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 Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data.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

Clinical impact ratings Mental health ★★★★★☆ Psychiatry ★★★★★☆ Paediatrics ★★★★★☆
GP/FP/Primary care ★★★★★☆

Q Are selective serotonin reuptake inhibitors (SSRIs) safe and effective 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 randomised controlled trials (RCTs) or RCTs with English abstracts that compared SSRIs with placebo in children (5–18 y) with depression; had adequate blinding, concealed allocation, and a description of withdrawals; and were published in peer reviewed journals or reviewed by the Committee on Safety of Medicines.

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

MAIN RESULTS

6 published and 6 unpublished RCTs were reviewed.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 venlafaxine had no effect; adverse events were increased for both drugs (table).

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.

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Commentary

Whittington *et al* have highlighted 3 key issues in the evaluation of the evidence base for antidepressant treatment in children and adolescents: effectiveness, safety, and the role of access to published versus unpublished data. A consistently high placebo response is noted, which emphasises the importance of undertaking controlled clinical trials for antidepressants in young people rather than assuming efficacy based on adult studies. Adverse effects also appear to be higher in children. The authors concluded that except for fluoxetine, the evidence does not support a favourable risk-benefit balance for SSRIs in child and adolescent depression. In addition to including unpublished negative trials, Whittington *et al* also criticised the interpretation of marginal results to produce apparently positive published studies (eg, sertraline, paroxetine) which, on reanalysis, do not show effectiveness and for which the impact of the risk-benefit ratio has also been ignored. The authors' conclusions are essentially the same as those reached by regulatory agencies that had access to the full data set^{1,2} and by other authors who have reviewed the published studies.^{3,4} This review illustrates the problem of publication bias in "evidence-biased medicine,"⁵ which includes biased interpretation of published data in favour of the drug and inability to weigh the full body of evidence because of lack of access to unpublished data.

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- University of British Columbia, Vancouver, British Columbia, Canada
- Medicines and Health Care Products Regulatory Agency. Use of Selective Serotonin Reuptake Inhibitors (SSRIs) in children and adolescents with major depressive disorder (MDD)—only fluoxetine (Prozac) shown to have a favourable balance of risks and benefits for the treatment of MDD in the under 18s, Dec 10, 2003. <http://www.mhra.gov.uk/news/2003.htm> (accessed 27 Oct 2004).
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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 AE (1)	0.9% v 3.6%	75% (–122 to 97)	NS
			Weighted RRI (CI)	NNH (CI)
	Suicide attempt (1)†	2.4% v 1.9%	26% (–64 to 340)	NS
	Discontinuation (2)‡	5.7% v 6.3%	19% (–82 to 685)	NS
Paroxetine	Serious AE (2)	12% v 4.4%	155% (23 to 430)	15 (8 to 50)
	Suicide attempt/ideation (2)	3.7% v 2.5%	51% (–38 to 269)	NS
	Discontinuation (1)	9.7% v 6.9%	40% (–48 to 278)	NS
Sertraline	Serious AE (2)	3.7% v 3.3%	14% (–61 to 232)	NS
	Suicide attempt/ideation (2)	2.6% v 1.1%	143% (–52 to 1139)	NS
	Discontinuation (2)	9.0% v 2.7%	236% (27 to 793)	17 (9 to 50)§
Citalopram	Suicide attempt (2)	7.1% v 3.6%	99% (–17 to 377)	NS
	Treatment emergent AE (2)	79% v 70%	13% (1 to 27)	12 (6 to 100)
	Discontinuation (2)	8.6% v 7.1%	20% (–38 to 135)	NS
Venlafaxine¶	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)

*AE = adverse events; NS = not significant. Other abbreviations defined in glossary. †Includes unpublished data. ‡Studies combined using random effects model; fixed effects model used for all others. §Data supplied by author. ¶Serotonin and noradrenaline reuptake inhibitor.