Adolescent Health, Medicine and Therapeutics

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

The use of cognitive behavioral therapy in the treatment of resistant depression in adolescents

This article was published in the following Dove Press journal:
Adolescent Health, Medicine and Therapeutics
7 September 2012
Number of times this article has been viewed

Sarah Hamill-Skoch[1]
Paul Hicks[2]
Ximena Prieto-Hicks[1]

[1]Department of Psychiatry, [2]Department of Family and Community Medicine, University of Arizona, Tuscon, AZ, USA

Abstract: Major depressive disorder often begins in adolescence, is chronic and recurrent, and heightens an individual's risk for major depressive disorder in adulthood. Treatment-resistant depression is a problem for a significant minority of adolescents. Few studies have examined treatments for treatment-resistant depression among adolescents, and even fewer have examined the use of cognitive-behavioral therapy as a monotherapy or in combination with pharmacological treatments. Mental health professionals have a strong interest in understanding what treatments are appropriate for adolescents who are treatment resistant. Preliminary evidence from current published trials indicates that the use of cognitive-behavioral therapy in combination with antidepressant medication yields the best outcome for treatment-resistant depression in adolescents. Secondary analyses also suggest that the utility of cognitive behavioral therapy can be increased by ensuring adolescents receive a therapeutic dose of treatment sessions (more than nine sessions) and the inclusion of two treatment components: social skills and problem solving training. Guidelines for clinicians as well as areas for future research are discussed.

Keywords: cognitive behavior therapy, treatment-resistant depression, adolescent depression

Introduction

Depression is one of the most frequently occurring psychological disorders and it is often referred to as the "common cold" of psychopathology.[1] Research demonstrates that between 5%–25% of the general population will experience depression in their lifetime, and up to 15% of severely depressed individuals will go on to commit suicide.[2] The World Health Organization reports that depression is currently the number one cause of disability among industrialized countries, and is the third most burdensome disease in terms of disability and mortality, second only to heart and cerebrovascular disease.[3]

These facts are especially true for youth. Major depressive disorder (MDD) often begins in adolescence, is chronic and recurrent, and heightens an individual's risk for MDD in adulthood.[4] Depressive disorders for youth includes MDD, dysthymic disorder, cyclothymic disorder, bipolar disorder (I and II), mood disorder due to a general medical condition, substance-induced mood disorder, and mood disorder not otherwise specified and depressive disorder not otherwise specified.[5] Lifetime prevalence rates are estimated between 1.5% for children and 7% among adolescents.[6,7] Seventy-five percent of adults with MDD report that their first episode of depression occurred during childhood or adolescence.[4]

Given these data, it is not surprising that researchers are interested in examining psychosocial and pharmacological treatments for depressed youth. Well-established

Correspondence: Sarah Hamill-Skoch
University of Arizona Medical Center,
1501 N Campbell Avenue,
PO Box, Tucson, AZ, USA
Tel +1 520 626 7739
Fax +1 520 626 2004
Email shamill@email.arizona.edu

treatments for adolescent depression include medication management, cognitive-behavior therapy (CBT), and interpersonal therapy (IPT).[8] However, despite these efforts towards treating adolescent depression, approximately 40% of adolescents will fail to adequately respond to treatment and only one-third will enter remission.[9] Although treatment-resistant depression (TRD) is not a diagnostic category defined in the *Diagnostic and Statistical Manual of Mental Disorders*, depressive symptoms that are resistant to treatment are a serious concern for many depressed youth. Predictors of treatment failure include more chronic depression, older age, suicidality, comorbid conditions including anxiety, higher rates of hopelessness, and functional impairment.[9]

TRD typically refers to a lack of adequate response after an appropriate dose of evidence-based treatment for MDD.[10] What constitutes an "adequate response" and an "appropriate dose" has been a source of significant contention in the field of psychiatry and psychology. While some researchers define inadequate response as patients who report minimal or no improvement with a course of antidepressants at the highest dose tolerated for a minimum of 6 weeks, other researchers argue that complete remission should be the goal of treatment in order for patients to return to their level of functioning prior to illness.[11,12] Most clinicians and researchers now define an adequate response as a "50% reduction in depressive symptoms or a global rating of 'much' or 'very much' improved during an adequate treatment course."[13] An adequate pharmacologic treatment consists of 8–12 weeks of medication management, with at least 4 weeks of fluoxetine (20 mg) or a medication equivalent.[13,14] Dose increases are recommended for an additional 4 weeks if the patient has not responded to the 4-week dose of 20 mg of fluoxetine or its equivalent.[13] Typically, an adequate course of CBT is defined as 8–16 sessions; however, dosing is more varied in CBT as psychotherapy effectiveness depends in part on the skill of the clinician, the specific type of treatment being used, and the developmental age of the child.[13] Patient adherence should be assessed in both treatment modalities (drug metabolite levels for pharmacotherapy and the patient's understanding of psychotherapy concepts), as well as clinician fidelity to the evidence-based psychotherapy treatment.

To date, few studies have examined psychosocial and pharmacological treatments for TRD among adolescents. In light of the serious implications of depressive symptoms, understanding what treatments might be most effective for adolescents with TRD is an area of research that can yield significant practical benefit. A better understanding of treatments that are the most effective for adolescents with TRD is needed, as poorly treated depressive symptoms result in disrupted functioning and increased suicidality.[15] Increasing the understanding of treatments for adolescent TRD may lead to improved clinical outcomes for this population. As a preliminary step in addressing such concerns, a review was completed examining the findings of how CBT can be used to treat resistant depression. First, an overview of depressive disorders in adolescents is discussed as well as the challenges associated with ongoing depression in youth. Next, a review of current pharmacotherapy options and the present evidence-based guidelines for medication management is discussed. Then, cognitive theories of adolescent depression and the available research literature examining CBT for TRD among adolescents is presented. Conclusions regarding how the current empirical literature informs our knowledge of adolescent depressive psychopathology are presented as well as directions for future research.

Depressive disorders in youth

Prevalence rates for depression increase with age and rates dramatically increase through late adolescence.[16,17] Among preschool children in the general population, depressive disorders are relatively uncommon and most typically associated with significant abuse or neglect.[18] It is estimated that prevalence rates for major depression for primary school-age children range from 0.4%–1.85%.[19] Among high school students prevalence rates range from 2.9% to as high as 8%.[20,21] In addition to these findings, a large percentage of youth report symptoms of dysphoria and low self-esteem, which may be precursors to the development of a major depressive episode.[16]

Several factors appear to consistently predict the duration of a depressive episode for youth. One consistent factor is gender, with more female adolescents and adults experiencing more severe and prolonged episodes of depressive disorder.[22,23] Prior to adolescence, rates of depression are fairly equivalent in girls and boys, with some evidence suggesting a higher risk among boys.[24–26] The emergence of a gender difference may begin prior to puberty, and by early to mid-adolescence, the rate of depressive symptoms rises dramatically in girls with females being two to three times more likely to experience depression than boys.[27,28] A second consistent risk factor is the disease severity at initial diagnosis, with more severe episodes at initial diagnosis predicting worse prognosis. The course of depressive disorders in youth is typically reported to be between 32 and 36 weeks, with recovery not occurring until the 24th to the 36th week.[28,29]

Depressive disorders have serious consequences for youth.[30] Depression results in disruptions in academic, social, and familial functioning for adolescents. Even after

symptoms are in remission, episodes tend to recurr and interfere with an adolescent's ability to function both at home and at school and meet developmentally appropriate expectations.[30,31] Longitudinal studies have demonstrated that youth who have experienced one depressive episode are 54% more likely to have another episode within 3 years and 72% more likely to experience another episode over a 5-year period.[31]

Depression is the most significant predictor of adolescent suicidal behavior, and adolescent suicide remains a significant public health problem throughout the world.[32] Research suggests that, globally, up to 100,000 adolescents (ages 15–24 years) commit suicide each year.[33] In the United States among individuals aged 10–24 years, suicide is the third leading cause of death, second only to accidents and homicide.[33] In 2002, approximately 4000 adolescents aged 15–24 years commit suicide each year, with an overall prevalence rate of eleven per 100,000.[33] Among 45,806 high school students aged 15–16 years in 17 European countries, the median prevalence rate of suicide attempts was 10.5%.[34] Suicidal thoughts and suicidal ideation are precursors to suicidal attempts, and the median frequency of any self-harm thoughts (at least five times) in a recent study was 7.4% (range 2.1%–15.3%).[34] Suicidal behavior is highly correlated with substance use, violent aggression, and depressive symptoms.[35]

Methodology for literature review

For the present review, studies were identified combining the terms "antidepressants," "treatment resistant," "major depression," "adolescence," "selective serotonin reuptake inhibitor (SSRI)," and "adolescent suicide" through Academic Search Premier and PubMed. Articles were selected if they examined pharmacological or CBT for resistant depression in pediatric samples. Studies that examined other forms of psychotherapy (ie, psychodynamic, supportive therapy) were excluded, as were treatment studies conducted in adult populations. Studies were limited to English language publications, age range 0–18 years, and further limited to clinical trials, randomized controlled trials, meta-analyses, review articles, and practice guidelines. For the medication management section of this review, 58 articles were identified. Of these 58 articles retrieved, each was reviewed to determine if it included unipolar MDD, treatment resistance, and included an adolescent patient population. For the cognitive behavioral review component of this article, 96 articles were initially identified through Academic Search Premier. Each of these papers was reviewed for its relevance to the topic of CBT of adolescent depression. Eight additional articles were reviewed that cover more general aspects of CBT treatment for adolescent depression (ie, evidence-based treatments for child/adolescent depression, CBT for adolescent depression) that were not initially captured in the original search.

Medication management for adolescent TRD

Recent data from the National Health and Nutrition Examination Surveys, looking at antidepressant use among Americans from 2005 to 2008 demonstrated that 11% of Americans aged 12 years and older are taking antidepressant medications, and one-third of individuals aged 12 years and older with severe depressive symptoms are currently taking antidepressant medications.[36] While these data combined both children, adolescents, and adults, it is clear that a significant percentage of Americans across all ages are using antidepressants. The current guidelines for the treatment of uncomplicated pediatric MDD recommend an 8 to 12-week course of an SSRI, counseling, or both as the initial interventions of choice.[37] Several controlled trials have documented the efficacy of specific pharmacological treatments for depressed adolescents including fluoxetine (Prozac®), paroxetine (Paxil®), sertraline (Zoloft®), and escitalopram (Lexapro®).[38–41] Despite empirical efficacy, the Food and Drug Administration has currently only provided approval for the use of fluoxetine for child and adolescent depression and escitalopram is approved only for MDD in adolescents.[8,9] Additionally, in 2004 the Food and Drug Administration issued a directive for a black box warning for the use of SSRIs in children and adolescents secondary to an increased risk of suicidality.[42] Since the original ruling, much has been published both in support and refutation.[43–46] Adding to the complexity of this issue is the fact that there is a high baseline risk of suicidality among adolescents with MDD and TRD, the contribution of poor control and treatment response for MDD, and a lack of adherence to treatment in approximately one-half of adolescents.[47–49] There is also only limited data examining the effects of antidepressants on the developing brain.[50] Questions regarding long-term side effects of SSRIs on brain development is an understudied area and one that requires further research.[50]

The best therapy for those adolescents who fail pharmacologic treatment, however, is not well addressed in current guidelines. Similar to other conditions such as generalized anxiety disorder and posttraumatic stress disorder, where the adult literature is more well-developed, the state of the pediatric depression literature is not as robust

and few controlled trials exist for TRD in adolescents. Most studies are small, unblinded, and vary considerably in the way in which response and remission is defined.[51–54] The Treatment of SSRI-resistant Depression in Adolescents (TORDIA) trial is a notable exception.[55] The TORDIA study conducted by Brent et al describes 334 adolescent patients (aged 12–18 years; mean = 15.9, standard deviation = 1.6) recruited from six sites within the United States who had failed to respond to 8 weeks of an SSRI, with the last 4 weeks being at recommended doses (with the exception of those adolescents who were unable to tolerate higher doses). Participants were 70% female, 82% Caucasian, and had a median household income of $61,000. The authors did not specify which SSRI was used in the initial care. Patients were excluded if they had previously failed two or more trials of SSRIs or treatment with venlafaxine, were engaged in ongoing CBT, had current substance abuse, or other mental health conditions including bipolar disorder, eating disorder, autism, and others. Participants were also excluded if they were taking other medications such as stable doses of stimulants and hypnotics, antipsychotics, mood stabilizers, and non-SSRI antidepressants at study entry. However, those medications could be started at the discretion of the psychiatrist. The four treatment groups included in the study were: (1) a change in SSRI alone, (2) a change in SSRI plus CBT, (3) venlafaxine alone, and (4) venlafaxine plus CBT. Treatment duration was 12 weeks and standardized assessments of ongoing symptoms of MDD were made throughout the study period including the Children's Depression Rating Scale-Revised, Clinical Global Impression Scale, and the Children's Global Assessment Scale. In addition, the Beck Depression Inventory-II, Beck Hopelessness Scale, and Suicide Ideation Questionnaire-Junior High School Version were used to assess adolescents at baseline and every 6 weeks throughout the study. Clinical response was defined as both a Clinical Global Impression-Improvement subscale of at least two (rated on a scale of one to seven) and a change in the Children's Depression Rating Scale-Revised score of 50% or more.

Results of the TORDIA study demonstrated that CBT in combination with medication improved clinical response (54.8%) more so than medication alone (40.5%). Combined CBT and medication was more efficacious compared to medication alone in Caucasian children, older children (aged 18–19 years), those who had been taking an SSRI prior to study entry, and those with coexisting anxiety disorder without nonsuicidal self-injury. Of the 334 participants enrolled, there were 18 suicide attempts among 17 participants, and no enrolled participants completed suicide. No differences among treatment groups existed with respect to suicidal ideation, self-injurious behavior, or suicide attempts. The authors report 78.1% (n = 261) completed the week-24 assessment, with similar proportions in each of the treatment groups.[56] The TORDIA study did not find significant differences in treatment response among the various SSRIs used nor between SSRIs and venlafaxine on depressive symptoms. However, differences in the safety and tolerability between these medications were noted. For those patients taking venlafaxine, 31.7% of adolescents reported skin problems (primarily itching and rash) compared to 16.9% in the SSRI group (95% confidence interval 11%–23%; $\chi^2 = 9.78$; $P = 0.002$). Four participants in the venlafaxine group terminated their participation in this study due to cardiovascular events, compared to one participant assigned to SSRI medications. Participants in the venlafaxine group evidenced increased diastolic blood pressure ($P = 0.004$) and pulse ($P = 0.001$).

Despite the benefits of combined therapy of CBT and medication in the TORDIA study, approximately 17% of adolescents – or about one in six adolescents – remained depressed even with aggressive treatment. Follow-up studies have looked at predictors to nonresponse as well as ongoing data from the original TORDIA cohort to examine the question of why a proportion of adolescents did not improve with treatment. Asarnow et al examined adolescents from the TORDIA study who had not improved to advance the understanding of predictors and moderators of treatment response. The adolescent participants reported moderately severe and chronic depression, with 14.9% reporting suicide attempts and 58.5% presenting with clinically significant suicidal ideation. Results show that those adolescents who were nonresponders were more often patients who were more severely or chronically depressed, had higher levels of suicidal ideation, hopelessness, more severe family conflict, and histories of nonsuicidal self-injury.[15] This study also found that the CBT/combined treatment was more effective among adolescents who had increased comorbidity (ie, attention deficit hyperactivity disorder and anxiety disorders), no history of abuse, and lower self-reported hopelessness measured by the Beck Hopelessness Scale.

A second follow-up study conducted by Emslie et al followed the TORDIA cohort for an additional 12 weeks and offered open treatment to the nonresponders in the original cohort.[56] Overall, 38.9% of patients achieved remission by 24 weeks and response rate was unaffected by combined treatment or medication choice. Not surprisingly, initial clinical response predicted remission at 24 weeks

(61.6% in responders versus 18.3% in nonresponders). Of note, those patients who went on to remit had quicker and more profound improvement in their Children's Depression Rating Scale-Revised scores such that response by 6 weeks in the original study predicted long-term success. Initial nonresponders were more likely to remit in the subsequent 12 weeks if treatment was augmented by their psychiatrists during the initial study period. Augmentation agents used were atypical antipsychotics or mood stabilizers and non-CBT therapy (ie, supportive psychotherapy) for those not assigned to CBT. However, this effect did not hold true if those interventions were begun after the initial 12-week study period, suggesting an effect, but perhaps one that takes longer to appear. The risk of relapse was unrelated to initial treatment group and occurred in 14.9%–23.3% of patients. Among those who had initially responded, 19.6% had relapsed by week 24. The best predictors of relapse were the self- and interviewer-reported rate of depression at intake.

Cognitive theories of adolescent depression and the use of CBT for adolescents TRD

CBT is considered a well-established treatment for adolescent depression.[8,57] CBT was developed based on cognitive theories of mood disorders that have been critical in the understanding of both adult and adolescent depression.[58] Although several cognitive theories exist, they share the general hypothesis that the way in which an individual interprets, attends to, and remembers life events contribute to the likelihood they will experience depression.[3]

CBT was developed to change an individual's thoughts, feelings, and behaviors that stem from dysfunctional cognitive patterns (ie, "I made a mistake and therefore I am a failure") as well as maladaptive behavioral patterns (ie, withdrawal, social isolation). CBT is a "here and now," approach that is goal oriented and designed to reduce a client's presenting symptoms.[59] Although CBT is heterogeneous and comprised of several different treatment components, common components include cognitive restructuring, behavioral activation, social skills training, and problem solving.[8] CBT for depression is an evidence-based treatment, and several studies have established the effectiveness of CBT for the treatment of adolescent depression.[8,57] CBT can be delivered individually or in group sessions, and is typically delivered in a time-limited fashion.[60]

To date, published studies reveal that CBT and IPT meet criteria for well-established treatments for adolescent depression and a multitude of controlled trials have shown that CBT and IPT are more efficacious when compared to no-treatment controls or alternative treatments (for a review of IPT for depressed adolescents, see David-Ferdon and Kaslow).[8] "Well-established" treatments refer to those where at least two well-conducted, between-group design experiments demonstrate efficacy by one of two ways: (1) superior to pill or psychological placebo or to another treatment, or (2) equivalent to an already established treatment in experiments with adequate sample sizes.[8] Within the umbrella of CBT, there are three prominent CBT approaches for youth with MDD: Adolescent Coping with Depression course (CWD-A), the Cognitive Therapy Manual from the Pittsburgh CBT trial, and the CBT manual of Treatment for Adolescents with Depression Study (TADS).[61–63] CWD-A is the only specific psychosocial protocol that currently meets criteria for a "probably efficacious" monotherapy.[8] For an intervention to be "probably efficacious," it must meet either of the following criteria: (1) two experiments must demonstrate that the invention is more effective than a no-treatment control group, or (2) the studies meet all criteria for a well-established treatment except for the requirement that treatment effects are shown by two different research teams.[8] For an intervention to be "probably efficacious," it must also be tested using a treatment manual and the researchers need to clearly define sample characteristics.[8]

CWD-A is an adolescent version of a program originally designed for adults. This approach consists of sixteen 2-hour group sessions, conducted over an 8-week period.[62] The protocol consists of mood monitoring, social skills, pleasant activities, relaxation training, constructive thinking, communication skills, negotiation skills, and problem solving. Parents are actively involved in this program and are presented with sessions specifically designed to provide psychoeducation and enhance communication and problem solving with the depressed adolescent. Several studies have examined the CWD-A program, and all but one have found this program to be efficacious.[8]

Although few studies have compared these different active treatments to each other, randomized controlled trials have found CBT effective at reducing depressive symptoms among adolescents.[59] Brent et al demonstrated that 12–16 weeks of individual CBT for depressed adolescents reduced depressive symptoms by 64.7% compared to systematic behavioral family therapy (37.9%) and nonspecific psychotherapy (39.4%). Participants in the CBT group recovered more rapidly based on client and rater reports. Fewer studies have examined the effectiveness of CBT for

adolescents with severe depression or TRD. Exceptions to this include the previously described TORDIA, TADS, and the Time for a Future adolescent depression program.

The TADS study, started in 1998, was designed to evaluate 12-week (short) and 36-week (long) efficacy of fluoxetine, CBT, fluoxetine plus CBT, and pill placebo for adolescents with MDD.[62] The CBT intervention used in this study consisted of 15 sessions over the course of 12 weeks, and the protocol used was based on CWD-A and an individual CBT intervention for depression.[62] The CBT program in TADS was a skill-based program that emphasized psychoeducation about depression, setting goals, mood monitoring, increasing pleasant activities, social problem solving, cognitive restructuring, and improving social skills.[8] Among the 439 adolescent participants, results demonstrated that the combined treatment of medication and CBT was more effective than either medication alone or pill placebo. When examining monotherapy in TADS, fluoxetine alone was superior to CBT alone, and no significant difference existed between adolescents in the CBT alone group and pill placebo group. Adolescents in the CBT group experienced significantly decreased suicidal ideation as compared to the fluoxetine group, indicating that CBT may protect adolescents against suicidal ideation.[8,64] The TADS study was unique in that it was a multisite study and examined treatment options among a large sample of adolescents. In addition, both a limitation and strength of TADS was that the sample consisted of adolescents with a long duration of depression and episodes characterized by moderate to marked severity.[64]

A second study with a similar design to TADS is the Time for a Future adolescent depression program.[65] This study examined three arms of treatment: (1) CBT alone, (2) sertraline alone, and (3) a combination treatment of CBT plus sertraline, among adolescents who met criteria for MDD, depressive disorder, or depression not otherwise specified. Unlike the findings presented by the TADS team, the Time for a Future adolescent depression program demonstrated that combined treatment was not superior to monotherapy.[8] Although participants in all three conditions improved in functioning, adolescents in the CBT alone condition demonstrated superior improvement at postintervention compared to participants in the medication arm.[8] The authors and others note caution in these findings given the relatively low dose of sertraline used in the medication condition.[65] Contrary to the TADS study, adolescent participants in Time for a Future adolescent depression program evidenced fewer depressive symptoms at intake.

As described previously, the TORDIA study is the only large controlled trial to examine the use of CBT for TRD among adolescents. The adolescents in TORDIA who received CBT in combination with either antidepressant demonstrated a 50% response rate to treatment. The main effect for CBT persisted even after controlling for baseline differences in the Beck Depression Inventory-II and comorbid psychiatry diagnoses.[55] In addition to the main effects of this study, a secondary analysis of the TORDIA results evaluated those participants who received 12 weeks of acute CBT and medication treatment to evaluate if specific treatment components are linked to depression remission among adolescents with severe depression.[61] Adolescent participants who had received more than nine CBT sessions were 2.5 times more likely to have an adequate treatment response in the TORDIA study than those participants who received nine or fewer sessions. Additionally, youth who received the social skills and problem solving modules of the CBT protocol were 2.3 and 2.6 times more likely to have a positive response to treatment. An interesting finding was that only about 50% of the adolescents in TORDIA received social skills and problem solving training modules, as these modules were typically presented in the latter part of the TORDIA treatment protocol (see Table 1 for the way this secondary analysis recategorized the TORDIA modules based on coding systems used to examine CBT manual content). Those participants who dropped out of the study early would not have received those modules presented in the latter part of treatment.[61] In fact, only 51.4% of participants received the problem solving component and 54.2% received the social skills component. Although the protocol was structured, certain modules were given to the participants based on family and adolescent characteristics (ie, substance use, nonsuicidal self-injury), such that the modules given were not randomly assigned. Such findings suggest that these two components are quite valuable in treating adolescents with TRD. Although problem solving and social skills are CBT modules used to treat a variety of child and adolescent disorders (ie, schizophrenia, autism spectrum disorders), they hold promise as especially potent modules in treating adolescent resistant depression.[61] Rates of response to the CBT component may have been even higher in the TORDIA study if more participants received adequate doses of therapy sessions and if more adolescents had received the problem solving and social skills modules.

Conclusion and directions for future research

Adolescent depression is chronic, recurrent, and results in significant academic and interpersonal impairment.[55] Clinical

Table 1 Cognitive-behavioral therapy taxonomy of treatment of SSRI-resistant depression in adolescents (TORDIA) modules

TORDIA module	Treatment component	Description of the module
Psychoeducation	Defining depression; causes; benefits of treatment	General therapy processes
Taking stock	Identifying helpful skills; progress made, work still to be done	
Mood monitoring	Self-rating of daily mood; evaluating progress over time	
Automatic thoughts and cognitive distortions	Identifying unrealistic thoughts and underlying beliefs; examining evidence for and against; testing reality of beliefs	Cognitive restructuring
Realistic counter-thoughts	Creating and implementing realistic alternatives to unrealistic thoughts and beliefs	
Increasing pleasant activities	Selecting target activities; establishing baseline; setting small incremental goals; self-reward for meeting goals	Behavioral activation
Reengagement	Overcoming inertia and avoidance; reengagement in reinforcing activities	
Emotion regulation	Interrupting chain of events leading to distressing emotions; self-soothing	Emotion regulation
Relaxation	Progressive muscle relaxation, deep breathing, imagery to reduce tension	
Family emotion regulation	Introducing emotion regulation skills to the family	
Assertion	Avoiding passivity and aggressiveness; "I" statements	Social skills
Communication and compromise	Active listening and reflecting; negotiation and conflict resolution	
Social interaction	Starting conversations; joining groups; listening	
Family communication	Reducing blame; clearly identifying objective problems/goals without name calling; increase trust, active listening, and reflecting	
Problem solving	Operationalizing problems/goals; brainstorming solutions; seeking compromise; evaluating	Problem solving
Family problem solving	Introducing problem solving skills to the family	
Family high expectations and positive reinforcement	Manage high expectations; strategies for positive reinforcement	Family-oriented components
Family contingency management	Introducing behavioral contracting between the child and family	
Family attachment and commitment	Helping parents identify strengths and positive attributes of the child; planning positive interactions	
Motivational interviewing	Pros/cons of alternative choices; readiness for change	Motivational interviewing
Relapse prevention	Self-monitoring; action plan for relapse	Relapse prevention
Family relapse prevention	Involving family in relapse prevention planning	

Abbreviation: SSRI, selective serotonin reuptake inhibitor.

guidelines for treating adolescent depression recommend the use of SSRI medications, psychotherapy, or both, with the most well-studied and efficacious psychotherapy being CBT.[55] Although there is evidence that such treatments are efficacious, it is also known that approximately 40% of adolescents will not respond to treatment. To date, few studies and clinical guidelines have been published to guide clinicians in the best management of adolescents with nonresponsive depressive symptoms.

The present review suggests that adolescents who are CBT-naive and experience TRD are more likely to respond to the combination of CBT and a switch in antidepressant medication when compared to switching medications alone.[55] For adolescents with significant suicidal ideation, the combination of CBT plus medication management varies in its effectiveness, and this appears to depend on the level of suicidality at intake, with higher levels of suicidality resulting in decreased response to treatment. It may also be the case that as early as 6 weeks into this course of treatment, clinicians can identify patients who are not likely to remit and intervene to improve those remission rates. This suggests that the "current clinical guidelines, which recommend pursuing a given treatment strategy for at least 8–12 weeks, may need to be revisited."[66] Further study using several tiers of interventions, similar to the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study in adults with TRD is needed to better answer these questions.[67] Results from the TORDIA study suggest that clinicians consider the use of early intervention for nonresponders including augmentation with psychotherapy, addressing comorbid anxiety, substance use, and family conflict, and/or augmentation with mood stabilizers or antipsychotics.[56] The literature to date suggests the need for correct dosing of CBT sessions (more than nine sessions) as well as the benefits of including problem solving and social skills treatment modules. The duration and time point of psychotherapy appear to be critical issues in the treatment of TRD, and it is important that adolescents receive both the correct dose of therapy and intervention as early as possible to minimize impairment.

It is important to remember that in the trials described above CBT has been well controlled and administered by

trained clinicians adhering to detailed protocols. Continued research on the effectiveness of psychotherapy interventions is needed, as well as research examining moderators of treatment.[8] What is also clear from the studies conducted thus far is that current treatments do a poor job of matching the patient to the best treatment.[32] When adolescents are not responsive, it is known that repeated trials of treatment eventually yield clinical outcome, although the yield decreases with every additional step in treatment, and a minority remain persistently treatment resistant.[32] When CBT is not effective, third wave psychotherapy approaches such as cognitive behavioral analysis system of psychotherapy (CBASP), acceptance and commitment therapy (ACT), and mindfulness-based cognitive therapy (MBCT) may be considered as treatment alternatives.

Future research directions

Substantial benefit will be gained by clarifying the definition of what is meant by TRD and researchers utilizing a consistent definition of what constitutes an inadequate response to first-line treatment. In addition, adherence and effective dosing of medication and psychotherapy remains an issue. Among adult populations, 66% of patients with depression are noncompliant with psychotherapy and poor adherence among adolescents contributes to lack of treatment response. Careful assessment, diagnostic clarification, and examination of medical causes of mood disorders and other comorbidities that may be contributing to an adolescent's depressive symptoms are essential. Future research is also needed to examine the quality of the therapeutic alliance between the adolescent and clinician in CBT when treating TRD. The therapeutic alliance is one of several nonspecific factors in psychotherapy, and such "common" factors account for a significant portion of response to treatment across therapeutic approaches.[68] Recent meta-analyses have demonstrated that youth involvement in CBT for anxiety predicted improvements at the end of treatment compared to youth who were less engaged.[69] Improving attendance and in-session engagement is challenging with adolescents, and this is likely to be especially true among treatment-resistant adolescents who may come to treatment feeling both hopeless and frustrated with mental health professionals.[70] Future studies are needed to examine the therapeutic alliance in CBT for treatment-resistant adolescents and whether improving this relationship in therapy enhances treatment response.

The present review also suggests the importance of examining predictors and moderators of treatment response. Examination of family stressors, parental psychopathology, and ongoing stressful life events is a necessary step when working with adolescents with TRD. We know that a history of childhood trauma is associated with an increased risk of chronic depression, and several studies have found that traumatic events early in life may lead to worse treatment outcomes.[71,72] Individual factors such as increased hopelessness and history of abuse has been linked to poorer response to CBT/combined treatment among adolescents with TRD.[15] Future research examining such moderators may allow for a more personalized and specific approach to the treatment of depressed youth.[15]

Clinical considerations

The progress made in the last few years in testing combined treatments for depressed adolescents has been significant. Although small in number, the published trials examining depression among adolescents have been large scale, multisite, and well controlled.[61] Questions remain regarding who will benefit the most from combined treatment versus monotherapy as well as the continued need to evaluate specific CBT protocols. The studies that have been conducted suggest that clinicians remain hopeful with their adolescent patients and families who have failed to respond to initial treatment. Additional interventions can lead to successful management of TRD and clinical improvement in these patients. *Healthy People 2020*, a national health initiative, highlights the importance of continuing to increase treatment rates for depression and expand the current treatment options for children and adolescents.[36] Future studies examining moderators of response to treatment will assist clinicians in providing empirically supported treatments for adolescents with TRD and tailor those treatments to the individual.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Ingram RE, Scott WD, Hamill S. Depression: social and cognitive aspects. In: Blaney PH, Millon T, editors. *Oxford Textbook of Psychopathology*. New York, NY: Oxford University Press; 2009:230–252.
2. Lakdawalla Z, Hankin BL, Mermelstein R. Cognitive theories of depression in children and adolescents: a conceptual and quantitative review. *Clin Child Fam Psychol Rev*. 2007;10(1):1–24.
3. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet*. 2006;367(9524):1747–1757.
4. Jacobs RH, Reinecke MA, Gollan JK, Kane P. Empirical evidence of cognitive vulnerability for depression among children and adolescents: a cognitive science and developmental perspective. *Clin Psychol Rev*. 2008;28(5):759–782.
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (Text Revisio)*. 4th ed. Washington, DC: American Psychiatric Association; 2000.

6. Costello EJ, Angold A, Burns BJ, Erkanli A, Stangl DK, Tweed DL. The Great Smoky Mountains study of youth. Functional impairment and serious emotional disturbance. *Arch Gen Psychiatry*. 1996;53(12): 1137–1143.
7. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):593–602.
8. David-Ferdon C, Kaslow NJ. Evidence-based psychosocial treatment for child and adolescent depression. *J Clin Child Adolesc Psychol*. 2008;37(1):62–104.
9. 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 Adolesc Psychiatry*. 2006;45(12):1427–1439.
10. Fava M. Diagnosis and definition of treatment-resistant depression. *Biol Psychiatry*. 2003;53(8):649–659.
11. Botteron KN, Geller B. Refractory depression in children and adolescents. *Depress Anxiety*. 1997;5(4):212–223.
12. Bakish D. New standard of depression treatment: remission and full recovery. *J Clin Psychiatry*. 2000;62(Suppl 26):5–9.
13. Maalouf FT, Atwi M, Brent DA. Treatment-resistant depression in adolescents: review and updates on clinical management. *Depress Anxiety*. 2011;28(11):946–954.
14. Birmaher B, Brent DA, 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(11):1503–1526.
15. 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(3):330–339.
16. Stark KD, Sander JB, Yancy MG, Bronik MD, Hoke JA. Treatment of depression in childhood and adolescence: cognitive-behavioral procedures for the individual and family. In: Kendall PC, editor. *Child and Adolescent Therapy: Cognitive-Behavioral Procedures*. New York, NY: The Guilford Press; 2000:173–234.
17. Kashani JH, Beck NC, Hoeper EW, et al. Psychiatric disorders in a community sample of adolescents. *Am J Psychiatry*. 1987;144(5): 584–589.
18. Domenech-Llaberia E, Vinas F, Pla E, et al. Prevalence of major depression in preschool children. *Eur Child Adolesc Psychiatry*. 2009; 18(10):597–604.
19. Anderson JC, Williams S, McGee R, Silva PA. DSM-III disorders in preadolescent children. Prevalence in a large sample from the general population. *Arch Gen Psychiatry*. 1987;44(1):69–76.
20. Lewinsohn PM, Hops H, Roberts RE, Seeley JR, Andrews JA. Adolescent psychopathology: I. Prevalence and incidence of depression and other DSM-III-R disorders in high school students. *J Abnorm Psychol*. 1993;102(1):133–144.
21. Kashani JH, Carlson GA, Beck NC, et al. Depression, depressive symptoms, and depressed mood among a community sample of adolescents. *Am J Psychiatry*. 1990;144(7):931–934.
22. Angold A, Costello EJ, Worthman CM. Puberty and depression: the roles of age, pubertal status and pubertal timing. *Psychol Med*. 1998; 28(1):51–61.
23. Silberg J, Pickles A, Rutter M, et al. The influence of genetic factors and life stress on depression among adolescent girls. *Arch Gen Psychiatry*. 1999;56(3):225–232.
24. Garber J. Depression in children and adolescents: linking risk research and prevention. *Am J Prev Med*. 2006;31(6):S104–S125.
25. Merry S, McDowell H, Wild CJ, Bir J, Cunliffe R. A randomized placebo-controlled trial of a school-based depression prevention program. *J Am Acad Child Adolesc Psychiatry*. 2004;43(5):538–547.
26. Pattison C, Lynd-Stevenson RM. The prevention of depressive symptoms in children: the immediate and long-term outcomes of a school based program. *Behav Change*. 2001;18:92–102.
27. Cote SM, Boivin M, Liu X, Nagin DS, Zoccolillo M, Tremblay RE. Depression and anxiety symptoms: onset, developmental course and risk factors during early childhood. *J Child Psychol Psychiatry*. 2009; 50(10):1201–1208.
28. Garber J. Development and depression. In: Sameroff AJ, Lewis M, Miller SM, editors. *Handbook of Developmental Psychopathology*. 2nd edition. New York, NY: Springer. 2000:467–490.
29. Stober M, Lampert C, Schmidt S, Morrell W. The course of major depressive disorder in adolescents: I. Recovery and risk of manic switching in a follow-up of psychotic and nonpsychotic subtypes. *J Am Acad Child Adolesc Psychiatry*. 1993;32(1):34–42.
30. Cicchetti D, Toth SL. The development of depression in children and adolescents. *Am Psychol*. 1998;53(2):221–241.
31. Kovacs M, Feinberg TL, Crouse-Novak MA, Paulauskas SL, Finkelstein R. Depressive disorders in childhood. I. A longitudinal prospective study of characteristics and recovery. *Arch Gen Psychiatry*. 1984;41(3): 229–237.
32. Brent DA. The treatment of SSRI-resistant depression in adolescents (TORDIA): in search of the best next step. *Depress Anxiety*. 2009;26(10): 871–874.
33. Graydanus D, Patel D, Pratt H. Suicide risk in adolescents with chronic illness: implications for primary care and specialty pediatric practice: a review. *Dev Med Child Neurol*. 2010;52(12):1083–1087.
34. Kokkevi A, Rotsika V, Arapaki A, Richardson C. Adolescents' self-reported suicide attempts, self-harm thoughts and their correlates across 17 European countries. *J Child Psychol Psychiatry*. 2012;53(4): 381–389.
35. Madge N, Hawton K, McMahon EM, et al. Psychological characteristics, stressful life events and deliberate self-harm: findings from the Child and Adolescent Self-harm in Europe (CASE) study. *Eur Child Adolesc Psychiatry*. 2011;20(10):499–508.
36. Pratt LA, Brody DJ, Gu Q. Antidepressant use in persons aged 12 and over: United States, 2005–2008. *NCHS Data Brief*. 2011;76:1–8.
37. National Institute for Clinical Excellence (NICE). Depression in children and young people: identification and management in primary, community, and secondary care. 2005. Available from: http://www.nice.org.uk/nicemedia/live/10970/29859/29859.pdf. Accessed June 27, 2011.
38. Emslie GJ, Heiligenstein JH, Wagner KD, et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry*. 2002;41(10):1205–1215.
39. Keller MB, Ryan ND, Strober M, et al. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2001;40(7):762–772.
40. Wagner KD, Ambrosini P, Rynn M, et al. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials. *JAMA*. 2003;290(8):1033–1041.
41. Wagner KD, Jonas J, Findling RL, Ventura D, Saikali K. A double-blind, randomized, placebo-controlled trial of escitalopram in the treatment of pediatric depression. *J Am Acad Child Adolesc Psychiatry*. 2006; 45(3):280–288.
42. United States Food and Drug Administration. FDA launches a multi-pronged strategy to strengthen safeguards for children treated with antidepressant medications. October 15, 2004. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108363.htm. Accessed February 26, 2012.
43. Hetrick S, Merry S, McKenzie J, Sindahl P, Proctor P. Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. *Cochrane Database Syst Rev*. 2007;3:CD004851.
44. Masi G, Liboni F, Brovedani P. Pharmacotherapy of major depressive disorder in adolescents. *Expert Opin Pharmacother*. 2010;11(3): 375–386.
45. 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(10):1132–1143.
46. Dudley M, Goldney R, Hadzi-Pavlovic D. Are adolescents dying by suicide taking SSRI antidepressants? A review of observational studies. *Australas Psychiatry*. 2010;18(3):242–245.
47. Asarnow JR, Porta G, Spirito A, et al. Suicide attempts and nonsuicidal self-injury in the treatment of resistant depression in adolescents: findings from the TORDIA study. J *Am Acad Child Adolesc Psychiatry*. 2011;50(8):772–781.

48. Vitello B, Silva SG, Rohde P, et al. Suicidal events in the Treatment for Adolescents with Depression Study (TADS). *J Clin Psychiatry*. 2009; 70(5):741–747.
49. Woldu H, Porta G, Goldstein T, et al. Pharmacokinetically and clinician-determined adherence to an antidepressant regimen and clinical outcome in the TORDIA trial. *J Am Acad Child Adolesc Psychiatry*. 2011;50(5):490–498.
50. Gaffrey MS, Shenoy R, Luby JL. Effects of stimulants and SSRIs on brain function in children: emerging clues from fMRI studies. *Child and Adolescent Psychopharmacology News*. 2011;16(5):3–5.
51. Strober M, Freeman R, Rigali J, Schmidt S, Diamond R. The pharmacotherapy of depressive illness in adolescence: II. Effects of lithium augmentation in nonresponders to imipramine. *J Am Acad Child Adolesc Psychiatry*. 1992;31(1):16–20.
52. Pathak S, Johns ES, Kowatch RA. Adjunctive quetiapine for treatment-resistant adolescent major depressive disorder: a case series. *J Child Adolesc Psychopharmacol*. 2005;15(4):696–702.
53. Birmaher B, Waterman GS, Ryan ND, et al. Randomized controlled trial of amitriptyline versus placebo for adolescents with "treatment-resistant" major depression. *J Am Acad Child Adolesc Psychiatry*. 1998; 37(5):527–535.
54. Strober M, Rao U, DeAntonio M, et al. Effects of electroconvulsive therapy in adolescents with severe endogenous depression resistant to pharmacotherapy. *Biol Psychiatry*. 1998;43(5):335–338.
55. 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(8):901–913.
56. Emslie GJ, Mayes T, Porta G, et al. Treatment of Resistant Depression in Adolescents (TORDIA): week 24 outcomes. *Am J Psychiatry*. 2010; 167(7):782–791.
57. Weisz JR, McCarty CA, Valeri SM. Effects of psychotherapy for depression in children and adolescents: a meta-analysis. *Psychol Bull*. 2006;132(1):132–149.
58. Blount T, Epkins C. Exploring modeling-based hypotheses in preadolescent girls' and boys' cognitive vulnerability to depression. *Cognit Ther Res*. 2009;33(1):110–125.
59. Ghaziuddin N, Barbosa V, King C. Treatment resistant depression in adolescents. In: Greden JF, Riba MB, McInnis M, editors. *Treatment Resistant Depression: A Roadmap for Effective Care*. Washington, DC: American Psychiatric Publishing; 2011:51–88.
60. Vitiello B. Combined cognitive-behavioral therapy and pharmacotherapy for adolescent depression: does it improve outcomes compared with monotherapy? *CNS Drugs*. 2009;23(4):271–280.
61. Kennard BD, Clark GN, Weersing VR, et al. Effective components of TORDIA cognitive-behavioral therapy for adolescent depression: preliminary findings. *J Consult Clin Psychol*. 2009;77(6):1033–1041.
62. Lewinsohn PM, Clarke GN, Hops H, Andrews JA. Cognitive-behavioral treatment for depressed adolescents. *Behav Ther*. 1990;21:385–401.
63. March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression. Treatment for Adolescent Depression Study (TADS) randomized controlled trial. *JAMA*. 2004;292(7):807–820.
64. 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(12): 1427–1439.
65. Melvin GA, Tonge BJ, King NJ, Heyne D, Gordon MS, Klimkeit E. A comparison of cognitive-behavioral therapy, sertraline, and their combination for adolescent depression. *J Am Acad Child Adolesc Psychiatry*. 2006;45(10):1151–1161.
66. TORDIA follow-up study indicates important of early treatment response. *Child Adol Psych Update*. 2011;13(3):1–3.
67. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D Report. *Am J Psychiatry*. 2006;163(11):1905–1917.
68. Kazdin AE. Psychosocial treatments for conduct disorder in children and adolescents. In: Nathan PE, Gorman JM, editors. *A Guide to Treatments that Work*. 2nd ed. New York, NY: Oxford University Press; 2002:57–85.
69. Chu BC, Kendall PC. Positive association of child involvement and treatment outcome within a manual-based cognitive-behavioral treatment for children with anxiety. *J Consult Clin Psychol*. 2004;72(5): 821–829.
70. Nock MK, Kazdin AE. Randomized controlled trial of a brief intervention for increasing participation in parent management training. *J Consult Clin Psychol*. 2005;73:872–879.
71. Wiersma JE, Hovens JG, van Oppen P, et al. The importance of childhood trauma and childhood life events for chronicity of depression in adults. *J Clin Psychiatry*. 2009;70(7):983–989.
72. Nemeroff CB, Heim CM, Thase ME, et al. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *Proc Natl Acad Sci U S A*. 2003;100(24):14293–14296.