Interventions for self-harm in children and adolescents (Protocol)

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[Intervention Protocol]

Interventions for self-harm in children and adolescents

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A B S T R A C T

Objectives

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

To assess the effects of psychosocial or pharmacological interventions for self-harm (SH) compared to comparison types of care (e.g. treatment as usual, routine psychiatric care, enhanced usual care, active comparator, placebo, alternative pharmacological treatment, or a combination of these) for children and adolescents (up to 18 years of age) 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), is a significant problem in children and adolescents up to 18 years of age (Hawton 2012a). Rates of SH in children and adolescents have been increasing over recent decades across a number of comparable countries, according to the number of presentations to general hospitals and primary care (Cairns 2019; Griffin 2018; Morgan 2017). This increase may be attributable to a number of factors; younger age of onset of SH behaviours (Gardner 2019; Griffin 2018; Jung 2018; Perera 2018), changes in the potential lethality of methods of SH used by children and adolescents (Griffin 2018), increased risk of SH repetition in children and adolescents, relative to young adults (i.e. 20 to 24-year-olds; Bennardi 2016), changes in clinical documentation and improved administrative coding of cases of SH in children and adolescents, resulting in a higher detection rate of young people who engage in SH (McGill 2018).

In most countries, rates of hospital-presenting SH are higher in young females in contrast to suicide. The female to male ratio peaks at approximately five to six times in 12 to 14-year-olds, before decreasing with age (Diggins 2017; Griffin 2018; McMahon 2014). While reasons for the differential prevalence of SH behaviours in young females compared to young males are complex, an earlier age of onset of psychiatric disorders in young females may represent an important factor (Rhodes 2014). However, only about 1:28 young males, and 1:18 young females who SH ever present to hospital (Geulayov 2018). Therefore, it is apparent that SH in children and adolescents in the community (i.e., without hospital presentation) is very common, although less is known about the treatment needs of these youth (Hawton 2012a; Madge 2008; McMahon 2014).

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 (Cairns 2019; Hawton 2012b; Sheen 2002). 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 (Geulayov 2018; Müller 2016; Madge 2008).

While suicide is relatively uncommon in younger children, rates have been increasing across a number of countries in recent years, particularly among young females (Bould 2019; Lahti 2011; Roh 2018; Skinner 2012; Stefanac 2019; Sullivan 2015). SH is associated with increased risk of future suicide. For example, recent data from the UK showed that children and adolescents who presented to hospital on at least one occasion following an episode of SH were 30 times more likely to die by suicide within a year (Hawton 2020). A history of SH, particularly with frequent repetition, is the strongest risk factor for suicide across a range of psychiatric disorders (Zahl 2004).

SH and suicide in children and adolescents is the result of a complex interplay between genetic, biological, psychiatric, psychosocial, social, cultural, and other factors (Hawton 2012a). Psychiatric disorders, particularly mood disorders, are associated with the largest population attributable risk for SH in children and adolescents. While personality disorders should not be diagnosed in younger children, emergent traits consistent with those in adult borderline personality disorder have also been found to be associated with a significant population attributable risk for SH in this population (Witt 2019a), particularly those who engage in frequent repetition of SH (Crowell 2012).

Poor emotion regulation abilities, or poor emotional intelligence may also contribute to the risk of SH in this population (Brausch 2019; Mikolajczak 2009). Psychological influences on children and adolescents who engage in SH include feelings of entrapment, lack of belonging, and perceiving oneself as a burden (O'Connor 2012). Other contributors include perfectionism, low self-esteem, social isolation, impulsivity, hopelessness, and poor parent-child attachment (Hawton 2012a). Alcohol and illicit drug misuse may also play an important role.

Relationship problems are common in children and adolescents who engage in SH, especially problems with family members (Fortune 2016). Relationship problems with partners are more common in older adolescents (i.e. 15 to 18-year-olds) than in younger children (i.e. 10 to 14-year-olds; Hawton 2012b). A history of emotional, physical, or sexual abuse has been associated with a significant population attributable risk of SH (Liu 2018; Madge 2011; Witt 2019a). Bullying and victimisation (Heerde 2019), including cyber-bullying (Heerde 2019; John 2018), can also increase the risk of SH. Exposure to suicidal behaviour in others, either through personal contact, or through portrayals in traditional (e.g. films or television dramas) or new media (including social media), may also be an important factor as SH in children and adolescents often has a 'contagious' quality (McMahon 2013).

Description of the intervention

Treatment for SH in children and adolescents may involve psychosocial interventions, pharmacological interventions, or a combination of the two approaches.

Psychosocial interventions

Psychological approaches used to treat children and adolescents who engage in SH typically involve brief individual- or group-based psychological therapy. Treatment may vary in initial management, location of treatment, continuity, intensity, and frequency of contact with therapists. There is also considerable variation among countries in the availability of services to provide such interventions. Consequently, there is no standard psychosocial treatment of SH in children and adolescents. However, in high-income countries, treatment generally consists of a combination of assessment, support, involvement of parents, family, and caregivers, and individual psychological therapies.

Pharmacological interventions

Given the prevalence of psychiatric disorders in children and adolescents who present to hospital following an episode of SH, pharmacological treatments may include antidepressants, antipsychotics, anxiolytics (including both benzodiazepines and non-benzodiazepine anxiolytics), and mood stabilisers (including anticonvulsants) (Hawton 2013). Other pharmacological agents may also be trialled. However, treatment with pharmacological agents is generally less common than treatment with psychosocial

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interventions in this population, partly due to concerns about the risk of exacerbating SH (Miller 2014).

Combined psychosocial and pharmacological interventions

Treatment may also involve a combination of both psychosocial and pharmacological approaches, such as cognitive behavioural therapy combined with fluoxetine (Gilbert 2020).

How the intervention might work

Psychosocial interventions

Mood disorders, in particular, have been identified as key modifiable risk factors for children and adolescents who engage in SH (Witt 2019a). Psychosocial interventions may address some of the underlying psychological risk factors associated with SH. The mechanisms of action of these interventions might help children and adolescents improve their coping skills and tackle specific problems, manage psychiatric disorders, improve self-esteem, increase a sense of social connectedness, and reduce impulsivity and harmful reactions to distressing situations. What follows, is a description of the psychosocial interventions that are typically available for children and adolescents who engage in SH.

Cognitive behavioural therapy-based psychotherapy

Cognitive behavioural therapy (CBT)-based psychotherapy helps people to identify and critically evaluate the ways in which they interpret and evaluate disturbing emotional experiences and events, and aims to help them change the ways in which they deal with problems (Westbrook 2008). This is achieved in three steps: first, people are helped to change the ways in which they interpret and evaluate distressing emotions; second, they learn strategies to help them change the way in which they think about the meanings and consequences of these emotions; finally, with the benefit of modified interpretation of emotions and events, they are helped to change their behaviour and develop positive functional behaviour (Jones 2012).

Problem-solving therapy (PST) is an integral part of CBT, although it can be delivered as a therapy in and of itself. PST assumes that ineffective and maladaptive coping behaviours that drive SH might be overcome by helping the person to learn skills to actively, constructively, and effectively solve the problems he or she faces in their daily lives (Nezu 2010). PST typically involves identification of the problem, generation of a range of solutions, implementation of chosen solutions based on appraisal, and the evaluation of these solutions (D'Zurilla 2010). Treatment goals include helping people to develop a positive problem-solving orientation, use rational problem-solving strategies, reduce the tendency to avoid problem-solving, and reduce the use of impulsive problem-solving strategies (Washburn 2012).

Dialectical behaviour therapy

In contrast to CBT and PST, which focus on changing behaviour and cognitive patterns, the focus of dialectical behavioural therapy (DBT) is to provide people with the skills to develop an awareness and acceptance of thoughts and emotions, including painful or distressing internal experiences, without judgement or attempts to alter, suppress, avoid, or otherwise change these experiences (Lynch 2006). The primary treatment goals of DBT are three-fold: to reduce SH, reduce behaviours that interfere with the success of treatment, such as treatment non-adherence, and reduce any

other factors that may adversely affect the person's quality of life (e.g. frequency or duration of psychiatric hospitalisations) (Linehan 1993).

Miller 2007 adapted dialectical behaviour therapy for adolescents (DBT-A) from Linehan's initial conceptualisation of DBT, which was developed for adults diagnosed with borderline personality disorder. DBT-A typically includes a combination of weekly individual and family therapy sessions, and telephone support as needed. As the aim of DBT-A is to help children and adolescents adjust to maladaptive personality characteristics, the treatment is intensive and relatively prolonged, although usually less so than in adults (James 2008; Miller 2007).

Mentalisation-based therapy

Mentalisation refers to the ability to understand the behaviour of both one's self and others in terms of motivational and emotional states (Allen 2008). Maladaptive and impulsive coping behaviours, including SH, are presumed to arise from a disrupted ability to engage in these processes. In mentalisation-based therapy (MBT), the goal is to help people understand their emotions and behaviours, and develop strategies to regulate them to minimise the risk that they will engage in SH during times of distress (Rossouw 2018).

Mentalisation-based therapy for adolescents (MBT-A) is a relatively prolonged (one year) treatment which typically includes weekly individual sessions, and monthly family sessions (Fonagy 2019).

Group-based psychotherapy

Group-based psychotherapy treatment of children and adolescents who have self-harmed integrates techniques from several therapies, including CBT, DBT-A, MBT-A, and specific group techniques. Group-based psychotherapy may be more effective for children and adolescents than individual psychotherapy, as it provides them with a chance to work on skills related to developing interpersonal relationships and problem-solving, which have been identified as important modifiable proximal risk factors for SH behaviours in this age group (Kaess 2020).

Enhanced assessment approaches

Enhanced therapeutic assessment approaches combine standard psychosocial history and risk assessment techniques with brief cognitive analytic therapy and PST. Children and adolescents learn to identify sources of psychological pain and their connection to problem behaviours, such as SH, and identify ways to break this cycle (Ougrin 2012). The aim is to enhance adherence with subsequent treatment, and the potential benefit from it.

Compliance enhancement approaches

Of particular concern regarding after-care of children and adolescents who present to hospital following an episode of SH, is the fact that adherence to recommended treatment tends to be relatively poor; between 25% and 50% of children and adolescents will not attend any follow-up outpatient treatment sessions (Granboulan 2001; Taylor 1984). Efforts to maintain contact with children and adolescents, such as following up with them in the community, as well as efforts to address factors likely to impede attendance at treatment sessions, may be effective in improving treatment engagement and adherence in this population (Yuan 2019).

Family interventions

Family interventions typically involve conjoint therapy sessions with the child or adolescent and family members. It includes negotiation of goals, exploration of the episode of SH, communication between family members, problem solving, and discussion of developmental issues and their impact on the family. The basis of this therapy is that SH in children and adolescents may relate to family dysfunction, and therefore, efforts to improve family cohesion, attachment, adaptability, support, and parental warmth could help families function better and hence, reduce the risk of SH (Fortune 2016).

Remote contact interventions

Remote contact interventions, which may include letters, brief text messages delivered by telephone, telephone calls, and postcards, are low resource and non-intrusive interventions that seek to maintain long-term contact with children and adolescents. These interventions provide a sense of ongoing concern, and may mitigate the sense of social isolation reported by many children and adolescents who engage in SH. They may also help to improve their knowledge about triggers and warning signs for SH, provide them with information on alternative coping behaviours to SH, and where they can access help (Milner 2016).

These interventions may also be combined with emergency card interventions, which encourage children and adolescents to seek help when they feel distressed, and offer on-demand emergency contact with psychiatric services or inpatient care. The aim is to reduce the risk of SH by facilitating rapid access to care.

Pharmacological interventions

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]). Antidepressants might improve mood in children and adolescents diagnosed with depression, and hence, reduce thoughts and acts of SH. 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 a child or adolescent 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 children and adolescents 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).

In children and adolescents, there have been significant concerns that certain classes of antidepressants, particularly SSRIs, may increase suicidal ideation (Healy 2003). As a result, regulatory agencies in both the UK (Medicines and Healthcare products Regulatory Agency; MHRA 2003), and the US (US Food and Drug Administration; FDA 2004) have issued warnings. More recently, review evidence suggests that risks may be elevated regardless of antidepressant class (Hetrick 2012). However, warnings from regulatory agencies may have had unintended consequences, such as increases in suicide attempts among children and adolescents (Gibbons 2007; Lu 2014; Plöderl 2019).

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. Low potency second generation antipsychotics may reduce SH in children and adolescents diagnosed with major depression (Good 2006), and schizophrenia (Ma 2018).

Anxiolytics, including both benzodiazepines and non-benzodiazepine anxiolytics

Anxiolytics, including benzodiazepines and non-benzodiazepine anxiolytics, might reduce SH through their specific effects on anxiety (Tyrer 2012). However, because of their GABAminergic effects, benzodiazepines may increase aggression and disinhibition (Albrecht 2014). In children and adolescents, data from case series describe an increased risk of suicidal ideation and SH in those prescribed benzodiazepines (Kandemir 2008). Therefore, it is usually recommended that benzodiazepines are used very cautiously, if at all, in children and adolescents at risk of SH.

Mood stabilisers (including antiepileptics)

Mood stabilisers may have benefits for children and adolescents diagnosed with bipolar disorder or unipolar depression, especially to prevent the recurrence of episodes of mood disorder (Cipriani 2013b). Therefore, these drugs may reduce the risk of SH. However, to date, this effect has only been found for lithium in adults (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 treatment 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

In adults, the main focus with natural products and suicidal behaviour has been on 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).

Combined psychosocial and pharmacological interventions

A growing number of trials have investigated the effectiveness of combined psychosocial and pharmacological interventions, particularly in children and adolescents diagnosed with major depression. Given that achieving treatment response for psychosocial therapy alone may take up to four weeks or longer, combined approaches may provide a faster treatment response, and may have a superior effect to psychosocial intervention alone (Cox 2014). However, the effect of combined approaches on SH remains unclear (Cox 2014).

Why it is important to do this review

SH in children and adolescents 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 children and adolescents who engage in SH (WHO 2014). SH also leads to substantial healthcare costs (Kinchin 2017; Sinclair 2011).

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 subsequently 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 in order to provide contemporary evidence to guide clinical policy and practice (Hawton 2015).

OBJECTIVES

To assess the effects of psychosocial or pharmacological interventions for self-harm (SH) compared to comparison types of care (e.g. treatment as usual, routine psychiatric care, enhanced usual care, active comparator, placebo, alternative pharmacological treatment, or a combination of these) for children and adolescents (up to 18 years of age) 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 psychosocial or pharmacological treatments versus treatment as usual, routine psychiatric care, enhanced usual care, active comparator, placebo, alternative pharmacological treatment, or a combination of these, in the treatment of children and adolescents 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 2019b), we will include participants of both sexes and all ethnicities up to 18 years of age, 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, particularly in children and adolescents (Andover 2012). Attempted suicide and non-suicidal self-injury 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:

Psychosocial interventions

These could include:

1. Individual CBT-based psychotherapy;
2. Dialectical behavioural therapy;
3. Mentalisation therapy;
4. Group-based psychotherapy;
5. Enhanced assessment approaches;
6. Compliance enhancement approaches;
7. Family interventions;
8. Remote contact interventions.

Comparators

Treatment as usual (TAU) is likely to vary widely both between settings and between trials conducted over different time periods (Witt 2018). Following previous work, we defined TAU as routine clinical service provision that children and adolescents would receive had they not been included in the trial (i.e. routine care or 'standard disposition'; Hunt 2013). Other comparators could include no specific treatment or enhanced usual care, which refers to TAU that has in some way been supplemented, such as providing psychoeducation, assertive outreach, or more regular contact with case managers, and standard assessment approaches.

Pharmacological 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.

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 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 children and adolescents 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 children and adolescents 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 children and adolescents 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 children and adolescents 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 children and adolescents 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.

Other

We remain open to including additional secondary outcomes, based on current outcome prioritisation work being undertaken by the author team.

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 interventions for SH in children and adolescents.

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 children and adolescents 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 or psychopharmacological treatment is compared with a comparator (e.g. treatment as usual, routine psychiatric care, enhanced usual care, active comparator, placebo, alternative pharmacological treatment, or a combination of these);
2. Ineligable 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 treatments were permitted and details of these treatments, and any excluded treatments;
4. Comparators(s): details on the comparator, including dose, duration, route of administration, whether concomitant treatments were permitted and details of these treatments, and any excluded treatments;
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. Individual CBT-based psychotherapy (e.g. CBT, PST) versus treatment as usual (TAU) or other comparator;
2. Dialectical behaviour therapy (DBT) versus TAU or other comparator;
3. Mentalisation-based therapy versus TAU or other comparator;
4. Group-based psychotherapy versus TAU or other comparator;
5. Enhanced assessment approaches versus TAU or other comparator;
6. Compliance enhancement approaches versus TAU or other comparator;
7. Family interventions versus TAU or other comparator;
8. Remote contact interventions versus TAU or other comparator;
9. Tricyclic antidepressants versus placebo or other comparator drug or dose;
10. Newer generation antidepressants versus placebo or other comparator drug or dose;
11. Any other antidepressants versus placebo or other comparator drug or dose;
12. Antipsychotics versus placebo or other comparator drug or dose;
13. Anxiolytics, including both benzodiazepines and non-benzodiazepine anxiolytics, versus placebo or other comparator drug or dose;
14. Mood stabilisers, including antiepileptics and lithium, versus placebo or other comparator drug or dose;
15. Other pharmacological agents versus placebo or other comparator drug or dose;
16. Natural products versus placebo or other 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 at 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 points. For treatment adherence, we also plan to use within-treatment period 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 2019b). 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 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, or 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 Chi² or I² statistics. However, in this review, we will only use only the I² statistic to quantify inconsistency, as this is considered to be more reliable (Deeks 2019). The I² 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 I²).

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).

Given the increasing use of enhanced usual care rather than TAU in trials in the field (Witt 2019b), we also plan to undertake sub-group analyses to determine whether comparator choice influenced the pattern of results observed. 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 at 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 availablity 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.

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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 PsycInfo, Embase and MEDLINE (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