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Treatment-Resistant Depression in Adolescents

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Case Example

Roberta is a 16-year-old girl with a two-year history of depression. She reports treatment with multiple antidepressants and psychotherapy without effect. In addition to having major depression, she also reports symptoms consistent with attention deficit disorder hyperactivity, inattentive type (ADHD).

Definition of the Problem

"Treatment-resistant depression" is depression that does not respond to an adequate dose of evidence-based treatment. In this paper, we review the definition, significance, assessment, and management of treatment-resistant depression in youth.

Adequate Clinical Response

Adequate clinical response is commonly defined as at least a 50 percent reduction in depressive symptoms by eight to 12 weeks of treatment. Around 60 percent of depressed youth show an adequate clinical response to an evidence-based treatment by 12 weeks, and reach remission by 24 weeks.[1,2] Therefore, around 40 percent of depressed youth who receive evidence-based treatments will have "treatment-resistant depression."

Evidence-based treatments for adolescent depression that are superior to either placebo or nondirective clinical management are selective serotonin reuptake inhibitors (SSRIs), cognitive behavior therapy (CBT), and interpersonal therapy (IPT), with medication showing a faster rate of response than CBT.[3,4]

Adequate Dose and Duration

An adequate trial with 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.

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Clinical Significance

Treatment-resistant depression frequently becomes chronic. Chronicity increases the likelihood of adverse sequelae, which include educational and occupational underattainment, interpersonal problems, alcohol and substance abuse, suicidal behavior, and completed suicide.[3] However, with additional treatment, the majority of depressed patients eventually achieve remission.[5,6]

Predictors of Nonresponse (Table 1)

Poorer treatment response is predicted by greater severity, chronicity, and comorbidity, although for comorbid cases, the combination of CBT and an antidepressant is superior to medication monotherapy.[7,8] Alcohol or substance use, even at subdiagnostic thresholds, is associated with a lower probability of response.[9] Hopelessness predicts a poorer response to treatment, and a greater likelihood of dropout.[10] Family discord is associated with nonresponse and relapse, and both a history of abuse and current parental depression predict nonresponse to CBT with or without medication.[5,7,10-12]

Assessment (Table 2)

Document Improvement or Lack Thereof

After weeks of treatment, chronically depressed 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 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, rather than beginning anew.

Roberta had not had a standardized assessment by her previous treating therapist and psychiatrist. However, a review of symptoms of depression revealed that neither functioning nor symptomatology had changed much since the onset of her depressive episode three years ago.

Determine Adherence and Adequacy of the Previous Treatment Trial

Adherence to medication treatment can be assessed through medication diaries, pill counts, or obtaining a trough level of drug plus metabolites. A large proportion of prescribed pills remaining (e.g., > 30 percent) represents clinically significant

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 as stressor not addressed in treatment

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

nonadherence and is associated with a greater likelihood of nonresponse.[13] Low plasma levels of antidepressant are associated with lower rate of response.[14] We recommend obtaining a trough level of an SSRI for patients who report multiple unsuccessful antidepressant 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.[14,15] Because adolescents metabolize several antidepressants more rapidly than adults (e.g., sertraline, citalopram, venlafaxine), dosages should be adjusted accordingly.[16]

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, 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.

Roberta previously had been treated with venlafaxine 75 mg per day for four weeks, sertraline, 50 mg per dayfor 3 weeks, and citalopram 20 mg per day for four weeks followed by another four weeks' treatment at 40 mg. The patient reported weekly psychotherapy in which she "got things off her chest." Therefore, the patient has had one adequate medication trial, whereas the first two were too short and underdosed; the patient has not previously been exposed to an evidence-based psychotherapy. A pill count of Roberta's remaining pills showed a remainder of 15 percent, which shows relatively good adherence. A trough level of citalopram was in the therapeutic range.

Determine if the Primary Diagnosis is Correct

Bipolar, psychotic, and seasonal depressions require 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 must be preceded by treatment with a mood stabilizer. Psychotic depression, often associated with a bipolar diathesis, requires the 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.

A patient may present with depressive symptoms that are either secondary to, or complicated by another condition that leads to treatment resistance. Depressed patients with attention deficit disorder, hyperactivity (ADHD) may be demoralized by peer rejection and school failure, and may have a better chance for recovery if their ADHD is treated. In a similar fashion, learning disabilities can contribute to depressed mood. Eating-disordered patients are often depressed due to battles about weight or due to being malnourished. Restoration of adequate weight and nutrition is a necessary precursor to successful treatment of the 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 necessary 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.

Roberta was doing well in school until she became depressed, and reported that her past difficulty with attention was no longer a major problem by the time she became depressed. Therefore, the primary problem did indeed appear to be depression rather than secondary to her ADHD. However, although she did not meet criteria for alcohol or drug abuse, she admitted to using marijuana twice week, along with some alcohol.

Assess for Concomitant Health Risk Behaviors

Adolescents with chronic depression often have concomitant, intercorrelated health risk behaviors (HRBs) such as fighting, weapon carrying, having unprotected sex, self-harm, binge eating, alcohol, drug or tobacco use, and not engaging in physical activity.[17] These HRBs 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 for depression because membership leads to life events, such as legal and disciplinary actions, that in turn increase the risk for depression. Depressed adolescents are at higher risk for obesity, which may then affect their self-image and social interactions.[18] Because drug concentration is inversely proportional to weight, a depressed adolescent who gains weight may "outgrow" his or her medication dose.

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
- B12 and folate
- Urine screen for drugs

Rule Out Covert Medication 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 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.[19] Specific chronic illnesses that have been shown to have increased rates of depression include epilepsy, asthma and other atopic illnesses, inflammatory bowel disorder, migraine, and diabetes.[20] Medications used to treat asthma (steroids), epilepsy (phenobarbitol, lamotrogine), inflammatory bowel disease (interferon, steroids), as well as the use of oral contraceptives also may increase the risk for depression.[20] Other undiagnosed medical conditions that can mimic depression or contribute to treatment resistance include hypothyroidism, mononucleosis, iron-deficiency anemia, or deficiency of B12 or folate.

The patient reported significant fatigue. She had a very heavy menstrual flow, and laboratory tests showed that she had a hematocrit of 9, consistent with iron-deficiency anemia.

Differentiate Side Effects of Antidepressants from Symptoms of Depression

In order to differentiate potential side effects from depressive symptoms, these adverse effects, such as 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 present, the antidepressant should be

withdrawn and treatment with a mood stabilizer initiated. If agitation occurs in patients treated with either higher doses of antidepressants, or more than one serotonergic agent, serotonin syndrome should be ruled out. Nonadherent patients treated with antidepressants with relatively short half-lives (e.g., sertraline, citalopram, venlafaxine) may experience withdrawal symptoms, which usually consist of fatigue, malaise, anxiety, and dysphoria.

Assess Sleep Quality

Insomnia and sleep deprivation are predictors of the onset of depressive symptoms.[21] While treatment of depression often normalizes sleep, often poor sleep habits and patterns persist. Sleep deprivation and insomnia contribute to daytime impulsiveness, poor concentration, dysphoria, and even suicidality. Sleep difficulties are one of the most common residual symptoms in adolescent depression, and conversely, the addition of treatments that improve sleep to SSRI antidepressants results in more rapid and complete treatment response in depressed adults.[22,23] Contributors to poor sleep, like anxiety at bedtime, an overstimulating bedtime routine, using alcohol or caffeine in the evening, daytime napping, and medications that interfere with sleep (e.g., stimulants, bupropion, steroids) should be assessed and targeted. In addition, specific sleep disorders like sleep apnea, restless leg syndrome, and narcolepsy should be ruled out either by history or by referral to a sleep clinic or laboratory.

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 be either divided 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 medication otherwise has been of benefit, then we suggest the addition of diphenhydramine, melatonin, or low-dose mirtazapine at bedtime.

Roberta napped after coming from school, and then had difficulty getting to sleep in the evening and waking up for school the next day.

Psychosocial 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 psychotherapy.[5,7,10-12,24] 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 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. In all these instances, systemic and/or psychotherapeutic interventions can target these sources of nonresponse prior to engaging in multiple switches in medication.

Roberta's mother completed a screening self-report that was consistent with major depressive disorder. Roberta also was the target of teasing at her school.

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 detect the condition early, and for co-location of mental health services in primary care, to improve access.[25] Once depression is identified, the goal of treatment should be complete remission, as patients with residual symptoms have a much greater risk of relapse and development of chronic depression.[26] Combined treatment with medication and CBT has been shown to result in the most rapid and complete response, in most, but not all studies.[4,27,28]

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. The best results have been reported for continuation treatment that is a combination of medication and wellness-focused CBT.[29] 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 health habits, physical activity, positive peer interactions, and connection to family and school should play an important role in continuation treatment in depressed youth, particular those with significant HRBs.

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

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 interventions 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, we can reliably assess response and side effects and our decisions about whether to continue or change treatments will be largely based on these assessments. It is important to instill hope, since the majority of patients with treatment-resistant depression eventually will achieve clinical response and remission.[1,6,22]

Partial Response (Table 4)

A partial clinical response is defined as a clinically significant improvement without achievement of remission, meaning that the patient could be substantially improved from intake, but still symptomatic and functionally impaired. The most common residual symptoms after acute treatment are anhedonia, sleep difficulties, irritability, and difficulty concentrating.[22]

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 partially responding patients and continuing psychotherapy in those showing steady improvement have both been shown to result in favorable clinical outcomes.[14,15,30]

The advantage of the optimization approach is that it does not expose the patient to any additional treatments, and continues those known to be both tolerated and effective. The disadvantage is that the endpoint of slow steady improvement could still be in an incomplete response. Therefore, the clinician must, in collaboration with patient and family, compare the likely outcome of continuation with the same intervention to the advantages and disadvantages of the other strategies discussed below.

Augmentation

Multiple 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.[4,27] Therefore, if a patient has shown a partial response to medication that has been optimized, the additional of CBT is likely to be beneficial; the same may be true of IPT, but IPT in combination with medication has not been studied in adolescents. Psychosocial treatments also may be brought to target specific risk factors for lack of complete response, namely, comorbid disorders (e.g., exposure therapy for anxiety disorder), family discord (with family therapy), or treatment of parental depression. Interventions may also target specific residual symptoms, such as psychosocial treatments for insomnia, behavior activation or "savoring" for anhedonia, or emotion regulation strategies for irritability.[23]

While there are no studies in adolescents, adult studies support the use of pharmacological augmentation strategies. There are data in adults showing that augmentation of antidepressants with thyroxine, mirtazapine, bupropion, atypical antipsychotics, and lithium in treatment resistant depression is effective, and well-tolerated.[6,31,32]

We recommend pharmacological augmentation after exhausting psychosocial alternatives. Sleep difficulties can be targeted with diphenhydramine, melatonin, or low doses of mirtazapine. Daytime fatigue, low energy, poor concentration, and low motivation may be targeted by augmentation with bupropion. Residual irritability may be targeted with a mood stabilizer such as atypical antipsychotics 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) was developed to answer the question of how to handle adolescent nonresponders to SSRIs. 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, citalopram), or switch to venlafaxine XR, and then to each of these cells with the addition of CBT. The short-term response rates were similar across medication options,

TABLE 5:

Management of Treatment-Resistant Depression: Nonresponse to Previous Treatment

- **Step 1**
  - Switch to another SSRI
  - Add CBT
  - Switch to SNRI (if has comorbid pain syndrome)
- **Step 2**
  - Switch to an SNRI (especially if has pain syndrome, comorbid anxiety)
  - Switch to bupropion (if has ADHD, low energy, fatigue)
- **Step 3a**
  - Augmentation (see Partial Response list)
- **Step 3b**
  - Switch to other agents (nefazadone, lamotrigine, MAOIs)
- **Step 4**
  - ECT (works best in those with mania, psychosis)

although overall venlafaxine was associated with more side effects, and higher levels of self-reported suicidal ideation and depression.[22,27] The addition of CBT to either medication switch improved outcome, both as part of the clinical trial, and when it was added openly during the first 12 weeks of treatment.[2,27] Open augmentation with a mood stabilizer during the first 12 weeks of treatment was also associated with response and remission.

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 also be beneficial, especially for more functionally impaired, depressed youth. Due to the higher rate of side effects, and slightly higher levels of self-reported depression and suicidal ideation over time compared to SSRIs, we recommend SSRIs as the first choice for an antidepressant switch over venlafaxine.

If a patient presents with a history of nonresponse to two SSRIs, and none of the above-noted 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 combinations of SSRIs with other agents (lithium, T3, bupropion, mirtazapine, atypical antipsychotics) are equally effective.[6,31,32] For a "third-step intervention," we extrapolate from adult data and the efficacy profile of the specific agent: for those with comorbid anxiety and/or a migraine or fibromyalgia, we recommend venlafaxine or duloxetine, whereas for 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. None of these agents has been carefully studied for the treatment of resistant adolescent depression. 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.[33] It is effective against both anxiety and depression and relatively sedating, and therefore may be useful for anxious, depressed patients for whom a sedating agent might be advantageous. Clomipramine, a tricyclic antidepressant, has been shown to be efficacious in the treatment of pediatric obsessive-compulsive disorder, and one small study showed that IV clomipramine was helpful in the management of treatment-resistant depression in adolescents.[34] Lamotrigine is a mood stabilizer that has been shown to be useful in the prophylaxis of depressive episodes in adult bipolar patients, and might be considered in a patient with a family history of bipolarity. It is relatively well-tolerated but is rarely associated with a very severe adverse outcome, Stevens-Johnson syndrome. Monoamine oxidase inhibitors have been shown to be useful in adults with atypical or bipolar depression, but have not been tested or frequently used in adolescents, due to the required dietary restrictions and side effects.

Patients who remain symptomatic after three to 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 who do the least well have prominent symptoms of personality disorder.[35] Other nonpharmacological procedures that have been used for treatment-refractory depression in adults, such as vagusnerve stimulation, transmagnetic stimulation, or deep brain stimulation, have not been studied in adolescents.

Roberta showed nonresponse to an adequate trial with citalopram. We observed her for an additional two weeks while she abstained from marijuana, with no significant improvement in mood. We then cross-tapered citalopram and initiated treatment with fluoxetine 10 mg for one week, followed by three weeks at 20 mg; treatment with CBT also was initiated. The patient was referred to her primary care physician for treatment of her iron-deficiency anemia. She was asked to stop napping in the afternoon in order to help normalize her sleep. Her mother was referred for evaluation and treatment of her likely depressive disorder. The clinician coached the patient and her mother about how to approach to school in order to address and stop the teasing. Roberta showed a partial response to treatment, and after four weeks, the dosage of fluoxetine was increased to 40 mg. After four weeks, the patient was reassessed, and described marked improvement except for some residual fatigue and suboptimal concentration. The fluoxetine was again increased without benefit and with some increased agitation, and so was reduced again to 40 mg. Subsequently, in light of her comorbid ADHD and symptom profile, bupropion XL 300 mg was added, resulting in a complete remission. The patient was maintained on 40 mg of fluoxetine, 300 mg of bupropion XL, and monthly CBT sessions for the next nine months.

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 comorbidity, sleep quality, and psychosocial stressors that may influence treatment response. Those adolescents who have not responded to adequate treatment with an SSRI should be switched to a second SSRI, and receive in addition, cognitive behavioral therapy. If a patient shows a partial or complete lack of response, subsequent steps include switching to an SNRI, or augmentation with agents that have been investigated in adult treatment resistant depression. The most important ingredients for success are continuing, thorough assessment, patient education, persistence, and maintenance of hope.

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