

# Review: most selective serotonin reuptake inhibitors lead to adverse events that appear to outweigh the benefits in children

Whittington CJ, Kendall T, Fonagy P, *et al*. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet* 2004;**363**:1341–5.

## Q Are selective serotonin reuptake inhibitors (SSRIs) safe for treating depression in children?

### METHODS



**Data sources:** Medline, CINAHL, EMBASE/Excerpta Medica, and PsycINFO (to April 2003); *Cochrane Library*; reference lists; tables of contents; previous systematic reviews; Guideline Development Group information; and written requests to experts.



**Study selection and assessment:** English language RCTs (or RCTs with English abstracts) that compared SSRIs with placebo in children (5–18 y) with depression; had adequate blinding, concealed allocation, and description of withdrawals; and were published in peer reviewed journals or reviewed in a report by the Committee on Safety of Medicines.



**Outcomes:** adverse events, remission, response, and mean depression level.

### MAIN RESULTS

5 published and 9 unpublished RCTs were reviewed. Fluoxetine showed a benefit for remission and response, and the adverse event data were not statistically significant (table). Paroxetine increased remission but not response and increased serious adverse events (table). Sertraline did not show a benefit for remission and led to more dropouts because of adverse events (table); a treatment effect for response had borderline significance. Citalopram led to a small reduction in depressive symptoms, and no effect was seen for venlafaxine; adverse events were increased for both drugs (table).

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### CONCLUSIONS

In children with depression, fluoxetine improves symptoms without increasing adverse events. For paroxetine, sertraline, venlafaxine, and citalopram, the risks appear to outweigh the benefits.

### Commentary

The review by Whittington *et al* tackles 2 important issues simultaneously: the questionable safety of SSRIs in children and young people and the often overlooked problem of publication bias.

With regard to safety, fluoxetine appears to be the only SSRI with a relative risk reduction of “serious adverse events,” although this finding is questionable given that the 95% confidence intervals (CIs) cross zero. Although fluoxetine is also associated with relative risk increases for the outcomes “suicide attempt” and “discontinuation,” the CIs for both these outcomes also cross zero, making firm conclusions about the safety of fluoxetine difficult. On the other hand, for each of the remaining 4 SSRIs, significant relative risk increases are identified without any clear evidence of benefits such as improved remission rates or depression ratings.

With regard to publication bias, what is striking about this review is the different conclusions drawn when unpublished trials are combined with published trials. In particular, as is the case for paroxetine and sertraline, the risk-benefit profiles that are ambivalent or weakly positive (profiles that do not necessarily detract from prescribing these drugs for children and young people) become somewhat negative once the unpublished data are added. Moreover, the reasons for “non-publication bias” are important and warrant identification and balance against the recommendations for such treatments, which are potentially ineffective, cause harm, or both.

On a methodological point, it is worth noting the lack of uniform outcome definitions across the studies reviewed (eg, remission). It would be useful for study authors to use their influence to call for standardised outcome measures. Furthermore, as only depression outcomes were explored, it is worth considering the possibility that additional outcomes, such as changes in commonly occurring comorbid anxiety, educational performance, or family dynamics, might be considered in future reviews.

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Selective serotonin reuptake inhibitors (SSRIs) v placebo for depression in children\*

SSRI	Outcomes at ≥12 weeks (number of studies)	Event rates	RRR (95% CI)	NNT (CI)
Fluoxetine	Serious adverse events (1)	0.9% v 3.6%	75% (–122 to 97)	Not significant
			<b>Weighted RRI (CI)</b>	<b>NNH</b>
Paroxetine	Suicide attempt (1)†	2.4% v 1.9%	26% (–64 to 340)	Not significant
	Discontinuation (2)‡	5.7% v 6.3%	19% (–82 to 685)	Not significant
	Serious adverse events (2)	1.2% v 4.4%	155% (23 to 430)	15 (8 to 50)
Sertraline	Suicide attempt/ideation (2)	3.7% v 2.5%	51% (–38 to 269)	Not significant
	Discontinuation (1)	9.7% v 6.9%	40% (–48 to 278)	Not significant
	Serious adverse events (1)	3.7% v 3.3%	14% (–61 to 232)	Not significant
Citalopram	Suicide attempt/ideation (1)	2.6% v 1.1%	143% (–52 to 1139)	Not significant
	Discontinuation (1)	9.0% v 2.7%	236% (27 to 793)	16 (9 to 59)§
	Suicide attempt (2)	7.1% v 3.6%	99% (–17 to 377)	Not significant
Venlafaxine	Treatment emergent adverse events (2)	7.9% v 7.0%	13% (1 to 27)	12 (6 to 100)
	Discontinuation (2)	8.6% v 7.1%	20% (–38 to 135)	Not significant
	Suicide related events (2)	7.7% v 0.6%	1277% (83 to 10261)	15 (10 to 34)
	Discontinuation (2)	10% v 3.0%	246% (30 to 821)	15 (9 to 50)

\*Abbreviations defined in glossary.

†Includes unpublished data.

‡Studies combined using random effects model; fixed effects model used for all others.

§Calculated from data in article.