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Review article

Is cognitive behavioural therapy an effective complement to antidepressants in adolescents? A meta-analysis

Calati R, Pedrini L, Alighieri S, Alvarez MI, Desideri L, Durante D, Favero F, Iero L, Magnani G, Pericoli V, Polmonari A, Raggini R, Raimondi E, Riboni V, Scaduto MC, Serretti A, De Girolamo G. Is cognitive behavioural therapy an effective complement to antidepressants in adolescents? A meta-analysis.

Objective: Evidence on effectiveness of combined treatments versus antidepressants alone in adolescents consists on a few studies in both major depressive and anxiety disorders. A meta-analysis of randomised 12-week follow-up studies in which antidepressant treatment was compared to combined treatment consisting of the same antidepressant with cognitive behavioural therapy has been performed.
Methods: Data were entered into the Cochrane Collaboration Review Manager software and were analysed within a random effect framework. A quality assessment has been performed through Jadad Scale.
Results: Higher global functioning at the Children's Global Assessment Scale was found in the combined treatment group ($p < 0.0001$) as well as higher improvement at the Clinical Global Impressions Improvement Scale ($p = 0.04$). No benefit of combined treatment was found on depressive symptomatology at the Children's Depression Rating Scale – Revised.
Conclusion: Combined treatment seems to be more effective than antidepressant alone on global functioning and general improvement in adolescents with major depressive and anxiety disorders.

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Summations

- Evidence of the superiority of combined treatment [antidepressant and cognitive behavioural therapy (CBT)] in comparison with antidepressant alone in both depressive and anxiety disorders has been found after 12-week treatment.
- A higher global functioning [Children's Global Assessment Scale (CGAS)] and a more marked improvement [(Clinical Global Impressions Improvement (CGI-I)] was found in patients treated with the combined treatment for 12 weeks.
- Combined treatment seems to have an unspecific effect on global functioning and general improvement rather than on depressive symptomatology.

Considerations

- The pooling of studies on both major depression and anxiety disorders obviously represents a limitation from the point of view of diagnostic homogeneity.
- The reported results pertain to the acute treatment outcome (12 weeks) and could not be extended to longer follow-up.
- The use of different antidepressant classes and molecules represents a further source of heterogeneity.

Introduction

The research evidence on the effectiveness of antidepressants and their risk-benefit ratio in adolescents is a debated issue (1–6). High caution has been suggested regarding antidepressant administration in this age group (2,5) and specific indications for psychological or at least combined therapies as first-line treatments in young patients have been reported (6).

However, according to guidelines, the prescription of antidepressants in adolescents should be considered in the case of moderate-to-severe depression or anxiety which fails to respond to psychological therapy (7–11), always within the context of a comprehensive management of the patient. This raises the issue if antidepressants should be prescribed in combination with psychological therapies or alone.

A few recent studies focused on the comparison between antidepressant alone versus combined therapy (12), filling up the gap of earlier research (13). In particular, three multi-centre, controlled, publicly funded clinical trials have been performed on this topic on major depressive disorder (MDD) patients: the Treatment of Adolescent Depression Study (TADS) (14), the Treatment of Resistant Depression in Adolescents (TORDIA) (15), and the Adolescent Depression and Psychotherapy Trial (ADAPT) (16).

The National Institutes of Health-funded TADS study investigated the efficacy of 12-week cognitive behavioural therapy (CBT) in comparison with fluoxetine alone, fluoxetine plus CBT, and placebo in 439 adolescents with moderate-to-severe depression (14). According to the reduction in the Children's Depression Rating Scale – Revised (CDRS-R), combined treatment was superior to all other treatments, while according to the rate of Clinical Global Impressions Improvement (CGI-I) responders, fluoxetine alone and combined treatment did not differ but they have been found to be both superior to CBT alone and placebo. In the same line of evidence, the National Institute of Mental Health-funded TORDIA study showed that in 334 depressed adolescents who have failed to respond to a selective serotonin reuptake inhibitor (SSRI) at adequate dose and duration, a switch to a 12-week combined therapy consisting in another antidepressant plus CBT resulted in a higher response than a switch to another antidepressant alone (15). However, from the National Health Service-funded ADAPT trial emerged a contrasting result: fluoxetine plus routine monitoring has been compared to fluoxetine plus CBT in 208 depressed adolescents who did not respond to a brief psychosocial intervention and the combined treatment was not associated with an improved outcome in comparison with SSRI alone (16).

In another MDD study comparing a treatment as usual (TAU) control condition consisting primarily of SSRI medication and the combined treatment with brief CBT, the combined treatment did not show detectable improvement on the Children's Global Assessment Scale (CGAS) (17).

Pertaining to anxiety, results run in the same direction of studies on MDD: a randomised controlled trial (RCT) on 488 adolescent patients with a primary diagnosis of separation anxiety disorder, generalised anxiety disorder or social phobia reported that the combination of sertraline and CBT were more effective in comparison with sertraline alone, CBT alone and placebo (18).

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Recently, an extensive meta-analysis of RCTs focused on newer-generation antidepressants and CBT in adolescent depression has been performed (19).

Aims of the study

We performed a new meta-analysis with the purpose of providing a more in depth estimation of combined treatment effect after 12-week treatment (comparison data with the previously published meta-analysis (19) are available on request). Moreover, we focused on the comparison between antidepressant alone versus combined treatment with antidepressant plus CBT not only in major depressed but also in anxiety disorder adolescents. In fact, our specific aim was to evaluate antidepressant impact on the global functioning of young patients throughout different diagnoses. However, we further performed sensitivity analyses on diagnostic homogeneous samples.

Methods

Search strategy

An electronic search of the literature was performed to identify studies having as a primary outcome the investigation of the effectiveness of antidepressants alone versus combined treatments in adolescents.

PubMed, PsychINFO and Cochrane databases were searched for articles published until April 2011 using any combination of the terms 'depressive disorder', 'antidepressant', 'combined treatment', 'CBT' and 'randomised controlled trials'. Reference lists from identified articles and reviews were used as well to find additional studies to be included.

Study selection

Fifteen reviewers independently screened the yield from the searches to identify potentially relevant studies. Studies were included if they: (a) were written in English language; (b) included adolescent patients affected by a psychiatric disorder diagnosed with the Diagnostic and Statistical Manual of Mental Disorders or the International Classification of Diseases and treated with an antidepressant; (c) showed comparison between antidepressant alone versus combined therapy; (d) include CBT therapy in the combined arm; (e) showed scores of at least one of the most used scales to assess symptom severity or clinical improvement in this population; and (f) showed a follow-up at 12 weeks. Moreover, we decided to perform the analyses on a specific scale in the presence of at least three studies reporting the related scores.

Studies were excluded if: (a) they were performed on overlapping samples and (b) no scores of symptomatological improvement or severity scales were separately given for the two trial arms.

Outcome measures

Primary outcome. The primary outcome was the comparison between antidepressant alone versus combined treatment groups in terms of scores at the CGAS through different diagnoses. Mean scores and standard deviations have been compared.

Secondary outcomes. The secondary outcomes were the comparison between antidepressant alone versus combined treatment groups in terms of scores at the CDRS-R and at the CGI-I. For CDRS-R mean scores and standard deviations have been compared, while for the CGI-I the number of patients reporting a CGI improvement score of 1 (very much improved) or 2 (much improved) has been compared with the total. Moreover, as secondary outcomes we performed some sensitivity analyses to separately consider MDD patients for each scale.

Data extraction

For each study, the following information were extracted: first author, publication year, total sample size and sample sizes for each sub-group, diagnostic status, gender ratio, mean age and age ranges, reported ethnicity, treatment and daily dose, CBT number of sessions and duration, duration of follow-up, scales used for the assessment and main results (Table 1).

Assessment of quality

The quality of the included studies has been assessed using the Jadad Scale (20). This instrument assesses the quality of (RCTs) allocating a total score comprised between zero (very poor) and five (rigorous). It assessed the randomisation, the blinding and the withdrawal description. Furthermore, potential publication bias was assessed using both funnel plots and Egger test (21).

Data analysis

Data were entered into the Cochrane Collaboration Review Manager software (RevMan version 5.1). Individual and pooled 95% confidence intervals (CIs) were calculated. Heterogeneity between studies was assessed with chi-squared test of fit. The significance of the pooled effect size was determined using a Z-test.

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Table 1. Studies included in the meta-analysis

References	Study design	Sample size	Diagnosis	Gender (males%)	Age (mean and age range)	Ethnicity	Treatments	CBT	Follow-up	Instruments	Results	Quality assessment – Jadad score
14		$N = 439$	MDD	45.6%	14.6 ± 1.5 (12–17 years)	White: 73.8%	Fluoxetine, 10–40 mg/day	15 sessions, 50–60 min each	12 weeks	CDRS-R	Combined > others	5
	CBT	$N = 111$								CGI-I		
	SSRI	$N = 109$								CGAS		
	SSRI + CBT	$N = 107$								RADS		
	Placebo	$N = 112$								SIQ		
17		$N = 152$	MDD			—	TAU SSRI	9 sessions, 60 min each	52 weeks	CES-D	Weak CBT effect after 52 weeks	2
	CBT + TAU SSRI	$N = 77$		22.7%	15.3 ± 1.60					YSR		
	TAU SSRI	$N = 75$		22.1%	15.3 ± 1.62 (12–18 years)					CGAS		
										SAS-SR		
										SF-12		
										CBCL		
16		$N = 208$	MDD	26.0%	11–17 years	White: 97.4%	Fluoxetine, 10–40 mg/day	19 sessions	12 weeks	CDRS-R	NS	NA
	SSRI + routine care	$N = 103$								CGI-I		
	SSRI + routine care + CBT	$N = 105$								CGAS		
										MFQ		
										HNOS		
15		$N = 334$	Resistant	30%	12–18 years	White: 82%	Paroxetine, citalopram or fluoxetine, 20–40 mg/day Venlafaxine, 150–225 mg/day	12 sessions, 60–90 min each	12 weeks	CDRS-R	Combined > others	5
	SSRI	$N = 85$	MDD							CGI-I		
	SSRI + CBT	$N = 83$								CGI-S		
	Venlafaxine	$N = 83$							CGAS			
	Venlafaxine + CBT	$N = 83$								SIQ		
										BDI		

Table 1. Continued

References	Study design	Sample size	Diagnosis	Gender (males%)	Age (mean and age range)	Ethnicity	Treatments	CBT	Follow-up	Instruments	Results	Quality assessment – Jadad score
18		$N = 488$	Anxiety disorders (separation anxiety, generalised anxiety, social phobia)	50.4%	10.7 ± 2.8 (7–17 years)	White: 78.9%	Sertraline, 25–200 mg/day	14 sessions, 60 min each	12 weeks	CGI-I	Combined > others	5
	CBT	$N = 139$								CGI-S		
	SSRI	$N = 133$								PARS		
	SSRI + CBT	$N = 140$								CGAS		
	Placebo	$N = 76$										

BDI, Beck Depression Inventory; CBCL, Child Behaviour Checklist; CES-D, Center for Epidemiological Studies–Depression Scale; CGI-S, Clinical Global Impressions Severity; HNOS, Health of the Nation Outcome Scales; MFQ, Mood and Feelings Questionnaire; NA, not applicable; NS, not significant; PARS, Pediatric Anxiety Rating Scale; RADS, Reynolds Adolescent Depression Scale; SAS-SR, Social Adjustment Scale-Self Report for Youth; SF-12, Short Form-12; SIQ, Suicidal Ideation Questionnaire; YSR, Youth Self-Report.

Data were analysed within a random effect framework because of the assumption of the presence of significant between-study heterogeneity. In the first analysis we included the whole studies. In further sensitivity analyses we removed some studies as described to reduce the heterogeneity.

Results

Inclusion/exclusion process and study description

The initial search yielded 2023 articles. Titles and abstracts were carefully revised in order to investigate if they fulfilled inclusion criteria. Of these articles, 1974 have been excluded because they were not performed on adolescent samples, they were not RCTs or they were reviews. The full texts of the 49 remaining studies were obtained and the reviewers independently applied inclusion/exclusion criteria. Forty-four studies were then excluded because they did not show two arms in which antidepressant alone versus combined therapy were tested or they were performed on overlapping samples (see Fig. 1 for the flow diagram).

Five studies met the criteria for inclusion in this meta-analysis. A summary of the included studies is provided in Table 1. Of these, four studies included MDD samples (14–17) and one included anxiety disorder sample (18).

The methodological quality of the included studies according to the Jadad Scale (20) is shown in Table 1. Three of the four included studies were

Fig. 1. Flow diagram of the study inclusion/exclusion process.

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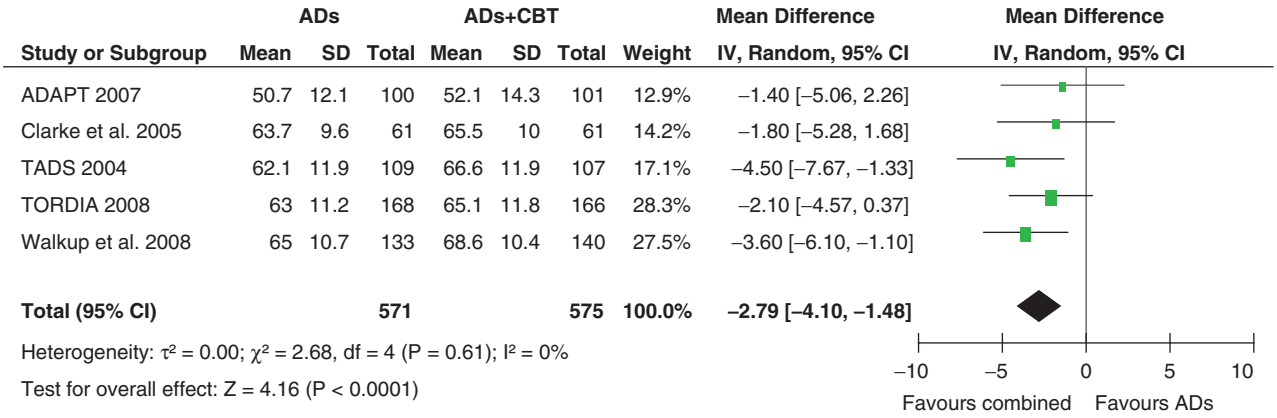

Fig. 2. Children's Global Assessment Scale scores in antidepressant versus combined treatment groups.

RCTs with a high methodological quality (score of 5). One study (16) could not be evaluated as it was a pragmatic randomised superiority trial.

Primary outcome

We firstly performed an analysis including both MDD and anxiety diagnoses for the CGAS scale. Random effects indicated an association between higher CGAS scores (higher global functioning) in the combined treatment group ($Z = 4.16$, $p < 0.0001$) without evidence of between-study heterogeneity ($\chi^2 = 2.68$, df = 4, $p = 0.61$, $I^2 = 0\%$) (Fig. 2). The funnel plot showed a symmetric inverted shape. Egger's test indicated no evidence of publication bias ($p = 0.32$).

Removing the anxiety disorder study in a further sensitivity analysis the association remained significant ($Z = 3.16$, $p = 0.002$) without heterogeneity ($\chi^2 = 2.13$, df = 3, $p = 0.55$, $I^2 = 0\%$).

Secondary outcomes

Considering the CGI-I scale, significantly higher rate of improved patients has been found in the combined treatment group ($Z = 2.02$, $p = 0.04$) (Fig. 3). Nevertheless, as expected, there was evidence of between-study heterogeneity ($\chi^2 = 11.28$, df = 3, $p = 0.01$, $I^2 = 73\%$). The funnel plot showed a symmetric inverted shape. Egger's test indicated no evidence of publication bias ($p = 0.88$).

In a sensitivity analysis, we removed the only study performed on anxiety disorder patients to observe if it consistently affected the heterogeneity. Random effects indicated no more between-study heterogeneity ($\chi^2 = 2.65$, df = 2, $p = 0.27$, $I^2 = 25\%$) with results in the same direction but with a reduced significance level ($Z = 1.75$, $p = 0.08$).

Finally, considering the CDRS-R scale, no difference has been found between antidepressant alone and combined treatment ($Z = 0.74$, $p = 0.46$), without evidence of between-study heterogeneity ($\chi^2 = 4.18$, df = 2, $p = 0.12$, $I^2 = 52\%$) (Fig. 4). In this

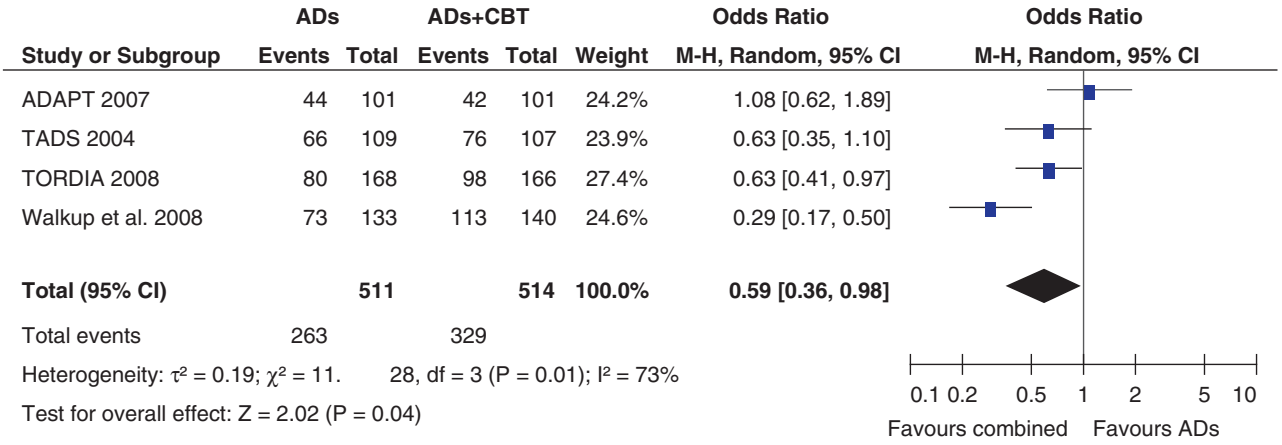

Fig. 3. Clinical Global Impressions Improvement in antidepressant versus combined treatment groups [patients reporting a CGI improvement score of 1 (very much improved) or 2 (much improved) have been compared with the total].

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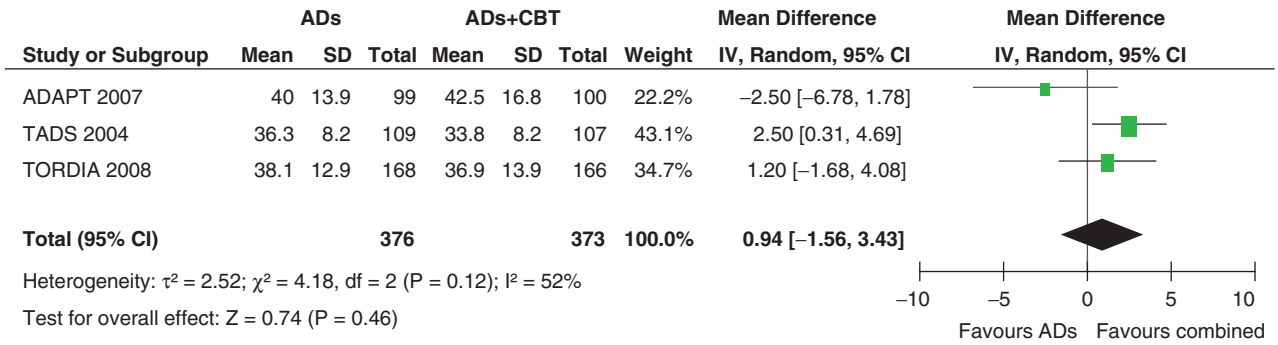

Fig. 4. Children's Depression Rating Scale – Revised scores in antidepressant versus combined treatment groups.

case, the funnel plot showed a non-symmetric shape and Egger's test indicated evidence of publication bias ($p = 0.04$).

Discussion

Higher global functioning in patients treated with the combined treatment. The aim of this meta-analysis was to compare the efficacy of antidepressant treatment alone versus the combination of an antidepressant with CBT in adolescent population with different psychiatric diagnoses (MDD and anxiety disorders). Present results are similar to the ones reported in adult samples (22,23): a mild evidence of the superiority of the combined treatment in both depressive and anxiety disorders has been found after 12-week treatment.

In detail, a higher global functioning (CGAS) was found in patients treated with the combined treatment for 12 weeks. Similarly, a more marked improvement (CGI-I) has been found in the same group. On the contrary, when depressive symptomatology has been considered, no effect of combined treatment was found. These findings substantially confirmed the ones reported by Dubicka end colleagues (19), but with a higher significance regarding global functioning ($p < 0.0001$ considering anxiety disorders and $p = 0.002$ without considering them).

Consequently, combined treatment seems to have an unspecific effect on global functioning and general improvement rather than on depressive symptomatology. This result could be due to a plausible CBT specific effect on the promotion of coping strategies and healthy behaviours rather than on the correction of cognitive distortions associated with depression in this population. This is in line with evidence of a higher efficacy of CBT in patient subgroups characterised by milder depression (24).

Anxiety disorders seem to have the most favourable outcome, in line with findings from TORDIA trial, in which the number of comorbid anxiety diagnoses was a positive moderator of combined treatment effects (25).

The fact that ADAPT results run in the opposite direction from other studies (Figs 3 and 4) could be interpreted considering that only non-responders to an initial psychotherapy were randomised into this trial and consequently patients less responsive to psychotherapy might have been selected.

Limitations

To the best of our knowledge, this is the first meta-analysis on this topic covering both depressive and anxiety disorders. A strength of this study was the quality assessment of the included trials through a specific scale.

However, several limitations have to be listed. First of all, the pooling of four studies on major depression together with a trial on anxiety disorders obviously represents a limitation from the point of view of diagnostic homogeneity, also considering the small total number of included trials. However, the primary aim of the present meta-analysis was to specifically evaluate the global functioning after 12 weeks of combined treatment versus antidepressant alone throughout different diagnoses. Moreover, some sensitivity analyses were performed to separately consider MDD patients.

Similarly, in the included studies different kinds of CBT treatments have been offered, especially considering specific interventions for major depressive and anxiety disorders. Moreover, fewer sessions were attended in the study by Clarke et al. (17) in comparison with others (Table 1).

Another limitation is represented by the difference in age ranges among the studies: in fact the article on anxiety (18) was different from the others (Table 1) since presented results of children between the ages of 7 and 17 years.

Furthermore, the reported results pertain to the acute treatment outcome (12 weeks) and could not be extended to longer follow-up. In fact at the end of

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the 36-week treatment, the rate of clinical response in TADS trial was similar across fluoxetine, CBT, and combined treatment, thus indicating that the benefit of the combination of antidepressant and CBT may be limited to the acceleration of the improvement process (26). Furthermore, baseline scores for each scale have not been included in the analyses.

Moreover, even if fluoxetine, the only SSRI currently approved by the US Food and Drug Administration for the treatment of adolescent depression, is the molecule administered in three of the five studies, some considerations should be taken into account in the evaluation of results: (a) the use of a different molecule (sertraline) in the study on anxiety disorders (18), (b) the inclusion of venlafaxine in the TORDIA trial (15), and (c) and the fact that in the study by Clarke et al. (17) the administered molecule was not specified but only the antidepressant class (SSRIs).

Finally, in the whole studies, the combined treatment with CBT has been evaluated and the results cannot be generalised to alternative psychosocial treatments.

In conclusion, combined treatment seems to be more effective than antidepressant treatment alone on global functioning and general improvement in adolescents with major depressive and anxiety disorders. Future studies should focus on different psychotherapeutic treatments, such as interpersonal psychotherapy.

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References

1. Michael KD, Crowley SL. How effective are treatments for child and adolescent depression? A meta-analytic review. Clin Psychol Rev 2002;**22**:247–269.
2. Papanikolaou K, Richardson C, Pehlivanidis A, Papadopoulou-Daifoti Z. Efficacy of antidepressants in child and adolescent depression: a meta-analytic study. J Neural Transm 2006;**113**:399–415.
3. Reinblatt SP, Riddle MA. The pharmacological management of childhood anxiety disorders: a review. Psychopharmacology 2007;**191**:67–86.
4. Tsapakis EM, Soldani F, Tondo L, Baldessarini RJ. Efficacy of antidepressants in juvenile depression: meta-analysis. Br J Psychiatry 2008;**193**:10–17.
5. Masi G, Liboni F, Brovedani P. Pharmacotherapy of major depressive disorder in adolescents. Expert Opin Pharmacother 2010;**11**:375–386.
6. Gentile S. Antidepressant use in children and adolescents diagnosed with major depressive disorder: what can we learn from published data? Rev Recent Clin Trials 2010;**5**:63–75.
7. Connolly SD, Bernstein GA. Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. J Am Acad Child Adolesc Psychiatry 2007;**46**:267–283.
8. Birmaher B, Brent D, Bernet W et al. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. J Am Acad Child Adolesc Psychiatry 2007;**46**:1503–1526.
9. NICE. Depression in Children and Young People. Identification and Management in Primary, Community and Secondary Care. 2005. URL http://www.nice.org.uk [accessed on April 2011].
10. Baldwin DS, Anderson IM, Nutt DJ et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2005; **19**:567–596.
11. Thorpe L, Whitney DK, Kutcher SP, Kennedy SH. Clinical guidelines for the treatment of depressive disorders. VI. Special populations. Can J Psychiatry 2001;**46**(Suppl. 1):63S–76S.
12. Tandon M, Pruett JR Jr. An overview of the use of antidepressants in children and adolescents. Mo Med 2008;**105**:79–84.
13. van Engeland H. Pharmacotherapy and behaviour therapy–competition or cooperation? Acta Paedopsychiatr 1993;**56**:123–127.
14. 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**:807–820.
15. Brent D, Emslie G, Clarke G et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. JAMA 2008;**299**:901–913.
16. Goodyer I, Dubicka B, Wilkinson P et al. Selective serotonin reuptake inhibitors (SSRIs) and routine specialist care with and without cognitive behaviour therapy in adolescents with major depression: randomised controlled trial. BMJ 2007; **335**:142.
17. Clarke G, Debar L, Lynch F et al. A randomized effectiveness trial of brief cognitive-behavioral therapy for depressed adolescents receiving antidepressant medication. J Am Acad Child Adolesc Psychiatry 2005;**44**:888–898.
18. Walkup JT, Albano AM, Piacentini J et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. N Engl J Med 2008;**359**:2753–2766.
19. Dubicka B, Elvins R, Roberts C, Chick G, Wilkinson P, Goodyer IM. Combined treatment with cognitive-behavioural therapy in adolescent depression: meta-analysis. Br J Psychiatry 2010;**197**:433–440.
20. Jadad AR, Moore RA, Carroll D et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;**17**:1–12.

21. Egger M, Smith GD, Phillips AN. Meta-analysis: Principles and procedures. BMJ 1997;**315**:1533–1537.
22. Molenaar PJ, Dekker J, Van R, Hendriksen M, Vink A, Schoevers RA. Does adding psychotherapy to pharmacotherapy improve social functioning in the treatment of outpatient depression? Depress Anxiety 2007;**24**:553–562.
23. Sharp DM, Power KG, Simpson RJ, Swanson V, Anstee JA. Global measures of outcome in a controlled comparison of pharmacological and psychological treatment of panic disorder and agoraphobia in primary care. Br J Gen Pract 1997;**47**:150–155.
24. Curry J, Rohde P, Simons A et al. Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). J Am Acad Child Adolesc Psychiatry 2006;**45**:1427–1439.
25. Asarnow JR, Emslie G, Clarke G et al. Treatment of selective serotonin reuptake inhibitor-resistant depression in adolescents: predictors and moderators of treatment response. J Am Acad Child Adolesc Psychiatry 2009;**48**:330–339.
26. March JS, Silva S, Petrycki S et al. The Treatment for Adolescents With Depression Study (TADS): long-term effectiveness and safety outcomes. Arch Gen Psychiatry 2007;**64**:1132–1143.

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