NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology Appraisals and Guidance Information Services

Static List Review (SLR)

Title and TA publication number of static topic:	**TA114; Methadone and buprenorphine for the management of opioid dependence, and TA115; Naltrexone for the management of opioid dependence**
Final decision:	The guidance for both TA114 and TA115 should remain on the static list.

1. Publication date:	TA114: January 2007 TA115: January 2007
2. Date added to static list:	TA114: November 2010 TA115: November 2010
3. Date the last searches were run:	TA114: May 2014 TA115: February 2010
4. Current guidance:	**TA114:** 1.1 Methadone and buprenorphine (oral formulations), using flexible dosing regimens, are recommended as options for maintenance therapy in the management of opioid dependence.

	1.2 The decision about which drug to use should be made on a case by case basis, taking into account a number of factors, including the person's history of opioid dependence, their commitment to a particular long-term management strategy, and an estimate of the risks and benefits of each treatment made by the responsible clinician in consultation with the person. If both drugs are equally suitable, methadone should be prescribed as the first choice. 1.3 Methadone and buprenorphine should be administered daily, under supervision, for at least the first 3 months. Supervision should be relaxed only when the patient's compliance is assured. Both drugs should be given as part of a programme of supportive care. **TA:115** 1 .1 Naltrexone is recommended as a treatment option in detoxified formerly opioid-dependent people who are highly motivated to remain in an abstinence programme. 1.2 Naltrexone should only be administered under adequate supervision to people who have been fully informed of the potential adverse effects of treatment. It should be given as part of a programme of supportive care. 1.3 The effectiveness of naltrexone in preventing opioid misuse in people being treated should be reviewed regularly. Discontinuation of naltrexone treatment should be considered if there is evidence of such misuse.
5. Research recommendations from original guidance:	**TA114:** 6.1 Randomised controlled trials conducted in the UK comparing methadone and buprenorphine using flexible dosing are required. 6.2 Randomised controlled trials conducted in the UK comparing high-dose methadone and high-dose buprenorphine are required.

	6.3 Research examining the impact of supervised consumption on the prevention of overdose is needed **TA:115** None
6. Current cost of technology/ technologies:	**TA114:** Methadone (Non-proprietary) Schedule 2 controlled drug Oral solution 1 mg/mL, methadone hydrochloride 1 mg/mL, net price 100 mL = £1.35, 500 mL = £6.75, 2.5 L = £32.10. Label: 2 Sugar free oral solution 1 mg/mL, methadone hydrochloride 1 mg/mL, net price 30 mL = 62p, 50 mL = £1.04, 100 mL = £2.08, 500 mL = £6.30, 2.5 L = £32.50. Label: 2 Buprenorphine (Non-proprietary) Schedule 3 controlled drug Tablets (sublingual), buprenorphine (as hydrochloride) 400 micrograms, net price 7-tab pack = £1.60; 2 mg, 7-tab pack = £1.93; 8 mg, 7-tab pack = £3.61. Label: 2, 26 **TA115** Tablets, naltrexone hydrochloride 50 mg, net price 28-tab pack = £22.34
7. Cost information from the TA (if available):	**TA114:** The cost of methadone oral solution (1 mg/ml) is £1.35 per 100 ml excluding VAT. The cost of methadone oral concentrate (10 mg/ml) is £12.01 per 150 ml excluding VAT (BNF, edition 51). The cost of buprenorphine is £2.88 per 8 mg tablet excluding VAT (BNF, edition 51).

	Buprenorphine is also available in 2 mg (£0.96 per tablet) and 400 micrograms (£0.23 per tablet) strengths (BNF, edition 51). **TA:115** The cost of naltrexone is £1.52 per 50-mg tablet excluding VAT ('British national formulary' [BNF], edition 51). People should receive 25 mg naltrexone on day 1 followed by 50 mg daily thereafter for an initial period of 3 months.
8. Alternative company(ies):	None
9. Changes to the original indication:	**TA114** Methadone: None Buprenorphine: None **TA115** Naltrexone: naltrexone is licensed for use as an adjunctive prophylactic treatment for detoxified formerly opioid-dependent people (who have remained opioid free for at least 7–10 days). 2015: naltrexone is licensed for use as an additional therapy within a comprehensive treatment program including psychological guidance for detoxified patients who have been opioid-dependent.
10. New relevant trials:	Neurocognitive Effects of Opiate Agonist Treatment (NCT01733693) Estimated Enrolment: 160 Estimated Study Completion Date: October 2016

	This study is currently recruiting participants Comparison of Different Methods of Pain Control After Cesarean Section for Patients on Buprenorphine or Methadone (NCT02091297) Estimated Enrolment: 180 Estimated Study Completion Date: April 2017 This study is not yet open for participant recruitment Buprenorphine to Improve HIV Care Engagement and Outcomes (NCT01936857) Estimated Enrolment: 450 Estimated Study Completion Date: April 2018 This study is currently recruiting participants Optimal Prevention of Overdose Deaths and Opioid Relapse Following Discharge: A Multi-Center RCT of Naltrexone Versus Buprenorphine in Norway (NCT01717963) Estimated Enrolment: 220 Estimated Study Completion Date: May 2016 This study is currently recruiting participants Health Services Research: Extended Release Naltrexone for Opioid-Dependent Youth (NCT01843023)

	Estimated Enrolment: 340 Estimated Study Completion Date: January 2019 This study is currently recruiting participants Extended-Release Naltrexone Opioid Treatment at Jail Re-Entry (NCT01999946) Estimated Enrolment: 255 Estimated Study Completion Date: May 2018 This study is currently recruiting participants. CTN-0051: Extended-Release Naltrexone vs. Buprenorphine for Opioid Treatment (NCT02032433) Estimated Enrolment: 1200 Estimated Primary Completion Date: April 2016 This study is currently recruiting participants. A Phase 3 Study to Evaluate the Safety, Tolerability, and Efficacy of Naltrexone for Use in Conjunction With Buprenorphine in Adults With Opioid Use Disorder Prior to First Dose of VIVITROL® (NCT02537574) Estimated Enrolment: 330 Estimated Study Completion Date: January 2017 This study is currently recruiting participants

	Biomarkers of Disease and Response to Treatment in Opioid Addiction (NCT02324725) Estimated Enrolment: 32 Estimated Study Completion Date: October 2016 This study is enrolling participants by invitation only Depot Pharmacotherapies for Opioid-Dependent Offenders: Outcomes and Costs (NCT02110264) Estimated Enrolment: 150 Estimated Study Completion Date: May 2017 This study is not yet open for participant recruitment. Opioid Relapse & HIV Risk: 48 Versus 24 Weeks of Injectable Extended Release Naltrexone (NCT01882361) - phase II/III so relevant? Enrolment: 130 Estimated Study Completion Date: June 2018 This study is ongoing, but not recruiting participants. Improving Treatment Outcomes for Prescription Opioid Dependence (NCT02543944) - again phase II/III so relevant? Estimated Enrolment: 200

	Estimated Study Completion Date: June 2020 This study is not yet open for participant recruitment.
11. Relevant NICE guidance (published or in progress):	Needle and syringe programmes (2014) NICE guidelines [PH52] Drug misuse in over 16s: opioid detoxification (2007) NICE guidelines [CG52] Drug misuse in over 16s: psychosocial interventions (2007) NICE guidelines [CG51]
12. Relevant safety issues:	None.
13. Any other additional relevant information or comments:	None.
14. Technical Lead comments and recommendation:	Since TA114 was issued, there have been no changes to the marketing authorisations for methadone and buprenorphine. Since TA115 was issued, the marketing authorisation for naltrexone has been extended to include alcohol dependent people: 'for use as an additional therapy within a comprehensive treatment program including psychological guidance for detoxified patients who have been opioid-dependent.' The original remit of TA114 was for drug misusers only, therefore this extension does not affect the guidance for TA115. The marketing authorisation for naltrexone also no longer specifies that the formerly opioid dependent population must have been opioid-free for 7 to10 days; however, this was not included in the recommendations of TA115 so this change would not impact the guidance. The recommendations of TA115 also state naltrexone 'should be given as part of a programme of supportive care' which is broadly in line with the new marketing authorisation wording 'within a comprehensive treatment program'. Overall the change to the marketing authorisation would be unlikely to impact the recommendations for TA115 regarding formerly opioid dependent people. Review of the ongoing clinical trials for TA114 found 3 trials that are currently recruiting, and 1 that is not yet recruiting. One ongoing trial could potentially provide relevant

	evidence (NCT01733693; currently recruiting), which aims to compare the effects of buprenorphine (8-32 mg per day) and methadone (60-100mg per day) on the ability to think and reason among people addicted to opiates (stratified according to people who are either HIV negative or HIV positive). However, the study is only looking at neurocognitive function outcomes, and it is questionable whether such limited outcomes (as opposed to more general health-related quality of life outcomes) in this open label study would result in a change to the recommendations. The other studies found do not address the research recommendations for TA114 and would be unlikely to result in a change to the recommendations. Review of the ongoing clinical trials for TA115 found 6 trials that are currently recruiting, and 3 that are not yet recruiting. Most of these studies however are investigating unlicensed long-lasting formulations of naltrexone (depot preparations and implants), but, as stated in section 3.1 of the final guidance, "these do not fall within the scope of this appraisal". There are also other out of scope formulations such as combinations of the drug with buprenorphine (suboxone) and some studies are in a different population to that of TA115. Overall, there were no studies that would be likely to influence the recommendations. Evidence suggests that there has been a significant drop in the NHS price of buprenorphine. However in TA114 the Committee agreed that buprenorphine should be recommended as a treatment option with an ICER of £26,400 per QALY gained. Therefore the drop in the price of buprenorphine would not change the guidance as it stands. The cost of 1 mg/mL methadone oral solution remains the same as when TA114 was issued (£1.35 per 100 ml). The cost of naltrexone when TA115 was issued was £1.52 per 50-mg tablet. The cost of a 28-tab pack (50 mg) is now £22.34, which is about £0.80 per 50-mg tablet. The reduction in price of naltrexone is only likely to further substantiate the Committee's conclusion that for people who preferred an abstinence programme, who were fully informed of the potential adverse effects and benefits of treatment, and who were highly motivated to remain on treatment,

	naltrexone treatment would fall within acceptable cost-effectiveness limits. Regarding the review of TA114, given that no substantial new evidence has been identified, the costs of methadone and buprenorphine have stayed similar or reduced, and the marketing authorisations have stayed the same, the treatments are likely to still be considered a cost effective use of NHS resources, as was found in the original appraisal. Therefore it is considered that the guidance for TA114 should remain on the static list. Likewise, no substantial new evidence has been identified in this review regarding TA115, and the cost of naltrexone has reduced considerably, meaning it would be likely to fall even further within acceptable cost-effectiveness limits. The marketing authorisation for naltrexone has changed since TA115 was issued but the change is unlikely to impact the recommendations for the formerly opioid dependent population appraised in TA115. Therefore, the guidance for TA115 should also remain on the static list.

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Appendix 1 – explanation of options

Options	Consequence	Selected – 'Yes/No'
The guidance will remain on the 'static guidance list'	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes
The decision to review the guidance will be deferred to specify date or trial	NICE will consider whether a review is necessary at the specified date. NICE will actively monitor the evidence available to ascertain when a consideration of a review is more suitable.	
A full consideration of a review will be carried out through the Review Proposal Process	There is evidence that could warrant a review of the guidance. NICE will schedule a consideration of a review, including a consultation with relevant consultees and commentators.	
The guidance will be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. NICE will schedule a consideration of a review, including a consultation with relevant consultees and commentators.	
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. NICE will schedule a consideration of a review, including a consultation with relevant consultees and commentators.	