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REVIEW ARTICLE

# Are antidepressants effective in quality of life improvement among children and adolescents? A systematic review

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There is some evidence indicating that psychotropic medications might lead to health-related quality of life (QOL) improvements among children and adolescents with psychiatric disorders. The aim of this systematic review is to assess evidence regarding whether antidepressant treatment improves QOL among children and adolescents with depressive or anxiety disorders. A comprehensive search resulted in 5 clinical trials to be included in this review: 4 trials with major depressive disorder (MDD) and 1 trial with social anxiety disorder (SAD). In one MDD trial, fluoxetine combined with cognitive behavior therapy (CBT) significantly improved QOL compared to fluoxetine or CBT alone (effect sizes were 0.53 and 0.69, respectively). In 2 combined trials, sertraline alone significantly improved QOL among adolescents with MDD (effect size was 0.29), but not among children with MDD. Essentially, it was observed that antidepressants in these trials had minor positive effects on QOL improvement, which were lower than their potential to improve depressive symptoms. Although fluoxetine with CBT or sertraline monotherapy were shown to have some potential to improve QOL, this systematic review found inconclusive evidence that antidepressant treatments improve QOL among children and adolescents with depressive or anxiety disorders. More research is required, considering that QOL is currently under-evaluated in clinical trials with antidepressants among children and adolescents and available trials have limited methodological quality when reporting QOL data.

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## Introduction

Since the 1990s, health-related quality of life (QOL) has been acknowledged as one of the best indicators of psychological dysfunction and disabilities associated with chronic as well as infectious diseases, injuries, and other health problems.[1–4] As a multidimensional concept that simultaneously assesses physical, mental, and social functioning domains, QOL goes beyond directly measuring population health, life expectancy, and causes of death, focusing on how the patient perceives impacts of a current health status on everyday well-being and functioning.[1]

Among children and adolescents with mental health problems, QOL gained significant research attention in the early 2000s.[5] Sawyer *et al.*[6] were the first to show in a standardized way that in children and adolescents with attention deficit/hyperactivity disorder (ADHD), major depressive disorder (MDD), or conduct disorder (CD), QOL was significantly impaired across various domains. Later studies have confirmed these findings, but also have shown that in particular disorders, specific QOL domains could be more impacted than others, such as emotional functioning in mood disorders or school functioning in ADHD.[7–12] Additionally, it was observed that QOL in children and adolescents with psychiatric problems might be improved by reducing psychiatric symptoms, though it was also possible to improve QOL without psychiatric symptom reduction.[13] So far, a QOL assessment has been acknowledged to provide a more comprehensive picture of the impacts that a mental health problem has on different aspects of well-being and functioning, going beyond simple symptoms evaluations and providing more data in diagnostic evaluations and treatment planning.[5,14]

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Together with other patient-reported outcomes (PROs), QOL has been recognized by the regulatory bodies to have an added value when reporting treatment efficacy of interventions in clinical trials, drugs registration, or marketing processes.[2,3,15–17] Providing QOL data about the impacts of specific treatments extends the efficacy data, because these data go beyond simply reporting about treatment effects they have on symptoms reduction to focusing on treatment effects they have on different aspects of well-being and functioning.[2] Therefore, primary measures, such as symptom-rating scales, have been more frequently supplemented with QOL measures in clinical trials among different populations with chronic disorders/conditions in order to assess the efficacy of specific interventions more comprehensively.[18] Over the past decade, QOL has also been recognized as a measure of efficacy in clinical trials among people with psychiatric disorders, although QOL is used to a lesser extent in trials with psychiatric disorders than in those with other disorders.[14] Considering the efficacy of specific psychotropic medications in terms of QOL data is particularly relevant because some emerging evidence suggests that various psychological and psychopharmacological interventions might lead to QOL improvements among adults with psychiatric disorders,[14,19,20] but also among children and adolescents, predominantly with ADHD and MDD.[21–23]

Although some variations in the prescribing patterns exist between clinicians, antidepressants are becoming increasingly used among children and adolescents for mood and anxiety disorders, where selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are gaining popularity compared with tricyclic/tetracyclic antidepressants (TCAs).[24–27] Currently, much of what is known about efficacy, tolerability, and safety of different antidepressants is based largely on measures that directly assess levels of specific symptoms, on global clinician's ratings of symptom severity or improvement, or global levels of functioning. To date, no systematized data about QOL as a measure of efficacy in clinical trials of antidepressants has been published, and the treatment impact of antidepressants on QOL remains uncertain. Therefore, the aim of this systematic review of clinical trials is to assess evidence on whether antidepressant treatments improve QOL in children and adolescents with depressive or anxiety disorders.

## Review of Antidepressant Clinical Trials Including QOL

Criteria needed for study inclusion in this systematic review were as follows: (1) a clinical trial must have evaluated the use of at least 1 antidepressant among children and/or adolescents up to 18 years of age with a depressive or anxiety disorder diagnosis, and (2) a clinical trial must have included a QOL instrument as an efficacy outcome measure. The QOL instrument used should be a psychometrically sound measure that assesses health-related QOL in children and/or adolescents.[28,29] At a minimum, the study must have provided an appropriate comparison for QOL values post-antidepressant intervention.

In order to ensure a comprehensive search for all clinical trials published until February 2013, multiple electronic databases and manual literature searches were taken into consideration. Three independent electronic database searches were performed, including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PsychInfo, Scopus, CINAHL Plus, Clinical Trials, and pharmaceutical companies' Web sites. Reference sections of pertinent review articles and meta-analyses were separately searched by the principal author, as were reference sections of included studies.[30–32] The following keywords with variations were combined in the searches: "antidepressant," "specific antidepressant group," generic names of all available antidepressants, "child," and "adolescent." No language restrictions were applied.

Data from selected trials were extracted by two coders (DS and IT). The following variables were included: (1) type of disorder; (2) type of antidepressant used in the trial, with allocated groups if applicable; (3) type of study; (4) length of treatment; (5) the main primary efficacy outcome measure; and (6) the QOL instrument used, with all mean value scores (M) and respective standard deviations (SD) or standardized effect size values (SE). Considering that the main object of this review is the QOL assessment, the methodological quality of reporting QOL data was assessed in each trial as an indication of the study's quality. Due to the lack of formal standards for reporting QOL data in clinical trials using psychotropic medications, the criteria known as the Minimum Standard Checklist for Evaluating Health-Related Quality of Life Outcomes was applied.[33] This is an 11-item checklist that was developed on the basis of good practice in conducting a QOL evaluation, and it was aimed at evaluating the reported quality of the QOL assessment methodology in a clinical trial. Although the checklist was primarily developed for cancer clinical trials, it is not cancer research specific and it is recognized as a general checklist for evaluating the QOL assessment methodology in any clinical trial.[34] This checklist addresses conceptual, measurement instrumentation, methodological, and interpretation issues that a given trial should report in order to have methodologically sound QOL outcomes. The checklist items were devised to have a dichotomous answer; these can be scored as "yes" (giving a score of 1) or "no" (giving a score of 0), and

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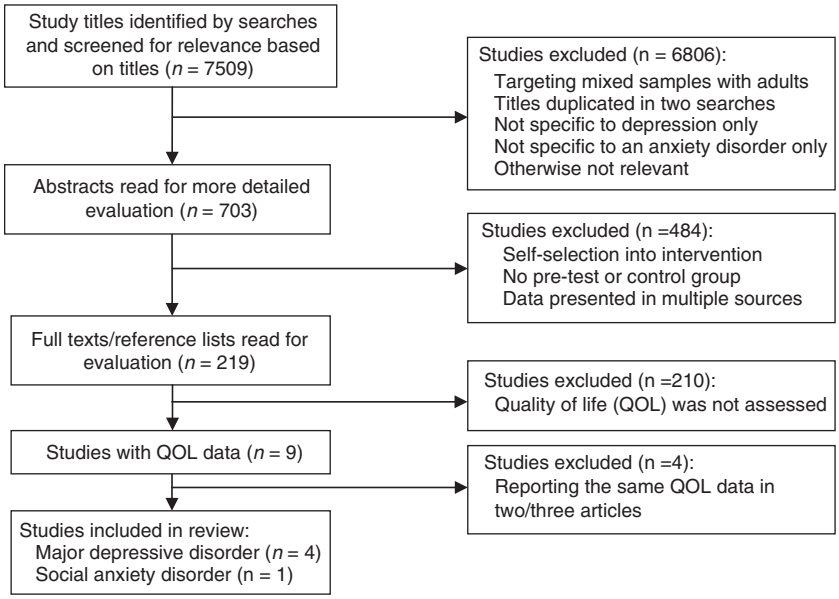


**FIGURE 1.** Flow diagram of study selection.

higher scores are related to greater robustness of the outcomes. Each study with a QOL prospective evaluation was also categorized, according to the summed checklist score, into one of the following descriptive categories: probably robust (with a score between 8 and 11), limited (with a score between 5 and 7), and very limited (with a score between 0 and 4). See the Appendix for details on the checklist and scores for all trials included.

Due to only 3 randomized clinical trials (RCT) available, with 2 different antidepressants used for MDD, it was inappropriate to conduct a meta-analysis. Therefore, it was decided to present only the magnitude of change regarding improvement (ie, effect size) in treatment with a specific antidepressant, as assessed with QOL measure and primary outcome measure as efficacy outcomes. Specific antidepressant treatment effects on QOL improvement and symptoms reduction were compared. If statistical information was not provided in a publication, this was extracted from the trial in order to calculate effect sizes for the specified variables. Effect size was interpreted as follows: 0.2 = small, 0.5 = moderate, and 0.8 = large.[35]

A comprehensive search for clinical trials that evaluated QOL as an outcome of antidepressant treatment yielded 9 articles that were published between 2003 and 2009 (Figure 1).[22,23,36–42] However, 2 articles reported the same QOL data from the Treatment for Adolescents with Depression Study (TADS),[22,41] 3 articles reported the same QOL data from the Adolescent Depression Antidepressant and Psychotherapy Trial (ADAPT),[36–38] and 1 reported combined QOL data from 3 sertraline trials.[23] Therefore, 5 studies reporting the original QOL data were included in this review (Table 1).[22,37,39,40,42]

Effects of fluoxetine and sertraline on depression and anxiety outcomes were evaluated in three RCTs (with a placebo and/or CBT group), while sertraline and escitalopram were carried-out in 2 open-label trials.[22,37,39,40,42] Two trials with fluoxetine considered only adolescents.[22,37] In all trials, QOL was the secondary efficacy outcome self-rated with the Euro-QOL questionnaire (EQ-5D),[43] Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q),[44] or Youth Quality of Life Instrument–Research Version (Y-QOL-R).[45] The primary efficacy measure was the Children's Depression Rating Scale–Revised (CDRS-R)[46] in 4 trials with MDD, while the Screen for Child and Anxiety Related Emotional Disorders (SCARED)[47] was used in the trial with SAD.

Details in reporting of QOL data were limited in all trials. Some examples are lack of a priori hypothesis regarding how antidepressants affect QOL, different QOL domain scores not considered, missing data not documented, and clinical significance of QOL improvements not addressed (see the Appendix).

In all trials, QOL significantly improved over the study period when antidepressant treatment was considered (effect size was small to moderate, ranging 0.4–0.8), but also when CBT alone or in a combination with an antidepressant was considered, and even placebo in RCTs (Table 2). The same trend was observed for the primary efficacy measure outcome in all trials, but the magnitude of improvement with antidepressant treatment in depressive/anxiety symptoms was greater than in QOL (effect size was high ranging 1.10–3.52).

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**TABLE 1. Main characteristics of included studies**

| Reference Year | Disorder | Antidepressant | Control group | Design | N | Age group | QOL measure | Duration | Main QOL outcome |
|---|---|---|---|---|---|---|---|---|---|
| Vitiello *et al.*[22] 2006 (TADS) | MDD | Fluoxetine | CBT, fluoxetine + CBT, placebo | RCT | 439 | Adolescents | PQ-LES-Q, self-rated | 12 weeks | Only fluoxetine + CBT provided statistically significant QOL improvement. |
| Goodyer *et al.*[37] 2008 (ADAPT) | MDD | Fluoxetine | Fluoxetine + CBT | RCT | 188 | Adolescents | EQ-5D, self-rated | 28 weeks | There was no statistically significant difference between 2 groups in QOL improvement. |
| Wagner *et al.*[39] 2003 | MDD | Sertraline | Placebo | RCT | 376 | Children and adolescents | PQ-LES-Q, self-rated | 10 weeks | There was statistically significant difference in QOL improvement between the groups for adolescents. |
| Rynn *et al.*[40] 2006 | MDD | Sertraline | None | Open-label | 216 | Children and adolescents | PQ-LES-Q, self-rated | 24 weeks | There was statistically significant QOL improvement over the study period. |
| Isolan *et al.*[42] 2007 | SAD | Escitalopram | None | Open-label | 20 | Children and adolescents | Y-QOL-R, self-rated | 12 weeks | There was statistically significant QOL improvement over the study period. |

Note: TADS = Treatment for Adolescents with Depression Study; ADAPT = Adolescent Depression Antidepressant and Psychotherapy Trial; MDD = major depressive disorder, SAD = social anxiety disorder; CBT = cognitive behavior therapy; RCT = randomized controlled trial; EQ-5D = The EuroQOL measure; PQ-LES-Q = Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire; Y-QOL-R = Youth Quality of Life Instrument–Research Version; QOL = quality of life.

In the TADS, fluoxetine combined with CBT significantly improved QOL compared to fluoxetine alone, CBT alone, or placebo (effect size was moderate, ranging from 0.53–0.69).[22] This is contrary to the main efficacy findings with the CDRS-R, where fluoxetine was also found to be significantly superior to CBT alone or placebo. However, fluoxetine combined with CBT in the ADAPT did not significantly improve QOL compared to fluoxetine alone.[37] In the 2 combined trials with sertraline that included children and adolescents, significant improvements in QOL were reported compared to placebo among adolescents with MDD only (effect size was low, 0.29), which was in line with the data for the main efficacy findings with the CDRS-R (effect size was low, 0.35).

## Limited Evidence that Antidepressants Improve QOL in Children and Adolescents

This is the only systematic review available that has synthesized findings from clinical trials on the effects of antidepressant treatment on QOL improvements among children and adolescents with depression and anxiety disorders. As data could only be obtained from 5 clinical trials, which used fluoxetine, sertraline, and escitalopram in treatment of MDD or SAD, evidence at this time largely remains inconclusive. The main results of this review of antidepressant effects on QOL indicate the following. When antidepressants alone, CBT alone, or CBT in combination with an antidepressant or even a placebo were considered, the results across the trials consistently showed QOL improvements and reduction in depressive and anxiety symptom ratings. However, the effects of antidepressants in QOL improvements from the baseline to the study endpoint were found to be small to moderate, and were much lower in comparison to depression and anxiety symptoms improvement, in which case the magnitude of improvement was high. Limited evidence existed on QOL improvements when comparing an antidepressant with other treatments used in the trials included. The results indicate that fluoxetine combined with CBT showed moderate QOL improvement in the TADS,[22] but not in the ADAPT,[37] while sertraline alone showed only small QOL improvements for adolescents with MDD, but not among children with MDD.[39,40] Considering the primary efficacy measure in the TADS, fluoxetine alone also moderately improved depressive symptoms, while in a sertraline trial only small improvements were observed. Therefore, if we consider data from RCTs only, we might conclude that fluoxetine with CBT and sertraline monotherapy have the potential to improve QOL among adolescents with MDD, although to a lesser extent than their potential to improve depressive symptoms.

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**TABLE 2. Main results on the efficacy outcomes in the included studies**

| Questionnaire | Intervention | Score change from baseline, M (SE), d | Between-groups comparisons (d) |
|---|---|---|---|
| ***Vitiello et al.*[22] *(TADS)*** | | | |
| CDRS-R | Fluoxetine + CBT | −27 (0.92)*, 3.98 | Fluoxetine + CBT vs. placebo* (0.98); fluoxetine vs. placebo* (0.68); CBT vs. placebo (ns); fluoxetine + CBT vs. fluoxetine (ns); fluoxetine + CBT vs. CBT* (0.69); fluoxetine vs. CBT* (0.46) |
| | Fluoxetine | −22.6 (0.87)*, 3.52 | |
| | CBT | −17.6 (0.97)*, 2.31 | |
| | Placebo | −19.4 (0.85)*, 3.03 | |
| PQ-LES-Q | Fluoxetine + CBT | 12.2 (1.51)*, 1.19 | Fluoxetine + CBT vs. placebo* (0.58); fluoxetine vs. placebo (ns); CBT vs. placebo (ns); fluoxetine + CBT vs. fluoxetine* (0.53); fluoxetine + CBT vs. CBT* (0.69); fluoxetine vs. CBT (ns) |
| | Fluoxetine | 6.3 (1.31)*, 0.69 | |
| | CBT | 4.5 (1.49)*, 0.48 | |
| | Placebo | 5.7 (1.36)*, 0.59 | |
| ***Goodyer et al.*[37] *(ADAPT)*** | | | |
| CDRS-R | Fluoxetine + CBT | −17.8 (1.51)*, 1.68 | Fluoxetine + CBT vs. fluoxetine (ns) |
| | Fluoxetine | −19.5 (1.47)*, 1.95 | |
| EQ-5D | Fluoxetine + CBT | 17 (2.89)*, 0.85 | Fluoxetine + CBT vs. fluoxetine (ns) |
| | Fluoxetine | 13 (3.17)*, 0.60 | |
| ***Wagner et al.*[39] *and Rynn et al.*[40]** | | | |
| CDRS-R | Sertraline | −22.8 (0.99)*, 1.66 | Sertraline vs. placebo* (0.19); for children (ns); for adolescents* (0.35) |
| | Placebo | −20.2 (0.99)*, 1.49 | |
| PQ-LES-Q | Sertraline | 6.5 (0.68)*, 0.69 | Sertraline vs. placebo (ns); for children ns; for adolescents* (0.29) |
| | Placebo | 4.7 (0.68)*, 0.50 | |
| CDRS-R | Sertraline open label | −34.8 (2.13)*, 1.11 | / |
| PQ-LES-Q | | 6.2 (1.12)*, 0.40 | |
| ***Isolan et al.*[42]** | | | |
| SCARED | Escitalopram Open label | −18.5 (3.51)*, 1.10 | / |
| YQOL | | 11.9 (5.52)*, 0.80 | |

Note: *$p < 0.01$; ns = not significant; d = effect size; TADS = Treatment for Adolescents with Depression Study; ADAPT = Adolescent Depression Antidepressant and Psychotherapy Trial; CBT = cognitive behavior therapy; EQ-5D VAS = The EuroQOL measure; PQ-LES-Q = Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire; SCARED = Screen for Child and Anxiety Related Emotional Disorders.

The trend noted above, that the positive effects of psychopharmacological treatments on QOL reflect their effects on improving/reducing core psychiatric symptoms, but with smaller clinical significance, was previously observed in previous studies. As recently reviewed, there is emerging evidence from clinical trials that QOL improves significantly following effective medication treatment among children and adolescents with ADHD, but improvements were greater in the core ADHD symptoms than in QOL.[21] Additionally, findings of clinical trials with adults who were treated with antidepressants indicate greater improvements in depressive or anxiety symptoms and much smaller improvements in QOL.[19,48] Considering the evidence that antidepressants offer mild-to-moderate treatment benefit in adolescents and children, with notable exceptions depending on medication and indication,[31,32] why these treatments have limited effects on QOL improvement remains to be explored.

Several issues should be taken into account when considering these observations. First, contrary to core symptoms that might improve with medications in several weeks, such as in depressive symptoms, QOL might require a longer time to improve. Therefore, clinical trials should last longer than 8–12 weeks in order to properly judge QOL improvements with a particular antidepressant. Second, it might be that improvements in core symptoms by treatment with antidepressants explained a relatively small proportion of the overall variance in QOL, as shown in the general population,[49] whereas the side effects of antidepressants and other clinical and sociodemographic variables are also important factors in QOL improvements as reported for adults.[19] This would be best explored using structural equation modeling. Additionally, although the TADS showed a mediating role of depressive symptoms on QOL,[22] associations between core symptoms and QOL domains considering antidepressant treatment might be necessary to differentiate. Furthermore, it might be insufficient to treat depressive/anxiety disorders among adolescents only with an antidepressant, and it might be necessary to combine the antidepressant with CBT in order to improve QOL, as indicated by the TADS data.[22] Finally, it might also be necessary to develop pharmacological treatments that target QOL

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domains and not only core symptom improvements. This idea has been supported by observations from previous studies with adults, where QOL improvements were substantial in the early phases of antidepressant treatment, and despite symptom remission, QOL did not reach ratings observed in the general populations over episode duration.[50,51] Nevertheless, our findings are consistent with earlier observations that symptoms measurement might not be the most influential factor in determining QOL, and adding QOL as an additional factor in diagnostic evaluation and treatment planning may be beneficial.[52]

The limitations of this review and available clinical trials should be put into perspective before drawing conclusions. First, the key limitation of our review is the possibility of publication bias, in that only data from 4 published clinical trials with MDD and 1 with SAD were available, with only 3 being RCTs. This strongly limits the generalizability of the findings. Additionally, we used an approach to assess the methodological quality of the QOL aspects of all trials, which suggested that only those that were evaluated as probably robust or robust are likely to provide useful data to facilitate clinical decision making.[33,34] None of the trials obtained a score indicating probable robustness, which limits the value of the studies under review as sources from which conclusive evidence can be drawn. Second, QOL was measured with the PQ-LES-Q or EQ-5D in the trials with MDD. They are both generic QOL measures with a single, overall QOL score. Although the PQ-LES-Q has multiple items on various domains of functioning and well-being, a structured multidimensional use of QOL, which covers different life domains in separate scales, is necessary for planning interventions and assessing the outcome in clinical trials.[2,14,18] Moreover, the EQ-5D is a utility measure for QOL assessments in adults, and although it might be/has been used in studies with children, a child-rated version has been only recently developed.[53] In the SAD trial with escitalopram, the Y-QOL-R, which has multiple domains, was used, but only its overall score was reported.[42] Third, none of the trials considered QOL assessments by proxy, which is important because in pediatric populations, children and parents largely disagree in providing information on specific QOL domains,[54] which has also been observed in studies of children and adolescents with mental health problems, such as ADHD.[21] Fourth, QOL has been analyzed to determine statistical significance between two groups or assessments, with or without effect size values being determined. A parameter for detecting clinical significance or clinically meaningful change in a QOL measure with antidepressant treatments was not considered.[55] In other words, it has not been stated how big a change in a questionnaire score from baseline to follow-up/endpoint assessment would be the minimal clinical difference above which QOL improvements would be claimed.

Several possible reasons could account for these drawbacks when using QOL measures as efficacy outcomes in the available trials. First, although QOL has been recognized to provide a more comprehensive picture of the impacts that a mental health problem has on different aspects of functioning, and not just simple symptoms evaluations, we still lack sound research on the conceptual underpinnings of associations between QOL and psychological symptoms. Second, we are still far away from the consensus about QOL measurements in clinical trials with psychotropic medications. Recently, formal guidelines for clinical trials in general have been developed, which should be followed.[56] Finally, although QOL and other PRO measures are recognized by the regulatory bodies as important outcome measures in clinical trials with medications, and their use is encouraged, QOL data are still not found among the main requirements during the drug labeling process.[2,3,15–17]

This systematic review found inconclusive evidence to suggest that antidepressant treatment improves QOL among children and adolescents with depressive or anxiety disorders. Sertraline monotherapy and fluoxetine in combination with CBT were shown to have limited effects on QOL improvement in MDD. However, caution is needed when interpreting the results from these studies, as QOL measures are under-evaluated in clinical trials using antidepressant treatment. Only 5 trials were available, and each had limitations in methodological quality when reporting QOL data. More research using QOL and standards related to assessment is needed before a claim can be made that antidepressants are effective in improving QOL in children and adolescents.[4,18,56,57]

## Disclosures

Dejan Stevanovic has the following disclosures: ACTAVIS Serbia, consultant, consulting fees. Ivana Tadic does not have anything to disclose. Rajna Knez has the following disclosures: Affins, study on AFFITOPE AD02, honoraria.

## Supplementary materials

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S1092852913000576

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