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Pharmacological interventions for self-harm in adults (Review)

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Pharmacological interventions for self-harm in adults.
Cochrane Database of Systematic Reviews 2021, Issue 1. Art. No.: CD013669.
DOI: 10.1002/14651858.CD013669.pub2.

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[Intervention Review]

Pharmacological interventions for self-harm in adults

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Editorial group: Cochrane Common Mental Disorders Group.
Publication status and date: Edited (no change to conclusions), published in Issue 3, 2021.

Citation: Witt KG, Hetrick SE, Rajaram G, Hazell P, Taylor Salisbury TL, Townsend E, Hawton K. Pharmacological interventions for self-harm in adults. *Cochrane Database of Systematic Reviews* 2021, Issue 1. Art. No.: CD013669. DOI: 10.1002/14651858.CD013669.pub2.

ABSTRACT

Background

Self-harm (SH; intentional self-poisoning or self-injury regardless of degree of suicidal intent or other types of motivation) is a growing problem in most countries, often repeated, and associated with suicide. Evidence assessing the effectiveness of pharmacological agents and/or natural products in the treatment of SH is lacking, especially when compared with the evidence for psychosocial interventions. This review therefore updates a previous Cochrane Review (last published in 2015) on the role of pharmacological interventions for SH in adults.

Objectives

To assess the effects of pharmacological agents or natural products for 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.

Search methods

We searched the Cochrane Common Mental Disorders Specialised Register, the Cochrane Library (Central Register of Controlled Trials [CENTRAL] and Cochrane Database of Systematic Reviews [CDSR]), together with MEDLINE. Ovid Embase and PsycINFO (to 4 July 2020).

Selection criteria

We included all randomised controlled trials (RCTs) comparing pharmacological agents or natural products with placebo/alternative pharmacological treatment in individuals with a recent (within six months of trial entry) episode of SH resulting in presentation to hospital or clinical services. The primary outcome was the occurrence of a repeated episode of SH over a maximum follow-up period of two years. Secondary outcomes included treatment acceptability, treatment adherence, depression, hopelessness, general functioning, social functioning, suicidal ideation, and suicide.

Data collection and analysis

We independently selected trials, extracted data, and appraised trial quality. For binary outcomes, we calculated odds ratios (ORs) and their 95% confidence internals (CIs). For continuous outcomes we calculated the mean difference (MD) or standardised mean difference (SMD) and 95% CI. The overall certainty of evidence for the primary outcome (i.e. repetition of SH at post-intervention) was appraised for each intervention using the GRADE approach.

Main results

We included data from seven trials with a total of 574 participants. Participants in these trials were predominately female (63.5%) with a mean age of 35.3 years (standard deviation (SD) 3.1 years). It is uncertain if newer generation antidepressants reduce repetition of SH compared to placebo (OR 0.59, 95% CI 0.29 to 1.19; N = 129; k = 2; very low-certainty evidence). There may be a lower rate of SH repetition for antipsychotics (21%) as compared to placebo (75%) (OR 0.09, 95% CI 0.02 to 0.50; N = 30; k = 1; low-certainty evidence). However, there was no evidence of a difference between antipsychotics compared to another comparator drug/dose for repetition of SH (OR 1.51, 95% CI 0.50 to 4.58; N = 53; k = 1; low-certainty evidence). There was also no evidence of a difference for mood stabilisers compared to placebo for repetition of SH (OR 0.99, 95% CI 0.33 to 2.95; N = 167; k = 1; very low-certainty evidence), or for natural products compared to placebo for repetition of SH (OR 1.33, 95% CI 0.38 to 4.62; N = 49; k = 1; lo- certainty) evidence.

Authors' conclusions

Given the low or very low quality of the available evidence, and the small number of trials identified, there is only uncertain evidence regarding pharmacological interventions in patients who engage in SH. More and larger trials of pharmacotherapy are required, preferably using newer agents. These might include evaluation of newer atypical antipsychotics. Further work should also include evaluation of adverse effects of pharmacological agents. Other research could include evaluation of combined pharmacotherapy and psychological treatment.

PLAIN LANGUAGE SUMMARY

Drugs and natural products for self-harm in adults

We have reviewed the international literature regarding pharmacological (drug) and natural product (dietary supplementation) treatment trials in the field. A total of seven trials meeting our inclusion criteria were identified. There is little evidence of beneficial effects of either pharmacological or natural product treatments. However, few trials have been conducted and those that have are small, meaning that possible beneficial effects of some therapies cannot be ruled out.

Why is this review important?

Self-harm (SH), which includes intentional self-poisoning/overdose and self-injury, is a major problem in many countries and is strongly linked with suicide. It is therefore important that effective treatments for SH patients are developed. Whilst there has been an increase in the use of psychosocial interventions for SH in adults (which is the focus of a separate review), drug treatments are frequently used in clinical practice. It is therefore important to assess the evidence for their effectiveness.

Who will be interested in this review?

Hospital administrators (e.g. service providers), health policy officers and third party payers (e.g. health insurers), clinicians working with patients who engage in SH, patients themselves, and their relatives.

What questions does this review aim to answer?

This review is an update of a previous Cochrane Review from 2015 which found little evidence of beneficial effects of drug treatments on repetition of SH. This updated aims to further evaluate the evidence for effectiveness of drugs and natural products for patients who engage in SH with a broader range of outcomes.

Which studies were included in the review?

To be included in the review, studies had to be randomised controlled trials of drug treatments for adults who had recently engaged in SH.

What does the evidence from the review tell us?

There is currently no clear evidence for the effectiveness of antidepressants, antipsychotics, mood stabilisers, or natural products in preventing repetition of SH.

What should happen next?

We recommend further trials of drugs for SH patients, possibly in combination with psychological treatment.

Summary of findings 1. Newer generation antidepressants (NGAs) compared to placebo for self-harm in adults

Newer generation antidepressants (NGAs) compared to placebo for self-harm in adults

Patient or population: Self-harm in adults
Intervention: Newer generation antidepressants (NGAs)
Comparison: Placebo

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without Newer generation antidepressants (NGAs)	With Newer generation antidepressants (NGAs)	Difference		
Repetition of SH by post-intervention (NGA class) № of participants: 129 (2 RCTs)	OR 0.59 (0.29 to 1.19)	Study population			⊕⊝⊝⊝ VERY LOW [1 2 3]	The evidence is very uncertain about the effect of newer generation antidepressants (NGAs) on repetition of self-harm by post-intervention.
		50.0%	37.1% (22.5 to 54.3)	12.9% fewer (27.5 fewer to 4.3 more)		
Repetition of SH by post-intervention (NGA class) - Mianserin vs. Placebo № of participants: 38 (1 RCT)	OR 0.67 (0.18 to 2.41)	Study population			⊕⊝⊝⊝ VERY LOW [1 2 3]	The evidence is very uncertain about the effect of newer generation antidepressants (NGAs) on repetition of self-harm by post-intervention by NGA class (i.e., mianserin vs. placebo).
		57.1%	47.2% (19.4 to 76.3)	10.0% fewer (37.8 fewer to 19.1 more)		
Repetition of SH by post-intervention (NGA class) - Paroxetine vs. Placebo № of participants: 91 (1 RCT)	OR 0.55 (0.24 to 1.29)	Study population			⊕⊕⊝⊝ LOW [2 3]	Further research is very likely to have an important impact on our confidence in the estimate of the effect of newer generation antidepressants (NGAs) on repetition of self-harm by post-intervention by NGA class (paroxetine vs. placebo), and may change the estimate.
		46.7%	32.5% (17.4 to 53)	14.2% fewer (29.3 fewer to 6.4 more)		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] We downgraded this domain by one level as we rated any of the sources of risk of bias (as described in Assessment of risk of bias in included studies) at high risk for one of the trials included in the pooled estimate.
[2] We downgraded this domain as these were relatively older agents and, in one trial, no information on how SH was ascertained was reported.
[3] We downgraded this domain by one level as the 95% CI for the pooled effect included the null value.

Summary of findings 2. Antipsychotics compared to placebo for self-harm in adults

Antipsychotics compared to placebo for self-harm in adults

Patient or population: Self-harm in adults
Intervention: Antipsychotics
Comparison: Placebo

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without Antipsychotics	With Antipsychotics	Difference		
Repetition of SH by post-intervention № of participants: 30 (1 RCT)	OR 0.09 (0.02 to 0.50)	Study population 75.0%	21.3% (5.7 to 60)	53.7% fewer (69.3 fewer to 15 fewer)	⊕⊕⊖⊖ LOW [1] [2]	Further research is very likely to have an important impact on our confidence in the estimate of the effect of antipsychotics as compared to placebo on repetition of self-harm by post-intervention, and may change the estimate.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] We downgraded this domain by one level as we rated any of the sources of risk of bias (as described in Assessment of risk of bias in included studies) at high risk for one of the trials included in the pooled estimate.
[2] We downgraded this domain as this was a relatively older agent and, for one trial, no information on how SH was ascertained was reported.

Summary of findings 3. Antipsychotics compared to another comparator drug or dose for self-harm in adults

Antipsychotics compared to another comparator drug or dose for self-harm in adults

Patient or population: Self-harm in adults
Intervention: Antipsychotics
Comparison: Another comparator drug/dose

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without Antipsychotics	With Antipsychotics	Difference		
Repetition of SH by post-intervention № of participants: 53 (1 RCT)	OR 1.51 (0.50 to 4.58)	Study population 34.6%	44.4% (20.9 to 70.8)	9.8% more (13.7 fewer to 36.2 more)	⊕⊕⊖⊖ LOW [1,2]	Further research is very likely to have an important impact on our confidence in the estimate of the effect of antipsychotics as compared to another comparator drug or dose on repetition of self-harm by post-intervention, and may change the estimate.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] We downgraded this domain as this was a relatively older agent.
[2] We downgraded this domain by one level as the 95% CI for the pooled effect included the null value.

Summary of findings 4. Mood stabilisers, including antiepileptics and lithium compared to placebo for self-harm in adults

Mood stabilisers, including antiepileptics and lithium compared to placebo for self-harm in adults

Patient or population: Self-harm in adults
Intervention: Mood stabilisers, including antiepileptics and lithium
Comparison: Placebo

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without Mood stabilisers, including antiepileptics and lithium	With Mood stabilisers, including antiepileptics and lithium	Difference		
Repetition of SH by post-intervention № of participants: 167 (1 RCT)	OR 0.99 (0.33 to 2.95)	Study population 8.4%	8.4% (2.9 to 21.4)	0.1% fewer (5.5 fewer to 12.9 more)	⊕⊖⊖⊖ VERY LOW [1 2 3]	The evidence is very uncertain about the effect of mood stabilisers, including antiepileptics and lithium, on repetition of self-harm by post-intervention.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] We downgraded this domain by one level as we rated any of the sources of risk of bias (as described in Assessment of risk of bias in included studies) at high risk for one of the trials included in the pooled estimate.
[2] We downgraded this domain as previous work has demonstrated that self-harm prevalence estimates derived from self-report may be underestimated, and supplementing prevalence estimates with medical or clinical record information is advisable (Mitchell 2016).
[3] We downgraded this domain by one level as the 95% CI for the pooled effect included the null value.

Summary of findings 5. Natural products compared to placebo for self-harm in adults

Natural products compared to placebo for self-harm in adults

Patient or population: Self-harm in adults
Intervention: Natural products

Comparison: Placebo

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without Natural products	With Natural products	Difference		
Repetition of SH by post-intervention № of participants: 49 (1 RCT)	OR 1.33 (0.38 to 4.62)	Study population 25.9%	31.8% (11.7 to 61.8)	5.8% more (14.2 fewer to 35.9 more)	⊕⊕⊖⊖ LOW [1] [2]	Further research is very likely to have an important impact on our confidence in the estimate of the effect of natural products as compared to placebo on repetition of self-harm by post-intervention, and may change the estimate.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] We downgraded this domain as previous work has demonstrated that self-harm prevalence estimates derived from self-report may be underestimated, and supplementing prevalence estimates with medical or clinical record information is advisable (Mitchell 2016).
[2] We downgraded this domain by one level as the 95% CI for the pooled effect included the null value.

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 2014a).

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, with a particularly high risk in men (Carroll 2014; 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, particularly 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, and mood stabilisers (including anticonvulsants and lithium). SH also arises in the context of anxiety and general distress and thus anxiolytics (including both benzodiazepines and non-benzodiazepine anxiolytics) may be trialled. Other pharmacological agents may also be trialled.

How the intervention might work

Antidepressants

In relation to the prevention of SH and suicidal behaviour, the primary mechanism would be the effect of antidepressants on depression. However, there might also be other relevant specific effects, such as with drugs acting on the serotonin system, it having been suggested that serotonin levels are relevant to impulsivity, which is a feature sometimes associated with suicidal behaviour (van Heeringen 2014).

While different classifications of antidepressants have been suggested, a currently accepted classification is non-selective monoamine inhibitors (e.g., amitriptyline, imipramine, dosulepin), selective serotonin reuptake inhibitors (e.g., fluoxetine, sertraline, citalopram), monoamine oxidase inhibitors, sub-grouped as non-selective monoamine oxidase inhibitors (e.g., phenelzine) and monoamine oxidase A inhibitors (e.g., moclobemide), and other antidepressants (e.g,. venlafaxine, mirtazapine, trazadone) (WHO 2014b).

An earlier approach was to group antidepressants as tricyclics, newer generation antidepressants (NGAs) (while recognising that many specific drugs in this category were introduced many years ago), and other antidepressants. This approach was used in the previous version of this review (Hawton 2015). For pragmatic reasons, we have therefore continued to use this categorisation in this update.

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 are generally preferred (Hawton 2010), especially in people thought to be at risk of suicide.

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 anxiolytics, may be used to reduce suicidal behaviour (Tyrer 2012). However, because of their GABAminergic effects, benzodiazepines may increase aggression and disinhibition (Albrecht 2014). Current evidence is that benzodiazepines are associated with increased risk of suicidal behaviour (Dodds 2017). 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; Smith 2017). 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 2020a). 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 2020a).

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 2014a). SH is also associated with 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. This guidance was updated 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 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 considered all randomised controlled trials (RCTs) 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) presentation for self-harm (SH). All RCTs (including cluster-RCTs and cross-over

trials) were eligible for inclusion regardless of publication type or language; however, we excluded quasi-randomised trials.

Types of participants

While exact eligibility criteria often differ both within and between regions and countries (Witt 2020b), we included participants of both sexes and all ethnicities, who were 18 years and older, with a recent (i.e. within six months of trial entry) presentation to hospital or clinical services for SH.

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

Types of interventions

Interventions

These included the following.

1. Tricyclic antidepressants (TCAs, 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), norepinephrine-dopamine reuptake inhibitors (NDRIs, e.g., bupropion), 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. We also included trials in which another pharmacological intervention (such as another standard pharmacological agent, reduced dose of the intervention agent, or active comparator) was used.

Combination interventions

We also planned 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 only included such trials if both the intervention and control groups received the same psychological therapy, to ensure that any potential effect of the psychosocial therapy was 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 were 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 was the occurrence of repeated SH over a maximum follow-up period of two years. Repetition of SH was identified through self-report, collateral report, clinical records, or research monitoring systems. As we wished to incorporate the maximum data from each trial, we included both self-reported and hospital records of SH, where available. Preference was given to clinical records over self-report where a study reported both measures. We also reported proportions of participants repeating SH, frequency of repeat episodes, and time to SH repetition (where available).

Secondary outcomes

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

Treatment acceptability

This was measured by differences in discontinuation rates for any reason.

Treatment adherence

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

Search methods for identification of studies

Electronic searches

An information specialist searched the following databases (to 4 July 2020), using relevant subject headings (controlled vocabularies) and search syntax as appropriate for each resource: Cochrane Common Mental Disorders Specialised Register (Appendix 1), Cochrane Library (Central Register of Controlled Trials; CENTRAL), Cochrane Database of Systematic Reviews (CDSR), MEDLINE Ovid, Embase Ovid, and PsycINFO Ovid (Appendix 2).

A date restriction was applied as the search was to update an earlier version of this review (Hawton 2015). However, we did not apply any further restrictions on language or publication status to the searches.

We searched for retraction statements and errata once the included studies were selected.

We also searched 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 also screened 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 also checked 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 (Hawton 2015).

Correspondence

We consulted 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 pharmacological treatment of adults who engage in SH that were not identified by the electronic searches.

Data collection and analysis

Selection of studies

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

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

All trials identified as potentially eligible for inclusion then underwent a second screening. Pairs of review authors, working independently from one another, screened the full text of eligible or potentially eligible trials to identify whether the trial met our inclusion criteria. We resolved disagreements in consultation with the senior review author (KH). Where disagreements could not be resolved from the information reported in the trial, or where it was unclear whether the trial satisfied our inclusion criteria, we contacted corresponding trial authors for additional clarification.

We identified and excluded duplicate records, and collated multiple reports of the same trial, so that each trial, rather than each report, represented the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Liberati 2009), and completed a 'Characteristics of excluded studies' table.

Data extraction and management

Review author KW and one of either SH, or GR independently extracted data from the included trials, using a standardised extraction form. Where there were any disagreements, they were resolved in consensus discussions with KH.

Data extracted from each eligible trial included the following.

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 extracted both dichotomous and continuous outcomes data from eligible trials. As the use of non-validated psychometric scales is associated with bias, we extracted continuous data only if the psychometric scale used to measure the outcome of interest had 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 planned 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). Review author KW and one of either SH, or GR independently evaluated the risk of bias for the primary outcome (i.e. repetition of SH post-intervention) by using version 2 of the Cochrane Risk of Bias tool, RoB 2 (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 also evaluated the following.

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

Signalling questions in the RoB 2 tool provided the basis for the tool's domain-level judgements about the risk of bias. Two review authors independently judged each source of potential bias low risk, high risk, or some concerns. An overall 'Risk of bias' judgement was then made for each study by combining ratings across these domains. Specifically, if any of the above domains were rated at high risk, the overall 'Risk of bias' judgement was rated at high risk. We reported 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 were provided in the original report, we contacted corresponding trial authors to provide clarification. We resolved disagreements through discussions with KH.

We entered and organised our RoB 2 assessments on an Excel spreadsheet (Microsoft Excel RoB2 Macro), and made them available as electronic supplements.

Measures of treatment effect

Dichotomous outcomes

We summarised 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 used mean differences (MDs) and accompanying 95% CI where the same outcome measure was used. Where different outcome measures were used, we used the standardised mean difference (SMD) and its accompanying 95% CI.

We aggregated trials in a meta-analysis only where treatments were sufficiently similar. For trials that could not be included in a meta-analysis, we provided narrative descriptions of the results.

Hierarchy of outcomes

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

Timing of outcome assessment

The primary end point for this review was post-intervention (i.e, at the conclusion of the treatment period). We also reported outcomes for the following secondary end points (where data were 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 was more than one outcome assessment within a time period, we used data from the last assessment in the time period, unless different outcomes are assessed at different time points. For treatment adherence, we also planned 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 2020b). 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).

Although no trial included in this review used Zelen's design, should we identify a trial using Zelen's method in future updates of this review, we plan to extract data for all randomised participants as this is consistent with Zelen's original intention (Zelen 1979), and preserves randomisation. This will typically be possible for our primary outcome, repetition of SH, as this will generally be ascertained from clinical, hospital, and/or medical records. However, for certain self-reported outcome measures, data may only be reported on the basis of those who consented to participation. We therefore 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).

Although no trial included in this review used cluster randomisation, should we identify a trial using cluster randomisation in future updates of this review, 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).

No trial included in this review used cross-over methodology. However, should we identify any cross-over trials in future updates of this trial, 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

One trial in the current review included multiple treatment arms (Hirsch 1982). As both intervention arms in this trial investigated the effectiveness of newer generation antidepressants (i.e. mianserin or nomifensine), we combined dichotomous data from these two arms. For continuous outcomes, we combined data using the formula reported in Higgins 2011.

Studies with adjusted effect sizes

Where trials reported both unadjusted and adjusted effect sizes, we included only observed, unadjusted effect sizes.

Dealing with missing data

We did not impute missing data, as we considered 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 contacted corresponding authors to request missing data. Where missing data could not be provided, we calculated missing SDs 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 only used 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 used 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 also took the magnitude and direction of effects and strength of evidence for heterogeneity into account (e.g. the CI for I^2).

Where substantial levels of heterogeneity were found, we explored 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 were affected by reporting bias, we planned to enter data into a funnel plot when a meta-analysis includes results of at least 10 trials. Should evidence of any small study effects be identified, we planned 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 calculated the pooled odds ratio (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 used the Mantel-Haenszel method for dichotomous data, and the inverse variance method for continuous data. We conducted all analyses in Review Manager 5.4 (Review Manager 2020).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses

We planned to undertake the following subgroup analyses where there were sufficient data to do so:

1. sex (males versus females);
2. repeater status (first SH episode versus repeat SH episode).

Formal tests for subgroup differences were undertaken in Review Manager 5.4 (Review Manager 2020). However, it is only 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. Given that randomisation was not stratified by these factors in the included studies, we found there were insufficient data to undertake these subgroup analyses in the current update.

Investigation of heterogeneity

Although no meta-analysis was associated with substantial levels of between-study heterogeneity (i.e., $I^2 \geq 75\%$), in future updates, should any meta-analysis be associated with substantial levels of between-study heterogeneity two review authors 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 planned to undertake 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).

However, as no included trial made use of Zelen's method of randomisation, and furthermore, no meta-analysis was associated with substantial levels of between-study heterogeneity, we were unable to undertake these sensitivity analyses.

Summary of findings and assessment of the certainty of the evidence

For each comparison we planned 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 certainty of the evidence from all included trials that measured the outcome. We assessed 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 downgraded the evidence from high certainty by one level (for serious) or by two levels (for very serious). For risk of bias, we downgraded 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 considered the extent to which trials included in any meta-analysis use proxy measures to ascertain repetition of SH; we downgraded this domain by one level if one study used proxy measures, and by two levels if multiple studies used proxy measures. For unexplained heterogeneity or inconsistency of results, we downgraded this domain by one level where the I^2 value indicated substantial levels of heterogeneity, or by two levels where the I^2 value indicated considerable levels of heterogeneity. For imprecision, we downgraded this domain by one level where the 95% CI for the pooled effect included the null value. Finally, for the potential publication bias domain, we considered any evidence of funnel plot asymmetry (if available), as well as other evidence such as suspected selective availability of data, and downgraded by one or more levels where publication bias was suspected.

We then used these domains to rate the overall certainty of evidence for the primary outcome according to the following.

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

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

Reaching conclusions

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

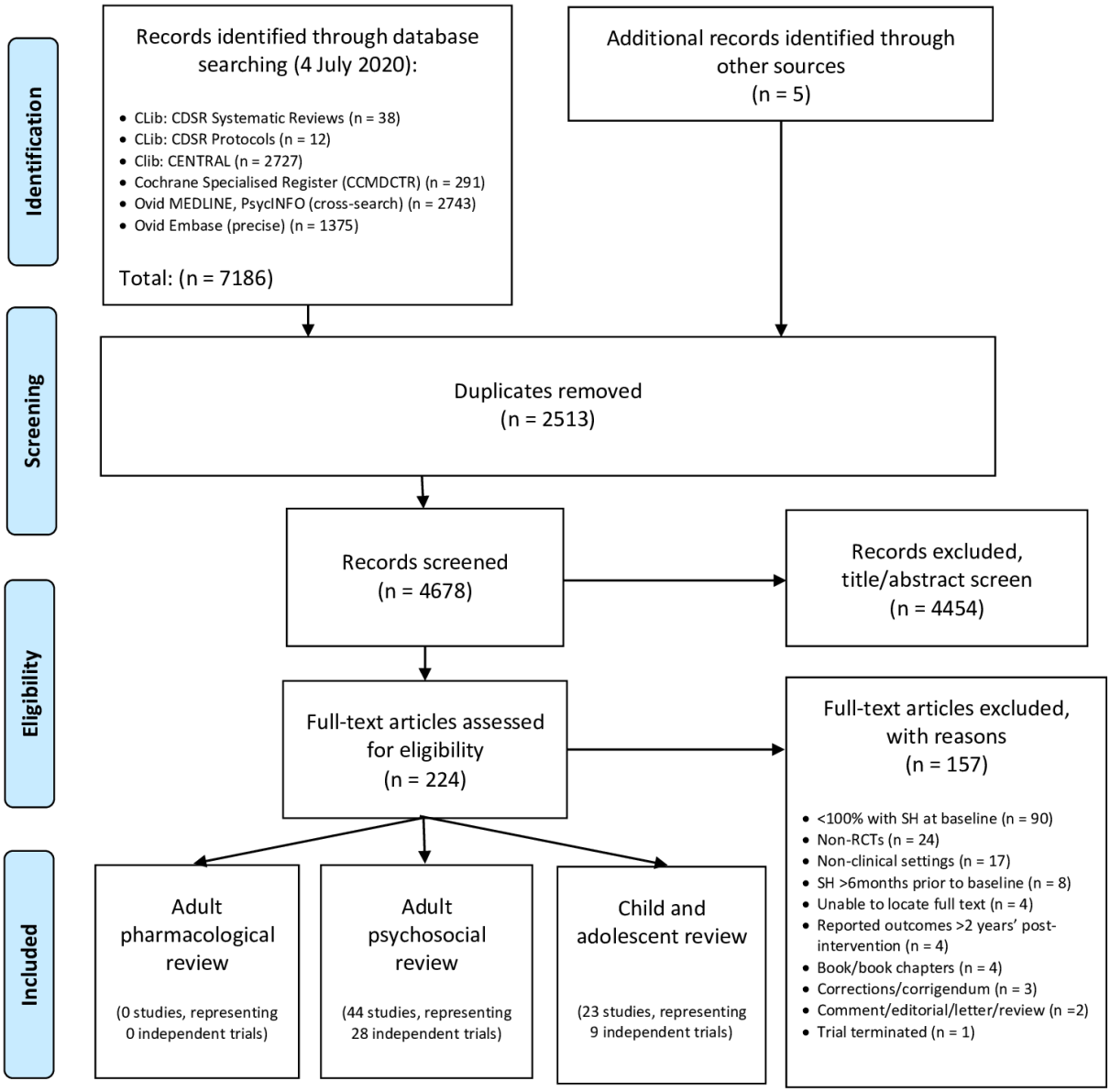
RESULTS

Description of studies

Results of the search

For this update, a total of 7186 records were found using the search strategy as outlined in Appendix 1 and Appendix 2. Five further records were identified following correspondence and discussion with researchers in the field. After deduplication, the initial number was reduced to 4678. Of these, 4454 were excluded following title/abstract screening, whilst a further 157 were excluded after reviewing the full texts (Figure 1).

Figure 1. Study Flow Diagram



Included studies

In the previous version of this review (Hawton 2015), seven trials of pharmacological interventions for self-harm (SH) in adults were included. The present update did not locate any additional trials of pharmacological interventions or natural products for SH in adults. The present review therefore includes seven non-overlapping trials (Battaglia 1999; Hallahan 2007; Hirsch 1982; Lauterbach 2008; Montgomery 1979; Montgomery 1983; Verkes 1998). No further reports provided any additional data on these trials.

Two of these trials have not been published (Montgomery 1979; Hirsch 1982). Unpublished data were obtained from study authors for three of these trials (Battaglia 1999; Hallahan 2007; Verkes 1998) (see the Characteristics of included studies tables for further information on these trials).

Design

Of these seven trials, five were placebo-controlled RCTs (Hallahan 2007; Hirsch 1982; Lauterbach 2008; Montgomery 1983; Verkes 1998). The remaining two trials compared the effectiveness of the intervention agent to an active comparator drug/dose (Battaglia 1999; Montgomery 1979). All seven trials employed a simple randomisation procedure based on individual allocation to the intervention and comparator arms.

Setting

Of the seven independent RCTs included in this review, three were from the UK (Hirsch 1982; Montgomery 1979; Montgomery 1983), and one was from each of the USA (Battaglia 1999), Germany (Lauterbach 2008), the Netherlands (Verkes 1998), and the Republic of Ireland (Hallahan 2007).

Although all participants were identified following a hospital admission for SH, five trials did not clearly specify if treatment was delivered on an inpatient or outpatient basis. For the remaining two trials (Lauterbach 2008; Verkes 1998), participants were treated in outpatient settings.

Participants and participant characteristics

The included trials comprised a total of 574 participants. All had engaged in at least one episode of SH prior to trial entry. A history of SH prior to the index episode (i.e. a history of multiple episodes of SH) was a requirement for participation in five trials (Battaglia 1999; Hallahan 2007; Lauterbach 2008; Montgomery 1979; Montgomery 1983).

Information on the methods of SH for the index episode was not reported in the majority of trials (Battaglia 1999; Hallahan 2007; Montgomery 1979; Montgomery 1983; Verkes 1998). In one trial, only those who had engaged in self-poisoning (i.e, not illicit substances or poison) were eligible to participate (Hirsch 1982), whilst in the remaining trial (Lauterbach 2008), a variety of different methods were used, including: self-poisoning (73.2%), self-injury (14.4%), jumping from a height (2.5%), and attempted hanging, attempted shooting, or attempted drowning (5.0%). The methods used by the remaining 4.9% of participants in this trial were not reported. Whilst the predominance of participants engaging in self-poisoning in these two trials is reflective of the typical pattern observed in those who present to hospital, in the community, SH more often involves self-cutting and other forms of self-injury (Müller 2016).

All trials included both male and female participants. Of the six trials that reported information on sex, the majority of participants were female (63.5%), reflecting the typical pattern for SH (Hawton 2008). Of the five trials that reported information on age, the weighted mean age of participants at trial entry was 35.3 years (standard (SD): 3.1 years). Two trials included a small number of adolescent participants (i.e. those under 18 years of age), but the precise number was not reported in either (Hallahan 2007; Hirsch 1982).

In the five trials that reported information on psychiatric diagnoses (Battaglia 1999; Hallahan 2007; Lauterbach 2008; Montgomery 1983; Verkes 1998), participants were most commonly diagnosed with major depression (34.5%), followed by any personality disorder (29.3%), and substance use disorder (24.8%). Around one-in-five (22.0%) were diagnosed with borderline personality disorder specifically. Information on comorbid diagnoses were reported in one trial (Lauterbach 2008). For this trial, the most common comorbidity was for any personality disorder (33.%), followed by substance use disorder (8.4%), and any anxiety disorder (7.2%). In a second trial (Verkes 1998), one-quarter (25.3%) of the sample were diagnosed with more than one psychiatric disorder from the following: any anxiety disorder, any depressive disorder, dysthymia, any dissociative disorder, any adjustment disorder, and alcohol use disorder. However, the proportion diagnosed with each comorbid condition was not reported.

Interventions

The trials included in this review investigated the effectiveness of various pharmacological agents.

1. Newer generation antidepressants (NGAs) versus placebo (Hirsch 1982; Montgomery 1983; Verkes 1998).
2. Antipsychotics versus placebo (Montgomery 1979).
3. Antipsychotics versus another comparator drug/dose (Battaglia 1999).
4. Mood stabilisers, including antiepileptics, versus placebo (Lauterbach 2008).
5. Natural products (omega-3 essential fatty acid; n-3EFA) versus placebo (Hallahan 2007).

Outcomes

Primary outcome

All trials reported data on the primary outcome of this review, repetition of SH. In two trials this was based on self-reported information (Battaglia 1999; Lauterbach 2008), and in two further trials on re-presentation to hospital (Hallahan 2007; Hirsch 1982). For the remaining three trials the source of information for this outcome was unclear (Montgomery 1979; Montgomery 1983; Hirsch 1982).

Secondary outcomes

Treatment acceptability

Treatment acceptability was measured as the proportion of participants that discontinued treatment for any reason in six trials (Battaglia 1999; Hirsch 1982; Lauterbach 2008; Montgomery 1979; Montgomery 1983; Verkes 1998). For the remaining trial, only data on the proportion of participants that discontinued treatment due to the development of adverse effects was reported (Hallahan 2007).

Treatment adherence

Treatment adherence was assessed using pill counts in the two trials that reported data on this outcome (Hallahan 2007; Verkes 1998).

Depression

Depression was assessed using the Beck Depression Inventory (BDI) (Hallahan 2007; Verkes 1998) or the Hamilton Depression Rating Scale (HDRS; Hamilton 1960) (Hallahan 2007; Lauterbach 2008).

Hopelessness

Hopelessness was assessed using the Beck Hopelessness Scale (BHS) (Lauterbach 2008; Verkes 1998).

General functioning

No trial reported data on general functioning.

Social functioning

No trial reported data on social functioning.

Suicidal ideation

Suicidal ideation was assessed using the sub-scale of the Modified Overt Aggression Scale (MOAS; Sorgi 1991) in one trial (Hallahan 2007), and the Scale for Suicidal Ideation (SSI) in one further trial (Lauterbach 2008).

Suicide

It was unclear how suicide was ascertained in any of the trials that reported data on this outcome.

Excluded studies

A total of 157 studies were excluded from this update. The most common reason for exclusion was that not all trial participants had engaged in SH within six months of trial entry (90 studies). Reasons for exclusion for the remaining studies are reported in Figure 1.

Details on the reasons for exclusion for those trials related to pharmacological interventions for SH in adults identified by this update are reported in the Characteristics of excluded studies section.

Ongoing studies

Of the two ongoing trials identified in the previous version of this review (Hawton 2015), one of oral lithium was subsequently terminated (NCT01928446), whilst the second, of oral ketamine, upon publication, did not meet inclusion criteria (Domany 2019). Two ongoing studies were identified in this update (see Characteristics of ongoing studies section for further information on these trials).

Studies awaiting classification

We identified one trial that is awaiting classification (see Characteristics of studies awaiting classification section for further information on this trial).

Risk of bias in included studies

Risk of bias was evaluated for the primary outcome repetition of SH at post-intervention. The results of the 'Risk of bias' assessments can be seen in Figure 2 and Figure 3. Full 'Risk of bias' assessments, including the evidence we used to justify our ratings, are available in Appendix 3.

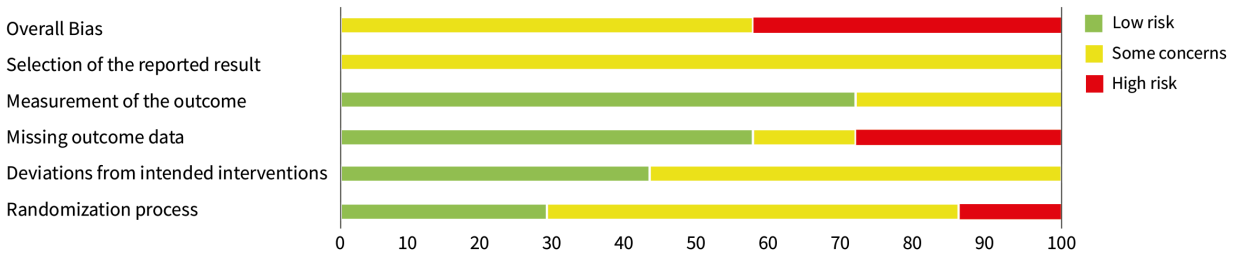
Figure 2. Results of 'Risk of bias' assessments for each study

Study ID	Experimental	Comparator	D1	D2	D3	D4	D5	Overall
Battaglia 1999	Antipsychotics	Alternative dose	?	?	?	+	?	?
Hallahan 2007	Natural products	Placebo	+	+	+	+	?	?
Hirsch 1982	NGAs	Placebo	?	?	+	?	?	?
Lauterbach 2008	Mood stabilisers	Placebo	−	+	+	?	?	−
Montgomery 1979	Antipsychotics	Placebo	?	?	−	+	?	−
Montgomery 1983	NGAs	Placebo	?	?	−	+	?	−
Verkes 1998	NGAs	Placebo	+	+	+	+	?	?

+ Low risk
? Some concerns
− High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

Figure 3. Summary of 'Risk of bias' assessments



Bias arising from randomisation process

Although all trials used random allocation to assign participants to the intervention and comparator arms, only two trials were rated as low risk of bias for this domain (Hallahan 2007; Verkes 1998). There were some concerns regarding bias arising from the randomisation process for over half (57.1%) of the trials included in this review. For some older trials, insufficient information on the method used to generate the randomisation sequence was reported. Additionally, no information on allocation concealment was reported in a number of these trials (Battaglia 1999; Hirsch 1982; Montgomery 1979; Montgomery 1983). One trial was rated as high risk of bias for this domain (Lauterbach 2008). For this trial, a very significantly greater proportion of those assigned to the intervention arm were diagnosed with a personality disorder and had a history of multiple suicide attempts, whilst those assigned to the comparator arm had higher scores on the Suicide Intent Scale at baseline. Given these differences, there may have been a problem with the randomisation process.

Bias due to deviations from intended interventions

Three trials were rated as low risk of bias for this domain as participants and clinical personnel were blind to allocation, no deviations from the intended intervention were apparent, and analyses were conducted on an intention-to-treat (ITT) basis (Hallahan 2007; Lauterbach 2008; Verkes 1998). For the remaining trials, either no specific information on participant and clinical personnel were reported (Hirsch 1982; Montgomery 1983), or analyses excluded eligible trial participants post-intervention (Battaglia 1999; Montgomery 1979). These four trials (57.1%) were therefore rated as at some concerns for this domain.

Bias due to missing outcome data

Over half (57.1%) of the trials included in this review were at low risk of bias for those domain. One trial (14.3%) was rated as some concerns for this domain as greater than 5% of the data were missing at the post-intervention assessment, there was some evidence of a larger proportion of missing data for the intervention arm as compared to the comparator arm, and further, sensitivity analyses were not undertaken to understand the impact missing data may have had on the estimate of treatment effectiveness (Battaglia 1999). Two trials (28.6%) were rated as high risk of bias for this domain as greater than 5% of the data were missing at the post-intervention assessment and either no information on causes of missingness were reported, or alternatively, missingness may have been related to the development of side-effects (Montgomery 1979; Montgomery 1983).

The majority of trials included in this review were rated as at low risk of bias for this outcome (71.4%). However, two trials were rated as some concerns for this domain; this was typically either because insufficient information was reported on how repetition of SH was ascertained (Hirsch 1982), or because repetition of SH was ascertained from self-reported information and participant blinding was incomplete due to safety considerations (Lauterbach 2008).Bias in measurement of the outcome

Bias in selection of the reported result

All trials included in this review were rated as at some concerns for this domain as these trials had been published prior to the International Committee of Medical Journal Editors' (ICMJE) requirement in 2015 that all trials be pre-registered in a publicly available clinical trials registry. It was therefore difficult to determine whether data had been analysed according to a pre-specified plan, although there were no apparent departures from the analyses outlined in the methods section of these trials (Battaglia 1999; Hallahan 2007; Hirsch 1982; Lauterbach 2008; Montgomery 1979; Montgomery 1983; Verkes 1998).

Overall bias

As a consequence, just under half of the trials (42.9%) included in this review were rated as at high risk of bias overall, whilst the remainder (57.1%) were rated as at some risk of bias.

Effects of interventions

See: **Summary of findings 1** Newer generation antidepressants (NGAs) compared to placebo for self-harm in adults; **Summary of findings 2** Antipsychotics compared to placebo for self-harm in adults; **Summary of findings 3** Antipsychotics compared to another comparator drug or dose for self-harm in adults; **Summary of findings 4** Mood stabilisers, including antiepileptics and lithium compared to placebo for self-harm in adults; **Summary of findings 5** Natural products compared to placebo for self-harm in adults

Comparison 1: Tricyclic antidepressants versus placebo

There were no eligible trials in which tricyclic antidepressants were compared with placebo identified by this review.

Comparison 2: Tricyclic antidepressants versus another comparator drug or dose

There were no eligible trials in which tricyclic antidepressants were compared with another comparator drug or dose identified by this review.

Comparison 3: Newer generation antidepressants (NGAs)versus placebo

Three trials evaluated the effectiveness of different NGAs in adults (weighted mean age: 35.6 ± 6.8 years; 51.2% female) admitted to general hospitals following SH. The first compared 30 mg to 60mg mianserin or 75 mg to 150mg nomifensine against placebo (Hirsch 1982, N = 114), the second compared 30mg mianserin against placebo (Montgomery 1983, N = 58), and the third compared 40 mg paroxetine per day plus weekly/fortnightly supportive psychotherapy to placebo plus supportive psychotherapy (Verkes 1998, N = 91). We acknowledge that these antidepressants are from different drug classes (i.e. tetracyclic, atypical, and selective serotonin reuptake inhibitors (SSRIs), respectively); however, we have combined results for these agents into one comparison in order to address the question of whether antidepressant treatment using NGAs might be of general benefit in this patient population. We have also subgrouped the individual agents in a *post hoc* analysis.

Primary outcome

3.1 Repetition of SH

While data from two trials did not show that NGAs may reduce risk of repetition of SH (23/63 versus 33/66; odds ratio (OR) 0.59, 95% CI 0.29 to 1.19; N = 129; k = 2; I^2 = 0%; Analysis 1.1), the direction of effect favoured NGAs over placebo but the pooled estimate was imprecise. However, the overall risk of bias was high for one trial

(Montgomery 1979) and there were some concerns for the other trial (Verkes 1998). According to GRADE criteria, we judged the evidence to be of very low certainty.

There was also no evidence of an effect for mianserin or nomifensine at 12 weeks in a single trial (15/76 versus 6/38; OR 1.31, 95% confidence interval (CI) 0.46 to 3.71; N = 114; k = 1; I^2 = not applicable).

A *post-hoc* analysis was conducted combining data from all three of these trials at the final follow-up assessment (i.e. 12 weeks for Hirsch 1982, six months for Montgomery 1983, and 12 months for Verkes 1998) in order to investigate whether there is any evidence of a difference by agent. To assess the efficacy of each agent, the intervention arms in Hirsch 1982 were separated into nomifensine versus placebo (n = 76) and mianserin versus placebo (n = 76) using the approach outlined in Higgins 2011. However, there was no evidence of a difference between agents (test for subgroup differences: Chi^2 = 1.25, df = 2, P = 0.53, I^2 = 0%; Analysis 1.2).

Secondary outcomes

3.2 Treatment acceptability

There was no evidence of an effect for NGAs on treatment acceptability in two trials (Analysis 1.3). In the third trial, just over one-third (34.5%) of participants discontinued treatment; however, results were not disaggregated by trial arm (Montgomery 1983).

3.3 Treatment adherence

Data on treatment adherence was reported in one trial (Verkes 1998); however, no numerical data were provided. However, the trial authors report that "...analysis of capsule counts at each visit revealed no statistically significant differences between treatments" (p.545).

3.4 Depression

Two trials reported outcome data for depression (Hirsch 1982; Verkes 1998). Although mean scores on the Hamilton Depression Rating Scale(HDRS) were reported in Hirsch 1982, insufficient information was provided to enable calculation of accompanying SDs via imputation. In Verkes 1998, no numerical data were provided. However, the trial authors report there was "...no significant treatment effect" for this outcome by the post-intervention assessment (p.545).

3.5 Hopelessness

Information on hopelessness was reported in one trial (Verkes 1998). Once again, however, no numerical data were provided. However, the trial authors state there was also "...no significant treatment effect" for this outcome by the post-intervention assessment (p.545).

3.6 General functioning

No data available.

3.7 Social functioning

No data available.

3.8 Suicidal ideation

No data available.

3.9 Suicide

Numbers of suicides were reported for two trials (Hirsch 1982; Verkes 1998). In the first, one suicide occurred in the placebo group by the post-intervention period (Verkes 1998); however, there was no evidence of an effect for NGAs on suicide in this trial (0/46 versus 1/45; OR 0.32, 95% CI 0.01 to 8.04; N = 91; k = 1; I^2 = not applicable). In the second, no participant died by suicide by the six month follow-up period (Hirsch 1982).

Subgroup analyses

No included trial stratified randomisation by sex or repeater status.

Sensitivity analyses

Not applicable.

Comparison 4: Newer generation antidepressants versus another comparator drug or dose

There were no eligible trials in which NGAs were compared with another comparator drug or dose identified by this review.

Comparison 5: Any other antidepressants versus placebo

There were no eligible trials in which any other antidepressants were compared with placebo identified by this review.

Comparison 6: Any other antidepressants versus another comparator drug or dose

There were no eligible trials in which any other antidepressants were compared with another comparator drug or dose identified by this review.

Comparison 7: Antipsychotics versus placebo

The effectiveness of 'prophylactic' injections of the depot antipsychotic flupenthixol was compared to placebo in one small trial of adults (mean age 35.3 years, SD not reported; 70.3% female) without depression or schizophrenia and who were admitted to a general hospital following SH (Montgomery 1979, N = 37).

Primary outcome

7.1 Repetition of SH

Flupenthixol may reduce repetition of SH compared with placebo by post-intervention based on evidence from one trial (3/14 versus 12/16; OR 0.09, 95% CI 0.02 to 0.50; N =30; k = 1; I^2 = not applicable). According to GRADE criteria, we judged the evidence to be of low certainty.

Secondary outcomes

7.2 Treatment acceptability

There was no evidence of an effect for flupenthixol on treatment acceptability by the post-intervention assessment (4/18 versus 3/19; OR 1.52, 95% CI 0.29 to 8.01; N = 37; k = 1; I^2 = not applicable).

7.3 Treatment adherence

There was no evidence of an effect for the number of participants who completed the full course of treatment (14/18 versus 16/19; OR 0.66, 95% CI 0.12 to 3.45; N = 37; k = 1; I^2=not applicable).

7.4 Depression

No data available.

7.5 Hopelessness

No data available.

7.6 General functioning

No data available.

7.7 Social functioning

No data available.

7.8 Suicidal ideation

No data available.

7.9 Suicide

No data available.

Subgroup analyses

No included trial stratified randomisation by sex or repeater status.

Sensitivity analyses

Not applicable.

Comparison 8: Antipsychotics versus another comparator drug or dose

A single small trial investigated the effectiveness of lo- dose (i.e. 12 mg/day) fluphenazine compared to ultra-low dose (i.e, 1.5 mg/day) fluphenazine in adults (mean age: 30.4 ± 7.0 years; 43.9% female) admitted to an emergency psychiatric unit following a suicide attempt (Battaglia 1999, N = 58). However, "one patient was dropped after randomization due to unreliable reporting of excessive (greater than 500) S-HB [self-harm behaviours]" (p.363).

The authors of this trial report that "[t]he 'ultra-low' (1.5 mg) was chosen to represent the extreme low end of possible pharmacologic effect for fluphenazine treatment" (p.363).

Primary outcome

8.1 Repetition of SH

There was no evidence of an effect on repetition of SH by post-intervention for low-dose fluphenazine in this trial (12/27 versus 9/26; OR 1.51, 95% CI 0.50 to 4.58; N = 53; k = 1; I^2 =not applicable). According to GRADE criteria, we judged the evidence to be of low certainty.

Secondary outcomes

8.2 Treatment acceptability

There was no evidence of an effect for low-dose fluphenazine on treatment acceptability (18/30 versus 15/27; OR 1.20, 95% CI 0.42 to 3.44; N=57; k=1; I^2=not applicable).

8.3 Treatment adherence

No data available.

8.4 Depression

No data available.

8.5 Hopelessness

No data available.

8.6 General functioning

No data available.

8.7 Social functioning

No data available.

8.8 Suicidal ideation

No data available.

8.9 Suicide

No participant died by suicide in either arm by the post-intervention period.

Subgroup analyses

No included trial stratified randomisation by sex or repeater status.

Sensitivity analyses

Not applicable.

Comparison 9: Anxiolytics, including benzodiazepines and non-benzodiazepine anxiolytics, versus placebo

There were no eligible trials in which anxiolytics (including benzodiazepines and non-benzodiazepine anxiolytics) were compared with placebo identified by this review.

Comparison 10: Anxiolytics, including benzodiazepines and non-benzodiazepine anxiolytics, versus another comparator drug or dose

There were no eligible trials in which anxiolytics (including benzodiazepines and non-benzodiazepine anxiolytics) were compared with another comparator drug or dose identified by this review.

Comparison 11: Mood stabilisers, including antiepileptics and lithium, versus placebo

In a single trial, the effectiveness of lithium was compared to placebo in adults (mean age: 39.4 ± 9.5 years; 57.5% female) who had engaged in SH in the context of a depressive spectrum disorder (Lauterbach 2008, N = 167).

Primary outcome

11.1 Repetition of SH

There was no evidence of an effect on repetition of SH by the post-intervention period in a single trial of lithium (7/84 versus 7/83; OR 0.99, 95% CI 0.33 to 2.95; N = 167; k = 1; I^2 = not applicable). According to GRADE criteria, we judged the evidence to be of very low certainty. Please note that these ORs differ modestly from those reported by the trial authors in correspondence; however, there is no material difference in either the overall direction, magnitude, or significance of these results.

Secondary outcomes

11.2 Treatment acceptability

There was no evidence of an effect in favour of lithium for treatment acceptability, as measured by the proportion of participants who discontinued treatment, at both the six month (i.e. during treatment) (30/84 versus 32/83; OR 0.89, 95% CI 0.47 to 1.66; N = 167; k = 1; I^2 = not applicable) and by the post-intervention (48/84

versus 49/83; OR 0.93, 95% CI 0.50 to 1.71; N = 167; k = 1; I^2 = not applicable) assessments.

11.3 Treatment adherence

No data available.

11.4 Depression

There was also no evidence of an effect for lithium on depression scores at post-intervention (mean 8.48, SD 7.50, N = 31 versus mean 8.87, SD 8.10, N = 33; mean difference (MD) -0.39, 95% CI -4.21 to 3.43; N = 64; k = 1; I^2 = not applicable). It should be noted that these(MDs differ modestly from those reported by the authors; however, there is no material difference in either the overall direction, magnitude, or significance of these results.

11.5 Hopelessness

There was no evidence of an effect for lithium on hopelessness scores at post-intervention (mean 8.88, SD 5.40, n = 26 versus mean 9.04, SD 6.10, n = 25; MD -0.16, 95% CI -3.33 to 3.01; N = 51; k = 1; I^2=not applicable). These MDs also differ modestly from those reported by the authors; however, there is no material difference in either the overall direction, magnitude, or significance of these results.

11.6 General functioning

No data available.

11.7 Social functioning

No data available.

11.8 Suicidal ideation

There was no evidence of an effect for lithium on the number of patients reporting suicidal ideation, defined as a score of greater than zero on the SSI, at post-intervention (8/31 versus 11/32; OR 0.66, 95% CI 0.22 to 1.97; N = 63; k =1; I^2 = not applicable) follow-up assessments. These ORs differ modestly from those reported by the trial authors in correspondence; however, there is no material difference in either the overall direction, magnitude, or significance of these results.

11.9 Suicide

There was no evidence of an effect for lithium on suicides (0/85 versus 3/83; OR 0.1, 95% CI 0.0 to 2.7; N = 167; k = 1; I^2 = not applicable).

Subgroup analyses

No included trial stratified randomisation by sex or repeater status.

Sensitivity analyses

Not applicable.

Comparison 12: Mood stabilisers, including antiepileptics and lithium, versus another comparator drug or dose

There were no eligible trials in which mood stabilisers (including antiepileptics and lithium) were compared with another comparator drug or dose identified by this review.

Comparison 13: Other pharmacological agents versus placebo

There were no eligible trials in which other pharmacological agents were compared with placebo identified by this review.

Comparison 14: Other pharmacological agents versus another comparator drug or dose

There were no eligible trials in which other pharmacological agents were compared with another comparator drug or dose identified by this review.

Comparison 15: Natural products versus placebo

One trial investigated the effectiveness of dietary supplementation with omega-3 essential fatty acid (n-3EFA) as compared to placebo in adults (mean age 30.6 years, SD not reported; 65.3% female) admitted to accident and emergency facilities following an episode of SH (Hallahan 2007, N = 49).

Primary outcome

15.1 Repetition of SH

There was no evidence of an effect for natural products at post-intervention in a single small trial (7/22 versus 7/27; OR 1.33, 95% CI 0.38 to 4.62; N = 49; k = 1; I^2 = not applicable). According to GRADE criteria, we judged the evidence to be of low certainty.

Additionally, there was no difference between groups in the mean number of SH episodes per participant between those receiving the supplement and those receiving placebo (mean 0.41 versus mean 0.41). However, insufficient information was provided to enable imputation of SDs.

Secondary outcomes

15.2 Treatment acceptability

There was no evidence of an effect for natural products on treatment acceptability as measured by the proportion of participants who discontinued treatment for any cause (3/22 versus 7/27; OR 0.45, 95% CI 0.10 to 2.00; N = 49; k=1; I^2 = not applicable), although the trial authors note that "[n]o patients discontinued the study because of adverse events" (Hallahan 2007, p.120).

15.3 Treatment adherence

There was no evidence of an effect for natural products on treatment adherence as measured by pill counts (19/22 versus 20/27; OR 2.22, 95% CI 0.50 to 9.85; N = 49; k = 1; I^2 = not applicable).

15.4 Depression

Mean and SD scores on the BDI and HRSD were reported as adjusted improvement scores. The authors report there were "significant improvements in BDI scores at 12 weeks [i.e. post-intervention] (p = 0.004) in the [omega-3] group. Moreover, more patients in the [omega-3] group attained more than 50% (p = 0.001) and 70% (p = 0.001) reduction (response and remission, respectively) in symptoms...Similar data were observed for the HRSD" (Hallahan 2007, p.119).

15.5 Hopelessness

No data available.

15.6 General functioning

No data available.

15.7 Social functioning

No data available.

15.8 Suicidal ideation

There may be evidence of a reduction in the proportion of participants reporting suicidal ideation at the post-intervention assessment for natural products compared with placebo (8/22 versus 19/27; OR 0.24, 95% CI 0.07 to 0.80; N = 49; k = 1; I^2 = not applicable).

15.9 Suicide

No participant died by suicide in either arm during the treatment period.

Subgroup analyses

No included trial stratified randomisation by sex or repeater status.

Sensitivity analyses

Not applicable.

Comparison 16: Natural products versus another comparator drug or dose

There were no eligible trials in which natural products were compared with another comparator drug or dose identified by this review.

DISCUSSION

This review included seven trials, and failed to identify any newer trials since the previous version (Hawton 2015). Previously, we commented on the paucity of evidence on which to make firm conclusions about the most effective form of pharmacological treatment for patients who have recently engaged in self-harm (SH). This update reinforces these conclusions.

Summary of main results

Newer generation antidepressants

On the basis of data from two trials in which different classes of antidepressants (i.e. mianserin and paroxetine) were evaluated in SH patients, the evidence remains uncertain as to whether (newer generation antidepressants NGAs) have any effect on repetition of SH compared with placebo by the post-intervention assessment (Montgomery 1983; Verkes 1998). There was no apparent effect by the 12-week assessment in a further trial of a different NGA (i.e. nomifensine) (Hirsch 1982). However, it should be noted that the trials were relatively small and the confidence intervals around the point estimate of the treatment effect were relatively wide. This therefore increases uncertainty about the estimates found for antidepressants in this review. Additionally, as only one death by suicide was recorded in these trials, it was not possible to determine whether there is an effect of NGAs on suicide in adults who engage in SH.

We combined results of three trials of antidepressants from different drug classes in this review (i.e. tetracyclic, atypical, and selective serotonin reuptake inhibitors (SSRIs)). Although we acknowledge that these agents have different mechanisms of action, we chose to combined them for the purposes of meta-analysis in this review on the basis that their potential impacts on SH through reducing levels of depression are likely to be similar and to establish whether there is evidence of a generalised effect of antidepressants in this clinical population. A *post-hoc* analysis, furthermore, suggested that no one antidepressant agent was superior to the others in reducing repetition of SH.

Antipsychotics

Based on data from a single relatively old and small trial in patients with a history of multiple episodes of SH without depression or schizophrenia, use of the depot antipsychotic medication flupenthixol may reduce repetition of SH compared with placebo by the post-intervention assessment (Montgomery 1979).

Based on another single trial, there is probably little or no effect of low-dose fluphenazine as compared with ultra-low dose fluphenazine on repetition of SH at post-intervention (Battaglia 1999).

Mood stabilisers, including lithium

On the basis of data from a single trial of lithium versus placebo (Lauterbach 2008), the evidence remains uncertain as to whether lithium has any effect on repetition of SH compared with placebo. However, the authors claimed there was an effect for suicide. This was based on a *post-hoc* analysis of very limited data (i.e. there being no suicides in the lithium treated group, and three in the placebo group), and by taking into account exposure time in each group.

Natural products

Based on a single trial, there is probably little or no effect of omega-3 essential fatty acids compared with placebo on repetition of SH at post-intervention. However, fewer patients who received the supplement reported suicidal ideation at follow-up (Hallahan 2007).

Overall completeness and applicability of evidence

Completeness of evidence

There have been few trials of pharmacological interventions for SH patients (we identified just seven), especially when compared with the number of trials of psychosocial interventions. Therefore, our conclusions are limited to a small range of pharmacological agents.

Three trials focused on drugs from three different classes of antidepressants (Hirsch 1982; Montgomery 1983; Verkes 1998). This is consistent with the high prevalence of depression found in SH patients presenting to clinical services (Hawton 2013), and with evidence that antidepressants are commonly prescribed to SH patients (Carr 2016). However, these trials included relatively older agents (i.e. mianserin, nomifensine, and paroxetine), one of which (i.e. nomifensine) is no longer used in the UK. The antidepressants now most commonly recommended for the treatment of adults diagnosed with moderate to severe depression are SSRIs (Qaseem 2016; Malhi 2015; NICE 2009), but only one drug from this class (i.e. paroxetine) has been specifically evaluated in SH patients to date. Increasingly, serotonin and noradrenaline reuptake inhibitors (SNRIs) are also used for the treatment of depression but no agents from this antidepressant class have so far been evaluated in this clinical population. In addition, there is little evidence that antidepressants reduce the risk of suicide, except in older adults (Stone 2009).

Unfortunately, presence of publication bias could not be evaluated as no meta-analysis in the present review included 10 or more trials. However, it is notable that one trial was never published in full (Hirsch 1982), whilst a second was not published in a peer-reviewed journal (Montgomery 1979). Therefore, we cannot rule out the possibility that publication bias may have affected the studies within this review. This is a problem that commonly affects clinical data (Easterbrook 1991).

Whilst all of the included trials reported information on repetition of SH, publication bias may have been more common for the secondary outcomes assessed by this review. However, formal testing of publication bias was not possible due to the small number of trials. None of the trials included further information on adverse effects of pharmacological therapy, other than further SH and suicidal behaviour.

Applicability of evidence

The majority of participants in these trials were female, reflecting the typical pattern for SH in hospital-presenting populations (Hawton 2008). As no included trial stratified randomisation by sex, however, we were unable to undertake subgroup analyses to investigate whether there was any difference in treatment response between females and males. Given that there are some differences in the motives for SH in as compared to females (Claes 2007), further work on the treatment needs and preferences of males who engage in SH, as well as their experiences of clinical services, and how these may differ from females who engage in SH, is warranted.

The majority of trials included either patients who had all engaged in intentional drug overdoses or self-poisoning, or samples where the majority had, again reflecting the typical pattern observed in patients who present to general hospitals following SH (Hawton 2007). However, there are other important patient subgroups, such as those who engage in self-cutting, who may have different treatment needs (Hawton 2004). None of the trials included in this review specifically focused on these patients; although it should be noted that method switching is common in those who engage in repeat episodes of SH (Witt 2019). Five of the seven trials focused on those with a history of repeated SH, which is a particular issue in this clinical population given the association of individuals with a history of repeat episodes having a greater risk of suicide (Zahl 2004). However, no trial investigated impacts of pharmacological interventions for those with an initial episode of SH versus those engaging in repeated SH. We were therefore unable to undertake subgroup analyses to investigate the impact of these interventions by repeater status.

This review focused exclusively on those who engaged in SH. As a result, we have excluded trials in which participants were diagnosed with conditions such as borderline personality disorder but where SH was not required for trial entry. We also excluded trials in which participants engaged in repetitive self-injurious behaviour in the context of an intellectual disability or developmental disorder (e.g, an autism spectrum disorder). Readers interested in the use of pharmacological interventions for these patient groups are referred to the relevant reviews (Rana 2013; Stoffers-Winterling 2020).

Quality of the evidence

Certainty of evidence, as assessed using the GRADE approach, was generally low to very low suggesting that further research is likely to have an important impact on our confidence in the estimate of treatment effectiveness, and may in fact change the estimates. This is particularly likely to affect results for those interventions that so far have only been assessed in single trials.

Additionally, using the Cochrane 'Risk of bias' tool, version 2 (Sterne 2019), all trials included in this review possessed some concerns or a high risk of bias in relation to at least one aspect of trial design, with weaknesses most commonly observed with selection of the reported result and measurement of the outcome.

In 2015, the International Committee of Medical Journal Editors (ICMJE) recommended all clinical trials should be pre-registered in a public trials registry (Witt 2020b). However, as all trials included in this review were published prior to 2015, it was difficult to determine whether data were analysed in accordance with a pre-specified analysis plan; although no substantial departures were noted for any of these trials. Future trials should provide sufficient detail within the clinical trial register to determine how key outcome(s) are defined and measured to aide in the determination as to whether there has been any substantive changes to the proposed analysis plan, and if so, the reasons for any such departures.

There were also some concerns relating to bias in the measurement of the outcome. This was typically because repetition of SH was based on self-reported information. Given that around two-thirds of SH episodes recorded in medical and clinical records are not reported by participants, prevalence estimates derived from self-reported information alone may underestimate the true rate of SH (Mitchell 2016). By supplementing data on self-reported SH with information from clinical or medical records, future trials could compare results based on self-reported information with that obtained from objective sources to investigate what impact, if any, this bias may have had on the estimate of treatment effectiveness.

Lastly, the trials included in this review were, in general, relatively small to detect significant differences in proportions of patients who engage in a repeat episode of SH. We have previously calculated that trials in this field may need to recruit up to a minimum of 1862 participants per arm to detect a significant effect for repetition of SH with 80% power at the conventional alpha level (Witt 2020b). Future trials should therefore supply *a priori* power calculations to justify their sample size.

Potential biases in the review process

We are confident we have identified all relevant trials of pharmacological interventions for SH in adults. However, we cannot rule out the possibility that some relevant outcome data may be missing from this review. Although data on repetition of SH were available for all of the included trials, limited data were available on secondary outcomes. Only three trials included information on depression, and two on hopelessness and suicidal ideation. Information on suicide was only published in one trial (Lauterbach 2008), and had to be requested from trial authors for the remaining trials. Nevertheless, by using the random-effects model in all analyses, our results possess greater generalisability than if we had used the fixed-effect model (Erez 1996).

Agreements and disagreements with other studies or reviews

This review is an update of the 2015 Cochrane Review on pharmacological interventions for SH in adults (Hawton 2015). The previous review included seven trials of four different approaches, finding that there was little evidence of beneficial effects of drug treatments on repetition of SH.

We identified only one other comprehensive review of pharmacotherapy for SH (Smith 2005). This included a wide range of evidence, not just from randomised controlled trials (RCTs). Whilst there were encouraging findings, particularly with regards to mood stabilisers and antipsychotics in this review, effects were less strong in randomised as compared to non-randomised trials. Two further reviews considered pharmacological interventions for borderline personality disorder including participants both with and without a history of SH (Turner 2014; Stoffers-Winterling 2020). Whilst one concluded there was some evidence of benefit for atypical antipsychotics in reducing SH on the basis of findings from a single RCT (Turner 2014), the second concluded there was little robust evidence of benefit for any one particular pharmacological agent for SH in this clinical population (Stoffers-Winterling 2020).

Given the positive effects found for lithium with regard to SH repetition in patients diagnosed with affective disorders (Cipriani 2013a; Smith 2017), there may be a role for lithium for some SH patients. While the negative results of the Lauterbach 2008 trial, which included patients with an 'affective spectrum disorder', would appear to be contrary to this suggestion, it should be noted that there were no suicides in the lithium-treated group in this trial. Alternatively, as studies in which beneficial effects for lithium have been found have focused on patients diagnosed with either depression or bipolar disorder, rather than those with a history of SH specifically, it may also be that the primary indication for lithium in the prevention of SH is in patients with either of these disorders, rather than SH alone.

AUTHORS' CONCLUSIONS

Implications for practice

It is not possible to reach firm conclusions regarding pharmacological interventions for those who engage in self-harm (SH). While depression may be common in these patients, we found only uncertain evidence that newer generation antidepressants (NGAs) prevent repetition of SH. In addition, the agents evaluated in these trials are older and one, nomifensine, is no longer used in the UK. While there may be low-certainty evidence of benefit in a single early trial of the depot antipsychotic flupenthixol in those with a history of multiple episodes of SH, this requires replication, preferably involving more modern antipsychotic agents. Additionally, further exploration of the potential mechanism of this effect (e.g. it is possible that depot delivery was a reason for this apparent effect though maintaining stable blood plasma levels) is required.

Clinicians treating SH patients with pharmacological agents must be aware of the extra risks of overdose in this population (Gjelsvik 2014), and especially the relative toxicity of the different agents that might be used. Pharmacological agents associated with lower case fatality indices should therefore be preferred (Hawton 2010).

Implications for research

While the results of this review did not indicate any benefit of NGAs, the high prevalence of depression in patients who self-harm (Hawton 2013), the strong association between both depression and SH and suicide, and the frequency with which antidepressants are prescribed to patients following SH (Carr 2016), suggest that there should be further evaluation of antidepressants in this clinical population. This would preferably involve the use of more modern and less toxic antidepressants, which should also be combined with psychosocial interventions. Further evaluation of the potential of lithium is also warranted given encouraging results of trials in patients with affective disorders (i.e. both with and without SH) (Cipriani 2013a; Smith 2017), as well as the uncertainty around the impact of lithium on suicide in the one trial included in this review. Emerging evidence also suggests that lithium may have a superior antisuicidal effect as compared to other mood stabilisers (Hayes 2016). Favourable findings of intravenous ketamine and nasal esketamine in relation to short-term reductions in suicidal ideation in those with treatment-resistant depression also suggest a potential role for these agents in SH prevention (Witt 2020a), possibly combined with psychosocial interventions that may help to enhance and sustain these effects.

In view of the paucity of andomised controlled trials (RCTs) of pharmacological agents in patients who engage in SH, perhaps reflecting difficulties in conducting these trials due to safety considerations, valuable information about the potential impacts of pharmacological treatments on suicidal behaviour might be gained from the analysis of linked population-wide registry data in which information about prescriptions, hospital presentations for SH, and suicide are routinely recorded (House 2020). Additionally, future trials in clinically-diverse populations (e.g. those with treatment-resistant depression, suicidal ideation, etc.) could consider stratifying randomisation by presence of SH. That way, relevant data relating to repetition of SH in those with a history of SH could be included in future updates of this review.

Any pharmacological interventions for adults who engage in SH should include a range of outcome measures, not just SH and suicide, but also acceptability, adherence, and attitudes to treatment as these may help to identify contributors to any apparent benefit or lack of impact. In particular, the inclusion of outcomes that matter to those who engage in SH is required to further inform intervention development (Owens 2020). It is also important that adverse effects of treatment medication, both short- and long-term, are carefully evaluated, including possible use of the medication in episodes of further SH (Ferrey 2018; Gjelsvik 2014).

Additionally, from a service planning perspective, future trials should also include economic evaluations in order to determine which interventions may be most feasible to routinely implement in health service settings (Bustamante-Madsen 2018).

ACKNOWLEDGEMENTS

The authors thank the following trial authors for providing us with unpublished data: Brian Hallahan and John Rush.

The authors and the CCMD Editorial Team are also grateful to the following peer reviewers for their time and comments: Gregory Carter, Nick Meader, Hector Pardo-Hernandez, Sue Rees and Mark

Sinyor. They would also like to thank Cochrane Copy Edit Support for the team's help and Phil Roberts from the University of York for graphic design support in the production of Figure 4 to 11.

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) Emeritus Senior Investigator and used personal funding from NIHR to help 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.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Battaglia 1999

Study characteristics	
Methods	Double-blind RCT. Participants were individually assigned to either 'low' dose (i.e., 12.5 mg/monthly) or 'ultra-low' dose (i.e., 1.5 mg/monthly) of intramuscular fluphenazine decanoate injections. *Follow-up period:* 6 months. *N lost to follow-up:* 5/58 (8.6%) for repetition of SH.
Participants	*Number of total participants:* 58 participants were randomised, 30 were allocated to the intervention arm (i.e., 12.5 mg/monthly of intramuscular fluphenazine decanoate) and 28 to the control arm (i.e., 1.5 mg/monthly of intramuscular fluphenazine decanoate). *Profile of participants:* all (n = 58; 100%) had multiple episodes of SH prior to trial entry. Almost one-half (n = 28; 44%) were female. The majority were diagnosed with substance misuse disorders (n = 45; 79%), followed by any mood disorder (n = 20; 35%), and any anxiety disorder (n = 17; 29%). *Source of participants:* patients presenting to a psychiatric hospital screened for a history of suicide attempts. *Inclusion criteria:* i) aged between 18-65 years; ii) receiving treatment for a suicide attempt that occurred within 30 days prior to trial entry; iii) ≥ 2 prior suicide attempts; iv) able to read English. *Exclusion criteria:* i) allergic/hypersensitive to fluphenazine; ii) diagnosed with tardive dyskinesia; iii) a history of neuroleptic malignant syndrome; iv) diagnosed with narrow angle glaucoma; v) diagnosed with schizophrenia; vi) diagnosed with any terminal illness with less than 1 year life expectancy; vii) pregnant or of childbearing age and not using effective birth control; viii) current/expected to continue with treatment using medications with psychotropic effects.
Interventions	*Intervention:* 12.5 mg/monthly of intramuscular fluphenazine decanoate administered by intramuscular injection. *Control:* 1.5 mg/monthly of intramuscular fluphenazine decanoate administered by intramuscular injection. *Concomitant medication(s):* benztropine was administered, as necessary, to prevent extra-pyramidal symptoms. It is unclear what proportion of the intervention and control groups were using concomitant medications, however. *Length of treatment:* six months. *Location:* Dallas, Texas, USA.
Outcomes	*Primary outcome(s):* repetition of SH according to self-report. *Secondary outcome(s):* i) adverse effects, as measured by the Abnormal Involuntary Movement Scale; ii) alcohol and other drug use, as measured by an idiosyncratic checklist developed by the authors; iii) suicide (unclear how ascertained).
Notes	*Funding:* "This research was supported in part by a grant from The National Institute of Mental Health (MH-53799) and by Mental Health Connections, a partnership between Dallas County Mental Health Mental Retardation and the Department of Psychiatry at the University of Texas South-Western Medical Centre. Funding was from the Texas State Legislature and Dallas Country Mental Health and Mental Retardation" (Battaglia 1999, p.370). *Conflict(s) of interest:* no details provided.

Battaglia 1999 *(Continued)*

Other: data on suicides were obtained following correspondence with authors.

Hallahan 2007

Study characteristics	
Methods	Double-blind placebo-controlled RCT. Participants were individually assigned via a computer generated list to either 2128mg/day of EPA plus DHA (i.e., participants received four capsules each containing 305mg EPA and 227 DHA) or four capsules containing 99% corn oil and a 1% EPA/DHA mixture (to control for the 'fishy breath' side effect associated with the intervention treatment). *Follow-up period:* 12 weeks. *N lost to follow-up:* 0/49 (0%) for repetition of SH.
Participants	*Number of total participants:* 49 participants were randomised, 22 were allocated to the intervention arm (i.e., 2128 mg/day of EPA plus DHA) and 27 to the control arm (i.e., four capsules containing 99% corn oil and a 1% EPA/DHA mixture). *Profile of participants:* all (n = 49; 100%) had multiple episodes of SH prior to trial entry. The majority were female (n = 32; 65%). The majority were diagnosed with any personality disorder (n = 40; 81.6%), followed by borderline personality disorder specifically (n = 35; 71.4%), and alcohol misuse disorder (n = 20; 41%). Around one-half (n = 26; 53%) were taking psychotropic medication. *Source of participants:* patients presenting to hospital following an episode of SH. *Inclusion criteria:* i) presenting to hospital following an episode of SH; ii) at least one previous episode of SH; iii) living inside the catchment area. *Exclusion criteria:* i) current history of addiction, substance abuse, psychosis, or any eating disorder; ii) currently receiving psychotherapy; iii) history of dyslipidaemia; iv) involved with any treatment, diet, or illness known to interfere with lipidorn-3EFA metabolism; v) weight loss greater than 10% over the previous 3 months; vi) taking supplements containing n-3 EFAs or have consumed fish more than once per week; vii) changes to, or introduction of, psychotropic medication during the previous 6 weeks.
Interventions	*Intervention:* four capsules containing 305 mg EPA and 227mg DHA. Total dose equalled 2128 mg per day of EPA plus DHA. *Control:* four capsules per day consisting of 99% corn oil and a 1% EPA/DHA mixture. *Concomitant medication(s):* were permitted, however, details of these were not provided. Around one-half of both the intervention (n = 13; 59.1%) and placebo (n = 13; 55.6%) groups were using concomitant psychiatric medications. *Length of treatment:* 12 weeks. *Location:* Dublin, Republic of Ireland.
Outcomes	*Primary outcome(s):* i) repetition of SH according to hospital records. *Secondary outcome(s):* i) depression, as measured by the BDI; ii) suicidal ideation, as measured by the Overt Aggression Scale, Modified (OAS-M); iii) suicide (unclear how ascertained); iv) treatment adherence, as measured by pill counts; v) aggressive behaviour, as measured by the OAS-M; vi) impulsivity, as measured by the Immediate and Delayed Memory Tasks; vii) daily stresses, as measured by the Perceived Stress Scale and the Daily Hassles and Uplifts Scale.
Notes	*Funding:* "B.H. received salary support from the Department of Psychiatry, University of Illinois at Chicago, USA" (Hallahan 2007, p.122).

Hallahan 2007 *(Continued)*

	Conflict(s) of interest: "Pronova (now Epax) AS, Lysaker, Norway, provided the active preparation and placebo but were not otherwise involved in the study" (Hallahan 2007, p.118). No other conflicts of interest were stated.

Hirsch 1982

Study characteristics	
Methods	Double-blind placebo-controlled RCT. Participants were individually assigned to either 30-60mg/day of mianserin, 75-150mg/day of nomifensine, or placebo (no further information on placebo provided). *Follow-up period:* 12 weeks. *N lost to follow-up:* 0/114 (0%) for repetition of SH.
Participants	*Number of total participants:* 114 participants, 38 were allocated to the mianserin arm, 38 were allocated to the nomifensine arm, and 38 to the placebo arm. *Profile of participants:* not stated. *Source of participants:* patients admitted to hospital following an episode of intentional drug overdose. *Inclusion criteria:* i) General Health Questionnaire (GHQ) score of over 20. *Exclusion criteria:* i) currently receiving antidepressant or antipsychotic medication.
Interventions	*Intervention:* oral administration of either 30 mg/day tp 60 mg/day of mianserin or 75 mg/day t 150 mg/day of nomifensine. *Control:* placebo. No further information provided. *Concomitant medication(s):* no information on whether concomitant medication(s) were permitted was provided. *Length of treatment:* six weeks. *Location:* London, UK.
Outcomes	*Primary outcome(s):* i) repetition of SH (unclear how ascertained). *Secondary outcome(s):* i) depression, as measured by the HDRS, ii) adverse events, as measured by the Symptoms Emergent Checklist; iii) life events, as measured by the Brief Life Events Scale; iv) general health, as measured by the GHQ; v) treatment adherence, as measured by pill counts; vi) suicide (unclear how ascertained).
Notes	*Funding:* no details on funding provided. *Conflict(s) of interest: no details on conflicts of interest provided.* *Other:* data on depression and treatment adherence had to be excluded due to an inability to collect unpublished data from the trial authors for these outcomes.

Lauterbach 2008

Study characteristics

Lauterbach 2008 *(Continued)*

Methods	Double-blind placebo-controlled RCT. Participants were individually assigned via a computerised sequence to either oral administration of lithium carbonate or placebo (no further information on placebo provided). *Follow-up period:* 14 weeks. *N lost to follow-up:* 22/169 (13.0%) at one month; 50/169 (29.6%) at three months; 62/169 (36.7%) at six months; 97/169 (57.4%) at 12 months.
Participants	*Number of total participants:* 167 participants, 84 were allocated to the lithium arm, and 83 were allocated to the placebo arm. *Profile of participants:* 44.3% (n = 74) had multiple episodes of SH prior to trial entry. Over one-half (n = 96; 57.5%) were female. Around three-quarters (n = 123; 76%) were diagnosed with major depression. *Source of participants:* patients admitted to one of five participating emergency departments following a suicide attempt. *Inclusion criteria:* i) at least 18 years of age; ii) suicide attempt within three months prior to first drug administration; iii) suicide attempt occurred within the context of a depressive spectrum disorder; iv) able to complete the screening and baseline assessment protocols; v) able to provide written informed consent. *Exclusion criteria:* i) diagnosed with a disorder associated with frequent suicidal behaviour (e.g., schizophrenia, borderline personality disorder, severe SH and/or substance-related disorders, including current substance addictions); ii) diagnosed with any disorder indicated for long-term lithium treatment; iii) diagnosed with any disorder for which lithium treatment is contraindicated; iv) any other contraindications (e.g., pregnant, breast-feeding, etc.)
Interventions	*Intervention:* oral administration of lithium carbonate according to a fixed schedule of dose augmentation (i.e., 200 mg/week) until an effective blood level of between 0.6 mm/L to 0.8 mmol/L had been achieved. For most participants, this level was achieved in 34 weeks. Participants received, in addition, TAU involving consultations with physicians in the community and referral to psychiatric treatment as necessary. *Control:* oral administration of a placebo capsule in addition to TAU involving consultations with physicians in the community and referral to psychiatric treatment as necessary. Ingredients for the placebo capsule are not provided. *Concomitant medication(s):* were permitted, however, details of these were not provided including details on the proportion of the intervention and placebo groups using concomitant medications. *Length of treatment:* 12 months. *Location:* Germany.
Outcomes	*Primary outcome(s):* i) repetition of SH according to self-report; ii) suicide (unclear how ascertained). *Secondary outcome(s):* i) depression, as measured by the HDRS; ii) hopelessness, as measured by the BHS; iii) suicidal ideation, as measured by the SSI.
Notes	*Funding:* "This research was supported by grants 01GI 9920 and 01GI 0220 from the German Ministry for Education and Research within the promotional emphasis 'German Research Network on Depression' (subproject 1.2), and German Research Foundation grant LA 1975/2-1 to Erik Lauterbach. Additional funding was granted by Sanofi-Aventis" (Lauterbach 2008, p.477). *Conflict(s) of interest:* "Dr. Ahrens has received a research grant from Sanofi Aventis" (Lauterbach 2008, p.477). *Other:* data for depression, hopelessness, and suicidal ideation had to be requested from the trial authors.

Montgomery 1979

Study characteristics	
Methods	Double-blind placebo-controlled RCT. Participants were individually assigned to either an intramuscular injection of 20 mg/month flupenthixol decanoate or placebo (no further information on placebo provided). *Follow-up period:* six months. *N lost to follow-up:* 7/37 (18.9%) for repetition of SH.
Participants	*Number of total participants:* 37 participants, 18 were allocated to intramuscular flupenthixol decanoate and 19 to placebo. *Profile of participants:* all (n = 37; 100%) had multiple episodes of SH prior to trial inclusion. The majority (n = 26; 70.3%) were female. *Source of participants:* patients admitted to a general hospital following a suicidal act. *Inclusion criteria:* i) documented history of two or more episodes of SH. *Exclusion criteria:* i) diagnosis of depression or schizophrenia; ii) diagnosis of an organic illness.
Interventions	*Intervention:* intramuscular administration of 20 mg/month of flupenthixol decanoate. *Control:* placebo. No further information provided. *Concomitant medication(s):* no information on whether concomitant medication(s) were permitted was provided. *Length of treatment:* six months. *Location:* Maidstone, UK.
Outcomes	*Primary outcome(s):* i) repetition of SH (unclear how ascertained). *Secondary outcome(s):* i) treatment adherence, as measured by the number of participants who completed the full course of treatment; ii) adverse effects (unclear how ascertained).
Notes	*Funding:* no details on funding were provided. *Conflict(s) of interest:* no details on author interests were provided.

Montgomery 1983

Study characteristics	
Methods	Double-blind placebo-controlled RCT. Participants were individually assigned to either 30mg/day mianserin or placebo (no further information on placebo provided). *Follow-up period:* six months. *N lost to follow-up:* 0/58 (0%) for repetition of SH.
Participants	*Number of total participants:* 58 participants, 17 were allocated to the mianserin arm, and 21 to the placebo arm.

Montgomery 1983 *(Continued)*

	Profile of participants: all (n = 58; 100%) had multiple episodes of SH prior to trial entry. Two-thirds (n = 38; 66%) were female. All (n = 58; 100%) had been diagnosed with borderline or histrionic personality disorder. *Source of participants:* patients admitted to a medical ward following SH. *Inclusion criteria:* i) multiple previous episodes of SH; ii) diagnosis of personality disorder. *Exclusion criteria:* i) diagnosis of depression or schizophrenia.
Interventions	*Intervention:* oral administration of 3 0mg/day mianserin. *Control:* placebo. No further information provided. *Concomitant medication(s):* no information on whether concomitant medication(s) were permitted was provided. *Length of treatment:* six months. *Location:* London, UK.
Outcomes	*Primary outcome(s):* i) repetition of SH (unclear how ascertained). *Secondary outcome(s):* i) depression, as measured by the MADRS; ii) treatment adherence, as measured by pill counts.
Notes	*Funding:* no details on funding were provided. *Conflict(s) of interest:* no details on author interests were provided. *Other:* data on depression had to be excluded due to an inability to collect unpublished data from the trial authors for this outcome.

Verkes 1998

Study characteristics	
Methods	Double-blind placebo-controlled RCT. Participants were individually assigned to either 40mg/day paroxetine plus weekly/fortnightly TAU or placebo (no further information on placebo provided) plus TAU. *Follow-up period:* 12 months. *N lost to follow-up:* 0/91 (0%) for repetition of SH data.
Participants	*Number of total participants:* 91 participants, 46 were allocated to the paroxetine arm, and 45 were allocated to the placebo arm. *Profile of participants:* all (n = 91; 100%) had engaged in multiple episodes of SH prior to trial entry. Over one-half (n = 54; 59.3%) were female. The majority (n = 84; 92%) were diagnosed with a personality disorder, followed by an alcohol use disorder (n = 40; 44%), any depressive disorder (n = 23; 25.3%), adjustment disorder (n = 19; 20.9%), any dissociative disorder (n = 8; 8.8%), dysthymia (n = 6; 6.5%), any anxiety disorder (n = 4; 4.4%). A minority (n = 15; 16.5%) had no formal psychiatric diagnosis. *Source of participants:* patients were recruited from outpatient departments in accident and emergency wards of university hospitals. *Inclusion criteria:* i) aged 18 years and over; ii) previous history of SH. *Exclusion criteria:* i) current diagnosis of major depression.

Verkes 1998 *(Continued)*

Interventions	*Intervention:* oral administration of paroxetine 40 mg/day, plus weekly or fortnightly psychotherapy TAU. *Control:* placebo (no further information provided) plus weekly or fortnightly psychotherapy TAU. *Concomitant medication(s):* one-half (n = 24; 52.2%) of the intervention group used concomitant benzodiazepine medications during the trial, compared to 62.2% (n = 28) of those allocated to placebo. *Length of treatment:* 12 months. *Location:* Leiden and Rotterdam, the Netherlands.
Outcomes	*Primary outcome(s):* i) repetition of SH (unclear how ascertained). *Secondary outcome(s):* i) depression, as measured by the BDI; ii) hopelessness, as measured by the BHS; iii) anger, as measured by the State-Trait Anger Expression Inventory; iv) treatment adherence, as measured by pill counts and platelet serotonin levels; v) adverse events (unclear how ascertained); vi) side effects (unclear how ascertained); vii) suicide (unclear how ascertained).
Notes	*Funding:* "Supported by grant 89-110 CRO 012859 from the Dutch Ministry of Welfare, Health, and Cultural Affairs and a grant from SmithKline Beecham Pharmaceuticals" (Verkes 1998, p.543). *Conflict(s) of interest:* no details on author interests are provided. *Other:* trial authors note that "the number of previous suicide attempts...was manifestly associated with the risk of another suicide attempt.... With adjustment for this important predictive characteristic, paroxetine proved to reduce the recurrence of suicidal behaviour significantly" (Verkes 1998, p.544-555).

BDI: Beck Depression Inventory; **BHS:** Beck Hopelessness Scale; **DHA:** docosahexaenoic acid; **EFA:** essential fatty acid; **EPA:** eicosapentaenoic acid; **GHQ:** General Health Questionnaire; **HDRS:** Hamilton Depression Rating Scale; **MADRS:** Montgomery Åsberg Depression Rating Scale; **mmol/L:** millimoles per litre; **mg:** milligrams; **RCT:** randomised controlled trial; **SH:** self-harm; **SSI:** Scale for Suicidal Ideation; **TAU:** treatment as usual.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bozzatello 2017	At baseline, < 100% of the sample had engaged in SH.
Crawford 2018	At baseline, 53.3% had engaged in SH within six months of trial entry.
Domany 2019	At baseline, < 100% of the sample had engaged in SH.
Grant 2016	Participants were diagnosed with skin-picking disorder.
Grunebaum 2012	At baseline, < 100% of the sample had engaged in SH.
Marriott 2016	Study protocol. However, unlikely that all participants will have engaged in SH at baseline.
McCall 2018	At baseline, < 100% of the sample had engaged in SH.
NCT00065936	Trial registration record last verified 1 May 2003. Current trial status therefore unknown.
NCT00533117	At baseline, < 100% had engaged in SH within six months of trial entry.
NCT00539188	Trial terminated early due to poor participant adherence.

Study	Reason for exclusion
NCT01103180	Trial terminated due to feasibility problems in identifying and recruiting participants.
NCT01928446	Trial terminated early due to Data Monitoring Committee (DMC) recommendations.
NCT02039479	Trial registration record last verified 1 March 2018. Current trial status therefore unknown.
Oquendo 2011	At baseline, < 100% had engaged in SH within six months of trial entry.
Yovell 2016	At baseline, 64.5% of the sample had engaged in SH.

DMC: data monitoring committee; **SH:** self-harm.

Characteristics of studies awaiting classification *[ordered by study ID]*

NCT00834834

Methods	*Study name:* Comparing treatments for self-injury and suicidal behavior in people with borderline personality disorder. *Study design:* Single (outcome assessor) blind, active-controlled, RCT. Participants were individually assigned to either either up to 40 mg/day fluoxetine, up to 60mg/day citalopram, or six months of manualised DBT, consisting of weekly (60 min) sessions of individual therapy and weekly (90 min) sessions of group-based therapy sessions. *Follow-up period:* 12 months.
Participants	*Number of total participants:* 84 participants, 28 were allocated to the fluoxetine arm, 28 were allocated to the citalopram arm, and 28 were allocated to the DBT arm. *Source of participants:* patients were recruited from outpatient departments. *Inclusion criteria:* i) aged 18 to 65 years; ii) suicide attempt in the two months prior to trial entry; ii) ≥1 additional suicide attempt and/or episode of SH (including NSS) in the year prior to trial entry; iii) reports current suicidal ideation; iv) able to be managed on an outpatient basis; v) not currently receiving optimum psychiatric treatment and agrees to notify study staff if any psychiatric care outside this study is sought; vi) has a stable living arrangement; vii) sufficient language ability; viii) willing and judged to be clinically able to undergo wash-out of psychotropic medications, except for occasional benzodiazepines use, for two to six weeks before treatment; ix) willing to use an effective method of birth control (female participants). *Exclusion criteria:* i) meets DSM-IV criteria for mental retardation, bipolar I disorder, schizophrenia, delusional disorder, schizophreniform disorder, schizoaffective disorder, or psychosis NOS; ii) requires treatment for an acute medical illness, including severe substance dependence and anorexia; iii) clinically too unstable to be managed in an outpatient setting; iv) requiring care other than that permitted by the protocol; v) failed adequate trials of fluoxetine and citalopram for an episode of major depression in the two years prior to trial entry; vi) history of severe allergies, adverse drug reactions, or known allergy to fluoxetine or citalopram; vii) has a heart pacemaker body implant, and/or other metal implants that may present a risk to the participant and/or interfere with the fMRI scan; viii) has claustrophobia or significant discomfort in enclosed space; ix) diagnosed with hypertension, cardiovascular disease, or abnormal EKGs; x) diagnosed with Raynaud's disorder; xi) pregnant.
Interventions	*Intervention (fluoxetine):* participants received a starting dose of 20 mg/day increased over four weeks, depending on tolerability, to a maximum of 40 mg/day. *Intervention (citalopram):* participants received a starting dose as determined by the study psychiatrist increased to up to a maximum of 60 mg/day.

NCT00834834 *(Continued)*

	Active comparator: manualised DBT consisting of weekly (60 min) individual therapy sessions and weekly (90 min) group therapy sessions delivered over a six month period. *Length of treatment:* six months.
Outcomes	*Primary outcome(s):* i) frequency of repeat episodes of SH ascertained using the Columbia Suicide History Interview (CSHI). *Secondary outcome(s):* i) repetition of SH ascertained using the CSHI.
Notes	*Source(s) of funding:* National Institute of Mental Health (NIMH). *Conflict(s) of interest:* none reported. *Other:* whilst preliminary data for this trial has been published on ClinicalTrials.gov, we were unable to confirm trial eligibility despite several efforts to contact the trial authors.

CSHI: Columbia Suicide History Inventory; **DBT:** dialectical behaviour therapy; **DSM-IV:** Diagnostic and Statistical Manual of Mental disorders, Fourth version; **EKG:** electrocardiogram; **fMRI:** functional Magnetic Resonance Imagining; **mg:** milligrams; **NOS:** not otherwise specified; **NSSI:** non-suicidal self-injury; **SH:** self-harm.

Characteristics of ongoing studies *[ordered by study ID]*

NCT04005053

Study name	Identifying biological signatures of N-Acetylcysteine for non-suicidal self-injury in adolescents and young adults.
Methods	Triple-blind placebo-controlled RCT. *Assignment:* parallel, individual-level.
Participants	*Inclusion criteria:* i) aged 16 to 24 years; ii) at least one episode of NSSI in the two months preceding trial entry; iii) ≥5 past episodes of NSSI with evidence of significant tissue damage (e.g., scars); iv) if in receipt of any psychotropic medications, participants need to be dose-stable for at least one month prior to trial entry; v) able to understand and comply with study procedures. *Exclusion criteria:* i) any MRI contraindications (e.g. metal plates, claustrophobia, braces, implanted devices); ii) current serious medical illness; iii) current substance use disorder (except tobacco use); iv) diagnosed with any psychosis; v) diagnosed with any neurodevelopmental disorder; vi) have taken N-acetylcysteine or glutathione regularly in the 6 months preceding study entry; vii) currently pregnant, planning to become pregnant, breast-feeding, or unwilling to use contraception; viii) allergy/sensitivity to N-acetylcysteine; ix) unable or unwilling to provide written informed consent.
Interventions	*Intervention 1:* oral low-dose (3600 mg/day) N-acetylcysteine delivered over an 8-week period. *Intervention 2:* oral high-dose (5400 mg/day) N-acetylcysteine delivered over an 8-week period. *Control:* oral placebo delivered over an 8-week period.
Outcomes	*Primary outcome(s):* i) glutathione concentrations in the anterior cingulate cortex, as measured by the number of participants who achieve a 5% increase in glutathione concentrations according to MRS. *Secondary outcome(s):* i) glutathione reduced-to-oxidized ratio, as measured by the number of participants who achieve an increase of at least 50% in the reduced-to-oxidized ratio of glutathione in the blood; ii) glutathione concentrations in the anterior cingulate cortex, as measured by the number of participants who achieve a 5% decrease in glutathione concentrations according to MRS.
Starting date	1 August, 2019.

NCT04005053 *(Continued)*

Contact information	Principal investigator: Assoc/Prof Kathryn Cullen, Department of Psychiatry, University of Minnesota, MN, USA (rega0026@umn.edu).
Notes	We are grateful to Assoc/Prof Cullen for confirming the above details were correct, 6 August, 2020.

NCT04242914

Study name	The effect of intravenous ketamine on non suicidal self injuries.
Methods	Double-blind placebo-controlled RCT. *Assignment:* parallel, individual-level.
Participants	*Inclusion criteria:* i) females; ii) aged between 18 and 65 years; iii) inpatients on the psychiatric ward of a general hospital; iv) self-reporting NSSI and/or active NSSI on hospital admission or in the preceding week. *Exclusion criteria:* i) males; ii) unable to provide written informed consent in Hebrew; iii) pregnant or breast-feeding; iv) history of substance misuse; v) diagnosed with a psychotic disorder and/or major physical condition, including hypertension, arrthymias, or a severe or active neurological condition; vi) previous treatment involving ketamine in which no improvement was observed.
Interventions	*Intervention:* intravenous infusion of ketamine (0.5mg/kg) in addition to midazolam (0.03mg/kg) over 40 minutes. *Control:* intravenous infusion of midazolam (0.03mg/kg) over 40 minutes.
Outcomes	*Primary outcome(s):* i) NSSI, as measured by the Brief Non-Suicidal Self-Injury Assessment. *Secondary outcome(s):* i) ketamine biomarkers, as measured by levels of interleukin 6, high sensitive C-Reactive Protein, and brain dendritic neurotrophic factor; ii) depression, as measured by the BDI; iii) anxiety, as measured by the DASS; iv) suicidal ideation, as measured by the C-SSRS and the BSSI; v) impulsivity, as measured by the BIS-11; vi) well-being, as measured by the WHO-5; vii) NSSI attitudes, as measured by the VAS; viii) adverse effects, as measured by an idiosyncratic scale developed by the authors.
Starting date	25 February, 2019.
Contact information	Principal investigator: Dr Lior Dvorak, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel (liordv@tlvmc.gov.il).
Notes	We are grateful to Dr Dvorak for confirming the above details were correct, 6 August, 2020.

BDI: Beck Depression Inventory; **BIS-11:** Barratt Impulsiveness Scale, 11 item; **BSSI:** Beck Scale of Suicidal Ideation;**C-SSRS:** Columbia Suicide Severity Rating Scale; **DASS:** Depression Anxiety Stress Scale; **kg:** kilograms; **mg:** milligrams; **MRI:** magnetic resonance imaging; **MRS:** magnetic resonance spectroscopy; **NSSI:** non-suicidal self-injury; **RCT:** randomised controlled trial; **VAS:** Visual Analogue Scale; **WHO-5:** World Health Organization, Five Well-Being Index.

RISK OF BIAS

Legend: Low risk of bias | High risk of bias | Some concerns

Risk of bias for analysis 1.1 Repetition of SH by post-intervention (NGA class)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.1.1 Mianserin vs. Placebo						
Montgomery 1983	~	~	✗	✓	~	✗
Subgroup 1.1.2 Paroxetine vs. Placebo						
Verkes 1998	✓	✓	✓	✓	~	~

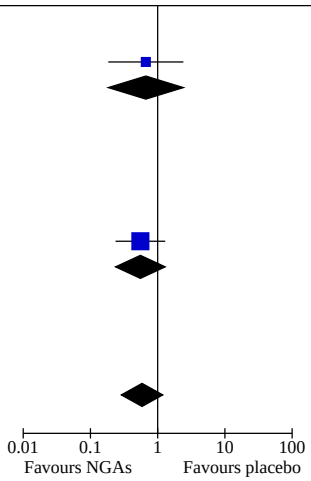
DATA AND ANALYSES

Comparison 1. Newer generation antidepressants (NGAs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Repetition of SH by post-intervention (NGA class)	2	129	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.29, 1.19]
1.1.1 Mianserin vs. Placebo	1	38	Odds Ratio (M-H, Random, 95% CI)	0.67 [0.18, 2.41]
1.1.2 Paroxetine vs. Placebo	1	91	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.24, 1.29]
1.2 Repetition of SH at final follow-up (by NGA class)	3	243	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.42, 1.35]
1.2.1 Mianserin vs. Placebo	2	95	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.39, 2.99]
1.2.2 Nomifensine vs. Placebo	1	57	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.17, 3.81]
1.2.3 Paroxetine vs. Placebo	1	91	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.24, 1.29]
1.3 Treatment acceptability	2	205	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.29, 1.71]

Analysis 1.1. Comparison 1: Newer generation antidepressants (NGAs), Outcome 1: Repetition of SH by post-intervention (NGA class)

Study or Subgroup	NGAs Events	NGAs Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
1.1.1 Mianserin vs. Placebo							
Montgomery 1983	8	17	12	21	30.4%	0.67 [0.18 , 2.41]	? ? - + ? -
Subtotal (95% CI)		**17**		**21**	**30.4%**	**0.67 [0.18 , 2.41]**	
Total events:	8		12				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.62 (P = 0.54)							
1.1.2 Paroxetine vs. Placebo							
Verkes 1998	15	46	21	45	69.6%	0.55 [0.24 , 1.29]	+ + + + ? ?
Subtotal (95% CI)		**46**		**45**	**69.6%**	**0.55 [0.24 , 1.29]**	
Total events:	15		21				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.37 (P = 0.17)							
Total (95% CI)		**63**		**66**	**100.0%**	**0.59 [0.29 , 1.19]**	
Total events:	23		33				
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%							
Test for overall effect: Z = 1.48 (P = 0.14)							
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%							



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Repetition of SH by post-intervention (NGA class)

(C) Bias due to missing outcome data: Repetition of SH by post-intervention (NGA class)

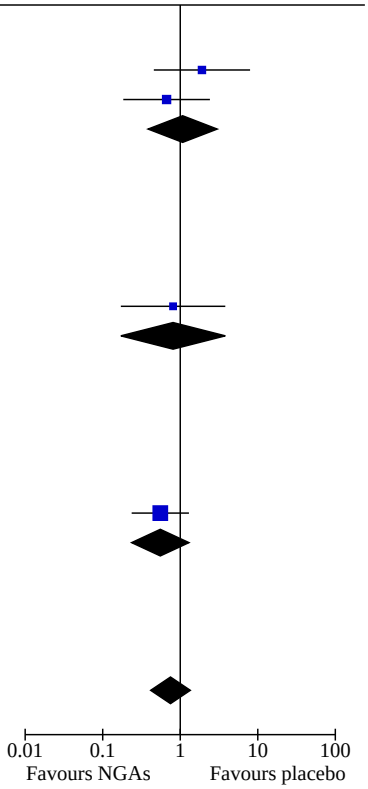
(D) Bias in measurement of the outcome: Repetition of SH by post-intervention (NGA class)

(E) Bias in selection of the reported result: Repetition of SH by post-intervention (NGA class)

(F) Overall bias: Repetition of SH by post-intervention (NGA class)

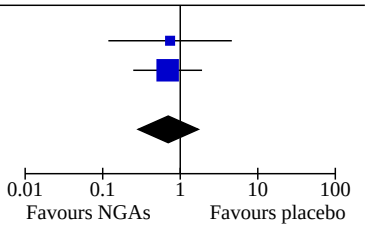
Analysis 1.2. Comparison 1: Newer generation antidepressants (NGAs), Outcome 2: Repetition of SH at final follow-up (by NGA class)

Study or Subgroup	NGAs Events	NGAs Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 Mianserin vs. Placebo						
Hirsch 1982	10	38	3	19	16.9%	1.90 [0.46 , 7.95]
Montgomery 1983	8	17	12	21	20.9%	0.67 [0.18 , 2.41]
Subtotal (95% CI)		**55**		**40**	**37.8%**	**1.07 [0.39 , 2.99]**
Total events:	18		15			
Heterogeneity: Tau² = 0.07; Chi² = 1.15, df = 1 (P = 0.28); I² = 13%						
Test for overall effect: Z = 0.14 (P = 0.89)						
1.2.2 Nomifensine vs. Placebo						
Hirsch 1982	5	38	3	19	14.4%	0.81 [0.17 , 3.81]
Subtotal (95% CI)		**38**		**19**	**14.4%**	**0.81 [0.17 , 3.81]**
Total events:	5		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						
1.2.3 Paroxetine vs. Placebo						
Verkes 1998	15	46	21	45	47.8%	0.55 [0.24 , 1.29]
Subtotal (95% CI)		**46**		**45**	**47.8%**	**0.55 [0.24 , 1.29]**
Total events:	15		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.37 (P = 0.17)						
Total (95% CI)		**139**		**104**	**100.0%**	**0.75 [0.42 , 1.35]**
Total events:	38		39			
Heterogeneity: Tau² = 0.00; Chi² = 2.17, df = 3 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Chi² = 0.97, df = 2 (P = 0.62), I² = 0%						



Analysis 1.3. Comparison 1: Newer generation antidepressants (NGAs), Outcome 3: Treatment acceptability

Study or Subgroup	NGAs Events	NGAs Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Hirsch 1982	3	76	2	38	23.7%	0.74 [0.12 , 4.63]
Verkes 1998	35	46	37	45	76.3%	0.69 [0.25 , 1.91]
Total (95% CI)		**122**		**83**	**100.0%**	**0.70 [0.29 , 1.71]**
Total events:	38		39			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						
Test for overall effect: Z = 0.78 (P = 0.43)						
Test for subgroup differences: Not applicable						



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

An information specialist with CCMD cross-searched 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*) (2015-June-2016) n=291

Appendix 2. MEDLINE, Embase, PsycINFO Ovid search strategy

An information specialist with CCMD searched the main bibliographic, biomedical databases using the terms listed below from January 2015 to 4-July-2020. [N.B. CCMDCTR is current to June 2016 only]

Search summary

Date-of-search: 4-July-2020

- Cochrane Library (CDSR) Systematic Reviews, n=38
- Cochrane Library (CDSR) Protocols, n=12
- Cochrane Library CENTRAL, n=2727
- Cochrane Specialised Register (CCMDCTR), n=291
- Ovid MEDLINE, PsycINFO (cross-search), n=2743
- Ovid Embase (precise), n=1375

Total=7186
Duplicates removed, n=2483
To screen, n=4703
[Cochrane Library CENTRAL-Trial Register Records (removed) n=1969]
Cochrane Library (Issue 7 of 12, 2020) [Date limited, 2015 onwards]

#1 MeSH descriptor: [Self-Injurious Behavior] explode all trees
#2 (overdose* and prevent*):kw or (overdos* near/3 prevent*):ti,ab
#3 ((nonfatal or non-fatal) near/2 (overdose* or over dose*)):ti,ab,kw
#4 (NSSI* or ((nonsuicid* or non-suicid*) near/2 (self* or injur*))):ti,ab
#5 (suicid* or parasuicid* or (auto next mutilat*) or automutilat* or (self next destruct*) or selfdestruct* or self-harm* or selfharm* or (self next harm*) or (self next immolat*) or selfimmolat* or (self next inflict*) or selfinflict* or (self next injur*) or selfinjur* or selfmutilat* or (self next mutilat*) or (self next poison*) or selfpoison* or (self near/2 (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 next bang*) or headbang*):ti,ab,kw
#6 (#1 or #2 or #3 or #4 or #5)
Limited 2015 to date
CDSR-reviews (38); CDSR-protocols (12); CENTRAL (2727); CENTRAL-TR (1969)
****

PsycINFO/MEDLINE cross-search

Ovid APA PsycInfo <1806 to June Week 5 2020>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to July 02, 2020> [Date limited, 2015 onwards]
Search Strategy:
---

1 Automutilation/ or Self-injurious Behavior/ or Self-destructive Behavior/ or Self-mutilation/ or Self-inflicted Wounds/ (19601)
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/ (97875)
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. (164244)
4 (NSSI? or ((nonsuicid* or non-suicid*) adj2 (self* or injur*))).ti,ab,kf,kw,id. (3469)
5 (Overdose/ or Drug Overdose/ or Drug Overdoses/) and prevent*.af. (3529)
6 ((nonfatal or non-fatal) adj2 (overdose? or over dose?)).mp. (571)
7 or/1-6 (183505)
8 Randomized Controlled Trial/ (509272)
9 Randomized Controlled Trial.pt. (508805)
10 Randomization/ (103117)
11 Random Allocation/ (103117)
12 Controlled Clinical Trial/ (93744)
13 Controlled Clinical Trial.pt. (93744)
14 Double-blind Method/ or Single-blind Method/ (186347)
15 (randomi#ed or randomi#ation or randomi#ing).ti,ab,kf,kw,id. (726423)
16 (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. (667814)
17 trial.ti. (251482)
18 placebo/ or (placebo and (allocat* or assign* or control* or group*)).ti,ab,kf,kw,id. (204672)
19 (control* adj3 group*).ab. (634930)
20 (control* and (trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,kf,kw,id. (32182)
21 ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,kf,kw,id. (200109)
22 treatment effectiveness evaluation/ (24511)
23 or/8-22 (1833008)
24 7 and 23 (9906)
25 (2015* or 2016* or 2017* or 2018* or 2019* or 2020*).yr,dc,dp,dt,ep,ez. (7909383)
26 24 and 25 (3732)
27 remove duplicates from 26 (2743)
****

Ovid Embase <1974 to 2020 Week 26> [Date limited, 2015 onwards]
Search Strategy:
---

1 Automutilation/ (17795)
2 suicidal behavior/ or self immolation/ or self poisoning/ or suicidal ideation/ or suicide/ or suicide attempt/ (101066)
3 Drug Overdose/ and prevent*.af. (4897)
4 (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,kw. (62383)

5 (NSSI? or ((nonsuicid* or non-suicid*) adj2 (self* or injur*))).ti,ab,kw. (1786)
6 ((nonfatal or non-fatal) adj2 (overdose? or over dose?)).mp. (418)
7 or/1-6 (125188)
8 randomized controlled trial/ (608057)
9 randomization.de. (87068)
10 controlled clinical trial/ and (Disease Management or Drug Therapy or Prevention or Rehabilitation or Therapy).fs. (253859)
11 *clinical trial/ (17606)
12 placebo.de. (351476)
13 placebo.ti,ab. (307193)
14 trial.ti. (301646)
15 (randomi#ed or randomi#ation or randomi#ing).ti,ab,kw. (917476)
16 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or control* or crossover or cross-over 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,kw. (769731)
17 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$ or dummy)).mp. (309225)
18 (control* and (study or group?) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,kw,hw. (39665)
19 or/8-18 (1732296)
20 ((animal or nonhuman) not (human and (animal or nonhuman))).de. (5683745)
21 19 not 20 (1575127)
22 7 and 21 (8502)
23 (2015* or 2016* or 2017* or 2018* or 2019* or 2020*).yr,dc,dp. (9329153)
24 22 and 23 (3277)
25 limit 24 to exclude medline journals (353)
26 *Automutilation/ (7770)
27 *suicidal behavior/ or *self immolation/ or *self poisoning/ or *suicidal ideation/ or *suicide/ or *suicide attempt/ (49956)
28 *Drug Overdose/ and prevent*.af. (984)
29 4 or 5 or 6 or 26 or 27 or 28 (72349)
30 21 and 29 (2692)
31 23 and 30 (1132)
32 25 or 31 (1375)
****

Appendix 3. Full 'Risk of bias' assessments for each study

Full 'Risk of bias' assessments for each study, including the evidence we used to justify our ratings can be found in Figure 4; Figure 5; Figure 6; Figure 7; Figure 8; Figure 9; and Figure 10.

Figure 4. 'Risk of bias' assessment for Battaglia 1999

Study ID	Battaglia 1999	Aim	assignment to intervention (the 'intention-to-treat' effect)
Experimental	Antipsychotics	Comparator	Alternative dose
Outcome	Repetition of SH	Results	OR 1.51, 95% CI 0.50 to 4.58
Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1	NI	"Participants...were randomized" (p.363). Although it is likely the random sequence was adequately generated, without further information on the method used, this cannot be ascertained. Additionally, no details on allocation sequence were reported.
	1.2	NI	
	1.3	N	"The two dose groups were comparable with regards to gender, race, marital status, education, substance abuse, age, and age at onset" (p.364; Table 1).
	Risk of bias judgement	Some concerns	
Bias due to deviations from intended interventions	2.1	PN	Trial authors describe the trial as "double-blinded" (p.364). Additionally, "[t]he research nurse and research psychiatrist...[were] both blinded to dose group" (p.364).
	2.2	N	
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	PN	"[O]ne patient was dropped after randomization due to unreliable reporting of excessive (greater than 500) S-HB [self-harm behaviours]" (p.363).
	2.7	PN	It is unlikely the failure to analyse participants in the group to which they were randomised substantially impacted the results observed.
	Risk of bias judgement	Some concerns	
Bias due to missing outcome data	3.1	N	Data were available for 91.4% of those randomised.
	3.2	PN	Analysis methods did not correct for bias, nor were sensitivity analyses undertaken to investigate the potential effect of missing data.
	3.3	PY	Data were available for 90.0% of those allocated to the intervention arm, and 96.3% of those allocated to the comparator arm.
	3.4	PN	
	Risk of bias judgement	Some concerns	
Bias in measurement of the outcome	4.1	PN	"...the Parasuicide History Interview...documented the time, circumstances, motivations, and treatment of suicidal behaviour...[t]he PHI was modified for monthly follow-up" (p.363-4). However, previous work has demonstrated that self-harm prevalence estimates derived from self-report may be underestimated, and supplementing prevalence estimates with medical or clinical record information is advisable (Mitchell 2016).
	4.2	N	Repetition of SH was ascertained in the same way for both the intervention and comparator arms.
	4.3	PN	"The research nurse and research psychiatrist...[were] both blinded to dose group" (p.364). However, the authors also note that measurement of side-effects may have potentially unblinded the clinician raters to dose group..." (p.364), nevertheless, the authors suggest that "...these low rates [of side-effects] suggest the impact was minimal" (p.364). Whilst repetition of SH was ascertained from participant self-report, participants were blind to treatment allocation.
	4.4	NA	
	4.5	NA	
	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1	NI	No information reported.
	5.2	PN	"Outcomes were assessed with the Parasuicide History Interview...monthly for six months" (p.361). All eligible outcome measurements within the outcome domain were reported.
	5.3	PN	All eligible analyses of the data were reported.
	Risk of bias judgement	Some concerns	

Figure 4. (Continued)

result	Risk of bias judgement	Some concerns	
Overall bias	Risk of bias judgement	Some concerns	

Figure 5. 'Risk of bias' assessment for Hallahan 2007

Study ID	Hallahan 2007	Aim	assignment to intervention (the 'intention-to-treat' effect)
Experimental	Natural products	Comparator	Placebo
Outcome	Repetition of SH	Results	OR 1.33, 95% CI 0.38 to 4.62
Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1	Y	"An independent colleague dispensed either active or placebo capsules according to a computer-generated list" (p.119). Although no details about allocation concealment were provided, however, the colleague responsible for allocation was referred to as 'independent' suggesting that allocation may have been adequately concealed.
	1.2	PY	
	1.3	PN	"Baseline socio-demographic characteristics were similar in both groups, except for marital status: more patients were married in the [intervention arm] than the placebo group" (p.119) (OR 26.61, 95% CI 1.42 to 498.20, p=0.04). The trial authors also report "[w]ith the exception of the BDI (mean placebo group score 32.22, mean [intervention] group score 38.41, p=0.04), the mean baseline scores for all psychometric instruments were similar for both groups" (p.119). These differences could have been attributable to chance.
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1	N	"Participants were prescribed four identical capsules of either active agent or placebo" (p.119). Additionally, "[p]lacebo contained 99% corn oil and a 1% EPA/DHA mixture. This ensured a degree of equality in the incidence of 'fishy breath', the most frequent side-effect of taking active treatment" (p.119). This suggests that participant and clinical personnel blinding could also have been convincingly achieved.
	2.2	N	
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	PY	Not clearly reported. However, on the basis of the information available, these were probably neither a naïve per protocol nor as treated analyses.
	2.7	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1	PY	Data were available for 100% of those randomised (following correspondence). Although, "[a]nalyses were performed using...the last observation carried forward...method" (p. 119). use of the last observation carried foward method may introduce bias (Engles 2003).
	3.2	NA	
	3.3	NA	
	3.4	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1	PN	"...patients reported episodes of self-harm during the study" (p.122). Further correspondence with trial authors revealed this was self-reported re-presentation to hospital. However, previous work has demonstrated that self-harm prevalence estimates derived from self-report may be underestimated, and supplementing prevalence estimates with medical or clinical record information is advisable (Mitchell 2016).
	4.2	N	Repetition of SH was ascertained in the same way for both the intervention and comparator arms.
	4.3	N	Repetition of SH was ascertained from participant self-report.
	4.4	NA	
	4.5	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1	NI	No information reported.
	5.2	PN	All eligible outcome measurements within the outcome domain were reported.
	5.3	PN	All eligible analyses of the data were reported.

Figure 5. (Continued)

the reported result	5.3	PN	All eligible analyses of the data were reported.
	Risk of bias judgement	Some concerns	
Overall bias	Risk of bias judgement	Some concerns	

Figure 6. 'Risk of bias' assessment for Hirsch 1982

Study ID	Hirsch 1982	Aim	assignment to intervention (the 'intention-to-treat' effect)
Experimental	NGAs	Comparator	Placebo
Outcome	Repetition of SH	Results	OR 1.31, 95% CI 0.46 to 3.71
Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1	NI	"...randomised..." (p.307). Although it is likely the random sequence was adequately generated, without further information on the method used, this cannot be ascertained. Furthermore, no details on allocation concealment were reported.
	1.2	NI	
	1.3	NI	Data on relevant socio-demographic and clinical characterstics at baseline by arm were not reported.
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1	N	"Patients were blind to the contents of the capsules as was the research psychiatrist" (p.4). However, no information on clinical personnel blinding was reported.
	2.2	NI	
	2.3	NI	There were no apparent deviations from the intended intervention.
	2.4	NA	
	2.5	NA	
	2.6	PY	Not clearly reported. However, on the basis of the information available, these were probably neither a naïve per protocol nor as treated analyses.
	2.7	NA	
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1	Y	Data were available for 100% of those randomised.
	3.2	NA	
	3.3	NA	
	3.4	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1	NI	"...repeat overdoses" (p.8). However, no further information as to how this outcome was
	4.2	N	Repetition of SH was ascertained in the same way for both the intervention and comparator
	4.3	NI	No information reported.
	4.4	NI	No information reported.
	4.5	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1	NI	No information reported.
	5.2	PN	All eligible outcome measurements within the outcome domain were reported.
	5.3	PN	All eligible analyses of the data were reported.
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Figure 7. 'Risk of bias' assessment for Lauterbach 2008

Study ID	Lauterbach 2008	Aim	assignment to intervention (the 'intention-to-treat' effect)
Experimental	Mood stabilisers	Comparator	Placebo
Outcome	Repetition of SH	Results	OR 0.99, 95% CI 0.33 to 2.95
Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1	Y	"Participants were randomly assigned...using a computerised randomisation sequence" (p.471). However, no information on allocation concealment were reported.
	1.2	NI	
	1.3	PY	"Participants in the [intervention] and placebo...group were well matched with respect to demographic variables. However, in the [intervention] group there was a higher incidence of personality disorders [OR 2.65, 95% CI 1.36 to 5.18, p=0.0043] as well as a higher number of subjects with multiple suicide attempts [OR 2.92, 95% CI 1.55 to 5.51, p=0.0009] whereas individuals in the placebo group had a higher score.
	Risk of bias judgement	**High**	
Bias due to deviations from intended interventions	2.1	PY	"Double-blind assessment was conducted...although in some cases this procedure could not be maintained because of emergencies in relation to suicidal acts or insufficient drug compliance" (p.471). However, "...monitoring of lithium blood levels occurred in an independent laboratory...to ensure the double-blind design, fake values on a randomised basis were provided for blood samples from individuals belonging to the placebo group" (p.472), suggesting that clinical personnel could have been blind to treatment allocation.
	2.2	PN	
	2.3	PN	There were no apparent deviations from the intended intervention.
	2.4	NA	
	2.5	NA	
	2.6	Y	"The evaluation of efficacy was based on an intention-to-treat analysis, including all participants randomised in the trial" (p.472).
	2.7	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1	N	Data were available for 41.9% of those randomised.
	3.2	PY	Analyses included all randomised participants, but no information on the method used for the imputation of missing data reported.
	3.3	NA	
	3.4	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1	PN	"Suicidal acts were assessed by participant report" (p.472). However, previous work has demonstrated that self-harm prevalence estimates derived from self-report may be underestimated, and supplementing prevalence estimates with medical or clinical record information is advisable (Mitchell 2016).
	4.2	N	Repetition of SH was ascertained in the same way for both the intervention and comparator arms.
	4.3	PY	"Double-blind assessment was conducted...although in some cases this procedure could not be maintained because of emergencies in relation to suicidal acts or insufficient drug
	4.4	PY	Repetition of SH was ascertained by participant self-report.
	4.5	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1	NI	No information reported.
	5.2	PN	All eligible outcome measurements within the outcome domain were reported.
	5.3	PN	All eligible analyses of the data were reported.
	Risk of bias judgement	**Some**	

Figure 7. (Continued)

result	5.3	PN	All eligible analyses of the data were reported.
	Risk of bias judgement	Some concerns	
Overall bias	Risk of bias judgement	High	

Figure 8. 'Risk of bias' assessment for Montgomery 1979

Study ID	Montgomery 1979	Aim	assignment to intervention (the 'intention-to-treat' effect)
Experimental	Antipsychotics	Comparator	Placebo
Outcome	Repetition of SH	Results	OR 0.09, 95% CI 0.02 to 0.50
Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1	NI	"Patients were randomly allocated..." (p.227). Although it is likely the random sequence was adequately generated, without further information on the method used, this cannot be ascertained. Additionally, no details on allocation concealment were provided.
	1.2	NI	
	1.3	NI	Data on relevant socio-demographic and clinical characterstics at baseline by arm were not reported.
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1	PY	"Patients...remained blind to actual treatment" (p.227). However, "[t]wo of the patients on active treatment complained of parkinsonian side effects...and were withdrawn to maintain blindness" (p.228). However, no information on clinical personnel blinding were provided.
	2.2	NI	
	2.3	PN	There were no apparent deviations from the intended intervention.
	2.4	NA	
	2.5	NA	
	2.6	N	"Two of the patients on active treatment complained of Parkinsonian side effects at 1 month and were withdrawn to maintain blindness" (p.228). Analyses therefore excluded participants
	2.7	PN	It is unlikely there was a substantial impact on the results of the failure to use an appropriate analysis to estimate the effect of assignment to the intervention.
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1	N	"There were 7 drop outs during this trial..." (p.228). Data were therefore available for 81.1% of those randomised.
	3.2	PN	Analysis methods did not correct for bias, nor were sensitivity analyses undertaken to investigate the potential effect of missing data.
	3.3	PY	"There were 7 drop outs during this trial, 3 on placebo and 4 on active" (p.228). Data were therefore reported for 77.8% of those allocated to the intervention arm, and 84.2% of those allocated to the comparator arm. Additionally, "[t]wo of the patients on active treatment complained of Parkinsonian side effects at 1 month and were withdrawn to maintain blindness" (p.228). Reasons for missing data for the remaining five participants were not reported.
	3.4	PY	
	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1	NI	"...any patient who made a suicidal act during the six months was counted..." (p. 227). However, no further information as to how this outcome was ascertained was reported.
	4.2	N	Repetition of SH was ascertained in the same way for both the intervention and comparator arms.
	4.3	PN	"...raters remained blind to actual treatment" (p.227).
	4.4	NA	
	4.5	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1	NI	No information reported.
	5.2	PN	All eligible outcome measurements within the outcome domain were reported.
	5.3	PN	All eligible analyses of the data were reported.
	Risk of bias judgement	**Some concerns**	

Figure 8. (Continued)

	Risk of bias judgement	Some concerns
Overall bias	Risk of bias judgement	High

Figure 9. 'Risk of bias' assessment for Montgomery 1983

Study ID	Montgomery 1983	Aim	assignment to intervention (the 'intention-to-treat' effect)
Experimental	NGAs	Comparator	Placebo
Outcome	Repetition of SH	Results	OR 0.67, 95% CI 0.18 to 2.41
Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1	NI	"Patients were randomly allocated..." (p.184S). Although it is likely the random sequence was adequately generated, without further information on the method used, this cannot be ascertained. Additionally, no information on allocation concealment were reported.
	1.2	NI	
	1.3	PN	"...there were no significant differences in distribution of sex, age or number of prior attempts, or diagnoses between the groups" (pp.184S-5).
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1	N	"Randomly allocated to treatment under double-blind conditions..." (p. 184S). However, no details on clinical personnel blinding were provided.
	2.2	NI	
	2.3	PN	There were no apparent deviations from the intended intervention.
	2.4	NA	
	2.5	NA	
	2.6	NI	No information reported.
	2.7	PN	It is unlikely there was a substantial impact on the results of the failure to use an appropriate
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1	N	"Fifty-eight patients entered the study. There were 20 drop-outs..." (p.185S). Data were therefore available for 65.5% of those randomised.
	3.2	PN	Analysis methods did not correct for bias, nor were sensitivity analyses undertaken to investigate the potential effect of missing data.
	3.3	NI	No information reported.
	3.4	NI	
	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1	NI	Repetition of SH was based on those who "...repeated their suicidal behaviour" (p.185S).
	4.2	PN	Repetition of SH was likely ascertained in the same way for both the intervention and comparator arms.
	4.3	N	The trial was conducted "...under double-blind conditions..." (p.184S).
	4.4	NA	
	4.5	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1	NI	No information reported.
	5.2	PN	All eligible outcome measurements within the outcome domain were reported.
	5.3	PN	All eligible analyses of the data were reported.
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Figure 10. 'Risk of bias' assessment for Verkes 1998

Study ID	Verkes 1998	Aim	assignment to intervention (the 'intention-to-treat' effect)
Experimental	NGAs	Comparator	Placebo
Outcome	Repetition of SH	Results	OR 0.55, 95% CI 0.24 to 1.29

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1	Y	"Patients were randomly assigned..." (p.544). Correspondence with trial authors further clarified that all the medication was packed in a series of blisters with consecutive numbers. This was done before the start of the study. A patient who entered the study got a consecutive number and subsequently received the medication blisters with the corresponding number. Correspondance with trial authors also revealed that randomisation was conducted remotely at the pharmacy of SmithKline Beecham.
	1.2	Y	
	1.3	N	"Random assignment produced comparable groups" (p.544).
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1	PN	"Patients in the placebo group received matching placebo" (p.544). The nature of this trial means that participants and clinical personnel could have been blinded to allocation, possibly through the use of identical capsules for both the active agent and placebo arms.
	2.2	PN	
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	"Efficacy was analyzed on an intention-to-treat basis..." (p.544).
	2.7	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1	Y	Data were available for 100% of those randomised (following correspondance). Additionally, "[e]fficacy was analyzed on an intention-to-treat basis; all available observations were used without the last point carried forward or estimating missing values. We also analyzed efficacy excluding the non-compliant visits" (p.544).
	3.2	NA	
	3.3	NA	
	3.4	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1	NI	"Recurrence of suicidal behavior..." However, no further information as to how this outcome was ascertained was reported.
	4.2	PN	Repetition of SH was likely ascertained in the same way for both the intervention and comparator arms.
	4.3	PN	The trial is described as a "...double-blind...study (p.546).
	4.4	NA	
	4.5	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1	NI	No information reported.
	5.2	PN	"Recurrence of suicidal behavior...were assessed at baseline, after weeks 2, 4, 6, 8, 10, and 12 of treatment, and at monthly intervals thereafter until 52 weeks" (p.544). All eligible outcome measurements within the outcome domain were reported.
	5.3	PN	All eligible analyses of the data were reported.
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Figure 10. (Continued)

See Figure 11 for the signalling questions.

Figure 11.

Signalling Questions

Bias arising from the randomization process	1.1 Was the allocation sequence random?
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?
	4.1 Was the method of measuring the outcome inappropriate?
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?

Figure 11. (Continued)

	differed between intervention groups?
Bias in measurement of the outcome	4.3 Were outcome assessors aware of the intervention received by study participants?
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?
	5.3 ... multiple eligible analyses of the data?

WHAT'S NEW

Date	Event	Description
3 March 2021	Amended	Minor text edit to add clarity to risk of bias methods and results.

HISTORY

Protocol first published: Issue 7, 2020
Review first published: Issue 12, 2020

Date	Event	Description
2 February 2021	Amended	Typo corrected and additional risk of bias table added.
13 January 2021	Amended	Typo corrected in Summary of findings 5.
7 January 2021	New citation required and conclusions have changed	A new protocol including updated methodology was applied (Witt 2020c). No new studies were included in this review compared to the earlier version (Hawton 2015).
7 January 2021	New search has been performed	This review updates and replaces the Cochrane Review '*Pharmacological interventions for self-harm in adults*' (Hawton 2015).
1 July 2020	Amended	We updated the protocol developed for Hawton 2015

CONTRIBUTIONS OF AUTHORS

KH had the idea for the review. All authors screened studies for inclusion. KGW, SEH, GR, and KH extracted data and assessed risk of bias for included studies. KGW, SEH, and TLTS conducted the statistical analyses. KGW and KH wrote the initial version of the review and all authors contributed to the writing of drafts. All authors approved the final version of the review for publication.

DECLARATIONS OF INTEREST

KGW: is an editor for the Cochrane Common Mental Disorders Group, and senior editor for the Self-Harm and Suicide Satellite of the group.
SEH: is the joint co-ordinating editor of the Cochrane Common Mental Disorders Group. She is funded by an Auckland Medical Research Foundation Douglas Goodfellow Repatriation Fellowship to develop and test a digital intervention for young people who engage in self-harm. She is the Principal Clinical Advisor of the Suicide Prevention Office of the Ministry of Health for the New Zealand Government.
GR: no declarations of interest to report in relation to this review
PH: no declarations of interest to report in relation to this review
TLTS: no declarations of interest to report in relation to this review
ET: no declarations of interest to report in relation to this review
KH: no declarations of interest to report in relation to this review

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).

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.