Umbrella Systematic Review of Systematic Reviews of Opioid Use Disorder in Primary Care: Setting, Diagnosis, Treatment, and Management of Comorbidities.

Abstract

Objective: To summarize the best available evidence regarding a variety of topics related to primary care management of opioid use disorder (OUD).

Data Sources: MEDLINE, Cochrane Library, Google, references of included studies and relevant guidelines.

Study Selection: Systematic reviews and newer randomized controlled trials (RCTs) from the last 5-10 years that investigated patient-oriented outcomes across 23 areas related to: managing OUD in primary care, diagnosis, pharmacotherapies (including buprenorphine, methadone, and naltrexone), tapering strategies, psychosocial interventions, prescribing practices, and management of co-morbidities.

Synthesis: From 8626 articles, 39 systematic reviews and an additional 26 RCTs were included. New meta-analyses were performed where possible. RCT evidence was either non-existent or inadequate for 10 areas. One cohort study suggests one case-finding tool may be reasonable to assist with diagnosis (positive likelihood ratio (10.3). Meta-analysis demonstrated that retention in treatment improves: 1) when buprenorphine or methadone are used (65-70% versus 22-40% control), 2) when OUD is treated in primary care [86% versus 67% specialty care, RR 1.25 (95%CI 1.07, 1.47)], and 3) when counselling is added to pharmacotherapy [75% versus 61% control, RR 1.23 (95%CI 1.08,1.39)]. Retention was also improved with naltrexone [33% versus 26% control, RR 1.32 (95%CI 1.09, 1.60)], and reduced with medication-related contingency management (example: loss of take-home doses as a punitive measure) [68% versus 77% no contingency, RR 0.86 (95%CI 0.76-0.98)].

Conclusion: There is reasonable evidence that primary care should manage patients with OUD. Diagnostic criteria for OUD remain elusive, with 1 reasonable case-finding tool. Methadone and buprenorphine improve treatment retention, both are better than naltrexone, and all should be continued long-term. Counselling is beneficial when added to pharmacotherapy.

Introduction

Opioids and opioid use disorder (OUD) are a major public health concern.[1] While various organizations have responded to this crisis with a variety of guidelines and educational resources, none have done so with an exclusive primary care audience in mind, or with the information necessary to allow for shared, informed, decision-making.[2,3] With their broad scope of practice, primary care clinicians require information on all aspects of OUD management (examples contracts and urine drug screens), and management of comorbidities (examples anxiety and pain). In some cases, they might have limited access to more specialized, wrap-around services available in larger and more specialized centres, furthering the need for accessible evidence-based information.

We completed 16 systematic reviews to answer key questions regarding management of OUD that are relevant to primary care according to a committee tasked with writing a OUD guideline for primary care,[4] related to:

1) Treatment Setting
    a. The management of OUD in primary care
    b. Residential treatment programs
2) Diagnosis of OUD
3) Treatment
    a. Pharmacotherapeutic management of OUD, including buprenorphine, methadone, naltrexone and cannabinoids
    b. Tapering off of drug therapy in OUD:
        i. Tapering off opioids,
        ii. Tapering off opioid agonist therapy (OAT)compared to long-term maintenance,
        iii. In patients discontinuing OAT, comparing fast and slow tapering regimens.
    c. Psychosocial interventions for OUD
        i. Counselling
        ii. Motivational interviewing
        iii. Cognitive Behavioral Therapy (CBT)
        iv. Contingency Management
        v. Technology-based psychosocial interventions
    d. Prescribing practices, including use of daily witnessed ingestion, urine drug screening and contracts.
4) Management of comorbidities in patients with OUD (acute pain, chronic pain, insomnia, anxiety and ADHD).

Two additional topics (the use of sustained release oral morphine and the role of OAT without any additional supports) were also investigated with an abbreviated systematic search. Results are available in Appendix YY.

Methods

To complete this review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the systematic review of systematic reviews protocol.[5,6]

Data Sources

The evidence team created a search strategy with guidance from an experienced librarian for each of the clinical questions created. Two authors (DP, JT) performed the search of systematic reviews and randomized, controlled trials (RCTs) for each clinical question with no language restrictions. The search was restricted to non-animal studies. The databases and resources used to search for relevant systematic reviews included MEDLINE, Cochrane Library, Google, published guidelines on opioid use disorder and reference lists of the included systematic reviews. The search included any articles up to June 2018, but was generally limited to the last 5-10 years. Keywords of "opioid or opiate" were used for all searches. Specifics for each question and the corresponding keywords, timelines, and search strategies used can be found in Appendix YY (full evidence review). After the search for systematic reviews was complete, an additional search of Medline was undertaken to find RCTs published since the most recent systematic review for each clinical question. Reference lists of included articles were hand searched to identify potentially missed articles.

Study Selection

Beyond systematic reviews and newer RCTs, inclusion criteria were adult patients with opioid use disorder reporting on at least one of the following outcomes: morbidity and mortality, social outcomes, quality of life and symptoms, or opioid use outcomes (definitions in Box XX). Systematic reviews of observational studies were included, although observational data was only utilized when RCTs did not exist. Exclusion criteria were studies on detoxification from opioids, studies in pediatric, pregnant or cancer patients, and studies completed within a prison setting. Any exceptions made were recorded (Appendix YY).

Dual title, abstract, and full-text review were completed for all systematic review and RCT searches to determine study eligibility. A single reviewer assessed titles and abstracts from guidelines and reference lists, with dual assessment if full-text review was required. Disagreements over inclusion were resolved by consensus.

Synthesis

Data Extraction

Dual data extraction was completed using templates created by two authors (CF, JT), one specifically for systematic reviews and one for RCTs. For systematic reviews, data extracted included author, year, title, study design, general characteristics, setting, gender, mean age, mean duration, duration range, outcomes reported (along with number of studies, RCTs and patients for each outcome), values associated with the outcomes, intervention and control. If no usable data was found in a given systematic review, authors attempted to obtain that data from the included trials.

Following extraction, data tables of systematic reviews and RCTs were created with headings for: total studies, age, population, relevant studies, duration of studies, intervention, outcomes and risk of bias quality assessment. The data tables created can be found in Appendix YY.

Risk-of-bias assessment

Risk-of-bias was assessed using a modified AMSTAR rubric for systematic reviews, focusing on the six most relevant questions:[7,8] 1) Was study selection and data extraction performed by dual reviewers? 2) Was the literature search comprehensive? 3) Were the included study characteristics described? 4) Was quality of the included studies assessed and reported? 5) Were the methods used to combine results appropriate? 6) Was conflict of interest reported? For systematic reviews, each question was scored as 1 (completed) or 0 (not completed). These individual scores were then summated with a higher total score suggesting a lower risk of bias. For RCTs, the JADAD 5-point scoring rubric was used.[9] The risk of bias assessment for each article was completed by at least two independent authors and disagreement was resolved by consensus or a third author. The scores for each rubric are reported in conjunction with their associated study in the data tables (Appendix XX).

Analysis

Following data extraction, we used study outcomes and meta-analyses to answer each clinical question. We reported study characteristics and outcomes descriptively using means and other statistical results as per the original paper. We prioritized systematic reviews of RCTs and individual RCT results over those of observational data. Where outcomes were measured in a variety of ways, we preferentially reported on the more objective outcomes. For example, for the outcome of continued opioid use in studies of pharmacotherapy, we report on the results of urine drug tests over self-report.

Performing New Meta-Analysis

If no relevant meta-analyses existed or if relevant RCTs had been published since the most recent systematic review, a new meta-analysis was completed using the RevMan 5 software. We used a Mantel-Haenszel statistical method and focused on reporting risk ratios when appropriate. Not wanting to overweigh smaller studies, we chose a fixed effects analysis if there was no reason to speculate that the effect of the intervention would deviate meaningfully between studies. Additionally, we performed an exploratory meta-analysis of the effects on buprenorphine, methadone and naltrexone on mortality. Due to the low event rate, mortality events from the 3 treatments were combined and meta-analyzed using the exact method with odds ratios.[10]

Synthesis

Details of study flow (PRIMSA) are provided in Appendix YY. All searches combined identified a total of 8626 articles, with 39 systematic reviews and an additional 26 RCTs being included. Table XX outlines the characteristics of the included systematic reviews. Reasons for exclusion of systematic reviews after full-text review are available in Table YY. Modified AMSTAR scores and JADAD scores are outlined in Tables XX and XX, respectively. Details on GRADE evaluation and Risk-of-Bias assessment are available in Table YY.

We preferentially report meta-analysis for treatment retention, ongoing drug-use and select key outcomes. All other outcomes are available in Appendix YY. Details of our meta-analyses, such as which RCTs contributed to which meta-analysis, are available in Table YY.

No RCT Data Available

Overall, 10 topics had either no RCT data available for the specified outcomes, or the data was considered inconclusive (Table XX). No topic had RCT data to support all outcomes, and no individual topic provided adequate data on morbidity and mortality.

Treatment Setting

No systematic review was available, however four RCTs were identified that compared the management of OUD in primary care compared to specialty care (n=46-221). Three of these looked at patient satisfaction rates and found statistically significantly higher rates (ie. more satisfaction) with primary care (example: 77% versus 38%). We meta-analyzed the effect of treatment setting on retention and found program retention was 86% in primary care versus 67% in a specialty clinic [Risk Ratio (RR) 1.25, p = 0.005 (95%CI 1.07 to 1.47) I^2 = 18%). Figure XX. Street opioid abstinence was also higher in primary care settings (53% versus 35%, (RR 1.50, p = 0.007, 95%CI 1.12 to 2.01, I^2 = 74%), although this included both self-reported as well as urine drug screen data. Figure XX.

Diagnosis

Fourteen systematic reviews were found. However, only two case-finding tools were compared to the Diagnostic and Statistical Manual (DSM IV or 5): the Current Opioid Misuse Measure (COMM), a 17-question scale, and the Prescription Opioid Misuse Index (POMI), a 6-question checklist. Both have been assessed in only 1 cohort study (238 and 74 patients, respectively),-reporting positive likelihood ratios of 3.35 and 10.3, respectively .

Treatment

a. Pharmacotherapy

I. Buprenorphine

We found 2 systematic reviews and an additional 5 RCTs (as 8 publications) of buprenorphine alone or combined with naloxone. Compared to placebo/detoxification only/psychotherapy, buprenorphine significantly retained more patients in treatment (65% versus 40% control, number needed to treat (NNT)=4 at 22 weeks) (see, ref YY).

II. Methadone

One systematic review and 1 RCT of methadone were found. Retention in treatment was higher with methadone compared to no methadone (73% versus 22% control, NNT=2 at 16 weeks) (see ref YY).

Our meta-analysis of 24 RCTs directly comparing buprenorphine to methadone revealed higher retention rates with methadone [45% versus 60% methadone, NNT=7, RR 0.75 (0.71, 0.80)]. Figure XX. However, substantial heterogeneity was present (I^2=72%) due to the inclusion of 1 open-label RCT designed to compare the effects of buprenorphine and methadone on liver indices. This also differed from Neilsen's systematic review that found no difference in retention rates between buprenorphine and methadone.[11] Neilsen's systematic review meta-

analyzed sub-groups of patients from 3 of the above studies who used prescription opioids, rather than heroin.[11]

Overall, opioid abstinence appears higher with methadone than buprenorphine (Figure XX). However, there was a statistically significant difference between subgroups of studies that measured abstinence objectively and those that relied on self-report (P<0.00001). If only studies that used objective measures are included, there is no difference in abstinence between buprenorphine and methadone [RR 0.99 (0.78, 1.24), I^2=0].

Adverse effects were poorly reported in both the buprenorphine and methadone literature. Two RCTs found no difference between drugs, except for more sedation with methadone (58% versus 26% buprenorphine), in 1 RCT. Two RCTs found fewer adverse effects with buprenorphine than controls.

III. Naltrexone

Two systematic reviews and 6 RCTs were found on the opioid antagonist naltrexone. Indirect comparison reveals lower rates of retention than OATs, but naltrexone is still better than placebo or usual care [33% versus 26% control, RR 1.32 (1.09, 1.60)]. Although subgroup analysis of oral naltrexone was not statistically significant [RR 1.28 (0.97, 1.68)], it was numerically similar to the injectable results, and the test for subgroup differences between oral and injectable forms was not significant (P=0.74). Naltrexone also increased abstinence from opioids [39% versus 27% control, RR 1.48 (95%CI 1.11, 1.98)] (Figure XX). Based on 4 small RCTs, naltrexone decreases re-incarceration [24% versus 33% control, RR 0.69 (95%CI 0.51, 0.94)] (figure XX).

Since mortality rates were very low across buprenorphine, methadone and naltrexone studies, we performed an exploratory meta-analysis combining event rates for all 3 drugs and found a statistically significant reduction in overall mortality with the use of pharmacotherapy in patients with OUD [Odds Ratio=0.29 (95%CI 0.08, 0.88), 6 RCTs].

b. Tapering

There were no systematic reviews or RCTs of tapering off of opioids versus the use of OAT for treating OUD. Two RCTs compared tapering off of OAT compared to long-term maintenance. Abstinence was not reported; however, the group that was maintained on treatment had a greater number of opioid-negative urines in 1 RCT (53% versus 35% tapered, significance not reported) (ref YY).

c. Psychosocial Supports

Eight systematic reviews were identified on psychosocial supports. There was substantial variation with regards to inclusion criteria and analysis, thus we prioritized 5 key interventions and assessed individual RCTs identified from the systematic reviews.

The addition of standard counselling to OAT is more effective in retaining people in treatment than no or minimal counselling [75% versus 61% control, RR 1.23 (95%CI 1.23, 1.39), NNT=8, 3 RCTs], although the heterogeneity was high (I^2=80%). No difference was noted between extended counseling sessions (45-60 mins) compared to "standard" sessions of 15-20 mins) [RR 0.93 95%CI 0.68, 1.26)].

The use of contingency Management, defined as either "rewards" for desired behaviour, (example: vouchers or prizes) or loss privileges for undesired behavior (example: loss of medication carries for positive urine drug screens), increases retention in treatment [RR 1.11 (95%CI 1.06, 1.17)] (Figure XX). Subgroup analysis suggests the benefits are primarily from positive contingencies [RR 1.15 (95%CI 1.09, 1.21)], with negative or medication related contingencies worsening retention [RR 0.86 (95%CI 0.76, 0.99)] (test for subgroup difference P<0.0001). Methods of reporting opioid use were too heterogeneous to be meta-analyzed.

d. Prescribing Practices

I. Contracts

All RCTs of contracts in patients with OUD incorporated contingency management. Therefore, it is not possible to differentiate the effects of contracts from the contingencies on patient outcomes.

II. Daily Witnessed Ingestion ("carries")

Both treatment retention and continued drug use are no different between daily witnessed and unsupervised ingestion (Figures XX and XX). However, none of the included RCTs had a completely unsupervised arm; rather, they compared various levels of supervision (example 2 versus 5 times per week).

III. Urine Drug Screening

No RCTs were found. One retrospective cohort study found all-cause mortality was lower in patients who underwent urine testing [Hazard Ratio 0.33 (95%CI 0.22, 0.49)]. However, this finding has significant potential for bias.

Management of Comorbidities in Patients with OUD

There was inadequate RCT evidence in all searched areas (Appendix YY).

Results of other systematic reviews, such as residential treatment, cannabinoids, fast versus slow tapering, motivational interviewing, cognitive behavioural therapy and technology-based psychosocial interventions are available in Appendix YY.

Discussion

There is a surprising lack of RCT data for a variety of topics important to the management of OUD in primary care. Of the 23 areas investigated, 10 had either no RCT evidence or RCT evidence that was impossible to make conclusive statements on.

While systematic reviews of observational data suggest that ongoing use of OAT results in a reduction in mortality,[12,13] we found no RCT powered to investigate this outcome. Our

exploratory meta-analysis of the combined effects of buprenorphine, methadone and naltrexone suggests that medication-assisted treatment may reduce mortality. However, adequately powered RCTs are needed for confirmation. Methadone is superior to buprenorphine for treatment retention, but opioid abstinence rates do not differ between methadone and buprenorphine when objective reporting measures are used. The majority of patients in pharmacotherapy studies were using heroin, not prescription opioids. Thus, outcomes in patients using prescription opioids may vary from what we have reported. One small meta-analysis using subgroups of patients on prescription opioids found no difference in retention rates between the 2 drugs. Some provinces maintain prescribing restrictions on methadone, and methadone typically requires more supervision to achieve therapeutic doses. RCTs of naltrexone typically only included patients who had undergone complete detoxification off of opioids before enrollment. This drastically limits its use as a first-line agent in primary care.

Despite finding numerous systematic reviews on the diagnosis of OUD, only one questionnaire with strong predictive ability for OUD that may be useful in primary care settings (POMI) was identified. The currently used Diagnostic and Screening Manual for Mental Disorders (DSM 5) criteria for OUD is difficult to apply to patients on prescription opioids for the management of chronic pain.[14] Diagnosis of OUD in these patients remains challenging.

Primary care is an appropriate setting for management of OUD, with improved patient outcomes compared to specialty care. While most of the included RCTs provided some type of supportive team and/or training, other RCTs have shown that OAT alone, without any additional supports, also improves outcomes, particularly retention in treatment (ref YY).

Our results for counselling and contingency management differ significantly from other systematic reviews. The most frequently cited systematic review of contingency management combined RCTs of both positive and negative contingencies, reporting no benefit on retention in treatment.[15] Since negative or medication-related contingencies may be viewed as disciplinary measure, it may be more appropriate to meta-analyze positive and negative contingencies separately. When analyzed separately, positive contingencies (example being given the opportunity to work on days where urine drug screens are negative) are noted to improve treatment retention, whereas negative or medication related contingencies (example loss of medication carries or lowering OAT doses) negatively affect retention in treatment. This is relevant for optimal OUD management, as negative contingencies are often used when patients are “caught” using opioids. It is notable that complete abstinence was rarely achieved even in carefully monitored trials and positive urine samples may be a sign of suboptimal treatment. Best practices need to be carefully balanced with the safety of the patient and public in a non-punitive manner.

Conclusion

Evidence supports primary care as a treatment setting for OUD. While diagnosing OUD remains a challenge for patients on chronic prescription opioids for pain, the POMI may be a useful tool. Buprenorphine and methadone may help patients stay in treatment, particularly if used long-term, although the optimal length of treatment is unknown. The addition of counselling to OAT, even brief, helps patients stay in treatment even longer. Punitive measures

should be avoided for ongoing drug use. Rather, changes to treatment may be required to help the patient reach their treatment goals, or to ensure the safety of the patient and the public.

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Appendix YY=full evidence review

Table XX. Outcomes Considered Relevant for Study Inclusion (outcome hierarchy)

The Outcome	**What the Outcome Includes**
Morbidity and Mortality	Mortality, fatal and nonfatal overdose, suicide, hospitalization/ER visits, and acquiring infection such as Hepatitis B and C.
Societal Outcomes	Crime, incarceration, employment, housing, and transmission of infection such as Hepatitis B and C.
Quality of Life and Symptoms	Incidence of adverse events, withdrawal symptoms, patient satisfaction, quality of life scales, and scales related to guideline question (eg. pain, anxiety).
Opioid Use and Treatment Retention	Ongoing opioid use (from urine toxicology preferentially), and abstinence from opioids.

Box XX. Topics With No or Inconclusive RCT Evidence for Any Outcome

Residential Treatment
Cannabinoids for OUD
Implementation of contract versus usual care
Urine Drug Screening
Tapering to discontinue prescription opioids without OAT
Management of acute pain in patients with OUD
Management of chronic pain in patients with OUD
Management of insomnia in patients with OUD
Management of ADHD in patients with OUD
Management of anxiety in patients with OUD

Table XX. Characteristics of Included Systematic Reviews

Systematic Review	Core Topic	Subgroup	Number of RCTs	Number Observational Studies	Total Patients	Total RCT Patients	Meta-analyses	Modified AMSTAR Score
King 2014	Primary Care	Not Applicable	0	47	NR	0	N	2
Lagisetty 2017	Primary Care	Not Applicable	10	25	7924	NR	N	5
Maree 2016	Primary Care	Not Applicable	1	14	NR	NR	N	4
Simoens 2005	Primary Care	Not Applicable	45 included (study design not reported)	NR	NR	N	3	
Argoff 2013	Diagnosis	Not Applicable	0	50	NR	0	N	1
Balbale 2017	Diagnosis	Not Applicable	0	12	1884	0	N	4
Becker 2013	Diagnosis	Not Applicable	0	14	1754	0	N	5
Blanchard 2016	Diagnosis	Not Applicable	0	14	2278	0	N	2
Canan 2017	Diagnosis	Not Applicable	0	15	190 - 2.3million	0	N	4
Chou 2009	Diagnosis	Not Applicable	0	16	2136	0	N	4
Cochran 2015	Diagnosis	Not Applicable	0	7	134603	0	N	4
Dowell 2016	Diagnosis	Not Applicable	0	6	1339	0	N	5
Lawrence	Diagnosis	Not Applicable	0	34	5234	0	N	6

2017								
Shmulewitz 2015	Diagnosis	Not Applicable	0	NR	11458	0	N	2
Smith 2013	Diagnosis	Not Applicable	0	11	NR	0	N	2
Smith 2015	Diagnosis	Not Applicable	0	6	1036	0	N	2
Solanki 2011	Diagnosis	Not Applicable	0	5	~5000	0	N	2
Turk 2008	Diagnosis	Not Applicable	0	9	16420	0	N	3
Mattick 2014	Pharmacotherapy	Buprenorphine	31	0	5430	5430	Y	6
Neilsen 2016	Pharmacotherapy	Buprenorphine	6	0	607	607	Y	6
Mattick 2009	Pharmacotherapy	Methadone	11	0	1969	1969	Y	6
Jarvis 2018	Pharmacotherapy	Naltrexone (injectable)	12	6	NR	NR	Y	4
Minozzi 2011	Pharmacotherapy	Naltrexone (oral)	13	0	1358	1358	Y	6
Frank 2017	Tapering (Duration of Therapy)	Not Applicable	11	56	12546	NR	N	5
Gowing 2017	Tapering (Duration of Therapy)	Not Applicable	27	0	3048	3048	Y	5
Amato 2011	Psychosocial	All Psychosocial Interventions	35	0	4319	4319	Y	6
Chou 2016	Psychosocial	All Psychosocial Interventions	28 included (study design not reported)		NR	NR	N	4
Gilchrist 2017	Psychosocial	All Psychosocial Interventions	32	0	12840	12840	Y	6
Timko 2016	Psychosocial	All Psychosocial	55 included (study design		NR	NR	N	4

		Interventions	not reported)					
DiClemente 2017	Psychosocial	Motivational Interviewing	34 included (study design not reported)		NR	NR	N	3
Ainscough	Psychosocial	Contingency Management	22	0	2333	2333	Y	4
Davis 2016	Psychosocial	Contingency Management	69 included (study design not reported)		NR	NR	N	1
Dugosh 2016	Psychosocial	Contingency Management	27 included (study design not reported)		NR	NR	N	2
Saulle 2017	Prescribing Practices	Witnessed Ingestion	4	2	7999	707	Y	6
Chou 2014	Prescribing Practices	Urine Drug Screening	0	1	2378	0	N	5
Taveros 2016	Comorbidities	Acute Pain	0	7	142	0	N	5
Morasco 2011	Comorbidities	Chronic Pain	0	38	NR	0	N	5
Hassan 2017	Comorbidities	Anxiety	22	0	1416*	1416	Y	6

*From 19/22 studies reported in systematic review

Table XX. Characteristics of Included Randomized, Controlled, Trials

RCT	Topic	Intervention	Comparator	Number of Patients Randomized	JADAD Score
Carrieri 2014	Primary Care	Methadone maintenance therapy induction in Primary Care	Methadone maintenance therapy induction in Specialty Care	221	2
Fiellin 2001	Primary Care	Methadone maintenance therapy delivered by primary care physician	Methadone maintenance therapy delivered by a narcotic treatment program	46	3
Gibson 2003	Primary Care	Buprenorphine in primary care	Buprenorphine in specialty care	115	2
O'Connor 1998	Primary Care	Buprenorphine delivered through primary care	Buprenorphine delivered in traditional drug treatment program	46	2
Dunlop 2017	Pharmacotherapy	Buprenorphine-naloxone	Waitlist	50	3
Sigmon 2016	Pharmacotherapy	Buprenorphine-naloxone	Waitlist	50	1
Wilson 2010	Pharmacotherapy	Methadone	Waitlist	319	3
Otiashvili 2013	Pharmacotherapy	Buprenorphine-naloxone	Methadone	80	3
Neumann 2013	Pharmacotherapy	Buprenorphine-naloxone	Methadone	54	2
Potter 2013	Pharmacotherapy	Buprenorphine-naloxone	Methadone	1269	2
Coviello 2010	Pharmacotherapy	Oral naltrexone	Treatment as usual	111	1
Krupitsky 2012	Pharmacotherapy	Oral naltrexone+ Placebo implant	Placebo oral naltrexone + placebo implant	306	4
Krupitsky 2013	Pharmacotherapy	Oral naltrexone+ Placebo guanfacine	Placebo oral naltrexone + placebo guanfacine	301	4
Mokri 2016	Pharmacotherapy	Oral naltrexone	Buprenorphine/naloxone	129	5
Springer 2018	Pharmacotherapy	Injectable naltrexone	Placebo	93	4

Bisaga	Pharmacotherapy (Cannabinoids)	Dronabinol	Placebo	60	3
Blondell 2010	Tapering (Duration of Therapy)	Buprenorphine-naloxone taper	Buprenorphine-naloxone stable	12	3
Fiellin 2014	Tapering (Duration of Therapy)	Buprenorphine-naloxone taper	Buprenorphine-naloxone stable	113	3
Marsch 2016	Tapering (Duration of Therapy)	Buprenorphine-naloxone 28-day taper	Buprenorphine-naloxone 56-day taper	53	4
Ling 2009	Tapering (Duration of Therapy)	Buprenorphine-naloxone 7-day taper	Buprenorphine-naloxone 28-day taper	516	2
Sigmon 2013	Tapering (Duration of Therapy)	Buprenorphine-naloxone 1-week taper or Buprenorphine-naloxone 2-week taper	Buprenorphine-naloxone 4-week taper	70	4
Abbott 1998	Psychosocial	Community Reinforcement Approach	Standard Care	180	2
Chawarski 2011	Psychosocial	Counseling + Methadone maintenance therapy	Methadone maintenance therapy	37	2
Fiellin 2006	Psychosocial	Enhanced Medical Management (45-minute counseling sessions)	Standard Management (20-minute sessions)	166	3
Gu 2013	Psychosocial	Counseling + Methadone maintenance therapy	Methadone maintenance therapy	288	2
Liu 2018	Psychosocial	Counseling + Methadone maintenance therapy	Methadone maintenance therapy	125	3
Tetrault 2012	Psychosocial	Enhanced Medical	Standard Management	47	2

		Management (45-minute counseling sessions)	(15-minute counseling sessions)		
Weiss 2011	Psychosocial	Counseling (45-60 minutes)	Standard Management (15-20 minutes)	653	3
Bernstein 2005	Psychosocial	Motivational Interviewing	Standard Care	1175	5
Jaffray 2014	Psychosocial	Motivational Interviewing	Standard Care	542	2
Saunders 1995	Psychosocial	Motivational Interviewing	Education	116	0
Stein 2009	Psychosocial	Motivational Interviewing	Assessment	277	1
Abrahms 1979	Psychosocial	Cognitive Behavioral Therapy	Group Therapy	14	1
Fiellin 2013	Psychosocial	Physician Management + Cognitive Behavioral Therapy	Physician Management	141	3
Ling 2013	Psychosocial	Cognitive Behavioral Therapy	No Behavioral Therapy	104	3
Pan 2015	Psychosocial	Cognitive Behavioral Therapy + Methadone maintenance therapy	Methadone maintenance therapy	240	3
Scherbaum 2005	Psychosocial	Methadone Maintenance Therapy + Group Cognitive Behavioral Therapy	Methadone maintenance therapy	73	3
Abbott 1998	Psychosocial	Methadone + Contingency Management	Methadone with Standard Counseling	166	2
Bickel 2008	Psychosocial	Contingency Management	Standard counseling	135	2

Brooner 2004	Psychosocial	Motivated Stepped Care	Standard Stepped Care	127	1
Chen 2013	Psychosocial	Contingency Management	Usual Care	246	1
Chopra 2009	Psychosocial	Medication contingency with community reinforcement approach	Standard care with counseling	120	2
Chutuape 1999	Psychosocial	Contingency Management	Standard Care	14	3
Chutuape 2001	Psychosocial	Contingency Management	Weekly draws for take-home doses (not contingent)	53	2
DeFulio 2012	Psychosocial	Contingency Management in therapeutic workplace	Therapeutic workplace	38	2
Dunn 2013	Psychosocial	Employment-based contingency	Prescription for naltrexone	67	2
Epstein 2009	Psychosocial	High/Low Dose Methadone maintenance therapy with vouchers	High/Low Dose Methadone maintenance therapy	252	2
Everly 2011	Psychosocial	Contingency Management in therapeutic workplace	Therapeutic workplace	35	2
Ghitza 2008	Psychosocial	Contingency Management	Methadone maintenance therapy	116	1
Gross 2006	Psychosocial	Contingency Management for vouchers OR medication	Buprenorphine Maintenance Therapy with counseling	60	2
Hser 2011	Psychosocial	Incentives	Usual Care	320	2
Iguchi 1997	Psychosocial	Contingency Management	Standard Treatment	103	1

Jiang 2012	Psychosocial	Contingency Management	Usual Care	160	2
Katz 2002	Psychosocial	Vouchers	No Vouchers	52	1
Kidorf 1996	Psychosocial	Contingency Management	Methadone maintenance therapy	16	2
Kidorf 2013	Psychosocial	Reinforced on-site integrated care	Standard care	125	2
Kosten 2003	Psychosocial	Contingency Management	Buprenorphine	160	2
Ling 2013	Psychosocial	Contingency Management + Buprenorphine-naloxone	Buprenorphine-naloxone	202	3
Milby 1978	Psychosocial	Contingency Management	Methadone maintenance therapy	75	2
Neufeld 2008	Psychosocial	Contingency Management	Methadone maintenance therapy	100	1
Oliveto 2005	Psychosocial	Contingency Management	Standard Treatment	140	2
Peirce 2006	Psychosocial	Contingency Management	Standard Care	388	2
Petry 2002	Psychosocial	Contingency Management	Standard Treatment	42	2
Petry 2005	Psychosocial	Contingency Management	Methadone maintenance therapy	77	3
Petry 2007	Psychosocial	Contingency Management	Methadone maintenance therapy	74	2
Preston 2000	Psychosocial	Contingency Management	Methadone maintenance therapy	120	3
Schottenfeld 2005	Psychosocial	Contingency Management (with buprenorphine or	Methadone maintenance therapy OR Buprenorphine	162	3

		methadone)	Maintenance Therapy		
Silverman 2004	Psychosocial	Contingency Management	Methadone maintenance therapy	78	3
Stitzer 1992	Psychosocial	Contingency Management	Methadone maintenance therapy	53	1
Marsch 2014	Psychosocial	Web-based education	Standard Counselling	160	1
Bickel 2008	Psychosocial	Therapist-delivered community reinforcement approach OR Computer-delivered community reinforcement approach	Standard treatment	135	2
Bell 2007	Witnessed Ingestion	Supervised buprenorphine-naloxone (daily, second-daily or thrice-weekly)	Weekly take-home dosing	119	2
Fiellin 2006	Witnessed Ingestion	Enhanced medical management + thrice weekly buprenorphine-naloxone dispensing	Standard medical management + once weekly buprenorphine-naloxone dispensing	166	3
Holland 2012	Witnessed Ingestion	Twice weekly supervised methadone	Daily, unsupervised methadone	60	3
Holland 2014	Witnessed Ingestion	Supervised daily buprenorphine-naloxone	Unsupervised daily buprenorphine-naloxone	293	3
Rhoades 1998	Witnessed Ingestion	Supervised methadone (5 days per week)	Supervised methadone (2 days a week)	107	1
Solhi 2016	Comorbidities (Acute Pain)	Meperidine IV	Morphine IV	122	1
Blondell 2010	Comorbidities (Chronic Pain)	Buprenorphine-Naloxone Steady Dose	Buprenorphine-Naloxone Tapering Dose	12	3

Stein 2012	Comorbidities (Insomnia)	Trazodone	Placebo	137	4
McRae 2004	Comorbidities (Anxiety)	Buspirone	Placebo	36	5
Saedy 2015	Comorbidities (Anxiety)	Acceptance-Commitment Therapy (ACT) + Methadone maintenance therapy	Methadone maintenance therapy online	28	0
Levin 2006	Comorbidities (ADHD)	Sustained release methylphenidate or Sustained release bupropion	Placebo	97	4

Table XX. **RCT Evidence that is Available based on Outcomes.**

Intervention versus Control	Morbidity and Mortality[1]	Societal Outcomes[2]	Quality of Life and Symptoms[3]		Opioid Use and Treatment Retention[4]
Diagnosis/ Screening and Management Setting					
Primary care versus Specialty care	-	-	Primary care better (Patient Preference)		Primary care better
Residential Treatment	-	-	-		-
Medications					
Buprenorphine versus Placebo, detoxification or psychotherapy only	•	•	-	Buprenorphine possibly better (Inconsistent)	Buprenorphine better
Buprenorphine versus Methadone	•	No Difference	No difference (QoL Scales)	Inconclusive (Adverse Events)[5]	Methadone better
Buprenorphine versus Waitlist	•	•	Buprenorphine better (QoL)	Inconclusive (Adverse Events)[5]	Buprenorphine better
Methadone versus no methadone	•	No Difference	-		Methadone better
Oral Naltrexone versus placebo or usual care	-	Naltrexone better (Re-incarceration)	-	No Difference	No Difference
Oral Naltrexone versus buprenorphine	-	-	-	-	Naltrexone worse
Injectable Naltrexone versus placebo or usual care	•	No Difference	•	Naltrexone worse (Adverse Events)[6]	Naltrexone better
Injectable Naltrexone versus buprenorphine	•	-	-	•	No Difference
Dronabinol versus placebo	-	-	•		•
Management Tools					
Implementation of Contract versus Usual care	-	-	-		-
Unsupervised (with up to one week carry) versus Daily or near daily supervised	-	Unsupervised better	No Difference		No Difference
Urine Drug Screening	-	-	-		-
Medication Taper (Discontinuation)					
Tapering off Prescription Opioids without OAT[7]	-	-	-		-
OAT[7]- Tapering off versus OAT[7]- Maintenance	-	-	-		Tapering off worse
Fast versus Slow Taper of OAT[7]	-	-	No Difference		Slow taper better
Psychosocial Interventions in Addition to OAT					
Counseling versus minimal to no counselling	-	-	-		Counselling better
Extended Counseling versus Brief Counseling	-	-	-		No difference

Intervention versus Control	Morbidity and Mortality[1]	Societal Outcomes[2]	Quality of Life and Symptoms[3]	Opioid Use and Treatment Retention[4]
Motivational Interviewing versus Usual Care	-	-	No Difference (QoL)	Motivational Interviewing better
Cognitive Behavioral Therapy versus Usual Care	-	-	-	No difference
Contingency Management versus Usual Care	-	-	-	Positive Contingencies better[8] Medication Contingencies worse[9]
Technology-Based[10] Psychosocial Interventions versus Usual Care	-	-	-	No Difference
Management of Comorbidities in Patients on OAT[7]				
Acute Pain/Chronic Pain/Insomnia/ADHD/Anxiety	-	-	•	•

White - No RCT Evidence Available for this Outcome.
Grey - Inconclusive RCT Evidence Available for this Outcome.
Green – RCT Evidence Suggests Benefit in this Outcome.
Yellow – RCT Evidence Suggests No Difference in this Outcome.
Red - RCT Evidence Suggests Harm in this Outcome.

1 Morbidity and Mortality includes fatal and nonfatal overdose, suicide, hospitalization/ER visits, and infection such as HepB and HepC.
2 Societal Harms include crime, incarceration, employment, housing, and transmission of infection such as HepB and HepC.
3 Quality of Life and Symptoms include incidence of adverse events, withdrawal symptoms, patient satisfaction, quality of life scales, and scales related to guideline question (eg. pain, anxiety).
4 Opioid Use and Treatment Retention includes decreased opioid use (from urine toxicology and self-report), abstinence from opioids, and illicit and other substance abuse.
5 Adverse Events for buprenorphine and methadone were poorly reported and included sedation and changes in liver indices.
6 Adverse Events for naltrexone includes injection site reactions, headache, GI upset, and insomnia.
7 OAT = Opioid Agonist Therapy
8 Positive contingencies was defined as prizes or vouchers for ongoing nonprescribed drug abstinence.
9 Medication contingencies was defined as reduction of OAT dosing and/or loss of take home priveledges for undesirable behaviours.
10 Technology-based psychosocial interventions was defined as the use of established therapeutics tools on a computer or web-based format.

Figure XX, Modified AMSTAR Scores of Included Systematic Reviews

Systematic Review	Dual Selection and Extraction	Comprehensive Literature Search	Characteristics of Included Studies	Quality Assessment of Studies	Pooled Estimates	Conflicts of Interest Stated	AMSTAR (0-6)
Primary Care							
King 2014	1	1	0	0	0	0	2
Lagisetty 2017	1	1	1	1	0	1	5
Maree 2016	0	1	1	1	0	1	4
Simoens 2005	1	1	0	0	0	1	3
Diagnosis/Screening							
Argoff 2013	0	0	0	0	0	1	1
Balbale 2017	1	1	1	0	0	1	4
Becker 2013	1	1	1	1	0	1	5
Blanchard 2016	0	1	1	0	0	0	2
Canan 2017	0	1	1	0	1	1	4
Chou 2009	0	1	1	1	0	1	4
Cochran 2015	1	1	1	0	0	1	4
Dowell 2016	1	1	1	0	1	1	5
Lawrence 2017	1	1	1	1	1	1	6
Shmulewitz 2015	0	1	0	0	0	1	2
Smith 2013	0	1	0	0	0	1	2
Smith 2015	0	1	1	0	0	0	2
Solanki 2011	0	1	0	0	0	1	2
Turk 2008	0	0	1	0	1	1	3
Pharmacotherapy: Buprenorphine Naloxone							
Mattick 2014	1	1	1	1	1	1	6
Neilsen 2016	0	1	1	1	1	1	5
Pharmacotherapy: Methadone							
Mattick 2009	1	1	1	1	1	1	6
Pharmacotherapy: Naltrexone							
Minozzi 2011	1	1	1	1	1	1	6
Jarvis 2018	0	0	1	1	1	1	4
Pharmacotherapy: Cannabinoids							
None							
Witnessed Ingestion/Daily Dispensing							
Saulle 2017	1	1	1	1	1	1	6

Contracts							
Bosch-Capblanch 2007	1	1	1	1	1	1	6
Urine Drug Screening							
Chou 2014	1	1	1	1	0	1	5
Duration of Therapy							
Frank 2017	1	1	1	1	0	1	5
Gowing 2017	0	1	1	1	1	1	5
Psychosocial and Behavioural Therapy							
Ainscough 2017	0	1	0	1	1	1	4
Amato 2011	1	1	1	1	1	1	6
Chou 2016	1	1	1	0	0	1	4
Davis 2016	0	0	0	0	0	1	1
DiClemente 2017	0	1	1	1	0	0	3
Dugosh 2016	0	1	0	0	0	1	2
Gilchrist 2017	1	1	1	1	1	1	6
Timko 2016	1	1	1	0	0	1	4
Comorbidities: Acute Pain							
Taveros 2016	1	1	1	1	0	1	5
Comorbidities: Chronic Pain							
Morasco 2011	1	1	1	1	0	1	5
Comorbidities: ADHD							
None							
Comorbidities: Anxiety							
Hassan 2017	1	1	1	1	1	1	6
Comorbidities: Insomnia							
None							

Figure XX. JADAD Scores for Included RCTs

Randomized Controlled Trial	Was it randomized?	Was randomization process appropriate?	Was it double-blind?	Was blinding process appropriate?	Were drop-outs described?	Deductions (for inappropriate randomization or blinding)	JADAD (0-5)
Primary Care							
Carrieri 2014	1	0	0	0	1	0	2
Fiellin 2001	1	1	0	0	1	0	3
Gibson 2003	1	1	0	0	0	0	2
O'Connor 1998	1	0	0	0	0	0	1
Diagnosis/Screening							
None							
Pharmacotherapy: Buprenorphine Naloxone							
Dunlop 2017	1	1	0	0	1	0	3
Potter 2013	1	0	0	0	1	0	2
Neumann 2013	1	1	0	0	1	-1	2
Otiashvili 2013	1	1	0	0	1	0	3
Sigmon 2016	1	0	0	0	0	0	1
Pharmacotherapy: Methadone							
Wilson 2010	1	1	0	0	1	0	3
Pharmacotherapy: Naltrexone							
Springer 2018	1	1	1	0	1	0	4
Coviello 2010	1	0	0	0	0	0	1
Krupitsky 2012	1	1	1	1	0	0	4
Krupitsky 2013	1	1	1	1	0	0	4
Mokri 2016	1	1	1	1	1	0	5
Pharmacotherapy: Cannabinoids							
Bisaga 2015	1	0	1	1	1	0	4
Witnessed Ingestion/Daily Dispensing							
Bell 2007	1	1	0	0	0	0	2
Fiellin 2006	1	1	0	0	1	0	3
Holland 2012	1	1	0	0	1	0	3
Holland 2014	1	1	0	0	1	0	3
Rhoades 1998	1	0	0	0	0	0	1
Contracts							
None							
Urine Drug Screening							
None							
Duration of Therapy							
Blondell 2010	1	1	0	0	1	0	3
Fiellin 2014	1	1	0	0	1	0	3
Ling 2009	1	1	0	0	0	0	2
Marsch 2014	1	1	1	1	0	0	4
Sigmon 2013	1	1	1	1	0	0	4

Psychosocial and Behavioural Therapy							
Abbott 1998	1	1	0	0	0	0	2
Abrahms 1979	1	0	0	0	0	0	1
Avants 2004	1	1	0	0	1	0	3
Bernstein 2005	1	1	1	1	1	0	5
Bickel 2008	1	1	0	0	0	0	2
Brooner 2004	1	0	0	0	0	0	1
Chawarski 2011	1	1	0	0	0	0	2
Chen 2013	1	0	0	0	0	0	1
Chopra 2009	1	1	0	0	0	0	2
Chutuape 2001	1	1	0	0	0	0	2
Chutuape 1999	1	1	0	0	1	0	3
De Fulio 2012	1	1	0	0	0	0	2
Dunn 2012	1	1	0	0	0	0	2
Epstein 2009	1	1	0	0	0	0	2
Everly 2011	1	1	0	0	0	0	2
Fiellin 2006	1	1	0	0	1	0	3
Fiellin 2013	1	1	0	0	1	0	3
Ghitza 2008	1	0	0	0	0	0	1
Gross 2006	1	0	0	0	1	0	2
Gu 2013	1	1	0	0	0	0	2
Holtyn 2014	1	1	0	0	0	0	2
Hser 2011	1	1	0	0	0	0	2
Iguchi 1997	1	0	0	0	0	0	1
Jaffray 2014	1	0	0	0	1	0	2
Jiang 2012	1	1	0	0	0	0	2
Katz 2002	1	0	0	0	0	0	1
Kidorf 1996	1	0	0	0	1	0	2
Kidorf 2013	1	1	0	0	0	0	2
Kosten 2003	1	0	0	0	1	0	2
Ling 2013	1	1	0	0	1	0	3
Liu 2018	1	1	0	0	1	0	3
Marsch 2014	1	0	0	0	0	0	1
McLellan 1993	1	0	0	0	1	0	2
Milby 1978	1	1	0	0	0	0	2
Neufeld 2008	1	0	0	0	0	0	1
Oliveto 2005	1	0	0	0	1	0	2
Pan 2015	1	1	0	0	1	0	3
Peirce 2006	1	1	0	0	0	0	2
Petry 2002	1	1	0	0	0	0	2
Petry 2005	1	1	0	0	1	0	3
Petry 2007	1	1	0	0	0	0	2
Petry 2010	1	1	0	0	0	0	2
Preston 2000	1	1	0	0	1	0	3

Saunders 1995	1	0	0	0	0	-1	0
Scherbaum 2005	1	1	0	0	1	0	3
Schottenfeld 2005	1	1	0	0	1	0	3
Silverman 2004	1	1	0	0	1	0	3
Stein 2009	1	0	0	0	0	0	1
Stitzer 1992	1	0	0	0	0	0	1
Tetrault 2012	1	0	0	0	1	0	2
Wang 2014	0	0	0	0	0	0	0
Weiss 2011	1	1	0	0	1	0	3
Comorbidities: Acute Pain							
Solhi 2016	1	0	0	0	0	0	1
Comorbidities: Chronic Pain							
Blondell 2010	1	1	0	0	1	0	3
Neumann 2013	1	1	0	0	1	0	3
Weist 2015	1	1	0	0	0	0	2
Comorbidities: ADHD							
Levin 2006	1	0	0	0	1	0	4
Comorbidities: Anxiety							
McRae 2004	1	1	1	1	1	0	5
Comorbidities: Insomnia							
Stein 2012	1	1	1	1	0	0	4

Figure XX. Treatment Retention in Primary Care versus Specialty Care

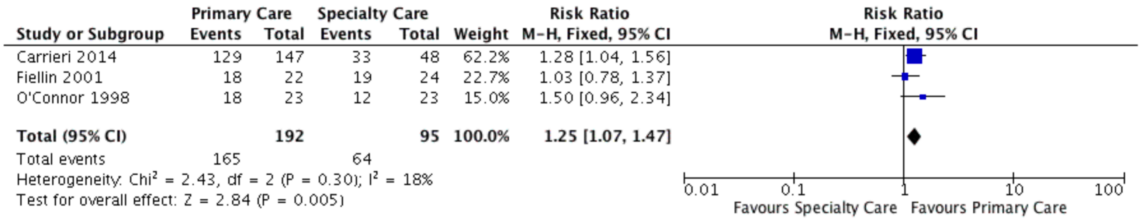

Figure XX. Street Opioid Abstinence in Primary Care versus Specialty Care

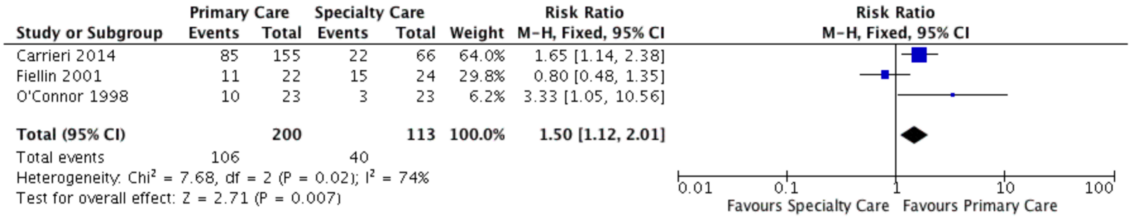

Figure XX. Retention in Treatment. Buprenorphine versus Methadone.

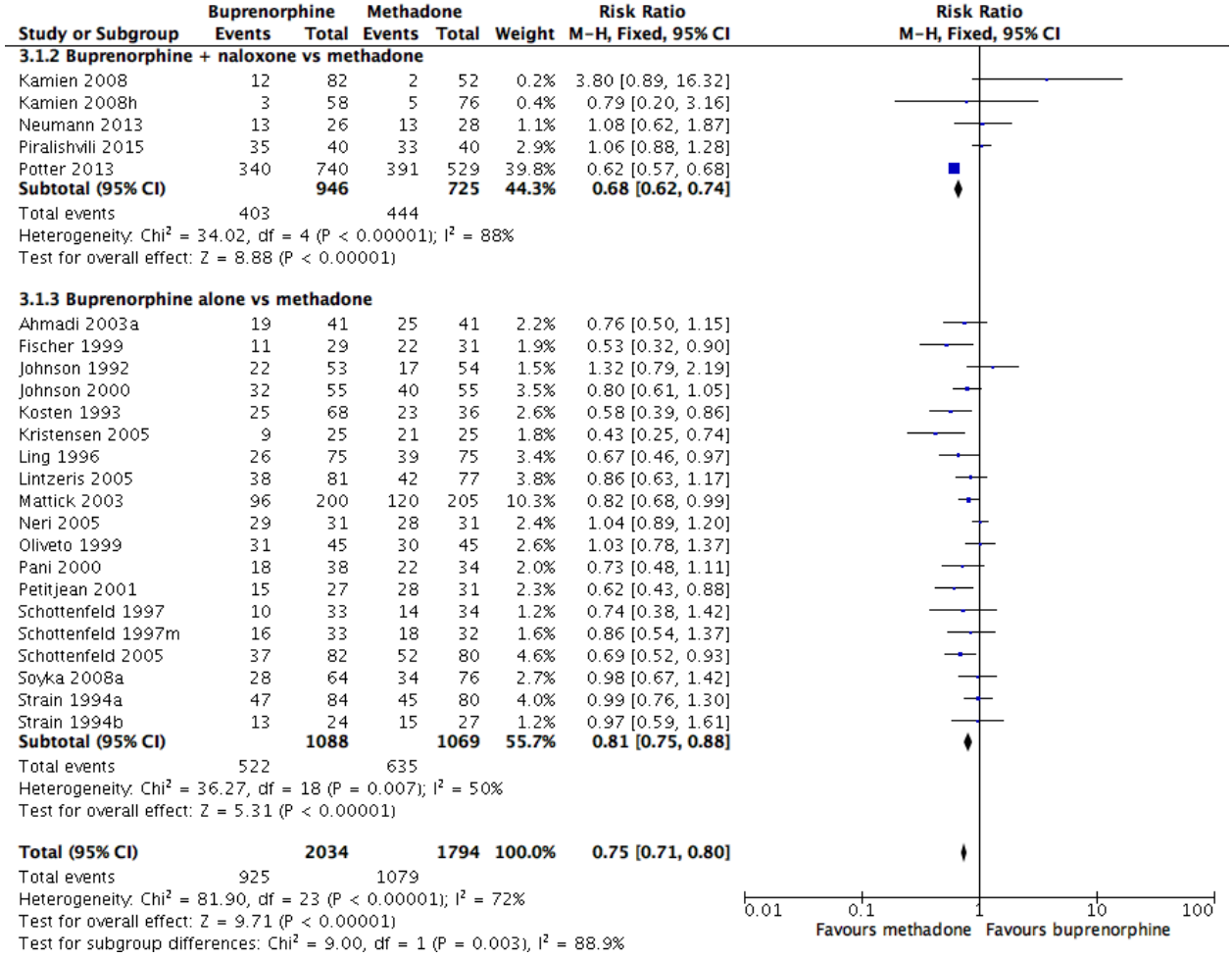

Figure XX. Abstinence. Buprenorphine versus Methadone.

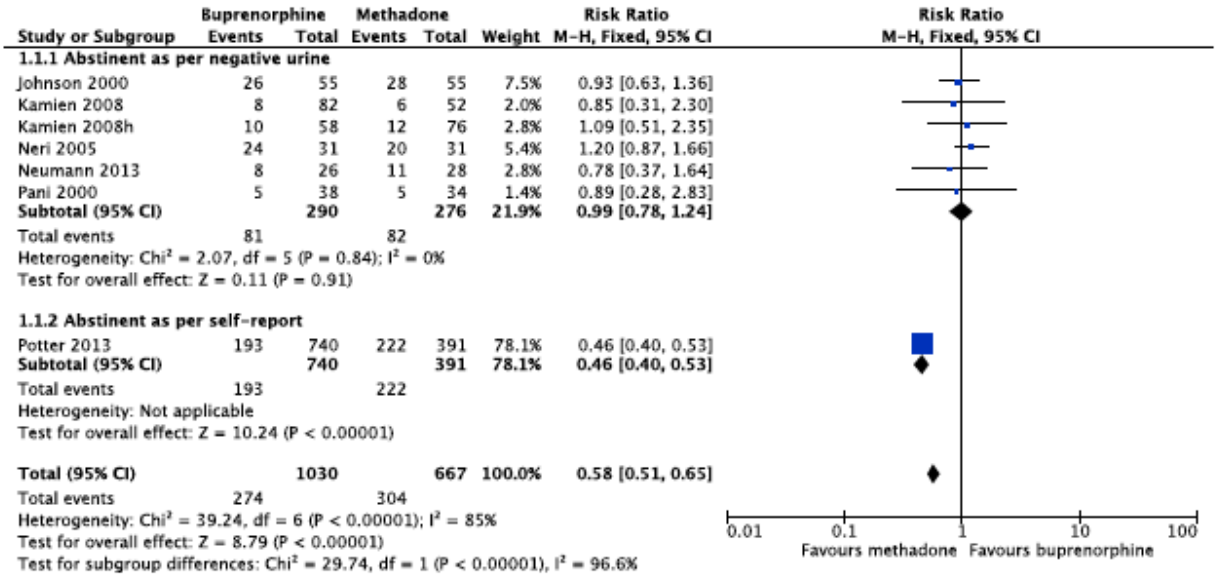

Figure XX. Retention in Treatment. Naltrexone versus placebo or usual care.

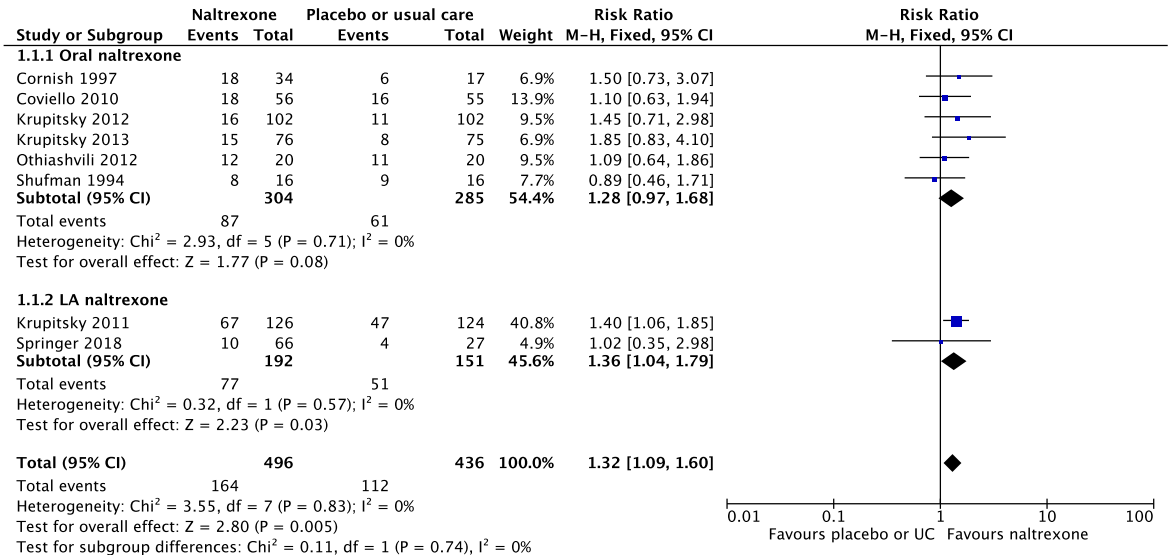

Figure XX. Abstinence. Naltrexone versus Placebo/Usual Care

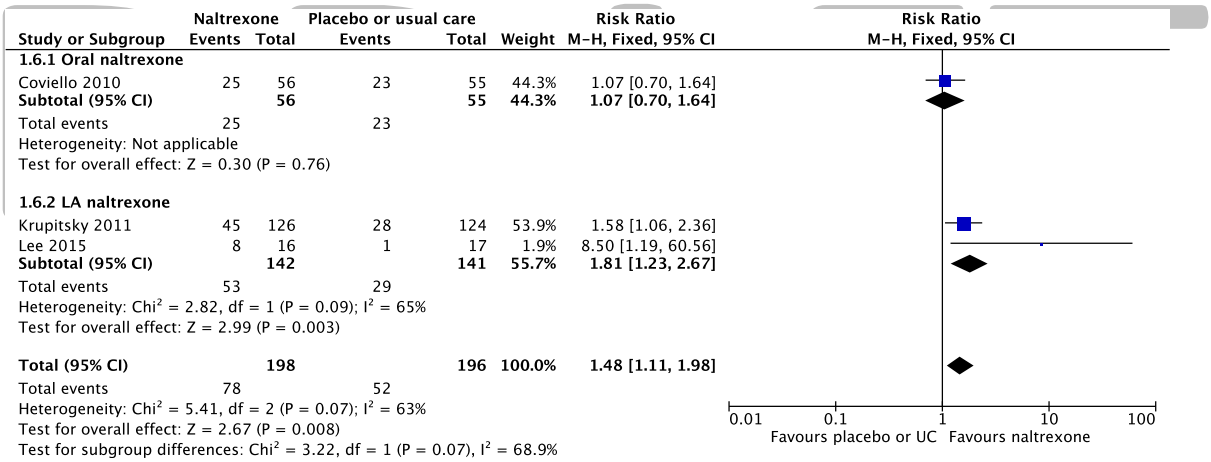

Figure XX. Re-incarceration. Naltrexone versus Placebo/Usual Care

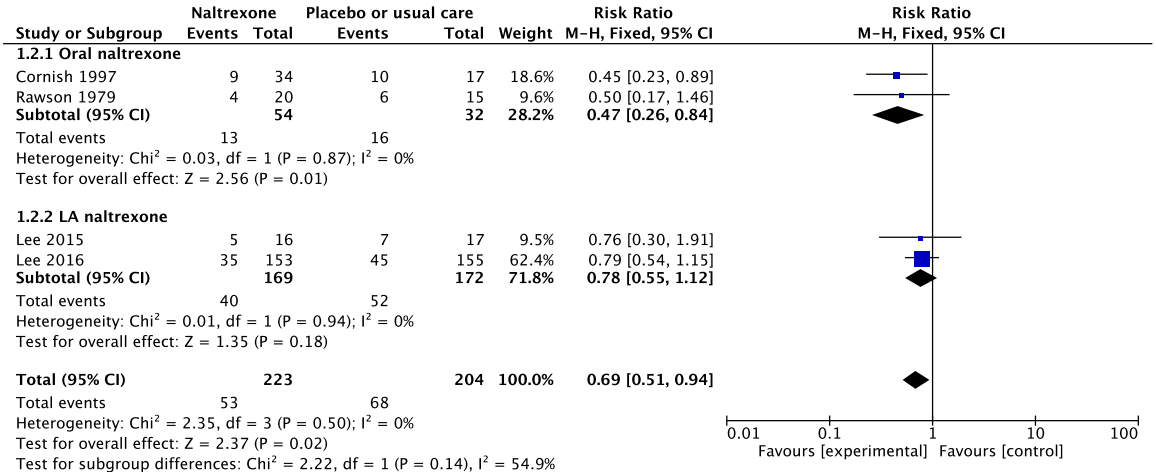

Figure XX. Retention in Treatment. Counselling versus Minimal to No Counselling

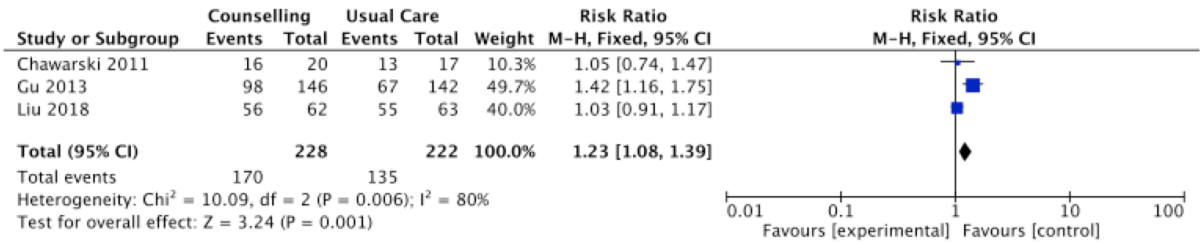

Figure XX. Retention in Treatment. Supervised versus Unsupervised Ingestion

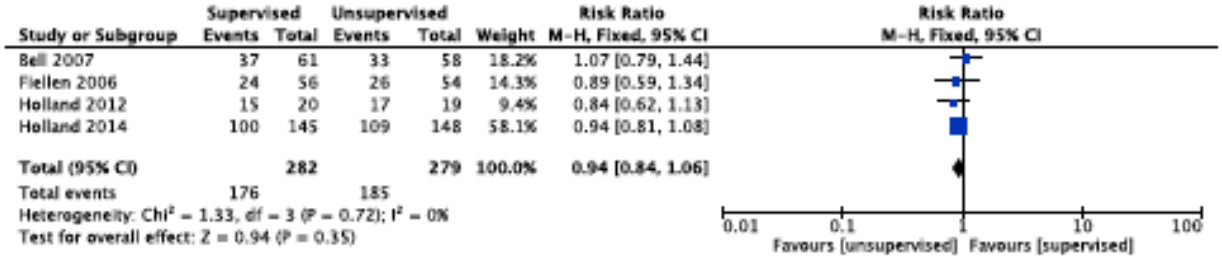

Figure XX. Illicit drug use. Supervised versus Unsupervised Ingestion.

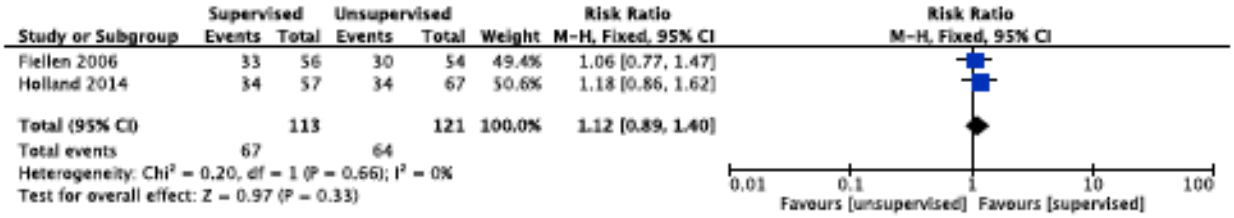

Figure XX. Retention in Treatment. Contingency Management versus No Contingency Management