Comprehensive Psychiatry 96 (2020) 152135

Contents lists available at ScienceDirect

Comprehensive Psychiatry

journal homepage: www.elsevier.com/locate/comppsych

Prevention of suicide and reduction of self-harm among people with substance use disorder: A systematic review and meta-analysis of randomised controlled trials

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ARTICLE INFO

Keywords:
Suicide
Substance use disorder
Addiction
Alcohol
Drug

ABSTRACT

Background: People with substance use disorder (SUD) are at significantly greater risk of suicide compared with the general population. In recent years the number of suicides resulting from drug poisoning in England and Wales has increased. We sought to identify and evaluate the effect of interventions to prevent suicide or reduce self-harm among people with SUD.
Methods: We conducted a systematic review of randomised controlled trials (RCTs) of interventions for people with SUD that included suicide or self-harm-related primary outcomes. We searched Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, PubMed, Embase and Web of Science from inception until 13th January 2019. Studies were assessed for bias using the Cochrane Risk of Bias 2 tool. A random effects meta-analysis of standardised mean differences (SMD) was conducted.
Results: We identified six RCTs from four countries (Australia, Iran, the United States of America and the United Kingdom) comprising 468 participants in total. All but one study investigated psychosocial interventions. On average across studies there was weak evidence of a small positive effect of interventions on suicide or self-harm outcomes ($d = -0.20$, 95% CI = −0.39–0.00).
Limitations: Studies were heterogeneous in terms of population, intervention, controls and outcome. There were some concerns regarding bias for all trials. All trials were liable to type II error.
Conclusions: Evidence is currently lacking regarding the effectiveness of interventions to prevent suicide and reduce self-harm amongst people with SUD.

1. Introduction

Globally, people with substance use disorder (SUD) are at significantly greater risk of suicide compared with the general population [1]. SUD is also widely recognised as an important modifiable risk factor for suicide [2], with 45% and 33% of those who died by suicide in England whilst in contact with services, having a history of alcohol or other drug misuse respectively [3]. Furthermore, in over half of National Health Service suicide-related compensation claims, the deceased had a history of substance misuse [4].

There are numerous biopsychosocial mechanisms, which may contribute to the increased risk of suicide amongst people with SUD. These include: 1) SUD leading to unemployment, social isolation and marginalisation; 2) substance use influencing cognition and behaviour, which may result in disinhibition and impulsivity; and 3) pain, distress and psychiatric conditions increasing the likelihood of both SUD and suicide [5–7]. In light of these specific mechanisms, it cannot be assumed that interventions targeting suicide and self-harm reduction in the general population can be applied to people with SUD; more specific strategies may need to be utilised in this particular population.

In recent years there has been a large increase in the incidence of drug-related deaths in England and Wales; the rate peaked in 2016 at the highest level since records began [8]. Although the majority of these deaths are considered accidental poisonings, suicidal

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https://doi.org/10.1016/j.comppsych.2019.152135

intent can be extremely difficult to determine [5], and an increase in the number of suicides resulting from drug poisoning has been identified as a contributory factor [9].

Current research and guidelines on co-existing severe mental illness and substance misuse provide minimal evidence regarding the management of suicide risk or self-harm in this population [10,11]. Furthermore, substance misuse is often an exclusion criterion when researching interventions. In two Cochrane reviews of interventions for self-harm, over a quarter of studies specified a type of substance misuse in their exclusion criteria [12,13]. In light of the absence of clear guidelines in this area, we sought to identify and evaluate the effect of interventions to prevent suicide or reduce self-harm specifically for people with SUD.

2. Method

This systematic review was conducted in accordance with the Cochrane Collaboration framework guidelines, [14] and reporting conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement) [15]. The review protocol is accessible on PROSPERO CRD42017076236.

The population of interest in this review was any person misusing at least one substance, which included alcohol but excluded tobacco. The intervention and comparison groups were unspecified. The outcomes of interest were suicide, suicidal ideation, suicide attempts or non-suicidal self-harm (or a combination of the latter two, commonly referred to as self-harm).

2.1. Search strategy

The following databases were searched for publications, without language restriction, from the inception of each database to 13th January 2019: Cochrane Central Register of Controlled Trials Register, PsycINFO, PubMed, Embase and Web of Science. Search terms broadly included: (substance (including alcohol)) AND (misuse) AND (suicide OR self-harm) AND (randomised controlled trial). The full search strategies are included in Supplementary File 1. Reference lists of all included studies and key systematic reviews of related interventions were screened to identify additional studies [10,12,13,16–20].

2.2. Eligibility criteria

Studies were included if they: 1) were individualised or cluster randomised controlled trials (RCTs); 2) included only participants who misused substances including alcohol but excluding tobacco; 3) investigated suicide, suicidal ideation, suicide attempts or non-suicidal self-harm as a primary outcome. Studies were excluded if the suicide- or self-harm-related outcomes were reported as secondary or supplementary outcomes. This distinction diverges from the pre-specified protocol, due to the difficulty in identifying all studies including relevant secondary outcomes and consequently the risk of publication bias. Reviews were excluded, but were used as a secondary source for relevant papers. No restrictions were applied based on participants' age or comorbidities.

2.3. Data extraction and quality assessment

Two authors (out of P.P., K.H., and V.C.) independently screened titles and abstracts, reviewed full texts of all potentially relevant studies, extracted data using a standardised extraction form (Supplementary File 2) and assessed included studies for bias using the Cochrane Risk of Bias 2 Assessment Tool (Supplementary File 3) [21]. The review aimed to assess the effect of introducing an intervention within a health system; therefore only intention-to-treat analyses were of interest. Authors were contacted to request study protocols to enhance the accuracy of the assessments. The overall risk of bias (ROB) for each study was classified as 'low' if all domains were judged to be low risk of bias, 'some risk of bias' if some concerns regarding bias were identified in one to four domains but no domains were considered to be high risk of bias, and 'high risk of bias' if one or more domains was judged to be at high risk of bias or there were some concerns regarding risk of bias for all five domains. Disagreements were resolved by discussion.

2.4. Data analysis

To maximise comparability of results, we present only follow-up data at six months (or as close to six months as possible).

We present tables of study-specific standardised mean differences (SMDs) for continuous outcomes and odds ratios (ORs) for binary outcomes, each with 95% confidence intervals (CIs). In order to pool across outcome types in a meta-analysis, we approximated SMDs and standard errors of SMDs from ORs using standard formulae [22].

As our eligibility criteria were broad, we anticipated heterogeneity in all aspects of the population, intervention, comparison and outcome (PICO) framework. We therefore performed a random effects meta-analysis as our primary analysis, with a fixed effect model as a sensitivity analysis. We tested for statistical heterogeneity using the Cochran Q test and estimated the proportion of variability in effect estimates due to heterogeneity using the I^2 statistic [23]. We have also presented a 95% prediction interval in addition to pooled estimates; this represents uncertainty about the likely true intervention effect in a future study, allowing for heterogeneity in the population of studies to date [24].

For one study, where there was more than one intervention group consisting of different doses of medication, the largest and smallest doses were compared due to ambiguity with regards to classification of the middle dose as an intervention or control [25]. Where a single study included two relevant primary outcome measures, these were averaged to form a composite SMD [22,26]. The correlation (r) between outcomes was unknown, and was assumed to be 0.5, as all outcomes were expected to be positively correlated.

The possibility of publication bias or other form of small study effects was assessed by inspection of a funnel plot (Supplementary File 4). Analyses were conducted using Stata [27].

3. Results

3.1. Search results

Our search (Supplementary File 1) identified 6862 references, of which 2214 were duplicates. After screening titles and abstracts, 4577 articles were excluded. Of 71 full-texts assessed for eligibility, seven were included, which described six RCTs [25,26,28–32]) (Fig. 1).

3.2. Study characteristics

Study characteristics are summarised in Table 1. All studies were individually randomised. Three of the included RCTs were based in the USA [29–32]. The remaining trials were based in Australia [26], the UK [28] and Iran [25]. With regards to the population included, three trials included people who misused alcohol only [28,30–32], two included people with alcohol and drug misuse [26,29], and one included only people with severe opioid use disorder [25]. Four studies restricted the population to those who reported suicidal ideation [26,29,32], had attempted suicide [26,29], or presented to hospital with self-harm [28]. Additional inclusion criteria in three trials were major depressive disorder [25], borderline personality disorder [30,31] and high emotional dysregulation [32]. All studies

Table 1
Summary of included studies (CBT: Cognitive behavioural therapy; DBT: dialectical behavioural therapy; DDT: dynamic deconstructive psychotherapy; FRAMES: Feedback about the adverse effects of excessive alcohol consumption, an emphasis on Responsibility for change lying with the individual, provision of Advice about reducing alcohol consumption, a Menu of options for further intervention if this is required, an Empathic stance towards the patient, and the enhancement of Self-efficacy).

Study	Country	Participants	Substance misuse	Mental health comorbidity	Age/ sex if restricted	Setting of recruitment and intervention	Intervention	Comparison group	Outcome	Risk of bias
Ahmadi et al. [25]	Iran	N = 51	Severe opioid use disorder	Major depressive disorder	Male	Recruited from and delivered on inpatient psychiatric ward	Single, sublingual dose of buprenorphine (96 mg)	Single, sublingual dose of buprenorphine (32 mg)	Beck Scale for suicide ideation	Some concerns
Crawford et al. [28]	UK	N = 103	Alcohol misuse	Nil specified	>18 years	Recruited from emergency department	'FRAMES' approach Single 1:1 session & leaflet	Leaflet	Re-attendance at emergency department with self-harm within 6 months	Some concerns
Esposito-Smythers et al. [29]	USA	N = 40	Alcohol/ cannabis use disorder	Nil specified	13-17 years	Recruited from inpatient units Outpatient intervention	CBT Separate 1:1 sessions for adolescents and parents with reducing frequency from twice weekly to monthly over 12 months	Enhanced treatment as usual	Suicidal ideation over previous month (Suicidal Ideation Questionnaire-Senior Version)	High
Gregory et al. [30,31]	USA	N = 30	Alcohol misuse/ dependence	Borderline personality disorder	18-45 years	Recruited through range of clinical settings including emergency department and hospital settings Outpatient intervention	DDT Weekly 1:1 sessions +/- group therapy over 12-18 months	Optimised community care	Self-harm (adapted 3 month version of the Lifetime Parasuicide Count)	High
Morley et al. [26]	Australia	N = 185	Alcohol/ drug misuse	Nil specified	18-65 years	Recruited from emergency dept. or outpatient drug and alcohol services Outpatient intervention	CBT 8 × 1:1 sessions with homework and 1x focus group session 3 months later	Treatment as usual	a) Presence of suicide ideation (weekly) b) Beck Scale for suicide ideation	High
Wilks et al. [32]	USA	N = 59	Heavy episodic alcohol intake	High emotional dysregulation	>17 years	Recruited through online forums and classifieds Delivered online	DBT Weekly modules with homework over 8 weeks	Waiting list for treatment	Beck Scale for suicide ideation	Some concerns

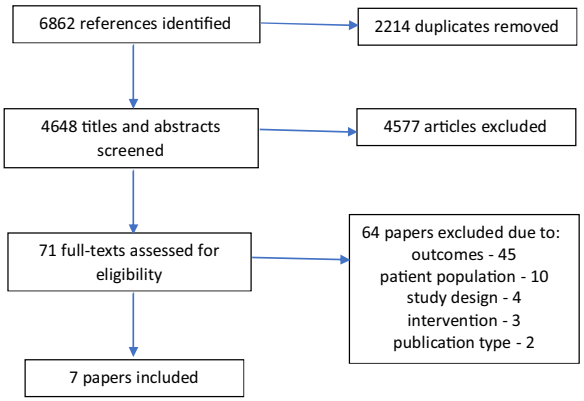

Fig. 1. Prisma diagram.

investigated interventions for adults, except for one which investigated cognitive behavioural therapy (CBT) in adolescents [29].

Five trials investigated psychosocial interventions: CBT [26,29], dynamic deconstructive psychotherapy (DDT) [30,31], brief intervention using Feedback about the adverse effects of excessive alcohol consumption, an emphasis on Responsibility for change lying with the individual, provision of Advice about reducing alcohol consumption, a Menu of options for further intervention if this is required, an Empathic stance towards the patient, and the enhancement of Self-efficacy (FRAMES) [28], and online dialectical behavioural therapy (DBT) [32]. The sixth trial, based in Iran, compared different high doses of buprenorphine (32 mg, 64 mg or 96 mg) specifically for men with severe opioid use disorder [25]. Preliminary evidence of effectiveness of low dose buprenorphine in reducing suicidal ideation amongst individuals without substance misuse was cited as justification for the trial [33,34].

In Ahmadi et al. [25], the comparison group received a lower dose (32 mg) of buprenorphine compared with the intervention group (96 mg). In two studies, the control group received optimised community care or enhanced treatment as usual. This involved referral to an alcohol rehabilitation centre and signposting to suitable clinics/therapists in Gregory et al. [31], whilst in Esposito-Smythers et al. [29] treatment as usual was determined by external providers, but supplemented with a diagnostic evaluation that was shared with community services, and medication management by the trial psychiatrist. In Morley et al. [26], the comparison group received treatment as usual only, which could include pharmacotherapy management and/or advice to seek support from community mental health services or the participants' general practitioner. Finally, in the trial by Crawford et al. [28], the control group received a leaflet, and in Wilks et al. [32] participants were allocated to a waiting list for treatment.

Suicidal ideation was an outcome in four trials [25,26,29,32]; self-reported self-harm [30,31] and emergency department re-attendance with self-harm [28] were outcomes in the remaining trials. Follow-up time for measuring outcomes ranged from three days to 18 months.

Although all studies described the efficacy of the interventions, three were pilot feasibility trials [29,31,32], for which formal hypothesis testing is not recommended [35]. The other three studies acknowledged their sample size and/or power to be a limitation [25,26,28]. Furthermore, of the six trials included, three were assessed to be at high risk of bias [26,29,30,31], whilst there were some concerns regarding risk of bias for the remaining studies (Table 2).

3.3. Study findings

Results from four studies, which included suicidal ideation (as a continuous variable) as the main outcome, are summarised in Table 3. These studies investigated CBT, online-DBT and different doses of buprenorphine. The SMD was estimated to be negative, favouring the intervention, in all studies. However, all estimates were small (absolute SMD < 0.2) and confidence intervals were very wide and inconclusive.

Results from three studies, which investigated a discrete primary outcome relating to suicide or self-harm, are summarised in Table 4. Amongst the intervention groups at six months, there was an estimated 43% reduction in the odds of re-attendance at the emergency department with self-harm following a brief intervention using the 'FRAMES' approach [28], and an estimated 52% reduction in self-reported self-harm following DDT [31]. However, confidence intervals around these results were very wide and inconclusive. In Morley's trial of an opportunistic CBT intervention there was an estimated 42% increase in the presence of suicidal ideation, but again the confidence intervals were wide and inconclusive. Furthermore, this contrasted with the reduction in mean difference of suicidal ideation scores noted in Table 3 [26].

The pooled estimate from a random effects meta-analysis of all six RCTs was an SMD of -0.20 (95% CI -0.39 to -0.00), indicating weak evidence of a small effect of the intervention versus control on suicide or self-harm. There was no statistical evidence for heterogeneity (I-squared = 21.1%, p = 0.27), although this may be due to low power. When allowing for potential heterogeneity, a 95% predictive interval for the true SMD in a future study ranged from -0.60 to 0.21. A sensitivity analysis with a fixed effect model gave a very similar pooled effect estimate but with a narrower confidence interval, indicating somewhat stronger evidence of a small intervention effect (SMD = −0.23 95% CI-0.36 to −0.09). Results are shown in Fig. 2. Visual inspection of the funnel plot did not highlight any concerns about publication bias or other small study effects (Supplementary File 4).

4. Discussion

We found little evidence of an effective intervention to prevent suicide or reduce self-harm among people with substance use disorders. The pooled standardised mean difference with regards to suicide or self-harm outcomes from a random effects meta-analysis was small.

4.1. Strengths and limitations

To our knowledge this is the first systematic review evaluating interventions aimed at reducing self-harm or preventing suicide amongst people with SUD. We followed standardised procedures for the assessment of bias and followed PRISMA guidelines in reporting our findings. Nevertheless, the findings must be interpreted in light of the following limitations.

The review identified only a small number of trials, all with limited sample sizes. Crawford et al. (2014) estimated that a sample size of 1400 would have been required to detect a 30% reduction in self-harm repetition at six months with 80% power and a 5% level of statistical significance. The combined total of all participants across all six trials is approximately a third of the number required to detect a potentially clinically important effect. Furthermore, we had at least some concerns of bias with regards to all studies included.

Trials were diverse in terms of population, interventions, comparison groups and outcomes. Somewhat surprisingly, there was no evidence of statistical heterogeneity, although this was likely

Table 2
Risk of bias summary (Green=low, yellow = some concerns, red=high).

	Study					
	Ahmadi et al. (2018)	Crawford et al. (2010)	Esposito-Smythers et al. (2011)	Gregory et al. (2008), (2009)	Morley et al. (2014)	Wilks et al. (2018)
Risk of bias arising from the randomization process						
Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)						
Risk of bias relating to missing outcome data						
Risk of bias in measurement of the outcome						
Risk of bias in selection of the reported result						
Overall risk of bias						

Table 3
Summary of continuous primary outcome data (SD: standard deviation; SMD: standardised mean difference; CI: confidence intervals).

Study	Measure, timepoint	Intervention, no. participants with outcome data	Intervention, mean (SD)	Control, no. participants with outcome data	Control, mean (SD)	Mean difference	SMD (95% CI)
Ahmadi et al. [25]	BSSI score, day 3	14	0.00 (0.00)	16	0.63 (2.50)	−0.63	−0.05 (-0.88, 0.77)
Esposito-Smythers et al. [29]	SIQ-S, 6 months	17	28.65 (22.17)	17	38.24 (35.54)	−9.59	−0.11 (-1.20, 0.99)
Morley et al. [26]	BSSI, 6 months	44	5.82 (5.58)	30	6.00 (6.61)	−0.18	0.00 (-0.47, 0.46)
Wilks et al. [32]	BSSI, 4 months	24	5.45 (6.62)	26	9.59 (8.99)	−4.14	−0.11 (-1.34, 1.12)

Table 4
Summary of discrete primary outcome data (SMD: standardised mean difference; CI: confidence intervals).

Study	Measure, timepoint	Intervention, n (% of those with outcome data at 6 months)	Control, n (% of those with outcome data at 6 months)	Odds ratio (95% CI)	SMD (95% CI)
Crawford et al. [28]	Re-attendance at emergency department with self-harm, 6 months	7 (13)	11 (21)	0.57 (0.17-1.78)	−0.31 (-0.48, -0.15)
Gregory et al. [31]	Self-reported self-harm, 6 months	5 (45)	7 (64)	0.48 (0.06-3.49)	−0.41 (-0.86, 0.04)
Morley et al. [26]	Presence of suicidal ideation (weekly), 6 months	6 (14)	3 (10)	1.42 (0.27-9.51)	0.19 (-0.14, 0.53)

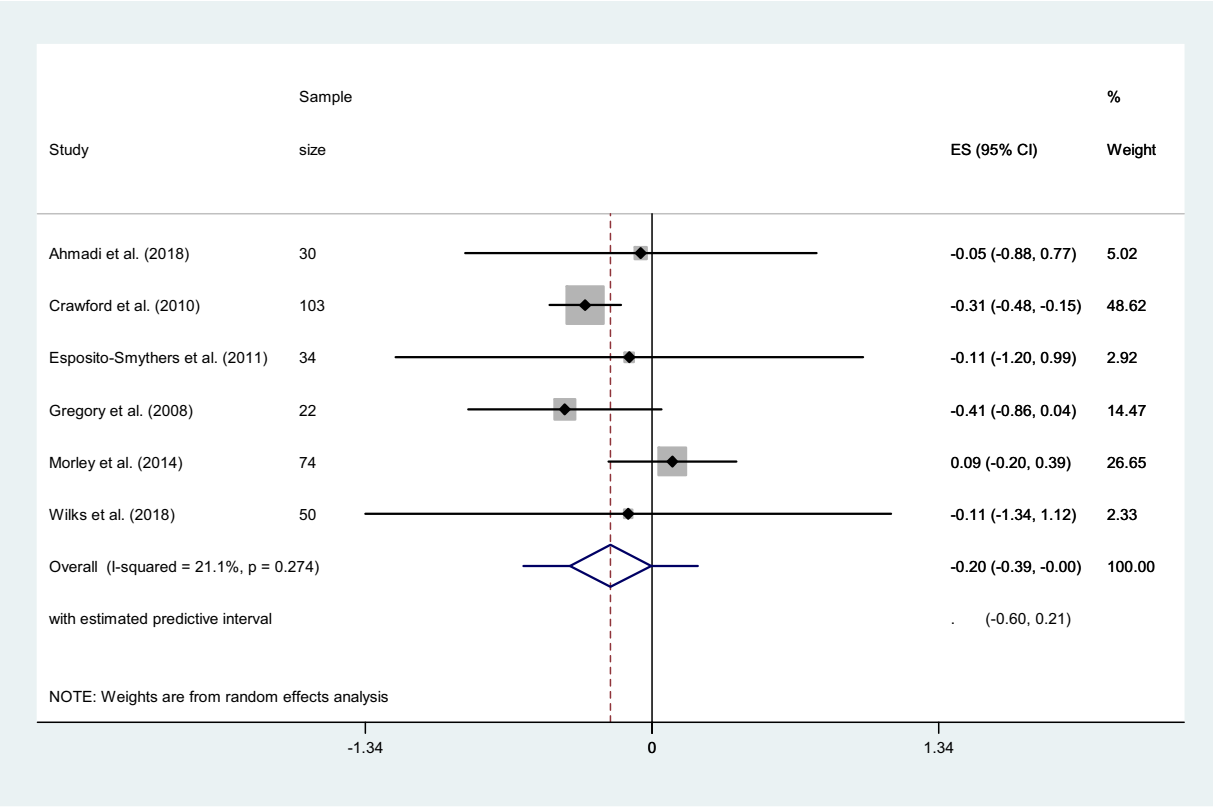

Fig. 2. Forest plot of standardised mean differences for suicide or self-harm outcomes in each included study (Below 0 favours intervention; composite outcome included for Morley et al. [26].

due to small sample sizes. The wider 95% predictive interval presented may be a better indication of the true amount of uncertainty we have at present about the effectiveness of interventions. The pooled result should therefore be interpreted with caution.

We considered the effect of treatment on two related but distinct phenomena: self-harm and suicide-related outcomes. There is, however, growing evidence of a distinction between non-suicidal self-injury, suicidal ideation and suicide attempts [36]. Nonetheless intent can often fluctuate and self-harm is a key risk factor for suicide [37], and for these reasons we grouped both outcomes together within one review.

4.2. Findings in the context of the wider literature

A broad review of suicide prevention interventions highlighted that evidence is limited for interventions other than means restriction, schools based awareness programmes and treatment of psychiatric conditions [20]. Two systematic reviews of psychosocial and pharmacological interventions for self-harm (irrespective of intent), in adults specifically, were also limited in their findings [12,13]. The review of psychosocial interventions found low-moderate quality evidence indicating a reduction in repetition of self-harm following CBT-based interventions, and low quality evidence regarding repetition of self-harm following DBT-based interventions. Evidence for a range of other approaches was inconclusive. The review of pharmacological interventions included only seven trials of 546 patients in total, and the quality of the evidence was low or very low, prohibiting conclusions being drawn. Many of the studies included in these reviews excluded people with a history of substance misuse. Furthermore, systematic reviews on dual diagnosis have not explored suicide- or self-harm-related outcomes [10,18].

In addition to the small number of identified trials measuring suicide- or self-harm-related outcomes as the primary outcome, several trials were found which investigated these as secondary or supplementary outcomes [38–46], or reported the suicide component of other scales separately, such as scales for depression or aggression [47,48] (Supplementary File 5). In keeping with the studies reviewed here, these studies also found little evidence for treatment effects but again were frequently subject to similar limitations as the studies included in this review. An uncontrolled pilot study of a suicide prevention module for patients attending group-based addiction treatment has had positive preliminary results [49]. A RCT of this module, with an estimated enrolment of 900 participants, is currently in progress [50].

4.3. Conclusion

Evidence is currently lacking regarding effective interventions to prevent suicide and reduce self-harm amongst people with SUD. RCTs investigating suicidality and self-harm are vulnerable to type II error, as well as bias resulting from inadequate blinding and the use of self-reported measures. Given the importance of suicide and self-harm among people with SUD, there is a pressing need for adequately powered and robustly conducted trials of new and existing interventions, examining suicide or self-harm-related primary outcomes.

Author contributions

P.P. conceived the idea for the review. P.P. drafted the proposal, all co-authors of the proposal provided feedback. The search strategy was first performed including all publications until September 2017. It was then re-run to include all publications between August 2017 and January 2019. In the first round, K.H. and P.P. independently screened titles and abstracts, reviewed full texts of all potentially relevant studies, extracted data using a standardised extraction form and assessed included studies for bias using the Cochrane Risk of Bias 2 Assessment Tool. V.C. and P.P. performed the same tasks for results obtained when the search strategy was re-run. P.P. performed the meta-analysis with advice from H.E.J.. P.P. drafted the paper with feedback from all co-authors.

Funding

This work was supported by the MRC Addiction Research Clinical Training programme. HEJ was supported by an MRC Career Development Award in Biostatistics (MR/M014533/1).

Declaration of Competing Interest

M.H. has received speaker honoraria from MSD, Gillead, Abbvie unrelated to this work.

Acknowledgements

We would like to acknowledge Martin Hewitt, librarian, for advice on the search strategy, Dr Clare French and Dr Jelena Savovic for providing feedback on the review protocol and Dr Jose Lopez-Lopez for statistical advice. PP's PhD Clinical Fellowship is funded by MRC Addiction Research Clinical Training programme. PM, DG and MH are supported by the NIHR Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol, England. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.comppsych.2019.152135.

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