Nalmefene for reducing alcohol consumption in people with alcohol dependence – NICE Single Technology Appraisal (STA)

11th August 2014; [redacted]

[redacted]

Competition of interest: I have received honoraria from:

- Turning Point
- Lundbeck
- Archimedes Pharmaceuticals
- Bayer Schering
- KJ Physiotherapy & Medical Consultancy Ltd
- Doctors.net UK
- Richmond Pharmacology
- Pfizer

Here is my input, please feel free to put this towards the items at your leisure:

Nalmefene is a relatively old drug and similar, but sufficiently different to Naltrexone to justify separate appraisal.

Naltrexone is not licensed for controlled reduction, but recommended by NICE CG115 for this indication. The use of Naltrexone instead of Nalmefene "PRN" is also known as the "Sinclair method"
Ref: Sinclair, John David (June 2001). Targeted Use of Naltrexone Without Prior Detoxification in the Treatment of Alcohol Dependence: A Factorial Double-Blind, Placebo-Controlled Trial". *Journal of Clinical Pharmacology* (Oxford Journal of Medicine) 21 (3): 287–292. PMID 11386491;
Sinclair, J.D. (January 14, 2000). "Evidence about the use of naltrexone and for different ways of using it in the treatment of alcoholism". *Alcohol and Alcoholism* (Oxford Journal of Medicine) 36 (1): 2–10. doi:10.1093/alcalc/36.1.2. PMID 11139409.

There is considerable confusion with regards to the definition of alcohol use disorders, worsened by relatively recent tries to make the terms used more acceptable to the public and patients.

The RCGP Substance Misuse Unit is recommending the use of the following terms, which are compatible with NICE CG115:

Low risk drinking
Hazardous drinking
Harmful drinking

In the RCGP Certificate in the Management of Alcohol Problems in Primary Care, which has trained over 3000 GPs and other healthcare professionals, we describe dependence as a

subform of harmful drinking, therefore all dependent drinkers are also harmful, but not all harmful drinkers would be seen as dependent.

Assessing the severity of alcohol dependence is important as it has direct consequences for patients and treatment choices. Mild dependency does not require the same treatment as moderate or severe dependency.

There is evidence that not everybody who drinks levels of alcohol that would usually result in developing physical dependence and therefore alcohol withdrawal syndrome (AWS, typically above 15-20 units) will develop AWS (Ref: Absence of alcohol withdrawal syndrome in a remote Indigenous community; Stephen A Margolis, Valmae A Ypinazar, Alan R Clough and Ernest Hunter; Med J Aust 2008; 189 (10): 596.).

The treatment for mild dependence and harmful drinking in the absence of elements of dependence is possibly very similar and often described as “extended brief intervention”, which is a conundrum derived from the term Brief Intervention which is used for hazardous drinking. As there is no standard definition of what a brief intervention entails, there is no definite agreement what an extended brief intervention should exactly look like. We therefore recommend the use of the term “Brief Treatment” for harmful drinking, which we suggest entails of a small number of sessions which are delivered by an appropriately trained individual.

Another complication is that in order to diagnose alcohol dependence, clinicians and other healthcare professionals must be appropriately trained; the use of assessment tools like AUDIT, SADQ or LDQ can aid decision making, however the more significant (or severe) the diagnosis is, the more important it is to ensure the person making the diagnosis to be competent in the assessment. As this is a clinical decision, we recommend taking a full history as part of a clinical interview and also cover areas like sleep duration, the use of “eye openers” (consuming alcohol in the morning), withdrawal symptoms, overall units consumed, blood test results and the use of a breathalyser. It is at the discretion of the clinician how much information is required to come to a preliminary or definite diagnosis.

	AUDIT	**SADQ**	**Sleep duration**	**Eye opener**	**With-drawal**	**Units/day**
Harmful	16+	<3	Normal	-	-	<15
Dependence						
Mild	16+	<15	8+ hrs	-	+	<15
Moderate	20+	15-30	6-8 hrs	+	++	15-30
Severe	20+	30+	4-6 hrs	++	+++	30+

Reference: RCGP Certificate in the Management of Alcohol Problems in Primary Care

We recognise that alcohol treatment is highly variable and service provision is patchy throughout England; alcohol treatment services might or might not be commissioned according to NICE clinical, public health or commissioning guidelines and there is a lack, often complete absence, of clinical advisors in public health England and local authority who can ensure that clinical treatment is commissioned safely. For example, NICE published guidelines on how to commission alcohol services (CMG38 “Services for the identification and treatment of hazardous drinking, harmful drinking and alcohol dependence in children, young people and adults”), but is possibly not used by commissioners.

It is likely that the majority of individuals should address their alcohol intake in a structured treatment that is not hazardous to drinkers who can be given a brief intervention, and who are either harmful or mildly dependent. The Adult Psychiatric Morbidity Survey 2007 gives a prevalence for alcohol dependence in England at 5.9%, of which the vast majority are mildly dependent (5.4% of the population). Only 0.5% of the population are either moderately or severely dependent.

If the case mix of a well-commissioned community alcohol service is offering appropriate treatment for all service users, it can be assumed that up to 90% of service user are mildly dependent and require a short treatment with or without pharmacotherapy, as currently recommended by NICE.

The typical GP (assuming 40-50 patient contacts per day) would encounter at least 2 alcohol dependent patients, who would be likely to be mildly dependent and suitable for treatment. This does not take into account the higher risk of both mental and physical health complications in harmful drinkers, which is again likely to increase presentation frequency for comorbidities.

Whilst NICE recommends structured psychosocial interventions (PSI) as first line treatment for alcohol use disorders, it also acknowledges the role of pharmacotherapy as an additional treatment option if PSI alone is insufficient or if a service user requests it specifically. CMG38 recommends assuming that 30% of service users will require pharmacotherapy, but does not detail what budget should be set aside.

There is overwhelming evidence that addiction is a brain disease (Leshner AI. Science. 2007;278:45-7, National Institute on Drug Abuse. 2010. http://www.drugabuse.gov/publications/science-addiction), like depression or Parkinson’s disease. Both psychosocial interventions (PSI) and pharmacotherapy are suitable treatment modalities and highly effective for some addictions, whilst others are less responsive.

The initial identification, assessment and treatment of alcohol use disorders is something all GPs are confronted with, however competence is difficult to assess. Addiction to alcohol is often seen as a failure or weakness of character rather than a treatable condition.

Most GPs would require additional training to clinically assess alcohol use disorder, including making the right diagnosis with regards to severity of dependence. The RCGP is confident that the RCGP Certificate in the Management of Alcohol Problems in Primary Care fulfils this as a minimum standard. As psychosocial interventions (PSI) are often delivered by other healthcare professionals like nurses or key workers (qualified according to DANOS – drugs and alcohol national occupational standards), it is safe to presume that treatment will only be delivered as part of a shared care scheme. The idea that GPs would treat alcohol dependence independently is unlikely. PSIs should be available according to NICE CG115 as a minimum.

11th August 2014; [redacted]

- Has all of the relevant evidence been taken into account?
  The evidence review group appear to have considered the relevant and available evidence and importantly highlighted areas where the evidence is lacking or not provided by the manufacturer

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
  Yes

- Are the provisional recommendations sound and a suitable basis for guidance to the NHS? (Please comment on the generalisability of the trial populations to clinical practice and whether this patient population could be easily identified)
  There does appear to be concerns around the generalisibilty of the population -in particular patients in primary care suffer from multimorbidty and polypharmacy and this must be considered in clinic trials

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
  The scope of the guidelines must take this into account and the equality assessment report suggests this.

- Given the requirement for relevant health bodies (clinical commissioning groups, NHS England and local authorities) to provide funding to ensure that the health technology is available within 3 months, from the date the recommendation is published by NICE (see section 5.1), is an extension to this normal period appropriate because any of the following circumstances apply:
  I don't think so
  - The health technology cannot be appropriately administered until training is in place?
  - The health technology cannot be appropriately administered until certain health service infrastructure requirements including goods, materials or other facilities are in place?
  - The health technology cannot be appropriately administered until other appropriate health services resources, including staff, are in place?

If so, please specify the reasons and an estimate of the time period within which the recommendation can be complied with.