Fluoxetine plus cognitive behavioural therapy was most effective for adolescents with major depressive disorder

March J, Silva S, Petrycki S, *et al*. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents with Depression Study (TADS) randomized controlled trial. *JAMA* 2004;**292**:807–20.

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

Q In adolescents with major depressive disorder (MDD), how do fluoxetine, cognitive behavioural therapy (CBT), and their combination compare for effectiveness?

METHODS

Design: 2 x 2 factorial randomised placebo controlled trial.

Allocation: {concealed*}†.

Blinding: blinded (patients and healthcare providers [fluoxetine *v* placebo comparison] and outcome assessors).*

Follow up period: 12 weeks.

Setting: outpatient clinic in the US.

Patients: 439 adolescents (mean age 14.6 y, 54% girls) who had a *DSM-IV* diagnosis of major depressive disorder, could attend an outpatient clinic, scored ⩾45 on the Children's Depression Rating Scale–Revised (CDRS–R), had a full scale IQ ⩾80, and were not taking antidepressants. Exclusion criteria included bipolar disorder, severe conduct disorder, substance abuse/dependence, 2 failed selective serotonin reuptake inhibitor trials (SSRI), and poor response to CBT.

Intervention: (1) fluoxetine, from 10 mg/day to a maximum of 40 mg/day by week 8 (n = 109); (2) CBT (n = 111); (3) CBT plus fluoxetine (n = 107); or (4) placebo (n = 112). CBT consisted of 15 sessions (50–60 mins each) for 12 weeks and aimed to correct depressive thought patterns and increase positive reinforcing behaviour patterns.

Outcomes: CDRS–R score (range 17–133; high scores = greater depression); Suicidal Ideation Questionnaire–Junior High School Version score; and Clinical Global Impressions–Improvement (CGI–I) response rate (much improved or very much improved).

Patient follow up: 82% (100% included in intention to treat analysis).

*See glossary.
†Information provided by author.

MAIN RESULTS

Combined treatment with fluoxetine plus CBT led to greater improvement in CDRS–R scores than did placebo ({mean difference 7.6}*, p = 0.001), fluoxetine alone ({mean difference 4.4}*, p = 0.02), or CBT alone ({mean difference 9.4}*, p = 0.001). Fluoxetine plus CBT also reduced suicidal thoughts. Fluoxetine plus CBT and fluoxetine had greater CGI–I response rates relative to placebo and CBT alone. Numbers needed to treat were 3 (95% CI 2 to 4) for fluoxetine plus CBT and 4 (CI 3 to 8) for fluoxetine alone relative to placebo. The 2 fluoxetine groups had more harm related events than the CBT alone and placebo groups {p = 0.04}* (table).

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CONCLUSION

In adolescents with major depressive disorder, fluoxetine plus cognitive behavioural therapy was most effective.

*Calculated from data in article.
A modified version of this abstract appears in Evidence-Based Nursing.

Commentary

TADS was published during a time of great controversy in the treatment of adolescent depression. Much previous research in this field, both published and unpublished, has been heavily criticised, and the safety and effectiveness of SSRIs is currently under close scrutiny, particularly with regard to suicidality. To date, TADS represents the largest treatment trial of adolescent depression and addresses some of the criticisms of earlier studies. TADS was a non-industry funded study, with predetermined measures of adverse events and relatively few exclusion criteria. It was also the first published study to directly compare CBT with antidepressant medication. The main finding was that combined treatment with CBT and fluoxetine had a greater effect on depressive symptoms than either treatment alone or placebo. However, these results are complicated by the fact that fluoxetine treated patients had an overall increased risk of "harm related" and other adverse events, and an excess of suicide attempts (although the numbers were too small to reach conventional statistical significance [7 in total]). CBT alone was not effective, although previous studies have shown it to be the treatment of choice in less depressed samples.[1]

How should the results of TADS influence clinician's treatment of adolescents with moderate to severe depression? Combined treatment appears to be most beneficial; however, CBT is not always readily available, and also we do not yet have information about its cost effectiveness. Despite recent concerns, fluoxetine is still the next treatment of choice in adolescents with a significant depressive illness, although a small proportion of patients will experience harm related adverse events, requiring careful monitoring. However, depression itself is associated with significant suicidality, and high risk cases were excluded from this study. Research still needs to explore the role of CBT and medication in the treatment of the most severely depressed, suicidal adolescents who are routinely seen in clinical practice.

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1 Harrington R, Whittaker K, Shoebridge P, *et al*. Systematic review of efficacy of cognitive behaviour therapies in childhood and adolescent depressive disorder. *BMJ* 1998;**316**:1559–63.

Fluoxetine or fluoxetine plus cognitive behavioural therapy (CBT) *v* placebo or CBT alone for major depressive disorder in adolescents*

Outcome at 12 weeks	Event rates	RRI (95% CI)	NNH (CI)
Harm related adverse events	10% *v* 4.9%	107% (2.8 to 292)	19 (7 to 713)

*Abbreviations defined in glossary; RRI, NNH, and CI calculated using odds ratio in article.