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Combined Cognitive-Behavioral Therapy and Pharmacotherapy for Adolescent Depression: Does it Improve Outcomes Compared with Monotherapy?

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Abstract

Adolescent depression can be effectively treated with selective serotonin reuptake inhibitor medications (SSRI), such as fluoxetine, or with specific forms of psychotherapy, such as cognitive-behavioral therapy (CBT) and interpersonal therapy. A single course of any of these treatments, however, leaves between one-third and one-half of the patients insufficiently improved and still depressed. In an effort to increase effectiveness, medication and CBT have been combined (COMB). A few controlled clinical trials have recently compared COMB to monotherapy. The Treatment for Adolescents with Depression Study (TADS) randomly assigned 439 adolescents with major depressive disorder to fluoxetine, CBT, COMB, or clinical management with placebo. After 12 weeks of treatment, both fluoxetine and COMB reduced depression more than CBT or placebo did, but only COMB was effective in inducing remission, achieving functional recovery, and reducing suicidal ideation. After 36 weeks of treatment, there was no difference in improvement among treatments, but the rate of suicidal events was lower in COMB than in the medication only group. However, in another trial, the Adolescent Depression and Psychotherapy Trial (ADAPT), involving 208 youths, no advantages of COMB over usual care with SSRI could be detected. In a third trial, the Treatment of Resistant Depression in Adolescence (TORDIA), which randomized 334 patients unresponsive to previous SSRI treatment, COMB produced a greater response rate than medication monotherapy. These and other, smaller trials of COMB in adolescent depression are here reviewed. It is concluded that, while there is no univocal support for the superiority of COMB, two controlled trials indicate that COMB has a more favorable benefit/risk balance than monotherapy in adolescent depression. It remains to be determined for which patient subgroups and in which clinical settings COMB may be most advantageous.

Depressive Disorders in Adolescence

Mood disorders are a major cause of morbidity in adolescence. In the U.S., these disorders rank first among the causes of hospitalization between age 13 and 17 years,[1] and constitute a major risk factor for suicide, which is the third leading cause of death in teen years.[2] Depression impairs functioning at home, school and in peer relationships, increases the risk for substance abuse, and portends adult depression and associated dysfunction.[3,4]

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As currently the case for most psychiatric disorders, there are no diagnostic biological makers for depression, which remains a clinically defined condition. According to the current nosology, depressive disorders include major depressive disorder, dysthymic disorder, and depressive disorder not otherwise specified.[5] The diagnostic criteria for major depressive disorder are substantially the same across the lifespan, even though the diagnostic process needs to be developmentally appropriate. Depression is uncommon and difficult to diagnose in preschool years, and remains infrequent until puberty when its prevalence rapidly increases to reach adult levels in the teen years. It is estimated that major depressive disorder affects at any time about 4–6% of adolescents between 13 and 17 years of age.[6]

Major depressive disorder is characterized by a distinct episode of depressed or irritable mood causing significant distress and/or functional impairment, lasting at least two weeks, and occurring in a patient who does not have history of mania. [5] An episode of depression can last months, occasionally years.[7] Even when depression eventually abates, residual symptoms can persist and functional recovery remain incomplete. Furthermore, recurrence is common. In a study, about 40% of youths who had recovered from one episode of MDD had another episode in the following 12 months.[8] Thus, despite the tendency of depression towards spontaneous improvement in at least one third of the cases, especially those with milder symptoms, there is general agreement that youths with moderate to severe depression should be vigorously treated.[9]

Evidence-Based Treatments of Adolescent Depression

Effective treatments of adolescent depression exist. In particular, randomized controlled clinical trials support the efficacy of serotonin reuptake medications (SSRIs) and two types of psychotherapy, cognitive-behavioral therapy (CBT) and interpersonal therapy, for the treatment of adolescents with major depressive disorder.[10,11] Fluoxetine was found to be better than placebo in three clinical trials, [7,12,13] and is currently the only SSRI approved by the U.S. Food and Drug Administration for the treatment of depression in children age 8 and older. For other SSRIs, such as sertraline and citalopram, the evidence is less strong, being limited to one controlled trial each. CBT, a form of psychotherapy that attempts to correct cognitive distortions associated with depression and promote healthy behaviors, is the best investigated specific therapy for depression, and was found to be of greater efficacy than non-specific supportive psychotherapy and family therapy. [11]

CBT can be delivered either individually or as group therapy, and several CBT manuals for the treatment of depressed adolescents are available. In fact, the term CBT indicates a psychotherapeutic approach that is essentially based on cognitive restructuring and behavioral activation, but there is considerable variability among the various treatment manuals. Most commonly, CBT includes an acute treatment consisting of 12– 15 hourly sessions, usually delivered on weekly basis, followed by biweekly sessions for a two-month consolidation phase and a gradual termination with monthly sessions.

Though effective, SSRIs and CBT have, on average, a small effect size when used as monotherapy, [10,11] and still leave between one-third and one-half of the patients insufficiently improved and still depressed. There has been therefore interest in combining pharmacological and psychotherapeutic interventions in an attempt to enhance effectiveness. In fact, for adult depression, combined treatment was found to be more effective than medication or CBT alone.[14,15] Combined treatment, however, has also drawbacks. It obviously requires more resources and is more expensive.¹⁶ It often requires the involvement of two separate clinicians, one prescribing and monitoring the medication treatment and the other providing the psychotherapy, so that good coordination between clinicians is needed for optimal success. Implementing this approach, however, may not be practically possible due to

a dearth of CBT-trained clinicians in many communities and the higher cost of combined treatment versus monotherapy .

This review briefly examines and discusses the available data comparing SSRI medication and CBT monotherapy with their combination in the treatment of adolescent depression.

Methodological Challenges in Evaluating Combined Treatment

Clinical trials that compare pharmacotherapy, psychotherapy and their combination are by necessity rather complex, methodologically challenging, and expensive to conduct. First, the expected difference in outcome between active treatments is smaller than that between an active treatment and placebo. Thus, the sample size must be large enough to ensure adequate statistical power and avoid false negative conclusions (i.e., statistical type II error). Second, the inclusion of a placebo arm is desirable as it can help with the interpretation of the results. [17] If there is not difference between the active treatments, but these are better than placebo, one can be reassured of the assay sensitivity of the study and thus conclude that both treatments are similarly effective.

Third, while medication can be fully masked with a matched placebo pill, psychotherapy cannot be administered under double blind conditions. Adding a pill placebo to psychotherapy creates problems by introducing an artificial and extraneous element in the patient-therapist relationship. Clearly, different levels of compromise are possible, none of which is completely satisfactory in removing potential biases. In addition, this type of study requires interdisciplinary collaborations between investigators with expertise in psychopharmacology and researchers in psychotherapy. Industry has little interest in sponsoring these studies, which are usually funded with public funds.

Thus, it is not surprising that relatively few large controlled clinical trials have been conducted to compare the effectiveness of combination vs. monotherapy in adolescent depression. In recent years, three such studies have been reported and will be here briefly reviewed together with other, smaller randomized controlled trials (Table 1).

The Treatment for Adolescents with Depression Study (TADS)

TADS was a publicly funded controlled trial to directly compare the effectiveness of fluoxetine, CBT, and their combination (COMB) with clinical management with pill placebo. [18] TADS was conducted at 13 clinical sites in the U.S., of which most were university clinics. A little more than half of the patients were recruited through direct advertising to the public. Inclusion criteria were quite broad, and common comorbidities, such as anxiety disorders and attention deficit/hyperactivity disorder, were allowed. However, patients who were actively suicidal, abusing alcohol or drugs, psychotic, with severe conduct problems, or in need of hospitalization were excluded.

In the fluoxetine and placebo groups, patients were treated by a pharmacotherapist, while COMB patients had each two clinicians, a pharmacotherapist and a CBT therapist. There was ongoing communication and coordination of treatment between the two clinicians. Fluoxetine and placebo were delivered under double-blind conditions, but CBT and COMB were not masked. Thus, as it happens when comparing pharmacological and psychotherapeutic interventions, there was an imbalance in masking across treatment groups, with a potential bias in favor of the psychotherapy containing conditions. [19] To attenuate potential biases, all primary outcomes were assessed by independent evaluators blinded to treatment assignment.

After 12 weeks of treatment, a statistically significantly greater rate of improvement was observed on fluoxetine (61%) or COMB (71%) than on CBT (43%) or placebo (35%) (Figure

1).[7] While fluoxetine and COMB were not statistically different in improvement rate, COMB was superior in inducing remission of the depression, decreasing suicidal ideation, and improving functioning, global health, and feelings of well being (Figure 2 and 3). Only COMB resulted in greater rates of remission (37% and normalization of functioning (35%) than placebo (17% and 19% respectively). [20,21] At the end of the 36-week treatment, the rate of clinical response was similar across fluoxetine, CBT, and COMB, thus indicating that the benefit of COMB is in accelerating the improvement process. [22]

An added benefit was that COMB treated patients achieved a high rate of response on a lower dose of fluoxetine (28 mg/day) than those on fluoxetine monotherapy (32 mg/day). [7] No suicide occurred in TADS, but some patients had episodes of suicidal ideation or attempts during the 36 week trial. [23] These episodes were more common in the fluoxetine group (14.7%) than in COMB (8.4%) or CBT (6.3%). Thus, overall, COMB showed a more favorable benefit/risk ratio than medication monotherapy. The mechanism through which CBT, given concomitantly with SSRI medication, may attenuate the risk for suicidal behavior is unknown, but it is possible that it provides patients with skills that help diffuse tension and cope with stressful situations in more appropriate, non-destructive ways.

Exploratory secondary analyses of the TADS database at week 12 suggest that a certain types of patient may be more likely to benefit from COMB than monotherapy.[24] The advantage of COMB over fluoxetine was evident in the subgroup with less severe depression or greater degree of cognitive distortion, while for the most severe patients there was no apparent benefit from adding CBT. These results are to be considered with caution as they come from secondary analyses and require prospective studies in order to be confirmed.

An analysis of the TADS data has indicated that, while both fluoxetine alone and COMB can be considered cost-effective using standard criteria for health care, fluoxetine is much more cost effective, at least after 12 weeks of treatment. [16] Thus, the relative advantages of COMB in terms of efficacy and safety must be weighed against a substantially greater cost and complexity of treatment. If, however, the protective effect of COMB against suicidal behavior is confirmed by future studies, COMB may be considered also economically advantageous given the high costs often associated with suicidal events.

The Adolescent Depression and Psychotherapy Trial (ADAPT)

ADAPT was a randomized controlled trial of SSRI medication vs. the combination of SSRI plus CBT. [25] The study, which was primarily funded by the National Health System in the U.K., was conducted in community clinical settings. Patients were clinically referred and treatment was delivered using routine care practices. All patients received an initial brief psychotherapeutic intervention, and only those who had not shown improvement were randomized into the trial. Thus, all patients in ADAPT received some type of psychotherapy, although not necessarily CBT. The fact that only non-responders to the initial psychotherapy were randomized into the trial might have selected not only the more severe patients, but also those less responsive to psychotherapy. A total of 208 outpatients aged 11–17 years were randomly assigned to routine care with an SSRI medication (primarily, but not exclusively fluoxetine) or the same but with the addition of CBT. The acute treatment phase lasted 12 weeks and was followed by a less intensive 16-week maintenance phase. At the end of the 28-week treatment, patients in both groups were improved with no differences between treatment arms in terms of symptom reduction, remission, or incidence of suicidal behavior. [25] The response rate was 61% in the usual care with fluoxetine group as compared with 53% in the combined fluoxetine plus CBT group, a non-significant difference. Obviously, adding CBT resulted in a higher cost for the combination with no evidence of greater cost-effectiveness. [26]

ADAPT was a pragmatic trial, conducted in “real world” clinical practices, as opposed to academic settings, using typical clinicians rather than research staff. The sample of ADAPT was somewhat more severe than that of TADS, and included also patients with recent suicidal behavior (who were excluded from TADS). Thus, the different conclusions emerging from TADS and ADAPT may be due to differences in severity of depression, comorbidity, or treatment delivery.

The Treatment of Resistant Depression in Adolescents (TORDIA)

TORDIA was also a publicly funded, controlled clinical trial in 12–17 year old youths with major depressive disorder. [27] In this study, which was conducted at six sites in the U.S., including also a managed care practice setting, patients had been previously treated with an SSRI medications but without success, and were still depressed. They were randomly assigned to receive a different antidepressant medication either alone or together with CBT. On a random basis, the medication consisted of another SSRI or venlafaxine. Acute treatment lasted 12 weeks and was followed by another 12-week continuation phase. At the end of first 12 weeks, more patients met response criteria in COMB (54.8%) than in the medication alone groups (40.5%, $p=0.009$). [27] In addition to the responder rate, the trajectory of depressive symptoms during TORDIA was also analyzed: symptoms significantly declined over time, but without differences between treatment groups.

Unlike TADS, but in agreement with ADAPT, there was no indication that CBT had a superior effect in decreasing suicidal ideation or preventing suicidal events compared with the medication only treatment. Patients who participated in TORDIA and ADAPT were more severe due to greater comorbidity, suicidality, or previous treatment resistance at study entry. These differences in study sample might have accounted for the observed differences in outcome.

TORDIA is a unique study that addresses the important issue of which treatment to use for depressed adolescents for whom SSRI monotherapy has not been helpful. The results of the study are remarkable in indicating that there is about a fifty percent likelihood of improvement with subsequent treatment and that COMB works better than monotherapy for these patients.

Other Randomized Studies

Three other controlled comparisons of CBT plus medication versus medication alone have been recently reported in depressed adolescents. Like the previously described trials, these too were mainly funded by public research agencies or not-for-profit foundations. Only a weak effect of CBT was found in a randomized trial of brief CBT added to a background of antidepressant medication in practice settings in the U.S. [28] This study had a relatively small sample size (total $N=152$), which may explain the difficulty in finding statistically significant differences. Like the ADAPT, this study was a pragmatic trial that enrolled clinically referred patients and maintained usual practice treatment as background for the experiment. It is interesting, and perhaps not entirely coincidental, that neither this study nor the ADAPT could not find added benefit from CBT over existing clinical care with SSRI. A possible conclusion is that it may be difficult to “export” successfully specialized psychotherapies such as CBT into usual practice settings.

Another, smaller, controlled study was conducted in community clinics in Australia.[29] A total of 73 adolescents aged 12–18 years with a diagnosis of major depressive disorder, dysthymia, or depressive disorder not otherwise specified were randomly assigned to CBT, sertraline, or their combination. The primary outcome was presence of depressive diagnosis assessed by the clinician using a standard semistructured interview. There was no evidence of superiority of the combination over monotherapy. Actually, the CBT monotherapy group had

lower rate of depression at the end of the first three months of treatment. Sertraline dosage was rather low and this might have been a disadvantage for the SSRI arm. The result of this study is apparently at odds with that obtained in TADS, where CBT was not better than clinical management with placebo at three months.[7] Moderator analyses of TADS, however, have indicated that there was substantial individual variability in treatment response and that CBT worked best for certain patient subgroups characterized by milder depression and higher family income. [24]

The third trial has unique features that make it substantially different from the previous studies. It enrolled 126 youths aged 13–19 years who met diagnostic criteria for both major depressive disorder and substance abuse disorder (other than tobacco use) in addition to having had a conduct disorder. [30] In this study, which was funded by the National Institute of Drug Abuse, patients were randomized to receive a 16-week treatment of CBT plus fluoxetine or CBT plus placebo. It is important to consider that the CBT was primarily addressed to the substance abuse and not to the depression. Analyses of the continuous ratings of depression showed a significantly greater decline in depressive symptoms in COMB than in CBT alone. At the end of treatment, 76% of the patients in COMB were deemed improved as to their depression vs. 67% in CBT, but the difference was not statistically significant. No treatment effect on self-reported substance use was detected, and the CBT only group was more likely to have a substance-free urine screen than the combined group. Clearly, the study population of this trial is substantially different from that of other studies, and these results cannot be generalized or easily integrated into those from other trials in non substance abusing depressed teens.

Conclusions

There has been much interest in developing and testing treatments for depressed adolescents that combine pharmacological and psychosocial interventions. Recently, a number of well-designed and carefully conducted clinical trials have been reported. The studies are rather heterogeneous with respect to patient characteristics, treatment setting, and outcome measure, and these differences make comparisons across studies difficult. Perhaps not surprisingly, the picture that emerges from these studies is not amenable to univocal interpretations, but likely reflects the considerable heterogeneity of clinical situations and treatment delivery. Despite these limitations, a number of informative conclusions can be drawn.

The results of two large trials provide support for the superior efficacy of the combination SSRI medication plus CBT for adolescents with moderately severe depression and in those who had not improved on SSRI monotherapy. [7,27] Trials conducted in usual practice settings, however, could not find evidence of added benefit from CBT to standard clinical care with SSRI medication. [25,28,29]

The finding from TADS that CBT decreased suicidal ideation and protected from the emergence of suicidal behavior is especially important vis-à-vis the increased incidence of suicidality events with SSRI as compared to placebo. [31] The fact that this effect was not detected in other trials suggests that multiple, still unrecognized, clinical and contextual variables influence the relationship between treatment and suicidal behavior in youth.

The rate of progress achieved in testing combined treatments for depressed adolescents is indeed remarkable, with several large multisite trials being reported in the last few years. It remains to be clarified which patients tend to do better with combined treatment than with monotherapy, and which sequential treatment approaches are most effective and under which circumstances. There are suggestions that clinical characteristics, such as severity of illness or degree of cognitive distortions, moderates treatment response, and further research to develop more personalized approaches to treatment is warranted.

References

- Owens, PL.; Thompson, J.; Elixhauser, A.; Ryan, K. Care of Children and Adolescents in U.S. Hospitals. Agency for Healthcare Research and Quality.; Rockville, MD: 2003. HCUP Fact Book NO.4, AHRQ Publication No. 04-0004
- Centers for Disease Control and Prevention: 2005 United States Suicide Injury Deaths and Rates. National Center for Injury Prevention and Control. 2007 [June 26, 2008]. Available at Website http://webappa.cdc.gov/sasweb/ncipc/mortrate10_sy.html
- Weissman MM, Wolk S, Goldstein RB, Moreau D, Adams P, Greenwald S, Klier CM, Ryan ND, Dahl RE, Wickramaratne P. Depressed adolescents grow up. *JAMA* 2000;281:1707–13. [PubMed: 10328070]
- Fombonne E, Wostear G, Cooper V, Harrington R, Rutter M. The Maudsley long-term follow-up of child and adolescent depression. 2. Suicidality, criminality and social dysfunction in adulthood. *Br J Psychiatry* 2001;179:218–223. [PubMed: 11532798]
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Vol. 4th edition. American Psychiatric Association; Washington, DC: 1994.
- Kessler RC, Avenevoli S, Merikangas KR. Mood disorders in children and adolescents: an epidemiological perspective. *Biol Psychiatry* 2001;49:1002–14. [PubMed: 11430842]
- TADS Team. The Treatment for Adolescents with Depression Study (TADS): Short-Term Effectiveness and Safety Outcomes. *JAMA* 2004;292:807–20. [PubMed: 15315995]
- Emslie GJ, Heiligenstein JH, Hoog SL, Wagner KD, Findling RL, McCracken JT, Nilsson ME, Jacobson JG. Fluoxetine treatment for prevention of relapse of depression in children and adolescents: a double-blind, placebo-controlled study. *J Am Acad Child Adolesc Psychiatry* 2004;43:1397–405. [PubMed: 15502599]
- Birmaher B, Brent D, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad Child Adolesc Psychiatry* 2007;46(11):1503–26. [PubMed: 18049300]
- Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, Ren L, Brent DA. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA* 2007;297:1683–96. [PubMed: 17440145]
- Weisz JR, McCarthy CA, Valeri SM. Effects of psychotherapy for depression in children and adolescents: a meta-analysis. *Psychol Bull* 2006;132:132–49. [PubMed: 16435960]
- Emslie GJ, Rush AJ, Weiberg WA, Kowatch RA, Hughes CW, Carmody T, Rintelmann J. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry* 1997;54:1031–7. [PubMed: 9366660]
- Emslie GJ, Heiligenstein JH, Wagner KD, Hoog SL, Ernest DE, Brown E, Nilsson M, Jacobson JG. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry* 2002;41:1205–15. [PubMed: 12364842]
- Keller MB, McCulloch JP, Klein DN, Asarnow B, Dunner DL, Gelenberg AG, Markowitz JC, Nemeroff CB, Russell JM, Thase ME, Trivedi MH, Zajecka J. 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(20):1462–70. [PubMed: 10816183]
- Pampallona S, Bollini P, Tibaldi G, Kupelnick B, Munizza C. Combined pharmacotherapy and psychological treatment for depression: a systematic review. *Arch Gen Psychiatry* 2004;61:714–9. [PubMed: 15237083]
- Domino ME, Burns BJ, Silva SG, Kratochvil CJ, Vitiello B, Reineke MA, Mario J, March JS. Cost-effectiveness of treatments for adolescent depression: Results from TADS. *Am J Psychiatry* 2008;165:588–596. [PubMed: 18413703]2008
- Temple R, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments. *Ann Intern Med* 2000;133:455–63. [PubMed: 10975964]
- TADS Team. Treatment for Adolescents with Depression Study (TADS): rationale, design, and methods. *J Am Acad Child Adolesc Psychiatry* 2003;42:531–42. [PubMed: 12707557]

19. March JS, Silva SG, Vitiello B. The Treatment for Adolescents with Depression Study (TADS): Methods and Message at Twelve Weeks. *J Am Acad Child Adolesc Psychiatry* 2006;45:1393–403. [PubMed: 17135984]
20. Kennard BD, Silva S, Vitiello B, Curry J, Kratochvil CJ, Simons A, Hughes JL, Feeny N, Weller E, Sweeney M, Reinecke M, Pathak S, Ginsburg G, Emslie GJ, March J. Remission and residual symptoms after acute treatment of adolescents with major depressive disorder. *J Am Acad Child Adolesc Psychiatry* 2006;45:1404–11. [PubMed: 17135985]
21. Vitiello B, Rohde P, Silva SG, Wells KC, Casat C, Waslick BD, Simons A, Reinecke MA, Weller EB, Kratochvil CJ, Walkup J, Pathak S, Robins M, March JS, the TADS Team. Effects of treatment on level of functioning, global health, and quality of life in depressed adolescents. *J Am Acad Child Adolesc Psychiatry* 2006;45:1419–26. [PubMed: 17135987]Ph.D.
22. TADS Team. The Treatment for Adolescents with Depression Study (TADS): long-term effectiveness and safety outcomes. *Arch Gen Psychiatry* 2007;64:1132–44. [PubMed: 17909125]
23. Emslie GJ, Kratochvil CJ, Vitiello B, Silva SG, Mayes TL, McNulty S, Weller E, Waslick B, Casat C, Walkup J, Pathak S, Rohde P, March J. Treatment for Adolescents with Depression Study (TADS): safety results. *J Am Acad Child Adolesc Psychiatry* 2006;45:1440–55. [PubMed: 17135989]
24. Curry JF, Rohde P, Simons A, Silva S, Vitiello B, Kratochvil CJ, March JS, Reinecke MA, Feeny N, Wells KC, Pathak S, Rosenberg D, Kennard BD, Robins M, Ginsburg GS. Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry* 2006;45:1427–39. [PubMed: 17135988]
25. Goodyer I, Dubicka B, Wilkinson P, Kelvin R, Roberts C, Byford S, Breen S, Ford C, Barrett B, Leech A, Rothwell J, White L, Harrington R. Selective serotonin reuptake inhibitors (SSRIs) and routine specialist care with and without cognitive behaviour therapy in adolescents with major depression: randomized controlled trial. *BMJ* 2007;335:142. [PubMed: 17556431]Epub doi: 10.1136/bmj.39224.494340.55
26. Byford S, Barrett B, Roberts C, Wilkinson P, Dubicka B, Kelvin RG, White L, Ford C, Breen S, Goodyer I. Cost-effectiveness of selective serotonin reuptake inhibitors and routine specialist care with and without cognitive behavioural therapy in adolescents with major depression. *Br J Psychiatry* 2007;191:521–7. [PubMed: 18055956]
27. Brent D, Emslie G, Clarke G, Wagner K, Asarnow J, Keller M, Vitiello B, Ritz L, Satish Iyengar S, Abebe K, Birmaher B, Ryan N, Kennard B, Hughes C, DeBar L, McCracken J, Strober M, Suddath R, Spirito A, Leonard H, Porta G, Onorato M, Zelazny J. The Treatment of Adolescents with SSRI-Resistant Depression (TORDIA). A Comparison of Switch to Venlafaxine or to another SSRI, with or without additional Cognitive Behavioral Therapy. *JAMA* 2008;299:901–13. [PubMed: 18314433]
28. Clarke G, DeBar L, Lynch F, Powell J, Gale J, O'Connor E, Ludman E, Bush T, Lin EHB, Von Korff M, Hertert S. A randomized effectiveness trial of brief cognitive-behavioral therapy for depressed adolescents receiving antidepressant medication. *J Am Acad Child Adolesc Psychiatry* 2005;44:888–98. [PubMed: 16113617]
29. Melvin GA, Tonge BJ, King NJ, Heyne D, Gordon Ms, Klimkeit E. A comparison of cognitive-behavioral therapy, sertraline, and their combination for adolescent depression. *J Am Acad Child Adolesc Psychiatry* 2006;45:1151–61. [PubMed: 17003660]
30. Riggs PD, Mikulich-Gilbertson SK, Davies RD, Lohman M, Klein C, Stover SK. A randomized controlled trial of fluoxetine and cognitive behavioral therapy in adolescents with major depression, behavior problems, and substance use disorders. *Arch Pediatr Adolesc Med* 2007;161:1026–1034. [PubMed: 17984403]
31. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry* 2006;63:332–9. [PubMed: 16520440]
32. Poznanski, EO.; Mokros, HB. Manual for the Children's Depression Rating Scale-Revised. Western Psychological Services; Los Angeles, LA: 1995.
33. Guy, W. ECDEU Assessment Manual for the Psychopharmacology. Vol. 2nd ed.. Washington, DC: 1976. Dept. of Health and Human Services Publication No. (ADM) 91–338
34. Gowers SG, Harrington RC, Whitton A, Lelliott P, Beevor A, Wing J, Jezzard R. Brief scale for measuring the outcomes of emotional and behavioural disorders in children. Health of the Nation Outcome Scales for children and Adolescents (HoNOSCA). *Br J Psychiatry* 1999;174:413–416. [PubMed: 10616607]

Figure 1. Response Rates in TADS [7,22]

Response: a score of “much “or very much” improved on the Clinical Global Impression-Improvement Scale.

CBT: cognitive-behavioral therapy

PBO: placebo

FLX: fluoxetine

COMB: fluoxetine plus CBT

At week 12, COMB and FLX were better than PBO and CBT ($p < 0.001$). Treatment groups did not differ at week 36. Last available observation was carried forward. PBO treatment lasted 12 weeks. [7]

Figure 2. Remission from Depression in TADS after 12 Weeks of Treatment [20]

Remission: a total score of 28 or lower on the Child Depression Rating Scale-Revised[32]

CBT: cognitive-behavioral therapy

PBO: placebo

FLX: fluoxetine

COMB: fluoxetine plus CBT

Wald $\chi^2=21.5$, $df=12$, $p=.04$. Only CBT was significantly different from PBO ($p=0.0009$) [20]

Figure 3. Level of Functioning in TADS [21]

CGAS: Children's Global Assessment Scale

CBT: cognitive-behavioral therapy

PBO: placebo

FLX: fluoxetine

COMB: fluoxetine plus CBT

CBT was superior to PBO and CBT ($p < 0.0001$), and to FLX ($p < 0.05$). FLX was better than PBO and CBT ($p < 0.05$). 19]

Table 1
Randomized Controlled Clinical Trials of Combination vs. Monotherapy in Adolescent Depression

Study	Inclusion	Exclusion	Design & Treatments	Duration	Primary outcome measures	Response Rate and Main Findings
Treatment for Adolescents with Depression Study (TADS) [7,18]	439 outpatients. Age: 12–17 years. Major depressive disorder.	Psychosis. Bipolar. Mental retardation. Substance abuse.	Four parallel groups: fluoxetine, placebo, CBT, and COMB.	12 weeks of acute treatment followed by a 24 week continuation.	CDRS-R CGI-I	At week 12: COMB: 73% Medication: 62% CBT: 48% Placebo: 35%
		Recent suicidal attempt. Suicidal intention.	Multi-site. Flexible dose. Individual CBT.		Response: CGI-I=1 or 2.	At week 36: COMB: 86% Medication: 81% CBT: 81% Medication, but not COMB, increased risk for suicidal events.
Adolescent Depression Antidepressant & Psychotherapy Trial (ADAPT) [25]	208 outpatients Age: 11–17 years. Major depressive disorder.	Bipolar. Schizophrenia. Mental retardation. Need for hospitalization.	Two parallel groups: SSRI and COMB.	12-week acute treatment followed by 12-week continuation	HoNOSCA	At week 12: COMB: 42% Medication: 44%
			Multi-site. Flexible dose. Individual CBT.		Response: CGI-I=1 or 2.	At week 28: COMB: 53% Medication: 61% No difference on HoNOSCA.
Treatment of Resistant Depression in Adolescents (TORDIA) [27]	334 outpatients Age: 12–18 years. Major depressive disorder	Psychosis. Bipolar. Pervasive developmental disorders Substance abuse.	Factorial with 4 parallel groups: other SSRI or venlafaxine, with or without CBT.	12 weeks acute treatment followed by 12-week continuation	CDRS-R CGI-I	At week 12: COMB: 55% Medication: 41%

Study	Inclusion	Exclusion	Design & Treatments	Duration	Primary outcome measures	Response Rate and Main Findings
	unresponsive to one SSRI treatment.					
			Multi-site. Flexible dosing. Individual CBT.		Response: $\geq 50\%$ decrease in CDRS-R and CGI-I=1 or 2	No difference on CDRS-R
Brief CBT for Depressed Adolescents Receiving SSRI [28]	152 outpatients Age: 12–18 years. Major depressive disorder.	Schizophrenia. Mental retardation.	Two parallel groups: SSRI vs. COMB	CES-D	52 weeks	At week 12: COMB: 77% Medication: 72%
			Multiple practice settings. Flexible dosing. Individual CBT.		Response: no current major depression episode	At week 52: COMB: 89% Medication: 94%
Comparison of CBT, Sertraline, and Their Combination [29]	73 outpatients Age: 12–18 years. Major depressive disorder, dysthymia, or depression not otherwise specified.	Psychosis. Bipolar. Mental retardation. Substance abuse. Active suicidality.	Three parallel groups: sertraline, CBT, and COMB	12 weeks with a 6-month follow-up	DSM-IV Diagnosis	At week 12: COMB: 52% Medication: 46% CBT: 86%
			Multi-site. Flexible dosing. Individual CBT.		Response: remission or partial remission	
Fluoxetine and CBT in Adolescents with Depression, Behavior Problems and Substance Use [30]	126 outpatients Age: 13–19 years. Major depressive disorder and substance abuse with history of conduct disorder.	Psychosis. Bipolar. High risk for suicidality.	Two parallel groups: CNT plus fluoxetine vs CBT plus placebo	16 weeks	CDRS-R CGI-I	At week 16: COMB: 76% CBT: 67%

Study	Inclusion	Exclusion	Design & Treatments	Duration	Primary outcome measures	Response Rate and Main Findings
Single-site Fixed dose (20 mg/day) Individual CBT (focused on substance abuse).						
Response: CGI-I=1 or 2.					COMB better than CBT on CDRS-R	

CBT: cognitive-behavioral therapy (different manuals were used)

SSRI: selective serotonin reuptake inhibitor

COMB: combination of medication and CBT

CDRS-R: Child Depression Rating Scale-Revised [32]

CGI-I: Clinical Global Impression-Improvement[33]

HoNOSCA: Health of the Nation Outcome Scales for Children and Adolescents[34]