

BMJ Open Adverse effects information in clinical guidelines on pharmacological treatment of depression in children and adolescents: a systematic review

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ABSTRACT

Objectives To analyse to what extent clinical practice guidelines on drug treatment of depression in children and adolescents mention the risk of adverse effects, to characterise the citations in the guidelines and to assess to what extent data from a major study (Treatment for Adolescents With Depression Study, TADS) was used as basis for information about adverse effects.

Design Systematic review of clinical guidelines and clinical decision support tools.

Data sources PubMed, EMBASE, guideline collections, Health libraries.

Eligibility criteria We included national guidelines on depression in children and adolescents from European and/or English-speaking countries, published in English, German, French or any Scandinavian language since 2008. We also included well-known, international clinical decision support tools.

Data extraction and synthesis Guidelines were examined by all authors to identify and classify information on adverse effects. Citations for statements on adverse effects were extracted and classified by category. The extent of citations about suicidality risk versus other adverse effects was assessed.

Results 19 guidelines were assessed. All guidelines discussed risk of suicidal behaviour connected with use of antidepressants. Most guidelines mentioned some other psychiatric adverse effects. Several guidelines did not include information on well-known and common somatic adverse effects. Most references concerned risk of suicidality. Adverse effects identified in underlying studies were not always presented. The TADS study was referred to, directly or indirectly, by 18/19 guidelines, but some only referred to TADS with regard to suicidality without citing the study's findings of somatic adverse effects. No guideline commented on the lack of long-term adverse effects data from TADS.

Conclusions Guidelines for treatment of depression in children and adolescents vary widely regarding information on adverse effects. Many guidelines do not provide information on common somatic adverse effects. There is no consensus as to what extent risks of adverse effects connected with use of antidepressants should be described in guidelines.

INTRODUCTION

The use of antidepressants in children and adolescents with depression is the topic of

Strengths and limitations of this study

- The search for guidelines was extensive.
- Inclusion of guidelines was not limited to English texts.
- The main limitation is that some guidelines may have been overlooked and that the cut-off for guideline inclusion can be debated on a geographical and local level.
- The guideline committee mandate and scope may have varied between guidelines.
- Guidelines were searched for all relevant statements about adverse effects and corresponding citations, but some statements or text excerpts may have been overlooked.

several national and international guidelines which appear to differ considerably in extent, quality and information on potential harms.

As defined by the US Institute of Medicine in 2011, clinical practice guidelines are statements that include recommendations intended to optimise patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options. Guidelines should provide a clear description of potential benefits and harms for each recommendation.^{1 2} However, compliance with standards has been shown to be low for several parameters, including more focus on benefits than on potential harms.³ Other researchers have assessed the quality of clinical guidelines regarding benefits of antidepressants^{4 5} using the Appraisal of Guidelines for Research & Evaluation II (AGREE II) tool.⁶ We have not identified any specific appraisals of the adverse effects information provided in guidelines on antidepressant therapy.

For fluoxetine, which is the suggested medication of first choice, few high-quality

clinical trials are available to assess risk–benefit.⁷ The largest randomised controlled clinical trial on fluoxetine in children and adolescents with depression is a National Institute of Mental Health (NIMH)-funded study (Treatment for Adolescents With Depression Study (TADS)),⁸ which is considered a high-quality trial.⁹ We have previously analysed the adverse effects reporting in the TADS study¹⁰ and found that little data had been published concerning adverse effects profile during treatment for more than 12 weeks, with the exception of suicidality.

Based on our previous study,¹⁰ we had reason to believe that adverse effects descriptions in many guidelines on treatment of depression in children and adolescents would focus primarily on suicidality, with less attention given to the risk of other adverse effects and the risk–benefit balance. The adverse effects profile of the most commonly used medications, the selective serotonin reuptake inhibitors (SSRIs), is generally assumed to be similar in adults and children/adolescents and similar between the different SSRIs. This includes psychiatric effects such as suicidality, mania, anxiety, agitation and sleep disorders, as well as gastrointestinal effects such as nausea, diarrhoea and anorexia/weight loss. In this review, we aimed to analyse to what extent adverse effects data on SSRIs were mentioned in clinical practice guidelines on treatment of depression in children and adolescents. We also aimed to characterise the documentation provided as references in the clinical guidelines, and to assess to what extent data from the TADS study, with the identified data gaps, was used as basis for information about adverse effects.

METHODS

To identify guidelines and clinical evidence summaries on treatment of depression in children and adolescents, a search was performed according to the Norwegian Health Library guidelines on literature searches for development of clinical procedures.¹¹

Literature database search

Searches in PubMed and guideline collections were carried out in the period 30 October 2018 to 17 February 2019. An EMBASE search with time limits 2008–2019 was performed 5 December 2019.

Several PubMed searches were performed, using the search terms:

- ▶ (“depressive disorder”[MeSH Terms] OR (“depressive”[All Fields] AND “disorder”[All Fields]) OR “depressive disorder”[All Fields] OR “depression”[All Fields] OR “depression”[MeSH Terms]) AND (“guideline”[Publication Type] OR “guidelines as topic”[MeSH Terms] OR “guideline”[All Fields]) OR (“practice guideline”[Publication Type] OR “practice guidelines as topic”[MeSH Terms] OR “clinical practice guideline”[All Fields])) AND (“humans”[MeSH Terms] AND (“infant”[MeSH

Terms] OR “child”[MeSH Terms] OR “adolescent”[MeSH Terms]))

- ▶ “Depressive Disorder/drug therapy”[MAJR] AND “Antidepressive Agents/therapeutic use”[MAJR] AND (Guideline[ptyp] OR Practice Guideline[ptyp])
- ▶ ((practice guidelines as topic) AND adolescent psychiatry) AND depressive disorder

Filters: Humans, Child: birth-18 years

EMBASE search terms were: (exp adolescent depression/ OR exp major depression/ OR exp depression/) AND practice guideline/. Limits: (child <unspecified age>or adolescent <13 to 17 years>) and yr=“2008–2019”

Searches in clinical guidelines collections

Clinical treatment guidelines were identified through searches in Guidelines International Network, McMaster Plus, Epistemonikos, UpToDate, BMJ Best Practice, DynaMed Plus, International Network of Agencies for Health Technology Assessment, National Institute for Health and Care Excellence (UK), Cochrane library, the Norwegian Health Library, Sundhetsstyrelsen (Denmark), Socialstyrelsen (Denmark), Center for Clinical Guidelines (Denmark), Socialstyrelsen (Sweden), AHRQ website (USA), IQWiQ website (Germany), Psychenet website (Germany), guidelines.gov (USA), SIGN website (Scotland), Health Canada website, CADTH website (Canada). In addition, a manual reference search was performed on identified studies and guidelines. The guideline search and selection process is described in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.¹²

Inclusion and exclusion criteria

We included national guidelines from European and/or English-speaking countries, published in English, German, French and any Scandinavian language since 2008, covering the last 10 years. We also included well-known and widely used international decision support tools. Local hospital or county guidelines were not included.

The guidelines and decision support tools (hereafter referred to as guidelines) should specifically address depression in children and adolescents. In cases where we retrieved multiple guidelines from the same organisation, the most recent version was analysed.

Data extraction

The guidelines were examined to identify information on safety or adverse effects. All authors made an overall assessment of the full guidelines. Text excerpts and corresponding references concerning safety or adverse effects were initially extracted by TW. Data extraction from all guidelines was checked by SN and MK. Text excerpts were assessed in detail by all authors. Information on adverse effects provided in each guideline was analysed and classified by organ system, in accordance

with the classification used in the product monograph for Prozac (fluoxetine) by Eli Lilly.¹³ In order to distinguish suicidality or self-harm from other psychiatric adverse effects, these were registered as a separate category. Analysis was limited to adverse effects occurring during treatment and did not include mention of withdrawal reactions.

We assessed whether the guidelines provided information on the quality of the underlying evidence (high, moderate, low or very low) and strengths of recommendations (strong or weak) by use of the Grading of Recommendations Assessments, Development, and Evaluation (GRADE) tool^{14 15} or similar criteria for quality ratings.

We also evaluated the guidelines regarding presentation and risk–benefit assessment. To our knowledge, there are no explicit criteria for such evaluations. The guidelines were assessed by all authors independently, according to whether the guideline provided an overall discussion on risks, made an attempt to assess risks and benefits together, gave information on handling adverse effects, provided frequency estimates on risks or gave recommendations on monitoring patients. Any discrepancies in judgement were discussed by all authors.

Classification of adverse effects

References that were provided as basis for statements on adverse effects were extracted from all guidelines, and the most cited references were identified. Adverse effects were mainly classified by System Organ Class according to the MedDRA classification, as used in European Summaries of Product Characteristics.¹⁶ In this classification, appetite disorders are classified under Metabolism and nutrition disorders; sleep disorders, restless, anxiety, mania and mood disorders are classified under psychiatric disorders and headache, dizziness, and somnolence are classified under nervous system disorders. Suicidal thoughts and behaviour are classified under psychiatric disorders in MedDRA, but has been noted separately in this review. Reproductive system and breast disorders include sexual dysfunction and erectile and ejaculation disorders. Libido changes are classified under Psychiatric disorders in MedDRA, we have, however, included any such information in the Reproductive system and breast disorders category, in order to show a comprehensive view on all sexual adverse effects. An overview of the System Organ Classes and the included adverse effects can be found in the online supplementary material table S1.

The references were assessed and classified by category. Analysis by category and type of adverse effects was performed to assess to what extent the citations were used to discuss risk of suicidality versus other adverse effects.

Patient and public involvement

No patients were involved in this review.

RESULTS

Inclusion of guidelines

Nineteen guidelines were included in the final analysis (table 1). A PRISMA flow diagram describing the search and screening process is shown in figure 1.

Adverse effects mentioned in guidelines

We identified 20 adverse effects categories in the summary of product characteristics for Prozac.¹³ The guidelines' mention of these adverse effects categories were highly variable (table 2).

The 19 guidelines mentioned an average of 5.3 adverse effects categories (median 4.0, range 1–15). All 19 guidelines included information on suicidal risk. Fifteen of 19 mentioned other types of psychiatric adverse reactions, including mention of manic switching or manic/hypomanic episodes in seven guidelines.

Seven of 19 guidelines limited their information on adverse effects to suicidality and/or psychiatric reactions. Three guidelines mentioned risk of suicidal behaviour only (figure 2). Nervous system adverse effects including headache was mentioned by 10/19 guidelines, as was also the case for gastrointestinal reactions. Several possible adverse effects were only mentioned in a few guidelines, as an example, the risk of sexual adverse effects was mentioned in 5/19 guidelines. Four guidelines mentioned adverse effects in 10 organ categories or more.^{17–20}

The overall assessments of somatic and nervous adverse effects varied widely, as illustrated by different descriptions of the SSRI risk profile. While one guideline stated that studies have shown somatic adverse effects to have small significance,²¹ another guideline stated that SSRI treatment causes significantly more nausea, diarrhoea, anorexia and stimulatory side effects (agitation, insomnia and anxiety) than tricyclic antidepressants.²² In our evaluation of the guidelines regarding presentation and risk–benefit assessment, we judged that 9/19 guidelines could be classified as having a sufficiently extensive and balanced consideration of adverse effects in their overall recommendations, while 10 guidelines did not (see online supplementary material table S2). Nine of 19 guidelines presented grading of evidence and strength of recommendations by the GRADE tool or similar, though the evidence grading mostly reflected efficacy documentation (see online supplementary material table S3).

References in guidelines as basis for adverse effects information

We identified 124 specific references as basis for statements in the 19 guidelines (see online supplementary material table S4). Some guidelines mentioned general sources of information, such as 'FDA warnings', 'Cochrane reviews', or 'Product monographs'. The guidelines had a mean number of adverse effects references of 9.3 (range 0–32).

**Table 1** Clinical practice guidelines on treatment of depression in children and adolescents

No	Title	Publisher	Country	Year	Category
1	Guidelines for Adolescent Depression in Primary Care: Part II. Treatment, Ongoing Management. ³⁰	American Academy of Pediatrics	USA	2018	Guideline
2	Depression in children and adolescents. ³¹	DynaMed Plus, EBSCO Health	USA	2018	Decision support tool
3	Pediatric unipolar depression and pharmacotherapy: Choosing a medication. ¹⁷	UpToDate	USA	2017	Decision support tool
4	Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 6. ³²	Canadian Network for Mood and Anxiety Treatments	Canada	2016	Guideline
5	Anxiety and Depression in Children and Youth - Diagnosis and Treatment. ¹⁸	British Columbia Guidelines Protocols Advisory Committee	Canada	2010	Guideline
6	Depression in children. ²⁴	BMJ Best Practice	UK	2018	Decision support tool
7	Depression in children and young people: identification and management (CG28). ³³	NICE (UK) National Institute for Health and Care Excellence	UK	2017	Guideline
8	Evidence-based guidelines for treating depressive disorders with antidepressants. ²²	British Association for Psychopharmacology	UK	2015	Guideline
9	Treating depression in young people. ³⁴	Orygen National Centre of Excellence in Youth Mental Health	Australia	2017	Guideline
10	Identification of Common Mental Disorders and Management of Depression in Primary Care. ³⁵	New Zealand Guidelines Group/Ministry of Health	New Zealand	2008	Guideline
11	Manifestations dépressives à l'adolescence : repérage, diagnostic, prise en charge en soins de premier recours. ¹⁹	Haute Autorité de Santé	France	2014	Guideline
12	S3-Leitlinie. Behandlung von depressiven Störungen bei Kindern und Jugendlichen. ²⁰	Deutsche Gesellschaft Kinder- und Jugendpsychiatrie, Psychosomatik, Psychotherapie	Germany	2013	Guideline
13	Håndbok for barn og unges psykiske helse. ³⁶	Center for Child and Adolescent Mental Health. Eastern, Southern Norway	Norway	2019	Guideline
14	Pediatriveilederen. Psykiske lidelser og psykososiale tilstander. 12.3 Angst og depresjon. ³⁷	Norwegian Pediatric Association	Norway	2018	Guideline
15	Vejledning om medikamentel behandling af børn og unge med psykiske lidelser. ³⁸	Danish Health Authority	Denmark	2013	Guideline
16	Landsdækkende klinisk retningslinje vedrørende udredning og behandling af depression hos børn og unge. ³⁹	Børne-og Ungdomspsykiatrisk Selskab	Denmark	2011	Guideline
17	Nationella riktlinjer för vård vid depression och ångestsyndrom. ²¹	The National Board of Health and Welfare	Sweden	2017	Guideline
18	Childhood depression. ⁴⁰	EBM Guidelines Duodecim	Finland	2018	Guideline
19	Depression of adolescents. ²⁵	EBM Guidelines Duodecim	Finland	2018	Guideline

EBM, evidence based medicine; NICE, National Institute for Health and Care Excellence.

The 124 references were cited 177 times, as some references had multiple citations (table 3). The largest group of references was single studies, followed by review articles, statements or warnings from medicinal authorities and systematic reviews (see online supplementary material table S4). Most references to review articles, authorities, systematic reviews and guidelines concerned risk of suicidality. For the single studies, however, 22/52 citations (42,3%) referred to adverse effects in other organ systems (see online supplementary material table S4). These included 14 clinical trials. Somatic adverse effects were referred to

in 3.2 organ categories for each citation (mean value), minimum value 1, maximum value 10.

Forty-one of 177 citations concerned adverse effects other than suicidality and/or other psychiatric adverse effects (see online supplementary material table S4). Most of those referred to somatic adverse effects in few organ systems (mean value 2.8, median 2.0, minimum value 1, maximum value 10).

Overall, 116 citations concerned risk of suicidal behaviour and 54 citations concerned risk of other psychiatric adverse effects, while fewer citations

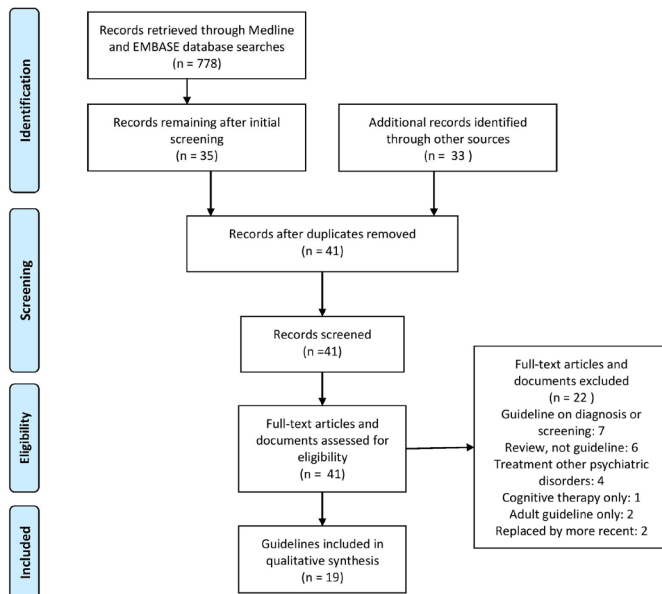


Figure 1 Identification of guidelines for treatment of depression in children and adolescents. PRISMA flowchart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

concerned somatic adverse effects. For some known adverse effects according to the product monograph,¹³ no guidelines provided any citations (figure 3).

Data from the TADS study as basis for information about adverse effects

Of the 19 guidelines, seven referred directly to publications from the TADS study, while 11 referred to sources that cited TADS as part of their assessment. One guideline did not provide any references and consequently did not refer to the TADS study.

Adverse effects data from the TADS study were published by March *et al*⁸ and in more detail by Emslie *et al* in 2006.²³ Both publications describe a broad range of adverse effects, including risk of suicidal behaviour, psychiatric adverse effects such as mania, sedation or sleeping problems, abdominal pain, diarrhoea and vomiting during the first 12 weeks of treatment. These articles were cited by seven and two guidelines, respectively. Most guidelines referring to TADS, directly or indirectly, described psychiatric, nervous, gastrointestinal and respiratory adverse effects. However, three guidelines^{20 24 25} that cited the TADS publication from March 2004⁸ did not cite the study's findings of somatic adverse effects. No guideline commented on the lack of long-term adverse effects data from TADS beyond 12 weeks.

DISCUSSION

Our analysis of 19 treatment guidelines of depression in children and adolescents shows that the guidelines vary widely regarding information on adverse effects. The most commonly used medications, the SSRIs, may have multiple adverse effects involving several organ

systems, but few guidelines described the full adverse effect profile. Several guidelines mentioned only risk of suicidal behaviour with or without mention of other psychiatric adverse effects. In many guidelines where adverse effects are mentioned, the frequency or the benefit-risk assessment is missing. Overall, somatic adverse effects were mentioned to little extent in the guidelines, and mention was often limited to few organ systems. The reporting of adverse effects in the guidelines appears to be selective and arbitrary. Several guidelines give the impression that suicidality is the only safety issue of consequence, and that there is a minor and limited risk of other adverse effects. We have not been able to identify a current, accepted standard for inclusion of adverse effects information in guidelines. It is possible that the varying descriptions of adverse effects in the guidelines are due to a lack of consensus as to what should be included. It can be argued that a full spectrum of adverse effects should be described. However, limitations may be necessary due to readability and format, in which case selection criteria should be stated.

All guidelines indicated suicidality as a major risk factor, reflecting that this has been a major topic of safety discussions. This was also the case for the underlying literature references. Most citations concerned suicidality with or without other psychiatric adverse effects. Far fewer citations concerned adverse effects in other organ systems. The fact that most references to review articles, authorities, systematic reviews and guidelines concerned risk of suicidality indicate that suicidality risk has been the main focus when addressing adverse effects of SSRIs. There were indications of selective citing, where the underlying articles provided more details of adverse effects than was referred to in the guidelines. The most frequently cited reference, the Cochrane database review by Hetrick *et al*,⁷ provides details on several adverse effects observed in the included studies, but most guidelines referred to this review only in the context of suicidality risk. Likewise, the TADS publication by March *et al*⁸ describes several somatic adverse effects which were not mentioned in many guidelines that cited the study on suicidality risk. A later publication on the range of adverse effects observed in the TADS study²³ was cited by two guidelines only. We found that most of the known somatic adverse effects were not mentioned in the majority of the guidelines, thereby giving users a biased and skewed impression of the risk of harms. This lack of adverse effect information may affect treatment of children and adolescents with depression.

Guidelines should include descriptions of benefits and harms for the recommendations, however, this is a general statement and does not specify to what extent possible harms and adverse drug reactions should be described. The recommended tool for assessment of guideline quality, the AGREE II tool⁶ includes the criterion 'The health benefits, side effects and risks



Table 2 Adverse effects categories mentioned in guidelines

Guideline	At least one adverse effect in category mentioned in guideline														Investigations					
	Suicidality	Other psychiatr.	Blood, lymphat	Immune	Endocrine	Metabol, nutrit	Nervous system	Eye	Ear	Cardiac	Vascular	Respiratory	Gastro-intestin	Hepatobiliary		Skin	Muskulo-skeletal	Renal, urinary	Reprod, breasts	General
Manifestations dépressives à l'adolescence. Haute Autorité Santé, France ¹⁹																				
Behandlung von depressiven Störungen bei Kindern und Jugendlichen. Deutsche Gesellschaft Kinder Jugendpsychiatrie ²⁰																				
Pediatric unipolar depression and pharmacotherapy: UpToDate, USA ¹⁷																				
Anxiety and Depression in Children and Youth. British Columbia, Canada ¹⁸																				
Evidence-based guidelines for treating depressive disorders with antidepressants. British Ass. Psychopharmacol. ²²																				
Depression in children. BMJ Best Practice, UK ²⁴																				
Guidelines for Adolescent Depression in Primary Care: Part II. American Acad Pediatrics ³⁰																				
Depression in children and young people: identification and management (CG28). NICE, UK ³³																				
Vejledning om medikamentel behandling af børn og unge med psykiske lidelser. Danish Health Authority ³⁸																				
Landsdækkende klinisk retningslinje vedrørende udredning og behandling af depression hos børn og unge. BUP-DK ³⁹																				
Nationella riktlinjer för vård vid depression och ångestsyndrom. National Board of Health and Welfare, Sweden ⁴¹																				
Håndbok for barn og unges psykiske helse. Center Child Adolescent Mental Health, Norway ³⁵																				
Treating depression in young people. Orygen, Australia ³⁴																				
Identification of Common Mental Disorders and Management of Depression in Primary Care. New Zealand Ministry of Health ³⁵																				

Continued

Table 2 Continued

Guideline	At least one adverse effect in category mentioned in guideline																				
	Suicidality	Other psychiatric	Blood, lymphat	Immune	Endocrine	Metabol, nutrit	Nervous system	Eye	Ear	Cardiac	Vascular	Respiratory	Gastro-intestin	Hepatobiliary	Skin	Muskuloskeletal	Renal, urinary	Reprod, breasts	General	Investigations	
Pediatrivelederen. Angst og depression Norwegian Pediatric Association ³⁷																					
Depression of adolescents. Duodecim, Finland ²⁵																					
Childhood depression. Duodecim, Finland ⁴⁰																					
Clinical Guidelines for the Management of Adults with Major Depressive Disorder. CANMAT, Canada ³²																					
Depression in children and adolescents. DynaMed Plus, USA ³¹																					

BUP-DK, Berne-og Ungdomspsykiatrisk Selskab; CANMAT, Canadian network for mood and anxiety treatments; NICE, National Institute for Health and Care Excellence.

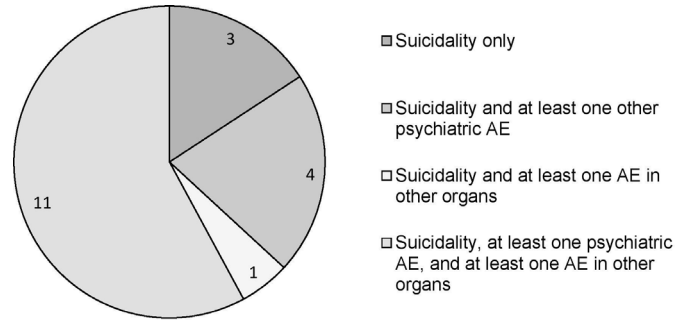


Figure 2 Information on adverse effects (AE) in clinical treatment guidelines (n=19).

have been considered in formulating the recommendations'. This should include descriptions of supporting data and reports of side effects, reports of the balance between benefits and side effects, and recommendations reflecting considerations of both benefits and side effects.²⁶ The tool does not, however, specify what should be considered a sufficient level of risk information. We have not identified any quality assessment studies of adverse effect information in clinical guidelines.

For systematic reviews, which sum up the literature and form a basis for guidelines, a framework has been proposed to include relevant harms data in a more comprehensive way.²⁷ However, research still show failings in the reporting of harms in systematic reviews.^{28 29} Despite having procedures and checklists for developing guidelines, there is no guarantee that adverse effects identified in underlying clinical trials will be reflected in the finished guideline.

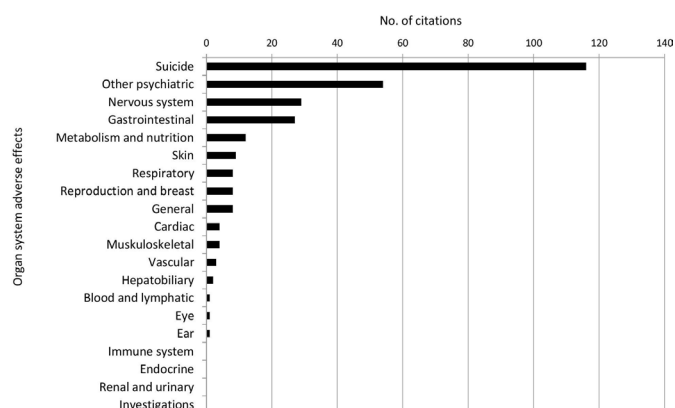
In conclusion, we found that many guidelines on treatment of depression in children and adolescents did not provide a thorough risk assessment with information on well-known and common adverse effects. There is currently no international standard regarding the extent of adverse effects information that should be included in guidelines. Development of such standards would give clinicians better accounts of risks and benefits as basis for therapy decisions.

Strengths and limitations

We conducted an extensive search for guidelines, however, some older guidelines were not found in electronic full text due to closure of the US National Guideline Clearinghouse. In many cases, we were able to identify updates that were available elsewhere. Inclusion of guidelines was not limited to English texts. Due to our geographical location and language issues, many included guidelines are of European or American origin. The cut-off for guideline inclusion can be debated on a geographical and local level. We have included guidelines on a national level, but did not aim to include guidelines from all countries. Local hospital or county guidelines were not included. There is, however, a possibility that we have not identified all relevant guideline collections, and that some guidelines may have been overlooked. We included

Table 3 Most cited references

Reference	No guidelines citing (n=19)
Hetrick SE, McKenzie JE, <i>et al.</i> Newer generation antidepressants for depressive disorders in children and adolescents. <i>Cochrane Database</i> 2012 ⁷	9
March J, Silva S, <i>et al.</i> Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. <i>JAMA</i> 2004 ⁸	7
Bridge JA, Iyengar S, <i>et al.</i> Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. <i>JAMA</i> 2007 ⁴¹	6
NICE 2015:CG28 Depression in children and young people: identification and management in primary, community and secondary care ³³	5
Barbui C, Esposito E, Cipriani A. Selective serotonin reuptake inhibitors and risk of suicide: a systematic review of observational studies. <i>CMAJ</i> 2009 ⁴²	5

**Figure 3** Number of citations in guidelines as basis for statements on adverse effects in organ systems.

three well-known, international decision support tools as they are probably being used by professionals to an increasing extent, however, other similar tools may be commercially available. Guidelines were examined for text extracts concerning adverse effects, and the corresponding reference was noted. We cannot exclude the possibility that some statements or references may have been overlooked. Finally, we did not aim to perform a formal assessment of the overall quality of the guidelines and cannot assess whether this is correlated with the extent of adverse effects information provided in the guideline. It is possible that guideline committee mandates and local expectations varied between guidelines.

Contributors The research question was developed by all authors. All authors discussed and defined the project. TW researched the literature and made the initial assessments. All authors discussed the guidelines included in the study, including interpretation and classification of information in the guidelines. TW drafted and finalised the manuscript as lead author. SN and MK commented on the draft and revised the manuscript at all stages.

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Data availability statement Data are available on reasonable request. Tables of references used in guidelines and their corresponding text statements are available on request.

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