

## Treatment for self-harm – are RCTs the best evidence?

Kate E Saunders<sup>1,2</sup>

Katharine A Smith<sup>1,2,3</sup>

1. University Department of Psychiatry, Warneford Hospital, Oxford OX3 7JX
2. Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford OX3 7JX
3. NIHR Oxford cognitive health Clinical Research Facility, Warneford Hospital, Oxford OX3 7JX

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## INTRODUCTION

Self-harm refers to intentional self-poisoning or self-injury, irrespective of motive or the extent of suicidal intent (NICE 2011, Hawton 2003). Thus, it includes acts intended to result in suicide (sometimes referred to as 'attempted suicide'), those without suicidal intent (for example to communicate distress or reduce unpleasant feelings) and those with a mixed (or unclear) motivation. It is a major public health concern and a common cause of assessment, treatment and admission to general hospitals. However, the majority of those who self-harm do not present to hospital, and community prevalence is estimated to be as high as 20% in those aged 15 years (<http://www.hbsc.org/>). Self-harm presentations increase significantly from the age of 12 years and decline from the mid 20s onwards (Boeninger 2010, Guelayov 2016). Repetition of self-harm is common, with up to 25% of individuals who present to hospital following self-harm returning to the same hospital following further self-harm within a year. Repetition is also frequent (percentage??) in adolescents who do not present to clinical services (Hawton 2002). At least 80% of individuals presenting to hospital following self-harm are suffering from at least one mental disorder (Hawton 2013) (including major depression, bipolar disorder, anxiety and substance misuse, often in combination with personality disorders). However, the aetiology is complex; self-harm is often associated with acute life events, often against a background of longer-term social and personal difficulties (such as relationship problems, financial difficulties or social isolation).

A history of self-harm is associated with a significantly increased risk of subsequent suicide (Carroll 2014, Owens 2002). One to three percent of those who present to hospital after self-harm will die by suicide in the following year (Carroll 2014). Of those who die by suicide, over 50% have a history of self-harm and 15% have presented to hospital with self-harm in the preceding year (Gairin 2003)

Self-harm is not only a problem in terms of healthcare. It is also associated with poorer educational outcomes as well as significant health and social care costs (Mars 2014, Sinclair 2011). Improving the treatment of self-harm has been a focus of a number of national and international guidelines (for example, NICE 2011, NICE 2004), although the paucity of evidence for effective treatments has been

highlighted (Hawton 1999). Given the complex aetiology of self-harm, encompassing not only mental health problems, but also psychological and social influences, treatment options to be appraised should include pharmacological and psychological treatments, and studies of the role of social and societal change. As self-harm is a problem that often emerges during the teenage years, it is important to encompass studies in children and adolescents as well as adults.

## METHODS

To identify relevant evidence for the treatment and management (whether short or long-term) of self-harm we searched the National Library of Medicine PubMed, PsychInfo, Google Scholar and Cochrane databases for articles published between 1980 and May 2016. No language constraints were applied. The search included the key words 'self-harm', 'suicide attempt', 'non-suicidal self-injury', 'treatment'. We focussed on meta-analyses of randomised controlled trials. The reference lists of reports identified were used to find additional publications. Three Cochrane reviews were identified which focussed on pharmacological treatments, psychological treatments and interventions for children and adolescents. These Cochrane reviews are related. They were completed by the same group of authors (encompassing experts in suicide research in the UK, Ireland, Australia and Belgium), and the three together update a single Cochrane review originally published in 1999. The update was divided into 3 reviews to allow space for the assessment of secondary outcomes where possible.

## PHARMACOLOGICAL TREATMENTS FOR SELF-HARM (Hawton 2015a)

Given the high prevalence of depressive illness and depressive symptoms in people who self-harm (Hawton 2013), antidepressants would seem to be possible candidates for prevention of recurrence. Mood stabilisers may also be a possibility, as there is evidence of a specific anti-suicidal effect of lithium when used to treat people with affective disorders (Cipriani 2013). Antipsychotic medication,

particularly in low doses, might also be considered, especially in those who frequently repeat self-harm, and or those with a diagnosis of borderline personality disorder.

The Cochrane review included seven RCTs with a total of 546 patients. Interestingly, the reviewers did not find any new trials when they searched for this update, compared to their original search for the 1999 Cochrane review (Hawton 1999). It is not clear why this might be, the difficulties in conducting RCTs of in this group in general are particularly pronounced when considering drug treatment. Meta-analysis revealed no significant treatment effects on repetition of self-harm for antidepressants, lithium, low-dose fluphenazine or natural products. The antipsychotic flupenthixol was found to significantly reduce self-harm in a single trial but numbers were small (n=30). All studies were reported as being of low or very low quality and no data on adverse events other than the planned outcomes relating to suicidal behaviour were reported. Information on psychiatric diagnosis was reported only in some trials and additional comorbidity in only one trial. Thus, it was not possible to make any association between the effects of different types of pharmacological treatment on repetition of self-harm according to diagnostic group.

These findings are in contrast to the observational data, particularly for lithium. The Cochrane review's analysis (of 167 participants) found no beneficial effect for lithium on repetition of self-harm, or on the secondary outcomes of depression score, hopelessness, suicidal ideation or suicide. Although with such a relatively small number of participants, it is very unlikely that there was sufficient power to show an effect on a relatively rare event such as suicide, the other data are somewhat surprising, given the evidence supporting the role of lithium in the reduction of suicidal behaviour. A systematic review and meta-analysis of 48 randomised controlled trials of lithium in 6674 patients with mood disorders found that lithium was more effective than placebo at reducing suicides but had little discernible effect on self-harm (Cipriani 2013). However, the results of a number of observational studies suggest that lithium may reduce self-harm (Goodwin 2003, Smith 2009, Baldessarini 2006) when compared to other anticonvulsants. In the specific population of patients with bipolar disorder,

a recent large (n=14,396) population-based electronic health records study (Hayes 2016) showed that rates of self-harm and unintentional injury were lower in the group treated with lithium compared to other mood stabilisers (valproate, olanzapine, quetiapine). It has been argued that the findings may be confounded by the secondary benefits of being on lithium (such as repeated blood tests, more clinic attendances). However, in a large naturalistic longitudinal study of non-fatal self-harm in individuals with bipolar disorder which replicated the protective effects of lithium, no difference was observed in the number of physician contacts in patients on lithium compared to those on other medications.

Other potential treatments such as ketamine and buprenorphine are not included in the review. There is an emerging evidence to support a rapid antidepressant effect of ketamine, a glutamate N-methyl-D-aspartate receptor antagonist, in the treatment of unipolar and bipolar depression (Caddy 2015, McCloud 2015). In depressed patients in the emergency department a rapid reduction in suicidal ideation was observed following an intravenous infusion of ketamine with the reduction being maintained for up to 10 days. Suicidal cognition was eradicated in patients with depression given three times weekly infusions. More recent evidence suggests that these effects are mediated by the reduction in nonsuicide-related depressive symptoms (Price 2014). Open label studies investigating suicidal ideation and anhedonia suggest that both are reduced after acute intravenous ketamine (Schwartz 2016). Further studies are needed to assess whether this effect is related to the antidepressant effect or is independent of it. In a multisite randomized double-blind placebo controlled trial, ultra-low dose sublingual buprenorphine was associated with a significant reduction in Beck Suicidal Ideation Scores at both 2 and 4 weeks in severely suicidal patients without substance abuse (Yovell 2016). Electroconvulsive therapy (ECT) is widely acknowledged as an effective treatment for severe depressive episodes and is cited as a treatment for suicidal behaviour in a number of national guidelines (APA/Jacobs 2010). In observational studies ECT appears to significantly reduce the frequency of suicide attempts in depressed patients (Brådvik 2006). While none of these

approaches are included in the Cochrane review as no RCTs are yet available, initial findings suggest that they may be a helpful approach in the treatment of self-harm.

#### PSYCHOLOGICAL TREATMENTS (Hawton 2016)

This Cochrane review identified 55 RCTs for psychological interventions for self-harm. The most common treatment modality was CBT-based psychological therapy (18 trials). The majority of these trials explored the effects of a 1:1 intervention delivered in fewer than 10 sessions. The remaining 37 trials evaluated a range of other psychological interventions including dialectical behavioural therapy, mentalisation based therapy, group-based psychotherapy and remote contact interventions (postcards, emergency cards, telephone contact).

A significant treatment effect for CBT-based therapy compared to treatment as usual was observed with respect to repetition of self-harm (odds ratio 0.70 95% confidence interval 0.55-0.88) although no reduction in the frequency of self-harm was found. While just 6% fewer people repeated self-harm following CBT, improvements in mood, hopelessness and suicidal thoughts were also observed. Most studies were small in nature and there was considerable variability between trial outcomes. The effects of the other therapeutic approaches remain unclear as they were mostly evaluated in small single studies.

The evaluation of psychological treatments within an RCT is more challenging than that of pharmacological treatments as patients and therapists are aware of the treatment modality that they are receiving such that true blinding cannot be achieved. There is also the issue of the comparison arm of the trial. In the review all 'active' treatments were compared to 'treatment as usual'. Whilst this addresses to some extent the non-specific effects of any type of psychological treatment (face-to-face contact, feeling that another individual is listening etc.), treatment as usual varies between centres in

each country and between countries. This means that combining the studies together in a meta-analysis, whilst increasing the power, is not strictly comparing like with like.

In addition, the studies of psychological treatments did not routinely document the 'fidelity' to the treatments. In other words, we do not know for certain how many of the offered sessions (either active treatment or treatment as usual) the participant actually attended. In addition, we cannot be certain how closely therapists adhered to the manualised therapy. So, by drawing a parallel with pharmacological studies, we do not know the 'dose' of active or placebo treatment that the participants received.

Whilst the findings for brief CBT-like therapy are encouraging, the trials did not identify for whom this intervention would be most effective. This is important – whilst the data suggest the best evidence that we have is that CBT should be offered to those who self-harm, we do not know whether it should be offered to all or a subgroup. Given the finite resources in psychological services, identifying the 'active' elements of the CBT intervention is a key question. Only studies comparing the full CBT intervention with the same intervention but missing a defined key element could answer this question.

Implementing this strategy into clinical care also presents other problems. Only a small percentage present to services following self-harm (McMahon 2014), so hospital based interventions will inevitably miss a significant number of the target population. In addition, psychiatric services are focused on providing treatment resources to those with a diagnosed mental illness, and again many patients with self-harm will not meet standardised criteria. The most persuasive argument for implementing such a service would be an economic one. Self-harm carries a significant direct and indirect cost in healthcare (in addition to the costs to the individual and their family) (Sinclair 2011). Future studies of CBT would be enhanced by including assessments of healthcare costs as an integral part of the study.

While CBT is the most widely available modality of psychological treatment in the UK following the launch of the IAPT (improving access to psychological therapies) scheme ([http://cep.lse.ac.uk/textonly/research/mentalhealth/DEPRESSION\\_REPORT\\_LAYARD2.pdf](http://cep.lse.ac.uk/textonly/research/mentalhealth/DEPRESSION_REPORT_LAYARD2.pdf)), those who self-harm or are expressing suicidal ideation are often deemed too high risk to be eligible and are referred to specialist services where waiting times are often much longer.

The single trials of other psychotherapies that were associated with favourable outcomes for example Dialectical behavior therapy (DBT) and Mentalization-based treatment (MBT) were all conducted in patients diagnosed with borderline personality disorder. The use of a specified diagnostic group means that there is clearer and more consistent framework for psychological intervention and understanding of self-harm as well as a more homogenous patient group.

#### TREATMENTS FOR CHILDREN AND YOUNG PEOPLE (Hawton 2015b)

In their third Cochrane review Hawton et al identified only 11 trials of interventions for self-harm in children and adolescents. This was a surprisingly low number of trials, given that under 18s are a key target age group for self-harm interventions. Most interventions were limited to single trials and the quality of the evidence was mostly graded as low. No trials of pharmacological interventions were identified. Neither group-based therapy or DBT (adapted for use in adolescents) were found to be associated with a reduction in the proportion of participants engaging compared to treatment as usual, although a reduction in the frequency of self-harm over time was observed following DBT. There were also significantly greater reductions in depression, hopelessness, and suicidal ideation in this group. MBT was associated with fewer adolescents scoring above the cut-off for repetition of SH based on the Risk-Taking and Self-Harm Inventory 12 months post-intervention although this study was limited to individuals who had multiple episodes of SH or emerging personality problem.



School based interventions were not included in the review as they generally target individuals irrespective of whether they have self-harmed or not. In a recent multi-centre cluster randomised controlled trial a Youth Aware of Mental Health Programme intervention significantly reduced the incidence of suicide attempts and suicidal ideation at 12 month follow-up compared with the control group. The reported reduction was more than 50% compared with the control group. Similar reductions were not associated with a manualised gatekeeper programme or screening for high risk individuals by professionals (Wasserman 2015). However, there are concerns about large-scale implementation of interventions in schools. Whilst it is logical to focus on schoolchildren at an early age before self-harm is likely to start, careful assessment of risk needs to be undertaken. It is possible that interventions may harm as well as benefit. For the child and adolescent population, the issue of 'contagion' is particularly important (Hawton 2012).

## DISCUSSION

All three Cochrane reviews summarise relatively small numbers of studies which are of poor or moderate quality. Meta-analysis, where it was feasible, revealed small changes in self-harm but the majority of approaches evaluated involved single studies. The Cochrane methodology exclusively explores RCT data and in the area of self-harm this significantly limits their interpretation because of the many methodological challenges (see figure 1). Observational data may be just as informative and perhaps more generalizable to clinical practice. The best example of this is the overwhelming observational evidence supporting the anti-suicidal effects of lithium for which no RCT data exist.

Testing interventions for the prevention or reduction self-harm is limited by a number of methodological considerations. The ethics of randomising individuals who report suicidal ideation often means that trials can never be truly representative. The question of who to target an intervention towards is also an area of debate. The majority of studies focus on hospital presenters or those known to mental health services whereas the majority of self-harm (particularly in younger

people) occurs in individuals where this is not the case (McMahon 2014). Other studies chose to focus on those who repeatedly harm themselves or limited recruitment to individuals who had taken overdoses. More effective interventions may be those that target individuals prior to the emergence of self-harm or promote mental wellbeing in the population as a whole. The majority of completed suicides occur in individuals who are not known to mental health services at the time of their death such that there is an imperative for population intervention as opposed to focussing on high risk groups.

Self-harm describes a range of different behaviours and is associated with nearly all mental disorders (Hawton 2013). The reasons for self-harm vary widely as to the methods and lethality. While a number of models for the emergence of self-harm and suicidality have been proposed all highlight the complex nature of the behaviour and none provide a clear single focus for intervention. In view of the heterogeneous nature of the self-harm as well as the absence of a mechanistically valid treatment target it is not surprising that treatment effects are small at best. Data from the treatment of specific disorders, for example mood disorders indicate that significant reductions in self-harm can be achieved by targeting the disorder rather than the self-harm per se (Cipriani 2013 BMJ).

The setting in which individuals who self-harm are most commonly encountered the emergency department, general practice or in education. All of the treatment trials included in the three Cochrane reviews were limited to trials conducted in inpatient or outpatient settings which further limits the generalizability of the findings.

The three Cochrane reviews identified highlight the challenges of testing interventions for a self-harm that are generalizable to routine clinical practice. The reliance on randomised controlled trial data, while methodologically robust, leads to a very limited summary of the available evidence and overlooks a number of important interventions for the reduction of self-harm. Given the many ethical and methodological challenges inherent in RCTs for self-harm observational data is an important complementary source of evidence which is generalizable to clinical and non-clinical settings.

Figure 1: Methodological challenges in designing studies to assess the efficacy of interventions for self-harm

<b>Methodological challenges in assessing the efficacy of interventions for self-harm</b>
<b>Heterogeneity of a study population recruited on the basis of a behaviour.</b>
<b>Which population to study</b>
<b>Definitions of self-harm</b>
<b>Study context</b>
<b>Timing of intervention</b>
<b>Time to follow-up</b>
<b>Ethics of randomising suicidal patients</b>
<b>Finding an appropriate control intervention (particularly in psychological treatment trials)</b>

## REFERENCES

APA?

Baldessarini, R. J., Tondo, L., Davis, P., Pompili, M., Goodwin, F. K., & Hennen, J. (2006). Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. *Bipolar disorders*, 8(5p2), 625-639.

Boeninger DK, Masyn KE, Feldman BJ, Conger RD. Sex differences in developmental trends in suicide ideation, plans and attempts among European adolescents, Suicide and lifer-threatening behavior. 40(5) 451-464

Brådvik L, Berglund M. Long-term treatment and suicidal behavior in severe depression: ECT and antidepressant pharmacotherapy may have different effects on the occurrence and seriousness of suicide attempts. *Depress Anxiety*. 2006;23(1):34–41. doi:[10.1002/da.20134](https://doi.org/10.1002/da.20134)

Caddy C, Amit BH, McCloud TL, Rendell JM, Furukawa TA, McShane R, Hawton K, Cipriani A. Ketamine and other glutamate receptor modulators for depression in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 9.

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

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

Gairin I, House A, Owens D (2003) Attendance at the accident and emergency department in the year before suicide: retrospective study. *British Journal of Psychiatry*, 183: 28–33.

Goodwin F,K, Fireman B, Simon GE, Henkeler EM, Lee J, Revicki D. Suicide risk in bipolar disorder during treatment with lithium and divalproex. *JAMA* 2003;290:1467-73

Geulayov G, Kapur N, Turnbull P, Clements C, Waters K, Ness J, Townsend E, Hawton K. Epidemiology and trends in non-fatal self-harm in three centres in England, 200-2012: findings from the multicentre study of self-harm in England. *BMJ Open* 2016;6e010538

Joseph F. Hayes, MSc, MBChB<sup>1</sup>; Alexandra Pitman, PhD<sup>1</sup>; Louise Marston, PhD<sup>2</sup>; Kate Walters, PhD<sup>2</sup>; John R. Geddes, MD<sup>3</sup>; Michael King, PhD<sup>1</sup>; David P. J. Osborn, PhD<sup>1</sup> Self-harm, Unintentional Injury, and Suicide in Bipolar Disorder During Maintenance Mood Stabilizer Treatment A UK Population-Based Electronic Health Records Study *JAMA Psychiatry*. 2016;73(6): 630-637

Hawton K, Townsend E, Arensman E, Gunnell D, Hazell P, House A, et al. Psychosocial and pharmacological treatments for deliberate self harm. *Cochrane Database of Systematic Reviews* 1999, Issue 4. [DOI: [10.1002/14651858.CD001764](https://doi.org/10.1002/14651858.CD001764)]

Hawton K, Hall S, Simkin S, et al. Deliberate self-harm in adolescents: a study of characteristics and trends in Oxford, 1990–2000. *J Child Psychol Psychiatry* 2003; 44: 1191–98.

Hawton, Keith, Kate EA Saunders, and Rory C. O'Connor. "Self-harm and suicide in adolescents." *The Lancet* 379.9834 (2012): 2373-2382.

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

Hawton K, Witt KG, Taylor Salisbury TL, et al (2015a) Pharmacological interventions for self-harm in adults. *Cochrane Database of Systematic Reviews*, 7: CD011777.

Hawton K, Witt KG, Taylor Salisbury TL, Arensman E, Gunnell D, Townsend E, van Heeringen K, Hazell P (2015b). Interventions for self-harm in children and adolescents. *Cochrane Database of Systematic Reviews* 2015, Issue 12. Art. No.: CD012013.

Hawton K, Witt KG, Taylor Salisbury TL, Arensman E, Gunnell D, Hazell P, Townsend E, van Heeringen K. Psychosocial interventions for self-harm in adults. *Cochrane Database of Systematic Reviews* 2016, Issue 5. Art. No.: CD012189. DOI: 10.1002/14651858.CD012189.

Jacobs et al Practice guideline for the Assessment and Treatment of Patients With Suicidal Behaviors. American Psychiatric Association. 2010  
[http://psychiatryonline.org/pb/assets/raw/sitewide/practice\\_guidelines/guidelines/suicide.pdf](http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/suicide.pdf)

Mars B, Heron J, Crane C, Hawton K, Lewis G, Macleod J, Tilling K, Gunnell D Clinical and social outcomes of adolescent self harm: population based birth cohort study. *BMJ*. 2014 Oct 21; 349():g5954.

McCloud TL, Caddy C, Jochim J, Rendell JM, Diamond PR, Shuttleworth C, Brett D, Amit BH, McShane R, Hamadi L, Hawton K, Cipriani A. Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 9.

McMahon EM1, Keeley H, Cannon M, Arensman E, Perry IJ, Clarke M, Chambers D, Corcoran P. The iceberg of suicide and self-harm in Irish adolescents: a population-based study. *Soc Psychiatry Psychiatr Epidemiol*. 2014 Dec;49(12):1929-35. doi: 10.1007/s00127-014-0907-z. Epub 2014 Jun 15.

National Collaborating Centre for Mental Health (2004) *Self-Harm: The Short-Term Physical and Psychological Management and Secondary Prevention of Self-Harm in Primary and Secondary Care* (Clinical Guideline 16). NICE.

National Collaborating Centre for Mental Health. Self-harm: longer term management. NICE clinical guideline 133. London: National Institute for Clinical Excellence, 2011.

National Institute for Health and Care Excellence (2011) *Self-harm in over 8s: Long-Term Management* (Clinical Guideline 133). NICE.

Owens D, Horrocks J, House A. Fatal and non-fatal repetition of self-harm. *The British Journal of Psychiatry* Sep 2002, 181 (3) 193-199; DOI: 10.1192/bjp.181.3.193

Price, R. B., Iosifescu, D. V., Murrough, J. W., Chang, L. C., Al Jurdi, R. K., Iqbal, S. Z., ... & Mathew, S. J. (2014). Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. *Depression and anxiety*, 31(4), 335-343.

Jaclyn Schwartz, James W Murrough, Dan V Iosifescu Ketamine for treatment-resistant depression: recent developments and clinical applications *Evid Based Mental Health* 2016;19:35-38  
doi:10.1136/eb-2016-102355

Sinclair JM1, Gray A, Rivero-Arias O, Saunders KE, Hawton K. Healthcare and social services resource use and costs of self-harm patients. *Soc Psychiatry Psychiatr Epidemiol*. 2011 Apr;46(4):263-71. doi: 10.1007/s00127-010-0183-5. Epub 2010 Feb 21.

Smith, E. G., Søndergård, L., Lopez, A. G., Andersen, P. K., & Kessing, L. V. (2009). Association between consistent purchase of anticonvulsants or lithium and suicide risk: A longitudinal cohort study from Denmark, 1995–2001. *Journal of affective disorders*, 117(3), 162-167.

SEYLE study Wasserman D, Hoven CW, Wasserman C, et al. School-based suicide prevention programmes: the SEYLE cluster-randomised, controlled trial. *Lancet* 2015; 385: 1536–44.

Yovell Y1, Bar G1, Mashiah M1, Baruch Y1, Briskman I1, Asherov J1, Lotan A1, Rigbi A1, Panksepp J1. Ultra-Low-Dose Buprenorphine as a Time-Limited Treatment for Severe Suicidal Ideation: A Randomized Controlled Trial. *Am J Psychiatry*. 2016 May 1;173(5):491-8. doi: 10.1176/appi.ajp.2015.15040535. Epub 2015 Dec 18.