Suicidal behaviour in youths with depression treated with new-generation antidepressants

Meta-analysis

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Background   Concern exists that antidepressants can cause suicidality in youths with depression.

Aims   To determine the pooled risk of self-harm and suicidal behaviour from randomised trials of newer antidepressants.

Method   A meta-analysis was carried out to calculate odds ratios for the combined data.

Results   Self-harm or suicide-related events occurred in 71 of 1487 (4.8%) of depressed youths treated with antidepressants v. 38 of 1254 (3.0%) of those given placebo (fixed effects odds ratio 1.70, 95% CI 1.13–2.54, P=0.01). There was a trend for individual suicidal thoughts, attempts and self-harm to occur more often in youths taking antidepressants than in those given placebo, but none of these differences was statistically significant.

Conclusions   Antidepressants may cause a small short-term risk of self-harm or suicidal events in children and adolescents with major depressive disorder.

In 2003 the Committee on Safety of Medicines (CSM) in the UK advised that the majority of the selective serotonin re-uptake inhibitors (SSRIs) and another new-generation antidepressant, venlafaxine, were not suitable to be used as antidepressants by those aged under 18 years (see the safety information messages issued in 2003 by the Medicines and Healthcare Products Regulatory Agency; http://www.mhra.gov.uk). This warning was based on a review of reports from controlled trials that had been submitted by pharmaceutical companies, published in journals, or both. The review found that for many of these drugs efficacy was not clearly demonstrated. It also found that for several of them there was an increased rate of self-harm and suicidal thoughts in participants given antidepressants relative to those given placebo. The CSM concluded that with the exception of fluoxetine the balance of risks and benefits was unfavourable in young people under the age of 18 years. Conversely, in 2004 a further review by the CSM of the use of SSRIs in adults found the balance of risks and benefits to be in favour of SSRIs. These conclusions have also been supported by the National Institute for Clinical Excellence findings on the treatment of adult depression, whereby SSRIs are recommended for the treatment of moderate to severe adult depression (National Collaborating Centre for Mental Health, 2004).

The CSM's warning has generated a great deal of discussion, and the Committee's conclusion that antidepressants could increase the risk of suicidal behaviour in young people has been challenged. For example, a preliminary report from the American College of Neuropsychopharmacology Task Force on the SSRIs and Suicidal Behaviour in Youth (American College of Neuropsychopharmacology, 2004) pointed out that when the SSRI trials were considered individually the risk of suicidal behaviour or suicidal ideation was not significantly increased for any drug. However, a single study often cannot detect or exclude with certainty a modest, but nevertheless clinically relevant, difference between the side-effects of two treatments. Most clinical trials are powered to detect the effects of the intervention on clinical outcomes, not on side-effects, which are often relatively rare. The meta-analytic approach offers a way forward because data from patients in trials evaluating the effects of a similar drug in several smaller, but comparable, studies can be considered.

A number of meta-analyses of the antidepressant data have now been published. Jureidini et al (2004) pooled outcome measures from five published studies and found a small effect size for the drugs (0.26, 95% CI 0.13–0.40); however, they concluded that this was unlikely to be clinically significant, and also questioned the efficacy of fluoxetine. These authors did not meta-analyse the suicidality data, but raised concerns about the underreporting of serious adverse events. Whittington et al (2004) included the unpublished data from the CSM report in their review: they pooled results from individual drugs, and found that when the unpublished data were added, the risks outweighed the benefits for the new antidepressants, with the exception of fluoxetine. In that paper Whittington et al calculated the relative risk for suicidality for individual drugs, and found the greatest risk was for venlafaxine (RR=13.77, 95% CI 1.83–103.61 for suicide-related events) and the least risk was for fluoxetine (RR=1.26, 95% CI 0.36–4.40 for attempts; RR=0.94, 95% CI 0.37–2.40 for suicidal behaviour). The latter authors did not amalgamate these results, but more recently Gunnell & Ashby (2004) pooled the suicidality data from the CSM and found the overall odds ratio of suicidal thoughts or behaviour was 1.66 (95% CI 0.83–3.50). This result, however, does not discriminate between suicide attempts and ideation, as Gunnell & Ashby included the data for sertraline, which combined attempts and ideation; their review also excluded venlafaxine.

The most comprehensive meta-analysis of the suicidality data that has taken place so far has been by the US Food and Drug Administration (FDA). Following the CSM report, the FDA meta-analysed the published and unpublished results. The initial analysis examined all possible suicide-related events. In addition, because of concerns regarding misclassification of cases,

the FDA identified all possible events from the original data and reclassified them, in order to perform a further analysis (Food and Drug Administration Center for Drug Evaluation and Research, 2004a). After re-classification, the relative risk (fixed effects model) for definitive suicidal behaviour and ideation (excluding non-suicidal self-harm) for all SSRI trials in major depression was 1.41 (95% CI 0.84–2.37), but this increased to 1.71 (95% CI 1.05–2.77) when other newer-generation antidepressants (venlafaxine, mirtazapine and nefazodone) were also considered. For non-major depression trials the risk was higher still (RR=2.17, 95% CI 0.72–6.48) and the pooled estimate for all trials was 1.78 (95% CI 1.14–2.77).

In addition, the FDA analysed the relative risks (fixed effects model) for a variety of outcomes including definitive suicidal behaviour (suicide attempt or preparatory action), ideation and self-harm (Food and Drug Administration Center for Drug Evaluation and Research, 2004b). For the combined SSRI depression trials these results were highest for actual suicidal behaviour (RR=1.83, 95% CI 0.89–3.77), but did not show an excess risk for ideation (RR=1.0, 95% CI 0.52–1.94) and showed little excess risk for self-harm (RR=1.20, 95% CI 0.35–4.13).

When individual drugs were considered in depression (Food and Drug Administration Center for Drug Evaluation and Research, 2004c), venlafaxine had the highest risk for both suicidal behaviour (RR=2.77, 95% CI 0.11–67.10) and ideation (RR=7.89, 95% CI 0.99–62.59), and nefazodone had the least risk (no events). However, the increased risk of suicidal ideation accounted for most of the overall excess risk associated with venlafaxine, rather than actual suicidal behaviour. This was also the case with sertraline and mirtazapine, but the actual numbers involved were small. For venlafaxine (n=182), there were seven cases of suicidal thoughts in the venlafaxine group and one case each of suicidal behaviour and self-harm; there were no suicide-related events for placebo (n=179). Sertraline showed the next highest risk for both suicidal behaviour and ideation (RR=2.16, 95% CI 0.48–9.62). Again, most of this risk was accounted for by ideation (RR=3.88, 95% CI 0.44–34.54); there were three accounts of suicidal thoughts in the sertraline group, n=189 (none for placebo, n=184) and two cases of suicidal behaviour in each

group. There was no case of self-harm. The risk for mirtazapine was also driven by thoughts (RR=1.58, 95% CI 0.06–38.37), which was accounted for by one case (n=170). There were no cases of suicidal behaviour or self-harm and no suicide-related events with placebo (n=89).

Citalopram, paroxetine and fluoxetine trials demonstrated suicidal behaviour more frequently than ideation. Of these drugs, paroxetine was associated with the highest risk (RR=2.30, 95% CI 0.67–7.93): there were 9 cases of suicidal behaviour with the drug (n=377) v. 2 with placebo (n=285). With regard to self-harm, a total of 10 events occurred in 6 of the 15 major depression trials (citalopram, venlafaxine, nefazodone and 3 paroxetine trials). Again, paroxetine had the most events (3 v. 1 for placebo).

As a result of this analysis the FDA issued a 'black box' warning for all the new-generation antidepressants, including fluoxetine; however, this organisation stopped short of contraindicating the drugs on the grounds that access to these therapies was important to those who could benefit (Food and Drug Administration Center for Drug Evaluation and Research, 2004d).

Within its summary of the adult trials, the CSM also went on to analyse further the child suicidality data (Medicines and Healthcare Products Regulatory Agency, 2004). The Committee performed meta-analyses for individual drugs for all suicide-related events, and found the highest risk was for venlafaxine (OR=4.5, 95% CI 1.4–15.0, P<0.01), and the lowest was for citalopram (OR=1.2, 95% CI 0.6–2.5, P=0.55). The data for all drugs were not pooled, and individual suicide-related events were not examined separately.

This CSM review also included data from a new trial of fluoxetine that was not included in the FDA analysis. The Treatment for Adolescents with Depression Study (TADS) is the largest randomised controlled trial to date of adolescents with major depression (Treatment for Adolescents with Depression Study Team, 2004). It included treatment with fluoxetine alone, cognitive–behavioural therapy alone, combined treatment, and placebo. It was not industry-sponsored and was the first to prospectively define suicide-related events, thus addressing the principal criticisms of earlier studies. The findings of the TADS trial on suicidality are therefore important to consider when addressing the risk and

benefits of antidepressants in youths. The CSM analysis found that the addition of the TADS suicidality data contributed to an increased risk of suicide-related events (OR=1.1, 95% CI 0.4–3.1 v. previous OR=1.6, 95% CI 0.9–3.1); however, the Committee concluded that the benefits of fluoxetine still outweighed the risks.

Although the CSM reported that in adult depression SSRIs remain beneficial, the conclusions of the adult data have also been challenged. Gunnell et al (2005) performed a meta-analysis of data from the Medicines and Healthcare Products Regulatory Agency of published and unpublished randomised controlled trials (RCTs) of SSRIs compared with placebo. Although they found no evidence that SSRIs increased the risk of suicide or suicidal thoughts when compared with placebo, they found weak evidence for an increased risk of self-harm (OR=1.57, 95% CI 0.99–2.55). Fergusson et al (2005) meta-analysed published RCTs of SSRIs used in any disorder and found an increase in suicide attempts for patients receiving SSRIs when compared with placebo (OR=2.28, 95% CI 1.14–4.55) or when compared with therapeutic interventions other than tricyclic antidepressants (OR=1.94, 95% CI 1.06–3.57). Therefore, the safety profile of SSRIs in adults is also currently unresolved and the FDA has now ordered a further review of the adult data (Food and Drug Administration Center for Drug Evaluation and Research, 2005).

In this meta-analysis we re-examine the suicidality data on children and adolescents from the CSM. Combined results for the drugs are presented for all self-harm and suicide-related events; in addition, the available data on suicidal ideation and attempts as well as self-harm are analysed separately where possible, in order to differentiate the risks for behaviours and thoughts. We include the TADS data, which were not considered in the original FDA analysis; however, data are extracted from the fluoxetine-alone and placebo arms of the trial only, unlike the CSM analysis, which pooled data from both fluoxetine arms, including the arm with fluoxetine and cognitive–behavioural therapy. The rates of suicidality for the latter arm are not included as these results cannot be directly compared with the other trials without psychological treatment, particularly as the TADS results suggest that cognitive–behavioural therapy has a protective effect on suicidality.

METHOD

Sources of data

Not all of the trials of the new-generation antidepressants have been published and we did not have access to the primary data from the unpublished trials. The primary source of data in our meta-analysis was therefore the data published by the CSM. These data were arranged in three levels of detail: we used data from level 3, the most detailed. In the case of venlafaxine we used the data from level 2, as this provided more detail on suicide-related events. Additional information on events was supplemented by the information from published reports, including the GlaxoSmithKline website for paroxetine (http://www.gsk.com/ media/paroxetine. htm). A further search was made to ascertain whether any other new RCTs had been published since the CSM and FDA reviews. Medline and PsycINFO databases were searched for the period January 2004 to August 2005 using the terms ANTIDEPRESSANT, CHILD, ADOLESCENT, DEPRESSION and TRIAL, and leading researchers in the field were also contacted. A further search was performed of the Cochrane Database. No new relevant trial was found.

Study and participant characteristics

The studies included in our meta-analysis were all randomised, placebo-controlled clinical trials with an active treatment phase of 8–12 weeks. The participants were all diagnosed as having a major depressive disorder. The antidepressants evaluated were fluoxetine (three published trials, one unpublished trial and also one trial of obsessive–compulsive disorder that was included in the CSM data), sertraline (two trials, published as one), citalopram (two trials, one published), paroxetine (three trials, one published, all available online), venlafaxine (two unpublished trials) and mirtazapine (two unpublished trials). All of the antidepressants were evaluated in both children and adolescents, with an age range of 6–18 years. Some of the antidepressants were evaluated in trials that included both children and adolescents in the same trial. For other antidepressants (e.g. citalopram), children and adolescents entered separate trials.

Few other details were available in the CSM summaries about the characteristics of the participants in the unpublished trials. However, examination of the published papers (Emslie *et al*, 1997, 2002; Keller *et al*, 2001; Wagner *et al*, 2003, 2004; Treatment for Adolescents with Depression Study Team, 2004) and the GlaxoSmithKline website for paroxetine showed that in most trials rigorous exclusion criteria were applied, particularly with regard to suicidality. In both the sertraline trials (Wagner *et al*, 2003), the published citalopram study (Wagner *et al*, 2004) and one of the paroxetine trials (Keller *et al*, 2001) youngsters who had made a suicidal attempt or who were deemed at risk of making one were excluded. Likewise, the TADS study (Treatment for Adolescents with Depression Study Team, 2004) excluded patients if they were deemed to be 'high risk' because of a suicide attempt requiring medical attention within the previous 6 months, clear intent or an active plan to attempt suicide, or suicidal ideation with a disorganised family unable to guarantee monitoring. The remaining paroxetine studies excluded people who were a current suicide risk (see the GlaxoSmithKline website), as did one of the fluoxetine trials (Emslie *et al*, 2002). The remaining published fluoxetine trial did not list suicidality as an exclusion criterion (Emslie *et al*, 1997).

Definition of suicidal behaviour

The trials did not all use the same definition of suicidal behaviour, and only the TADS research prospectively defined suicidality. The published TADS data define suicide-related events as worsening suicidal ideation, a suicide attempt, or both. Non-suicidal self-harm was included in the definition of harm-related adverse events, which also included harm to others, and was therefore not included in our analysis. In the CSM report the studies of sertraline conflated suicidal behaviour and suicidal thinking, whereas the level-3 studies of venlafaxine reported only suicidal thinking and the paroxetine data commented non-specifically on 'emotional lability' and cases 'possibly related to suicidality'. In our analyses we focused initially therefore on the total number of all suicide-related events itemised in the CSM (attempted suicide, thoughts or self-harm) and TADS reports. A second analysis then considered attempted suicide, self-harm and suicidal thinking as individual outcomes, for those antidepressants for which separate data were available. Additional information on

individual events was added from the published papers and the paroxetine online data. Hence, the sertraline study (Wagner *et al*, 2003) described separate suicide attempts which were included in the analysis. The GlaxoSmithKline paroxetine website provides case summaries of all serious adverse events, and further separate events were extracted from these data; however, as the description of the events was not always clear, the only events recorded were under the category of suicide attempts (defined as a clear description of an intentional overdose, or serious preparations for a suicide attempt).

Statistical analysis

The data were analysed using a user-written Stata procedure (Bradburn *et al*, 1999).

RESULTS

Tests of homogeneity (DerSimonian & Laird, 1986) were carried out on each end-point or outcome to examine whether the treatment effect differed between compounds. There was little evidence of heterogeneity between drugs for all self-harm or suicide-related events ($\chi^2_5=6.52$, $P=0.259$), suicidal thoughts ($\chi^2_3=4.77$, $P=0.189$), self-harm ($\chi^2_2=1.86$, $P=0.395$) or suicidal attempts ($\chi^2_1=0.33$, $P=0.829$). A fixed effects estimate of the pooled odds ratio has been presented based on the Mantel–Haenszel method (Sutton *et al*, 2000) in Table 1. As the test of heterogeneity is known to lack power, the DerSimonian & Laird random effects estimate in which allowance is made for heterogeneity between compounds, is included, where the estimated between study variance was non-zero.

No suicide was reported in either trial arm for any of the compounds. Table 1 shows the presence or absence of all self-harm or suicide-related events on active and placebo treatments. Self-harm or suicide-related events occurred in 71 of 1487 (4.8%) young people with depression treated with antidepressants and in 38 of 1254 (3.0%) treated with placebo. If this result is expressed in terms of the number needed to treat (NNT), 57 young people would need to be treated with antidepressants in order for 1 to experience one additional such event. In the fixed effects analysis patients on the active drugs were significantly more likely to have

a self-harm or suicide-related event (OR=1.70, 95% CI 1.13–2.54, P=0.010; Fig. 1). The random effects analysis gave a non-significant odds ratio of 1.58 (95% CI 0.94–2.88, P=0.083).

Table 1 also gives results for suicidal thoughts, self-harm and suicide attempts. Suicidal thoughts occurred in 9 of 738 (1.2%) young people with depression treated with antidepressants (citalopram, mirtazapine, sertraline and venlafaxine) and in 5 of 634 (0.8%) treated with placebo, with an odds ratio of active drug compared with placebo of 1.45 (95% CI 0.54–3.88, P=0.46, NNT=232). Self-harm occurred in 19 of 569 (3.3%) young people with depression treated with antidepressants (citalopram, mirtazapine, sertraline) and in 12 of 469 (2.6%) treated with placebo (OR=1.44, 95% CI 0.70–2.97, P=0.325, NNT=128). Suicide attempts occurred in 19 of 992 (1.9%) young people with depression treated with antidepressants (mirtazapine, fluoxetine, paroxetine, sertraline) and in 9 of 773 (1.2%) treated with placebo (OR=1.70, 95% CI 0.76–3.81, P=0.194, NNT=133).

DISCUSSION

The results show that, overall, total events (suicidal thoughts, self-harm or attempted suicide) occurred more often in young people prescribed antidepressants than in those given placebo. The odds ratio of 1.70 represents a small, statistically significant increase. Thus, in a sample of 100 young people being treated with antidepressants, approximately 5 would demonstrate some form of self-harm or suicidality, as opposed to 3 on placebo. However, a random effects analysis gives a more equivocal result. The overall odds ratio found in this analysis is similar to that found in the FDA analysis. The risk ratio for definitive suicidal behaviour or ideation in all major depression trials after reclassification was 1.7 (95% CI 1.05–2.77). This definition did not include non-suicidal self-harm; however, an earlier FDA analysis of all possible suicide-related events (Food and Drug Administration Center for Drug Evaluation and Research, 2004a) found a slightly higher relative risk of 1.81 (95% CI 1.19–2.77).

There was also a trend for all events to be increased, although the individual results for suicidal thinking, self-harm or suicide attempts did not reach statistical

Table I Self-harm and suicide-related events and odds ratios in randomised placebo-controlled trials of antidepressants in children and adolescents with depression

Drug	Active drug n/N (%)		Placebo n/N (%)		OR	(95% CI)	
All self-harm and suicide-related events							
Paroxetine	14/378	(3.7)	7/285	(2.5)	1.53	(0.61–3.84)	
Citalopram	19/210	(9.0)	15/197	(7.6)	1.21	(0.60–2.45)	
Mirtazapine	1/170	(0.6)	1/88	(1.1)	0.51	(0.03–8.33)	
Sertraline	5/189	(2.6)	2/184	(1.1)	2.47	(0.47–12.9)	
Venlafaxine	14/182	(7.7)	1/179	(0.6)	14.83	(1.93–114.0)	
Fluoxetine	18/358	(5.0)	12/321	(3.7)	1.36	(0.65–2.88)	
Combined	71/1487	(4.8)	38/1254	(3.0)	1.70	(1.13–2.54)	F
					1.58	(0.94–2.88)	R
Suicidal thoughts							
Citalopram	2/210	(1.0)	5/197	(2.5)	0.37	(0.07–1.93)	
Mirtazapine	1/170	(0.6)	0/88	(0)	1.57	(0.06–38.9)	
Sertraline[1]	3/189	(1.6)	0/184	(0)	6.92	(0.36–135.0)	
Venlafaxine[1]	3/169	(1.8)	0/165	(0)	6.96	(0.36–135.8)	
Combined	9/738	(1.2)	5/634	(0.8)	1.45	(0.54–3.88)	F
					1.63	(0.32–8.39)	R
Self-harm							
Citalopram	17/210	(8.1)	10/197	(5.1)	1.65	(0.74–3.69)	
Mirtazapine	0/170	(0)	1/88	(1.1)	0.17	(0.01–4.24)	
Sertraline[1]	2/189	(1.1)	1/184	(0.5)	1.96	(0.18–21.8)	
Combined	19/569	(3.3)	12/469	(2.6)	1.44	(0.70–2.97)	F
Suicide attempts							
Mirtazapine	0/170	(0)	0/88	(0)			
Fluoxetine	8/358	(2.2)	4/321	(1.2)	1.81	(0.54–6.07)	
Paroxetine	9/275	(3.3)	3/180	(1.7)	2.00	(0.53–7.48)	
Sertraline	2/189	(1.1)	2/184	(1.1)	0.97	(0.14–6.98)	
Combined	19/992	(1.9)	9/773	(1.2)	1.70	(0.76–3.81)	F

F, fixed effects (Mantel–Haenszel); R, random effects (DerSimonian & Laird, 1986).
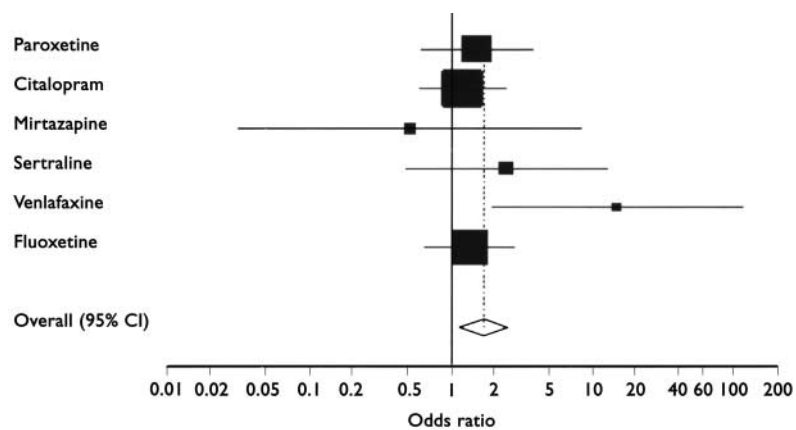1. Based on discontinuation data.

Fig. I Odds ratios for all self-harm and suicide-related events.

significance at the conventional level. The overall increase in risk for suicidal thinking was small, although venlafaxine and sertraline were associated with a higher risk, which was reflected in higher overall risk for both these drugs, as with the FDA analysis. Sertraline also showed an excess risk of self-harm, but no increased risk of suicide attempts, but this was based on very few events. Mirtazapine was associated with an overall risk reduction, but this was based on few events and relatively low study numbers. Fluoxetine showed an overall small risk of any event, and this was lower than the risk found in the CSM analysis (RR=1.6, 95% CI 0.9–3.1). However, the risk of attempts was higher and similar to that of paroxetine. A similar pattern was seen in the FDA analysis, although the relative risks were higher (suicidal behaviour: paroxetine, RR=2.30, 95% CI 0.67–7.93; fluoxetine, RR=2.15, 95% CI 0.50–9.26; Food and Drug Administration Center for Drug Evaluation and Research, 2004c). Citalopram appeared to confer a beneficial effect on suicidal thoughts but an increased risk of self-harm; this conflicts with the FDA analysis which reported equal numbers (2) of self-harm events in both groups. However, the results for individual drugs and events need to be interpreted cautiously, because they are based on small numbers with relatively few incidences of adverse events and there is no statistical evidence of heterogeneity between studies.

In interpreting these results overall a number of other issues need to be considered. First, our analyses were largely based on the information provided by the CSM. Because not all of the trials have been published we were unable to examine all the original reports, hence it is difficult to assess the quality of the unpublished trials. Second, when information was available from published trials it was clear that in many the entry criteria excluded children and adolescents if they had previously attempted suicide and/or were actively suicidal (Emslie et al, 2002; Keller et al, 2001; Wagner et al, 2003, 2004; Treatment for Adolescents with Depression Study Team, 2004; see also the GlaxoSmithKline website). Affective disorder is the most common psychiatric disorder in adolescence associated with both completed suicide and suicidal behaviour (Shaffer et al, 1996). A British epidemiological study found that 41.2% of adolescents with depression had tried to harm, hurt or kill themselves (Meltzer et al, 2001). Therefore, the results of the trials included in our study and previous meta-analyses may not generalise to routine clinical practice, as many depressed suicidal children would have been excluded. Third, most of these trials (with the exception of TADS) were not designed to measure suicidality prospectively, and the descriptions of suicide-related events are sparse and lacking in detail, making interpretation difficult (Food and Drug Administration Center for Drug Evaluation and Research, 2004e). Finally, comparison between studies is difficult because of numerous methodological differences; subsequent reviewers have commented on the problems with trial methodology and consequently the difficulties in drawing conclusions from the available data (Cheung et al, 2005). Hence, any conclusion on the basis of this data with regard to suicidality needs to be made with caution.

The results of this meta-analysis and others must therefore be seen as preliminary. Further studies are urgently required that are prospectively designed to measure suicidality, adequately distinguish self-harm, thoughts and attempts, and do not exclude the most depressed suicidal children. In the meantime, practitioners treating depressed children and adolescents with new-generation antidepressants should carefully monitor suicidal risk. It is important to bear in mind, however, that juvenile depression is itself a strong risk factor for both attempted and completed suicide (Marttunen et al, 1993; Rao et al, 1993; Harrington et al, 1994). Therefore, any decision to use antidepressants needs to balance the known risk of increased suicidality secondary to a depressive disorder against the apparent increased risk that may be attributed to the use of the antidepressant itself. Moreover, the results of our meta-analysis indicate that the absolute risk of suicidal events in patients taking antidepressants is small, and there was no recorded case of completed suicide. The apparent increase in suicide-related events found in this review needs therefore to be seen within the broader context of the management of a disorder that is potentially life-threatening and disabling.

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