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Treatment-Resistant Depression in Adolescents

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Introduction

In this review, the definition, predictors, approach, and management of treatment-resistant depression in adolescents are described. We conclude with descriptions of some novel interventions that may be treatments of the future for treatment-resistant depression.

Definition

We define "treatment-resistant depression" as a unipolar depressive disorder that does not respond to an adequate dose of evidence-based treatment.

Adequate Clinical Response

An adequate clinical response is frequently defined as at least a 50 percent reduction in depressive symptomatology after eight to 12 weeks of treatment. Around 60 percent of depressed youth show an adequate clinical response after 12 weeks of treatment, and a similar proportion will reach remission (i.e., the absence of depressive symptoms) by 24 to 36 weeks.[1,2] Therefore, around 40 percent of depressed youth who receive a single course of an evidence-based treatment will have treatment-resistant depression.

Evidence-based treatments for adolescent depression that are superior to either placebo or non-directive clinical management are selective serotonin reuptake inhibitors (SSRIs), cognitive

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behavior therapy (CBT), and interpersonal therapy (IPT), with medication showing a more rapid response rate than CBT.[1,3,4] Fluoxetine is the medication with the strongest and most consistent results in adolescent depression, and the only medication that is FDA-approved for use in prepubertal depression.[3]

Adequate Dose and Duration

An adequate trial of an SSRI should be at least eight weeks in duration, with the last four weeks at a dosage of the equivalent of 40 mg of fluoxetine. CBT or IPT should consist of eight to 16 sessions over as many weeks.

Clinical Significance

Treatment-resistant depression frequently becomes chronic. Chronicity increases the likelihood of adverse sequelae, which include educational and occupational under-attainment, interpersonal problems, alcohol and substance abuse, suicidal behavior, and suicide.[5] However, with additional treatment, the majority of depressed patients achieve remission even if they do not respond fully to the first intervention.[2,6-8]

Predictors of Nonresponse (Table 1)

Poorer treatment response is predicted by greater severity, chronicity, and comorbidity; for comorbid cases, the combination of CBT and an antidepressant is superior to medication monotherapy.[1,9-11] Prominent anhedonia predicts nonresponse, even after controlling for overall depressive severity, highlighting the importance of assessing and targeting this important domain.[12] Alcohol or substance use, even at sub-diagnostic thresholds, is associated with a lower probability of response.[13] Hopelessness predicts a poorer response to treatment and a greater likelihood of dropout.[14] Family discord is associated with nonresponse and relapse, and both a history of abuse and of current parental depression predict nonresponse to CBT with or without medication.[10,14-18]

TABLE 1:
Predictors of Nonresponse to Treatment in Adolescent Depression

Chronicity
Severity
Comorbidity, especially substance use
Nonadherence
Low blood concentration of antidepressant
History of abuse
Family discord
Parental depression
Bullying at school
Same-sex attraction accompanied by peer victimization or family rejection

Document Improvement or Lack Thereof

After weeks of treatment, patients with chronic depression may report that "nothing has improved." The symptoms of depression do not all improve at the same pace, and often, engagement and participation in activities improve prior to the relief of sad mood and anhedonia. The use of standardized self-report or interview ratings of depression on a regular basis will help the clinician, patient, and family to objectively judge clinical progress. If improvement is discernible, then the current treatment should be optimized (e.g., dose adjustment), rather than discontinuing a current treatment and initiating a new treatment.

Determine Adherence and the Adequacy of the Previous Treatment Trial (Table 2)

Adherence to medication treatment can be assessed through medication diaries, pill counts, or obtaining a trough level of drug plus metabolites. A large proportion (e.g., > 30 percent) of prescribed pills remaining over those expected if a patient was taking the medication as prescribed represents clinically significant nonadherence and is associated with a greater likelihood of nonresponse.[19] Low plasma levels of antidepressants are associated with a lower rate of response.[20] We recommend obtaining a trough level of an SSRI for patients who report multiple unsuccessful medication trials. A very low level of drug may indicate either nonadherence or, more rarely, extensive metabolism, which can be confirmed by genotyping of cytochrome P450 genes. If a nonadherent patient resumes taking a drug in anticipation of having a level drawn, so-called "white-coat compliance," then the level of parent compound will be high compared to that of the metabolites. An increase in the dose of an SSRI in the face of nonresponse is more likely to result in response, especially if the dose change leads to an increase in drug concentration and the drug concentration prior to the dose increase was low.[20,21] Because adolescents metabolize several antidepressants more rapidly than adults (e.g., sertraline, citalopram), dosages should be adjusted accordingly.[22] Meta-analyses show that the response rate in adult depression goes up with the dose, along with the likelihood of side effects.[23] A similar meta-analysis in youth was not able to demonstrate this, although these studies were for the most part not designed to test the effect of dose. Therefore, clinicians and researchers tend to base their approach on the few individual studies that do demonstrate a higher response related to increased dose.[20,21,24]

CBT and IPT both require eight to 16 sessions in 12 to 16 weeks. Adherence to these psychotherapies means that the patient regularly attended sessions, did the assigned homework, and learned the skills and therapeutic framework about depression — and was able to implement them. Sometimes patients are too depressed or otherwise unmotivated to be able to benefit from psychotherapy.

TABLE 2: Assessment of the Treatment-Resistant Adolescent
Document nonresponse
Assess adequacy of dose and duration of treatment
Assess adherence to previous treatment
Reassess primary and secondary diagnoses
Rule out contributory medical comorbidity
Reassess sleep quality
Assess potential psychosocial contributors to treatment resistance

Determine if the Primary Diagnosis Is Correct

Bipolar, psychotic, and seasonal depression requires different treatment approaches from those used for unipolar major depression. Pediatric bipolar disorder often presents in a mixed state. Treatment with an antidepressant alone can be dangerous and can precipitate a manic episode. Instead, antidepressant treatment must be preceded by treatment with a mood stabilizer. Even subsyndromal manic symptoms can be associated with prolonged depression and lowered rates of remission.[25] Psychotic depression, often associated with a bipolar diathesis, requires a combination of an antipsychotic medication along with an antidepressant. This condition must be differentiated from the prodromal symptoms of schizophrenia, which may include distress and sad affect. Treatment of early-onset schizophrenia involves the use of antipsychotic medication and patient and family support. Seasonal affective disorder may respond to antidepressants, but light therapy is the most specific and effective treatment.[26]

A patient may present with depressive symptoms that are either secondary to, or complicated by, another condition that contributes to treatment resistance. Depressed patients with attention deficit hyperactivity disorder (ADHD) may be demoralized by peer rejection and school failure, and may have a better chance of recovery if their ADHD is properly managed. Patients with eating disorders are often depressed due to battles about weight or due to being malnourished. Restoration of adequate weight and nutrition are a necessary precursor to the successful treatment of depression. Patients with anxiety disorders may be so restricted in their social activities that they find it difficult to engage in meaningful and pleasurable activities helpful for recovery. Alcohol and substance abuse may mimic or complicate a depressive picture, as well as confer treatment resistance. In each of these circumstances, treatment of the primary or complicating condition is necessary in order to achieve remission of depressive symptomatology.

Assess for Concomitant Health Risk Behaviors

Adolescents with chronic depression often have concomitant, intercorrelated health risk behaviors, such as fighting, weapon-carrying, having unprotected sex, nonsuicidal self-injury, binge eating, alcohol, drug, or tobacco use, or not engaging in physical activity.[27] These health risk behaviors can be life-threatening, damage long-term health, interfere with treatment response, and result in life events that are depressogenic. Belonging to an antisocial peer group is a risk factor for depression because membership leads to life events, such a legal or disciplinary actions, that in turn increase the risk for depression.[28] Depressed adolescents are at increased risk for obesity, which may then affect their self-image and social interactions.[29] Because drug concentration is inversely proportional to weight, a depressed adolescent who gains weight may "outgrow" his or her medication dose.[20]

TABLE 3: Possible Screening Laboratory Tests for Treatment-Resistant Depression in Adolescents
Trough drug level and metabolites (if suspect nonadherence, extensive or slow metabolism)
CBC
C-reactive protein
TSH
Vitamins B2, B6, B12, Vitamin D, and folate
Urine screens for drugs

Rule Out Covert Medical Illness (Table 3)

A careful medical history and physical examination and selected laboratory tests are appropriate as clinically indicated for a patient with chronically unresponsive depression. Chronic medical illness may contribute to an increased risk of depression by interfering with the ability to participate in pleasurable and meaningful activities and by its general effect on well-being.[18] Specific chronic illnesses that have been shown to increase rates of depression include diseases of the central nervous system, such as migraine and epilepsy, and those that involve inflammation, such as asthma and inflammatory bowel disease.[30-32] Medication used to treat asthma (corticosteroids), epilepsy (phenobarbital), and inflammatory bowel disease (cortico-steroids, interferon), as well as the use of oral contraceptives, may also increase the risk for depression.[33] Other undiagnosed medical conditions that can mimic or contribute to depression and treatment resistance include hypothyroidism, mononucleosis, iron-deficiency anemia, and deficiencies in Vitamin D, B2, B6, B21, or folate.[31,32]

Differentiate Side Effects of Antidepressants From the Symptoms of Depression

In order to differentiate potential side effects of antidepressants from depressive symptoms, these adverse effects, such as fatigue, agitation, anxiety, hostility, suicidality, irritability, and akathisia, must be mapped against the time course of initiation of treatment and dosage changes. The decision about whether to switch medications or to reduce or divide the dosage should be based on balancing these side effects against any benefit that the patient has derived from the treatment. Patients who experience greater agitation, anxiety, or irritability after starting an antidepressant should be carefully evaluated to rule out mania; if mania occurs, the antidepressant should be withdrawn and treatment with a mood stabilizer initiated. If agitation occurs in patients treated with either higher doses of an antidepressant, or more than one serotonergic agent, serotonin syndrome should be ruled out and the dose of the antidepressant should be reduced or completely stopped. Nonadherent patients treated with antidepressants with relatively short half-lives (e.g., sertraline, citalopram, venlafaxine) may experience withdrawal symptoms, which usually consistent of fatigue, malaise, anxiety, and dysphoria.

Assess Sleep Quality

Insomnia and sleep deprivation are predictors of the onset of depressive symptoms.[34] While treatment of depression may normalize sleep, often poor sleep habits and patterns persist. Sleep deprivation and insomnia contribute to daytime impulsiveness, poor concentration, dysphoria, and risk for nonsuicidal self-injury and suicidal behavior.[35-37] Sleep difficulties are one of the most common residual symptoms in adolescent depression. Conversely, the addition of treatments that improve sleep, such as cognitive therapy for insomnia, can result in more rapid and complete treatment response in depressed adults and youth.[7,38,39] Poor sleep also appears to interfere with depressed adolescents' responses to antidepressant treatment.[40] Contributors to poor sleep, like anxiety at bedtime, an overstimulating bedtime routine, use of alcohol or caffeine in the evening, daytime napping, and medication that may interfere with sleep (e.g., stimulants, bupropion, steroids), should be assessed and targeted. In addition, specific sleep disorders, like sleep apnea, restless legs syndrome, and narcolepsy, should be ruled out either by history or by referral to a sleep specialist.[41]

Pilot studies show that "triple chronotherapy" holds promise for treatment-resistant depressed and suicidal adolescent patients. Triple chronotherapy has primarily been conducted on inpatient units and involves sleep deprivation, phase advance, and morning bright light, and has resulted in rapid short-term reduction in depression and suicidal ideation.[42,43]

Patients treated with SSRIs may complain of daytime fatigue, difficulty falling asleep, sleep disruption, and vivid, sometimes unpleasant dreams. Vivid dreams are a side effect of SSRIs, and if they are intolerable, then the patient should be switched to an alternative agent. In the case of antidepressant-induced fatigue, the dosage can either be divided between day and night or switched to the evening. When patients report difficulty falling asleep or sleep disruption, the clinician should make sure that the patient is not taking the antidepressant too late in the day.

If psychosocial interventions do not help the medication-induced sleep difficulties, and the antidepressant has otherwise been of benefit, then we recommend the addition of diphenhydramine, melatonin, or low-dose mirtazapine one hour prior to bedtime. Although many clinicians continue to find trazodone to be of benefit for depressed patients with sleep difficulties, we tend to avoid its use for two reasons. First, in boys, there is an increased risk of priapism, and second, in the TORDIA trial, the addition of trazodone to an antidepressant regimen resulted in an extremely low treatment response (around 15 percent vs. around 50 to 60 percent overall).[9,44] One possible explanation for these findings is that trazodone is metabolized to m-CPP (meta-chlorophenylpiperazine), which is known to induce dysphoria. In the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA), the response rate was particularly low in those patients treated with the combination of trazodone and either fluoxetine or paroxetine, both of which are potent inhibitors of cytochrome 2D6 metabolism. Since cytochrome 2D6 is required to metabolize m-CPP, the inhibition of cytochrome 2D6 activity by fluoxetine or paroxetine could have led to an accumulation of m-CPP, resulting in dysphoria and lack of a therapeutic response.[44]

Issues Contributing to Nonresponse

Parental depression, family discord, and a history of abuse all have been shown to predict poor response to treatment, including the combination of medication and CBT.[10,14-17,45,46] While not as carefully studied, clinical experience has taught us that youth who are being bullied at school, coping with same-sex attraction, or experiencing school failure are unlikely to recover until these stressors are addressed. The clinician can help the family advocate for the school to implement mandated anti-bullying policies, and to accommodate the depressed teen's educational needs with the expectations that are appropriate for his or her current level of functioning. Youth with same-sex attraction may experience distress due to bullying, peer, or family rejection, or guilt due to conflicts with family and cultural expectations.[47,48]

These dynamics are particularly prominent in transgendered youth, and it is encouraging that those transgendered youth who are supported in their transition by their family and school setting are no more symptomatic than controls.[49]

Excessive internet or social media use (defined as 2.5 or more hours of use per day) may contribute to treatment-resistant depression through at least three mechanisms: (1) youth who use social media excessively have lower total sleep times; (2) depressed youth are especially sensitive to rejection and social comparison, which are prominent in social media use; and (3) greater social media use is associated with a greater risk for cyberbullying, which often co-occurs with and has similar effects to traditional bullying with regard to impact on mood, anxiety, and suicidal ideation.[50-55] Parental monitoring of social media use is protective against these negative impacts of dysfunctional social media use that may be contributing to the youth's prolonged depressive episode. [56,57]

In all these examples of psychosocial stressors contributing to treatment resistance, systemic and/or psychotherapeutic interventions should be implemented to target these sources of nonresponse prior to engaging in multiple switches in medication.

It is rare for depressed patients to present to clinicians with a single set of problems, and, in fact, it is much more common for depressed patients to have several comorbidities, along with family or peer conflict and academic difficulties. Weisz and Chorpita demonstrated that using an algorithm that prioritizes and sequences clinical problems (e.g., treating family conflict and conduct problems first, because family violence or legal problems might ensue and upend treatment for depression and anxiety) is superior to clinicians using their own judgment in how to combine different evidence-based treatments.[58,59]

Prevention of Treatment-Resistant Depression

The best way to manage treatment-resistant depression is to prevent it from ever occurring. The biggest single risk factor for treatment-resistant depression is chronicity. In recognition of this, the American Academy of Pediatrics now recommends screening for adolescent depression in order to promote early detection of this condition, and endorses co-location of mental health services in primary care to enhance access. Collaborative care for adolescent depression has been shown to dramatically increase uptake into treatment, improve outcome, and reduce health care costs associated with untreated depression.[60,61] Once depression is identified, the goal of treatment should be to achieve complete remission, as patients with residual symptoms have a much greater risk of relapse and the development of chronic depression.[62] Combined treatments of medication and CBT have been shown to result in the most rapid and complete response in most, but not all, studies.[1,9,63] To prevent relapse, continuation treatment with the same intervention that resulted in remission (medication at the same dose, CBT booster sessions) should be offered for six to 12 months after achieving remission.[62,64] The addition of wellness-focused CBT to continuation antidepressant therapy substantially improves the likelihood of sustained recovery over continuation treatment with medication monotherapy alone.[65]

If a patient already has experienced a chronic and/or recurrent course, then a longer period of prophylaxis may be indicated. Increasing the patient's overall resilience by improving sleep habits, physical activity, positive peer interactions, and connection to family and school can play an important role in continuation treatment for depressed youth, particularly those with significant health risk behaviors.

Recent meta-analyses have examined the efficacy of different antidepressants in adolescent depression, finding the most consistent effect in those treated with fluoxetine.[66] Although the effect size for fluoxetine's impact on depression reported in this recent meta-analysis was moderate (d= –0.51), Cipriani and colleagues expressed reservations about the use of fluoxetine for adolescent depression, and evinced a strong preference for use of psychotherapy, despite much weaker effects for psychotherapies in depression (d= 0.29).[67] All things being equal, initial treatment with psychotherapy monotherapy may make sense. However, in light of the larger effect size for fluoxetine than for CBT and the 11:1 ratio of adolescents who respond to antidepressants vs. those who experience suicidal events, there is room for greater optimism about the use of antidepressants in adolescent depression than was conveyed in this meta-analysis.[3,66]

Management

Education

Patients and their families should understand that depression is a brain illness. They should learn about the benefits and side effects of various treatments, and be actively involved in choosing which intervention to implement. It is important to prepare the chronically depressed teen and his or her family for the possibility that finding the proper treatment or combinations thereof may take time, and unfortunately, can involve trial and error. However, better outcome can be obtained using "measurement-based care," in which patients are systematically monitored for side effects and treatment response using standard assessments with set strategies for making treatment changes.[68] It is important to instill hope, since the majority of patients with treatment-resistant depression eventually will achieve clinical response and remission, and hopelessness predicts dropout from treatment.[6,7,14]

Development of a Safety Plan

Adolescents with treatment-resistant depression are frequently suicidal; in the TORDIA study, 58 percent of participants had clinically significant levels of suicidal ideation.[9] Best practice recommends the development of a safety plan to reduce the risk that suicidal patients will act on their suicidal thoughts. A safety plan is a structured, individualized plan that the suicidal individual can implement to cope with suicidal urges.[69] First, adolescents should identify possible triggers for suicidal urges, and then, in collaboration

with the clinician, develop plans for either avoiding these triggers or coping with them. These strategies can be intrapersonal, interpersonal, or reaching out to professionals. Intrapersonal techniques include reviewing reasons for living, distraction, and techniques for distress tolerance, such as deep breathing or relaxation.

Interpersonal strategies involve reaching out to friends or trusted adults for distraction and support; we urge adolescents not to rely on their friends for discussion of suicidal urges but to go only to trusted adults for these issues. If the patient does not think he or she can manage with the first two approaches, then the patient can contact professional help, which could be the treating clinician, the emergency room, crisis or text services, or the police. Finally, the parents, patient, and clinician then review the safety plan and try to identify possible barriers to its implementation and modify the plan if necessary.

Partial Response (Table 4)

A partial clinical response is defined as a clinically significant improvement without the achievement of remission, meaning that the patient could be substantially improved from intake, but still symptomatic and showing some evidence of functional impairment. The most common residual symptoms after acute treatment are anhedonia, sleep difficulties, irritability, and difficulty concentrating, all of which can contribute to functional impairment and relapse.[2,7]

TABLE 4:
Management of Treatment-Resistant Depression: Partial Response

Optimize initial treatment
Add psychotherapy
Address psychosocial stressors
Pharmacological targeting of residual symptoms
Augmentation
• T3
• Antipsychotic
• Lithium
• Bupropion

Optimization

If the patient is showing a trajectory of steady improvement that is likely to result in remission, then it makes sense to maintain or increase the dose and/or duration of the current treatment. Increasing the dose of an SSRI in patients showing a partial response and continuing psychotherapy in those showing steady improvement have been shown to result in favorable clinical outcomes.[20,21] The advantage of the optimization approach is that it does not expose the patient to any additional treatments and continues those interventions known to be both tolerated and at least partially effective. The disadvantage is that the endpoint of slow steady improvement could still be an incomplete response. Therefore, the clinician must, in collaboration with the patient and family, compare the likely outcome of continuation with the same intervention with the advantages and disadvantages of the other strategies discussed below, namely augmentation or switching to a different treatment.

Augmentation

Most, although not all, studies in depressed adolescents and adults have shown that the combination of CBT and antidepressant medication results in a faster and more complete response than either monotherapy alone.[1,9,63,70] Therefore, if a patient has shown a partial response to medication that has been optimized, the addition of CBT is likely to be beneficial; the same may be true of IPT, but the combination of IPT and antidepressant medication has not been studied in adolescents. Psychosocial treatments may also be implemented in order to target specific risk factors for incomplete remission, such as comorbid anxiety or family discord. Interventions may also target specific residual symptoms, such as psychosocial treatments for insomnia, behavior activation or "savoring" for anhedonia, and emotion regulation therapy for irritability. [38,71,72]

While there are no studies of augmentation strategies in adolescent depression, studies in adults support the use of pharmacological augmentation strategies. There are studies of adults whose data demonstrates the efficacy of augmentation of antidepressants with thyroxine, mirtazapine, bupropion, atypical antipsychotics, and lithium in treatment-resistant depression.[73,74]

We recommend pharmacological augmentation after exhausting psychosocial alternatives. Sleep difficulties can be targeted with diphenhydramine, melatonin, or low dose mirtazapine. Daytime fatigue, low energy, poor concentration, and low motivation may be targeted by bupropion. Residual irritability may be targeted with a mood stabilizer, such as a second-generation antipsychotic or lithium, although the possibility of weight gain and other side effects makes many adolescents reluctant to accept this treatment strategy.

Nonresponse (Table 5)

The Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) study was developed to help inform clinicians about the best next steps to take if a depressed adolescent did not respond to an adequate trial with an SSRI. In TORDIA, 334 depressed adolescents who had not responded to an adequate trial of an SSRI were randomized to one of four cells: switch to another SSRI (fluoxetine, paroxetine, or citalopram) or switch to venlafaxine XL, with or without the addition of CBT.[9] The short-term response rates were similar across medication groups, although venlafaxine was associated with more side effects and higher levels of self-reported suicidal ideation and depression.[9,39] The addition of CBT to medication switch to either an SSRI or venlafaxine improved outcome, both as part of the clinical trial and when it was added openly during the first 12 weeks of treatment.[6,9] Open augmentation with a mood stabilizer during the first 12 weeks of treatment was also associated with an increased likelihood of response and remission.[6]

TABLE 5: Management of SSRI-Treatment-Resistant Depression: Nonresponse to Previous Treatment
Step 1
• Switch to another SSRI
• Add CBT
Step 2
• Switch to an SNRI (especially if patient has pain syndrome, comorbid anxiety)
• Switch to buproprion (if patient has ADHD, low energy, fatigue)
Step 3
• Switch to other agents (nefazodone, lamotrigine, MAOIs)
Step 4
• ECT (works best in those with mania, psychosis)

Therefore, when a depressed adolescent has not responded to an adequate trial with an SSRI, we recommend a switch to a second SSRI and the addition of CBT. Higher "doses" of psychotherapy such as are available in intensive outpatient or partial hospital settings may be beneficial, especially for more functionally impaired, depressed youth. Due to the higher rate of side effects, and the slightly higher levels of self-reported suicidal ideation and depression over time in serotonin noradrenergic reuptake inhibitors (SNRIs) compared to SSRIs, we recommend SSRIs as the first line choice for an antidepressant switch over venlafaxine.[7]

If a patient presents with a history of nonresponse to two SSRIs, and none of the above-noted psychosocial risk factors were contributory, there are no data in adolescents to guide the clinician. Studies in adults show that a switch from a second SSRI to either venlafaxine, bupropion, or a combination of an SSRI and other agents (lithium, thyroxine, bupropion, mirtazapine, second generation antipsychotic) are equally effective.[73-75] For a third-step intervention, we extrapolate from adult data and the efficacy profile of the specific agent: for those with comorbid anxiety or migraine, we recommend venlafaxine or duloxetine, whereas those with comorbid ADHD and/or low motivation, fatigue, difficulty concentrating, or hypersomnia, we recommend bupropion.

Additional medications that might be considered if the above-noted strategies either do not work or cannot be tolerated include nefazodone, clomipramine, lamotrigine, and monoamine oxidase inhibitors (MAOIs). None of these agents have been carefully studied in adolescents. Nefazodone has been shown to be efficacious in the treatment of adolescent depression in one clinical trial, and while the drug continues to be available, it is no longer marketed by the parent company because it has a low but increased rate of hepatotoxicity compared to other antidepressants.[3] It is effective against both anxiety and depression and is relatively sedating, and therefore may be useful for depressed and anxious patients who have difficulty getting to sleep. Lamotrigine is a mood stabilizer that is useful in adults for the prevention of bipolar depression. It has a fairly benign side effect profile except for the increased risk of Stevens-Johnson syndrome. Monoamine oxidase inhibitors have been shown to be useful in adults with bipolar or atypical depression, but have not been carefully tested or evaluated in adolescents due to required dietary restrictions and side effects.

Patients who remain symptomatic after three or four medication trials along with evidence-based psychotherapy should be considered for electroconvulsive therapy (ECT). Adolescents who respond best to ECT are those who have bipolar or psychotic depression, and those with the most suboptimal outcomes are those with prominent personality disorder symptoms.[76]

Novel Treatments

Meta-analyses show that intravenous ketamine can have a rapid and profound effect on depressed mood and suicidal ideation, especially in adults.[77,78] There is even some evidence supporting a role of ketamine in improving the likelihood that a patient will respond to ECT or an antidepressant.[79] However, while ketamine is beginning to be used clinically on a fairly widespread basis, ketamine still has two major disadvantages. First, the duration of the effect is measured in days, meaning that in order to maintain the effect, regular infusions of ketamine are required. Second, ketamine has some serious side effects, include potential for abuse and relatively high rates of dissociation.

Transcranial magnetic stimulation (TMS) has been shown to be beneficial for medication-resistant depression in adults, and in open trials this intervention is promising, but has not been definitively assessed in depressed adolescents. However, it appears to be less effective, either in the short or long-term, than ECT.[80,81]

There is some evidence in adults to support nutraceutical augmentation of antidepressant treatment in treatment-resistant depression, specifically with regard to s-adenosyl-L-methionine (SAMe) and omega-3 fatty acids,[82] but there is little evidence one way or the other in youth.[83] N-acetyl cysteine was found to be helpful in reducing nonsuicidal self-injury in adolescents in one open trial.[84] L-methylfolate augmentation has been shown to be beneficial relative to placebo in treatment-resistant depression in adults, but those who are most likely to benefit have a genetic polymorphism that interferes with the conjugation of folic acid into a form that can cross the blood-brain barrier.[82,85,86] Anti-inflammatory agents, such as COX-2 inhibitors may be useful as an augmenting agent in treatment-resistant depression in adults, but may be most promising in those with evidence of higher levels of pro-inflammatory cytokines.[87]

The use of fMRI-guided interventions shows promise in the treatment of depression. One small randomized clinical trial demonstrated that depressed adults who increased their amygdala responses to positive autobiographical memories showed improvement in their depressive symptoms.[88]

Finally, recent work on metabolomic characterization of adolescent and young adults with treatment-resistant depression has identified metabolic correlates that may give clues to treatment.[89] In participants with low cerebrospinal fluid (CSF) biopterin, open trials of replacement with sapropterin (a precursor of biopterin) resulted in improvement in chronic and severe treatment-resistant depression.[89] Another condition that was found in treatment-resistant depression was cerebral folate deficiency, in which patients present with normal serum folate but low CSF tetrahydrofolate, due to an inability to conjugate folic acid so that it can cross the blood-brain barrier. In a series of participants treated openly, treatment with folinic acid resulted in improvement in the majority of these individuals, all of whom had a history of chronic and severe depression.[89]

Conclusion

The majority of adolescents with treatment-resistant depression can eventually find relief from their symptoms. Patients presenting with treatment-resistant depression should be carefully assessed with respect to adherence, adequacy of previous treatments, medical and psychiatric comorbidities, sleep quality, and psychosocial stressors that may influence treatment response. Those adolescents who have not responded to an adequate trial with an SSRI should be switched to a second SSRI and also be treated with CBT. If a patient shows a partial or complete lack of response to a second SSRI, subsequent steps include switching to an SNRI, switching to bupropion, or augmentation with agents shown to be helpful in adults with treatment-resistant depression. The most important ingredients for success are continued monitoring, thorough assessments, provision of patient education, persistence, and maintenance of hope. Future work should clarify the potential roles of ketamine and related compounds, triple chronotherapy, nutraceuticals, neuromodulation, and metabolomic approaches to the relief of treatment-resistant depression.

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