

## Articles

## ⊕ Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data

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### Summary

**Background** Questions concerning the safety of selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression in children led us to compare and contrast published and unpublished data on the risks and benefits of these drugs.

**Methods** We did a meta-analysis of data from randomised controlled trials that evaluated an SSRI versus placebo in participants aged 5–18 years and that were published in a peer-reviewed journal or were unpublished and included in a review by the Committee on Safety of Medicines. The following outcomes were included: remission, response to treatment, depressive symptom scores, serious adverse events, suicide-related behaviours, and discontinuation of treatment because of adverse events.

**Findings** Data for two published trials suggest that fluoxetine has a favourable risk-benefit profile, and unpublished data lend support to this finding. Published results from one trial of paroxetine and two trials of sertraline suggest equivocal or weak positive risk-benefit profiles. However, in both cases, addition of unpublished data indicates that risks outweigh benefits. Data from unpublished trials of citalopram and venlafaxine show unfavourable risk-benefit profiles.

**Interpretation** Published data suggest a favourable risk-benefit profile for some SSRIs; however, addition of unpublished data indicates that risks could outweigh benefits of these drugs (except fluoxetine) to treat depression in children and young people. Clinical guideline development and clinical decisions about treatment are largely dependent on an evidence base published in peer-reviewed journals. Non-publication of trials, for whatever reason, or the omission of important data from published trials, can lead to erroneous recommendations for treatment. Greater openness and transparency with respect to all intervention studies is needed.

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### Introduction

Researchers have estimated that 2–6% of children and adolescents in the community suffer from depression,<sup>1,2</sup> and suicide is now the third leading cause of death in 10–19 year olds.<sup>3</sup> There is, therefore, a clear need for safe and effective treatments for this group of people. Although evidence of such treatments for depression in children exists,<sup>4</sup> the lack of efficacy and poor side-effect profile for tricyclic antidepressants<sup>5</sup> leaves selective serotonin reuptake inhibitors (SSRIs) as the only class of antidepressants for pharmacological therapy.

The Expert Working Group of the Committee on Safety of Medicines (CSM) undertook a review of the efficacy and safety of SSRIs in paediatric major depressive disorder. In view of the CSM review, the Medicines and Healthcare products Regulatory Agency (MHRA) released a statement contraindicating the use of all SSRIs other than fluoxetine as new treatment for patients younger than 18 years of age with depressive illness.<sup>6</sup> This advice followed an earlier recommendation by the CSM that both paroxetine and venlafaxine should be contraindicated for use in this context.

The CSM review was initiated because of concerns about the safety of SSRIs; in particular, the possibility that these drugs might be associated with an increased risk of suicidal behaviour and that important withdrawal reactions can happen on stopping treatment.<sup>7</sup> Similar concerns in the USA about the safety of SSRIs prompted reviews by the US Food and Drug Administration<sup>8</sup> and the American College of Neuropsychopharmacology.<sup>9</sup> Although both these organisations raised concerns about the validity of the suicide data and called for further analyses, neither recommended contraindicating SSRIs.

In parallel to the reviews described above, in the UK, the National Collaborating Centre for Mental Health (NCCMH), commissioned by the National Institute for Clinical Excellence (NICE), produced a similar review restricted to published evidence for a national clinical guideline that is being developed for the management of depression in children and young people.

In view of the ongoing debate about publication bias and the serious concerns about withholding unfavourable trial data and under-reporting of adverse events,<sup>10–16</sup> we decided to investigate the risk-benefit profile of individual SSRIs using published data, unpublished data, and the combined dataset.

### Methods

The full review protocol is available from the authors and will be published in the full guideline on depression in children (for more information, see <http://www.nice.org.uk>). Briefly, we searched four electronic bibliographic databases (EMBASE, MEDLINE, PsycINFO, CINAHL) and the Cochrane Library for published trials in which any antidepressant was compared with placebo in participants aged 5–18 years who were diagnosed with depression.

Every database was searched from inception to April, 2003, and restricted to English language papers or those with English language abstracts. We found additional papers by searching the references of retrieved articles, tables of contents of relevant journals, and previous systematic reviews and meta-analyses of depression treatments; from Guideline Development Group knowledge; and by written requests to experts. Only randomised controlled trials published in peer-reviewed journals or reviewed in the CSM report<sup>17</sup> were eligible.

We assessed all published studies that met our eligibility criteria for methodological quality, with the following criteria: adequate random sequence generation, concealment of allocation, blinding, and description of withdrawals.<sup>18</sup> The adequacy of every criterion is described in the webtable (<http://image.thelancet.com/extras/04art3423webtable.pdf>). We excluded studies that were not clearly described as randomised. One of us (EB) entered study details into a Microsoft Access database (version 2000), applied the quality criteria, and extracted outcome data directly into Review Manager version 4.2.3.<sup>19</sup> Another author (CW) double-checked the assessment of study quality and all outcome data for accuracy, with disagreements resolved by discussion.

We extracted data for the following efficacy outcomes: remission and response (as long as appropriate criteria were used), and mean depression level (endpoint or change from baseline to end of treatment). With respect to safety, we restricted our analysis to serious adverse events (including related suicidal behaviour) and discontinuation attributable to any adverse event. What constituted an adverse event depended on the individual trials. We then used meta-analysis, where appropriate, to synthesise the evidence, with Review Manager.

We extracted intention-to-treat and last observation carried forward data where possible. For consistency of presentation, we entered all data into Review Manager in such a way that negative effect sizes or relative risks of less than one represented an effect that favoured the active drug—for example, we entered remission data into Review Manager as non-remission, so that a relative risk of 0.50 would be interpreted as a 50% reduction in the risk of non-remission favouring the active drug. For continuous data, we calculated the standardised mean difference and for binary data, the relative risk and the number needed to treat (benefit/harm; NNTB/NNTH).<sup>20</sup> We pooled data from more than one study with a fixed-effects meta-analysis, unless important heterogeneity was present, in which case we used a random-effects model. To detect heterogeneity, we used both the  $I^2$  test of heterogeneity<sup>21</sup> and the  $\chi^2$  test of heterogeneity ( $p < 0.10$ ), as well as visual inspection of forest plots. Where possible, NNTs were calculated from the meta-analytical estimates.

We assessed outcome data for clinical importance, taking into account both the point estimate of the effect and the associated 95% CI. We calculated the risk-benefit profile of every drug by examining the balance between risks and benefits with both relative and absolute statistics. We then extracted unpublished data from the CSM report<sup>17</sup> with our guideline methodology and then entered them directly into Review Manager and double-checked them for accuracy.

#### Role of the funding source

NICE provide general guidance for undertaking systematic reviews during the development of clinical guidelines, but had no specific role in the design, analysis, or writing of this review. A draft was seen by senior staff at NICE who agreed the review should be submitted for publication.

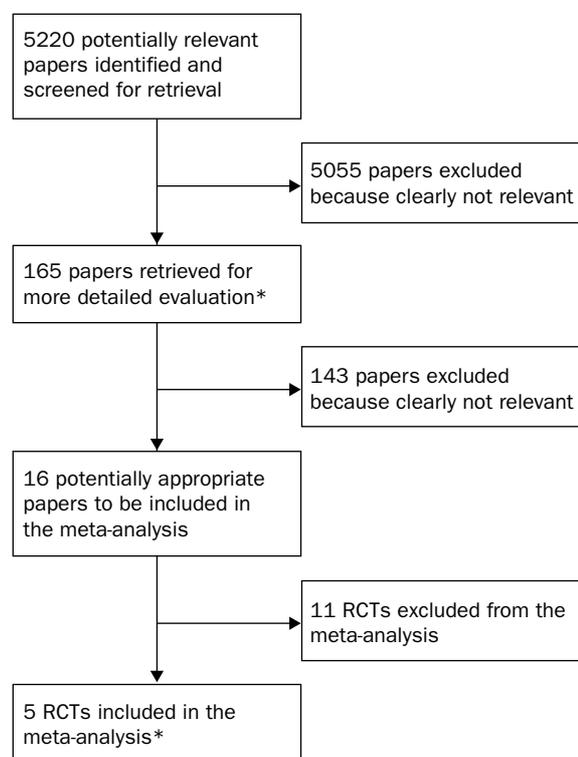
## Results

Of 5220 potentially relevant papers, 165 were retrieved for more detailed evaluation. Of these, 143 were excluded as clearly not relevant. Further inspection of the remaining papers revealed five randomised controlled trials that met our inclusion criteria (figure). The most usual reason for exclusion was that the study only compared a tricyclic antidepressant with placebo. Further details of the five included studies and reasons for excluding studies are shown in the webtable.

### Fluoxetine

For fluoxetine, we identified two published randomised controlled trials providing data for 315 participants diagnosed with major depressive disorder (aged 7–18 years).<sup>22,23</sup> Fluoxetine was more likely than placebo to bring about remission by the end of 7–8 weeks of treatment (NNTB for one extra patient to achieve remission, 6 [95% CI 4–15]; table). Fluoxetine also led to a clinically meaningful treatment response (NNTB 5 [4–13]) and a small reduction in depressive symptoms, as measured with the children's depression rating scale-revised (CDRS-R;  $n=310$ ; standardised mean difference  $-0.43$  [95% CI  $-0.65$  to  $-0.20$ ]). In terms of safety, fewer serious adverse events were reported in the fluoxetine group than in the placebo group ( $<1\%$  vs  $3.6\%$ ; NNTB 34 [95% CI NNTB 15 to  $\infty$  to NNTH 100]), although this finding should be interpreted cautiously in view of the wide confidence intervals around the effect. The rate of discontinuation because of adverse events was similar in both groups ( $5.7\%$  vs  $6.3\%$ ; NNTB 100 [NNTB 10 to  $\infty$  to NNTH 12]), but again with wide confidence intervals. No data on suicidal behaviour were reported, although no deaths were recorded in either trial.

Although no unpublished trials were found of fluoxetine, the CSM review included unpublished data



#### Trial flowchart for published data

RCT=randomised controlled trial. \*Includes trials reported in several publications.

Outcome	Publication status	Study	Active treatment (n/N)	Placebo (n/N)	Relative risk (95% CI)	
<b>Fluoxetine*</b>						
Non-remission	Published	Emslie 1997 <sup>22</sup>	33/48	37/48	0.78 (0.67–0.90)	
		Emslie 2002 <sup>23</sup>	64/109	88/110		
Non-response	Published	Emslie 2002 <sup>23</sup>	46/109	69/110	0.67 (0.52–0.87)	
Any serious adverse event	Published	Emslie 2002 <sup>23</sup>	1/109	4/110	0.25 (0.03–2.22)	
Suicidal behaviour	Unpublished†	Fluoxetine study 1 and 2	9/249	8/209	0.94 (0.37–2.40)	
Suicide attempts	Unpublished†	Fluoxetine study 1 and 2	6/249	4/209	1.26 (0.36–4.40)	
Discontinuation because of adverse events	Published	Emslie 1997 <sup>22</sup>	4/48	1/48	Random effects	
		Emslie 2002 <sup>23</sup>	5/109	9/110	1.19 (0.18–7.85)	
<b>Paroxetine‡</b>						
Non-remission	Published	Keller 2001 <sup>24</sup>	36/93	47/87	0.72 (0.52–0.99)	
Non-response	Published	Keller 2001 <sup>24</sup>	33/93	39/87	0.79 (0.55–1.13)	
		Unpublished	Paroxetine study 2 <sup>17</sup>	70/177	38/91	0.95 (0.70–1.28)
		Combined	–	–	–	0.88 (0.70–1.11)
Any serious adverse event	Published	Keller 2001 <sup>24</sup>	11/93	2/87	5.15 (1.17–22.56)	
		Unpublished	Paroxetine study 2 <sup>17</sup>	22/182	6/93	1.87 (0.79–4.46)
		Combined	–	–	–	2.55 (1.23–5.30)
Suicide attempt or ideation	Published	Keller 2001 <sup>24</sup>	5/93	0/87	10.30 (0.58–183.53)	
		Combined	–	–	–	1.51 (0.62–3.69)
Discontinuation because of adverse events	Published	Keller 2001 <sup>24</sup>	9/93	6/87	1.40 (0.52–3.78)	
<b>Sertraline§</b>						
Non-remission	Unpublished	Sertraline study 1 <sup>17</sup>	60/97	51/91	Random effects	
		Sertraline study 2 <sup>17</sup>	31/92	44/96	0.92 (0.62–1.38)	
Non-response	Published	Wagner 2003 <sup>25</sup>	74/189	92/187	0.80 (0.63–1.00)	
Any serious adverse event	Published	Wagner 2003 <sup>25</sup>	7/189	6/184	1.14 (0.39–3.32)	
Suicide attempt or ideation	Published	Wagner 2003 <sup>25</sup>	5/189	2/184	2.43 (0.48–12.39)	
Discontinuation because of adverse events	Published	Wagner 2003 <sup>25</sup>	17/189	5/187	3.36 (1.27–8.93)	
<b>Citalopram¶</b>						
Suicide attempt	Unpublished	Citalopram study 1 <sup>17</sup>	1/89	2/85	1.99 (0.83–4.77)	
		Citalopram study 2 <sup>17</sup>	14/121	5/112		
Treatment-emergent adverse events	Unpublished	Citalopram study 1 <sup>17</sup>	75/89	59/85	1.13 (1.01–1.27)	
		Citalopram study 2 <sup>17</sup>	91/121	79/112		
Discontinuation because of adverse events	Unpublished	Citalopram study 1 <sup>17</sup>	5/89	5/85	1.20 (0.62–2.35)	
		Citalopram study 2 <sup>17</sup>	13/121	9/112		
<b>Venlafaxine</b>						
Suicide-related events	Unpublished	Venlafaxine study 1 <sup>17</sup> and 2 <sup>17</sup>	14/182	1/179	13.77 (1.83–103.61)	
Discontinuation because of adverse events	Unpublished	Venlafaxine study 1 <sup>17</sup>	9/68	4/73	3.46 (1.30–9.21)	
		Venlafaxine study 2 <sup>17</sup>	8/101	1/92		

n=number of patients with outcome; N=number of patients in the group; \*Remission was defined as children's depression rating scale-revised (CDRS-R) <29; response was defined as at least 50% reduction in CDRS-R score from baseline to endpoint. †Includes one trial of obsessive-compulsive disorder. ‡Remission was defined as Hamilton depression rating scale (HDRS) ≤8; response was defined as HDRS ≤8 or at least 50% reduction in HDRS/Montgomery-Asberg depression rating scale score from baseline to endpoint. §Remission was defined as no longer meeting DSM-IV criteria for current major depressive disorder at endpoint. ¶Suicide attempt included any of the following: suicide, suicide tendency, non-accidental overdose, and thoughts of self-harm. ||Includes patients with major depressive disorder treated in a 24-week uncontrolled open-label study.

#### Benefits and harms for fluoxetine, paroxetine, sertraline, citalopram, and venlafaxine versus placebo from both published and unpublished evidence, and the combination where available

(not included in the two published trials) on suicidal behaviour. No increased risk of this behaviour (3.6% *vs* 3.8%; NNTB ∞ [95% CI NNTB 25 to ∞ to NNTH 34]) or attempted suicide (2.4% *vs* 1.9%; NNTB ∞ [NNTB 50 to ∞ to NNTH 34]) was noted in either group, but again these data are difficult to interpret in view of the wide confidence intervals (table).

In view of the evidence for efficacy and no increased risk of serious adverse effects, fluoxetine seems to have a favourable risk-benefit profile.

#### Paroxetine

We identified one published trial of paroxetine, providing data on 180 participants with major depressive disorder (aged 12–18 years).<sup>24</sup> By the end of 8 weeks of treatment, more patients given paroxetine met the criteria for remission than did those given placebo (NNTB 7 [95% CI 4–100]), although this apparent benefit of treatment is not lent clear support by response (NNTB 12 [95% CI NNTB 5 to ∞ to NNTH 20]) or a clinically meaningful reduction in depressive symptoms (Hamilton depression rating scale; n=177; standardised mean difference –0.21 [95% CI –0.51 to 0.08]; table). Moreover, patients on paroxetine had an increased risk of having a serious adverse event (11.8% *vs* 2.3%; NNTH 10 [95% CI

6–50]) and of suicidal ideation or attempting suicide (5.4% *vs* 0%; NNTH 20 [10 to ∞]).

The CSM review included two unpublished trials of paroxetine on 478 participants with major depressive disorder aged 7–18 years old (paroxetine study 2 and 3). As with the published data, the unpublished trials provided little evidence for the efficacy of paroxetine by the end of 8–12 weeks of treatment for either depressive symptoms measured with CDRS-R (n=203; standardised mean difference 0.05 [95% CI –0.22 to 0.33]) or response to treatment (NNTB 50 [95% CI NNTB 7 to ∞ to NNTH 10]). No data for remission were presented in the CSM's review. Importantly, findings of the unpublished studies did show evidence of an increased risk of serious adverse events (12.1% *vs* 6.5%; NNTH 17 [95% CI NNTH 8 to ∞ to NNTB 100]).

After pooling all available data, evidence continued to suggest that paroxetine does not improve depressive symptoms (n=380; standardised mean difference –0.07 [95% CI –0.27 to 0.13]) and has little effect on response (NNTB 20 [95% CI NNTB 7 to ∞ to NNTH 25]). Similarly, an increased risk of having a serious adverse event (12% *vs* 4.4%; NNTH 15 [95% CI 8–50]) and of suicidal ideation or attempting suicide (3.7% *vs* 2.5%; NNTH 100 [95% CI NNTH 25 to ∞ to NNTB 100])

remained with paroxetine, although the latter finding is difficult to interpret in view of the large confidence intervals.

Therefore, from published data on paroxetine, the clinical risk-benefit profile suggests that the clinical benefit may outweigh the clinical risk. However, when published and unpublished trial data were combined, little evidence remained for efficacy, and the increased risk for serious adverse events (including a small potential risk for suicidal ideation or attempts) was still present, suggesting that the risk outweighs the benefit.

### Sertraline

We identified two published randomised controlled trials of sertraline (published in one paper and reported in a combined analysis) providing data on 376 participants with major depressive disorder (aged 6–17 years).<sup>23</sup> Sertraline was more likely than placebo to bring about response by the end of 10 weeks of treatment (NNTB 10 [95% CI 5 to ∞]), but gave little improvement in mean depressive symptoms (standardised mean difference  $-0.28$  [95% CI  $-0.49$  to  $-0.08$ ]; table). No data for remission were reported. With respect to safety, slightly more sertraline-treated patients reported serious adverse events (3.7% *vs* 3.3%; NNTH ∞ [95% CI NNTH 34 to ∞ to NNTB 25]) and suicide attempts or ideation (2.6% *vs* 1.1%; NNTH 50 [NNTH 25 to ∞ to NNTB 100]); however, the wide confidence intervals make these data difficult to interpret.

The CSM review provided no new unpublished sertraline trials, but did provide additional data on remission that were not reported in the published trials (table). These findings give little support for a benefit of treatment (NNTB 34 [95% CI NNTB 5 to ∞ to NNTH 8]). Without the unpublished data, the risk-benefit profile would marginally favour use of sertraline. However, taken together, the question about efficacy highlighted by the unpublished remission data and a possible increase in suicidal ideation and attempts suggests an unfavourable risk-benefit balance.

### Citalopram

We did not identify any published randomised controlled trials of citalopram that met our review criteria. However, the CSM review provided data from two unpublished trials on 422 participants with major depressive disorder aged 7–18 years old (citalopram study 1 and 2). Efficacy data from these trials were limited, but suggested that citalopram was unlikely to produce a clinically important reduction in depressive symptoms (CDRS-R) by the end of 8–12 weeks of treatment ( $n=174$ ; standardised mean difference  $-0.34$  [95% CI  $-0.64$  to  $-0.04$ ]; table). In terms of safety, citalopram increased the risk of attempting suicide (7.1% *vs* 3.6%; NNTH 25 [95% CI NNTH 13 to ∞ to NNTB 100]) and was associated with a small increased risk of treatment-emergent adverse events (79.0% *vs* 70.1%; NNTH 12 [6–100]). With no good evidence for efficacy and the potential for increasing the risk for suicide, the risk-benefit balance is unfavourable.

### Venlafaxine

We identified one small randomised controlled trial of venlafaxine (a serotonin noradrenaline reuptake inhibitor) providing data for 40 participants with major depressive disorder aged 8–18 years.<sup>26</sup> The limited data included in the published report suggested that venlafaxine did not improve depressive symptoms (CDRS) by the end of 6 weeks of treatment ( $n=33$ ; standardised mean difference  $0.25$  [ $-0.44$  to  $0.93$ ]; table). No serious adverse events

were reported, although one patient receiving venlafaxine developed a manic episode and had to be admitted.

Two unpublished trials of venlafaxine were included in the CSM review, including 334 participants with major depressive disorder aged 6–17 years (venlafaxine study 1 and 2). Data from these trials were in keeping with the published evidence, suggesting that a clinically important improvement in depressive symptoms (CDRS-R) after treatment with venlafaxine was unlikely by the end of 8 weeks of treatment compared with placebo ( $n=334$ ; standardised mean difference  $-0.29$  [95% CI  $-0.51$  to  $-0.07$ ]). Moreover, patients on venlafaxine had an increased risk of discontinuation because of adverse events (10.1% *vs* 3.0%; NNTH 15 [95% CI 9–50]) and a raised risk of suicide-related events (7.7% *vs* 0.6%; NNTH 15 [10–34]). Again, unpublished data suggested an unfavourable risk-benefit profile.

### Discussion

Our analysis of published data from two trials<sup>22,23</sup> of fluoxetine suggested a favourable risk-benefit profile for the treatment of depression in children and young people; unpublished safety data<sup>17</sup> lent support to this view. Published data from one trial<sup>24</sup> of paroxetine and two trials<sup>25</sup> of sertraline suggested equivocal or weak positive risk-benefit profiles; however, in both cases, addition of unpublished data<sup>17</sup> indicated that risks outweighed benefits. Further, our analyses of unpublished data from two trials<sup>17</sup> of citalopram and two trials<sup>17</sup> of venlafaxine suggested unfavourable risk-benefit profiles.

Questions have arisen about the quality of evidence on SSRIs for the treatment of depression in young people, especially with respect to safety, and most importantly whether data exist to suggest that these drugs might increase suicidal ideation. The studies included in our analysis were not designed to investigate rare events, such as suicide, and as such are unlikely to have sufficient statistical power to detect potential risk. Furthermore, both relative and absolute risks calculated from low event rates are problematic and could lead to spurious confidence intervals, false-positive results, or both. Studies designed to identify rare events are needed, and the US Food and Drug Administration is currently working on guidance that will enable researchers to undertake appropriate research.<sup>8</sup> Nevertheless, in view of the high risk of suicide in this group of children and young people, the possibility that a drug might increase that risk without clear evidence of benefit, should, in our view, discourage its use.

A second important issue, raised previously,<sup>10–16</sup> is that of non-reporting of negative trials. We noted that the published data for paroxetine, sertraline, and venlafaxine provided some evidence of efficacy or little or no evidence of harm. The researchers<sup>24–26</sup> interpreted these positive risk-benefit profiles as evidence that these SSRIs are safe, effective, or both. On the basis of published evidence alone, we could have considered at least tentatively recommending use of these drugs for children and young people with depression. However, our review of combined published and unpublished data for paroxetine, sertraline, venlafaxine, and citalopram suggest that these SSRIs are not efficacious in this context. Moreover, a possible increased risk of suicidal ideation, serious adverse events, or both, although small, cannot be ignored. Without evidence for efficacy for all but one SSRI (fluoxetine), and in view of the fact that fluoxetine seems to be efficacious without showing an increased risk of suicidal ideation, our findings provide (meta-analytic) support for the conclusions reached by the MHRA. We should note,

however, that SSRIs might be safe and effective for treating other disorders seen in childhood, such as obsessive-compulsive disorder<sup>27</sup> and anxiety,<sup>28</sup> which raises the possibility that subgroups of depressed children—for example, those with comorbid anxiety—might benefit from these drugs.

The difference between the results derived from published and unpublished trials is important. In developing the NICE guideline for the treatment of depression in children and young people, we contacted all the pharmaceutical companies who manufacture antidepressants requesting unpublished data. None was forthcoming. We understand that some trials might have been submitted for publication, and that negative results could be more difficult to get published. Nevertheless, the possibility remains, that was raised elsewhere,<sup>10</sup> that researchers writing these reports might not have been able to disclose the findings from negative unpublished trials.

The clinical guideline programme developed by NICE is underpinned by an evidence-base published in peer-reviewed journals. Although NICE accept submissions of evidence from stakeholders, which might not be published, this acceptance is only done on the understanding that data are made publicly available.<sup>29</sup> Drug sponsors who withhold trial data (or do not make full trial reports available) undermine the guideline programme, which can ultimately lead to recommendations for treatments that are ineffective, cause harm, or both. Others have suggested that the pharmaceutical industry needs greater regulation, and in particular that all trial data—whether published or unpublished—should be fully accessible.<sup>11</sup> In any event, greater cooperation and openness between the pharmaceutical industry and guideline developers, including gaining access to unpublished full trial reports, is clearly a matter of some urgency; this access would allow critical appraisal of study methodology and inclusion of unpublished data that meet recognised standards of quality. The fact that the drugs reviewed here have previously been recommended for use in children on the basis of a very restricted published evidence base can only serve to increase that sense of urgency.

#### Contributors

P Fonagy had the idea for the review. All authors helped to design the review and contributed to interpretation of results. C Whittington and E Boddington developed the search strategy and extracted and analysed data. C Whittington and T Kendall wrote the paper, with contributions from all authors.

#### Conflict of interest statement

DC has a few shares in GlaxoSmithKline, the manufacturer of paroxetine. All authors are members of the Guideline Development Group for the Depression in Children Guideline currently being developed by the NCCMH and funded by NICE. All authors had full access to all data and had responsibility for the decision to submit for publication.

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