[New 2015]

Supervised dosing with a long acting opioid medication for the management of prescription opioid dependence [New 2015]

SCOPING QUESTION: In the management of prescription opioid dependence, does supervised dosing with a long-acting opioid medication result in less opioid use and related harms than non-prescription, detoxification or usual care?

BACKGROUND

Prescription opioid (PO) use has increased sharply in the United States, where more than 80% of the global opioid supply is consumed (Manchikanti et al., 2010). A similar increase has been noted in Canada, where opioid consumption doubled from 2001-2009 (Fischer et al., 2011). This trend has affected European countries to a lesser extent, although reports from the UK, Germany and Norway also identified an increase in the use of opioid analgesics (Schubert et al. 2013; Zin et al. 2014). Opioid prescription has also risen in Australia, with a reported 150% increase in oxycodone prescriptions between 2002 and 2008 (Roxburgh et al. 2011).

The need to improve access to pain relief has influenced this rise. Acute and chronic pain contribute significantly to the global disease burden and poor access to pain relief remains a problem in some parts of the world. But POs have been increasingly used to treat chronic non-cancer pain (Schubert et al., 2013), despite sparse evidence to support this practice (Kissin, 2013). Concerns regarding the use of opioids in the management of chronic pain have led to the development of specific guidance.

The rise in PO use has been followed by an increase in related harms, including fatal and non-fatal overdose. In the US, a strong correlation has been found between opioid sales and opioid related emergency department presentations (Wisniewski et al., 2009). In 2010, an estimated 16 651 people died from an overdose of prescription opioids in the US alone (Jones et al., 2010). There is also an upward trend in the prevalence of PO abuse and dependence. Presentations to US treatment services for PO dependence have increased six-fold in association with a four-fold increase in opioid prescription (Gilson et al., 20014; Novak et al., 2004). The prevalence of PO lifetime use and past-year use have also increased in the US (Martins et al., 2010), a trend also noted in other countries (Fischer et al., 2006; Nielsen et al. 2013).

The treatment of PO dependence has been mostly based on the evidence for heroin addiction treatment, which includes opioid substitution treatment (methadone and buprenorphine), detoxification and behavioural counselling (NIDA, 2011). However, it is not clear if the treatment and clinical outcomes for that population can be translated to patients dependent on prescription opioids. It has been suggested that this new group of patients have different socio-demographic characteristics to illicit opioid users, tending to have more years of education, being more frequently in employment and having less neuropsychiatric co-morbidities (Moore et al., 2007). These differences could indicate that patients dependent on PO could present greater treatment success and have preference for detoxification.

In summary, the current state of PO dependence and associated harms has been refereed as an 'American epidemic', raising concerns for countries planning to improve access to better pain management and also to countries modeling their health care system in the American one. There is an urgent need to better understand optimal treatment options and pathways to treat prescription opioid dependence, not only in North America, but globally. The aim of this scoping question is to incorporate the updated evidence into the assessment of optimal treatment options for PO dependence.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

- **Population:** Adults and adolescents dependent on prescription opioids – Specifically, morphine, oxycodone, tramadol and methadone (including patients receiving these for the treatment of chronic pain)
- **Interventions:** Supervised dosing with a long-acting medication, switching to a different opioid, detoxification
- **Comparison:** No treatment, continuing to prescribe the same opioid, non-supervised dosing, detoxification, usual care
- **Outcomes:**
    - **Critical –** Drug use, abstinence
    - **Important –** Treatment retention, psychosocial functioning, drug related harm and death

Search strategy

To identify relevant systematic reviews, the following databases were searched: MEDLINE, Embase, The Cochrane Library, BMJ Clinical Evidence and PsychINFO up to September 2014, using the search strategy found in Appendix 1. An additional search (see also Appendix 1) was conducted in order to identify individual studies.

Study selection

The search for systematic reviews identified 587 articles. These were screened by a single researcher, yielding 14 potentially relevant studies. Further screening of full texts by two researchers reduced these to 1 systematic review. However, this study only included one randomized controlled trial (RCT) and one guideline; therefore, it was decided to assess the single study directly and to look for other individual studies that could address the key question. The search for individual studies identified 372 articles. These were screened by a single researcher, yielding nine potentially relevant studies. Further screening of full texts by two researchers reduced these to four RCTs.

Results of the literature search

The four RCTs identified were conducted in the United States and compared different interventions for the treatment of prescription opioid dependence. Therefore, each intervention will be described individually. One of the studies (Weiss et al., 2011) is an RCT with a 2-phase adaptive treatment research design, so each phase of this study will be analyzed separately.

Included in GRADE tables or footnotes

- Fiellin D A et al. (2014). Primary Care–Based Buprenorphine Taper vs Maintenance Therapy for Prescription Opioid Dependence: A Randomized Clinical Trial. *JAMA Internal Medicine*, 174(12):1947-1954

- Neumann, A. M et al. (2013). A Preliminary Study Comparing Methadone And Buprenorphine In Patients With Chronic Pain And Coexistent Opioid Addiction. *Journal Of Addictive Diseases*, 32:68-78.

- Sigmon S C et al. (2013). A randomized, double-blind evaluation of buprenorphine taper duration in primary prescription opioid abusers. *JAMA psychiatry*, 70:1347-1354.

- Weiss R D et al. (2011). Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Archives of general psychiatry*, 68:1238-1246.

Excluded from GRADE tables and footnotes

Sigmon S C et al. (2009). Randomized, double-blind trial evaluating buprenorphine tapper for prescription opioid abuse, Proceedings of the 71th Annual Scientific Meeting of the College on Problems of Drug Dependence; 2009 June 20-25; Reno/Sparks, Nevada, USA: 141.
REASON FOR EXCLUSION: Single group study.

Nielsen S et al. (2013). A comparison of buprenorphine taper outcomes between prescription opioid and heroin users. *Journal of addiction medicine*, 7:33-38.
REASON FOR EXCLUSION: The data could not be used because the study did not analyze the 90 prescription opioid patients as a subgroup of the RCT.

Dreifuss J A et al. (2013). Patient characteristics associated with buprenorphine/naloxone treatment outcome for prescription opioid dependence: Results from a multisite study. *Drug and alcohol dependence*, 131:112-118.
REASON FOR EXCLUSION: Secondary data analysis of the Prescription Opioid Addiction Treatment Study (POATS).

Weiss R D et al. (2010). A multi-site, two-phase, Prescription Opioid Addiction Treatment Study (POATS): rationale, design, and methodology, *Contemporary clinical trials*, 31:189-199**.**
REASON FOR EXCLUSION: Description of the rationale, design, and methodology of the Prescription Opioid Addiction Treatment Study (POATS).

Griffin M L et al. (2014). Baseline characteristics and treatment outcomes in prescription opioid dependent patients with and without co-occurring psychiatric disorder. *American journal of drug and alcohol abuse*, 40:157-162.
REASON FOR EXCLUSION: Secondary data analysis of the Prescription Opioid Addiction Treatment Study (POATS).

[New 2015]

PICO Table

Population: Adults dependent on prescription opioids					
Intervention	**Comparison**	**Outcome***	**RCT used for GRADE**	**Justification for RCT use**	**Relevant GRADE table**
Long detoxification	Short detoxification	Opioid use Treatment retention	Sigmon et al. (2013) (2 comparisons)	Only RCT evidence available	Table 1
Detoxification	Maintenance	Opioid use Treatment retention	Fiellin et al. (2014)	Only RCT evidence available	Table 2a and 2b
Buprenorphine	Methadone	Opioid use Treatment retention Psychological functioning	Neumann et al. (2013)	Only RCT evidence available	Table 3
Detoxification + Counseling	Detoxification + Treatment as usual	Opioid use Treatment retention	Weiss et al. (2011) (Phase 1)	Only RCT evidence available	Table 4
Maintenance + Counseling	Maintenance + Treatment as usual	Opioid use Treatment retention	Weiss et al. (2011) (Phase 2)	Only RCT evidence available	Table 5

*Those outcomes not mentioned in this table did not have any associated evidence.

Narrative description of the studies that went into the analysis

Weiss et al. (2011): A sequential multi-assignment, nonblinded RCT conducted in 10 sites in the United States. In the first phase, 653 treatment-seeking outpatients dependent on prescription opioid started a brief buprenorphine/naloxone treatment, which included 2-week buprenorphine-naloxone stabilization, 2-week taper and 8-week follow-up. Patients who were unsuccessful in phase 1 entered phase 2, which consisted of an extended (12-week) buprenorphine-naloxone treatment, 4-week taper and 8-week follow-up. In both phases, patients were randomized to standard medical management (SMM) or SMM plus Opioid Dependence Counselling (ODC). Primary outcome was a composit score of minimal or no opioid use based on self-report, confirmed by urine test.

Neumann et al. (2013): A two-group, parallel-arm, nonblinded, RCT of Buprenorphine (sublingual buprenorphine/naloxone 4–16 mg/1–4 mg/day) versus Methadone (oral methadone tablets 10–60 mg/day) treatments for patients with chronic pain (originating from the spine or large joints) and coexistent opioid addiction. Patients with a history of methadone or buprenorphine maintenance treatment were not eligible. Fifty-four participants were randomly allocated to receive either Bup/nlx (N= 26) or Methadone (N=24) for 6 months. Primary outcome was self-reported analgesia at 6 months compared with the initial visit. Opioid use was measured by urine analysis.

Sigmon et al. (2013): A three-group, parallel-arm, double blinded, double dummy RCT of 1-, 2- and 4-week buprenorphine tapering regimens and subsequent naltrexone hydrochloride therapy in prescription opioid dependent outpatients. After a brief period of stabilization with Buprenorphine 70 patients were randomly assigned to receive a 1 (N=24), 2 (N=24) or 4 (N=22) weeks taper. Did not exclude patients with a history of opioid dependency. During phase 1 (weeks 1-5 after randomization), participants visited the clinic daily; during phase 2 (weeks 6-12), visits were reduced to thrice weekly. Participants received behavioral therapy and urine toxicology testing throughout the trial. There outcomes were percentage of participants negative for illicit opioid use, retention, naltrexone ingestion and favourable treatment response.

Fiellin et al. (2014): A two-group, parallel-arm, nonblinded, randomized controlled trial of buprenorphine taper vs ongoing maintenance therapy in primary care–based treatment for prescription opioid dependence in a sigle primary care setting. One-hundred and thirteen were randomized to either buprenorphine/naloxone taper condition (N=57) or to buprenorohine maintenace (N=56). The taper condition, initiated after 6 weeks of stabilization, lasted for 3 weeks, and included medications for opioid withdrawal, after which patients were offered naltrexone treatment. All patients received physician and nurse support and drug counseling. Outcomes were: Illicit opioid use via results of urine analysis and patient report, treatment retention, and reinitiation of buprenorphine therapy (taper group only).

[New 2015]

GRADE Tables

Table 1. Maintenance (with long-acting opioid) vs. detoxification for treatment of PO dependence

Authors: A Williams and N Clark
Question: Should opioid agonist maintenance treatment or detoxification be used for the treatment of prescription opioid dependence?
Bibliography: Fiellin DA et al. (2014). Primary Care–Based Buprenorphine Taper vs Maintenance Therapy for Prescription Opioid Dependence: A Randomized Clinical Trial. JAMA Internal Medicine, 174(12):1947-1954

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Detoxification**	**Maintenance**	**Relative (95% CI)**	**Absolute (95% CI)**		
Opioid use (assessed with percentage of negative urine samples during treatment)												
1	Randomized trials	Serious [1]	Not serious [2]	Not serious	Serious [2]	None	35.2	53.2	-	MD **18 lower** (30.32 lower to 5.68 lower)	⨁⨁⨁◯ LOW	CRITICAL
Opioid abstinence (assessed with mean maximum consecutive weeks of opioid abstinence)												
1	Randomized trials	Serious [1]	Not serious [2]	Not serious	Serious [2]	None	2.7	5.2	-	MD **2.5 lower** (3.9 lower to 1.1 lower)	⨁⨁⨁◯ LOW	CRITICAL
Treatment retention (assessed with mean number of days in treatment)												

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Detoxification**	**Maintenance**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	Randomized trials	Serious [1]	Not serious [2]	Not serious	Not serious	None	57.5	98.7	-	MD **41.2 lower** (55.86 lower to 26.54 lower)	⊕⊕⊕O MODERATE	IMPORTANT

1. Open-label.
2. Result comes from a small single study.

[New 2015]

Table 2a: Long detoxification (4 weeks) vs. short detoxification (1 week) for treatment of PO dependence

Authors: A Williams and N Clark
Question: Is long detoxification (4 weeks) more effective for the treatment of prescription opioid dependence when compared to short detoxification (1 week)?
Bibliography (systematic reviews): Sigmon S. C., Dunn K. E., Saulsgiver K., Patrick M. E., Badger G. J., Heil S. H. et al.. A randomized, double-blind evaluation of buprenorphine taper duration in primary prescription opioid abusers, JAMA psychiatry 2013: 70: 1347-1354.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Long detoxification (4 weeks)**	**Short detoxification (1 week)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Opioid abstinence at the end of treatment (assessed with negative urine test)												
1	Randomized trial	Not serious	Not serious	Not serious	Serious [1,2]	None	14/22 (63.6%)	7/24 (29.2%)	**OR 0.24** (0.07 to 0.81)	202 fewer per 1000 (from 42 fewer to 264 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
								29.17%		202 fewer per 1000 (from 42 fewer to 264 fewer)		
Opioid abstinence post-treatment (assessed with negative urine test)												

[New 2015]

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Long detoxification (4 weeks)**	**Short detoxification (1 week)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	Randomized trial	Not serious	Not serious [1]	Not serious	Serious [1] [2]	None	11/22 (50.0%)	5/24 (20.8%)	**OR 0.26** (0.07 to 0.96)	144 fewer per 1000 (from 7 fewer to 190 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
								20.83%		144 fewer per 1000 (from 7 fewer to 190 fewer)		
Treatment retention												
1	Randomized trial	Not serious	Not serious [1]	Not serious	Very serious [1] [3]	None	14/22 (63.6%)	10/24 (41.7%)	**OR 0.41** (0.12 to 1.34)	190 fewer per 1000 (from 72 more to 338 fewer)	⨁◯◯◯ LOW	IMPORTANT

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long detoxification (4 weeks)	Short detoxification (1 week)	Relative (95% CI)	Absolute (95% CI)		
								41.67%		190 fewer per 1000 (from 72 more to 338 fewer)		

1. Result comes from a single study.
2. Less than 100 individuals in both arms plus wide confidence interval.
3. Less 100 individuals in both arms plus wide confidence interval crossing the line of no effect.

[New 2015]

Table 2b. Long detoxification (4 weeks) vs. short detoxification (2 weeks) for treatment of PO dependence

Authors: A Williams and N Clark
Question: Is long detoxification (4 weeks) more effective for the treatment of PO dependence when compared to short detoxification (2 weeks)?
Bibliography (systematic reviews): Sigmon S. C., Dunn K. E., Saulsgiver K., Patrick M. E., Badger G. J., Heil S. H. et al.. A randomized, double-blind evaluation of buprenorphine taper duration in primary prescription opioid abusers, JAMA psychiatry 2013: 70: 1347-1354.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Long detoxification (4 weeks)**	**Short detoxification (2 weeks)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Opioid abstinence at the end of treatment (assessed with negative urine test)												
1	Randomized trial	Not serious	Not serious [1]	Not serious	Serious [2]	None	14/22 (63.6%)	7/24 (29.2%)	**OR 0.24** (0.07 to 0.81)	202 fewer per 1000 (from 42 fewer to 264 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
								29.17%		202 fewer per 1000 (from 42 fewer to 264 fewer)		
Opioid abstinence post-treatment (assessed with negative urine test)												

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Long detoxification (4 weeks)**	**Short detoxification (2 weeks)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	Randomized trial	Not serious	Not serious [1]	Not serious	Serious [2]	None	11/22 (50.0%)	4/24 (16.7%)	**OR 0.2** (0.05 to 0.78)	128 fewer per 1000 (from 32 fewer to 157 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
								16.67%		128 fewer per 1000 (from 32 fewer to 157 fewer)		
Treatment retention												
1	Randomized trial	Not serious	Not serious [2]	Not serious	Serious [2]	None	14/22 (63.6%)	7/24 (29.2%)	**OR 0.24** (0.07 to 0.81)	202 fewer per 1000 (from 42 fewer to	⨁⨁⨁◯ MODERATE	IMPORTANT

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long detoxification (4 weeks)	Short detoxification (2 weeks)	Relative (95% CI)	Absolute (95% CI)		
										264 fewer)		
								29.17%		202 fewer per 1000 (from 42 fewer to 264 fewer)		

1. Result comes from one study.
2. Less than 100 individuals in both arms and wide confidence interval.

[New 2015]

Table 3. Buprenorphine vs. methadone for the treatment of PO dependence

Authors: A Williams and N Clark
Question: Should buprenorphine vs. methadone be used in the treatment of PO dependence?
Bibliography (systematic reviews): Neumann, A. M., Blondell, R. D., Jaanimägi, U., Giambrone, A. K., Homish, G. G., Lozano, J. R., Kowalik, U. & Azadfard, M. 2013. A Preliminary Study Comparing Methadone And Buprenorphine In Patients With Chronic Pain And Coexistent Opioid Addiction. Journal Of Addictive Diseases, 32, 68-78.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Buprenorphine**	**Methadone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Opioids use (assessed with positive urine test)												
1	Randomized trial	Very serious [1] [2] [3]	Not serious [4]	Not serious	Very serious [4] [5]	None	5/13 (38.5%)	2/13 (15.4%)	**OR 3.44** (0.53 to 22.43)	231 more per 1000 (from 66 fewer to 649 more)	⨁◯◯◯ VERY LOW	CRITICAL
								15.38%		231 more per 1000 (from 66 fewer to 649 more)		
Opioid use (assessed with self-report of opioid use)												

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Buprenorphine**	**Methadone**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	Randomized trial	Very serious [1] [2] [3]	Not serious [4]	Not serious	Very serious [4] [5]	None	5/13 (38.5%)	0/13 (0.0%)	**OR 17.47** (0.85 to 357.84)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Psychological functioning (assessed with percentage change of functioning from baseline in a 0-10 point numerical rating scale)												
1	Randomized trial	Very serious [1] [2] [3]	Not serious [4]	Not serious	Very serious [4] [5]	None	121.9	113.8	-	MD **8.1 higher** (40.49 lower to 56.69 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Treatment retention												
1	Randomized trial	Very serious [1] [2] [3]	Not serious [4]	Not serious [4]	Very serious [4] [5]	None	13/26 (50.0%)	13/28 (46.4%) 46.43%	**OR 0.87** (0.3 to 2.52)	34 fewer per 1000 (from 222 more to 258 fewer) 34 fewer	⨁◯◯◯ VERY LOW	IMPORTANT

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Buprenorphine	Methadone	Relative (95% CI)	Absolute (95% CI)		
										per 1000 (from 222 more to 258 fewer)		

1. Small sample size.
2. No intention to treat (ITT) analysis.
3. High drop-out rate.
4. Result comes from a single study.
5. Very wide confidence interval crossing the line of no effect.

Table 4. Detoxification + counseling vs. detoxification + treatment as usual (TAU) for treatment of PO dependence

Authors: A Williams and N Clark
Question: Is detoxification + counseling effective for treatment of PO dependence compared to detoxification + TAU?
Bibliography (systematic reviews): Weiss R. D., Potter J. S., Fiellin D. A., Byrne M., Connery H. S., Dickinson W. et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial, Archives of general psychiatry 2011: 68: 1238-1246.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Detoxification + counseling	Detoxification + TAU	Relative (95% CI)	Absolute (95% CI)		
Opioid use at the end of treatment (assessed with minimal or no opioid use based on urine test and self-report)												
1	Randomized trials	Serious [1]	Not serious [2]	Not serious	Serious [2,3]	None	19/329 (5.8%)	24/324 (7.4%)		21 more per 1000 (from	⊕⊕OO LOW	CRITICAL

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Detoxification + counseling	Detoxification + TAU	Relative (95% CI)	Absolute (95% CI)		
									OR 1.31 (0.7 to 2.43)	21 fewer to 89 more)		
								7.41%		21 more per 1000 (from 21 fewer to 89 more)		
Treatment retention (assessed with mean number of treatment sessions attended)												
1	Randomized trials	Serious [1]	Not serious [2]	Not serious	Not serious [2]	None	6.6	4.5	-	MD **2.1 higher** (1.7 higher to 2.5 higher)	⊕⊕⊕O MODERATE	IMPORTANT

6. Open-label: lack of blinding may have resulted in performance bias.
7. Results come from a single study (Weiss et al., 2011).
8. Wide confidence interval crossing the line of no effect.

[New 2015]

Table 5. Maintenance + counseling vs. maintenance + TAU for treatment of PO dependence

Authors: A Williams and N Clark
Question: Is maintenance + counseling effective for treatment of PO dependence compared to maintenance + TAU?
Bibliography (systematic reviews): Weiss R. D., Potter J. S., Fiellin D. A., Byrne M., Connery H. S., Dickinson W. et al.. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial, Archives of general psychiatry 2011: 68: 1238-1246.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Maintenance + counseling	Maintenance + TAU	Relative (95% CI)	Absolute (95% CI)		
Opioid use at the end of treatment (assessed with minimal or no opioid use based on urine test and self-report)												
1	Randomized trials	Serious [1]	Not serious [2]	Not serious	Serious [2,4]	None	93/180 (51.7%)	84/180 (46.7%) 46.67%	**OR 0.82** (0.54 to 1.24)	49 fewer per 1000 (from 54 more to 146 fewer) 49 fewer per 1000 (from 54 more to 146 fewer)	⊕⊕OO LOW	CRITICAL
Opioid use post-treatment (assessed with minimal or no opioid use based on urine test and self-report)												
1	Randomized trials	Serious [1]	Not serious [2]	Not serious	Serious [2,3]	None	18/180 (10.0%)	13/180 (7.2%) 7.22%	**OR 0.7** (0.33 to 1.48)	21 fewer per 1000 (from 31 more to 47 fewer) 21 fewer per 1000 (from 31 more to 47 fewer)	⊕⊕OO LOW	CRITICAL
Abstinence during treatment (assessed with urine test and self-report)												
1	Randomized trials	Serious [1]	Not serious [2]	Not serious	Serious [2,4]	None	70/180 (38.9%)	61/180 (33.9%)	**OR 0.81**	45 fewer per 1000 (from 50 more to 128 fewer)	⊕⊕OO LOW	CRITICAL

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Maintenance + counseling**	**Maintenance + TAU**	**Relative (95% CI)**	**Absolute (95% CI)**		
								33.89%	(0.52 to 1.24)	45 fewer per 1000 (from 50 more to 128 fewer)		
Abstinence post-treatment (assessed with urine test and self-report)												
1	Randomized trials	Serious [1]	Not serious [2]	Not serious	Serious [2][3]	None	13/180 (7.2%)	11/180 (6.1%)	**OR 0.84** (0.36 to 1.92)	9 fewer per 1000 (from 38 fewer to 50 more)	⊕⊕OO LOW	CRITICAL
								6.11%		9 fewer per 1000 (from 38 fewer to 50 more)		
Treatment Retention (assessed with mean number of sessions attended)												
1	Randomized trials	Serious [1]	Not serious [2]	Not serious	Not serious [2]	None	11.6	14	-	MD **2.4 lower** (3.38 lower to 1.42 lower)	⊕⊕⊕O MODERATE	IMPORTANT

9. Open-label: lack of blinding may have resulted in performance bias.
10. Results come from a single study (Weiss et al., 2011).
11. Wide confidence interval crossing the line of no effect.
12. Crosses the line of no effect.

[New 2015]

Additional evidence not mentioned in GRADE tables

Nielsen S., Hillhouse M., Thomas C, Hasson A, Ling W. A comparison of buprenorphine taper outcomes between prescription opioid and heroin users, Journal of addiction medicine 2013: 7: 33-38.

This study comprised a secondary data analysis of an uncontrolled comparison that examined differences in outcomes between PO users (n = 90) and heroin users (n = 426) following a buprenorphine taper. After a 4-week buprenorphine induction/ stabilization phase, 516 opioid-dependent individuals were randomized into one of two taper lengths (7 days vs. 28 days) to assess the association between taper length and outcome. The primary outcome was measured by urine drug test for opioids at the end of the taper period. Results indicate that a higher percentage of the PO group (49%) provided an opioid-free urine drug specimen at the end of taper compared to the heroin group (36%; $\chi 2$ 6.592, $p < .010$). PO users appear to have favourable taper outcomes compared to heroin users.

Dreifuss J. A., Griffin M. L., Frost K., Fitzmaurice G. M., Potter J. S., Fiellin D. A. et al. Patient characteristics associated with buprenorphine/naloxone treatment outcome for prescription opioid dependence: Results from a multisite study, Drug and alcohol dependence 2013: 131: 112-118.

This study comprised a secondary analysis of data of POATS that examined baseline patient characteristics (N=360) associated with success during 12-week buprenorphine/naloxone treatment for prescription opioid dependence. Pre-treatment characteristics associated with successful opioid use outcome included: older age; past-year or lifetime diagnosis of major depressive disorder; initially obtaining opioids with a medical prescription to relieve pain; having only used opioids by swallowing or sublingual administration; never having used heroin; using an opioid other than extended-release oxycodone most frequently; and no prior opioid dependence treatment. In multivariate analysis, age, lifetime major depressive disorder, having only used opioids by swallowing or sublingual administration and receiving no prior opioid dependence treatment remained as significant predictors of successful outcome.

Griffin M. L., Dodd D. R., Potter J. S., Rice L. S., Dickinson W., Sparenborg S. et al. Baseline characteristics and treatment outcomes in prescription opioid dependent patients with and without co-occurring psychiatric disorder, American journal of drug and alcohol abuse 2014: 40: 157-162.

This secondary analysis of 360 patients entering a treatment study for dependence on prescription opioids (POATS) examined the association between the presence of a co-occurring Axis I psychiatric disorder and sociodemographic and clinical characteristics. Participants were receiving 12 weeks of buprenorphine-naloxone treatment. Half of the 360 participants who entered the second phase had a current co-occurring psychiatric disorder in addition to substance dependence. Women were 1.6 times more likely than men to have a co-occurring disorder. On several clinical indicators at baseline, participants with a co-occurring disorder had greater impairment. However, they had better opioid use outcomes at the conclusion of 12 weeks of buprenorphine-naloxone stabilization than did participants without a co-occurring disorder.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Summary of evidence table

OUTCOME	Long detoxification vs. Short detoxification *(Number of studies, OR or MD [95% CI] and Quality)*		Detoxification vs. maintenance *(Number of studies, OR or MD [95% CI] and Quality)*	Buprenorphine vs. methadone *(Number of studies, OR or MD [95% CI] and Quality)*	Detoxification + Counseling vs. detoxification + TAU *(Number of studies, OR or MD [95% CI] and Quality)*	Maintenance + Counseling vs. maintenance + TAU *(Number of studies, OR or MD [95% CI] and Quality)*
	4 weeks vs. 1 week	4 weeks vs. 2 weeks				
Opioid use: during treatment or at the end of treatment	1 study OR 0.24 (0.07 to 0.81) Favouring long detox MODERATE quality	1 study OR 0.24 (0.07 to 0.81) Favouring long detox MODERATE quality	1 study Mean urine test: MD -18 (-30.32 to -5.68) Abstinence MD -18 (-30.32 to -5.68) Favouring maintenance LOW quality	1 study Abstinence (+urine test): OR 3.44 (0.53 to 22.43) Abstinence (self-report): OR 17.47 (0.85 to 357.84) Favouring methadone VERY LOW quality	1 study OR 1.31 (0.7 to 2.43) No difference LOW quality	1 study Opioid use: OR 0.82 (0.54 to 1.24) Abstinence: OR 0.81 (0.52 to 1.24) No difference LOW quality
Opioid use: post-treatment	1 study OR 0.26 (0.07 to 0.96) Favouring long detox MODERATE quality	1 study OR 0.2 (0.05 to 0.78) Favouring long detox MODERATE quality	_____	_____	_____	1 study Opioid use: OR 0.7 (0.33 to 1.48) Abstinence: OR 0.84 (0.36 to 1.92) No difference LOW quality
Treatment retention	1 study OR 0.41 (0.12 to 1.34) Favouring long detox LOW quality	1 study OR 0.24 (0.07 to 0.81) Favouring long detox MODERATE quality	1 study MD -41.2 (-55.86 to -26.54) Favouring maintenance MODERATE quality	1 study OR 0.87 (0.3 to 2.52) No difference VERY LOW quality	1 study MD 2.1 (1.7 to 2.5) No difference MODERATE quality	1 study MD -2.4 (-3.38 to -1.42) No difference MODERATE quality

Psychological function	_____	_____	_____	1 study MD 8.1 (-40.49 to 56.69) No difference VERY LOW	_____	_____
Drug related harms	_____	_____	_____	_____	_____	_____
Death	_____	_____	_____	_____	_____	_____

Evidence to recommendation table

Benefits	There are very few trials of interventions for people with prescription opiod (PO) dependence. For strong PO dependence (that is, people dependent on morphine, oxycodone, etc.), one study compared detoxification with buprenorphine vs. buprenorphine maintenance treatment. There was 40-50% less drug use in the maintenance group, which shows a 2/3 reduction in heroin use with maintenance treatment and is consistent with the heroin dependence literature. A reduction in drug use can lead to less criminality (e.g., obtaining illegal supplies of drugs). There were no studies examining interventions for dependence on tramadol or other weaker opioids. In other related evidence for strong prescription opioids, there was one trial demonstrating that more gradual detoxification with buprenorphine (4 weeks) is better than shorter detoxification (1-2 weeks), one trial showing unsupervised methadone treatment was more effective than unsupervised buprenorphine (LOW quality evidence), one trial showing modest benefits of psychosocial support during detoxification, and one trial showing the same during buprenorphine maintenance. These findings support those of studies of heroin dependent patients, where opioid maintenance treatment produced better outcomes than detoxification, where supervision of treatment is more effective than unsupervised, and where psychosocial support in addition to opioid agonist treatment provides additional benefits (WHO, 2009).

Harms	No harms of long term buprenorphine use were identified in this study; however, other research has indicated that when prescribed buprenorphine, some people will inject their buprenorphine and put themselves at risk of infection from bloodborne viruses. This may be of particular concern in people with a history of drug injection. Both buprenorphine and methadone are medications that can be diverted from treatment to illicit sales. Diversion of these medications can produce substantial concerns among law enforcement and other public officials. At this time, findings cannot be extended to PO-dependent people who are also dependent on alcohol and cocaine and to patients with a history of heroin use, as patients with these characteristics were excluded from the sample.
Summary of the quality of evidence	The quality of the evidence is LOW.

Value and preferences	
In favour	Maintenance treatment might be the preferred option for patients who find it difficult to cease opioids, either because of pain recurrence or opioid dependence symptoms.
Against	Despite maintenance proving superior to detoxification in this study, a small number of highly motivated patients might still prefer to attempt detoxification and might benefit from it. In some countries, the political or societal position may not be akin to maintenance programmes and may prefer detoxification. Supervised dosing can be difficult for some patients (to attend the dispensing service on a daily or weekly basis), can be stigmatising and may be seen as reducing patient autonomy.
Uncertainty or variability?	There is high variability with regards to treatment preferences.

Feasibility (including resource use considerations)	In some countries, neither buprenorphine nor methadone are available and maintenance treatment is not possible due to supply chain issues. National legislation surrounding controlled drugs can also negatively impact availability. Medication costs are a consideration, with buprenorphine more costly than methadone. However, in many jurisdictions, methadone is only used with in specially licensed facilities and not in general health care settings. Research studies have been done with highly trained staff and there would be significant time and cost required for training to implement either medication.
Uncertainty or variability?	There is significant variability in the availability of opioid agonist treatment.

[New 2015]

Recommendation and remarks

Recommendation

When managing people who are dependent on strong prescription opioids (i.e. morphine-like), physicians can switch to a long acting opioid (such as methadone and buprenophine) which can be taken once daily, with supervised dispensing if necessary, either for maintenance treatment or for detoxification.

Rationale: There is low quality evidence regarding the benefits of long acting opioid medication for the management of prescription opioid dependence. However both buprenorphine and methadone are medications that can be diverted from treatment to illicit sales, which is a cause for concern. Maintenance treatment might be the preferred option for patients who find it difficult to cease opioids, either because of pain recurrence or opioid dependence symptoms. In some countries, neither buprenorphine nor methadone are available and maintenance treatment is not possible due to supply chain issues. National legislation surrounding controlled drugs can also negatively impact availability.

Remarks

The prescription of long acting opioids such as methadone and buprenorphine in the maintenance treatment of opioid dependence is most safely conducted following specific training, or under the supervision of a specialist in the treatment of opioid dependence. Within the category of "supervised long acting opioid medication", which includes methadone, buprenorphine and slow-release oral morphine, buprenorphine has most evidence of support and has a variety of advantages, including lower overdose risk and better harms profile. However, methadone can be another option, when buprenorphine is not available. If methadone and buprenorphine treatment are not

available, it may be possible to substitute methadone and buprenorphine with another long acting opioid which is available and to supervise the dispensing daily if necessary.

When deciding between maintenance and detoxification options, the duration and severity of the opioid dependence, past history of illicit drug use, and patient preference should be taken into consideration.

Patients should be advised that people with opioid dependence who detox are at a higher risk of overdose having completed detoxification, as their tolerance to opioids will have dropped.

The duration of maintenance treatment is difficult to determine, but generally the patient should not be encouraged to cease maintenance treatment until they have ceased other substance use.

For detoxification, it may be preferable to titrate the pace of reduction to the patients' capacity to manage the opioid withdrawal symptoms.

Judgements about the strength of a recommendation

Factor	Decision
Quality of the evidence	□ High **X Moderate** □ Low □ Very low

Balance of benefits versus harms	X Benefits clearly outweigh harms □ Benefits and harms are balanced □ Potential harms clearly outweigh potential benefits
Values and preferences	□ No major variability X Major variability
Resource use	□ Less resource-intensive X More resource-intensive
Strength	CONDITIONAL

OTHER REFERENCES

Barnett PG, Rodgers JH, Bloch DA (2001). A meta-analysis comparing buprenorphine to methadone for treatment of opiate dependence. Addiction.96:683–690.

Dreifuss JA, Griffin ML, Frost K, Fitzmaurice GM, Potter JS, Fiellin DA et al. (2013). Patient characteristics associated with buprenorphine/naloxone treatment outcome for prescription opioid dependence: Results from a multisite study. Drug and Alcohol Dependence.131:112-118.

Fiellin DA, Pantalon MV, Chawarski MC, Moore BA, Sullivan LE, O'Connor PG et al. (2006). Counselling plus Buprenorphine–Naloxone Maintenance Therapy for Opioid Dependence.New England Journal of Medicine.355:365-374.

Fiellin DA, Schottenfeld RS, Cutter CJ, Moore BA, Barry DT, O'Connor PG (2014). Primary Care–Based Buprenorphine Taper vs Maintenance Therapy for Prescription Opioid Dependence: A Randomized Clinical Trial. JAMA Intern Med.174(12):1947-1954.

Fischer B, Jones W, Krahn M, Rehm J (2011). Differences and over-time changes in levels of prescription opioid analgesic dispensing from retail pharmacies in Canada, 2005-2010. Pharmacoepidemiology and Drug Safety.20(12):1269–77.

Fischer B, Rehm J, Patra J, Firestone C (2006). Changes in illicit opioid use profiles across Canada. Canadian Medical Association Journal.175(11):1–3.

Gilson AM, Ryan KM, Joranson DE, Dahl JL (2004). A reassessment of trends in the medical use and abuse of opioid analgesics and implications for diversion control: 1997–2002. Journal of Pain and Symptom Management.28(2):176–88.

Griffin ML, Dodd DR, Potter JS, Rice LS, Dickinson W, Sparenborg S et al. (2014). Baseline characteristics and treatment outcomes in prescription opioid dependent patients with and without co-occurring psychiatric disorder. American Journal of Drug and Alcohol Abuse.40:157-162.

Jones CM, Mack KA, Paulozzi LJ (2013). Pharmaceutical overdose deaths, United States, 2010. JAMA.309(7):657-9.

Kakko J, Svanborg KD, Kreek MJ, Heilig M (2003). 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. The Lancet.361:662-668.

Kissin I (2013). Long-term opioid treatment of chronic nonmalignant pain; unproven efficacy and neglected safety? Journal of Pain Research.513.

Ling W, Amass L, Shoptaw S, et al. (2005). A multi-center randomized trial of buprenorphine–naloxone versus clonidine for opioid detoxification: findings from the National Institute on Drug Abuse Clinical Trials Network. Addiction.100(8):1090-1100.

Manchikanti L, Fellows B, Ailinani H (2010). Therapeutic use, abuse, and nonmedical use of opioids: a ten-year perspective. Pain Physician.13:401–35.

Martins SS, Keyes KM, Storr CL, Zhu H, Grucza RA (2010). Birth-cohort trends in lifetime and past-year prescription opioid-use disorder resulting from nonmedical use: results from two national surveys. Journal of Studies on Alcohol and Drugs.71(4):480.

Moore BA, Fiellin DA, Barry DT, et al. (2007). Primary Care Office-based Buprenorphine Treatment: Comparison of Heroin and Prescription Opioid Dependent Patients. Journal of General Internal Medicine.22(4):527-530.

National Institute on Drug Abuse (NIDA) (2011). Treating addiction to prescription opioids. NIDA Drug Publications. Available from http://www.drugabuse.gov/publications/research-reports/prescription-drugs/treating-prescription-drug-addiction/treating-addiction-to-prescription-opio (accessed Autumn 2014).

Neumann AM, Blondell RD, Jaanimägi U, Giambrone AK, Homish GG, Lozano JR, Kowalik U, Azadfard M (2013). A Preliminary Study Comparing Methadone And Buprenorphine In Patients With Chronic Pain And Coexistent Opioid Addiction. Journal Of Addictive Diseases.32:68-78.

Nielsen S, Bruno R, Degenhardt L, Stoove M, Fischer J, Carruthers S, et al. (2013). The sources of pharmaceuticals for problematic users of benzodiazepines and prescription opioids. Med J Aust.199(10):696–9.

Nielsen S, Hillhouse M, Thomas C, Hasson A, Ling W (2013). A comparison of buprenorphine taper outcomes between prescription opioid and heroin users, Journal of Addiction Medicine.7:33-38.

Novak S, Nemeth WC, Lawson KA (2004). Trends in Medical Use and Abuse of Sustained-Release Opioid Analgesics: A Revisit. Pain Medicine.5(1):59–65.

Sees KL, Delucchi KL, Masson C, et al. (2000). Methadone Maintenance vs 180-Day Psychosocially Enriched Detoxification for Treatment of Opioid Dependence: A Randomized Controlled Trial. JAMA.283(10):1303-1310.

Sigmon SC, Dunn KE, Saulsgiver K, Patrick ME, Badger GJ, Heil SH et al. (2013). A randomized, double-blind evaluation of buprenorphine taper duration in primary prescription opioid abusers. JAMA Psychiatry.70:1347-1354.

Sigmon SC, Dunn K, Saulsgiver K, Heil S, Higgins S (2009). Randomized, double-blinde trial evaluating buprenorphine tapper for prescription opioid abuse, Proceedings of the 71th Annual Scientific Meeting of the College on Problems of Drug Dependence. 141.

Strain EC, Stitzer ML, Liebson IA, Bigelow GE (1993). Dose-Response Effects of Methadone in the Treatment of Opioid Dependence. Ann Intern Med.119:23-27.

Weiss RD, Potter JS, Fiellin DA, Byrne M, Connery HS, Dickinson W et al. (2011). Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. Archives of General Psychiatry.68:1238-1246.

Weiss RD, Potter JS, Provost SE, Huang Z, Jacobs P, Hasson A et al. (2010). A multi-site, two-phase, Prescription Opioid Addiction Treatment Study (POATS): rationale, design, and methodology. Contemporary Clinical Trials.31:189-199.

Woody GE, Poole SA, Subramaniam G, et al. (2008). Extended vs Short-term Buprenorphine-Naloxone for Treatment of Opioid-Addicted Youth: A Randomized Trial. JAMA.300(17):2003-2011.

Zin CS, Chen L-C, Knaggs RD (2014). Changes in trends and pattern of strong opioid prescribing in primary care: Strong opioid prescribing in the United Kingdom. European Journal of Pain. n/a–n/a.

APPENDIX 1

Search Strategies

Search for systematic reviews

ID Search Hits
#1 MeSH descriptor: [Opioid-Related Disorders] explode all trees 1225
#2 (opiate or opioid* or morphin* or morfin* or methadone or oxycodone or hydrocodone or hydromorphone or tramadol or codeine or fentanyl or meperidine or oxymorphone or propoxyphene or tramadol) near (abuse* or abusing or addict* or misus* or depend* or disorder*):ti,ab,kw (Word variations have been searched) 2224*
#3 #1 or #2 2362
#4 MeSH descriptor: [Analgesics, Opioid] explode all trees 5213
#5 ((opioid or opiat*) near analges*):ti,ab,kw (Word variations have been searched) 6479*
#6 MeSH descriptor: [Prescription Drugs] explode all trees 87
#7 ((prescript or prescrib* or pharmaceutical) near (opioid* or opiate*)):ti,ab,kw (Word variations have been searched) 197*
#8 #4 or #5 or #6 or #7 6665
#9 #3 and #8 417

Search for individual studies

ID Search Hits
#1 MeSH descriptor: [Opioid-Related Disorders] explode all trees 1225
#2 (opiate or opioid* or morphin* or morfin* or methadone or oxycodone or hydrocodone or hydromorphone or tramadol or codeine or fentanyl or meperidine or oxymorphone or propoxyphene or tramadol) near (abuse* or abusing or addict* or misus* or depend* or disorder*):ti,ab,kw (Word variations have been searched) 2224*

#3 #1 or #2 2362
#4 MeSH descriptor: [Analgesics, Opioid] explode all trees 5213
#5 ((opioid or opiat*) near analges*):ti,ab,kw (Word variations have been searched) 6479*
#6 MeSH descriptor: [Prescription Drugs] explode all trees 87
#7 ((prescript or prescrib* or pharmaceutical) near (opioid* or opiate*)):ti,ab,kw (Word variations have been searched) 197*
#8 #4 or #5 or #6 or #7 6665
#9 #3 and #8 in Trials 365