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Review

TREATMENT-RESISTANT DEPRESSION IN ADOLESCENTS: REVIEW AND UPDATES ON CLINICAL MANAGEMENT

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Treatment-resistant depression (TRD) in adolescents is prevalent and impairing. We here review the definition, prevalence, clinical significance, risk factors, and management of TRD in adolescents. Risk factors associated with TRD include characteristics of depression (severity, level of hopelessness, and suicidal ideation), psychiatric and medical comorbidities, environmental factors (family conflict, maternal depression, and history of abuse), and pharmacokinetics and other biomarkers. Management options include review of the adequacy of the initial treatment, re-assessment for the above-noted factors that might predispose to treatment resistance, switching antidepressants, and augmentation with medication or psychotherapy. Other modalities, such as electroconvulsive therapy, vagal nerve stimulation, and repetitive transcranial magnetic stimulation, are also reviewed. Depression and Anxiety 28:946–954, 2011.

Key words: *depression; adolescent; treatment; treatment-resistant; psychotherapy; antidepressant*

INTRODUCTION

In this article, we review the definition, prevalence, clinical significance, risk factors, and management of treatment-resistant depression (TRD) in adolescents. This review was conducted using PubMed search engine. The following keywords were used: (Treatment-resistant depression AND adolescent) AND (treatment OR psychotherapy OR selective serotonin reuptake inhibitors (SSRI) OR Serotonin Reuptake Inhibitor OR Cognitive Behavioral Therapy OR Interpersonal Therapy (IPT)). The initial search was restricted for the period extending from January 1980 to October 2010, to English language and to studies with subjects under the age of 18 years. An additional search was conducted during the revision of this article covering the period from October 2010 to June 2011. Relevant studies were also identified through references of originally reviewed articles including the American Academy of Child and Adolescent Psychiatry practice parameters for the management of depressive disorders in children and adolescents.[1] Pubmed search yielded a total of 196 articles, which were screened. After the screening procedure, 21 articles were judged as relevant (15 original studies and 6 reviews) and we have summarized original articles in Table 1. Other articles were excluded either because they involved adult samples or the use of medications that are not available on the U.S. market (roboxetine) or because they were studies that were summarized in other systematic reviews and referenced as such. Added to the Pubmed search result were studies from the bibliography of the main review articles that although were not specific to a treatment-resistant population were large randomized controlled trials that contributed to the evidence body of pediatric depression treatment, namely the Treatment of Adolescent

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TABLE 1. Characteristics and key findings of treatment trials of resistant depression in adolescents reviewed in the text

	Population	Method/design/intervention	Key finding
TORDIA[17,18,23,24,26,29,35,39,41,56]	Three hundred and thirty-four adolescents with resistant depression	RCT with four arms	At 12 weeks, switch to another antidepressant and addition of CBT was superior to medication switch alone
	Age: 12–18	Switch to a different SSRI, switch to a different SSRI plus CBT, switch to Venlafaxine, switch to Venlafaxine plus CBT	Switch to another SSRI was associated with less side effects than switch to Venlafaxine
[70]	Nine adolescents with resistant depression Age:16–18	Open label trial of rTMS over 14 days	Improvement in depressive symptoms with rTMS, three patients had 30% improvement in symptoms
[57]	Ten adolescents with treatment-resistant depression Age:13–18	Case series with chart review to evaluate adjunctive use of Quetiapine	70% response rate with adjunctive use of Quetiapine
[52]	Fourteen adolescents diagnosed with treatment-resistant depression	Retrospective chart review of augmentation with lithium carbonate after TCA non-response.	Six of 14 patients had good response with combination of TCA and lithium
[65]	Ten adolescents with treatment-resistant psychotic depression	Open-label ECT trial	All but one patient had dramatic improvement within one week of treatment
[53]	Twenty-five adolescents with treatment resistant depression	Three-week open trial of augmentation with lithium carbonate after imipramine non-response	Ten of 24 patients responded or partially improved with combination of imipramine and lithium

TORDIA, Treatment of Resistant Depression in Adolescent Trial; ECT, electrocovulsive therapy; rTMS, repetitive transcranial magnetic stimulation; TCA, tricyclic antidepressant; RCT, randomized control trial; SSRI, selective serotonin reuptake inhibitors; CBT, cognitive-behavior therapy.

Depression Study (TADS) and the Adolescent Depression Antidepressant and Psychotherapy Trial (ADAPT) study in addition to adult studies that through the literature search were thought to be relevant to extrapolate to adolescents.

DEFINITION

TRD is defined as the lack of an "adequate clinical response" to an appropriate dose of evidence-based treatment. Many clinicians and research studies define an adequate response as at least 50% improvement in symptoms of depression or a global rating of improvement of "much" or "very much" improved during an adequate treatment course.[2] There are three evidence-based interventions for adolescent depression: cognitive-behavior therapy (CBT), IPT, and SSRIs. Adequate treatment means ensuring optimal dosage, duration, and patient adherence.[3] Adequate treatment is defined as 8–12 weeks of optimal pharmacological treatment that consists of at least 4 weeks of fluoxetine (20 mg) or its equivalent and a dose increase if no response is obtained for an additional 4 weeks.[1,4] Adequate psychotherapy course is defined as the use of CBT or IPT for 8–16 sessions.[4] Adherence to these treatments is assessed by attendance at sessions, by pill count remainder, or drug and metabolite levels for pharmacotherapy, and, for psychotherapy, completing homework and showing an understanding of the principles of either CBT or IPT.

PREVALENCE

In clinical trials, approximately 30–40% of adolescents do not respond to initial treatment of either combination of CBT and SSRI, SSRI alone, or psychotherapy alone.[2,5] Upon longer term follow-up, around 60% of adolescents who received evidence-based treatment achieve remission.[6–8] Consequently, around 40% of depressed adolescents can have what could be termed "TRD."

CLINICAL SIGNIFICANCE

Depression in adolescence is associated with impairments in functioning at home and at school, substance abuse, increased risk of hospitalization and other medical expenses, and an increased risk of nonsuicidal self-injury, suicide attempts, and completed suicide, the third leading cause of death in adolescence.[1]

RISK FACTORS FOR TRD

CHARACTERISTICS OF DEPRESSION

Clinical predictors of poor outcome in acute treatment of adolescent depression include chronicity and severity of depression, nonsuicidal self-injury, suicidal ideation, and hopelessness.[9,10] These characteristics also predict poor response within treatment-resistant samples.

PSYCHIATRIC COMORBIDITIES

A high rate of psychiatric disorders can co-occur with major depression in adolescents and can affect treatment response. Most common are diagnoses of Attention Deficit Hyperactivity Disorder (ADHD), dysthymic disorder, anxiety disorders, and substance abuse.[1,11,12] Comorbidities with dysthymic disorder is most highly correlated with poor prognosis and response to SSRI medication[13,14] and the presence of ADHD moderated treatment response in TADS.[15] In treating depressed adolescents with other psychiatric comorbidities, the current practice parameters recommend that treatment should first target the disorder which is most impairing and distressing to the individual.[1] In addition, if improvement of depressive symptoms is not likely until a comorbid condition is treated (e.g. severe malnutrition in anorexia, intravenous drug dependence), then the comorbid condition must be addressed first.

Comorbid anxiety has proven to predict poor response to acute treatment in previous studies.[9,15,16] The presence of anxiety has been, however, a positive moderator of CBT and combined treatment effect in some but not in all clinical trials.[9,17] This indicates that patients with comorbid depression and anxiety may be particularly in need of skills they learn through CBT in order to get better.

Further complicating treatment is substance abuse disorder, which is common in adolescents with TRD. Substance-related impairment was associated with depression severity and predicted poor response in the Treatment of Resistant Depression in Adolescent (TORDIA) study.[18]

MEDICAL COMORBIDITIES

Comorbidity with medical conditions, such as anemia, vitamin B12 deficiency, hypothyroidism, mononucleosis, insulin-dependent diabetes mellitus, migraine, fibromyalgia, or other chronic illnesses, is more common in depression and can contribute to the exacerbation of depressive symptoms in children and adolescents and requires attention and management.[19,20] Conversely, treatment of underlying depression may change the natural course of the medical comorbidity.

PHARMACOKINETICS AND PHARMACOGENETICS

CYP450 genes play a major role in the metabolism of antidepressants and determine the individual's metabolizer status which in turn affects exposure to antidepressants.[21] However, polymorphisms in these genes have not been shown to be related to clinical outcome in adults in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, although this has not been studied in pediatric depression.[22] In the TORDIA study, better outcome was associated with higher blood concentration of drug, at least for fluoxetine and citalopram, and higher adherence was also associated with a better outcome.[23,24]

In one study, depressed and anxious youth homozygous for the more functional allele of the serotonin transporter promoter gene are more likely to respond to citalopram.[25] This genotype did not predict response in the TORDIAs, although polymorphisms of the FKBP5 associated with greater glucocorticoid receptor subsensitivity was associated with an increased risk of suicidal events, which were much more common in depressed youth who did not respond to treatment.[26]

ENVIRONMENTAL FACTORS

Family conflict has been shown to be a risk factor for depression,[27] to predict poorer response and prolong time to remission to treatment in some but not in all studies.[9,15,28] Family conflict also is a predictor of suicidal events in both the ADAPT and TORDIA studies.[10,29] Maternal depression has been shown to be a predictor of poor response to treatment in general and cognitive behavior therapy in specific; conversely, treatment of maternal depression has been associated with a better response to child treatment.[30,31] History of abuse is a negative moderator of treatment response to CBT in both the TADS and TORDIA studies[32,33] and specifically it emerged as a negative moderator of response to antidepressant and psychotherapy in TORDIA.[17,34]

APPROACH TO A PATIENT WITH TREATMENT-RESISTANT DEPRESSION

When managing patients who are not responding to treatment, clinicians should consider the following clinical issues in addition to being cognizant of the above clinical factors that are associated with poor outcome: misdiagnosis and inadequate initial treatment due to low dose, lack of proper ingredients, or nonadherence.

MISDIAGNOSIS

Several psychiatric (e.g. anxiety, dysthymia, pervasive developmental disorder, schizophrenia, and substance abuse) and medical disorders (e.g. hypothyroidism, anemia, cancer, autoimmune diseases, inflammatory bowel disease, and chronic fatigue syndrome) as well as conditions such as bereavement and adjustment disorder may mimic or complicate major depressive disorder. These conditions should not be diagnosed as MDD and treated as such unless patients meet criteria for major depression that are not directly attributable to associated diseases. Since patients with bipolar disorder often present during a depressive episode, screening for symptoms of mania or hypomania should be done continuously and diligently because these symptoms are often denied and are pleasant feelings, which adolescents may associate with improved functioning[35] These symptoms can be confounded with ADHD symptoms in preadolescents or effects of substance use in adolescents.[35] Family history of bipolar disorder, psychosis, and history of pharmacologically induced mania or hypomania are associated with the development of bipolar disorder,[1,33,36] although not all children who develop pharmacologically induced hypomania have bipolar disorder.[37] Adolescents who are misdiagnosed as unipolar and treated with antidepressant only without the concomitant use of mood stabilizers are at a substantial risk of developing a manic episode or a mixed state.[38]

INADEQUATE PSYCHOTHERAPY OR PHARMACOTHERAPY

Inadequate psychotherapy can be due to lack of practice or expertise of the therapist, the lack of "active ingredients" in the therapy course, and/or insufficient frequency or duration of therapy or the use of a nonevidence-based intervention. For instance, in TORDIA both CBT dosage and specific components of the CBT treatment were associated with a more favorable treatment response. Participants receiving an adequate treatment dose (defined as nine CBT sessions) had better outcomes, as did participants who received the social skills and problem-solving modules.[39] The effects of CBT in TADS appeared to be partially mediated by an improvement in perceived problem-solving efficacy.[40]

When patients are treated with medications, however, it is important to evaluate their adherence to medication treatment and the presence of side effects that may contribute to poor adherence or premature discontinuation of treatment. There is some evidence that inadequate exposure to antidepressants can lead to a lower response rate and, conversely, that increasing exposure by increasing the dose of antidepressant can improve the response rate.[23] In certain instances, clinicians may want to obtain a medication level to make sure that their patient is taking the prescribed antidepressant, or is not a rapid metabolizer. Since concentration is very much inversely related to weight, dosing should take this into consideration, both at baseline, and also, over time, if the patient's weight changes significantly.[23] Nonadherence to medication, as established by the proportion of prescribed medication that should have been taken but has not been, has also been associated with poorer outcome.[24]

TREATMENT STRATEGIES FOR TRD

We discuss below the following treatment options that are available when a depressed adolescent does not respond to an adequate course of treatment: (1) medication switch; (2) augmentation with psychotherapy or medication; and (3) other nonpharmacological somatic treatments.

MEDICATION SWITCH

When adequate courses of treatment fail, or when side effects of the treatment hinder response, one can consider either within-class switching or between-class switching. TORDIA is a six-site trial that randomized 334 participants with unipolar major depression that has not responded to one adequate trial of SSRI to one of four treatments for 12 weeks: a switch to another SSRI (fluoxetine, paroxetine, or citalopram); a switch to venlafaxine; a switch to another SSRI with CBT, or a switch to venlafaxine with CBT.

Results from TORDIA revealed a response rate of 40% with medication monotherapy, with no difference between medication class, although participants switched to venlafaxine had more side effects, and under some conditions, higher rates of suicidal ideation, and self-injury.[41] Medication monotherapy was inferior to the switch to another antidepressant with the addition of CBT (54.8%). Thus, the recommendation from this study was, if a patient has not responded to an adequate treatment with one SSRI, that the next move should be to switch to a second SSRI with the addition of CBT. Before switching, it is important to ascertain that the patient received an adequate dose for a sufficient duration, that the patient received an adequate concentration of drug, and that the patient was adherent.[23,24]

After failure of two SSRIs, studies in adults show that a switch from a second SSRI to either venlafaxine, bupropion, or combinations of SSRIs with other agents (lithium, T3, bupropion, mirtazapine, and atypical antipsychotics) are equally effective.[6,31,32]

Switching to monoamine oxidase inhibitors (MAOIs) is less common but has been studied in adults in a number of randomized controlled trials (RCTs) reporting response rates between 12.1 and 45.5%.[42,43] It is, however, associated with high dropout rates because of adverse effects. Two case reports on the use of phenelzine in adolescents with treatment-resistant

melancholia have been documented by Strober et al.[36] In these case reports, phenelzine monotherapy lead to complete remission after multiple failed treatments. The risks of hypertensive crises and serotonin syndromes associated with the use of MAOIs however have discouraged their use.

To our knowledge, the only study for adolescent depression using an IV drug infusion was a small RCT comparing the effect of IV infusion of clomipramine to a sham infusion.[44] In this study, response was significantly better in those who received the infusion and this effect was sustained on follow-up.

AUGMENTATION WITH PSYCHOTHERAPY

A second finding from the TORDIA study was that the combination of a medication switch plus adding CBT was superior to a medication switch alone. These results are consistent with the findings from TADS that combination of CBT and fluoxetine was associated with the most rapid and complete response compared to other interventions. At 12 weeks, the combination of CBT and fluoxetine was vastly superior to CBT alone, was superior to both CBT and fluoxetine monotherapy, as well as placebo, with respect to the pace of decline in depressive symptoms, suicidal ideation, improvement in functional impairment, and achievement of remission.[5,45,46] The corresponding rates of "adequate clinical response" were: 71% for combination, 61% for fluoxetine, 43% for CBT, and 35% for placebo. However, combination treatment was not superior to fluoxetine alone for those with more severe depression, which is consistent with the British ADAPT study-where 61% response rate by week 28 for SSRI alone and 53% for the combination.[47,48] With respect to remission, 37% of those who received combination treatment achieved remission by 12 weeks in TADS, as compared to 23% of those treated with fluoxetine, 16% of those treated with CBT, and 17% of those treated with placebo.[45] Over time, all the different treatment options converged (at week 36, the estimated remission rates were 60% for combination treatment, 55% for fluoxetine, and 64% for CBT).[45] A meta-analysis of all available studies of combination treatment for adolescent depression concludes that combination treatment has no superiority over antidepressants for depressive symptoms and suicidality although it was superior to medication monotherapy for improvement in functional status.[47]

AUGMENTATION WITH MEDICATIONS

Augmentation is the use of a psychotropic agent, not usually clinically indicated for the treatment of depression, to increase the influence of an antidepressant. Using augmentation substitutes for the option of discontinuing the initial antidepressant and speed up response time.

Augmentation with lithium in adults has been reported to enhance the effect of tricyclic antidepressants, MAOIs, and SSRIs and has proven more effective than optimizing with placebo.[49] Nonetheless, in some more recent studies[50,51] lithium has not achieved the high response rates (50–60%) that were reported in earlier studies. Only scarce data have supported the use of lithium in children and adolescents.[52,53] Furthermore, it is associated with risks of toxicity, weight gain, and acne. Some other augmentation agents which have not been studied in adolescents include thyroid hormone (T3), atypical antipsychotics, buspirone, and bupropion.[54,55] Evidence for the efficacy of atypical antipsychotics as augmenting agents of SSRIs is documented in several adult studies that have shown that they may be particularly helpful in patients with residual mood lability and to decrease suicidality and impulsive aggression.[55] In adolescents, augmentation with antipsychotics was supported by post hoc analyses of the TORDIA study;[56] however, systematic studies have not been performed with adolescent population, and only some case studies have been published. In one case series report, Pathak et al. described 10 adolescent cases diagnosed with TRD who were treated with adjunctive quetiapine. Improvement ("much or "very much") on the CGI was reported in 70% of the patients and decrease in self-harm in 30% of them.[57] Disadvantages of the use of atypical antipsychotics in this population include risk of weight gain, obesity, and metabolic syndrome.[58]

Augmentation of SSRI with either sustained-release bupropion or buspirone appears to be useful in resistant depression in adults as demonstrated in STAR*D. Here, augmentation with sustained-release bupropion had certain advantages, including a greater reduction in the number and severity of symptoms and fewer side effects and adverse events.[59] Such augmentation strategies have not been systematically studied in adolescents although open-label studies have suggested the effectiveness of bupropion in acute treatment of depressed adolescents with and without ADHD.[60,61]

OTHER NONPHARMACOLOGICAL SOMATIC TREATMENTS

Electroconvulsive therapy (ECT). ECT is only considered in adolescents after failure of three or four medication trials and at least one psychotherapy trial[4] and is estimated to produce response rates between 60 and 80% in patients with bipolar or psychotic depression.[62] Neuroimaging studies have shown that ECT works by decreasing "auto-receptor inhibition in noradrenergic and dopaminergic neurons" and thus increasing the release of noradrenaline and dopamine.[63] Although ECT has been studied in RCTs in adults and has been proven effective for treatment-resistant depression, no RCT has been conducted in adolescents yet, who constitute only 1% of the patients receiving this treatment, due to possible associated side effects,[64] although an open-label trial suggested that it is effective in the treatment of resistant depression especially when associated with psychotic symptoms.[65]

Side effects range from headaches, nausea, muscle, and joint pains to disinhibition and disturbances in short-term memory.[62]

Vagus nerve stimulation (VNS). Initially used for the treatment of refractory epilepsy in both children and adults, VNS has shown to improve mood in patients receiving this treatment, which lead to it being approved by the FDA in 2005 for use in TRD only in adults.[66] The mechanism of action of VNS has not been well defined and no studies have been done in the young population yet. Common side effects that are usually transient include dyspnea, voice alterations, hoarseness neck pain, and cough.[67] In some studies of adults successfully treated with VNS, observed effects included enhanced neurocognitive functioning and improvement of pain symptoms.[68]

Repetitive Transcranial Magnetic stimulation (rTMS). rTMS has been proven to be an effective treatment for TRD in a number of studies done in adults with reported response rates ranging between 30 and 65%.[69] To date, Bloch et al.'s open-label study (2008) represents the largest sample of adolescents treated with rTMS. Out of nine patients, three patients had more than 30% reduction in symptom severity as measured by the CDRS and all patients reported the treatment as being a favorable option.[70] Side effects of rTMS include headache and scalp pain, rare seizures, and episodes of mania have also been reported.

PROMISING NEW DIRECTIONS

Family conflict has previously been reported to be associated with a slower response to treatment and an increased risk for relapse in clinical trials for the treatment of adolescent depression[71] and to moderate the response of depressed adolescents to CBT in the TADS study.[28] Family therapy, though not well studied in the treatment of children and adolescents with TRD can also play a role in improving outcome,[71] and family-based interventions have shown mixed results for depressed adolescents. The most promising findings come from interventions aimed at improving parent–child attachment bond.[72] Specifically, Attachment-Based Family Therapy consisting of individual and family sessions has been shown to decrease depressive symptoms in sample of suicidal adolescents.[72]

In addition, insomnia is a predictor of the onset of depressive symptoms[73] and is one of the most common residual symptoms in adolescent depression.[74] Conversely, psychotherapy to improve sleep has been shown to improve treatment response to SSRI in depressed adults with insomnia[75] but such an intervention has not been carefully studied in adolescents. The fact that the use of medications to improve sleep was associated with poor outcome in TORDIA[41] raises the questions of whether the presence of sleep disturbances is a proxy of clinical features of a subpopulation of depressed adolescents who are unlikely to respond to treatment or whether poor outcome was related to incomplete treatment of sleep difficulties as no psychotherapeutic interventions to improve sleep were used or whether it was due to an interaction between hypnotics and antidepressants.

Domains, such as neurocognitive deficits and abnormal neural correlates, have been shown to be present in pediatric depression and to predict treatment response in depressed adults.[76–78] These may also serve as treatment targets and future studies will probably investigate this question.

SUICIDALITY IN TREATMENT-RESISTANT DEPRESSED ADOLESCENTS

With high nonresponse rates and multiple trials of antidepressants in treatment-resistance depression, the likelihood of occurrence of suicidal events in depressed adolescents becomes of important clinical concerns. In both TADS and TORDIA, suicidal events happened very early in treatment, a median of around 3 weeks into treatment, and were most likely to occur in those with high levels of depression and suicidal ideation who were not responding to treatment.[29,79] In TORDIA, suicidal event was also predicted by family conflict, and drug and alcohol use.[29] These findings were similar to the ADAPT trial, in which ideation, family difficulties, and nonsuicidal self-injury were predictors of suicidal events.[80] In TORDIA, in addition, venlafaxine treatment was associated with a higher rate of self-harm adverse events in those with higher suicidal ideation and adjunctive use of benzodiazepines, while in a small number of participants ($N = 10$) it was associated with higher rate of both suicidal and nonsuicidal self-injury adverse events.[29] Reduction in suicidal events may be achieved by accelerating initial treatment response, addressing family conflict and drug and alcohol use, and psychosocial interventions such as developing a good safety plan and emotion regulation skills.[81]

SUMMARY

In summary, factors associated with treatment-resistant depression include inadequate dose or duration of treatment, misdiagnosis, treatment nonadherence, psychiatric and medical comorbidities, and psychosocial stressors. Treatment options for depressed adolescents who have failed a first SSRI trial include switching to another SSRI and addition of CBT and if this step fails or is suboptimal, next reasonable steps include augmentation and switching options that are evidence-based in adults.

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