

Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* **MH** *clinical question-answering service*

Question

“For opioid-dependent persons, how effective is buprenorphine maintenance versus placebo or methadone maintenance for substance abuse?”

Clarification of question using PICO structure

<i>Patients:</i>	Participants with opioid dependence
<i>Intervention:</i>	Buprenorphine maintenance
<i>Comparator:</i>	Placebo or methadone maintenance
<i>Outcome:</i>	Substance abuse

Clinical and research implications

One well conducted Cochrane review of 31 RCTs found that buprenorphine is effective in the maintenance treatment of heroin dependence, suppressing illicit opioid use at doses of at least 16 mg or greater compared to placebo. Flexibly administered buprenorphine has similar effectiveness to methadone for suppressing illicit opioid use, but flexibly administered methadone is superior to buprenorphine in retaining people in treatment. These findings are consistent with NICE guidance which recommends that buprenorphine, using flexible dose regimens, is recommended as an option for maintenance therapy in the management of opioid dependence.

What does the evidence say?

Number of included studies/reviews (number of participants)

One high quality Cochrane review of 31 studies (5430 participants) was included.

Main Findings

High dose buprenorphine ($\geq 16\text{mg}$) was associated with reduced opioid use compared to placebo as assessed by urinalysis (SMD -1.17, 95% CI -1.85, -0.49; 3 studies). There was no difference between low or medium dose and placebo. There was no difference in opioid use between buprenorphine and methadone measured by urinalysis (SMD -0.11, 95% CI -0.23, 0.02; 8 studies) or self-report (SMD -0.11, 95% CI -0.28, 0.07; 4 studies).

Buprenorphine was associated with better treatment retention than placebo at all doses assessed. Low dose (2-6mg): RR 1.50 (95% CI 1.19, 1.88; 5 studies), medium dose (7-15mg): RR 1.74 (95% CI 1.06, 2.87; 4 studies), high dose ($\geq 16\text{mg}$): RR 1.82 (95% CI 1.15, 2.90; 5 studies). However, buprenorphine in flexible doses adjusted to participant need was associated with lower treatment retention than methadone: RR 0.83, (95% CI 0.72, 0.95; 5 studies). Low dose methadone was also associated with greater retention than low dose buprenorphine (3 studies) but there was no difference between medium or high doses of the drugs.

Few studies reported on adverse effects and there was no evidence of a difference in adverse events between methadone and buprenorphine (2 studies).

Authors Conclusions

The authors' concluded that buprenorphine is an effective medication in the maintenance treatment of heroin dependence, suppressing illicit opioid use at doses of at least 16 mg or greater. However, when doses are delivered flexibly methadone is superior to buprenorphine in retaining people in treatment, and methadone equally suppresses illicit opioid use. Flexible dose results are most relevant to patient care as fixed doses are rarely used in practice.

Reliability of conclusions/Strength of evidence

This was a well conducted systematic review and the conclusions are likely to be reliable. The literature search was comprehensive, selection criteria were clearly defined, appropriate steps were taken to minimise bias and errors during the review, and the statistical synthesis was appropriate.

What do guidelines say?

National Institute for Health and Care Excellence (NICE) guidelines make the following recommendations:

“Methadone or buprenorphine should be offered as the first-line treatment in opioid detoxification. When deciding between these medications, healthcare professionals should take into account:

- whether the service user is receiving maintenance treatment with methadone or buprenorphine; if so, opioid detoxification should normally be started with the same medication
- the preference of the service user.” (p.6, 2007, CG52)

There is also a NICE technology appraisal guidance specifically about buprenorphine for the management of opioid dependence (2007, TA114), which recommends that buprenorphine (oral formulations), using flexible dose regimens, are recommended as options for maintenance therapy in the management of opioid dependence.

Date question received: 20/01/2015
Date searches conducted: 21/01/2015
Date answer completed: 03/03/2015

References

Systematic reviews

Mattick, R. P., Breen, C., Kimber, J., & Davoli, M. (2014). Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database of Systematic Reviews, Issue 2*. Art. No.: CD002207. DOI: 10.1002/14651858.CD002207.pub4.
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002207.pub4/pdf>

Guidelines

National Institute for Health and Care Excellence. (2007). *Drug misuse: Opioid detoxification. CG52*. London: National Institute for Health and Care Excellence.

<http://www.nice.org.uk/guidance/cg52/resources/guidance-drug-misuse-opioid-detoxification-pdf>

National Institute for Health and Care Excellence. (2007). *Methadone and buprenorphine for the management of opioid dependence. TA114*. London: National Institute for Health and Care Excellence. <http://www.nice.org.uk/guidance/ta114/resources/guidance-methadone-and-buprenorphine-for-the-management-of-opioid-dependence-pdf>

Results

Systematic reviews

Author (year)	Search date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Mattick et al. (2014)	01/2013	<p><i>Participants:</i> Individuals dependent on heroin or other opioids. Exclusions: Pregnant women.</p> <p><i>Intervention:</i> Buprenorphine (>1mg/day) maintenance therapy (BMT) administered as sublingual tablets, an ethanol-based solution, or implants</p> <p><i>Comparator:</i> Methadone maintenance therapy (MMT) (> 20mg/day), placebo, or 1mg/day buprenorphine (placebo dose). Exclusions: studies using methadone or buprenorphine for detoxification without a maintenance phase.</p> <p><i>Outcome:</i> Primary outcomes: retention; use of opioids (urinalysis positive for heroin metabolite; self-reported heroin use); use of other substances (urinalysis positive for cocaine; urinalysis positive for benzodiazepines); criminal activity; mortality. Secondary outcomes: physical health, psychological health, adverse medication effects.</p> <p><i>Study design:</i> Randomised controlled trials</p>	31 (5430 participants)	<p>Buprenorphine was associated with better treatment retention than placebo at all doses assessed. Low dose (2-6mg): RR 1.50 (95% CI 1.19, 1.88; 5 studies), medium dose (7-15mg): RR 1.74 (95% CI 1.06, 2.87; 4 studies), high dose (≥16mg): RR 1.82 (95% CI 1.15, 2.90; 5 studies). However, buprenorphine in flexible doses adjusted to participant need was associated with lower treatment retention than methadone: RR 0.83, (95% CI 0.72, 0.95; 5 studies). Low dose methadone was also associated with greater retention than low dose buprenorphine (3 studies) but there was no difference between medium or high doses of the drugs.</p> <p>High dose buprenorphine (≥16mg) was associated with reduced opioid use compared to placebo: SMD -1.17 (95% CI -1.85, -0.49; 3 studies). There was no difference between low or medium dose and placebo. There was no difference in opioid use between buprenorphine and methadone measured by urinalysis (SMD -0.11, 95% CI -0.23,</p>	Low


		(RCTs)		<p>0.02; 8 studies) or self-report (SMD -0.11, 95% CI - 0.28, 0.07; 4 studies).</p> <p>Benzodiazepine and cocaine positive urines generally showed no difference between treatment groups for any of the comparisons.</p> <p>Few studies reported on adverse effects. There was no difference in adverse events between methadone and buprenorphine in the two studies in which this was evaluated.</p>	
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
Risk of Bias:

Systematic reviews

Author (year)	RISK OF BIAS				
	Inclusion criteria	Searches	Review process	Quality assessment	Synthesis
Mattick et al. (2014)					

 Low Risk

 High Risk

 Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	buprenorphine opioid	17	
Primary studies			
CENTRAL	#1 MeSH descriptor: [Buprenorphine] explode all trees 671 #2 MeSH descriptor: [Narcotic Antagonists] explode all trees 901 #3 buprenorphine or buprenex or suboxone or bunavail or zubsolv 1416 #4 #1 or #2 or #3 2132 #5 MeSH descriptor: [Opioid-Related Disorders] explode all trees 1229 #6 (opiate* near dependen*) or (opiate* near abuse*) or (opiate* near addict*) 674 #7 #5 or #6 1661 #8 #4 and #7 #9 Jan 2013-Present	52	0
PsycINFO	32. PsycINFO; exp BUPRENORPHINE/; 0 results. 33. PsycINFO; NARCOTIC ANTAGONIST/; 1284 results. 34. PsycINFO; NARCOTIC AGENT/; 0 results. 35. PsycINFO; BUPRENORPHINE PLUS NALOXONE/; 0 results. 36. PsycINFO; (buprenorphine OR buprenex OR suboxone OR bunavail OR zubsolv).ti,ab; 1804 results. 37. PsycINFO; exp OPIATE ADDICTION/; 0 results. 38. PsycINFO; ((opiate* adj3 dependen*) OR (opiate* adj3 abuse*) OR (opiate* adj3 addict*)).ti,ab; 2382 results. 39. PsycINFO; 32 OR 33 OR 34 OR 35 OR 36; 2985 results. 40. PsycINFO; 37 OR 38; 2382 results. 41. PsycINFO; 39 AND 40; 275 results. 42. PsycINFO; CLINICAL TRIALS/ [Limit to: Publication Year 1860-2014]; 8256 results. 43. PsycINFO; random*.ti,ab [Limit to: Publication Year 1860-2014]; 136970 results.	9	0

	<p>44. PsycINFO; (doubl* adj3 blind*).ti,ab [Limit to: Publication Year 1860-2014]; 18909 results.</p> <p>45. PsycINFO; (singl* adj3 blind*).ti,ab [Limit to: Publication Year 1860-2014]; 1739 results.</p> <p>46. PsycINFO; EXPERIMENTAL DESIGN/ [Limit to: Publication Year 1860-2014]; 9432 results.</p> <p>47. PsycINFO; controlled.ti,ab [Limit to: Publication Year 1860-2014]; 84853 results.</p> <p>48. PsycINFO; (clinical adj3 study).ti,ab [Limit to: Publication Year 1860-2014]; 8286 results.</p> <p>49. PsycINFO; trial.ti,ab [Limit to: Publication Year 1860-2014]; 72071 results.</p> <p>50. PsycINFO; "treatment outcome clinical trial".md [Limit to: Publication Year 1860-2014]; 28691 results.</p> <p>51. PsycINFO; 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 [Limit to: Publication Year 1860-2014]; 259880 results.</p> <p>52. PsycINFO; 41 AND 51 [Limit to: Publication Year 1860-2014]; 70 results.</p> <p>53. PsycINFO; 52 [Limit to: Publication Year 2013-2014]; 9 results.</p>		
Embase	<p>1. EMBASE; exp BUPRENORPHINE/; 11530 results.</p> <p>2. EMBASE; NARCOTIC ANTAGONIST/; 482075 results.</p> <p>3. EMBASE; NARCOTIC AGENT/; 10943 results.</p> <p>5. EMBASE; BUPRENORPHINE PLUS NALOXONE/; 802 results.</p> <p>6. EMBASE; (buprenorphine OR buprenex OR suboxone OR bunavail OR subsolv).ti,ab; 5658 results.</p> <p>7. EMBASE; exp OPIATE ADDICTION/; 10896 results.</p> <p>8. EMBASE; ((opiate* adj3 dependen*) OR (opiate* adj3 abuse*) OR (opiate* adj3 addict*)).ti,ab; 4472 results.</p> <p>9. EMBASE; 1 OR 2 OR 3 OR 5 OR 6; 24108 results.</p> <p>10. EMBASE; 7 OR 8; 13107 results.</p> <p>11. EMBASE; 9 AND 10; 3230 results.</p> <p>13. EMBASE; CLINICAL TRIAL/; 837391 results.</p> <p>14. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 356075 results.</p> <p>15. EMBASE; RANDOMIZATION/; 64185 results.</p> <p>16. EMBASE; SINGLE BLIND PROCEDURE/; 19250 results.</p> <p>17. EMBASE; DOUBLE BLIND PROCEDURE/; 116908 results.</p> <p>18. EMBASE; CROSSOVER PROCEDURE/; 41027 results.</p> <p>19. EMBASE; "Randomi?ed controlled trial\$.ti,ab; 107148 results.</p> <p>20. EMBASE; rct.ti,ab; 15502 results.</p>	95	0

	<p>21. EMBASE; "Random allocation".ti,ab; 1355 results.</p> <p>22. EMBASE; "Randomly allocated".ti,ab; 21256 results.</p> <p>23. EMBASE; ((allocated adj2 random)).ti,ab; 720 results.</p> <p>24. EMBASE; "Single blind\$.ti,ab; 15025 results.</p> <p>25. EMBASE; "Double blind\$.ti,ab; 145845 results.</p> <p>26. EMBASE; (treble ADJ blind\$.ti,ab; 0 results.</p> <p>27. EMBASE; (triple ADJ blind\$.ti,ab; 410 results.</p> <p>28. EMBASE; Placebo\$.ti,ab; 206020 results.</p> <p>29. EMBASE; PROSPECTIVE STUDY/; 270436 results.</p> <p>30. EMBASE; 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 47 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29; 1407163 results.</p> <p>31. EMBASE; "case report".ti,ab; 270970 results.</p> <p>32. EMBASE; ABSTRACT REPORT/; 71432 results.</p> <p>33. EMBASE; LETTER/; 839280 results.</p> <p>34. EMBASE; 60 OR 31 OR 32 OR 33; 1205188 results.</p> <p>35. EMBASE; 30 not 34; 1368726 results.</p> <p>36. EMBASE; 11 AND 35; 811 results.</p> <p>37. EMBASE; 36 [Limit to: Publication Year 2013-2015]; 95 results.</p>		
Medline	<p>12. MEDLINE; exp BUPRENORPHINE/; 3739 results.</p> <p>13. MEDLINE; NARCOTIC ANTAGONIST/; 11076 results.</p> <p>14. MEDLINE; NARCOTIC AGENT/; 0 results.</p> <p>15. MEDLINE; BUPRENORPHINE PLUS NALOXONE/; 0 results.</p> <p>16. MEDLINE; (buprenorphine OR buprenex OR suboxone OR bunavail OR subsolv).ti,ab; 4340 results.</p> <p>17. MEDLINE; exp OPIATE ADDICTION/; 19142 results.</p> <p>18. MEDLINE; ((opiate* adj3 dependen*) OR (opiate* adj3 abuse*) OR (opiate* adj3 addict*)).ti,ab; 3549 results.</p> <p>19. MEDLINE; 12 OR 13 OR 14 OR 15 OR 16; 14930 results.</p> <p>20. MEDLINE; 17 OR 18; 20648 results.</p> <p>21. MEDLINE; 19 AND 20; 2993 results.</p> <p>22. MEDLINE; RANDOMIZED CONTROLLED TRIALS AS TOPIC/; 94496 results.</p> <p>23. MEDLINE; RANDOMIZED CONTROLLED TRIAL/; 381448 results.</p>	74	0

	<p>24. MEDLINE; RANDOM ALLOCATION/; 81580 results.</p> <p>25. MEDLINE; DOUBLE-BLIND METHOD/; 126702 results.</p> <p>26. MEDLINE; SINGLE-BLIND METHOD/; 19643 results.</p> <p>27. MEDLINE; CLINICAL TRIAL/; 488112 results.</p> <p>28. MEDLINE; "clinical trial, phase i".pt; 14407 results.</p> <p>29. MEDLINE; "clinical trial, phase ii".pt; 23256 results.</p> <p>30. MEDLINE; "clinical trial, phase iii".pt; 9274 results.</p> <p>31. MEDLINE; "clinical trial, phase iv".pt; 970 results.</p> <p>32. MEDLINE; "controlled clinical trial".pt; 88431 results.</p> <p>33. MEDLINE; "randomized controlled trial".pt; 381448 results.</p> <p>34. MEDLINE; "clinical trial".pt; 488112 results.</p> <p>35. MEDLINE; exp CLINICAL TRIALS AS TOPIC/; 282546 results.</p> <p>36. MEDLINE; (single\$ ADJ blind\$).ti,ab; 11903 results.</p> <p>37. MEDLINE; (doubl\$ ADJ blind\$).ti,ab; 117826 results.</p> <p>38. MEDLINE; (treb\$ ADJ blind\$).ti,ab; 0 results.</p> <p>39. MEDLINE; (trip\$ ADJ blind\$).ti,ab; 363 results.</p> <p>40. MEDLINE; (single\$ ADJ mask\$).ti,ab; 319 results.</p> <p>41. MEDLINE; (doub\$ ADJ mask\$).ti,ab; 2681 results.</p> <p>42. MEDLINE; (treb\$ ADJ mask\$).ti,ab; 0 results.</p> <p>43. MEDLINE; (trip\$ ADJ mask\$).ti,ab; 40 results.</p> <p>44. MEDLINE; PLACEBOS/; 32439 results.</p> <p>45. MEDLINE; placebo\$.ti,ab; 162055 results.</p> <p>46. MEDLINE; "randomly allocated".ti,ab; 17824 results.</p> <p>47. MEDLINE; (allocated adj2 random\$).ti,ab; 20445 results.</p> <p>48. MEDLINE; 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35; 954820 results.</p> <p>49. MEDLINE; 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47; 240252 results.</p> <p>50. MEDLINE; 48 OR 49; 1002908 results.</p> <p>51. MEDLINE; "case report".ti,ab; 212976 results.</p> <p>52. MEDLINE; LETTER/; 857605 results.</p> <p>53. MEDLINE; HISTORICAL ARTICLE/; 304761 results.</p>		
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	<p>54. MEDLINE; 51 OR 52 OR 53; 1363427 results.</p> <p>55. MEDLINE; 50 not 54; 975346 results.</p> <p>56. MEDLINE; 21 AND 55; 727 results.</p> <p>57. MEDLINE; 56 [Limit to: Publication Year 2013-2015]; 74 results.</p>		
Cinahl	<p>42. CINAHL; exp BUPRENORPHINE/; 1072 results.</p> <p>42. CINAHL; exp BUPRENORPHINE/; 1072 results.</p> <p>43. CINAHL; NARCOTIC ANTAGONIST/; 0 results.</p> <p>43. CINAHL; NARCOTIC ANTAGONIST/; 0 results.</p> <p>44. CINAHL; NARCOTIC AGENT/; 0 results.</p> <p>45. CINAHL; BUPRENORPHINE PLUS NALOXONE/; 0 results.</p> <p>46. CINAHL; (buprenorphine OR buprenex OR suboxone OR bunavail OR zubsolv).ti,ab; 919 results.</p> <p>47. CINAHL; exp OPIATE ADDICTION/; 0 results.</p> <p>48. CINAHL; ((opiate* adj3 dependen*) OR (opiate* adj3 abuse*) OR (opiate* adj3 addict*)).ti,ab; 429 results.</p> <p>49. CINAHL; 42 OR 43 OR 44 OR 45 OR 46; 1257 results.</p> <p>50. CINAHL; 47 OR 48; 429 results.</p> <p>51. CINAHL; 49 AND 50; 97 results.</p> <p>52. CINAHL; 51 [Limit to: Publication Year 2013-2015]; 11 results.</p>	11	0
Summary	NA	NA	

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