

Association Between Harm Reduction Strategies and Healthcare Utilization and Outcomes in Patients on Long-term Prescribed Opioid Therapy Presenting to Acute Healthcare Settings: A Systematic Review and Meta-analysis

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Abstract

Background

Long-term prescription of opioids by healthcare professionals has been linked to poor individual patient outcomes and high resource utilization. Harm reduction strategies in this population in regard to acute healthcare settings may have substantial impact.

Methods

We performed a systematic review and meta-analysis of primary studies. The studies were included according to the following criteria: 1) age 18 and older; 2) long-term/chronic prescribed opioid therapy; 3) acute healthcare setting presentation from a complication of opioid therapy; 4) evaluating a harm reduction strategy; 5) comparing the effectiveness of different interventions; 6) addressing patient or healthcare related outcomes. We performed a qualitative analysis of harm reduction strategies identified. We pooled patient and system related outcome data for each harm reduction strategy.

Results

A total of 5664 studies were screened and 21 studies were included. A total of 11 broad categories of harm reduction strategies were identified. Meta-analysis was performed for the “supports for patients in pain” harm reduction strategy on two system-related outcomes using a ratio of means. The number of emergency department (ED) visits were significantly reduced for cohort studies ($n=6$, 0.36, 95% CI [0.20-0.62], $I^2 = 87\%$) and randomized controlled trials (RCTs) ($n=3$, 0.71, 95% CI [0.61-0.82], $I^2 = 0\%$). The number of opioid prescriptions at ED discharge was significantly reduced for RCTs ($n=3$, 0.34, 95% CI [0.14-0.82], $I^2 = 78\%$).

Interpretation

For patients presenting to acute healthcare settings with complications related to long-term opioid therapy, the intervention with the most robust data is “supports for patients in pain”.

Study registration

CRD42018088962

Background

Description of the condition

The opioid epidemic is a major public health problem across the world. While not initially recognized as a crisis, it has become a public health emergency that is largely believed to have begun in 1996 when OxyContin® was approved by the FDA (1). Opioid prescription was initially thought to be the crux of the problem and multiple interventions were implemented in response over the years. A majority of these interventions were focused on reducing access to opioid prescriptions. The results of these interventions have had unforeseen and paradoxical consequences. As an example, reducing in prescription rates in Ontario (Canada) lead to a doubling of opioid mortality due to an increase in street opioids (2). This shift in the nature of the opioid crisis to illicit opioid use has indeed been seen in multiple locations over the years and paralleled these interventions (3). In light of such findings, illicit drug use has become the focus of most current efforts to limit the impact of the opioid crisis and the impact of opioid prescriptions has taken a backseat. However, it remains that there are patients on long-term opioids for chronic painful conditions that are also at risk for complications. This group has ultimately been somewhat neglected amidst the extensive literature available on the more obvious high-risk populations. It is however quite clear that individuals on long-term opioid therapy are at risk of poor outcomes, including hospitalization, overdose and death from the use or management of their opioids (4,5). These poor outcomes invariably lead to acute healthcare presentations that have significant system level

impacts on health services use including emergency department (ED) presentations, hospital and intensive care unit (ICU) admissions, as well important socio-economic consequences (6–10).

Description of the intervention

Harm reduction strategies are defined as “any policy or program designed to reduce drug-related harm without requiring the cessation of drug use; these interventions may be targeted at the individual, the family, community or society (11–19).” Harm reduction strategies are traditionally thought of and applied to patients demonstrating high risk behaviors and the term has not typically been applied in relation to individuals on long-term opioid therapy. These individuals may still benefit from harm reduction strategies as they require these medications for their well-being but may still suffer harmful consequences from their use. While evidence exists for harm reduction strategies in acute opioid overdoses, the evidence to support their impact in individuals on long-term opioid therapy is harder to discern but it may be substantial given the reported high risk of adverse events in these settings (7,20–22). The most important complications as a result of opioid therapy most often lead to a presentation to an acute healthcare setting, defined as a setting in which “health system components, or care delivery platforms, are used to treat sudden, often unexpected, urgent or emergent episodes of injury and illness that can lead to death or disability without rapid intervention (23).” Examples of these include emergency departments, acute health care clinics, hospital inpatient units. Accordingly, this may be the healthcare setting in which the most impactful harm reduction strategies may lie, and how this population can best be captured in studies. As such, the primary objective of this study was to identify the most effective harm reduction strategies for patients on long-term prescribed opioids presenting to acute care settings to decrease complications attributable to opioid use, to reduce avoidable health services use, and to improve outcomes.

Methods

Study design and registration

We performed a systematic review using the guidelines from Cochrane and the Centre for Reviews and Dissemination (24,25), and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines for observational studies(26,27). The study was registered with the PROSPERO (CRD42018088962 on 2018/02/19) International Prospective Register of Systematic Reviews (<http://www.crd.york.ac.uk/prospero>).

Criteria for considering studies for this review

Types of studies

We considered primary studies (i.e., randomized controlled trials (RCT), cohort studies, case-control studies) and secondary analyses or evidence syntheses (i.e., systematic reviews, meta-analyses). There were no language restrictions. We considered studies published after 1996 as this is when OxyContin® was introduced, and the current prescription opioid epidemic is believed to have largely began(1). We excluded editorials, case series, case reports and narrative reviews.

Eligibility of individual studies

Studies were eligible for inclusion if they satisfied the following criteria:

- Patient related criteria:
 - Age 18 years or older.
 - Long-term or chronic opioid therapy, reflecting prescribed opioid more than 70% of days for at least 3 months(28).
 - Presentation to acute healthcare setting secondary for a presumed or confirmed complication of prescribed opioid therapy.
- Study-related criteria

- Evaluating an intervention representing a harm reduction strategy.
- Comparing the effectiveness of different interventions between each other or individual interventions compared to current care
- Addressing patient or healthcare system related outcomes (i.e. number of opioid prescriptions, repeat presentations to ED or acute healthcare, number of overdoses).

We excluded studies that specifically addressed patients with non-prescription opioid use, or prescription opioid use not obtained through healthcare professionals. We excluded studies of patients with opioid use disorder or misuse that was not attributable to an established chronic pain disorder or disease.

Search methods

The search strategy was developed and executed by an information specialist (RF) and was peer-reviewed by a second research librarian (Figure 1). The information specialist searched electronic databases: Ovid MEDLINE (1946-), Ovid EMBASE (1996-), Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCOhost (1937-), and Wiley Cochrane Library (inception-), including the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (CENTRAL). We also searched reports from the National Information Center on Health Services Research and Health Care Technology (NICHSR) via the NICHSR ONEsearch portal. Study records were also searched via the trial registry platform ClinicalTrials.gov, guidelines via the National Guidelines Clearinghouse, and meeting abstracts via the Conference Proceedings Citation Index database (Clarivate Analytics). The following search themes was used: 1) opioids; 2) long-term drug therapy; and 3) acute healthcare settings (emergency departments, acute care surgery, critical care, urgent care and short-term inpatient stabilization). We additionally scanned the reference list of relevant included studies for additional articles. Bibliographic records were exported to an EndNote X9 (Clarivate Analytics, Philadelphia, Pennsylvania). Databases were searched up to and including April 11, 2019.

Study assessment

Articles were identified through two phases. First, two authors (JD and JG) independently reviewed the titles and abstracts of all retrieved articles for study inclusion. Second, full texts of the selected articles were retrieved, reviewed and selected based on inclusion criteria. All steps were performed in duplicate, and in each phase, disagreements were resolved through discussion. In the case of unresolved matters, a third author (OGR) was involved. Reasons for exclusion of full text articles were recorded and displayed in a PRISMA diagram format.

Quality assessment of studies

The methodological quality of each study was independently analyzed by two authors (JD and JG) using the Newcastle-Ottawa Quality Assessment Scale (NOS) for observational studies and the Cochrane Risk of Bias Tool for randomized controlled trials (24,29). Disagreements were resolved through discussion, and in the case of unresolved matters, a third author (OGR) was involved.

Data analysis and synthesis

An inventory of harm reduction strategies was developed from the included studies. Descriptive analysis and data extraction of patient and study characteristics, and of harm reduction strategies and their outcomes were performed using standardized electronic data forms (Supplementary Appendix 1 for variables extracted). We analyzed all available data qualitatively and, when possible, aggregate analysis was performed (30). For each study we extracted or computed the ratio of means between the intervention and usual care groups with 95% confidence interval (31). These ratios were then pooled using the DerSimonian-Laird random effects method with an inverse variance weighting. To minimize bias due to confounding, results for RCTs were pooled separately from results for cohort studies and the two were not combined in one meta-analysis. Heterogeneity was assessed using the I-squared statistic with values greater than 50% considered to be “substantial” heterogeneity.

Results

Our search yielded 5664 studies, of which 21 studies fulfilled our eligibility criteria (Figure 2, Supplementary Appendix 2). These included 19 full-text articles and 2 abstracts, of which 16 were cohort studies and 5 were randomized controlled trials (Table 1). No additional articles were identified for inclusion from the reference list of included articles. Study quality is reported in tables 2 and 3.

A total of 11 categories of harm reduction strategies were identified (Table 4). Most studies addressed multiple harm reduction strategies simultaneously making separation difficult. This is reflected and detailed in both Table 1 and Table 4. The 16 cohort studies included all assessed harm reduction strategies in a pre/post intervention model (Table 1). They either compared matched cohorts of different patients ($n = 9$) or cohorts of same patients before and after intervention ($n = 7$) in which each patient was his own control. Nearly all studies were performed in ED settings ($n = 14$). A single cohort study assessed mortality (11). The five RCTs (Table 1) were all performed in the ED, with the comparator being usual care. Outcomes assessed included ED opioid prescriptions, ED discharge opioid prescriptions, hospital length of stay (LOS), and overdose and opioid related ED visits. All cohort and RCT studies were conducted in the US other than the cohort study by Allen et al. in Canada (32).

Six cohort studies and three RCTs were suitable for meta-analysis (Figures 3 and 4). All studies included in the meta-analysis assessed outcomes for the “supports for patients in pain” harm reduction strategy. This strategy is characterized by the use of patient support groups, individual patient case management and pain clinic vetting and referrals. Two outcomes (number of ED visits and number of ED discharge opioid prescriptions) were meta-analyzed. The ED visits outcome refers to total number of visits to the ED after implementation of the strategy. The ED discharge opioid prescriptions outcome refers to the number of prescriptions dispensed at discharge of the patients from the ED. A significant reduction in number of ED visits for cohort studies (ratio of means 0.36, 95% CI [0.20-0.62], $I^2 = 87\%$) and for RCTs (ratio of means 0.71, 95% CI [0.61-0.82], $I^2 = 0\%$) was apparent. A significant reduction in number of ED discharge opioid prescriptions was noted for RCTs (ratio of means 0.34, 95% CI [0.14-0.82], $I^2 = 78\%$). No patient-centered outcomes could be meta-analyzed. The studies duration ranged from 6 to 52 months.

Discussion

This systematic review identified 11 harm reduction strategies for patients on long-term prescription opioids presenting to an ED with complications related to their opioid therapy. A pooled analysis of outcomes for “support for patients in pain” showed a clinically important decrease in the number of ED visits and ED discharge opioid prescriptions. Other harm reduction strategies could not be analyzed in a rigorous fashion and may be considered by healthcare providers until additional evidence becomes available.

Opioid use is an important and increasing problem in the US and Canada. Multiple harm reduction strategies for acute healthcare settings have been developed and studied, but the evidence had not been collated for an assessment of their impact. Most of the harm reduction strategies identified were from small, single center studies, were too heterogeneous to be meta-analyzed, or were infrequently studied (Table 4). While most reported positive results, a number of these are single-center studies with a small number of patients. These small studies often lack the scientific rigor or external validity to allow meaningful interpretation in a larger context, and to support widespread changes in practice (33).

We identified multiple studies with enough data to perform a meta-analysis for outcomes of the “supports for patient in pain” strategy (Table 4 for definitions). These studies were chosen due to their similarity in the coordinated care models used and the target populations. There was a clinically important decrease in system-related outcomes of ED visits and ED discharge opioid prescriptions for this strategy. For both outcomes, 3 RCTs were included, with the most compelling data for ED visits due statistical significance and uniform data ($I^2 0\%$), while ED discharge opioid prescriptions were significant but showed substantial heterogeneity ($I^2 87\%$). The ED visits outcome was also supported by the meta-analysis of cohort studies that all trended in the same direction despite substantial heterogeneity ($I^2 87\%$). Across all studies, there were only four instances of

patient-related outcomes being evaluated. In these cases, the decrease in system-related outcomes were associated with unfavorable patient-related outcomes. Faryar et al. and Fulton-Kehoe respectively showed an increase in heroin use and methadone poisonings as the number of opioid prescriptions and poisonings decreased (34,35). Alexandridis et al. was the only study with a favourable patient-related outcome, demonstrating lower overdose mortality related to healthcare professional education, but as a whole did not change the rate of ED visits (11). This highlights concerns by experts that harm reduction strategies that focus on decreasing opioid prescriptions might actually contributed to unanticipated increases in avoidable deaths and overdoses (36) as patients seek out non-prescribed opioids to replace the previously prescribed opioids. The outcomes meta-analyzed may thus represent a poor proxy for appropriately impactful harm reduction strategies.

The other harm reduction strategies listed in Table 4 represent a combination of frequently recurring well-defined harm reduction strategies as well as composite terms representing harm reduction strategies referred to with different names across studies. This was determined through careful review of the detailed intervention performed in each study in order to reclassify them under umbrella headings. Unfortunately, precise definitions for each harm reduction strategy identified were not present in most studies. This limits our ability to both have homogeneous interventions under each harm reduction strategy. As such, based on the analysis of the interventions performed, most studies have multiple simultaneous harm reductions strategies employed. Accordingly, this limits the rigorous analysis of each harm reduction strategy independently.

In a similar fashion, there are no comparative studies of harm reduction strategies to inform which strategies may be superior, in which specific context, and where to direct organization and resources. Alexandridis et al. was the only study to include multiple well-differentiated strategies but analyzed them as independent variables despite a simultaneous implementation (11). However, identifying a superior strategy may be of limited importance, as statistical superiority does not necessarily reflect the clinical reality in these complex patients. Indeed, the most appropriate strategy depends on multiple local factors such as individual patient's specific needs and availability as well as access to resources. This highlights the complexity of assessing these process of care interventions for successful implementation and effectiveness of intervention. Such interventions may not lead to statistical or clinical significance in traditional outcomes (i.e., mortality) but have wider ranging benefits in care processes, workflow and resource optimization, as in the case and wide adoption of medical emergency teams (MET) (37).

Strengths and limitations

While this study had several important strengths (i.e., breadth of scope, rigorously pre-defined methodology stretching across several medical domains, presence of patient advisors), several important limitations warrant discussion. First, important terms (i.e., long-term medical opioid therapy, opioid 'abuse' and misuse, harm reduction strategies) were heterogeneously defined across studies and may have been a barrier to study identification. Most importantly, the harm reduction strategies were overall poorly defined across studies. Despite a careful analysis of the interventions in order to regroup or reclassify them under umbrella terms, it was difficult to clearly identify separate harm reduction strategies in some studies. Accordingly, these studies then often used multiple harm reduction strategies simultaneously, which significantly limited our ability to have a rigorous analysis. This is reflected in the meta-analysis where the most important harm reduction strategy was analyzed, acknowledging that it may not be fully separated from other minor elements of the intervention that may be classified under another umbrella term. We attempted to mitigate these factors by independent screening by two authors to ensure the inclusion of all relevant studies and appropriately classify the harm reduction strategies. Second, the rate of study inclusion was only 0.4%. This was secondary to most identified studies either studied illicit drug use or did not adequately differentiate between illicit drug use and opioid misuse, or poorly defined their population. When unclear following full-text review of the relevant publications, we erred to exclude studies from this review, hence focusing the findings of this review to those patients on prescribed opioid therapy. Third, the wide scope of some harm reduction strategies lead to difficult decisions for study inclusion. Indeed, a number of harm reductions were part of a package organized at a state level. It was difficult to separate the specific impact of each strategy, the impact on acute versus non-acute healthcare settings and to discern which studies dealt with patients on appropriate long-term opioid therapy. In these situations, we opted to include these state level studies if there was a well-described significant proportion of long-term opioid users, and if number of acute healthcare presentations was an

outcome of interest. We do acknowledge that these studies reflect a very heterogeneous group in a lot of instances and limit the validity of the findings. This is not reflected well in the quality assessment of the cohort study who are technically for the most part of moderate to high methodological quality. The RCTs are for their part paradoxically at moderate to high risk of bias due to their design but represent a more homogeneous population. Fourth, most identified studies were from the US, limiting the generalizability of our findings to other jurisdictions that may have different policies and context that affect the outcomes of the identified harm reduction strategies. This is not surprising as the opioid epidemic was first recognized in the US, and many findings in the US are applicable across Canada and other high-income countries(1). Finally, while we decided to include studies from 1996, all of the studies included are from the last 15 years. This is likely explained by the delayed recognition of the public health crisis from the opioid epidemic.

Future directions

Our systematic review revealed that most of the studies have targeted patients presenting to the ED, with very little data on inpatient harm reduction strategies. This knowledge gap is reflected in the most recent Canadian guidelines for opioid use for chronic non-cancer pain, which do not address acute admissions in this population (38). These guidelines do reflect the importance of a multidisciplinary approach in the chronic non-cancer pain population, which would be similar to the “supports for patient in pain” harm reductions strategy. Studying this harm reduction strategy for non-ED acute healthcare settings would strengthen the current body of evidence. Importantly, studying these strategies using patient-related outcomes such as mortality, quality of life and pain is of paramount importance, as opioid prescriptions and ED visits appear to be poor or misleading surrogate endpoints. Future policy work informed by these results would lead to better resource utilization through a shift from reactionary processes (i.e., ED visits) to preventative strategies that prevent acute healthcare presentations.

Conclusion

We identified 11 harm reduction strategies for patients chronically prescribed opioids presenting to acute healthcare. The only harm reduction strategy that showed evidence of efficacy was “support for patients in pain” with clinically important decrease in the number of ED visits and ED discharge opioid prescriptions. Unfortunately, other harm reduction strategies were not evaluated in a rigorous fashion and may be considered by healthcare providers until additional evidence becomes available. These strategies have been studied almost exclusively in ED patients, and data on inpatient harm reduction is lacking and requires further study.

List Of Abbreviations

ED: Emergency Department

ICU: Intensive Care Unit

RCT: Randomized Control Trial

MET: Medical Emergency Team

Declarations

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable.

Availability of data and materials:

All data generated or analysed during this study are included in this published article.

Author contributions

JD was responsible for the manuscript preparation. JD and OGR were responsible for finalizing the manuscript. RF developed the search strategy in consultation with JD and OGR and conducted the search. SMB and OGR conceived the project, and all authors provided critical revision of the final manuscript. OGR will guarantee the content of the review. All authors read and approved the final manuscript.

Competing interests

a
SMB is supported by a Canada Research Chair in Critical Care Nephrology.

SS has received advisory board fees from Daiichi Sankyo, Inc. SS is a specialist in occupational medicine and some of the patients he assesses have painful conditions.

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References

1. DeWeerd S. Tracing the US opioid crisis to its roots. *Nature*. 2019 Sep;573(7773):S10–2.
2. Clarke H, Bao J, Weinrib A, Dubin RE, Kahan M. Canada's hidden opioid crisis: the health care system's inability to manage high-dose opioid patients. *Can Fam Physician*. 2019 Sep;65(9):612–4.
3. National Academies of Sciences E, Division H and M, Policy B on HS, Abuse C on PM and RS to APO, Phillips JK, Ford MA, et al. Trends in Opioid Use, Harms, and Treatment [Internet]. National Academies Press (US); 2017 [cited 2020 Feb 16]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK458661/>
4. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med*. 2010 Jan;152(2):85–92.
5. Shipton EE, Shipton AJ, Williman JA, Shipton EA. Deaths from Opioid Overdosing: Implications of Coroners' Inquest Reports 2008-2012 and Annual Rise in Opioid Prescription Rates: A Population-Based Cohort Study. *Pain Ther*. 2017 Dec;6(2):203–215.
6. Cannon R, Bozeman M, Miller KR, Smith JW, Harbrecht B, Franklin G, et al. The prevalence and impact of prescription controlled substance use among injured patients at a Level I trauma center. *J Trauma Acute Care Surg*. 2014

- Jan;76(1):172–175.
7. de Wit M, Gennings C, Zilberberg M, Burnham EL, Moss M, Balster RL. Drug withdrawal, cocaine and sedative use disorders increase the need for mechanical ventilation in medical patients. *Addiction*. 2008 Sep;103(9):1500–1508.
 8. Gomes T, Mamdani MM, Paterson JM, Dhalla IA, Juurlink DN. Trends in high-dose opioid prescribing in Canada. *Can Fam Physician Med Fam Can*. 2014 Sep;60(9):826–832.
 9. Burkes R, Pfister G, Guinn B, Cavallazzi R. Opioid overdose leading to intensive care unit admission: Epidemiology and outcomes. *J Crit Care*. 2017;37:261.
 10. White AM, Hingson RW, Pan I-J, Yi H-Y. Hospitalizations for alcohol and drug overdoses in young adults ages 18-24 in the United States, 1999-2008: results from the Nationwide Inpatient Sample. *J Stud Alcohol Drugs*. 2011 Sep;72(5):774–786.
 11. Alexandridis AA, McCort A, Ringwalt CL, Sachdeva N, Sanford C, Marshall SW, et al. A statewide evaluation of seven strategies to reduce opioid overdose in North Carolina. *Inj Prev J Int Soc Child Adolesc Inj Prev*. 2017 Aug;injuryprev–2017–042396.
 12. British Columbia Center on Substance Use, Health BCM of. A Guideline for the Clinical Management of Opioid Use Disorder. 2017 Jun;1–77.
 13. Kucukarslan SN, Peters M, Mlynarek M, Nafziger DA. Pharmacists on rounding teams reduce preventable adverse drug events in hospital general medicine units. *Arch Intern Med*. 2003 Sep;163(17):2014–2018.
 14. Leape LL, Cullen DJ, Clapp MD, Burdick E, Demonaco HJ, Erickson JI, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. *JAMA*. 1999 Jul;282(3):267–270.
 15. Lynch ME, Katz J. “One Size Fits All” Doesn’t Fit When It Comes to Long-Term Opioid Use for People with Chronic Pain. *Can J Pain*. 2017 Aug;1(1):2–7.
 16. Morley-Forster PK, Clark AJ, Speechley M, Moulin DE. Attitudes toward opioid use for chronic pain: a Canadian physician survey. *Pain Res Manag*. 2003;8(4):189–194.
 17. National Advisory Council on Prescription Drug Misuse. First Do No Harm: Responding to Canada’s Prescription Drug Crisis (Report). 2013 May;1–84.
 18. Rudd RA, Seth P, David F, Scholl L. Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015. *MMWR Morb Mortal Wkly Rep*. 2016 Dec;65(5051):1445–1452.
 19. Young A, Alfred KC, Davignon PP, Hughes LM, Robin LA, Chaudhry HJ. Physician survey examining the impact of an educational tool for responsible opioid prescribing. *J Opioid Manag*. 2012 Mar;8(2):81–87.
 20. Herzig SJ, Rothberg MB, Cheung M, Ngo LH, Marcantonio ER. Opioid utilization and opioid-related adverse events in nonsurgical patients in US hospitals. *J Hosp Med*. 2014 Feb;9(2):73–81.
 21. Van Hook C, Burneikiene S, Tangel D, Warner B. The relationship of outpatient prescription narcotic use to the early implementation and manner of assisted ventilation in a community hospital intensive care unit. *Intensive Care Med Exp*. 2015;3(Suppl 1):A311.
 22. Rootman DB, Mustard R, Kalia V, Ahmed N. Increased incidence of complications in trauma patients cointoxicated with alcohol and other drugs. *J Trauma Inj Infect Crit Care*. 2007 Mar;62(3):755–758.
 23. WHO | Health systems and services: the role of acute care [Internet]. WHO. [cited 2020 Feb 27]. Available from: <https://www.who.int/bulletin/volumes/91/5/12-112664/en/>
 24. Higgins J, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* [Internet]. The Cochrane Collaboration; 2011 [cited 2018 Oct 10]. Available from: <http://www.handbook.cochrane.org>
 25. Centre for Reviews Dissemination. Systematic review: CRD’s guidance for undertaking reviews in health care. CRD; University of York; 2009.
 26. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009 Jul 21;339:b2700.

27. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. In: JAMA. Centers for Disease Control and Prevention, Atlanta, GA 30333, USA. dfs2@cdc.gov; 2000. p. 2008–2012.
28. Yaffe PB, Green RS, Butler MB, Witter T. Is Admission to the Intensive Care Unit Associated With Chronic Opioid Use? A 4-Year Follow-Up of Intensive Care Unit Survivors. *J Intensive Care Med*. 2016 Aug;32(7):429–435.
29. Wells G, Shea B, O’Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. The Ottawa Hospital Research Institute.; Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
30. Rewa OG, Villeneuve P-M, Lachance P, Eurich DT, Stelfox HT, Gibney RTN, et al. Quality indicators of continuous renal replacement therapy (CRRT) care in critically ill patients: a systematic review. *Intensive Care Med*. 2017 Jun;43(6):750–763.
31. Friedrich JO, Adhikari NK, Beyene J. The ratio of means method as an alternative to mean differences for analyzing continuous outcome variables in meta-analysis: A simulation study. *BMC Med Res Methodol*. 2008 May 21;8(1):32.
32. Allen MA. P008: Addressing chronic pain and problematic substance use of opioids in the emergency department: can a comprehensive framework for care work? *Can J Emerg Med*. 2016 May;18(S1):S81–S81.
33. Bellomo R, Warrillow SJ, Reade MC. Why we should be wary of single-center trials. *Crit Care Med*. 2009 Dec;37(12):3114–9.
34. Fulton-Kehoe D, Sullivan M, Turner J, Garg R, Bauer A, Wickizer T, et al. (428) Opioid poisonings in Washington state Medicaid: trends, dosing, and guidelines. *J Pain*. 2015 Apr;16(4):S83.
35. Faryar KA, Freeman CL, Persaud AK, Furmanek SP, Guinn BE, Mattingly WA, et al. The Effects of Kentucky’s Comprehensive Opioid Legislation on Patients Presenting with Prescription Opioid or Heroin Abuse to One Urban Emergency Department. *J Emerg Med*. 2017 Dec;53(6):805–14.
36. Clarke H, Bao J, Weinrib A, Dubin RE, Kahan M. Canada’s hidden opioid crisis: the health care system’s inability to manage high-dose opioid patients: Fallout from the 2017 Canadian opioid guidelines. *Can Fam Physician*. 2019 Sep 1;65(9):612–4.
37. Hillman K, Chen J, Cretikos M, Bellomo R, Brown D, Doig G, et al. Introduction of the medical emergency team (MET) system: a cluster-randomised controlled trial. *Lancet Lond Engl*. 2005 Jun 18;365(9477):2091–7.
38. Busse J. The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain. *Cancer Pain*. 2017;105.

Tables

Table 1. Descriptive characteristics of included harm reduction intervention studies

Author and Year of Publication	Country of Origin	Setting	# of Subjects	Opioid Use Inclusion Criteria	Harm Reduction Intervention	Outcomes	Follow-up Post Intervention
Cohort studies							
Alburaih (2018)	U.S.	ED	314	Multi-ED, patients eligible for a standardized pain contract; only visits involving complaints of pain included.	Support for patients in pain.	# of ED visits	24-months
Alexandridis (2018)	U.S.	ED + Community	7200	Statewide, non-selective ER meta-data ; sub-analysis of chronic pain patients & opioid use related outcomes	Diversion control Naloxone policies Community education Provider education Support for patients in pain Hospital ED policy Addiction treatment	Overdose mortality Overdose-related ED visits	22-months
Alexandridis (2019)	U.S.	ED + Community	7200	Statewide, non-selective ER meta-data ; specific evaluation of opioid prescriptions and buprenorphine patients	Diversion control Naloxone policies Community education Provider education Support for patients in pain Hospital ED policy Addiction treatment	PDMP-derived counts of opioid prescriptions and buprenorphine	22-months
Allen (2016)%	Canada	ED + Community	13	>360 combined ER visits in prior 12-Mo with complex pain and problematic substance use	Support for patients in pain +/- pain management plan and referral	# of visits to ED Disposition of patients after ED visit	52-months

Faryar (2017)	U.S.	ED	2945	ER presentation with either Rx opioid or heroin abuse, not otherwise specified.	Opioid Prescribing Guideline	# and type of opioid used after ED visit.	33-months
Fulton-Kehoe (2015)	U.S.	Statewide	1809	1 or > opioid Rx & ER presentation of methadone or other opioid poisoning	Opioid Prescribing Guideline	Rates of non-methadone associated opioid poisonings	45-months
Ghobadi (2018)	U.S.	ED	19751@	Outpatient opioid use of > 50 MME per day for > 90 days	Opioid Prescribing Guideline	ED parenteral opioids ED oral opioids ED discharge prescription counts	12-months
Gugelmann (2013)	U.S.	ED	2462 ⁺⁺	ED presentations; subgroup analysis of chronic pain patients and Rx opioid users.	Provider Education + ED database tool	# of opioid discharge packs Change in opioid dispensing in patients with RF for dependence	12-months
Hartung (2018)	U.S.	Statewide	N/A	High-dose opioid use (>120 MME per day), with subdivision for 61-120, and <60 MME/day.	Opioid Prescribing Guideline	Probability of opioid prescription above 120mg MED	18-months
Jurecska (2012)	U.S.	ED	91	>3 ED visits in prior 3-Mo or 6 or > presentations in 6-Mo with chief complaint of chronic pain (defined as pain >6 Mo).	Opioid Prescribing Guideline	Recurrent visits to ED	36-months
Kahler (2017)	U.S.	ED	243	6 or > ED visits per 12 Mo + at least 1 visit identified as primarily opioid-seeking behavior + chart review of ED misuse.	Referral to chronic pain clinic + ED database tool + educated would no longer receive ED opioid Rx.	# of ED visits # of PDMP opioid prescriptions # of individual opioid prescribers # of diagnostic tests	12-months
Maughan (2015)	U.S.	ED	N/A	All ED visits involving query opioid analgesic drug mis-use, as	Prescription drug monitoring program (PDMP)	Rates of ED visits	84-months

coded through
DAWN (drug
abuse
monitoring
Network)

Olsen (2016)	U.S.	ED	46	>3 ED visits in prior 6-Mo or >6 ED visits in prior 12-Mo for a chronic painful condition + PDMP evidence of inappropriate opioid or benzodiazepine Rx(s).	ED pathway (protocol) + database tool with referral	# fo ED visits # of opioid pills prescribed	6-months
Pace (2017)	U.S.	ED	529	Pain present for > 3 Mos, no criterion or # of ED presentations or MME.	ED pathway + provider education prior.	MEQ dose administered in ED # of IV/IM prescriptions # of opioid prescriptions at discharge	6-months
Svenson (2007)	U.S.	ED	15	> 10 ED visits in prior 12-Mos for chronic non cancer pain	Support for patients in pain + educated would no longer receive ED opioid Rx.	# of ED visits # of outpatient clinic visits # of outpatient opioid prescriptions	12-months
Whiteside (2017)	U.S.	ED	29	Subgroup analysis of ED patients screened positive for risk of Rx opioid misuse in prior 6-Mo	"ED-LILNC" Support for patients in pain Opioid prescribing guidelines ED database/PDMP tool	Feasibility of intervention Substance use and mental health scores # of ED visits	6-months

-
Randomized controlled trials

Bohnert (2016)	U.S.	ED	204	Self reported opioid misuse in the prior 3-months determined via computerized screening survey (COMM)	Motivational Interviewing Session (30-mins) via therapist + education	Overdose risk behaviours Rate of non-medical opioid use	6-months
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Murphy (2017) [§]	U.S.	ED	165	5 or > ED visits in prior 12-Mo with > ½ pain complaints or drug-seeking behavior.	Multidisciplinary, individualized ED care plan	Total treatment cost differential	12-months
Neven (2016)	U.S.	ED	165	5 or > ED visits in prior 12-Mo with > ½ pain complaints or drug-seeking behavior.	Multidisciplinary, individualized ED care plan	# of ED visits Odds of receiving an opioid prescription at ED discharge MEQ of opioid dispensed	12-months
Rathlev (2016)	U.S.	ED	40	4 or > ED visits in prior 12-Mo with opioid use disorder (OUD) identified via SMS billing codes	ED database tool + opioid use care plan	MEQ prescribed at discharge MEQ administered in ED or inpatient Total medical charges # of ED visits # of ED visits with advanced imaging # of inpatient admission	12-months
Ringwalt (2015)	U.S.	ED	411	11 or > ED visits in prior 12-Mo and chronic noncancer pain determined via chart & Rx review	ED database tool + opioid use care plan + letter to patient & PCP	# of prescriptions received from ED. # of ED visits	12-months

%Abstract only. ++ Subgroup analysis of patients on opioids at ER presentation (pre=1512 and post=950). @ subgroup of chronic opioid use patients pre + post. § Murphy (2017) is an economic evaluation of the population and harm reduction strategy studied in Neven (2016). MINI: Mini-International Neuropsychiatric Interview as per DSM-IV criteria. Rx: prescriptions. MME: morphine milliequivalents (synonymous with mean morphine equivalent / MEQ). ED: Emergency department. PCP: primary care provider; RF: risk factors; #: number. All studies listed were compared to usual care as defined as standard practice in the institution.

See supplementary appendix 1 for full references.

Table 2 – Quality assessment of the studies included using the Newcastle-Ottawa Scale (NOS)

Author	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of harm reduction	Outcome of interest absent at start of study	Comparability of cohorts	Assessment of outcome with independency	Adequacy of follow-up length	Adequacy of loss to follow-up	Total Quality score
Albraith (2018)	*	*	*	*	**	*	*	*	7
Alexandridis (2017)	*	*	*	*	*	*	*	*	7
Alexandridis (2018)	*	*	*	*	*	*	*	*	7
Allen (2016)	*	*	*	*	*	*	*	*	7
Faryar (2017)	*	*	*	*	*	*	*	*	7
Fulson-Kehee (2015)	*	*	*	*	*	*	*	*	8
Ghobadi (2018)	*	*	*	*	*	*	*	*	7
Gugelmann (2013)	*	*	*	*	*	*	*	*	6
Hartung (2018)	*	*	*	*	*	*	*	*	8
Jurecska (2012)	*	*	*	*	*	*	*	*	0
Kahler (2017)	*	*	*	*	**	*	*	*	9
Maughan (2015)	*	*	*	*	*	*	*	*	5
Olsen (2016)	*	*	*	*	*	*	*	*	7
Pace (2017)	*	*	*	*	*	*	*	*	7
Svensson (2007)	*	*	*	*	*	*	*	*	7
Whiteside (2017)	*	*	*	*	*	*	*	*	5

A maximum score of 9 is possible. A score of 0 to 3 represent low quality; 4 to 6 represent moderate quality; 7 to 9 represent high quality.

Table 3. Quality assessment of randomized controlled trials using the Cochrane Risk of Bias Tool.

Author	Random sequence generation	Allocation concealment	Selective reporting	Other bias	Blinding of participants	Blinding of outcome	Incomplete outcome data	Final risk of bias
Rathlev (2016)	Low	Low	Low	Low	High	Unclear	Low	High
Neven (2016)	Low	Low	Low	Low	High	Low	Low	Mod
Murphy (2017)	Low	Low	Low	Low	High	Low	Low	Mod
Ringwalt (2015)	Low	High	Low	Low	High	Low	Low	Mod
Bohnet (2016)	Unclear	Unclear	Low	High	High	Low	High	High

Table 4. Harm reduction strategies identified

Harm Reduction strategy	Definition	Cohort	RCTs
Support for patients in pain	Support groups, case management and pain clinic vetting and referrals.	11	4
Hospital ED policy	Local practices to limit ED or inpatient OA prescribing and checking prescription drugs monitoring programs prior to prescribing	5	
Provider education	Education of medical professionals in chronic pain treatment	4	
Statewide prescription policies	Practices or wide-ranging regulations to limit OA prescription within a legislative territory	3	
Addiction treatment	Opioid agonist therapies and policies supporting their use	4	
Electronic alert system	Systems that alert providers to possible opioid abuse situations without mandating their use	2	
Community education	Promotion of public awareness of prescription opioid overdose	2	
Diversion control	Removal of unused medications and training of local law enforcement with OA diversion	2	
At-risk patient education	Tailored preventative interventions targeted at patients currently on opioid therapy	0	1
Naloxone policies	Promotion of the adoption of policies to disseminate the opioid antagonist naloxone to opioid users	2	
Multimodal	Composite approach that encompasses multiple elements of the previous harm reduction strategies as a combined package	2	

Figures

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

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5 demerol*.tw.kf. (231)
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7 dilaudid*.tw.kf. (69)
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9 fentanyl*.tw.kf. (16667)
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21 (oxy-contin* or oxycotin*).tw.kf. (226)
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32 Drug abuse/ (87805)
33 exp Drug Misuse/ (10703)
34 Drug Overdose/ (9457)
35 Neurotoxicity Syndromes/ (4428)
36 exp Opioid-Related Disorders/ (22304)
37 Poisoning/ (21631)
38 Psychoses, Substance-Induced/ (5082)
39 Self-Injurious Behavior/ (6447)
40 Street Drugs/ae [adverse effects] (1421)
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53 Hospital Medicine/ (119)
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55 Hospitalization/ (91123)
56 Intensive Care Units/ (45436)
57 exp Life Support Care/ (8408)
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59 Respiratory Care Units/ (579)
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Figure 1

Search strategy

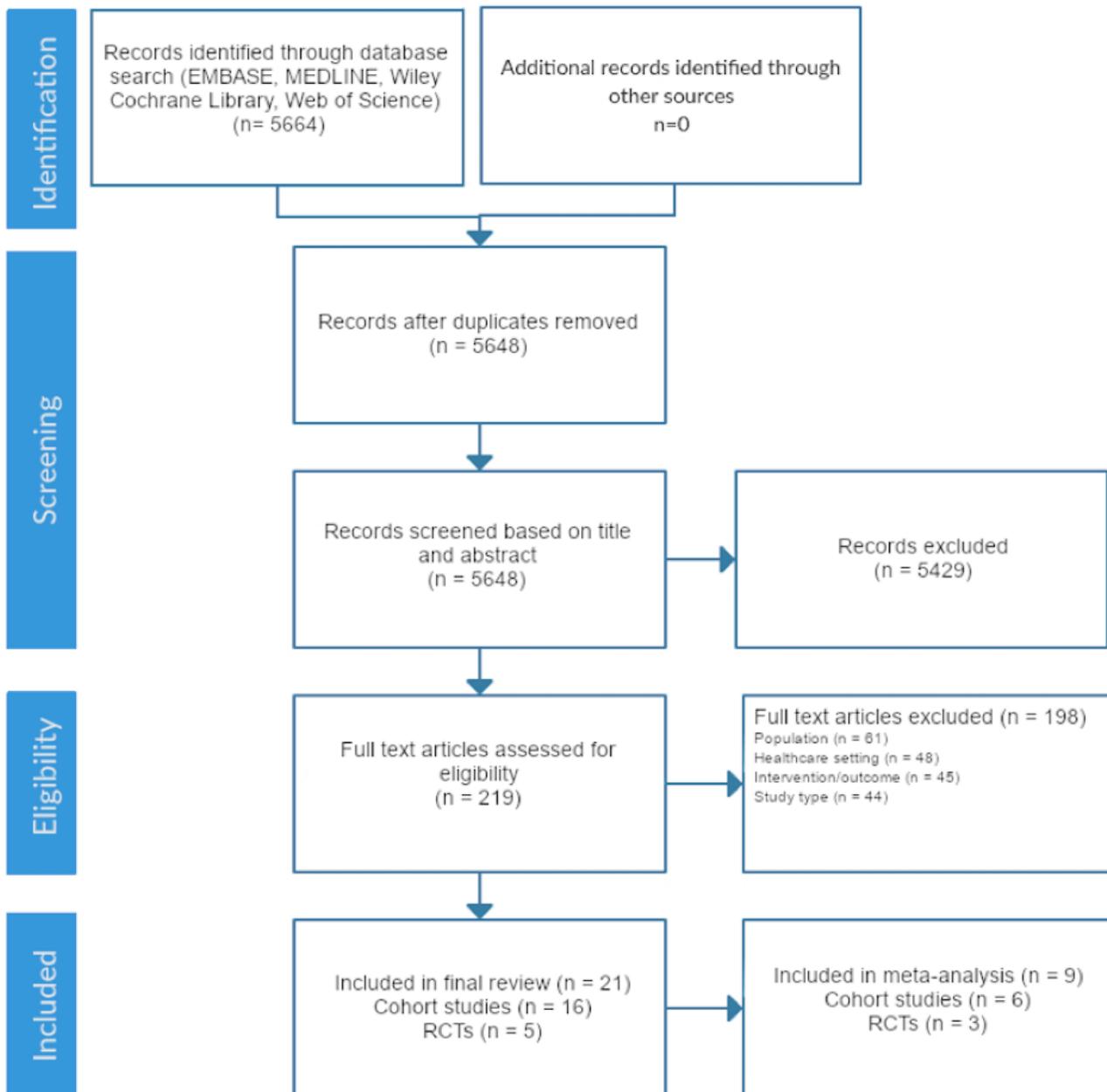


Figure 2

Flow diagram for study assessment

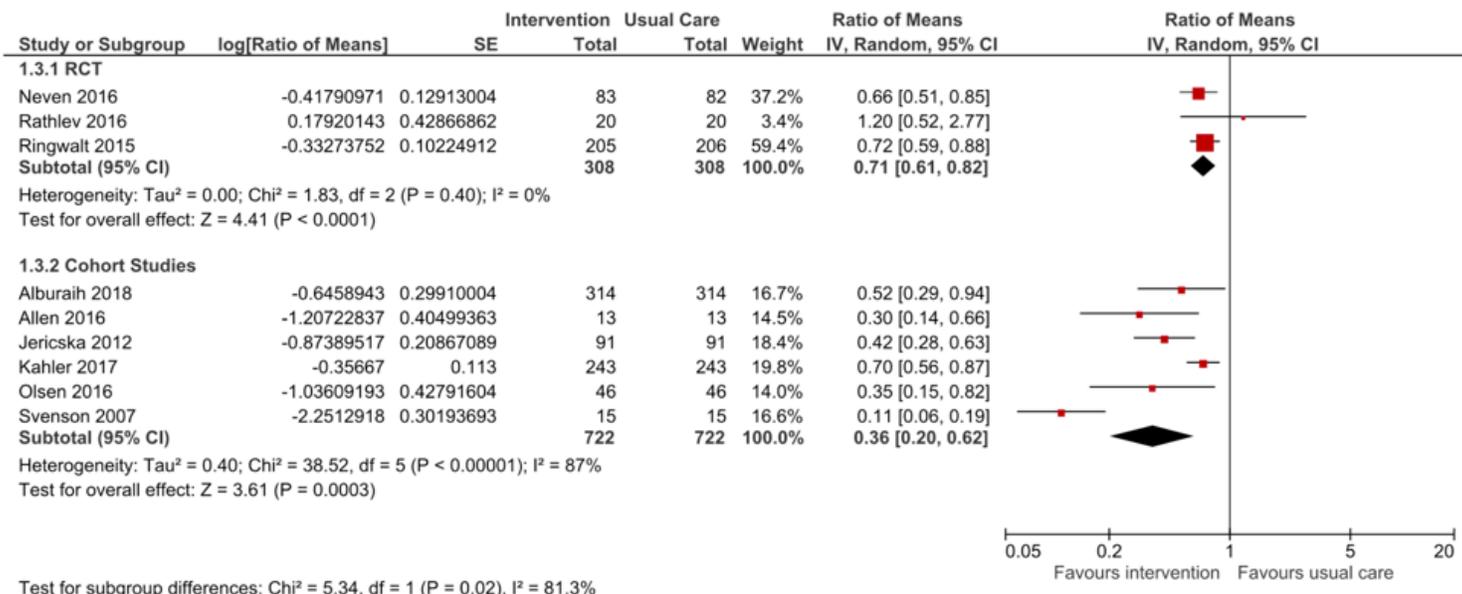


Figure 3

Meta-analysis of support for patients in pain harm reduction strategy for number of ED visits outcome.

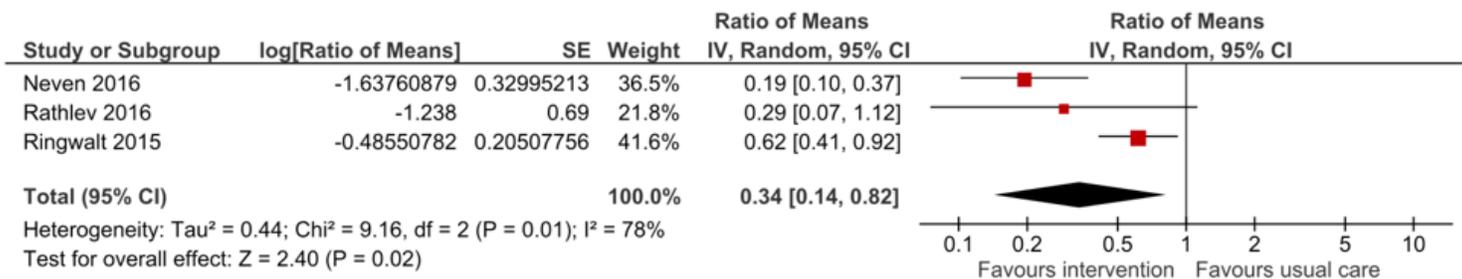


Figure 4

Meta-analysis of supports for patients in pain harm reduction for ED discharge opioid prescriptions outcome.

Supplementary Files

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- [AdditionalFile2.docx](#)