maintenance therapies (also known as 'substitution' or 'harm reduction' therapies). The aim of the maintenance approach is to provide stability by reducing craving and

	different for abstinence and withdrawal and detoxification. Lastly, in opiate dependence, substitution is generally followed by detoxification and then abstinence. 'Pharmacological treatments are broadly characterised as substitution or maintenance (also know as harm reduction and involves a substitution regimen), detoxification or abstinence. Abstinence means that a person has stopped taking that drug. Whilst abstinence generally refers to an individual stopping all drugs, ie. Including their substitute drug, abstinence may be used when the person is now abstinent from their 'street' or illicit drugs. Therefore when talking about abstinence one may need to qualify whether it is total abstinence from all drugs or from their 'street' drugs. The total abstinence definition is preferred.	preventing withdrawal, eliminating the hazards of injecting, freeing the person from preoccupation with obtaining illicit opioids and to enhance overall function. To achieve this, a substitution opioid regimen (a fixed or flexible dose of methadone or buprenorphine to reduce and stop illicit use) is prescribed in a dose higher than that required merely to prevent withdrawal symptoms. The aim is for opiate-dependent people to progress from maintenance to detoxification and then abstinence. Abstinence means that a person has stopped taking that drug. All detoxification programmes require relapse prevention strategies and psychological support after detoxification as relapse rates are high. In abstinence strategies, opioid-dependent people voluntarily refrain from using opioids. Some people can rapidly achieve total abstinence from opioids; others require the support of prescribed medication for longer than a few months. The opioid antagonist naltrexone can also be used to help maintain abstinence."
BAPS	2.11 Are these figures just for drug use since naltrexone is also prescribed for treatment of alcohol dependence and for other	Section 2.11 has been amended to clarify that the majority of these

	conditions, albeit less frequently.	prescriptions are for opioid dependence although naltrexone may also be used to treat alcohol dependence and other conditions.
BAPS	3.3 Clearly with Naltrexone, an opioid antagonist on board patients who then take diamorphine will not get euphoric. Its not clear whether they can ever overcome Naltrexone blockade to achieve euphoria as stated here – but acknowledge they do try. We are not aware of any such evidence. Fatal overdose results from respiratory depression. This is not made clear. If the diamorphine is taken in conjunction with other drugs such as alcohol and benzodiazepines, the risk of fatal respiratory depression is greater.	Section 3.3 has been reworded to highlight that fatal overdoses are due to respiratory depression (SPC). The Section now includes the statement "Patients may be at risk of fatal overdose caused by respiratory depression if they relapse while taking naltrexone (because patients may try a larger dose of diamorphine to achieve euphoria) and if they return to diamorphine use after naltrexone treatment (because of loss of tolerance to diamorphine)."
BAPS	4.3.5 It is stated that the committee heard that people taking Naltrexone may suffer a number of different adverse effects such as dysphoria, depression and insomnia. Some of these may be directly related to Naltrexone though some may be the effect of being abstinent – often for a significant period for the first time. It may be worth noting, because this would result in different clinical management.	Section 4.3.5 has been amended to include the following statement: "Experts advised that adverse effects may be caused by withdrawal from illicit drugs or by the naltrexone treatment itself and stressed the importance of prescribing naltrexone as part of a care programme that includes psychosocial therapy and general support."
SCAN	2.5, line 6 – it is not correct to say most people in treatment are there because of the availability of substitute medications. It would be more accurate to say that psychosocial treatments are poorly	The purpose of this sentence is to highlight that of people in drug treatment services most are

	developed and delivered for illicit substances but contrast this to services for people who misuse alcohol where there are huge numbers in treatment but no substitution therapy.	dependence on opioids. This sentence has been amended to clarify that “Most of the people in treatment were dependent on opioids.”
SCAN	Can we have dependence throughout the document – a dependency is a small country. What is meant by ‘medical’ interventions – I think this is referring to pharmacotherapies which would be a better term.	Comments noted. Medical editors have advised that the term dependency is appropriate as it .describes a “state of being dependent” Comment noted – This sentence has been amended to “Pharmacological and psychosocial interventions are provided in the community and the criminal justice system and include inpatient, residential, day-patient and outpatient services”
SCAN	2.8 – it is OK to compare methadone maintenance with buprenorphine maintenance but there should be caveats. While there is some overlap between the use of methadone and buprenorphine the two drugs are also targeted at different populations. Because methadone is generally more effective at a higher dose, that is a dose that achieves some receptor blockade, initiation of methadone is also a commitment to prescribing up to say 80mg. This may be a higher dose of opiate than the substance user was originally taking, moreover, reducing and come off 80mg of methadone is likely to be protracted and difficult. It follows that methadone is a less desirable drug for individuals with lower levels of	**No change** – methadone and buprenorphine are referred to for completeness. Detailed guidance on their use is given in the methadone/ buprenorphine appraisal.

	dependence and usage, notably young people. Buprenorphine has the advantage of that it can be used for maintenance, it is now first line treatment for detoxification, and it is always possible to switch to methadone which will be preferred by service users looking for an opiate effect. So, it is reasonable to compare the two drugs but it should also be made clear that they have some separate indications for their use.	
SCAN	3.2 – is it confusing to say that naltrexone has a half life of 4.5 hours when the previous paragraph states that it is possible to use a 3 times a week dosing schedule. Presumably the discrepancy arises because of the very high receptor affinity of naltrexone. It might be helpful to clarify this point	**No change** – information on drug half life and dosing regimens is taken from the SPC.
SCAN	3.3, line 5 – I am not aware of any evidence, nor does it make clinical sense, that naltrexone increases the risk of death. Certainly a high dose of heroin is required to overcome the naltrexone blockade but there would still be a significant amount of blockade. The loss of tolerance is due to stopping opiates rather than taking naltrexone and this is a problem that needs to be addressed whenever people achieve abstinence from opiates. Surely this cannot be used as a reason against prescribing naltrexone.	**No change** • Information provided in the SPC and naltrexone is contraindicated in opioid taking patients. • Comment noted – loss of tolerance will occur in all abstinent patients
SCAN	6.1 given that the review has identified a very poor quality of research I would have thought it reasonable to recommend a large multi centre trial of naltrexone with prospective economic evaluation.	**No change** Although there is lack of good quality RCTs in a non-selected opioid misusers, there is evidence of its effectiveness in highly motivated

		individuals.
SCAN	pg1, para 1 – It is not correct to say that opiate dependence causes spread of blood borne viruses or overdose – better to say 'may be associated with'.	This section has been amended to state that "Diamorphine is the most widely misused opiate, and dependence on illicit diamorphine can lead to accidental overdose and may be associated with the spread of blood-borne viruses when it is injected (for example, HIV and hepatitis B or C)."
SCAN	pg8, para 1 – retention is not particularly a good outcome measure for naltrexone. As far as the service user is concerned naltrexone may have a similar effect to placebo, namely nothing at all, unless the service user relapses into opiate use. This is really judging the quality of the relapse prevention work which should be a structured psychosocial therapy.	Comment noted – the following sentence has been added to section 4.3.3 "The Committee heard from clinical experts that the most important effectiveness outcome for naltrexone treatment is relapse prevention (continued abstinence from taking illicit opioids)."
SCAN	pg21, para 1 – detoxified service users have not necessarily reduced their dependence on opiates from a psychological point of view – this is the point of naltrexone. Suggest removing 'formerly opioid dependent'.	**No change** The phrase formerly opioid dependent patients refers to the licensed indications of naltrexone.

NHS QIS	I do consider that the paper covers all the relevant evidence. I feel the committee has weighed this up appropriately. The cost-effectiveness arguments/methodologies are complex and are beyond my level of expertise. However, my knowledge of the evidence and clinical experience meant that its not surprising that the findings were somewhat equivocal. Retention is not a good measure of effectiveness in this population - many successfully treated people do not wish to stay in contact with services. Abstinence is better and more relevant. Retention can only give an indicator of compliance with the treatment (ie taking it).	Comment noted. The clinical trials included retention on treatment as a clinical outcome measure.The Committee considered the evidence from the trials but noted that prevention of relapse was the principal goal of treatment (see FAD section 4.3.3). The following sentence was also added to the FAD “Experts advised that retention on treatment is problematic as an outcome of effectiveness because it is primarily a measure of treatment compliance (taking naltrexone medication) and noted that people who do not wish to remain in contact with drug treatment services may be still be compliant in taking naltrexone.” No change
NHS QIS	In terms of resource implications for the NHS, this is likely to be a small population so drug costs are low. Counselling/psychosocial interventions should be in place even if on no medications so reflect no additional burden to the NHS. Supervision costs may if pharmacy supervision was to be considered.	**Comment noted – no change**

NHS QIS	It is a shame that non-oral preparations have been left out of the review – I refer to the 3rd Berlin Stapleford International Addiction Conference (Latest developments in effective medical treatments for addiction) www.stapleford-berlin2006.de/conference	**Comment noted– no change** Unlicensed preparations of naltrexone do not fall within the scope of this appraisal.
NHS QIS	I still feel that the evidence is not clear for oral Naltrexone UNLESS it is taken in a highly supervised environment. The risks of overdose if clients drop out of treatment remain high. I would recommend that the cost of overdose training and the provision of take home Naltrexone both need to be factored into the clinical and cost equations. In light of the new pharmacy contract, I wonder if a price for supervision of Naltrexone has been negotiated?	Comment noted **– no change** Guidance specifies that naltrexone treatment should be supervised. Price negotiation does not fall within the remit of the Institute.
NHS QIS	I would also comment that there should be recommendations for further research both in the use of oral Naltrexone in the UK;- is there a demand, in what population, what is the best way to get on to Naltrexone, efficacy, deaths whilst in and after treatment. Role as an adjunct to rehabilitation (residential or structured day). Comparison of outcomes in oral, depot and implantable Naltrexone etc.	**No change** The Committee considered that further research was not required within the context of the remit for this appraisal. It considered that there is evidence of its effectiveness in highly motivated individuals
RCN	Nurses working in this area of health have reviewed the Appraisal Consultation Document for the use of naltrexone for the management of opiod dependence. They consider the document very comprehensive and have nothing further to add on behalf of the Royal College of Nursing at this stage.	**Comment noted – no change**
RCP	The Appraisal Consultation Document is a comprehensive and representative summary of the current evidence base.	**Comment noted – no change**

	The authors rightly point to the lack of strong data supporting the use of oral Naltrexone but balance this with the low economic impact and potential value in specific groups of patients. The need for further research is well made. Hopefully in time this document will be expanded to include the use of naltrexone in detoxification and the depot preparation.	
GP and Lead in substance misuse	Important to review use of other drugs eg cocaine - it has been argued this may increase. Useful to clarify how it may work as in 1.2 with psychosocial thearpy There are issues around the reality of care programmes - what does psychosocial therapy mean, is it available at all or free, how is the person"s attendance validated?? - many abstinence-based programmes wont encompass blocker users, I presume this would include 12 step related approaches and a range of others but it isnt clear to me what psychosocial therapy access means - Many people discharged from private detox institutions eg detox 5 have no follow up care arranged in psychosocial terms - but may be given trazodone antidepressant and naltrexone with an attempt to transfer to the GP. Lack of evidence for efficacy stands out from reviews below certainly with out specific psychosocial therapy- so indications need to be very clear. 2.10 would be usefully broken down into private and NHS sectors - to address the situation where people go to private detox clinics and may have private maintenance scripts. 2.9 is rather vague on psychosoc as above Useful - there is substantial public demand for injectable unlicensed naltrexone and some psychiatrists and centres are using	**Comment noted - no change** Specific guidance on the provision of psychosocial therapy does not fall within the remit of this appraisal as it is being considered by a separate guideline (Drug misuse: psychosocial management of drug misusers in the community and prison settings. NICE clinical guideline (publication expected July 2007). The remit to the Institute is to provide guidance to the NHS. The Institute only issues guidance

	it. Nice should make a public statement on this. Section 4 – quite difficult to select Kindly address the issue of private sector public sector transfers in care (a big problem for GPs not just in substance misuse and also a problem when local voluntary sector agencies such as community drugs teams are harm minimisation not abstinence based, and there are limited abstinence based facilities which may not allow people taking blockers. Prescribers may not be equal partners in care plans and can end up feeling pulled in a direction in which they do not feel confident, or be cavalier, or in appropriately not prescribe. It is appropriate for prescription to take place in general practice as part of reintegration of ex opiate users, so the practicalities of this need to be carefull considered. You are probably aware that there is a demand for depot naltrexone in the Bangladeshi community in East London. There is room for more research on this. There is also a need when Nice makes a recommendation to do evaluative research given the equivocal nature of the evidence for most individuals, and the attempt to focus on motivation and psychosocial support. This also needs to be tailored to particular groups in the population. It needs to address the normal culture of poly drug and often alcohol use, which may well be different from that in which naltrexone was evaluated in trials above. Psychosocial management does need to come out with naltrexone guidance. This is far to far away, profiles of substance misuse and methods of treatment change quite fast, a brief review in 3 years would be appropriate.	on the licensed indications of drugs which have received a UK marketing authorisation. The issue of private / public sector transfer falls outside the remit of guidance issued in a technology appraisal. **Comment noted – no change** • See comment on guideline above • **Comment noted – no change**
GP	Section 1.2 is unclear.Does ""adequate supervision"" mean daily supervised dispensing and administration in a pharmacy in the	Specific guidance on the level of supervision falls outwith the remit of

	same way as methadone and buprenorphine?If so this is rather restrictive for patients especially since oral naltrexone is likely to be used in drug free,stable,motivated patients who are more likely to be in employment.If ""adequate supervision"" means family,partner or friends then this should be stated more clearly.Also guidance should be given given on whether to prescribe in appropriate individuals where such supervision is not possible	this appraisal. Decisions as to the level of supervision deemed to be 'adequate' should be made on an individual patient basis using clinical judgement.
Private health care practitioner	Naltrexone The Summary of Product Characteristics (SPC)1, for Nalorex* recommends under contraindications, that Nalorex should not be given to patients with acute hepatitis or liver failure. Further it is noted under warnings, that it is not uncommon for opioid abusing individuals to have impaired liver function. Additionally, liver function test abnormalities have been reported in obese and elderly patients taking naltrexone, who have no previous history of drug abuse. It is recommended that liver function tests be carried out before and during treatment with naltrexone. The warnings mentioned are based on studies which used naltrexone at higher than licensed doses for its licensed indication. In practice, it is important that any patients considered for Nalorex treatment after opioid detoxification, are assessed for the presence of acute liver disease, and baseline liver function tests should be conducted, naltrexone should not be used in patients with acute liver failure or acute hepatitis. Klebers Guidelines Initiation of naltrexone treatment in patients with abnormal LFT"s Kleber HD2, reports that many addicts with minor liver abnormalities have been treated	Comments noted. The SPC contains information on administration of naltrexone and contraindications/ warnings associated with its use. The guidance applies to the use of naltrexone in accordance with its marketing authorisation.

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