1 Umbrella Systematic Review of Systematic Reviews of Opioid Use Disorder in

- 2 Primary Care: Setting, Diagnosis, Treatment, and Management of Comorbidities.
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- 5

6 Abstract

- 7 **Objective:** To summarize the best available evidence regarding a variety of topics related to
- 8 primary care management of opioid use disorder (OUD).
- 9 Data Sources: MEDLINE, Cochrane Library, Google, references of included studies and relevant
 10 guidelines.
- 11 Study Selection: Systematic reviews and newer randomized controlled trials (RCTs) from the
- 12 last 5-10 years that investigated patient-oriented outcomes across 23 areas related to:
- 13 managing OUD in primary care, diagnosis, pharmacotherapies (including buprenorphine,
- 14 methadone, and naltrexone), tapering strategies, psychosocial interventions, prescribing
- 15 practices, and management of co-morbidities.
- 16 **Synthesis:** From 8626 articles, 39 systematic reviews and an additional 26 RCTs were included.
- 17 New meta-analyses were performed where possible. RCT evidence was either non-existent or
- 18 inadequate for 10 areas. One cohort study suggests one case-finding tool may be reasonable to
- 19 assist with diagnosis (positive likelihood ratio (10.3). Meta-analysis demonstrated that
- 20 retention in treatment improves: 1) when buprenorphine or methadone are used (65-70%
- 21 versus 22-40% control), 2) when OUD is treated in primary care [86% versus 67% specialty care,
- 22 RR 1.25 (95%Cl 1.07, 1.47)], and 3) when counselling is added to pharmacotherapy [75% versus
- 23 61% control, RR 1.23 (95%Cl 1.08,1.39)]. Retention was also improved with naltrexone [33%
- versus 26% control, RR 1.32 (95%Cl 1.09, 1.60)], and reduced with medication-related
- 25 contingency management (example: loss of take-home doses as a punitive measure) [68%
- 26 versus 77% no contingency, RR 0.86 (95%Cl 0.76-0.98)].
- 27 **Conclusion:** There is reasonable evidence that primary care should manage patients with OUD.
- 28 Diagnostic criteria for OUD remain elusive, with 1 reasonable case-finding tool. Methadone and
- 29 buprenorphine improve treatment retention, both are better than naltrexone, and all should be
- 30 continued long-term. Counselling is beneficial when added to pharmacotherapy.
- 31
- 32 33

37 Introduction

38 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 39 40 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 41 42 their broad scope of practice, primary care clinicians require information on all aspects of 43 OUD management (examples contracts and urine drug screens), and management of 44 comorbidities (examples anxiety and pain). In some cases, they might have limited access 45 to more specialized, wrap-around services available in larger and more specialized centres, 46 furthering the need for accessible evidence-based information. 47 We completed 16 systematic reviews to answer key questions regarding 48 management of OUD that are relevant to primary care according to a committee tasked 49 with writing a OUD guideline for primary care,⁴ related to: 50 1) Treatment Setting 51 a. The management of OUD in primary care 52 b. Residential treatment programs 53 2) Diagnosis of OUD 54 3) Treatment 55 a. Pharmacotherapeutic management of OUD, including buprenorphine, methadone, naltrexone and cannabinoids 56 b. Tapering off of drug therapy in OUD: 57 58 i. Tapering off opioids, Tapering off opioid agonist therapy (OAT)compared to long-term 59 ii. maintenance, 60 iii. In patients discontinuing OAT, comparing fast and slow tapering 61 regimens. 62 c. Psychosocial interventions for OUD 63 i. Counselling 64 ii. Motivational interviewing 65 iii. Cognitive Behavioral Therapy (CBT) 66 iv. Contingency Management 67 v. Technology-based psychosocial interventions 68 d. Prescribing practices, including use of daily witnessed ingestion, urine 69 70 drug screening and contracts. 4) Management of comorbidities in patients with OUD (acute pain, chronic pain, 71 72 insomnia, anxiety and ADHD). Two additional topics (the use of sustained release oral morphine and the role of 73 74 OAT without any additional supports) were also investigated with an abbreviated systematic search. Results are available in Appendix YY. 75 76 77 Methods 78 To complete this review, we followed the Preferred Reporting Items for Systematic 79 Reviews and Meta-Analyses (PRISMA) and the systematic review of systematic reviews 80 protocol.^{5,6}

82

83 Data Sources

84 The evidence team created a search strategy with guidance from an experienced 85 librarian for each of the clinical questions created. Two authors (DP, JT) performed the search 86 of systematic reviews and randomized, controlled trials (RCTs) for each clinical question with no 87 language restrictions. The search was restricted to non-animal studies. The databases and 88 resources used to search for relevant systematic reviews included MEDLINE, Cochrane Library, 89 Google, published guidelines on opioid use disorder and reference lists of the included 90 systematic reviews. The search included any articles up to June 2018, but was generally limited 91 to the last 5-10 years. Keywords of "opioid or opiate" were used for all searches. Specifics for 92 each question and the corresponding keywords, timelines, and search strategies used can be 93 found in Appendix YY (full evidence review). After the search for systematic reviews was 94 complete, an additional search of Medline was undertaken to find RCTs published since the 95 most recent systematic review for each clinical question. Reference lists of included articles 96 were hand searched to identify potentially missed articles.

97

98 Study Selection

99 Beyond systematic reviews and newer RCTs, inclusion criteria were adult patients with 100 opioid use disorder reporting on at least one of the following outcomes: morbidity and 101 mortality, social outcomes, quality of life and symptoms, or opioid use outcomes (definitions in 102 Box XX). Systematic reviews of observational studies were included, although observational 103 data was only utilized when RCTs did not exist. Exclusion criteria were studies on detoxification 104 from opioids, studies in pediatric, pregnant or cancer patients, and studies completed within a 105 prison setting. Any exceptions made were recorded (Appendix YY).

106Dual title, abstract, and full-text review were completed for all systematic review and107RCT searches to determine study eligibility. A single reviewer assessed titles and abstracts from108guidelines and reference lists, with dual assessment if full-text review was required.

109 Disagreements over inclusion were resolved by consensus.

- 110
- 111 Synthesis
- 112 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.

- 124
- 125 Risk-of-bias assessment

- 126 Risk-of-bias was assessed using a modified AMSTAR rubric for systematic reviews,
- 127 focusing on the six most relevant questions:^{7,8} 1) Was study selection and data extraction
- 128 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
- 130 reported: 5) were the methods used to combine results appropriate? 6) was connect of 131 interest reported? For systematic reviews, each question was scored as 1 (completed) or 0 (not
- 132 completed). These individual scores were then summated with a higher total score suggesting a
- 133 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
- 136 reported in conjunction with their associated study in the data tables (Appendix XX).
- 137

138 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.

146

147 Performing New Meta-Analysis

If no relevant meta-analyses existed or if relevant RCTs had been published since the 148 149 most recent systematic review, a new meta-analysis was completed using the RevMan 5 150 software. We used a Mantel-Haenszel statistical method and focused on reporting risk ratios 151 when appropriate. Not wanting to overweigh smaller studies, we chose a fixed effects analysis 152 if there was no reason to speculate that the effect of the intervention would deviate 153 meaningfully between studies. Additionally, we performed an exploratory meta-analysis of the 154 effects on buprenorphine, methadone and naltrexone on mortality. Due to the low event rate, 155 mortality events from the 3 treatments were combined and meta-analyzed using the exact method with odds ratios.¹⁰ 156

157

158 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.

169 No RCT Data Available

- 170 Overall, 10 topics had either no RCT data available for the specified outcomes, or the 171 data was considered inconclusive (Table XX). No topic had RCT data to support all outcomes, 172 and no individual topic provided adequate data on morbidity and mortality.
- 173

174 Treatment Setting

175 No systematic review was available, however four RCTs were identified that compared 176 the management of OUD in primary care compared to specialty care (n=46-221). Three of these 177 looked at patient satisfaction rates and found statistically significantly higher rates (ie. more 178 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 179 67% in a specialty clinic [Risk Ratio (RR) 1.25, p = 0.005 (95%Cl 1.07 to 1.47) I² = 18%). Figure 180 181 XX. Street opioid abstinence was also higher in primary care settings (53% versus 35%, (RR 1.50, 182 p = 0.007, 95%CI 1.12 to 2.01, $I^2 = 74\%$), although this included both self-reported as well as 183 urine drug screen data. Figure XX.

- 184
- 185 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 6question 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.

192	Treatment	
193	a. Pharn	nacotherapy
194	I.	Buprenorphine
195		We found 2 systematic reviews and an additional 5 RCTs (as 8 publications) of
196		buprenorphine alone or combined with naloxone. Compared to
197		placebo/detoxification only/psychotherapy, buprenorphine significantly retained
198		more patients in treatment (65% versus 40% control, number needed to treat
199		(NNT)=4 at 22 weeks) (see, ref YY).
200		
201	١١.	Methadone
202		One systematic review and 1 RCT of methadone were found. Retention in
203		treatment was higher with methadone compared to no methadone (73% versus
204		22% control, NNT=2 at 16 weeks) (see ref YY).
205		
206		Our meta-analysis of 24 RCTs directly comparing buprenorphine to methadone
207		revealed higher retention rates with methadone [45% versus 60% methadone,
208		NNT=7, RR 0.75 (0.71, 0.80)]. Figure XX. However, substantial heterogeneity was
209		present (I ² =72%) due to the inclusion of 1 open-label RCT designed to compare
210		the effects of buprenorphine and methadone on liver indices. This also differed
211		from Neilsen's systematic review that found no difference in retention rates
212		between buprenorphine and methadone. ¹¹ Neilsen's systematic review meta-

213		analyzed sub-groups of patients from 3 of the above studies who used
214		prescription opioids, rather than heroin. ¹¹
215		
216		Overall, opioid abstinence appears higher with methadone than buprenorphine
217		(Figure XX). However, there was a statistically significant difference between
218		subgroups of studies that measured abstinence objectively and those that relied
219		on self-report (P<0.00001). If only studies that used objective measures are
220		included, there is no difference in abstinence between buprenorphine and
221		methadone [RR 0.99 (0.78, 1.24), I^2 =0].
222		methadone [mt 0.55 (0.76, 1.24), 1 =0].
223		Advarce offects were nearly reported in both the hyproperphise and methodope
		Adverse effects were poorly reported in both the buprenorphine and methadone
224		literature. Two RCTs found no difference between drugs, except for more
225		sedation with methadone (58% versus 26% buprenorphine), in 1 RCT. Two RCTs
226		found fewer adverse effects with buprenorphine than controls.
227		
228		III. Naltrexone
229		Two systematic reviews and 6 RCTs were found on the opioid antagonist
230		naltrexone. Indirect comparison reveals lower rates of retention than OATs, but
231		naltrexone is still better than placebo or usual care [33% versus 26% control, RR
232		1.32 (1.09, 1.60)]. Although subgroup analysis of oral naltrexone was not
233		statistically significant [RR 1.28 (0.97, 1.68)], it was numerically similar to the
234		injectable results, and the test for subgroup differences between oral and
235		injectable forms was not significant (P=0.74). Naltrexone also increased
236		abstinence from opioids [39% versus 27% control, RR 1.48 (95%Cl 1.11, 1.98)]
237		(Figure XX). Based on 4 small RCTs, naltrexone decreases re-incarceration [24%
238		versus 33% control, RR 0.69 (95%Cl 0.51, 0.94)] (figure XX).
239		
235		Since mortality rates were very low across buprenorphine, methadone and
240		naltrexone studies, we performed an exploratory meta-analysis combining event
241		
		rates for all 3 drugs and found a statistically significant reduction in overall
243		mortality with the use of pharmacotherapy in patients with OUD [Odds
244		Ratio=0.29 (95%Cl 0.08, 0.88), 6 RCTs].
245		
246	b.	Tapering
247		There were no systematic reviews or RCTs of tapering off of opioids versus the use of
248		OAT for treating OUD. Two RCTs compared tapering off of OAT compared to long-term
249		maintenance. Abstinence was not reported; however, the group that was maintained
250		on treatment had a greater number of opioid-negative urines in 1 RCT (53% versus 35%
251		tapered, significance not reported) (ref YY).
252		
253	c.	Psychosocial Supports
254		Eight systematic reviews were identified on psychosocial supports. There was
255		substantial variation with regards to inclusion criteria and analysis, thus we prioritized 5
256		key interventions and assessed individual RCTs identified from the systematic reviews.
		· · · ·

257	The addition of standard counselling to OAT is more effective in retaining people
258	in treatment than no or minimal counselling [75% versus 61% control, RR 1.23 (95%Cl
259	1.23, 1.39), NNT=8, 3 RCTs], although the heterogeneity was high (I^2 =80%). No
260	difference was noted between extended counseling sessions (45-60 mins) compared to
260	"standard" sessions of 15-20 mins) [RR 0.93 95%CI 0.68, 1.26)].
261	
	The use of contingency Management, defined as either "rewards" for desired
263	behaviour, (example: vouchers or prizes) or loss privileges for undesired behavior
264	(example: loss of medication carries for positive urine drug screens), increases retention
265	in treatment [RR 1.11 (95%CI 1.06, 1.17)] (Figure XX). Subgroup analysis suggests the
266	benefits are primarily from positive contingencies [RR 1.15 (95%CI 1.09, 1.21)], with
267	negative or medication related contingencies worsening retention [RR 0.86 (95%CI 0.76,
268	0.99)] (test for subgroup difference P<0.0001). Methods of reporting opioid use were
269	too heterogeneous to be meta-analyzed.
270	
271	d. Prescribing Practices
272	I. Contracts
273	All RCTs of contracts in patients with OUD incorporated contingency
274	management. Therefore, it is not possible to differentiate the effects of
275	contracts from the contingencies on patient outcomes.
276	
277	II. Daily Witnessed Ingestion ("carries")
278	Both treatment retention and continued drug use are no different between daily
279	witnessed and unsupervised ingestion (Figures XX and XX). However, none of
280	the included RCTs had a completely unsupervised arm; rather, they compared
281	various levels of supervision (example 2 versus 5 times per week).
282	
283	III. Urine Drug Screening
284	No RCTs were found. One retrospective cohort study found all-cause mortality
285	was lower in patients who underwent urine testing [Hazard Ratio 0.33 (95%CI
286	0.22, 0.49)]. However, this finding has significant potential for bias.
287	
288	Management of Comorbidities in Patients with OUD
289	There was inadequate RCT evidence in all searched areas (Appendix YY).
290	
291	Results of other systematic reviews, such as residential treatment, cannabinoids, fast versus
292	slow tapering, motivational interviewing, cognitive behavioural therapy and technology-based
293	psychosocial interventions are available in Appendix YY.
294	
295	Discussion
296	There is a surprising lack of RCT data for a variety of topics important to the
297	management of OUD in primary care. Of the 23 areas investigated, 10 had either no RCT
298	evidence or RCT evidence that was impossible to make conclusive statements on.
299	While systematic reviews of observational data suggest that ongoing use of OAT results
300	in a reduction in mortality, ^{12,13} we found no RCT powered to investigate this outcome. Our

301 exploratory meta-analysis of the combined effects of buprenorphine, methadone and 302 naltrexone suggests that medication-assisted treatment may reduce mortality. However, 303 adequately powered RCTs are needed for confirmation. Methadone is superior to 304 buprenorphine for treatment retention, but opioid abstinence rates do not differ between 305 methadone and buprenorphine when objective reporting measures are used. The majority of 306 patients in pharmacotherapy studies were using heroin, not prescription opioids. Thus, 307 outcomes in patients using prescription opioids may vary from what we have reported. One 308 small meta-analysis using subgroups of patients on prescription opioids found no difference in 309 retention rates between the 2 drugs. Some provinces maintain prescribing restrictions on 310 methadone, and methadone typically requires more supervision to achieve therapeutic doses. 311 RCTs of naltrexone typically only included patients who had undergone complete detoxification 312 off of opioids before enrollment. This drastically limits its use as a first-line agent in primary 313 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).

323 Our results for counselling and contingency management differ significantly from other 324 systematic reviews. The most frequently cited systematic review of contingency management 325 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 326 disciplinary measure, it may be more appropriate to meta-analyze positive and negative 327 328 contingencies separately. When analyzed separately, positive contingencies (example being 329 given the opportunity to work on days where urine drug screens are negative) are noted to 330 improve treatment retention, whereas negative or medication related contingencies (example 331 loss of medication carries or lowering OAT doses) negatively affect retention in treatment. This 332 is relevant for optimal OUD management, as negative contingencies are often used when 333 patients are "caught" using opioids. It is notable that complete abstinence was rarely achieved 334 even in carefully monitored trials and positive urine samples may be a sign of suboptimal 335 treatment. Best practices need to be carefully balanced with the safety of the patient and 336 public in a non-punitive manner.

337

338 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 344 should be avoided for ongoing drug use. Rather, changes to treatment may be required to help

- 345 the patient reach their treatment goals, or to ensure the safety of the patient and the public.
- 346

347 **References**:

348 1. Special Advisory Committee on the Epidemic of Opioid Overdoses. National report: 349 Apparent opioid-related deaths in Canada (January 2016 to March 2018) Web-based 350 Report. Ottawa: Public Health Agency of Canada; September 2018. 351 2. Government of Canada. Strengthening Canada's approach to substances use issues. 352 https://www.canada.ca/en/health-canada/services/substance-use/canadian-drugs-353 substances-strategy/strengthening-canada-approach-substance-use-issue.html, 354 Government of Canada. 3. Bruneau J, Ahamad K, Goyer M, et al. Management of opioid use disorders: a national 355 356 clinical practice guideline. CMAJ. 2018; 190: E247-57. 357 4. The Guideline. TBD. 358 5. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred Reporting Items for 359 Systematic Reviews and Meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535. 360 6. Smith V, Devane D, Begley CM, Clarke M. Methodology in conducting a systematic 361 review of systematic reviews of healthcare interventions. BMC Med Res Methodol. 362 2011;11:15. 363 7. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic 364 365 reviews.BMC Med Res Methodol. 2007 Feb 15;7:10. 366 8. Allan GM, Finley CR, Ton J, Perry D, Ramji J, Crawford K, et al. Systematic review of 367 systematic reviews for medical cannabinoids: Pain, nausea and vomiting, spasticity, and 368 harms. Can Fam Physician. 2018 Feb;64(2):e78-e94. 369 9. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds JM, Gavaghan DJ, et al. Assessing the 370 Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? Control Clin Trials. 371 1996 Feb;17(1):1-12. 372 10. Mehta CR, Patel NR, Gray R. Computing and exact confidence interval for the common 373 odds ratio in several 2 X 2 contingency tables. JASA. 1985: 80: 969-73. 374 11. Neilsen S, Larance B, Degenhardt L, Kehler C, Lintzeris N. Opioid agonist treatment for 375 pharmaceutical opioid dependent people. Cochrane Database System Rev. 2016; 376 5:CD011117. 377 12. Ma J, Bao YP, Wang RJ, Su MK, Liu MX, Li JQ, et al. Effects of medication-assisted 378 treatment on mortality among opioid users: a systematic review and meta-analysis. Mol 379 Psychiatry. 2018 Jun 22 [Epub ahead of print]. 380 13. Sordo L, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, et al. Mortality risk 381 during and after opioid substitution treatment: systematic review and meta-analysis of 382 cohort studies. BMJ. 2017;357:i1550. 383 14. Ton J, Korownyk C, Allan GM. Does this patient taking prescription opioids have opioid 384 use disorder? Tools for Practice #222 online publication. October 22, 2018. Available 385 at: https://gomainpro.ca/wp-content/uploads/tools-for-386 practice/1539789463 tfp222opioidscreeningfv.pdf Accessed 31-JAN-2019.

387 15. Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial combined with agonist
 388 maintenance treatments versus agonist maintenance treatments alone for treatment of
 389 opioid dependence. Cochrane Database Syst Rev. 2011 Oct 5;(10):CD004147.
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 391

DRAFT

392 Appendix YY=full evidence review

395 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.

398 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	

Systematic	Core Topic	Subgroup	Number	Number	Total	Total	Meta-	Modified
Review			of RCTs	Observational	Patients	RCT	analyses	AMSTAR
				Studies		Patients		Score
King 2014	Primary Care	Not Applicable	0	47	NR	0	Ν	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	NR	NR	N	3	
			not reported)					
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	Ν	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	Ν	6

Table XX. Characteristics of Included Systematic Reviews

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 include not report	d (study design ed)	NR	NR	N	4
Gilchrist 2017	Psychosocial	All Psychosocial Interventions	32	0	12840	12840	Y	6
Timko 2016	Psychosocial	All Psychosocial	55 include	d (study design	NR	NR	Ν	4

		Interventions	not reporte	ed)				
DiClemente 2017	Psychosocial	Motivational Interviewing	34 included not reported	d (study design ed)	NR	NR	N	3
Ainscough	Psychosocial	Contingency Management	22	0	2333	2333	Y	4
Davis 2016	Psychosocial	Contingency Management	69 included not reporte	d (study design ed)	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	Ν	5
Morasco 2011	Comorbidities	Chronic Pain	0	38	NR	0	N	5
Hassan 2017	Comorbidities	Anxiety	22	0	1416*	1416	Υ	6

*From 19/22 studies reported in systematic review

RCT	Торіс	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

Table XX. Characteristics of Included Randomized, Controlled, Trials

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

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

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

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

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



Intervention versus Control	of Life nptoms ³	Opioid Use and Treatment Retention ⁴			
	Diagnosi	s/ Screening and Mar	agement Setting		
Primary care versus Specialty care	-	-	Primary ca (Patient Pr	are better reference)	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 To	ols		
Implementation of Contract versus Usual care	-	-	-	-	-
Unsupervised (with up to one week carry) versus Daily or near daily supervised	-	Unsupervised better	No Diff	erence	No Difference
Urine Drug Screening	-	-	-		-
	Me	edication Taper (Disco	ntinuation)		·
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 Diff	erence	Slow taper better
	Psychos	ocial Interventions in	Addition to OAT		
Counseling versus minimal to no counselling	-	-	-	•	Counselling better
Extended Counseling versus Brief Counseling	-	-	-	-	No difference

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
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
	Managem	ent of Comorbidities i	n Patients on OAT $'$	
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, Gl 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.

		VISTAR Scores o	-		1	Conflicto					
Systematic	Dual	Comprehensive	Characteristics	Quality	Pooled	Conflicts	AMSTAR				
Review	Selection	Literature	of Included	Assessment	Estimates	of	(0-6)				
	and	Search	Studies	of Studies		Interest					
	Extraction					Stated					
		1	Primary Care			1					
King 2014	1	1	0	0	0	0	2				
Lagisetty	1	1	1	1	0	1	5				
2017											
Maree 2016	0	1	1	1	0	1	4				
Simoens	1	1	0	0	0	1	3				
2005											
Diagnosis/Screening											
Argoff 2013	0	0	0	0	0	1	1				
Balbale	1	1	1	0	0	1	4				
2017											
Becker	1	1	1	1	0	1	5				
2013					-		-				
Blanchard	0	1	1	0	0	0	2				
2016	C C	-	-	C C	· ·		_				
Canan 2017	0	1	1	0	1	1	4				
Chou 2009	0	1	1	1	0	1	4				
Cochran	1	1	1	0	0	1	4				
2015	-		-	Ŭ	Ū						
Dowell	1	1	1	0	1	1	5				
2016	+		-	Ŭ	-	-					
Lawrence	1	1	1	1	1	1	6				
2017	-	-	-		-	-	Ŭ				
Shmulewitz	0	1	0	0	0	1	2				
2015	U	-	Ŭ	Ŭ	Ű	-	-				
Smith 2013	0	1	0	0	0	1	2				
Smith 2015	0	1	1	0	0	0	2				
Solanki	0	1	0	0	0	1	2				
2011	Ŭ	-	Ū	Ũ	Ū	-	2				
Turk 2008	0	0	1	0	1	1	3				
	0		I herapy: Buprenor			L T					
Mattick	1					1	6				
2014	1	1	1	1	1	1	Ū				
Neilsen	0	1	1	1	1	1	5				
Nellsen 2016	0	L T	L L	1	L L		5				
2010	I	Dh -	rmacatheres	thadana			<u> </u>				
	1		rmacotherapy: Me		1	1	C				
Mattick	1	1	1	1	1	1	6				
2009											
N A ¹			rmacotherapy: Na								
Minozzi	1	1	1	1	1	1	6				
2011							-				
Jarvis 2018	0	0	1	1	1	1	4				
	1	Phar	macotherapy: Can	nabinoids			1				
None											
			sed Ingestion/Dail	y Dispensing		•					
Saulle 2017	1	1	1	1	1	1	6				

Figure XX, Modified AMSTAR Scores of Included Systematic Reviews

			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				
		Psychos	ocial and Behavio	ural 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				
		C	omorbidities: Acut	e Pain							
Taveros 2016	1	1	1	1	0	1	5				
		Co	morbidities: Chroi	nic Pain							
Morasco 2011	1	1	1	1	0	1	5				
1	1		Comorbidities: Al	OHD							
None											
	1		Comorbidities: An	xiety							
Hassan 2017	1	1	1	1	1	1	6				
			Comorbidities: Inso	omnia							
None											

Randomized	Was it	Was	Was it	Was blinding	Were	Deductions	JADAD
Controlled	randomized?	randomization	double-	process	drop-outs	(for	(0-5)
Trial	randomizeu:	process	blind?	appropriate?	described?	inappropriate	(0-5)
IIIdi			Dinu:	appropriate:	described!	randomization	
		appropriate?					
			Prim	ary Care		or blinding)	
Carrieri 2014	1	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	1	0	0	0	0	0	1
1998	-	Ũ	Ũ	Ũ	Ũ	Ū	-
2000			Diagnosi	s/Screening			
None							
	•	Pharmaco	therapy: B	uprenorphine Nal	oxone	•	
Dunlop 2017	1	1	0	0	1	0	3
Potter 2013	1	0	0	0	1	0	2
Neumann	1	1	0	0	1	-1	2
2013							
Otiashvili	1	1	0	0	1	0	3
2013							
Sigmon 2016	1	0	0	0	0	0	1
		Pha	armacothe	apy: Methadone			
Wilson 2010	1	1	0	0	1	0	3
		Ph	armacothe	rapy: 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	1	1	1	1	0	0	4
2013							
Mokri 2016	1	1	1	1	1	0	5
			rmacothera	py: Cannabinoids		1	1
Bisaga 2015	1	0	1	1	1	0	4
	1			ion/Daily Dispens		1	1
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
None			Cor	ntracts			
None			Liring D-	Ig Screening			
None				ig Juleelillig			
	1	1	Duration	of Therapy	1	1	1
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
SIGILIOU ZOTO	L	T	1	L 1	U	U	4

Figure XX. JADAD Scores for Included RCTs

		Psycho	social and I	Behavioural Thera	ру		
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	1	1	1	1	1	0	5
2005							
Bickel 2008	1	1	0	0	0	0	2
Brooner 2004	1	0	0	0	0	0	1
Chawarski	1	1	0	0	0	0	2
2011							
Chen 2013	1	0	0	0	0	0	1
Chopra 2009	1	1	0	0	0	0	2
Chutuape	1	1	0	0	0	0	2
2001							
Chutuape	1	1	0	0	1	0	3
1999							
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 Ghitza 2008	1	1	0	0	1	0	3
Gross 2008	1	0	0	0	1	0	2
Gross 2008 Gu 2013	1	1	0	0	0	0	2
Holtyn 2014	1	1	0	0	0	0	2
Holtyn 2014 Hser 2011	1	1	0	0	0	0	2
lguchi 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 Kidorf 2013	1	0	0	0	1 0	0	2
Kidori 2013 Kosten 2003	1	0	0	0	1	0	2
Ling 2013	1	1	0	0	1	0	3
Ling 2013	1	1	0	0	1	0	3
Marsch 2014	1	0	0	0	0	0	1
McLellan	1	0	0	0	1	0	2
1993	-			5	÷	5	~
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	1	0	0	0	0	-1	0			
1995										
Scherbaum	1	1	0	0	1	0	3			
2005										
Schottenfeld	1	1	0	0	1	0	3			
2005										
Silverman	1	1	0	0	1	0	3			
2004										
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			
		C	omorbiditie	es: Chronic Pain			_			
Blondell 2010	1	1	0	0	1	0	3			
Neumann	1	1	0	0	1	0	3			
2013										
Weist 2015	1	1	0	0	0	0	2			
			Comorbic	lities: ADHD			_			
Levin 2006	1	0	0	0	1	0	4			
			Comorbid	ties: Anxiety						
McRae 2004	1	1	1	1	1	0	5			
			Comorbidit	ies: Insomnia			_			
Stein 2012	1	1	1	1	0	0	4			

Figure XX. Treatment Retention in Primary Care versus Specialty Care

	Primary	Care	Specialty	Care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Carrieri 2014	129	147	33	48	62.2%	1.28 [1.04, 1.56]	
Fiellin 2001	18	22	19	24	22.7%	1.03 [0.78, 1.37]	+
O'Connor 1998	18	23	12	23	15.0%	1.50 [0.96, 2.34]	
Total (95% CI)		192		95	100.0%	1.25 [1.07, 1.47]	◆
Total events	165		64				
Heterogeneity. $Chi^2 =$	2.43, df =	= 2 (P =	0.30); l ² :	= 18%			0.01 0.1 1 10 100
Test for overall effect:	Z = 2.84	(P = 0.	005)				Favours Specialty Care Favours Primary Care

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

	Primary	Care	Specialty	Care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Carrieri 2014	85	155	22	66	64.0%	1.65 [1.14, 2.38]	
Fiellin 2001	11	22	15	24	29.8%	0.80 [0.48, 1.35]	
O'Connor 1998	10	23	3	23	6.2%	3.33 [1.05, 10.56]	
Total (95% CI)		200		113	100.0%	1.50 [1.12, 2.01]	◆
Total events	106		40				
Heterogeneity. Chi ² =	7.68, df =	= 2 (P =	0.02); I ²	= 74%			
Test for overall effect:	Z = 2.71	(P = 0.	007)				0.01 0.1 1 10 100 Favours Specialty Care Favours Primary Care



	Buprenor		Methac			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
3.1.2 Buprenorphine	+ naloxon	e vs me	thadone				
Kamien 2008	12	82	2	52	0.2%	3.80 [0.89, 16.32]	
Kamien 2008h	3	58	5	76	0.4%		
Neumann 2013	13	26	13	28	1.1%	1.08 [0.62, 1.87]	
Piralishvili 2015	35	40	33	40	2.9%	1.06 [0.88, 1.28]	+
Potter 2013	340	740	391	529	39.8%	0.62 [0.57, 0.68]	•
Subtotal (95% CI)		946		725	44.3%	0.68 [0.62, 0.74]	♦
Total events	403		444				
Heterogeneity. Chi ² =	34.02, df =	= 4 (P <	0.00001	$(); ^2 = 8$	38%		
Test for overall effect:	Z = 8.88 (P < 0.00	001)				
3.1.3 Buprenorphine	alone vs n	nethador	ne				
Ahmadi 2003a	19	41	25	41	2.2%	0.76 [0.50, 1.15]	
Fischer 1999	11	29	22	31	1.9%		
Johnson 1992	22	53	17	54	1.5%	1.32 [0.79, 2.19]	
Johnson 2000	32	55	40	55	3.5%	0.80 [0.61, 1.05]	
Kosten 1993	25	68	23	36	2.6%	0.58 [0.39, 0.86]	
Kristensen 2005	9	25	21	25	1.8%		
Ling 1996	26	75	39	75	3.4%	0.67 [0.46, 0.97]	
Lintzeris 2005	38	81	42	77	3.8%		_+ <u>+</u>
Mattick 2003	96	200	120	205	10.3%	0.82 [0.68, 0.99]	+
Neri 2005	29	31	28	31	2.4%	1.04 [0.89, 1.20]	+
Oliveto 1999	31	45	30	45	2.6%	1.03 [0.78, 1.37]	+
Pani 2000	18	38	22	34	2.0%	0.73 [0.48, 1.11]	
Petitjean 2001	15	27	28	31	2.3%	0.62 [0.43, 0.88]	
Schottenfeld 1997	10	33	14	34	1.2%	0.74 [0.38, 1.42]	
Schottenfeld 1997m	16	33	18	32	1.6%	0.86 [0.54, 1.37]	
Schottenfeld 2005	37	82	52	80	4.6%	0.69 [0.52, 0.93]	
Soyka 2008a	28	64	34	76	2.7%	0.98 [0.67, 1.42]	-+-
Strain 1994a	47	84	45	80	4.0%	0.99 [0.76, 1.30]	-+-
Strain 1994b	13	24	15	27	1.2%	0.97 [0.59, 1.61]	-+-
Subtotal (95% CI)		1088		1069	55.7%	0.81 [0.75, 0.88]	•
Total events	522		635				
Heterogeneity: Chi ² =				$ ^2 = 50$	0%		
Test for overall effect:	Z = 5.31 (P < 0.00	001)				
Total (95% CI)		2034		1794	100.0%	0.75 [0.71, 0.80]	•
Total events	925		1079				
Heterogeneity. Chi ² =	81.90, df =	= 23 (P <	0.0000	(1); ² =	72%		0.01 0.1 1 10 1
Test for overall effect:	Z = 9.71 (P < 0.00	001)				Favours methadone Favours buprenorphine

Figure XX. Retention in Treatment. Buprenorphine versus Methadone.

Test for subgroup differences: $Chi^2 = 9.00$, df = 1 (P = 0.003), $l^2 = 88.9\%$

Figure XX. Abstinence. Buprenorphine versus Methadone.

	Buprenor		Methad			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.1.1 Abstinent as p	er negative	urine					
Johnson 2000	26	55	28	55	7.5%	0.93 [0.63, 1.36]	
Kamien 2008	8	82	6	52	2.0%	0.85 [0.31, 2.30]	
Kamien 2008h	10	58	12	76	2.8%	1.09 [0.51, 2.35]	
Neri 2005	24	31	20	31	5.4%	1.20 [0.87, 1.66]	
Neumann 2013	8	26	11	28	2.8%	0.78 [0.37, 1.64]	
Pani 2000	5	38	5	34	1.4%	0.89 [0.28, 2.83]	
Subtotal (95% CI)		290		276	21.9%	0.99 [0.78, 1.24]	◆
Total events	81		82				
Heterogeneity: Chi ² =	2.07, df =	5 (P = 0)	.84); I ² =	0%			
Test for overall effect	z = 0.11 (P = 0.91)				
1.1.2 Abstinent as p	er self-rep	ort					
Potter 2013	193	740	222	391	78.1%	0.46 [0.40, 0.53]	
Subtotal (95% CI)	100	740		391	78.1%		
Total events	193		222				Ŧ
Heterogeneity: Not ap							
Test for overall effect		(P < 0.0	0001)				
T-+-1 (05% CI)		1020			100.00	0.50 (0.51, 0.55)	
Total (95% CI)		1030		667	100.0%	0.58 [0.51, 0.65]	•
			304				
Total events	274						
Total events Heterogeneity: Chi ² =	= 39.24, df =); I ² = 8	35%		0.01 0.1 1 10 10
Total events	= 39.24, df = t: Z = 8.79 (P < 0.00	001)				0.01 0.1 1 10 10 Favours methadone Favours buprenorphine

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

	Naltrex	one	Placebo or usua	al care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
1.1.1 Oral naltrexon	e						
Cornish 1997	18	34	6	17	6.9%	1.50 [0.73, 3.07]	+
Coviello 2010	18	56	16	55	13.9%	1.10 [0.63, 1.94]	_
Krupitsky 2012	16	102	11	102	9.5%	1.45 [0.71, 2.98]	
Krupitsky 2013	15	76	8	75	6.9%	1.85 [0.83, 4.10]	+
Othiashvili 2012	12	20	11	20	9.5%	1.09 [0.64, 1.86]	_ _
Shufman 1994 Subtotal (95% CI)	8	16 304	9	16 285	7.7% 54.4%	0.89 [0.46, 1.71] 1.28 [0.97, 1.68]	
Test for overall effect 1.1.2 LA naltrexone Krupitsky 2011 Springer 2018 Subtotal (95% CI)	: Z = 1.77 67 10	' (P = C 126 66 192	47 4	124 27 151	40.8% 4.9% 45.6%		
Total events Heterogeneity: Chi ² = Test for overall effect		= 1 (P		151	. 3.070	1.50 [1.04, 1.75]	
Total (95% CI) Total events	164	496	112	436	100.0%	1.32 [1.09, 1.60]	
Heterogeneity: Chi ² = Test for overall effect Test for subgroup dif	: Z = 2.80) (P = C	.005)	0.74), I ²	= 0%		0.01 0.1 1 10 100 Favours placebo or UC Favours naltrexone

Figure XX. Abstinence. Naltrexone versus Placebo/Usual Care

	Naltrex	one	Placebo or usua	l care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
1.6.1 Oral naltrexon	e						
Coviello 2010 Subtotal (95% CI)	25	56 56	23	55 55	44.3% 44.3%		
Total events Heterogeneity: Not ap	•		23				
Test for overall effect	Z = 0.30	(P = 0)	.76)				
1.6.2 LA naltrexone							
Krupitsky 2011	45	126	28	124	53.9%	1.58 [1.06, 2.36]	
Lee 2015 Subtotal (95% CI)	8	16 142	1	17 141	1.9% 55.7%		→
Total events	53		29				
Heterogeneity: Chi ² = Test for overall effect	,		.,				
Total (95% CI)		198		196	100.0%	1.48 [1.11, 1.98]	◆
Total events Heterogeneity: Chi ² = Test for overall effect Test for subgroup dif	: Z = 2.67	' (P = 0	.008)	0.07), I ²	= 68.9%		0.01 0.1 1 10 100 Favours placebo or UC Favours naltrexone

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

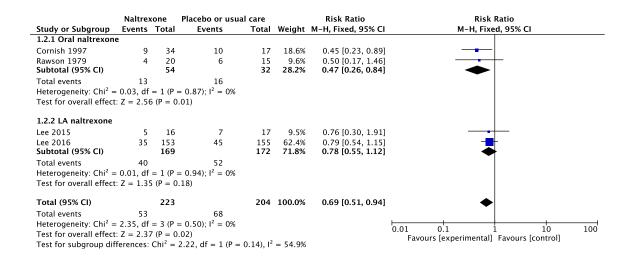


Figure XX. Retention in Treatment. Counselling versus Minimal to No Counselling

	Counse	lling	Usual (Care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Chawarski 2011	16	20	13	17	10.3%	1.05 [0.74, 1.47]	+
Gu 2013	98	146	67	142	49.7%	1.42 [1.16, 1.75]	*
Liu 2018	56	62	55	63	40.0%	1.03 [0.91, 1.17]	•
Total (95% CI)		228		222	100.0%	1.23 [1.08, 1.39]	•
Total events	170		135				
Heterogeneity: Chi ² =	10.09, d	f = 2 (P	= 0.006); $I^2 = 8$	0%		0.01 0.1 1 10 100
Test for overall effect	: Z = 3.24	(P = 0.	.001)				Favours [experimental] Favours [control]

0							1 8
	Superv	ised	Unsuper	vised		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Bell 2007	37	61	33	58	18.2%	1.07 [0.79, 1.44]	+
Fiellen 2006	24	56	26	54	14.3%	0.89 [0.59, 1.34]	
Holland 2012	15	20	17	19	9.4%	0.84 [0.62, 1.13]	
Holland 2014	100	145	109	148	58.1%	0.94 [0.81, 1.08]	•
Total (95% CI)		282		279	100.0%	0.94 [0.84, 1.06]	•
Total events	176		185				
Heterogeneity: Chi ² =	1.33, df	= 3 (P -	= 0.72); I ²	- 0%			0.01 0.1 1 10 100
Test for overall effect:	Z = 0.94	4 (P = 0	.35)				Favours [unsupervised] Favours [supervised]

Figure XX. Retention in Treatment. Supervised versus Unsupervised Ingestion

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

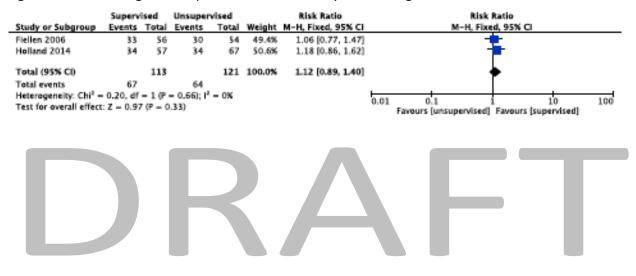


Figure XX. Retention in Treatment. Contingency Management versus No Contingency Management

	Contingency Man		Non-Cont			Risk Ratio	Risk Ratio
Study or Subgroup		Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% CI
1.1.1 Voucher/Prize					_		
Bickel 2008	52	90	26	60	3.3X	1.78 [1.24, 2.55]	
Chen 2013	103	126	61	120	10.0%	1.21 [1.04, 1.41]	*
Chopra 2009	35	41	14	19	2.3%	1.16 [0.86, 1.56]	
Chutuape 1999	7	7	5	7	0.7%	1.36 [0.83, 2.25]	+
Defulio 2012	14	19	5	19	0.6%	2.80 [1.26, 6.22]	
Dunn 2013	19	35	5	32	0.6%	3.47 [1.47, 8.22]	
Everly 2011	12	16	6	17	0.7%	1.69 [0.92, 3.69]	
Gross 2006	16	20	6	10	1.3%	1.00 [0.68, 1.46]	
Hser 2011	129	160	106	159	12.6%	1.21 [1.06, 1.38]	
jiang 2012	70	60	69	60	8.3%	1.01 [0.90, 1.14]	+
Kidorf 2013	51	62	52	63	6.2%	1.00 [0.85, 1.17]	+
Kosten 2003	37	40	38	40	4.6%	0.97 [0.87, 1.09]	+
Ling 2013	35	49	28	51	3.3%	1.30 [0.96, 1.77]	↓
Oliveto 2005	36	70	38	70	4.6%	0.95 [0.69, 1.30]	-
Peirce 2006	133	198	123	190	15.1%	1.04 [0.90, 1.20]	+
Petry 2002	18	19	21	23	2.3×	1.04 [0.88, 1.22]	+
Petry 2005	35	40	31	37	3.9%	1.04 [0.87, 1.26]	+
Petry 2007	45	55	14	20	2.5%	1.17 [0.85, 1.60]	<u>+</u>
Preston 2000	27	29	28	28	3.5%	0.93 [0.83, 1.05]	-
Subtotal (95% CI)		1158		1065	86.4%	1.15 [1.09, 1.21]	•
Total events	874		698				·
	= 54.72, df = 18 (P <	0.0001); f	- 67%				
	t: Z = 5.22 (P < 0.00		•				
1.1.2 Medication-S	pecific Contingencies						
		•					
Chonza 2009			14	18	24%	0 77 10 54 1 091	
	25	42	14 8	16 8	2.4% 1.4%	0.77 [0.54, 1.09]	+
Chutuape 1999	25 18	42 21	6	6	1.4%	0.89 [0.70, 1.13]	+
Chutuape 1999 Chutuape 2001	25 18 25	42 21 34	6 16	8 19	1.4% 2.6%	0.89 [0.70, 1.13] 0.78 [0.62, 0.97]	
Chutuape 1999 Chutuape 2001 Gross 2006	25 18 25 13	42 21 34 20	6 16 6	8 19 10	1.4% 2.8% 1.3%	0.89 [0.70, 1.13] 0.78 [0.62, 0.97] 0.81 [0.52, 1.27]	
Chutuape 1999 Chutuape 2001 Gross 2006 Kidorf 1996	25 18 25 13 14	42 21 34 20 16	8 18 8 16	8 19 10 16	1.4% 2.8% 1.3% 2.0%	0.89 [0.70, 1.13] 0.76 [0.62, 0.97] 0.81 [0.52, 1.27] 0.86 [0.71, 1.09]	
Chutuape 1999 Chutuape 2001 Gross 2006 Kidorf 1996 Silverman 2004	25 18 25 13 14 16	42 21 34 20 16 26	8 18 8 16 14	8 19 10 16 26	1.4% 2.8% 1.3% 2.0% 1.7%	0.89 [0.70, 1.13] 0.78 [0.62, 0.97] 0.81 [0.52, 1.27] 0.88 [0.71, 1.09] 1.14 [0.72, 1.82]	
Chutuape 1999 Chutuape 2001 Gross 2006 Kkdorf 1996 Silverman 2004 Stitzer 1992	25 18 25 13 14	42 21 34 20 16 26 26	8 18 8 16	8 19 10 16 26 27	1.4% 2.8% 1.3% 2.0% 1.7% 2.1%	0.89 [0.70, 1.13] 0.78 [0.62, 0.97] 0.81 [0.52, 1.27] 0.88 [0.71, 1.09] 1.14 [0.72, 1.82] 0.87 [0.57, 1.32]	
Chopra 2009 Chutuape 1999 Chutuape 2001 Gross 2006 Kidorf 1996 Silverman 2004 Stitzer 1992 Subtotal (95% Cl) Total events	25 18 25 13 14 16 15	42 21 34 20 16 26	6 16 16 16 14 16	8 19 10 16 26	1.4% 2.8% 1.3% 2.0% 1.7%	0.89 [0.70, 1.13] 0.78 [0.62, 0.97] 0.81 [0.52, 1.27] 0.88 [0.71, 1.09] 1.14 [0.72, 1.82]	
Chutuape 1999 Chutuape 2001 Gross 2006 Kidorf 1996 Silverman 2004 Stitzer 1992 Subtotal (95% CI) Total events	25 18 25 13 14 16 15 126	42 21 34 20 16 26 26 185	6 16 16 14 18 96	8 19 10 16 26 27	1.4% 2.8% 1.3% 2.0% 1.7% 2.1%	0.89 [0.70, 1.13] 0.78 [0.62, 0.97] 0.81 [0.52, 1.27] 0.88 [0.71, 1.09] 1.14 [0.72, 1.82] 0.87 [0.57, 1.32]	
Chutuape 1999 Chutuape 2001 Gross 2006 Kidorf 1996 Silverman 2004 Stitzer 1992 Subtotal (95% CI) Total events Heterogeneity: Chi ²	25 18 25 13 14 16 15	42 21 34 20 16 26 26 185 83); i ² = 0;	6 16 16 14 18 96	8 19 10 16 26 27	1.4% 2.8% 1.3% 2.0% 1.7% 2.1%	0.89 [0.70, 1.13] 0.78 [0.62, 0.97] 0.81 [0.52, 1.27] 0.88 [0.71, 1.09] 1.14 [0.72, 1.82] 0.87 [0.57, 1.32]	
Chutuape 1999 Chutuape 2001 Gross 2006 Kidorf 1996 Silverman 2004 Stitzer 1992 Subtotal (95% CI) Total events Heterogeneity: Chi ² Test for overall effect	25 18 25 13 14 16 15 126 = 2.64, df = 6 (P = 0.	42 21 34 20 16 26 26 185 83); i ² = 0;	6 16 16 14 18 96	8 19 10 16 26 27 124	1.4% 2.8% 1.3% 2.0% 1.7% 2.1%	0.89 [0.70, 1.13] 0.78 [0.62, 0.97] 0.81 [0.52, 1.27] 0.88 [0.71, 1.09] 1.14 [0.72, 1.82] 0.87 [0.57, 1.32]	
Chutuape 1999 Chutuape 2001 Gross 2006 Kidorf 1996 Silverman 2004 Stitzer 1992 Subtotal (95% CI) Total events Heterogeneity: Chi ²	25 18 25 13 14 16 15 126 = 2.64, df = 6 (P = 0.	42 21 34 20 16 26 26 185 83); r ² = 0?	6 16 16 14 18 96	8 19 10 16 26 27 124	1.4% 2.8% 1.3% 2.0% 1.7% 2.1% 13.6%	0.89 [0.70, 1.13] 0.78 [0.62, 0.97] 0.81 [0.52, 1.27] 0.88 [0.71, 1.09] 1.14 [0.72, 1.82] 0.87 [0.57, 1.32] 0.86 [0.76, 0.99]	
Chutuape 1999 Chutuape 2001 Gross 2006 Kidorf 1996 Silverman 2004 Stitzer 1992 Subtotal (95% CI) Total events Heterogeneity: Chi ² Total events Total (95% CI) Total events	25 18 25 13 14 16 15 126 = 2.84, df = 6 (P = 0. ;; Z = 2.19 (P = 0.03)	42 21 34 20 16 26 26 185 83); f ² = 0; 1343	6 16 16 14 18 96 4	8 19 10 16 26 27 124	1.4% 2.8% 1.3% 2.0% 1.7% 2.1% 13.6%	0.89 [0.70, 1.13] 0.78 [0.62, 0.97] 0.81 [0.52, 1.27] 0.88 [0.71, 1.09] 1.14 [0.72, 1.82] 0.87 [0.57, 1.32] 0.86 [0.76, 0.99]	
Chutuape 1999 Chutuape 2001 Gross 2006 Kidorf 1996 Silverman 2004 Stitzer 1992 Subtotal (95% CI) Total events Heterogeneity: Chi ² Total (95% CI) Total events Heterogeneity: Chi ²	25 18 25 13 14 16 15 126 = 2.84, df = 6 (P = 0. 3; Z = 2.19 (P = 0.03)	$42 \\ 21 \\ 34 \\ 20 \\ 16 \\ 26 \\ 26 \\ 185 \\ 83); r^2 = 0? \\ 1343 \\ 0.00001);$	6 16 16 14 18 96 4	8 19 10 16 26 27 124	1.4% 2.8% 1.3% 2.0% 1.7% 2.1% 13.6%	0.89 [0.70, 1.13] 0.78 [0.62, 0.97] 0.81 [0.52, 1.27] 0.88 [0.71, 1.09] 1.14 [0.72, 1.82] 0.87 [0.57, 1.32] 0.86 [0.76, 0.99]	0.01 0.1 10 Favours [non-contingent] Favours [contingent]