

# Sertraline improves symptoms in children and adolescents with major depressive disorder

Wagner KD, Ambrosini P, Rynn M, *et al.* Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials. *JAMA* 2003;**290**:1033–41.

## Q What are the effects of sertraline in children and adolescents with major depressive disorder (MDD)?

### METHODS

	<b>Design:</b> Two randomised controlled trials.
	<b>Allocation:</b> Concealed.
	<b>Blinding:</b> Double blinded (clinicians, patients).
	<b>Follow up period:</b> 10 weeks.
	<b>Setting:</b> Two identically designed trials run concurrently in 53 hospital, general practice and academic centres in USA, India, Canada, Costa Rica, and Mexico; enrolment December 1999 to May 2001.
	<b>Patients:</b> 376 children and adolescents aged 6 to 17 years with a current episode of MDD (DSM-IV criteria) lasting at least 6 weeks, and scoring at least 45 on the Children's Depression Rating Scale-Revised (CDRS-R) and at least 4 on the Clinical Global Impression Scale of Severity of Illness (CGI-S) during 3 visits within a 2 week screening period. Exclusions: attention-deficit/hyperactivity disorder, conduct disorder, obsessive compulsive disorder, panic disorder, or psychotic features; history of bipolar, psychotic, or autistic spectrum disorders; suicidal or homicidal risk; abnormal ECG, lab tests, vital signs, or body weight; pregnancy; previous enrolment in sertraline trial; contraindication to SSRIs and history of non-responsiveness to SSRIs. Participants needed to be free of psychotropic medication for at least 2 weeks (4 weeks for fluoxetine). Diphenhydramine or chloral hydrate were permitted as sleeping aids. Participants could continue with ongoing psychotherapy, but not cognitive behaviour therapy.
	<b>Intervention:</b> 25mg/day sertraline for 3 days, then 50mg/day until the end of the second week; dosage was then titrated up to a maximum of 200mg/day for optimum clinical response (n = 189); or placebo (n = 187).
	<b>Outcomes:</b> Severity of depressive symptoms (rated using the 17 item clinician rated CDRS-R (scores range from 17 = least severe to 113 = most severe), response (responders defined as having at least a 40% decrease in the adjusted CDRS-R total score) and adverse effects.
	<b>Patient follow up:</b> Efficacy analysis 97%; safety analysis 99%.

### MAIN RESULTS

Sertraline significantly improved depressive symptoms compared with placebo over 10 weeks (mean change in CDRS-R score: -22.8 with sertraline v -20.2 with placebo;  $p = 0.007$ ; analysis not by intention to treat). 69% of the sertraline group responded, compared with 59% of the placebo group ( $p = 0.05$ ). More participants in the sertraline group withdrew due to adverse effects than in the placebo

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group (17/189 (9%) with sertraline v 5/187 (3%) in the placebo group;  $p = 0.14$  (Fisher's exact, calculated from results as significance not stated in paper)). Adverse effects occurring in at least 5% of the sertraline group, and with an incidence of at least twice that of the placebo group were: insomnia, diarrhoea, anorexia, vomiting, agitation, urinary incontinence, and purpura.

### CONCLUSION

Sertraline is an effective and safe short term treatment for children and adolescents with MDD.

### Commentary

Given the high prevalence of major depressive disorder (MDD) among the young, the authors are to be commended for undertaking this research, which holds important implications for depressed children and adolescents. The current study appears particularly important given its large sample, wide age range, and use of a standard, parallel group placebo controlled design.

Responder criteria were met by 10% more of the sertraline group than the placebo group. This difference is statistically significant, and the authors suggest that it is clinically meaningful. Nevertheless, conclusions on the meaningfulness of this 10% difference should be drawn in the context of other RCTs on paediatric, as well as adult, mood, and anxiety disorders. In general, a 10% difference between an active medication and placebo is below the standard usually applied to identify treatments that are of substantial clinical benefit for mood and anxiety disorders.

The issue of whether the present findings indicate clinically meaningful benefits of sertraline for depressed children and adolescents must be evaluated in the context of several other relevant questions. Firstly, is the medication safe for youth? In light of the ongoing controversy regarding the safety of various SSRIs in paediatric populations, the present study yields reassuring findings. No evidence of treatment related differences emerged for clinically meaningful indices of adverse outcomes. Secondly, is sertraline alone just as or more efficacious than non-pharmacological or combined treatment for MDD? Based on findings that combined treatment benefits adults with chronic MDD,<sup>1</sup> research comparing combined and single modality treatment approaches in youth is currently underway.<sup>2</sup> Such research is all the more important given the modest difference between placebo and sertraline in the current study. Finally, the current study provides important information on acute treatment, but provides no data concerning length of treatment. Because MDD is associated with high risk for relapse or recurrence, studies are needed that compare risks and benefits of long term SSRI treatment, as opposed to placebo substitution for an initially effective SSRI.<sup>3</sup> Such "maintenance" studies appear all the more important given the role of serotonin in both general and specific aspects of brain plasticity as it relates to stress regulation across development.<sup>4</sup>

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- 1 Keller MB, McCullough JP, Klein DN, *et al.* A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med* 2000;**342**:1462–70.
- 2 The Treatment for Adolescents with Depression Study Team. Treatment for adolescents with depression study (TADS): rationale, design, and methods. *J Am Acad Child Adolesc Psychiatry* 2003;**42**:531–42.
- 3 Emslie GJ, Mayes TL. Mood disorders in children and adolescents: psychopharmacological treatment. *Biol Psychiatry* 2001;**49**:1082–90.
- 4 Pine DS. Treating children and adolescents with selective serotonin reuptake inhibitors: how long is appropriate? *J Child Adolesc Psychopharmacol* 2002;**12**:189–203.