Review article

Combined treatment with cognitive–behavioural therapy in adolescent depression: meta-analysis

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Background

The treatment of adolescent depression is controversial and studies of combined treatment (antidepressants and cognitive–behavioural therapy, CBT) have produced conflicting findings.

Aims

To address the question of whether CBT confers additional benefit to antidepressant treatment in adolescents with unipolar depression for depressive symptoms, suicidality, impairment and global improvement.

Method

Meta-analysis of randomised controlled trials (RCTs) of newer-generation antidepressants and CBT in adolescent depression.

Results

There was no evidence of a statistically significant benefit of combined treatment over antidepressants for depressive symptoms, suicidality and global improvement after acute treatment or at follow-up. There was a statistically significant advantage of combined treatment for impairment in the short-term (at 12 weeks) only. There was some evidence of heterogeneity between studies.

Conclusions

Adding CBT to antidepressants confers limited advantage for the treatment of an episode of depression in adolescents. The variation in sampling and methodology between studies, as well as the small number of trials, limits the generalisability of the findings and any conclusions that can be drawn. Future studies should examine predictors of response to treatment as well as clinical components that may affect outcome.

Declaration of interest

B.D., C.R., P.W. and I.M.G. participated in one of the studies analysed. R.E. attended symposia sponsored by Janssen-Cilag and Lilly.

The optimal treatment for an episode of adolescent depression is currently unclear. Concerns exist regarding both the efficacy and safety of the newer-generation antidepressants,[1] and more recently, the efficacy of psychological treatment has also been questioned.[2] The National Institute for Health and Clinical Excellence (NICE) has advised that selective serotonin reuptake inhibitors (SSRIs) should not be prescribed in adolescents without a concurrent specific psychological treatment (http://guidance. nice.org.uk/CG28/niceguidance/pdf/English). This advice was based on findings from the Treatment for Adolescents with Depression Study (TADS) whereby combined treatment (fluoxetine plus cognitive–behavioural therapy, CBT) was found to be superior to fluoxetine alone, and CBT appeared to offer additional protection against suicidality when combined with fluoxetine.[3] Adult data also suggest that combined treatment with psychological therapy is associated with a higher improvement rate (odds ratio, OR = 1.86, 95% CI 1.38–2.52) than drug treatment alone.[4] Since the publication of the NICE guidelines, further studies of combined treatment with CBT have been published with differing results to the TADS findings. This has brought into question the applicability of the guidance, particularly in view of the significant cost and resource implications involved. We have therefore reviewed the current available data on studies combining CBT and antidepressant treatment in adolescent depression.

Method

Search method

PsycINFO, Medline and the Cochrane databases were searched, using the terms 'depressive disorder', 'cognitive behavioural treatment', 'antidepressant treatment' and 'randomised controlled trials'. The search was not limited by age group to ensure that older adolescents were not excluded. Seven journals were also searched individually, and reference lists of relevant publications, including the NICE guidelines, were examined. Leading authors in the field were also contacted. Searches were performed from January 1980 to March 2009 for articles that had been published in the English language.

Selection criteria

Randomised controlled trials (RCTs) predominantly including adolescents aged 11–18 years with a DSM–IV defined episode of depression were selected where CBT was combined with a newer-generation antidepressant and compared with antidepressant treatment without CBT. The principle outcomes of interest were depression and impairment scores, overall improvement, suicidality and adverse events.

Validity assessment

Two of the authors, G.C. and R.E. independently reviewed abstracts of potentially relevant RCTs. This was followed by a consensus discussion with B.D. The quality of the RCTs was coded independently by G.C. and R.E. and disagreement was resolved by consensus discussions. The rating method was broadly based on schemes used by authors of relevant systematic reviews.[5,6] Nine features were rated on a 0–3 scale, with a maximum score of 27. The rated items were: quality of description of randomisation; inclusion of data on participants who subsequently withdrew from the study (intention-to-treat); degree to which assessors of outcome were masked to treatment allocation; degree to which expectancy of participants about treatment was assessed; clarity of description of improvement; use of multiple informants to assess outcome; description of dosage regime; manualised therapy and assessment of therapy adherence; and assessment of adherence with medication.

Data extraction

An *ad hoc* form was designed for data extraction which included diagnosis, gender, mean age, exclusions, suicidality, comorbidity, ethnicity, recruitment method, treatment duration and follow up, type of treatment, number of sessions offered and attended, medication type and dose, and adverse events.

Quantitative data synthesis

Acute and longer-term outcomes were examined where data were available. The principle outcomes of interest were interview-rated and self-report depression measures, impairment, overall improvement and suicidality. Spontaneous reports of suicidality were described inconsistently in the trials and, as this method of reporting also tends to underestimate events,[7] only systematic reports were included in the statistical analysis, and the spontaneous reports are described separately.

For quantitative outcome measures (Child Depression Rating Scale – Revised (CDRS–R); Hamilton Rating Scale for Depression (HRSD); Mood and Feelings Questionnaire (MFQ); Reynolds Adolescent Depression Scale (RADS); Beck Depression Inventory (BDI); Centre for Epidemiological Studies–Depression Scale (CES–D); Child Global Assessment Schedule (CGAS); Health of the Nation Outcome Scale in Children and Adolescents (HoNOSCA); Schedule for Affective Disorders and Schizophrenia for School Aged Children (Kiddie–SADS–PL); Suicidal Ideation Questionnaire – Junior High School Version (SIQ–Jr)) the estimate of the combined treatment effect is based on the weighted mean difference using the inverse variance method. As the test of heterogeneity between studies is known to lack power, a random effects estimate is also given where the estimated between-study variance τ^2 was non-zero. The I^2 statistic is also provided as a measure of heterogeneity, whereby low, moderate and high heterogeneity can be tentatively assigned to I^2 values of 25%, 50% and 75%. However, quantification of heterogeneity is only one component of a wider investigation of variability across studies, the most important being diversity in clinical and methodological aspects, and the observed degree of inconsistency across studies with regard to the direction of effect.[8] I^2 as a measure of heterogeneity also has limitations as it depends on sample size.[9] To allow pooling of studies using different measures, pooled analyses were carried out using the standardised mean difference.[10] For the Clinical Global Impressions – Improvement (CGI–I), a fixed effects estimate of the pooled odds ratio has been presented based on the Mantel–Haenszel method.[10] The DerSimonian and Laird random effects estimate is given where there was evidence of heterogeneity.[11]

Results

Literature search

The flow of the literature review is shown in Fig. 1. Five RCTs were included in the analysis (online Table DS1).[3,12–16] Three studies combined CBT with antidepressant medication alone,[3,12,15] and one of these recruited adolescents who were resistant to treatment with an SSRI, randomising to either venlafaxine or an alternative SSRI, with or without CBT.[12] Two trials provided CBT with antidepressants and routine care.[13,14] One study was excluded as, although participants were given routine care that may have involved the use of antidepressant medication and this was compared with CBT plus routine care,[17] antidepressants were not offered to all participants.

All included studies reported 12-week outcomes after acute treatment and, at the time of writing, all except one[12] have
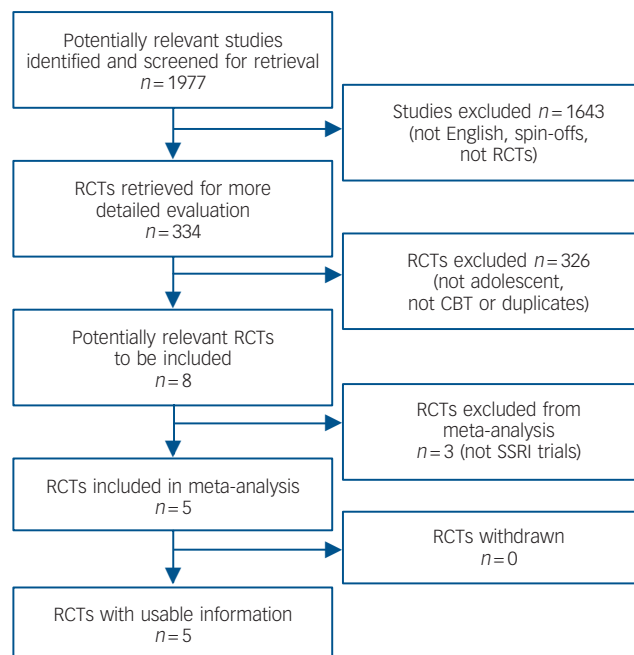

Fig. 1 Flow of literature review. RCT, randomised controlled trial; CBT, cognitive–behavioural therapy; SSRI, selective serotonin reuptake inhibitor.

published longer-term outcomes ranging from 26 weeks to 2 years. In this analysis, 26-week to 9-month outcomes were pooled.

Quality of trials

(a) Quality score: the mean rating score was 21 out of a maximum of 27. All studies scored well over half the maximum possible score (range 18–24).

(b) Randomisation: all studies described a randomisation process, but not all indicated an independent remote randomisation in their descriptions.

(c) Intention-to-treat analysis: all studies described an intention-to-treat analysis.

(d) Masking: all studies would have had a chance of assessor unmasking so maximum scores could not be given. Most studies made efforts to reduce this risk, although one study did not mention masking.

(e) Expectancy assessments: no study mentioned expectancy scores.

(f) Clarity of description of improvement: generally well-described in all studies.

(g) Informants: all trials used information from the adolescent and primary caregivers.

(h) Dosage regimes: although drug initiation regimes were described, no study commented on drug withdrawal regimes.

(i) Therapy manualisation and adherence: therapy was consistently manualised but adherence was not described in all studies.

(j) Medication adherence: assessment of medication adherence was not always reported.

Study characteristics

In total, 1206 adolescents were recruited with a mean age of 15.0 years (online Table DS1). Recruitment was largely from clinics in four studies. The TADS used the broadest recruitment strategy including juvenile justice facilities, schools and 56% of participants in TADS were recruited from advertisements. This did not appear to moderate outcomes in TADS,[18] in contrast to an earlier study.[19]

The percentage of female participants varied from 54 to 79%. The broader recruitment strategy in TADS may explain the greater preponderance of boys in this study. It also reported the highest proportion of participants from an ethnic minority background, as TADS participants were recruited in proportion to population values. The sample was therefore more representative of the ethnic mix of the American general population.[20]

Four studies focused on major depression,[3,12–14] although 16 cases of minor depression were included in the Adolescent Depression Antidepressant and Psychotherapy Trial (ADAPT). Adolescents with major and minor depression in ADAPT had similar levels of impairment on the CGAS but participants with major depression had significantly higher scores on the HoNOSCA.[21] In the Melvin et al trial, 60% of participants were diagnosed with major depression, and the remaining adolescents had dysthymic disorder or depressive disorder not otherwise specified.[15] However, baseline depression scores were greater in the Melvin trial when compared with TADS, and suicidality scores indicated almost double the levels of severity. In total, 96% of adolescents had major depression across all five trials.

With regard to severity of depression at baseline, TADS, ADAPT and the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) trial all demonstrated similarly high levels of depressive symptomatology on the CDRS–R. The Melvin et al study reported higher levels of self-reported depression than in TADS (84.4 v. 78.5) on the RADS, indicating that adolescents in the Melvin et al study also had significant levels of depression, comparable with participants in TADS and the other trials. The study by Clarke et al[13] used HRSD thus making direct comparisons difficult.

With regard to suicidality, TADS excluded active suicidality and adolescents who had attempted suicide within the previous 6 months; Melvin et al excluded active suicidality requiring admission; and Clarke et al excluded adolescents who were an 'extreme suicidal risk'. Both ADAPT and TORDIA did not exclude participants on the basis of suicide risk, although 6 out of 510 (1%) adolescents assessed for the ADAPT study were not randomised on the basis that they were too unwell and required immediate admission. The TADS was the only one that contained a placebo arm and therefore the more stringent exclusion criteria were a reflection of the inclusion of non-active treatment.

The ADAPT reported the highest levels of comorbidity (89%) and this was reflected in the high scores for impairment. At baseline, three of the studies[3,12,13] had similar levels of impairment on the CGAS (mean 50, 'obvious to noticeable problems'), despite the inclusion of more severe depression in TORDIA with a history of treatment resistance. The ADAPT study levels of impairment were greater (mean 41, 'serious to severe problems'), approaching the level for major impairment (cut-off 40). Similarly, HoNOSCA scores reflected poorer levels of functioning in ADAPT than TADS (mean scores 25 v. 17).

CBT intervention

A total of 480 adolescents received individual manualised CBT (online Table DS2). All studies offered some degree of parental participation, either jointly or as separate sessions. In the acute treatment phase, four studies offered weekly sessions for 12 weeks and the Clarke et al study provided five to nine sessions in the acute phase, although the time period was not specified or the frequency of sessions. The mean number of sessions attended in the acute phase varied from 5 (Clarke et al)[13] to 11 (TADS,[3] Melvin et al).[15] Four trials offered maintenance treatment. In ADAPT, four additional sessions were attended on average after acute treatment. Uptake was poor in the Melvin et al and Clarke et al studies. The TADS did not report on the take-up of maintenance treatment, and, at the time of writing, TORDIA only reported on acute 12-week outcomes.

With regard to type of therapists used, three trials employed at least master's level therapists;[3,12,13] ADAPT used predominantly psychiatrists; and the Melvin et al study, predominantly psychologists.

Antidepressant treatment

Fluoxetine[3,14] or sertraline[15] were selected as principle antidepressants in three studies; two studies did not specify a particular antidepressant,[12,13] and the TORDIA trial also used venlafaxine (online Table DS2). The mean daily dose prescribed was similar across the TADS and ADAPT trials and between arms (mean range 28–33 mg), and similar doses of SSRIs were used across the TORDIA study (mean 34 mg). There were no significant differences between arms in antidepressant prescribing days in the Clarke et al study, although mean doses were not reported. Fewer sessions were offered in the medication alone arms than for CBT, but only three studies reported mean attendance, which ranged from five sessions over 1 year to seven sessions over 18 or 28 weeks.[13–15] This is in contrast to the CBT arms where attendance was considerably greater in the acute phase (mean 8.4 CBT sessions attended).

Adjunct treatment

Two studies permitted 'treatment as usual' alongside study treatment;[13,14] two offered some additional psychological treatment sessions;[3,12] and one study offered additional treatment at the end of the acute phase.[15]

Depression outcomes

All trials used interviewer-rated and self-report depression measures. The results are given in online Table DS3 for 12-week outcomes and Table 1 for 26- to 36-week outcomes, and standardised effects shown in Fig. 2. The Melvin et al study[15] did not provide data for depression diagnosis outcomes, therefore this study was not included in the interview-rated analysis.

Self-report depression outcomes

The standardised analysis of all five studies for self-report depression outcomes (RADS, MFQ, BDI, CES–D) at 12 weeks did not show a significant difference between arms (standardised mean difference, SMD = 0.04, 95% CI −0.09 to 0.17, $P = 0.56$) or any evidence of heterogeneity ($\tau^2 = 0.0$, $I^2 = 0.0\%$). Data were available for three studies at follow-up (26–36 weeks),[13–15] and further analysis did not find a significant difference between arms (SMD = −0.03, 95% CI −0.29 to 0.24, $P = 0.84$) but some evidence of heterogeneity ($\tau^2 = 0.018$, $I^2 = 32.8\%$).

Interviewer-rated depression outcomes

Combining data from ADAPT, TADS, TORDIA and Clark et al, an analysis based on the standardised mean difference of interviewer-rated depression outcomes (CDRS and HRSD) at 12 weeks demonstrated that there was some evidence of between-study heterogeneity ($\tau^2 = 0.0094$; $I = 32.3\%$). Based on four studies, a DerSimonian–Laird random effects analysis gave a standardised

Table 1 Quantitative outcomes at follow-up (26–36 weeks)[a]

	Newer-generation antidepressant alone			Combined treatment			Newer-generation anti-depressant minus combined					
	n	Mean	s.d.	*n*	Mean	s.d.	MD	WMD	95% CI	*P*	τ^2	I^2, %
Children's Depression Rating Scale –Revised (CDRS–R)												
ADAPT	94	55.8	12.7	98	57.3	13.5	−1.50		−5.21 to 2.21			
TADS	74	29.2	11.2	82	27.9	9.3	1.27		−1.98 to 4.52			
Combined CDRS-R											0.68	17.7
Fixed effect								0.07	−2.37 to 2.51	0.96		
Random effect								0.04	−2.66 to 2.73	0.98		
Hamilton Rating Scale for Depression												
Clarke *et al*	61	7.8	6.9	61	6.5	6.7	1.30		−1.11 to 3.71			
Mood and Feelings Questionnaire												
ADAPT	93	15.5	15.0	98	18.9	15.5	−3.40		−7.73 to 0.93			
Reynolds Adolescent Depression Scale												
Melvin *et al*	23	67.1	20.3	24	63.3	17.9	3.76		−9.15 to 16.67			
Centre for Epidemiological Studies – Depression Scale												
Clarke *et al*	62	15.0	11.4	65	13.7	11.5	1.30		−2.68 to 5.21			
Children's Global Assessment Scale (CGAS)												
ADAPT	94	57.8	14.5	98	57.2	16.4	0.60		−3.77 to 4.97			
TADS	75	70.7	13.9	82	71.9	12.7	−1.19		−5.37 to 2.99			
Clarke *et al*	62	66.6	8.7	65	68.8	8.4	−2.20		−5.18 to 0.78			
Combined CGAS, fixed effect								−1.28	−3.40 to 0.84	0.24		
Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA)												
ADAPT	95	14.5	8.3	98	15.4	8.6	−0.90		−3.28 to 1.48			
Schedule for Affective Disorders and Schizophrenia for School-Aged Children – Present and Lifetime version – suicidality												
ADAPT	94	0.39	1.09	98	0.51	1.16	−0.12		−0.44 to 0.20			
Suicidal Ideation Questionnaire – Junior High School Version (SIQ–Jr)												
TADS	73	12.3	17.4	79	9.0	10.7	3.38		−1.26 to −1.26			
Melvin *et al*	23	20.7	26.1	24	19.3	17.7	1.41		−11.40 to −11.40			
Combined SIQ-Jr, fixed effect								3.15	−1.21 to 7.51	0.16		

MD, mean difference; WMD, weighted mean difference. ADAPT, Adolescent Depression Antidepressant and Psychotherapy Trial; TADS, Treatment for Adolescents with Depression Study.
a. Heterogeneity measures τ^2 and I^2 equal zero unless shown.

mean difference equal to 0.06 (95% CI −0.10 to 0.23, $P = 0.46$). At follow-up, data from three studies were available.[11,12,14] There was little evidence of heterogeneity ($\tau^2 = 0.0014$; $I^2 = 5.1\%$) and the standardised mean difference was again small (SMD = 0.05, 95% CI −0.14 to 0.23, $P = 0.64$).

Impairment outcomes

All trials used the same interviewer-rated impairment measure (CGAS), although data were not available for the Melvin *et al* trial. In addition, TADS and ADAPT used the HoNOSCA. At 12 weeks, pooled data for all four studies for CGAS, and a separate analysis for HoNOSCA in TADS and ADAPT, did not show any evidence of heterogeneity ($\tau^2 = 0.0$, $I^2 = 0.0\%$). This analysis did demonstrate a significant difference between arms: CGAS showed a benefit for combined treatment as compared with an anti-depressant alone (weighted mean difference, WMD = −2.32, 95% CI −3.91 to −0.74, $P = 0.004$), but this was less evident for HoNOSCA (WMD = 1.7, 95% CI −0.24 to 2.59, $P = 0.10$) (online Table DS3 and Fig. 2). Based on three studies there was no evidence of a treatment effect (WMD = −1.28, 95% CI −3.40 to 0.84, $P = 0.24$) at follow-up (Table 1 and Fig. 2), and no evidence of heterogeneity ($\tau^2 = 0.0$, $I^2 = 0.0\%$).

Improvement

Three studies used a categorical measure of improvement, CGI–I.[3,12,14] These are summarised in Table 2. At 12 weeks, there was some evidence of heterogeneity with the between-study

variance ($\tau^2 = 0.025$, $I^2 = 25\%$). In a random effects meta-analysis the pooled odds ratio of improvement in CGI–I for combined treatment compared with an SSRI was 1.35, which was not statistically significant (95% CI 0.95–1.92, $P = 0.09$). At follow-up, there was heterogeneity between studies ($\tau^2 = 0.11$, $I^2 = 43.8\%$), but no evidence of a treatment effect, with a corresponding pooled odds ratio of 0.97 (95% CI 0.49–1.92, $P = 0.93$).

Suicidality

Systematic data. With regard to suicidality, three studies used a self-report suicidal ideation questionnaire (SIQ–Jr)[3,12,15] and ADAPT reported on interviewer-rated suicidality items from the Kiddie–SADS–PL. Clarke *et al* did not report on suicidality.

At 12 weeks, in the standardised analysis there was no evidence of heterogeneity ($\tau^2 = 0.0$, $I^2 = 0\%$) or a significant difference between arms (SMD = 0.00, 95% CI −0.14 to 0.15, $P = 0.95$). Data were available for three studies at follow-up[14–16] and, similarly, there was again no evidence of a difference between arms (SMD = 0.05, 95% CI −0.18 to 0.28, $P = 0.66$), but some heterogeneity ($\tau^2 = 0.008$; $I^2 = 19.3\%$).

Spontaneously reported suicidal events. In TADS, ten suicidal events occurred in the fluoxetine alone arm (eight ideation, two attempts) *v.* six events in the combined arm (two attempts, three ideation, one self-harm), but this difference was not statistically significant at 12 weeks.[7] However, TADS reported significantly more suicidal events in the fluoxetine alone arm at 36 weeks when
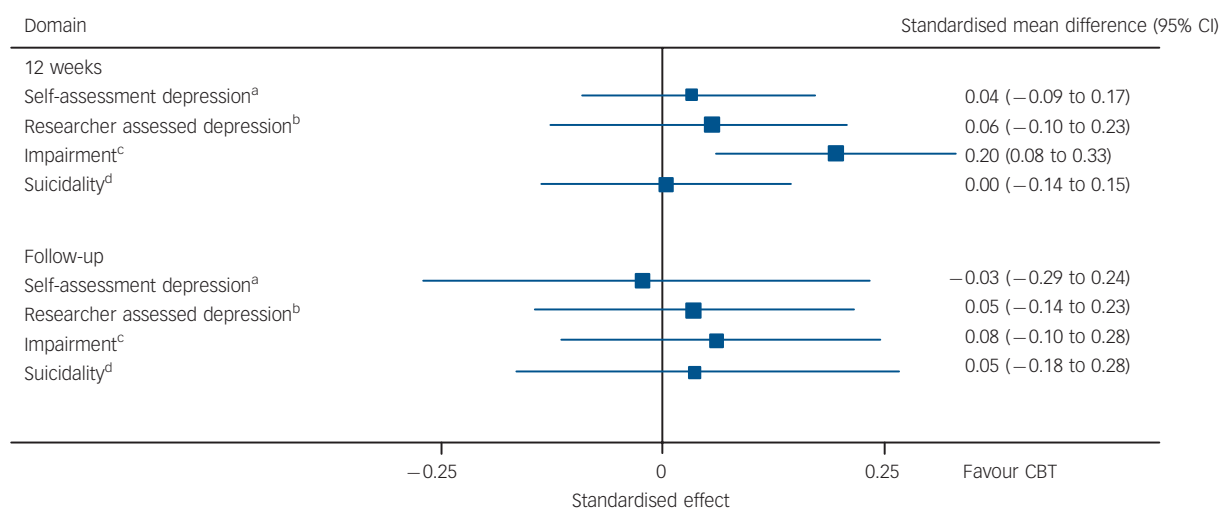
Fig. 2 Standardised effect by domain at 12 weeks and follow-up.

Positive effects represent benefit of combined cognitive–behavioural therapy (CBT) plus newer-generation antidepressant compared with antidepressant alone for all domains.
a. Mood and Feelings Questionnaire, Reynolds Adolescent Depression Scale, Centre for Epidemiological Studies or Beck Depression Inventory.
b. Children's Depression Rating Scale or Hamilton Rating Scale for Depression.
c. Children's Global Assessment Scale.
d. Schedule for Affective Disorders and Schizophrenia for School-Aged Children or Suicidal Ideation Questionnaire.

compared with the combined treatment arm.[16] The Melvin trial reported that one adolescent in the combined arm *v.* four in the SSRI arm had high levels of suicidality. The TORDIA trial reported higher rates of self-harm in those with higher suicidal ideation and receiving venlafaxine.[22]

Other adverse events

Only three trials presented adverse event data between groups. The ADAPT trial reported slightly more adverse events in the anti-depressant plus treatment as usual arm (185 *v.* 173), and reported one serious event. The most common events were headaches, nausea and tiredness, and disinhibition was reported by one participant. In TADS, sedation, insomnia, vomiting and upper abdominal pain occurred in at least 2% of participants in both medication arms, and at twice the rate of placebo. Reported numbers of psychiatric adverse events were too small to detect statistical significance, although rates were highest in the fluoxetine alone arm (11% *v.* 5.6% combined). In particular, there were four within the mania spectrum and four of irritability with

fluoxetine alone, compared with one and two respectively in the combined arm. In TORDIA, there were no significant differences between treatments with regard to the frequency of serious adverse events (14, 8.3% of participants in the no-CBT arm experienced more than one serious adverse event *v.* 23, 13.9% in the combined arm), adverse events or the frequency of removal from the study as a result of events. Sleep difficulties and irritability were the only psychiatric adverse events that occurred in at least 5% of participants, and there was only one incident of hypomania. Non-psychiatric events were more common with venlafaxine than with SSRIs.

Discussion

Key findings

There was no evidence of any significant additional benefit for CBT when combined with antidepressant medication for depressive symptoms, suicidality or global improvement in the short or longer term. There was, however, a statistically significant

Table 2 Improvement (Clinical Global Improvement Scale)

	Newer-generation antidepressant, n/N (%)	Combined, n/N (%)	OR	95% CI	P	τ²	I², %
12 weeks							
TADS	62/98 (63)	70/95 (73)	1.63	0.88–3.01			
ADAPT	44/101 (44)	42/101 (42)	0.92	0.53–1.61			
TORDIA	80/168 (48)	98/166 (59)	1.59	1.03–2.44			
Combined						0.025	25.0
Mantel–Haenszel estimate			1.37	1.01–1.84	0.04		
DerSimonian–Laird estimate			1.35	0.95–1.92	0.09		
28–36 weeks							
TADS	62/75 (83)	72/82 (88)	1.51	0.62–3.68			
ADAPT	57/94 (62)	52/98 (53)	0.73	0.41–1.30			
Combined						0.11	43.8
Mantel-Haenszel estimate			0.91	0.56 –1.47	0.69		
DerSimonian–Laird estimate			0.97	0.49–1.92	0.93		

TADS, Treatment for Adolescents with Depression Study; ADAPT, Adolescent Depression Antidepressant and Psychotherapy Trial; TORDIA, Treatment of SSRI-Resistant Depression in Adolescents.

benefit in impairment scores (CGAS) after acute treatment, although the clinical implications of this are not clear, and no benefits were seen using the HoNOSCA measure. There was some statistical evidence of heterogeneity between trial outcomes at 12 weeks and follow-up, but care needs to be taken not to over-interpret such differences as the number of studies involved in any of these analyses was small. However, the finding of no difference at follow-up was consistent across studies and populations, suggesting no additional benefit from combining CBT with antidepressant medication for the 26- to 36-week outcomes.

Comparison of study outcomes

Depression outcomes

At 12 weeks, only TADS reported a significantly favourable benefit for the combined arm over fluoxetine alone on continuous measures of depressive symptoms, and, although TORDIA did not find a significant effect of CBT with regard to change scores on the CDRS–R, significantly more adolescents responded on a pre-determined definition of response (change in CDRS–R score of 50% or more and CGI–I showing much/very much improvement).[12] Although TADS did not find a significant difference between arms in depression levels at follow-up, the combined treatment accelerated response times. None of the remaining three studies with follow-up data reported a significant difference between arms at any time point.

Impairment outcomes

Of the four studies that provided suitable data on impairment, only TADS reported a significant benefit of combined treatment over medication alone at 12 weeks for impairment with the CGAS, but not with the HoNOSCA.[23] Neither the Clarke et al study nor ADAPT found any significant differences in impairment at any time point.[13,14]

Improvement

At 12 weeks, TORDIA reported a significant benefit of combined treatment over medication alone on the CGI–I, but ADAPT and TADS did not. There were no significant differences at 28-week follow-up in ADAPT or at 36 weeks in TADS.

Suicidality

Of the four trials reporting on suicidality, all found a decrease with no significant differences between arms after acute treatment. The ADAPT found a reduction in all forms of suicidality in both arms (self-harm, thoughts, acts); TORDIA reported a significant reduction in suicidal ideation, with no differences between arms for self-harm and suicidality, although a secondary analysis found that adolescents with higher suicidal ideation and receiving venlafaxine had more self-harm adverse events; and the Melvin et al study similarly reported a reduction of suicidal thinking. At 12 weeks, TADS found that the reduction in suicidal thinking was greatest in the combined arm, and, although there were no significant differences between groups for emergent or worsening ideation after acute treatment,[7] at 36 weeks fluoxetine alone showed significantly higher rates of suicidal risk compared with combined treatment.[16] In contrast, neither of the remaining two studies that had available follow-up suicidality data demonstrated any significant differences in suicidality between arms.[14,15]

Adverse events

There was no evidence of a significant protective effect of CBT for adverse events in ADAPT and TORDIA, and although TADS found a significant protective effect at follow-up for suicidality, there was no evidence of a significant difference between arms after acute treatment for physical adverse events.[7] Antidepressant-induced manic symptoms appeared to be rare in all studies.

Similarities and differences between trials

In terms of study quality, no study scored below 50% of the total possible score and all studies scored within a relatively narrow range, therefore a sensitivity analysis was not performed.

Two of these five studies (TADS and TORDIA) concluded that combination treatment was superior to antidepressant alone, although this superiority was not consistent for all outcome measures. Two studies (ADAPT and Melvin et al) did not find any significant differences between arms and this was consistent for all outcome measures. The remaining study by Clarke et al did not find any advantage for combined treatment for depression outcomes or the CGAS, but did find a significant benefit in functioning on one measure (the Short Form–12 Functioning Mental Component Scale), together with a reduction in out-patient visits and prescription of medication. Therefore, the individual study findings have been mixed.

Cost–benefit analyses can further inform treatment decision-making; however, only two of these studies provide health economic data (ADAPT and TADS) and again the findings have been mixed.[24–26]

What could be the explanations for the conflicting findings between studies?

Exclusion criteria

These were relatively more stringent in TADS since this study included a placebo arm. This could partially explain the differing findings, particularly since a subsequent severity analysis did not find a significant difference between arms in the subsample with severe depression.[18] However, TORDIA recruited treatment-resistant adolescents, had few exclusion criteria and also found a benefit of combination treatment on some measures. Interestingly, this study did not find a protective effect of CBT on suicidality, like ADAPT, which also had few exclusion criteria. It is possible that this protective effect may only be seen in less impaired and complex cases whereby adverse effects of medication may be more apparent. Alternatively, pre-existing suicidality may reduce in severe (as defined in DSM) depression but show an increase in milder cases. Like TORDIA, ADAPT had few exclusion criteria, but had greater levels of impairment than other studies. The complexity of cases treated in ADAPT could also explain the lack of benefit seen in the combined arm, as this was a severely impaired sample, and perhaps were not able to engage with CBT in the acute phase, although neither the Clarke et al or Melvin et al studies found a significant effect on the principal measures.

Cognitive–behavioural therapy

Fewer sessions were attended in ADAPT and the Clarke et al study at 12 weeks compared with TADS, which could be another explanation for lack of effect; however, fewer sessions were also attended in TORDIA, where an effect was found. On the contrary, a similar number of sessions to TADS were attended in the Melvin et al trial, but no effect was found. Therefore, the number of sessions attended does not consistently explain the differences in findings. The quality of CBT offered could be an explanatory

variable; however, insufficient information is available on this to make comparisons between studies. Nevertheless, all trials used a manualised form of CBT in order to improve fidelity and quality.

Additional treatment

The ADAPT and the Clarke *et al* study offered routine care to all participants, which would make it more difficult to detect an additional benefit of CBT. However, the Melvin *et al* trial did not offer additional treatment and still found no effect.

Recruitment

Only TADS and TORDIA used advertisements to recruit participants, which could offer an explanation for the differing findings in these trials. However, a further analysis in TADS did not find that referral source either predicted or moderated outcome.[18]

Strengths and limitations

A large number of adolescents were included in this meta-analysis, including findings from two countries outside the USA. However, there were only a relatively small number of studies available for analysis, reflecting the difficulties of running psychological treatment trials in this field. The pool of available studies was smaller than the data available in adult depression, where combination treatment was deemed better than monotherapy,[4] so there is the possibility of a type II error in this study. The generalisability of the findings from this meta-analysis are also limited by the varying populations and methodologies used in each study. It is also likely that there was heterogeneity between studies with regard to the administration of CBT; however, unlike the prescription of antidepressants in medication trials, administration of psychological treatment is difficult to homogenise, even with manualised therapy within a single study. Heterogeneity of treatment delivery is also a reflection of real-life practice and therefore it is possible that these combined findings may in fact be a more accurate reflection of the wider spectrum of CBT delivery across services, rather than the results from one single study. With regard to outcome measures, these trials used response (i.e. improvement) as their main outcome, but full remission data may be more informative. Remission is a higher standard than response and there is some evidence to suggest that remission outcomes may confer a more favourable outcome for active treatment than response.[27] Not all data were available for all time points or for a severity subanalysis.

Implications

The results of this meta-analysis would suggest that adding CBT to antidepressants in adolescent major depression provides an additional benefit for reducing impairment in the short-term, but not for alleviating depressive symptoms, suicidality or for gains in overall improvement. Therefore, the advantages of combined treatment appear to be limited. However, there are a number of caveats to this finding. The samples studied were heterogeneous and it remains unclear whether there may be a differential effect in different subgroups. There is some evidence from TADS that the most impaired adolescents do less well with combined treatment in the acute treatment phase,[18] hence combined treatment may be differentially beneficial depending on severity and complexity. The context of treatment may also be important, and the addition of CBT to antidepressants may not improve outcomes in the short-term if high-quality 'routine

care' is readily available. However, the components of routine care in the relevant studies was not manualised and therefore it is not clear which aspects of routine clinical care were undertaken and which may be beneficial.

In conclusion, the results of this meta-analysis need to be considered in the light of certain limitations. The implications are that combined treatment with CBT may not always be necessary for all adolescents with depression who receive antidepressants in the first instance, in contrast to the current advice from NICE, but it remains unclear which aspects of adjunct clinical care may be important in achieving an optimal response. Although this study suggests that CBT may only have a limited effect, further research is necessary to determine individual predictors of response and non-response, together with health economic data, in order to target treatment most effectively and determine which youths are likely to gain most benefit in both the short and longer term.

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EXTRA CONTENT ONLINE

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psychiatry in pictures

The first psychiatric hospital in China

Jie Li

Founder of the first psychiatric hospital, Dr John G. Kerr (back row, left) and the male patients (1898)

The development of modern Chinese psychiatry was influenced by both Western medicine and colonialism. During the 19th century, Western psychiatrists and ministers established asylums for refugees and mentally ill people in Asia. One of them was Dr John Glasgow Kerr (1824–1901), a Presbyterian medical missionary, who in 1898 founded in Canton (now Guangzhou) the first psychiatric hospital in China. It was called Hui Ai Hospital, which means the fraternity from Christianity. Between 1898 and 1927, the hospital admitted 6599 individuals with mental disorders (4428 male and 2171 female). After Dr Kerr died in 1901, the hospital was renamed John Kerr Hospital. Since its founding, many other hospitals have been established in other places in China, such as Beijing (1906), Suzhou (1923) and Shanghai (1935). Patients with mental disorders gradually received humane solicitude and modern Chinese psychiatry has been developed. John Kerr's hospital is still in existence, now under a new name, Guangzhou Psychiatric Hospital. Dr Kerr, a pioneer of mental healthcare in China, is worthy of praise.

Jie Li, MD, President of Guangzhou Society of Psychiatry, Vice-President of Guangzhou Psychiatric Hospital.