Cochrane Library

Cochrane Database of Systematic Reviews

Pharmacological interventions for self-harm in adults (Protocol)

Witt KG, Hawton K, Hetrick SE, Taylor Salisbury TL, Townsend E, Hazell P

Witt KG, Hawton K, Hetrick SE, Taylor Salisbury TL, Townsend E, Hazell P.
Pharmacological interventions for self-harm in adults (Protocol).
Cochrane Database of Systematic Reviews 2020, Issue 7. Art. No.: CD013669.
DOI: 10.1002/14651858.CD013669.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Pharmacological interventions for self-harm in adults

Katrina G Witt[1,2], Keith Hawton[3], Sarah E Hetrick[4], Tatiana L Taylor Salisbury[5], Ellen Townsend[6], Philip Hazell[7]

[1]Orygen, Parkville, Melbourne, Australia. [2]Centre for Youth Mental Health, The University of Melbourne, Melbourne, Australia. [3]Centre for Suicide Research, Department of Psychiatry, University of Oxford, Oxford, UK. [4]Department of Psychological Medicine, University of Auckland, Auckland, New Zealand. [5]Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. [6]Self-Harm Research Group, School of Psychology, University of Nottingham, Nottingham, UK. [7]Discipline of Psychiatry, The University of Sydney School of Medicine, Sydney, Australia

Contact address: Katrina G Witt, katrina.witt@orygen.org.au.

Editorial group: Cochrane Common Mental Disorders Group.
Publication status and date: New, published in Issue 7, 2020.

Citation: Witt KG, Hawton K, Hetrick SE, Taylor Salisbury TL, Townsend E, Hazell P. Pharmacological interventions for self-harm in adults (Protocol). *Cochrane Database of Systematic Reviews* 2020, Issue 7. Art. No.: CD013669. DOI: 10.1002/14651858.CD013669.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects of pharmacological agents or natural products for self-harm (SH) compared to comparison types of treatment (e.g. placebo or alternative pharmacological treatment) for adults (aged 18 years or older) who engage in SH.

BACKGROUND

Description of the condition

Self-harm (SH), which includes all intentional acts of self-poisoning (such as intentional drug overdoses) or self-injury (such as self-cutting), regardless of degree of suicidal intent or other types of motivation (Hawton 2003), has been a growing problem in most countries. In Australia, for example, it is estimated that there are now more than 26,000 general hospitalisations for SH each year, or a rate of 116.7 per 100,000 persons (Harrison 2014), similar to rates observed in a number of other comparable countries (Canner 2018; Griffin 2014; Morthorst 2016; Ting 2012; Wilkinson 2002). However, it is notable that rates of emergency department presentations for SH are often higher than hospitalisations (Bergen 2010; Corcoran 2015). In the UK, for example, higher rates of emergency department presentations for SH in both females (442 per 100,000) and males (362 per 100,000) have been reported (Geulayov 2016). There are also many more episodes of SH occurring in the community that do not come to the attention of clinical services. Worldwide, for example, the World Health Organization (WHO) estimates that the rate of SH may be as high as 400 per 100,000, according to self-report data (WHO 2014).

In contrast to suicide rates, rates of hospital-presenting SH are higher in females than in males in most countries (Canner 2018; Griffin 2014; Masiran 2017; Morthorst 2016; Ting 2012; Wilkinson 2002), with rates peaking in younger adults up to 24 years of age (Perry 2012). However, this difference decreases over the life cycle (Hawton 2008). SH is less common in older people, but tends to be associated with higher suicidal intent (Hawton 2008), with consequent greater risk of suicide (Murphy 2012).

For those who present to hospital, the most common method of SH is self-poisoning. Overdoses of analgesics and psychotropics, especially paracetamol or acetaminophen, are common in some countries; particularly high-income countries. Self-cutting is the next most frequent method used by those who present to hospital. However, in the community, self-cutting and other forms of self-injury are far more frequent than self-poisoning (Müller 2016).

SH is often repeated. Up to one-quarter of those who present to hospital following SH return to the same hospital within a year (Carroll 2014; Owens 2002); although some individuals may present to another hospital. Others may not present to hospital at all given that studies identifying SH repetition via self-report suggest that as many as one in five report further SH episodes following a hospital presentation (Carroll 2014). Repetition is more common in individuals who have a history of previous episodes of SH, personality disorder, psychiatric treatment, and alcohol or drug misuse (Larkin 2014). Risks of repeat SH may also be associated with method. Rates of repetition are higher among those who present to hospital following self-injury alone (Carroll 2014; Lilley 2008), or combined self-injury and self-poisoning (Perry 2012), compared to those who present for self-poisoning alone.

SH is associated with suicide. The risk of death by suicide within one year among people who present to hospital with SH varies across studies from nearly 1% to over 3% (Carroll 2014; Owens 2002). This variation reflects the characteristics of the population, and the background national suicide rate. In the UK, for example, during the first year after an episode of SH, the risk of suicide is around 50 times that of the general population (Geulayov 2019). One quarter of these deaths are estimated to occur within one month after discharge, and almost 50% by three months (Forte 2019), although the risk of suicide appears to remain elevated for a number of years (Geulayov 2019). A history of SH is the strongest risk factor for suicide across a range of psychiatric disorders. Repetition of SH further increases the risk of suicide (Zahl 2004).

SH and suicide are the result of a complex interplay between genetic, biological, psychiatric, psychological, social, cultural, and other factors. Psychiatric disorders, paricularly mood and anxiety disorders, are associated with the largest contribution to the risk of both SH (Hawton 2013), and suicide in adults (Ferrari 2014). Personality disorders, including borderline personality disorder, are also associated with SH, particularly frequent repetition. Alcohol use may also play an important role (Ferrari 2014). Both psychological and biological factors appear to further increase vulnerability to SH. Psychological factors may include difficulties in problem-solving, low self-esteem, impulsivity, vulnerability to having pessimistic thoughts about the future (i.e. hopelessness), and a sense of entrapment. Biological factors include disturbances in the serotonergic and stress response systems (van Heeringen 2014).

Description of the intervention

Given the high prevalence of depression in people who engage in SH, pharmacological interventions may include antidepressants, antipsychotics, anxiolytics (including both benzodiazepines and non-benzodiazepine anxiolytics), and mood stabilisers (including anticonvulsants and lithium). Other pharmacological agents may also be trialled.

How the intervention might work

Antidepressants

Antidepressants can be divided into a number of classes, including: tricyclics, newer generation antidepressants (e.g. selective serotonin reuptake inhibitors [SSRIs]), and other antidepressants (e.g. monoamine oxidase inhibitors [MAOIs]). Tricyclic antidepressants primarily inhibit both serotonin and norepinephrine reuptake, whereas SSRIs specifically target synaptic serotonergic reuptake (Feighner 1999). Given the link between serotonin activity, impulsivity, and suicidal behaviour, both tricyclic and SSRI antidepressants may be associated with a serotonin-mediated reduction in impulsivity and enhanced emotion regulation, which might possibly reduce the likelihood that an individual will engage in SH (van Heeringen 2014).

Antidepressants are often prescribed in the same dose range used to treat major depression. However, owing to the increased risk of overdose in this population, including the likelihood that people who engage in self-poisoning may use their own medication (Gjelsvik 2014), antidepressants associated with lower case fatality indices (e.g. SSRIs) are generally preferred (Hawton 2010).

Antipsychotics

In people with a history of repeat SH, treatment with antipsychotics may be used to reduce heightened levels of arousal often experienced by them, especially in relation to stressful life events. By reducing this arousal, the urge to engage in SH may be reduced, although there is little evidence for their efficacy in reducing suicidal behaviour in adults (Stoffers 2010). Lower doses may

be prescribed to obtain this effect than is generally used in the treatment of psychotic disorders.

Anxiolytics, including both benzodiazepines and non-benzodiazepine anxiolytics

Given this population experiences a high prevalence of anxiety disorders (Hawton 2013) anxiolytics, including benzodiazepines and non-benzodiazepine anyiolytics, may be used to reduce suicidal behaviour (Tyrer 2012). However, because of their GABAminergic effects, benzodiazepines may increase aggression and disinhibition (Albrecht 2014). In some individuals, benzodiazepines may also increase the risk of repetition of SH. Therefore, it is usually recommended that benzodiazepines are used very cautiously, if at all, in people at risk of SH.

Mood stabilisers (including antiepileptics)

Mood stabilisers may have a role for people diagnosed with bipolar disorder or unipolar depression, especially to prevent the recurrence of episodes of mood disorder (Cipriani 2013b). Therefore, these drugs might reduce the risk of SH. However, to date, this effect has only been found for lithium (Cipriani 2013a). Lithium may reduce the risk of SH via a serotonin-mediated reduction in impulsivity and aggression. It is also possible that the long-term clinical monitoring, which all persons prescribed lithium must undergo might contribute to a reduction in SH (Cipriani 2013a).

Other pharmacological agents

Other pharmacological agents, particularly the N-Methyl-D-aspartate receptor antagonist, ketamine, may also be trialled. Ketamine has been shown to have an antisuicidal effect, independent of its antidepressant effects (Sanacora 2017). As a result, the FDA has recently granted approval for the use of both ketamine and esketamine, as adjunctive treatments to antidepressant therapy (FDA 2019). Ketamine has been associated with reduced suicidal ideation severity in the short term in adults with treatment-resistant mood disorders (Wilkinson 2018; Witt 2020). However, few trials have investigated the effect of ketamine over longer time periods. The effectiveness of ketamine on SH, and potential adverse effects of ketamine administration, such as dissociation, emergence psychosis, and rebound suicidal ideation, or behaviour, or both, remain under-studied (Witt 2020).

Natural products

There is some interest in the use of natural products, for example dietary supplementation of omega-3 fatty acids (fish oils; Tanskanen 2001). Omega-3 fatty acids have been implicated in the neural network, which is shown to correlate with the lethality of recent SH (Mann 2013). Blood plasma polyunsaturated fatty acid levels have also been implicated in the serotonin-mediated link between low cholesterol and SH, suggesting that low omega-3 fatty acid levels may have a negative impact on serotonin function (Sublette 2006). For those in whom SH is impulsive, omega-3 supplementation may stimulate serotonin activity, thereby reducing the likelihood of engaging in SH (Brunner 2002).

Why it is important to do this review

SH is a major social and healthcare problem. It represents significant morbidity, is often repeated, and is linked with suicide. Many countries now have suicide prevention strategies, all of which include a focus on improved management of people presenting with SH (WHO 2014). SH also leads to substantial healthcare costs (Sinclair 2011). In the UK, the overall median cost per episode of SH has been estimated to be £809, although costs are significantly higher for cases of combined self-injury and self-poisoning, compared to either self-injury or self-poisoning alone. These costs are mainly attributable to health-service level contact (i.e. inpatient stay or admission to intensive care; Tsiachristas 2017).

In the UK, the National Collaborating Centre for Mental Health (NCCMH) produced the first guideline on the treatment of SH behaviours in 2004 (NCCMH 2004). This guideline focused on the short-term physical and psychological management of SH. They updated this guidance in 2011, using interim data from a previous version of this review as the evidence-base, and focused on the longer-term psychological management of SH (NICE 2011). Subsequently, similar guidelines have been published by the Royal College of Psychiatrists (Royal College of Psychiatrists 2014), the Royal Australian and New Zealand College of Psychiatrists (Carter 2016), and a number of German Professional Associations and Societies (Plener 2016), amongst others (Courtney 2019).

In 2021, the guidance contained in the 2011 NICE guidelines for the longer-term management of SH will be due for updating. Therefore, we are updating our review (Hawton 2015), in order to provide contemporary evidence to guide clinical policy and practice.

OBJECTIVES

To assess the effects of pharmacological agents or natural products for self-harm (SH) compared to comparison types of treatment (e.g. placebo or alternative pharmacological treatment) for adults (aged 18 years or older) who engage in SH.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider all randomised controlled trials (RCT) of specific pharmacological agents or natural products versus placebo, or any other pharmacological comparisons in the treatment of adults with a recent (within six months of trial entry) hospital presentation for SH. We will include RCTs (including cluster-RCTs and cross-over trials) regardless of publication type or language; however, we will exclude quasi-randomised trials.

Types of participants

While exact eligibility criteria often differ both within and between regions and countries (Witt 2019), we will include participants of both sexes and all ethnicities, who are 18 years and older, with a recent (i.e. within six months of trial entry) hospital presentation for SH.

We define SH as all intentional acts of self-poisoning (such as intentional drug overdoses) or self-injury (such as self-cutting), regardless of degree of suicidal intent or other types of motivation (Hawton 2003). This definition includes acts intended to result in death ('attempted suicide'), those without suicidal intent (e.g. to communicate distress, to temporarily reduce unpleasant feelings; sometimes termed 'non-suicidal self-injury'), and those with mixed

motivation. We will not distinguish between attempted suicide and non-suicidal self-injury in this review, because there is a high level of co-occurrence between them, and the two cannot be distinguished in any reliable way, including on levels of suicidal intent (Klonsky 2011). Lastly, the motivations for SH are complex and can change, even within a single episode (De Beurs 2018).

We will exclude trials in which participants were hospitalised for suicidal ideation only (i.e. without evidence of SH).

Types of interventions

Categorisation of the interventions in this review will be informed by the trials themselves, and based on consensus discussions among members of the review team, who have considerable experience in both research and clinical practice related to SH. However, based on the previous version of this review (Hawton 2015), we anticipate the following groupings:

Interventions

These could include:

1. Tricyclic antidepressants (TADs, e.g. amitriptyline);
2. Newer generation antidepressants (NGAs), such as selective serotonin reuptake inhibitor (SSRIs, e.g. fluoxetine), serotonin and noradrenaline reuptake inhibitors (SNRIs, e.g. venlafaxine), norepinephrine reuptake inhibitors (NRIs, e.g. reboxetine), tetracyclic antidepressants (e.g. maprotiline), noradrenergic specific serotonergic antidepressants (NaSSAs, e.g. mirtazapine), serotonin antagonist or reuptake inhibitors (SARIs, e.g. trazodone), or reversible inhibitors of monoamine oxidase type A (RIMAs, e.g. moclobemide);
3. Other antidepressants, such as irreversible monoamine oxidase inhibitors (MAOIs, e.g. phenelzine);
4. Antipsychotics (e.g. quetiapine);
5. Anxiolytics, including both benzodiazepines (e.g. diazepam), and non-benzodiazepine anxiolytics (e.g. buspirone);
6. Mood stabilisers, including antiepileptics (e.g. sodium valporate) and lithium;
7. Other pharmacological agents (e.g. ketamine);
8. Natural products (e.g. omega-3 essential fatty acid supplementation).

Comparators

In pharmacological trials, where a comparison with the specific effects of a drug is being made, the comparator is typically placebo, which consists of any pharmacologically inactive treatment, such as sugar pills or injections with saline. In some trials, another pharmacological intervention (such as another standard pharmacological agent, reduced dose of the intervention agent, or active comparator) may be used.

Combination interventions

We also plan to include combination interventions, where any pharmacological agent of any class, as outlined above, is combined with psychological therapy. However, as the focus of this review is the effectiveness of pharmacological agents for people who self harm, we will only include such trials if both the intervention and control groups received the same psychological therapy, to ensure that any potential effect of the psychosocial therapy is balanced across both groups. The effectiveness of psychosocial therapy alone for adults who engage in SH behaviours is the subject of a separate review (Hawton 2016).

Types of outcome measures

For all outcomes, we are primarily interested in quantifying the effect of treatment assignment to the intervention at baseline, regardless of whether the intervention was received as intended (i.e. the intention-to-treat effect).

Primary outcomes

The primary outcome measure in this review will be the occurrence of repeated SH over a maximum follow-up period of two years. Repetition of SH may be identified through self-report, collateral report, clinical records, or research monitoring systems. As we wish to incorporate the maximum data from each trial, we will include both self-reported and hospital records of SH, where available. Preference will be given to clinical records over self-report where a study reports both measures. We will also report proportions of participants repeating SH, frequency of repeat episodes, and time to SH repetition (if available).

Secondary outcomes

Given increasing interest in the measurement of outcomes of importance to those who engage in SH, we plan to analyse data for the following secondary outcomes (where available) over a maximum follow-up period of two years (Owens 2020),

Treatment acceptability

This will be measured by differences in discontinuation rates for any reason.

Treatment adherence

This may be assessed using a range of measures of adherence, including: pill counts, changes in blood measures, and the proportion of participants that both started and completed treatment.

Depression

This will be assessed as either continuous data, by scores on psychometric measures of depression symptoms, for example total scores on the Beck Depression Inventory (BDI; Beck 1961), or scores on the depression sub-scale of the Hospital Anxiety and Depression Scale (HADS; Zigmond 1983), or as dichotomous data as the proportion of participants who meet defined diagnostic criteria for depression.

Hopelessness

This will be assessed as either continuous data, by scores on psychometric measures of hopelessness, for example, total scores on the Beck Hopelessness Scale (BHS; Beck 1974), or as dichotomous data as the proportion of participants reporting hopelessness.

General functioning

This will be assessed as either continuous data, by scores on psychometric measures of general functioning, for example, total scores on the Global Assessment of Functioning (GAF; APA 2000), or as dichotomous data as the proportion of participants reporting improved general functioning.

Social functioning

This will be assessed as either continuous data, by scores on psychometric measures of social functioning, for example, total scores on the Social Adjustment Scale (SAS; Weissman 1999), or as dichotomous data as the proportion of participants reporting improved social functioning.

Suicidal ideation

This will be assessed as either continuous data, by scores on psychometric measures of suicidal ideation, for example, total scores on the Beck Scale for Suicidal Ideation (BSS; Beck 1988), or as dichotomous data as the proportion of participants reaching a defined cut-off for ideation.

Suicide

This may include register-recorded deaths, or reports from collateral informants, such as family members or neighbours.

Search methods for identification of studies

Electronic searches

We will search the following databases, using relevant subject headings (controlled vocabularies) and search syntax as appropriate for each resource: Cochrane Common Mental Disorders Specialized Register (Appendix 1), Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE Ovid, Embase Ovid, and PsycINFO Ovid (Appendix 2).

As we are updating a previous version of this review (Hawton 2015), we will apply a date restriction of 2015 onwards. However, we will not apply any restrictions on language or publication status to the searches.

We will search for retraction statements and errata once we have selected the included studies, and will rerun all searches close to publication if the initial search date is longer than 12 months.

We will also search the World Health Organization International Clinical Trials Registry Platform, and the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov to identify ongoing trials.

Searching other resources

Conference abstracts

In addition to conference abstracts retrieved via the main electronic search, we will also screen the proceedings of recent (last five years) conferences organised by the largest scientific committees in the field:

1. International Association for Suicide Prevention (both global congresses and regional conferences), and;
2. Joint International Academy of Suicide Research and American Foundation for Suicide Prevention International Summits on Suicide Research.

Reference lists

We will check the reference lists of all relevant RCTs, and the reference lists of major reviews that included a focus on pharmacological interventions for SH in adults.

Correspondance

We will consult the corresponding authors of trials, and other experts in the field to find out if they are aware of any ongoing or unpublished RCTs on the treatment of adults who engage in SH which are not identified by the electronic searches.

Data collection and analysis

Selection of studies

Review authors KW, KH, and one of either SH, TTS, ET, or PH, will independently assess the titles of reports identified by the electronic search for eligibility. We will distinguish between:

1. Eligible or potentially eligible trials for retrieval, in which any psychosocial intervention is compared with a comparator (e.g., placebo or alternative pharmacological treatment);
2. Ineligible general treatment trials, not for retrieval (i.e. where there is no control treatment.

All trials identified as potentially eligible for inclusion will then undergo a second screening. Pairs of review authors, working independently from one another, will screen the full text of eligible or potentially eligible trials to identify whether the trial meets our inclusion criteria. We will resolve disagreements in consultation with the senior review author (KH). Where disagreements cannot be resolved from the information reported in the trial, or where it is unclear whether the trial satisfied our inclusion criteria, we will contact corresponding trial authors for additional clarification.

We will identify and exclude duplicate records, and collate multiple reports of the same trial, so that each trial, rather than each report, represents the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram, and will complete a 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

KW and one of either SH, TTS, ET, or PH will independently extract data from the included trials, using a standardised extraction form. Where there are any disagreements, we will resolve them in consensus discussions with KH.

Data extracted from each eligible trial will include:

1. Participant information: number randomised, number lost to follow-up or withdrawn, number analysed, mean or median age, sex composition, diagnoses, diagnostic criteria, inclusion criteria, and exclusion criteria;
2. Methods: trial design, total duration of the trial, details of any 'run in' period (if applicable), number of trial centres and their location, setting, and date;
3. Intervention(s): details of the intervention, including dose, duration, route of administration, whether concomitant medications were permitted and details of these medications, and any excluded medications;
4. Comparator(s): details of the comparator, including dose, duration, route of administration, whether concomitant medications were permitted and details of these medications, and any excluded medications;

5. Outcomes: raw data for each eligible outcome (see Types of outcome measures), details of other outcomes specified and reported, and time points at which outcomes were reported;
6. Notes: source of trial funding, and any notable conflicts of interest of trial authors.

We will extract both dichotomous and continuous outcomes data from eligible trials. As the use of non-validated psychometric scales is associated with bias, we will extract continuous data only if the psychometric scale used to measure the outcome of interest has been previously published in a peer-reviewed journal, and was not subjected to item, scoring, or other modification by the trial authors (Marshall 2000).

We plan the following main comparisons:

1. Tricyclic antidepressants versus placebo;
2. Tricyclic antidepressants versus another comparator drug or dose;
3. Newer generation antidepressants versus placebo;
4. Newer generation antidepressants versus another comparator drug or dose;
5. Any other antidepressants versus placebo;
6. Any other antidepressants versus another comparator drug or dose;
7. Antipsychotics versus placebo;
8. Antipsychotics versus another comparator drug or dose;
9. Anxiolytics, including benzodiazepines and non-benzodiazepine anxiolytics, versus placebo;
10. Anxiolytics, including benzodiazepines and non-benzodiazepine anxiolytics, versus another comparator drug or dose;
11. Mood stabilisers, including antiepileptics and lithium, versus placebo;
12. Mood stabilisers, including antiepileptics and lithium, versus another comparator drug or dose;
13. Other pharmacological agents versus placebo;
14. Other pharmacological agents versus another comparator drug or dose;
15. Natural products versus placebo;
16. Natural products versus another comparator drug or dose.

Assessment of risk of bias in included studies

Highly biased studies are more likely to overestimate treatment effectiveness (Moher 1998). KW and one of either SH, TTS, ET, or PH will independently evaluate the risk of bias for the primary outcome (i.e. repetition of SH post-intervention) by using the Cochrane Risk of Bias tool, version 2.0 (Sterne 2019). This tool encourages consideration of the following domains:

1. Bias in the randomisation process;
2. Deviations from the intended intervention (assignment to intervention);
3. Missing outcome data;
4. Bias in the measurement of the outcome;
5. Bias in the selection of the reported result.

For cluster-RCTs, we will also evaluate:

1. Bias arising from the timing of identification and recruitment of participants.

Two review authors will independently judge each source of potential bias low risk, high risk, or some concerns. They will then make an overall risk of bias judgement for each study, by combining ratings across these six domains. Specifically, if any of the above domains are rated at high risk, the overall risk of bias judgement will be rated at high risk. We will report this overall judgement, which can also be low risk, high risk, or some concerns, in the text of the review, and in the 'Risk of bias' tables.

Where inadequate details are provided in the original report, we will contact corresponding trial authors to provide clarification. We will resolve disagreements through discussions with KH.

We will process the 'Risk of bias' assessments using the recommended template, and make them available as electronic supplements.

Measures of treatment effect

Dichotomous outcomes

We will summarise dichotomous outcomes, such as the number of participants engaging in a repeat SH episode, or number of deaths by suicide, using the summary odds ratio (OR) and the accompanying 95% confidence interval (CI), as the OR is the most appropriate effect size statistic for summarising associations between two dichotomous groups (Fleiss 1994).

Continuous outcomes

For outcomes measured on a continuous scale, we will use mean differences (MD) and accompanying 95% CI where the same outcome measure is used. Where different outcome measures are used, we will use the standardised mean difference (SMD) and its accompanying 95% CI.

We will aggregate trials in a meta-analysis only if treatments are sufficiently similar. For trials that cannot be included in a meta-analysis, we will provide narrative descriptions of the results.

Hierarchy of outcomes

Where a trial measures the same outcome, for example depression, in two or more ways, we plan to use the most common measure across trials in any meta-analysis. We also plan to report scores from other measures in a supplementary table.

Timing of outcome assessment

The primary end point for this review will be post-intervention (i.e. at the conclusion of the treatment period). We will also report outcomes for the following secondary end points (where data are available):

1. Between zero and six months after the conclusion of the treatment period;
2. Between six and 12 months after the conclusion of the treatment period;
3. Between 12 and 24 months after the conclusion of the treatment period.

Where there is more than one outcome assessment within a time period, we will use data from the last assessment in the time period,

unless different outcomes are assessed at different time points. For treatment adherence, we also plan to use within-treatment results.

Unit of analysis issues

Zelen design trials

Trials in this area are increasingly using Zelen's method, in which consent is obtained subsequent to randomisation and treatment allocation (Witt 2019). This design may lead to bias if, for example, participants allocated to one particular arm of the trial disproportionally refuse to provide consent for participation or, alternatively, if participants only provide consent if they are allowed to cross over to the other treatment arm (Torgerson 2004). Given the uncertainty of whether to use data for the primary outcome based on all those randomised to the trial, or only those who consent to participation, should we identify a trial using Zelen's method, we plan to extract data using both sources of data, where possible. We also plan to conduct sensitivity analyses to investigate what impact, if any, the inclusion of these trials may have on the pooled estimate of treatment effectiveness.

Cluster-randomised trials

Cluster randomisation, for example by clinician or general practice, can lead to overestimation of the significance of a treatment effect, resulting in an inflation of the nominal type I error rate, unless appropriate adjustment is made for the effects of clustering (Donner 2002; Kerry 1998). Should any included trial use this design, we will follow the guidance outlined in Higgins 2019a. Specifically, where possible, we will analyse data using measures that statistically accounted for the cluster design. Where this is not possible, we will analyse data using the effective sample size.

Cross-over trials

A primary concern with cross-over trials is the carry-over effect, in which the effect of the intervention treatment (e.g. pharmacological, physiological, psychological) influences the participant's response to the subsequent control condition (Elbourne 2002). As a consequence, on entry to the second phase of the trial, participants may differ systematically from their initial state, despite a wash-out phase. In turn, this may result in a concomitant underestimation of the effectiveness of the treatment intervention (Curtin 2002a; Curtin 2002b). Should we identify any cross-over trials, we will only extract data from the first phase of the trial, prior to cross-over, to protect against the carry-over effect.

Studies with multiple treatment arms

Should any trial include multiple treatment groups where the intervention arms are sufficiently similar, for example where comparison is made between two interventions of the same type, we will combine dichotomous data. For outcomes reported on a continuous scale, we will combine data using the formula in Higgins 2011.

Where the interventions are not sufficiently similar, we will split the comparator arm data following the advice in Higgins 2011.

Studies with adjusted effect sizes

Where trials report both unadjusted and adjusted effect sizes, we will only include observed, unadjusted effect sizes.

Dealing with missing data

We will not impute missing data, as we consider that the bias that would be introduced by doing this would outweigh any benefit of increased statistical power that may have been gained by including imputed data. However, where authors omitted standard deviations (SD) for continuous measures, we first plan to contact corresponding authors to request missing data. If missing data are not provided, we will calculate missing SD using other data from the trial, such as CIs, based on methods outlined in Higgins 2019b.

Assessment of heterogeneity

Between-study heterogeneity can be assessed using either the Chi^2 or I^2 statistics. However, in this review, we will only use only the I^2 statistic to quantify inconsistency, as this is considered to be more reliable (Deeks 2019). The I^2 statistic indicates the percentage of between-study variation due to chance, and can take any value from 0% to 100% (Deeks 2019).

We will use the following values to denote relative importance of heterogeneity, as per Deeks 2019:

1. Unimportant: 0% to 40%;
2. Moderate: 30% to 60%;
3. Substantial: 50% to 90%;
4. Considerable: 75% to 100%.

We will take the magnitude and direction of effects and strength of evidence for heterogeneity into account (e.g. the CI for I^2).

Where we find substantial levels of heterogeneity, we will explore reasons for this heterogeneity (see Subgroup analysis and investigation of heterogeneity for details).

Assessment of reporting biases

Reporting bias occurs when the decision to publish a particular trial is influenced by the direction and significance of the results (Egger 1997). Research suggests, for example, that trials with statistically significant findings are more likely to be submitted for publication, and subsequently, be accepted for publication, leading to possible overestimation of the true treatment effect (Hopewell 2009).

To assess whether trials included in any meta-analysis are affected by reporting bias, we plan to enter data into a funnel plot when a meta-analysis includes results of at least ten trials. Should evidence of any small study effects be identified, we plan to explore reasons for funnel plot asymmetry, including the presence of possible publication bias (Egger 1997).

Data synthesis

For the purposes of this review, we will calculate the pooled OR and accompanying 95% CI using the random-effects model, as this is the most appropriate model for incorporating heterogeneity between studies (Deeks 2019). We will use the Mantel-Haenszel method for dichotomous data, and the inverse variance method for continuous data. We will conduct all analyses in Review Manager 5.4 (Review Manager 2020).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses

We plan to undertake the following subgroup analyses where there are sufficient data to do so:

1. Sex (males vs. females);
2. Repeater status (first SH episode versus repeat SH episode).

It will only be possible to undertake these subgroup analyses if randomisation was stratified by these factors, otherwise, there is the risk that doing so could lead to confounding.

Formal tests for subgroup differences will be undertaken in Review Manager 5.4 (Review Manager 2020).

Investigation of heterogeneity

Should any meta-analysis be associated with substantial levels of between-study heterogeneity (i.e. $I^2 \geq 75\%$), or visual inspection of the forest plot identifies a trial that has a very different result to the general pattern of the others, KW and KH will firstly independently triple-check data to ensure these were correctly entered. Assuming data were entered correctly, we will investigate the source of this heterogeneity using a formal statistical approach as outlined in Viechtbauer 2020.

Sensitivity analysis

We plan to carry out the following sensitivity analyses, where appropriate, to test whether key methodological factors or decisions may have influenced the main result:

1. Where a trial made use of Zelen's method of randomisation (see Unit of analysis issues);
2. Where a trial contributed to substantial between-study heterogeneity (see Subgroup analysis and investigation of heterogeneity).

Summary of findings and assessment of the certainty of the evidence

For each comparison we plan to construct a 'Summary of findings' table for our primary outcome measure, repetition of SH post-intervention, following the recommendations outlined in Schünemann 2019. These tables provide information concerning the overall quality of the evidence from all included trials that measured the outcome. We will assess the quality of evidence across the following domains:

1. Risk of bias assessment;
2. Indirectness of evidence;
3. Unexplained heterogeneity or inconsistency of results;
4. Imprecision of effect estimates;
5. Potential publication bias.

For each of these domains, we will downgrade the evidence from high quality by one level (for serious) or by two levels (for very serious). For risk of bias, we will downgrade this domain by one level when we rate any of the sources of risk of bias (as described in Assessment of risk of bias in included studies) at high risk for any of the studies included in the pooled estimate, or by two levels when we rate multiple studies at high risk for any of these sources. For indirectness of evidence, we will consider the extent to which trials included in any meta-analysis use proxy measures to ascertain repetition of SH; we will downgrade this domain by one level if one study uses proxy measures, and by two levels if multiple studies use proxy measures. For unexplained heterogeneity or inconsistency of results, we will downgrade this domain by one level where the I^2 value indicates substantial levels of heterogeneity, or by two levels where the I^2 value indicates considerable levels of heterogeneity. For imprecision, we will downgrade this domain by one level where the 95% CI for the pooled effect includes the null value. Finally, for the potential publication bias domain, we will consider any evidence of funnel plot asymmetry (if available), as well as other evidence such as suspected selective availability of data, and will downgrade by one or more levels where publication bias is suspected.

We will then use these domains to rate the overall quality of evidence for the primary outcome according to the following:

1. High quality: further research is very unlikely to change our confidence in the estimate of effect;
2. Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect, and may change the estimate;
3. Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect, and may change the estimate;
4. Very low quality: we are very uncertain about the estimate.

We will construct 'Summary of findings' tables using GRADEpro GDT software (GRADEpro GDT 2015).

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of the studies included in this review. Our recommendations for practice and research will suggest priorities for future research, and outline the remaining uncertainties in the area.

ACKNOWLEDGEMENTS

The authors and the CCMD Editorial Team are grateful to the following peer reviewers for their time and comments: Nuala Livingstone, Tess Moore, Ruth Simmonds, and Mark Sinyor. They would also like to thank Cochrane Copy Edit Support for the team's help.

This project has previously been supported by the National Co-ordinating Centre for NHS Service Delivery and Organisation R&D (NCCSDO). KH is funded by Oxford Health NHS Foundation Trust. He is a National Institute for Health Research (NIHR) Senior Investigator and personal funding from NIHR helped support this update.

The NIHR is the largest single funder of the CCMD Group.

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

REFERENCES

Additional references

Albrecht 2014

Albrecht B, Staiger PK, Hall K, Miller P, Best D, Lubman DI. Benzodiazepine use and aggressive behaviour: a systematic review. *Australian and New Zealand Journal of Psychiatry* 2014;**48**:1096-114.

APA 2000

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association, 2000.

Beck 1961

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Archives of General Psychiatry* 1961;**4**:561.

Beck 1974

Beck AT, Weissman A, Lester D, Trexler L. The measurement of pessimism: the Hopelessness Scale. *Journal of Consulting and Clinical Psychology* 1974;**42**:861-5.

Beck 1988

Beck AT, Steet RA, Ranieri WF. Scale for Suicidal Ideation: psychometric properties of a self-report version. *Journal of Clinical Psychology* 1988;**44**:499-505.

Bergen 2010

Bergen H, Hawton K, Waters K, Cooper J, Kapur N. Epidemiology and trends in non-fatal self-harm in three centres in England, 2000-2007. *British Journal of Psychiatry* 2010;**197**:493-8.

Brunner 2002

Brunner J, Parhofer KG, Schwandt P, Bronisch T. Cholesterol, essential fatty acids, and suicide. *Pharmacopsychiatry* 2002;**35**:1-5.

Canner 2018

Canner JK, Giuliano K, Selvaraiah S, Hammond ER, Schneider EB. Emergency department visits for attempted suicide and self harm in the USA, 2006-2013. *Epidemiology and Psychiatric Services* 2018;**27**:94-102.

Carroll 2014

Carroll R, Metcalfe C, Gunnell D. Hospital presenting self-harm and risk of fatal and non-fatal repetition: systematic review and meta-analysis. *PLoS One* 2014;**9**:e89944.

Carter 2016

Carter G, Page A, Large M, Hetrick S, Milner AJ, Bendit N, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guideline for the management of deliberate self-harm. *Australian and New Zealand Journal of Psychiatry* 2016;**50**:939-1000.

Cipriani 2013a

Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ* 2013;**346**:f3646.

Cipriani 2013b

Cipriani A, Reid K, Young AH, Macritchie K, Geddes J. Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. *Cochrane Database of Systematic Reviews* 2013, Issue 10. [DOI: 10.1002/14651858.CD003196.pub2]

Corcoran 2015

Corcoran P, Griffin E, O'Carroll A, Cassidy L, Bonner B. Hospital-treated deliberate self-harm in the western area of Northern Ireland. *Crisis* 2015;**36**:83-90.

Courtney 2019

Courtney DB, Duda S, Szatmari P, Henderson J, Bennett K. Systematic review and quality appraisal of practice guidelines for self-harm in children and adolescents. *Suicide and Life-Threatening Behavior* 2019;**49**:707-23.

Curtin 2002a

Curtin F, Elbourne D, Altman DG. Meta-analysis combining parallel and cross-over clinical trials. III. The issue of carry-over. *Statistics in Medicine* 2002;**21**:2161-73.

Curtin 2002b

Curtin F, Altman DG, Elbourne D. Meta-analysis combining parallel and cross-over trials. I. Continuous outcomes. *Statistics in Medicine* 2002;**21**:2131-44.

De Beurs 2018

De Beurs D, Vancayseele N, van Borkulo C, Portzky G, van Heeringen K. The association between motives, perceived problems and current thoughts of self-harm following an episode of self-harm: a network analysis. *Journal of Affective Disorders* 2018;**240**:262-70.

Deeks 2019

Deeks JJ, Higgins JPT, Altman DG, editor(s). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Donner 2002

Donner A, Klar N. Issues in the meta-analysis of cluster randomized trials. *Statistics in Medicine* 2002;**21**:2971-80.

Egger 1997

Egger M, Smith GD, Schneider M, Christoph M. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629.

Elbourne 2002

Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**:140-9.

FDA 2019

US Food and Drug Administration. FDA approves new nasal spray medication for treatment-resistant depression. www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified Accessed 18 March 2020.

Feighner 1999

Feighner JP. Mechanism of action of antidepressant medications. *Journal of Clinical Psychiatry* 1999;**60**:s4-11.

Ferrari 2014

Ferrari AJ, Norman RE, Freedman G, Baxter AJ, Pirkis JE, Harris MG, et al. The burden attributable to mental and substance use disorders as risk factors for suicide: findings from the Global Burden of Disease Study 2010. *PLoS One* 2014;**9**:e91936.

Fleiss 1994

Fleiss JL. Measures of effect size for categorical data. In: Cooper H, Hedges LV, editors(s). The Handbook of Research Synthesis. New York, NY: Russell Sage Foundation, 1994.

Forte 2019

Forte A, Buscaioni A, Fiorillo A, Pompii A, Baldessarini R. Suicidal risk following hospital discharge: a review. *Harvard Review of Psychiatry* 2019;**27**:209-16.

Geulayov 2016

Geulayov G, Kapur N, Turnbull P, Clements C, Waters K, Ness J, et al. Epidemiology and trends in non-fatal self-harm in three centres in England, 2000-2012: findings from the Multicentre Study of Self-harm in England. *BMJ Open* 2016;**6**:e010538.

Geulayov 2019

Geulayov G, Casey D, Bale L, Brand F, Clements C, Farooq B, et al. Suicide following presentation to hospital for non-fatal self-harm in the Multicentre Study of Self-Harm: a long-term follow-up study. *Lancet Psychiatry* 2019;**6**:1021-30.

Gjelsvik 2014

Gjelsvik B, Heyerdahl F, Lunn D, Hawton K. Change in access to prescribed medication following an episode of deliberate self-poisoning: a multilevel approach. *PLoS One* 2014;**9**:e98086.

GRADEpro GDT 2015 [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), accessed 26 June 2020.Available at gradepro.org.

Griffin 2014

Griffin E, Arensman E, Corcoran P, Wall A, Williamson E, Perry I. National Registry of Deliberate Self Harm Annual Report. Cork, Ireland: National Suicide Research Foundation, 2014.

Harrison 2014

Harrison JE, Henley G, AIHW. Suicide and hospitalised self-harm in Australia: trends and analysis. Injury research and statistics series no. 93. Cat. no. INJCAT 169. Canberra: AIHW 2014.

Hawton 2003

Hawton K, Hariss L, Hall S, Simkin S, Bale E, Bond A. Deliberate self-harm in Oxford, 1990-2000: a time of change in patient characteristics. *Psychological Medicine* 2003;**33**:987-96.

Hawton 2008

Hawton K, Harriss L. The changing gender ratio in occurrence of deliberate self-harm across the lifecycle. *Crisis* 2008;**29**:4-10.

Hawton 2010

Hawton K, Bergen H, Simkin H, Cooper K, Water K, Gunnell D, et al. Toxicity of antidepressants: rates of suicide relative to prescribing and non-fatal overdose. *British Journal of Psychiatry* 2010;**196**:354-8.

Hawton 2013

Hawton K, Saunders KEA, Topiwala A, Haw C. Psychiatric disorders in patients presenting to hospital following self-harm: a systematic review. *Journal of Affective Disorders* 2013;**151**:821-30.

Hawton 2016

Hawton K, Witt KG, Taylor Salisbury TL, Arensman E, Gunnell D, Hazell P, Townsend E, van Heeringen K. Psychosocial interventions for self-harm in adults. *Cochrane Database of Systematic Reviews* 2016;**5**:CD012189.

Higgins 2011

Higgins JPT, Deeks JJ. Chapter 7: Selecting studies and collecting data. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2019a

Higgins JPT, Eldridge S, Li T, editor(s). Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Higgins 2019b

Higgins JPT, Li T, Deeks JJ, editor(s). Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Hopewell 2009

Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.MR000006.pub3]

Kerry 1998

Kerry SM, Bland JM. Analysis of a trial randomised in clusters. *BMJ* 1998;**316**:54.

Klonsky 2011

Klonsky ED. Non-suicidal self-injury in United States adults: prevalence, socio-demographics, topography and functions. *Psychological Medicine* 2011;**41**:1981-6.

Larkin 2014

Larkin C, di Blasi Z, Arensman E. Risk factors for repetition of self-harm: a systematic review of prospective hospital-based studies. *PLoS One* 2014;**9**:e84282.

Liberati 2009

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine* 2009;**6**(7):e1000100.

Lilley 2008

Lilley R, Owens D, Horrocks J, House A, Noble R, Bergen H, et al. Hosptial care and repetition following self-harm: multicentre comparison of self-poisoning and self-injury. *British Journal of Psychiatry* 2008;**192**:440-5.

Mann 2013

Mann JJ. The serotonergic system in mood disorders and suicidal behaviour. *Philosophical Transactions of The Royal Society (B Biological Sciences)* 2013;**368**:20120537.

Marshall 2000

Marshall M, Lockwood A, Bradley C, Adamns C, Joy C, Fenton M. Unpublished rating scales: a major source of bias in randomised controlled trials of treatments for schizophrenia. *British Journal of Psychiatry* 2000;**176**:249-52.

Masiran 2017

Masiran R, Haniff J, Ali NH, Hamid AMA. Rates and profiles of self-harm presenting to Malaysian general hospitals: data from the Ministry of Health in 2011. *Malaysian Journal of Medicine and Health Sciences* 2017;**13**:39-45.

Moher 1998

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;**352**:609-13.

Morthorst 2016

Morthorst BT, Soegaard B, Nordentoft M, Erlangsen A. Incidence rates of deliberate self-harm in Denmark, 1994-2011: a nationwide register study. *Crisis* 2016;**37**:256-64.

Murphy 2012

Murphy E, Kapur N, Webb R, Purandare N, Hawton K, Bergen H, et al. Risk factors for repetition and suicide following self-harm in older adults: multicentre cohort study. *British Journal of Psychiatry* 2012;**200**:399-404.

Müller 2016

Müller A, Claes L, Brähler E, de Zwann M. Prevalence and correlates of self-harm in the German general population. *PLoS One* 2016;**11**:e0157928.

NCCMH 2004

National Collaborating Centre for Mental Health. Clinical Guideline 16. Self-harm: The short-term physical and psychological management and secondary prevention of self-harm in primary and secondary care. London, UK: National Institute for Clinical Excellence, 2004.

NICE 2011

National Institute for Health and Clinical Excellence. Self-harm: Longer-term management [National Clinical Practice Guideline Number 133]. Accessed 26 June 2020 from: https://www.nice.org.uk/guidance/cg133/evidence/full-guideline-pdf-184901581. London, UK: National Institute for Health and Clinical Excellence, 2011.

Owens 2002

Owens D, Horrocks J, House A. Fatal and non-fatal repetition of self-harm: systematic review. *British Journal of Psychiatry* 2002;**181**:193-9.

Owens 2020

Owens C, Fox F, Redwood S, Davies R, Foote L, Salisbury N, et al. Measuring outcomes in trials of interventions for people who self-harm: qualitative study of service users' views. *British Journal of Psychiatry Open* 2020;**6**:e22.

Perry 2012

Perry IJ, Corcoran P, Fitzgerald AP, Keeley HS, Reulback U, Arensman E. The incidence and repetition of hospital-treated deliberate self-harm: findings from the world's first national registry. *PLoS One* 2012;**7**:e31663.

Plener 2016

Plener PL, Brunner R, Fegert JM, Groschwitz RC, In-Albon T, Kaess M, et al. Treating nonsuicidal self-injury (NSSI) in adolescents: consensus based German guidelines. *Child and Adolescent Psychiatry and Mental Health* 2016;**10**:46.

Review Manager 2020 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.4. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2020.

Royal College of Psychiatrists 2014

Royal College of Psychiatrists. Managing Self-Harm in Young People (Guideline number CR192). London, UK: Royal College of Psychiatrists, 2014.

Sanacora 2017

Sanacora G, Frye MA, McDonald W, Mathew SJ, Turner MS, Schatzberg AF, et al, the American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments. A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry* 2017;**74**:399-405.

Schünemann 2019

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et

al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Sinclair 2011

Sinclair JMA, Gray A, Rivero-Arias O, Saunders KEA, Hawton K. Healthcare and social services resource use and costs of self-harm patients. *Social Psychiatry and Psychiatric Epidemiology* 2011;**46**:263-71.

Sterne 2019

Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898.

Stoffers 2010

Stoffers J, Völlm BA, Rücker G, Timmer A, Huband N, Lieb K. Pharmacological interventions for borderline personality disorder. *Cochrane Database of Systematic Reviews* 2010, Issue 6. [DOI: 10.1002/14651858.CD005653.pub2]

Sublette 2006

Sublette ME, Hibbeln JR, Galfalvy H, Oquendo MA, Mann JJ. Omega-3 polyunsaturated essential fatty acid status as a predictor of future suicide risk. *American Journal of Psychiatry* 2006;**163**:1100-02.

Tanskanen 2001

Tanskanen A, Hibbeln JR, Hintikka J, Haatainen K, Honkalampi K, Viinamaki H. Fish consumption, depression, and suicidality in a general population. *Archives of General Psychiatry* 2001;**58**:512-3.

Ting 2012

Ting SA, Sulivan AF, Boudreaux ED, Miller I, Camargo CA. Trends in US emergency department visits for attempted suicide and self-inflicted injury, 1993-2008. *General Hospital Psychiatry* 2012;**34**:557-65.

Torgerson 2004

Torgerson D. The use of Zelen's design in randomised trials. *British Journal of Obstetrics and Gynaecology* 2004;**111**:2.

Tsiachristas 2017

Tsiachristas A, McDaid D, Casey D, Brand F, Leal J, Park A-L, et al. General hospital costs in England of medical and psychiatric care for patients who self-harm: a retrospective analysis. *Lancet* 2017;**4**:759-67.

Tyrer 2012

Tyrer P. Why benzodiazepine are not going away: commentary on benzodiazepines for anxiety disorders. *Advances in Psychiatric Treatment* 2012;**18**:259-62.

van Heeringen 2014

van Heeringen K, Mann JJ. The neurobiology of suicide. *Lancet Psychiatry* 2014;**1**:63-72.

Viechtbauer 2020

Viechtbauer W, Cheung MW-L. Outlier and influence diagnostics for meta-analysis. *Research Synthesis Methods* 2020;**1**:112-25.

Weissman 1999

Weissman MM, Staff MHS. Social Adjustment Scale - Self-Report (SAS-SR) User's Manual. North Tonawanda, NY: Multi-Health Systems, 1999.

WHO 2014

World Health Organization. Preventing Suicide: A Global Imperative. Geneva, Switzerland: World Health Organization, 2014.

Wilkinson 2002

Wilkinson S, Taylor G, Templeton L, Mistral W, Salter E, Bennett P. Admissions to hospital for deliberate self-harm in England 1995-2000: an analysis of Hospital Episode Statistics. *Journal of Public Health* 2002;**24**:179-83.

Wilkinson 2018

Wilkinson ST, Ballard ED, Bloch MH, Mathew SJ, Murrough JW, Feder A, et al. The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. *American Journal of Psychiatry* 2018;**175**:150-8.

Witt 2019

Witt K, Townsend E, Arensman E, Gunnell D, Hazell P, Taylor Salisbury T, et al. Psychosocial interventions for people who self-harm: methodological issues involved in trials to evaluate effectiveness. Archives of Suicide Research 2019 Jul 10 [Epub ahead of print]:1-62. [DOI: 10.1080/13811118.2019.1592043]

Witt 2020

Witt K, Potts J, Hubers A, Grunebaum MF, Murrough JW, Loo C, et al. Ketamine for suicidal ideation in adults with psychiatric disorders: a systematic review and meta-analysis of treatment trials. *Australian and New Zealand Journal of Psychiatry* 2020;**54**:29-45.

Zahl 2004

Zahl DL, Hawton K. Repetition of deliberate self-harm and subsequent suicide risk: long-term follow-up study of 11 583 patients. *British Journal of Psychiatry* 2004;**185**:70-5.

Zigmond 1983

Zigmond AS, Snaith RP. The Hospital Anxeity and Depression Scale. *Acta Psychiatrica Scandinavica* 1983;**67**:361-70.

References to other published versions of this review

Hawton 2015

Hawton K, Witt KG, Taylor Salisbury TL, Arensman E, Gunnell D, Hazell P, et al. Pharmacological interventions for self-harm in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 7. [DOI: 10.1002/14651858.CD011777]

APPENDICES

Appendix 1. Cochrane Common Mental Disorders Group Specialized Register

The Cochrane Common Mental Disorders Group (CCMD) maintains an archived controlled trials register known as the CCMDCTR. This specialized register contains over 40,000 reference records (reports of RCTs) for anxiety disorders, depression, bipolar disorder, eating disorders, self-harm, and other mental disorders within the scope of this Group. The CCMDCTR is a partially studies-based register with more than 50% of reference records tagged to around 12,500 individually PICO-coded study records. Reports of studies for inclusion in the register were collated from (weekly) generic searches of key bibliographic databases to June 2016, which included: MEDLINE (1950 onwards), Embase (1974 onwards), PsycINFO (1967 onwards), quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), and review-specific searches of additional databases. Reports of studies were also sourced from international trials registries, drug companies, the handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Details of CCMD's core search strategies (used to identify RCTs) are on the Group's website, with an example of the core MEDLINE search displayed below.

[MeSH Headings]: eating disorders/ or anorexia nervosa/ or binge-eating disorder/ or bulimia nervosa/ or female athlete triad syndrome/ or pica/ or hyperphagia/ or bulimia/ or self-injurious behavior/ or self mutilation/ or suicide/ or suicidal ideation/ or suicide, attempted/ or mood disorders/ or affective disorders, psychotic/ or bipolar disorder/ or cyclothymic disorder/ or depressive disorder/ or depression, postpartum/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/ or seasonal affective disorder/ or neurotic disorders/ or depression/ or adjustment disorders/ or exp antidepressive agents/ or anxiety disorders/ or agoraphobia/ or neurocirculatory asthenia/ or obsessive-compulsive disorder/ or obsessive hoarding/ or panic disorder/ or phobic disorders/ or stress disorders, traumatic/ or combat disorders/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ or anxiety/ or anxiety, castration/ or koro/ or anxiety, separation/ or panic/ or exp anti-anxiety agents/ or somatoform disorders/ or body dysmorphic disorders/ or conversion disorder/ or hypochondriasis/ or neurasthenia/ or hysteria/ or munchausen syndrome by proxy/ or munchausen syndrome/ or fatigue syndrome, chronic/ or obsessive behavior/ or compulsive behavior/ or behavior, addictive/ or impulse control disorders/ or firesetting behavior/ or gambling/ or trichotillomania/ or stress, psychological/ or burnout, professional/ or sexual dysfunctions, psychological/ or vaginismus/ or Anhedonia/ or Affective Symptoms/ or *Mental Disorders/ OR *[Title/ Author Keywords]:* (eating disorder* or anorexia nervosa or bulimi* or binge eat* or (self adj (injur* or mutilat*)) or suicide* or suicidal or parasuicid* or mood disorder* or affective disorder* or bipolar i or bipolar ii or (bipolar and (affective or disorder*)) or mania or manic or cyclothymic* or depression or depressive or dysthymi* or neurotic or neurosis or adjustment disorder* or antidepress* or anxiety disorder* or agoraphobia or obsess* or compulsi* or panic or phobi* or ptsd or posttrauma* or post trauma* or combat or somatoform or somati#ation or medical* unexplained or body dysmorphi* or conversion disorder or hypochondria* or neurastheni* or hysteria or munchausen or chronic fatigue* or gambling or trichotillomania or vaginismus or anhedoni* or affective symptoms or mental disorder* or mental health).tw,kf. AND *[RCT filter]:* (controlled clinical trial.pt. or randomised controlled trial.pt. or (randomi#ed or randomi#ation).ab,ti. or randomly.ab. or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).ab. or placebo*.ab,ti. or drug therapy.fs. or trial.ab,ti. or groups.ab. or (control* adj3 (trial* or study or studies)).ab,ti. or ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp. or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or randomised controlled trial/ or pragmatic clinical trial/ or (quasi adj (experimental or random*)).ti,ab. or ((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group)).ab.)

Records were screened for reports of RCTs within the scope of the Cochrane Common Mental Disorders Group. Secondary reports of RCTs were tagged to the appropriate study record

The information specialist with CCMD will cross-search the CCMDCTR-Studies and References register using the following terms (all fields):

(suicid* or parasuicid* or "auto mutilat*" or automutilat* or "self destruct*" or selfdestruct* or self-harm* or selfharm* or "self immolat*" or selfimmolat* or "self inflict*" or selfinflict* or "self injur*" or selfinjur* or selfmutilat* or "self mutilat*" or "self poison*" or selfpoison* or (self adj2 (cut or cuts or cutting or cutter? or burn or burns or burning or bite or bites or biting or hit or hits or hitting)) or "head bang*" or headbang* or "over dose*" or overdos* or NSSI* or nonsuicid* or non-suicid*)

Appendix 2. MEDLINE, Embase, PsycINFO Ovid search strategy

We will perform an Ovid cross-search on MEDLINE, Embase, and PsycINFO (2015 onwards), using the following terms:
1. Automutilation/ or Self-injurious Behavior/ or Self-destructive Behavior/ or Self-mutilation/ or Self-inflicted Wounds/
2. Suicidal Behavior/ or Suicide/ or Suicidal Ideation/ or Attempted Suicide/ or Suicide, Attempted/ or Self Poisoning/ or Suicide Prevention/ or Suicide Prevention Centers/ or Suicidology/
3. (suicid* or parasuicid* or auto mutilat* or automutilat* or self destruct* or selfdestruct* or self-harm* or selfharm* or self immolat* or selfimmolat* or self inflict* or selfinflict* or self injur* or selfinjur* or selfmutilat* or self mutilat* or self poison* or selfpoison* or (self adj2 (cut or cuts or cutting or cutter? or burn or burns or burning or bite or bites or biting or hit or hits or hitting)) or head bang* or headbang*).ti,ab,kf,kw,id.
4. (NSSI? or ((nonsuicid* or non-suicid*) adj2 (self* or injur*))).ti,ab,kf,kw,id.
5. (Overdose/ or Drug Overdose/ or Drug Overdoses/) and prevent*.af.
6. or/1-5
7. Randomized Controlled Trial/

8. Randomized Controlled Trial.pt.
9. Randomization/
10. Random Allocation/
11. Controlled Clinical Trial/
12. Controlled Clinical Trial.pt.
13. Double-blind Method/ or Single-blind Method/
14. (randomi#ed or randomi#ation or randomi#ing).ti,ab,kf,kw,id.
15. (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or crossover or cross-over or control* or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or subsitut* or treat*))).ti,ab,kf,kw,id.
16. trial.ti.
17. placebo/ or (placebo and (allocat* or assign* or control* or group*)).ti,ab,kf,kw,id.
18. (control* adj3 group*).ab.
19. (control* and (trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,kf,kw,id.
20. ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,kf,kw,id.
21. treatment effectiveness evaluation/
22. or/7-21
23. 6 and 22
24. (2015* or 2016* or 2017* or 2018* or 2019* or 2020*).yr,dc,dp,dt,ep,ez.
25. 23 and 24
[De-duplicate line 25 within Ovid]

WHAT'S NEW

Date	Event	Description
1 July 2020	New citation required and major changes	We updated the protocol developed for Hawton 2015

HISTORY

Protocol first published: Issue 7, 2020

CONTRIBUTIONS OF AUTHORS

KH had the idea for the review. KW wrote the initial version of the protocol, and all authors contributed to the writing of drafts. All authors also approved the final version of the protocol for publication.

DECLARATIONS OF INTEREST

KW: no declarations of interest to report in relation to this protocol
KH: no declarations of interest to report in relation to this protocol
SH: no declarations of interest to report in relation to this protocol
TTS: no declarations of interest to report in relation to this protocol
ET: no declarations of interest to report in relation to this protocol
PH: no declarations of interest to report in relation to this protocol

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Health and Medical Research Council, Australia

  KW is supported by an Emerging Leadership 1 Fellowship awarded by the NHMRC (APP1177787).
- National Institute of Health Research (NIHR), UK

  KW received support from the NIHR (Award number: NIHR 131985).