

# BMJ Open Unwanted effects of treatments for depression in children and adolescents: a mapping of systematic reviews

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**To cite:** Eidet LM, Dahlgren A, Elvsåshagen M. Unwanted effects of treatments for depression in children and adolescents: a mapping of systematic reviews. *BMJ Open* 2020;**10**:e034532. doi:10.1136/bmjopen-2019-034532

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2019-034532>).

Received 25 September 2019  
Revised 10 December 2019  
Accepted 28 January 2020



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## ABSTRACT

**Objectives** To describe the results of a mapping review exploring the coverage of unwanted treatment effects in systematic reviews of the effects of various treatments for moderate to severe depression in children and adolescents.

**Setting** Any context or service providing treatment for depression, including interventions delivered in local communities and school settings, as well as services provided in primary or specialist care.

**Participants** Children and young people with moderate to severe depression (<18 years).

**Interventions** Systematic reviews published in 2011 or later comparing the effects of any treatment for children and adolescents with moderate to severe depression meeting the Database of Abstracts of Reviews of Effects criteria. The systematic search was performed in April 2018 and updated in December 2018.

**Primary outcomes** Any unwanted effects of treatments as defined in the systematic review.

**Results** We included 10 systematic reviews covering 19 treatment comparisons. Unwanted effects were assessed for seven of 19. Three comparisons were evaluations of pharmaceutical interventions or combination therapy, reporting effects on 'suicidal ideation' and 'suicide risk'. Two included therapy, reporting 'self-harm', and 'suicidal ideation', and two comparisons included transcranial magnetic stimulation and electroconvulsive treatment. Unwanted effects evaluated for these treatments were mostly symptoms of physical discomfort such as headache or cramps. For the remaining treatment comparisons evaluating psychological and psychosocial therapies, unwanted effects were not evaluated or found. A limitation of overviews of systematic reviews such as this mapping study is that data extraction is done based on the reporting of results by the review authors and not on the primary studies.

**Conclusion** The unwanted effects of widely used treatments for children and young people with depression is unknown. This is a major barrier for evidence informed decision making about treatment choices for children and young people. We suggest that unwanted effects should be a reporting standard in all protocols describing evaluations of treatments, including primary studies as well as systematic reviews.

## INTRODUCTION

Depression is a serious mood disorder that affects about 10% of the world population.<sup>1</sup>

## Strengths and limitations of this study

- A mapping review is an appropriate first step in identifying research gaps.
- To our knowledge, this is the first mapping review to explore occurrence and type of unwanted effects evaluated in systematic reviews on the effects for young people with depression.
- We have used systematic and transparent review methods, including only up-to-date systematic reviews.
- Our data extraction is based on the reporting of results by the review authors, thus primary studies may have evaluated other unwanted effects.
- Whether the problem is at the primary study level or in the execution of systematic reviews, their absence in systematic reviews is of major importance because of the reliance now placed on systematic reviews by practitioners and guideline developers.

It is associated with social and educational impairments and can predict suicide, self-harm and poor physical health. Depression can also mark the beginning of long-term mental health difficulties.<sup>2</sup>

Depression in children and adolescents can be treated in several ways. The most commonly used treatment options are psychological, psychosocial and pharmaceutical treatments. The large variety of therapeutic interventions give rise to questions of clinical effectiveness and side effects.<sup>2</sup>

Systematic reviews provide the most reliable evidence base for making informed treatment choices. Evidence summaries should also serve as a starting point when launching new research, such as the development of measures or evaluation tools.<sup>3–5</sup> Knowledge about the benefits and harms associated with treatments is essential for informed decision making and should be integrated with the practitioner's personal experience and through dialogue with the patient.<sup>3 6 7</sup> All treatments believed to be beneficial can also be harmful.<sup>8</sup> Any action to improve an outcome, whether psychological, dietary,



self-help groups or medication can also have unwanted effects, such as adverse events or reactions, harms, negative effects, toxicity or complications.<sup>9</sup>

Health and welfare services have sometimes failed to recognise the harms of some interventions. Although interventions are well-intentioned, systematic research has identified serious harmful effects; examples include thalidomide for morning sickness in pregnant women that led to fetus malformations in the 1960s,<sup>10</sup> the advice of baby sleeping on stomach before the 1990s even though evidence that it was harmful and led to the sudden infant death syndrome was available from the 1970s,<sup>11</sup> and the 'Scared Straight' crime prevention programme that likely had an opposite effect than intended and harmed the youths and increased delinquency relative to doing nothing.<sup>12</sup> It has also been reported that group treatment for self-harm, depression and suicidal ideation has sometimes been followed by an increase in self harm.<sup>13</sup>

Professionals have a responsibility to convey to patients the known benefits and harms associated with treatments and also if there are known uncertainties associated with treatment effects.<sup>4</sup> Such uncertainties result from lack of research or that the evidence supporting the treatment is weak.<sup>4</sup> Identifying evidence gaps in the existing literature should also be the starting point for new research initiatives and shaping future research priorities (EBRNetwork.org). The purpose of a mapping review is to describe a research field by finding and systematising existing literature.<sup>5</sup> It is also essential for identifying knowledge gaps and suggesting new research priorities. An overview of evaluations of potential unwanted effects associated with treatments for children and young people with depression should help to support patients, practitioners and researchers in making informed decisions.

## Objective

This study aims to map the occurrence of evaluations of unwanted effects in systematic reviews of the effects of various treatments for moderate to severe depression in children and adolescents. We will also describe which treatment comparisons included assessments of unwanted effects and report how these outcomes were evaluated.

## METHODS

We have recently developed an evidence portal for the Norwegian service providers and the general public summarising research assessing the effects of treatments for young people with mental illness.<sup>14</sup> The evidence portal has been developed according to national and international standards for systematic reviews and guideline development.<sup>15–18</sup> This work gives an opportunity to map reviews analysing methodological issues in the available evidence. This mapping review is a secondary analysis based on the evidence portal and our previous work summarising the effects of treatments for children and youth with depression.<sup>19</sup>

## Description of study design and search strategy

According to the typology of Grant and Booth,<sup>5</sup> a mapping review differs from other scoping assessments.<sup>8</sup> Whereas a scoping review is usually restricted to a systematic, criteria-led sorting of the results of a literature search according to a set of criteria, the objective of a mapping review is to quantify, describe and organise the literature according to theoretical perspectives or by population or other characteristics.<sup>5</sup> For many researchers, this is the first step to get an overview over a research field before imitating new research efforts. It is not intended to be used for evaluating the effects of a treatment. For this mapping review, we included all systematic reviews evaluating the effects of treatments for children and young people under 18 for any psychological, pharmaceutical or other relevant forms of treatment such as social interventions, physical activity or nutrition.

The evidence portal and consequently our search for studies for this mapping review was largely based on IN SUM: A database of systematic reviews on effects of child mental health and welfare interventions ([www.insum.no](http://www.insum.no)).<sup>20</sup> The search was performed in April 2018 and updated in December 2018. IN SUM is a recently developed database of systematic reviews on the effects of interventions relevant to children and young people's mental health and welfare. The database indexes systematic reviews from the following databases: Cochrane Database of Systematic Reviews, Campbell Library, PsycINFO, Medline, Embase, Web of Science, Database of Abstracts of Reviews of Effects (DARE) and Evidence-Based Mental Health. Online supplementary appendix 1 describes the search strategy of IN SUM. We reviewed all 1153 records in IN SUM for this study. Two authors independently screened all references, extracting all reviews potentially meeting our inclusion criteria (see [table 1](#)). In addition to IN SUM, we also hand searched the websites of the Norwegian Institute for Public Health, the Swedish Agency for Health Technology Assessment and Assessment of Social Services, the Danish Health Authority for Systematic Reviews and the National Institute for Health and Care Excellence for evidence-based guidelines.

Reviews included in IN SUM, and consequently this mapping review, must adhere to the DARE criteria to be considered a systematic review.<sup>21</sup> According to these criteria the review authors must provide:

1. Clear inclusion and exclusion criteria.
2. A comprehensive search strategy.
3. A compilation of results from included studies.
4. Quality assessment of included studies.

Furthermore, we only included systematic reviews published 2011 or later. This cut-off is pragmatic and based on a consideration that a review published earlier than this is obsolete and no longer a reliable basis for evidence and in need for being updated.

There is a high number of systematic reviews and guidelines available. In case of overlap between these systematic reviews, we based our prioritisation on the principles of quality and the review's date of search.

**Table 1** Inclusion criteria for search and retrieval by research design: systematic reviews and evidence-based guidelines

Design	Systematic reviews and evidence-based guidelines.
Populations	Children and adolescents from 0 to 18 years old with moderate to severe depression (as defined by the review authors).
Types of interventions	Psychological, medical and other relevant treatments such as social interventions, physical activity or nutrition.
Comparison	Other relevant interventions, treatment as usual or no intervention.
Outcomes	Unwanted effects of psychological treatments for depression.
Language	No restrictions.
Date	Published 2011 or later.
Quality	DARE criteria 1–4.

DARE, Database of Abstracts of Reviews of Effects.

We excluded reviews that did not meet the criteria mentioned above, only addressed adult patients or other patients with primary diagnoses other than depression. Preventive interventions were not included.

### Data collection and presentation of the findings

Unwanted effects or symptoms is defined as unwanted experiences in participants (unfavourable changes in health), which may or may not be caused by treatments.<sup>22</sup> We mapped all types of unwanted effects reported in the systematic reviews. These were sorted by treatment comparison and entered into an Excel spreadsheet for analysis. We also extracted information about how these effects were assessed (ie, the outcome measurements used). One of us extracted this information and another quality checked the first author's judgements. We considered measures of self-harm to be unwanted effects, although self-harm could also be part of the symptomatology associated with depression. For this outcome,

we also report the review authors' rationale for including this outcome.

Loss to follow-up may be associated with unwanted effects but may also be due to other reasons. For this review we did not consider this as an unwanted effect.

### Patient and public involvement

No patients were involved in conducting this mapping review.

## RESULTS

### Description of the included studies

We screened 1153 references indexed in IN SUM (the hand search of the other databases resulted in three additional publications). Of the 1153 references, 1125 were excluded in the initial screening. Thirty-one articles were assessed in full text for eligibility (see the Preferred Reporting Items for Systematic Review and Meta-Analysis flow diagram in figure 1). Ten reviews (see online supplementary appendix 2) evaluating 19 treatment comparisons met our inclusion criteria.

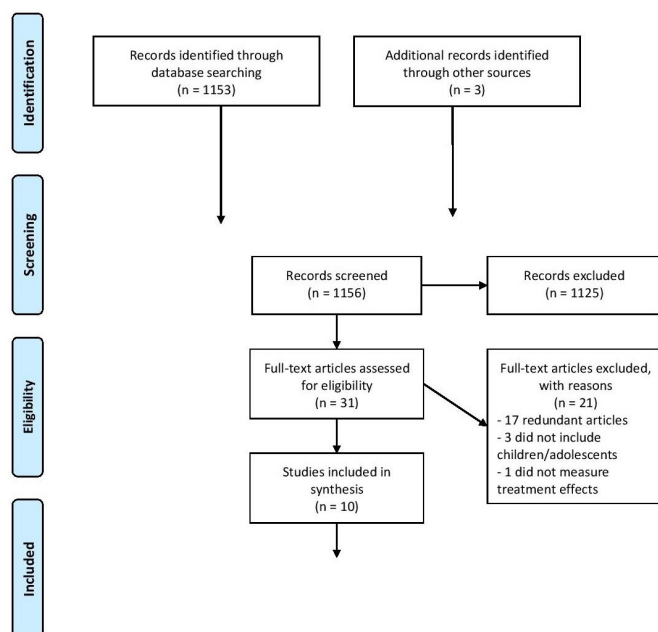
After finalising our mapping review, two additional reviews were identified with potential relevance to this analysis.<sup>23 24</sup>

### Treatment comparisons evaluated in the included reviews

Of 19 treatment comparisons, the reviews reported unwanted effects in seven (see table 2). Three of these seven were associated with a drug treatment or combination therapy, one evaluated unwanted effects of electroconvulsive therapy (ECT) and one evaluated unwanted effects of transcranial magnetic stimulation (rTMS). Two comparisons included therapy. See table 3 for instruments used for measuring unwanted effects.

The unwanted effects measured were 'suicidal ideation', 'suicidal risk', 'self-harm' and 'suicide',<sup>25–27</sup> 'tension headache', 'scalp discomfort', 'sleepiness' and 'hypomania' after rTMS<sup>27</sup> and 'discomfort', 'headache', 'memory loss' and 'cramps' after ECT.<sup>25</sup>

The treatment comparisons in which no unwanted effects were identified included evaluations of cognitive



**Figure 1** Preferred Reporting Items for Systematic Review and Meta-Analysis flow diagram.

**Table 2** Treatment comparisons evaluated in the included reviews

Study identification	Comparison of treatments	Unwanted effects
<b>Moderate and severe depression</b>		
Aalbers <i>et al</i> <sup>30</sup>	Music therapy versus cognitive behavioural therapy	No results identified
Bailey <i>et al</i> <sup>29</sup>	Physical activity versus treatment as usual, waitlist and attention/activity placebo condition	No results identified
Cook <i>et al</i> <sup>26</sup>	Dialectical behavioural therapy versus treatment as usual or no follow-up	Self-harm
Fleming <sup>28</sup>	Serious games versus treatment as usual or no follow-up	No results identified
Meekums <i>et al</i> <sup>31</sup>	Dance movement therapy versus treatment as usual or no follow-up	No results identified
Pu <i>et al</i> <sup>34</sup>	Interpersonal psychotherapy versus treatment as usual or no follow-up	No results identified
Tindall <i>et al</i> <sup>39</sup>	Behavioural activation versus treatment as usual, waitlist or no follow-up	No results identified
Socialstyrelsen <sup>25</sup>	Psychoeducation versus treatment as usual or waitlist	No results identified
Socialstyrelsen <sup>25</sup>	Cognitive behavioural therapy versus treatment as usual or no follow-up	No results identified
Socialstyrelsen <sup>25</sup>	Interpersonal therapy versus cognitive behavioural therapy	No results identified
Socialstyrelsen <sup>25</sup>	Psychodynamic therapy versus systemic family therapy	No results identified
Socialstyrelsen <sup>25</sup>	Systemic family therapy compared with individual or other therapy	No results identified
Socialstyrelsen <sup>25</sup>	Attachment-based family therapy versus no follow-up	Suicidal ideation
Socialstyrelsen <sup>25</sup>	Mindfulness based interventions versus treatment as usual or no follow-up	No results identified
Dalsbø <i>et al</i> <sup>33</sup>	Combination treatment versus psychological treatment	Suicidal ideation
Socialstyrelsen <sup>25</sup>	Medical treatment versus psychological treatment	Suicidal ideation
<b>Serious and treatment resistant depression</b>		
Donaldson <i>et al</i> <sup>27</sup>	Transcranial magnetic stimulation	Tension headache, scalp discomfort, sleepiness, hypomania and seizure
Socialstyrelsen <sup>25</sup>	Electroconvulsive therapy	Discomfort, headache, memory loss, cramps
Socialstyrelsen <sup>25</sup>	Combination treatment versus psychological treatment alone	Suicide risk

behavioural therapy,<sup>25</sup> interpersonal psychotherapy,<sup>25</sup> psychodynamic therapy,<sup>25</sup> systemic family therapy,<sup>25</sup> mindfulness-based interventions,<sup>25</sup> serious games,<sup>28</sup> physical activity,<sup>29</sup> music therapy<sup>30</sup> and dance movement therapy.<sup>31</sup>

The drug treatments covered included fluoxetine, paroxetine, sertraline and escitalopram.

## DISCUSSION

### Summary of findings

Overall, unwanted effects were reported for less than a third of the treatment comparisons. Of the seven comparisons that did include a potential measure of unwanted effects, three evaluated the effects of pharmacological interventions, with suicidal ideation and suicidal risk being the unwanted effects measured. However, the rationale for evaluating these outcomes may have been twofold; as drug treatment for depression theoretically may both reduce and increase the risk of suicidal behaviour. Whereas previous research has suggested that drug treatment for young people with depression may

increase suicidal risk, such behaviour may also be associated with depression itself.<sup>32</sup>

'Self-harm' was measured as a part of the symptomatology in the comparison 'dialectical behavioural therapy versus treatment as usual or no follow-up' by Cook *et al*.<sup>26</sup> Socialstyrelsen<sup>25</sup> measured 'suicidal ideation' from baseline to follow-up as a part of the symptomatology in the comparison 'attachment-based behavioural therapy versus no follow-up'. The five other comparisons (see tables 2–3) by Socialstyrelsen,<sup>25</sup> Donaldson *et al*<sup>27</sup> and Dalsbø *et al*<sup>33</sup> considered the outcomes 'suicidal ideation', 'suicide risk', 'discomfort', 'headache', 'memory loss', 'cramps', 'scalp discomfort', 'sleepiness', 'hypomania' and 'seizure' to be specific measures of unwanted effects.

Psychological therapy and other interventions can be effective in reducing depression.<sup>19 25 34</sup> However, our findings suggest that unwanted effects are seldom reported in systematic reviews for these young patients, particularly with respect to non-pharmaceutical interventions. This may be explained by less strict reporting guidelines for non-pharmacological interventions and because

**Table 3** Instruments used for measuring unwanted effects

Study identification	Comparison of treatments	Instruments
<b>Moderate and severe depression</b>		
Cook <i>et al</i> <sup>26</sup>	Dialectic behavioural therapy vs treatment as usual or no follow-up	LPC, K-SADS-DRS* 'deliberate self-harm- incidents per week' item, CBCL 'deliberate self-harm' item, LPC self-harm episodes per week
Dalsbø <i>et al</i> <sup>33</sup>	Combination treatment versus psychological treatment	SIQ-Jr
Socialstyrelsen <sup>25</sup>	Attachment-based family therapy versus no follow-up	SIQ-Jr
Socialstyrelsen <sup>25</sup>	Medical treatment versus psychological treatment	Unclear
<b>Serious and treatment resistant depression</b>		
Socialstyrelsen <sup>25</sup>	Combination treatment versus psychological treatment alone	SIQ-Jr
Socialstyrelsen <sup>25</sup>	Electroconvulsive therapy	Unclear
Donaldson <i>et al</i> <sup>27</sup>	Transcranial magnetic stimulation	Unclear

\*K-SADS-DRS is a subscale from the K-SADS-PL, a semistructured diagnostic interview to assess current and past episodes of psychopathology in children and adolescents.

CBCL, Child Behavior Checklist; LPC, Lifetime Parasuicide Count; SIQ-Jr, Suicidal Ideation Questionnaire Junior High School.

researchers and providers may assume that psychological and psychosocial treatments are unlikely to have unwanted effects. As mentioned earlier, any intervention with potential beneficial effects, may also have negative or unwanted effects.<sup>8</sup>

Healthcare professionals should engage with their patients and their treatment decisions and expectations so that they can give meaningful and properly informed consent for their chosen treatment.<sup>35</sup> This requires that children, young people and their next of kin are informed about the benefits and harms of available treatments, including any uncertainties.<sup>4</sup> Such information should be communicated at an appropriate time, as part of a collaborative and supportive relationship with healthcare professionals.<sup>35</sup>

Based on the findings of this review, we suggest that researchers should identify potential unwanted effects of interventions and that evaluate these appropriately. Qualitative research or other input from patients and their carers may provide important insights identifying such consequences.<sup>36</sup> Establishing core outcome sets covering what should be measured and reported in clinical trials should also be considered.<sup>37</sup> Furthermore, journals and funders should support the development of standards for evaluating potential unwanted effects of interventions.

### Strengths and limitations of this study

We have applied transparent, systematic methods informed by the published principles for mapping reviews. By systematising existing literature and identifying gaps in the evidence base<sup>5 38</sup> mapping reviews<sup>38</sup> are an appropriate starting point for initiating new research and reviews. This review makes clear that a majority of

the systematic reviews of treatments for depressed children and adolescents do not cover unwanted effects of treatments.

A limitation of overviews of systematic reviews such as this mapping study is that data extraction is done based on the reporting of results by the review authors and not on the primary studies. This means that the primary studies may have evaluated unwanted effects even though these were not reported in the reviews we included. However, whether the problem is at the primary study level or in the execution of systematic reviews, their absence in systematic reviews is of major importance because of the reliance now placed on systematic reviews by practitioners and those preparing information and guidelines for clinicians and families.

### CONCLUSION

Knowledge of unwanted effects associated with treatments for depression in children and adolescents is inadequate. Most systematic reviews that have evaluated the effects of treatments for depression in children and adolescents do not report unwanted effects. Information about potentially unwanted effects of interventions should be more readily available to support informed decisions about choice of treatment and for patient safety. Qualitative research or other input from patients and their carers may provide important insights identifying such consequences. Establishing core outcome sets covering what should be measured and reported in clinical trials should also be considered. Furthermore, journals and funders should support the development of standards

for evaluating potential unwanted effects of interventions in all protocols describing evaluations of treatments, including primary studies as well as systematic reviews.

**Contributors** LME and AD assessed all relevant references and considered them for inclusion. All full-text reviews were assessed by LME and AD. LME, AD and ME performed data extraction and the descriptive analysis. LME drafted this manuscript and all authors provided substantial contribution to this process.

**Funding** The study was funded by Helsedirektoratet and RBUP Øst og Sør.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information.

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