REVIEW

Achieving adolescent adherence to treatment of major depression

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Abstract: When treatments are ordered for adolescent major depression, or for other adolescent medical illnesses, adherence and clinical outcomes are likely to be unsatisfactory, unless 4 basic principles of the medical treatment of adolescent illness are implemented. These comprise providing effective patient and parent/caregiver education, establishing effective patient and caregiver therapeutic alliances, providing effective treatment, and managing other factors associated with treatment adherence as indicated. The goals of treatment are to achieve the earliest possible response and remission. Failure to treat adolescent major depression successfully has potentially serious consequences, including worsened adherence, long-term morbidity, and suicide attempt. Accordingly, prescribed treatment must be aggressively managed. Doses of an antidepressant medication should be increased as rapidly as can be tolerated, preferably every 1–2 weeks, until full remission is achieved or such dosing is limited by the emergence of unacceptable adverse effects. A full range of medication treatment options must be employed if necessary. Treatment adherence, occurrence of problematic adverse effects, clinical progress, and safety must be systematically monitored. Adolescents with major depression must be assessed for risk of harm to self or others. When this risk appears significant, likelihood of successful outcomes will be enhanced by use of treatment plans that comprehensively address factors associated with treatment nonadherence. Abbreviated and comprehensive plans for the treatment of potentially fatal adolescent illnesses are outlined in this review.

Keywords: adolescent, depression, antidepressant, treatment, adherence, safety

Introduction

Failure to treat adolescent major depression successfully has potentially serious consequences, including suicide, homicide/suicide (eg, school shooting), severely self-destructive behavior (eg, cutting, burning, allowing sexual victimization and pregnancy), or the development of chronic depression with psychosocial deterioration (eg, school failure, substance abuse, recurrent anger dyscontrol, and dysfunctional interpersonal interactions). A major contributor to treatment failure is nonadherence,[1–4] which can be enabled by clinician failure to attend to basic principles of the medical treatment of adolescents. The purpose of this review is to describe these principles and to outline treatment strategies that optimize likelihood of achieving satisfactory adherence, obtaining successful outcomes, and insuring safety.

Methods

Although there is a marked paucity of research about adolescent adherence to treatments for major depression, there are many studies of treatment adherence

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within other adolescent clinical populations.[5] These include studies of adolescents with human immunodeficiency virus (HIV) infection, type 1 diabetes, renal failure and transplant, asthma, cystic fibrosis, and inflammatory bowel disease. Data from the latter studies have been included where relevant. Accordingly, the conclusions of this review are intended to be applicable to understanding nonadherence encountered during treatment of any adolescent medical illness. Where information pertaining to adolescents is sparse or unavailable, results of studies of adult clinical populations (often including subjects aged 18 years and older) have been included in order to provide a comprehensive description of issues relevant to treatment nonadherence. The literature referenced in this review was identified using the US National Library of Medicine search engine and is generally limited to the most recently published articles. Older literature is referenced in the included publications. The current status of psychiatric treatment-adherence research is reviewed by Velligan et al[1,2] and is not addressed in this paper.

Literature review and discussion
Management of adolescent treatment adherence

Likelihood of achieving long-term remission of adolescent major depression and other adolescent illnesses is significantly enhanced by treatment adherence,[1,2,4,6,7] assuming correct diagnosis and efficacious treatment. Unfortunately, adolescent compliance with psychiatric and other medication regimens is commonly unsatisfactory.[8–11] When illness is accompanied by pessimism or hopelessness, achieving adherence may be particularly difficult. How should clinicians manage the probability that adolescent patients will be poorly compliant with treatment recommendations?

Successful management of adolescent treatment adherence has 4 primary components: (1) establishing effective therapeutic alliances,[12–19] (2) providing effective patient and parent/caregiver education,[20,21] (3) providing effective treatment,[22–25] and (4) attending to other relevant factors associated with treatment nonadherence.[22,26] These 4 components comprise the basic principles of the medical treatment of adolescents and are addressed later, seriatim. Subsequently, the importance of treatment adherence for insuring patient safety is addressed and alternative risk-based treatment protocols are proposed, including one for outpatient management of adolescents who present significant risk of harm to self or others.

Therapeutic alliances

An unsatisfactory clinician–patient relationship invites treatment nonadherence[27–32] and adversely impacts treatment outcome.[29,30,33] Establishing an effective therapeutic alliance requires development of a clinician–patient affective bond,[29,34] development of patient trust in the clinician's expertise,[14,16,19,30,35] and collaborative agreement about the treatment plan.[29,30,34]

Establishment of an affective bond is facilitated by clinician warmth, interest, empathy, nonjudgmental acceptance, and honesty,[29,30] coupled with adolescent patient capacity for interpersonal attachment.[36] Trust in the clinician's expertise, an important contributor to an effective therapeutic alliance and satisfactory adherence,[17–19,21,27,32,37,38] is engendered by careful explanatory communication and by early evidence of clinical improvement. Encouraging patient collaboration in treatment planning is important.[29,30,39–41] Adolescent acceptance of a collaborative role fosters successful coping with concerns about and inconveniences associated with treatment.[39] Patients with avoidant[36] or cold/detached[42] traits will find collaboration difficult and will manifest, at least initially, impaired relationships with clinicians, potentially adversely influencing treatment adherence and outcome.

Therapeutic alliances also must be established with patients' caretakers,[29,30] recruiting them for compliance support.[38,43] These alliances promote caretaker cooperation with treatment expectations,[29,44] more responsible adolescent treatment adherence,[29,43] and more favorable outcomes.[43]

Patient and parent education

Adolescents are more likely to comply with treatment if they understand and accept their need to do so.[39] The goals of patient and caregiver education, therefore, are to generate acceptance of need for treatment, while decreasing apprehension about adverse effects.[39] Depressed adolescents and their parents should be assumed to be poorly informed about depressive illness and its clinical management, as is the case with many depressed adults.[45] Individuals with other medical illnesses display widely differing levels of knowledge about their conditions.[46]

Clinicians should explain medical understanding of the illness and its treatment options, including the diagnosis or diagnoses, the known or presumed genesis of the disorder and the acute illness episode, the logic of the recommended treatment, common adverse effects, and the probable consequences of treatment failure vs success.[11,21,47–49]

Education should counter misconceptions about the illness, lack of concern about or denial of illness severity,[49] and misconceptions about the recommended treatment[12,23,50–52] (especially about the safety of antidepressant medications, discussed later). It also should address other barriers to compliance (eg, concern about cost).

Clinicians should elicit patients' and family members' experiences of problems associated with the illness, the impact of these problems,[21] and fears regarding the illness and its treatment. It is essential that patients and family members feel listened to and be given hope that the illness is comprehensible and treatable.[53] Finally, clinicians need to determine how well patient education information has been understood.[21]

Effective patient education also should (1) engender a positive, trusting clinician–patient relationship,[14,16,19,35,47] (2) engender patient confidence in a decision to accept medication treatment when indicated,[48] (3) engender a positive attitude about the treatment process and expectation of a successful outcome,[15,35,53,54] and (4) enhance the likelihood of treatment adherence.[15,21,35] Providing supportive, empathic clinician–patient dialog, over time, is the most effective means of promoting treatment adherence.

Effective treatment: pharmacotherapy

This review endorses a medical-model viewpoint that the most rapid, least expensive, and most effective monotherapy for adolescent major depression usually will be antidepressant medication,[52,55–58] if closely monitored and aggressively managed.[56,59,60] When there is a family history of mood disorder, including problematic anger dyscontrol, it is particularly sensible for treating clinicians to emphasize the apparent presence of genetic vulnerability for the occurrence of depression. This attributes primary causation to inherited (biologic) bad luck – not to a psychosocial circumstance, or a personality or parenting defect, or to maladaptive depressive thought patterns. It also implies that the condition is medically treatable, even when psychosocial precipitants are clearly present. When patients' symptom and/or family histories suggest underlying pediatric bipolar illness,[61,62] long-term pharmacotherapy should be anticipated.

Concern about adverse effects

Expectation of an adverse medication reaction increases the risk of nonadherence, the risk of nonremission of depressive symptoms, and the occurrence of suicidal ideation or attempt.[63] Expectation of a beneficial response to medication, on the other hand, predicts better treatment adherence.[64] Consequently, clinicians must effectively confront patient and/or caregiver apprehension about antidepressant medication, which may be reasonable (weight gain and sexual dysfunction)[65] or unreasonable (altered personality, permanent organ damage, dependence, and greater risk of suicide).[12,20,25,64]

Antidepressant medication and suicidal ideation

Antidepressant pharmacotherapy ameliorates suicidal ideation[55,57,66,67] and has a protective effect against completed suicide.[68–73] Paradoxically, use of antidepressant medication has been reported to have increased the incidence of suicidal thoughts and behaviors by 0.9%[68] in child, adolescent, and young adult subjects, in a large database of pharmaceutical-industry randomized controlled trials (RCTs).[51,66,68,71] This adverse finding was derived from spontaneously reported (not systematically tracked), retrospectively recovered data.[68,71,72,74] The limited amount of suicide-related data that was systematically collected during these RCTs revealed no association with antidepressant treatment.[71,72] Actual suicide attempts were uncommon[68] and there were no completed child or adolescent suicides in this database.[51,68,71]

No causal explanation for this paradoxical association has been established.[68] Adolescent reporting of recent suicidal thoughts during RCTs could reflect clinical improvement,[74] or ascertainment bias,[71,72,74] or an artifact of sample-selection bias, resulting from the strict inclusion/exclusion criteria of RCTs.[75] Moreover, conclusions from RCTs cannot be generalized unless they are specifically calibrated to characteristics of target clinical populations.[76]

Antidepressant use is associated with lower suicide rates in adolescents.[56,69,72] Substantially reduced use of antidepressant medication, since 2004, has been associated with a significant increase in the incidence of child and adolescent completed suicide.[71,77] In 2 large studies of depressed adolescents not funded by the pharmaceutical industry, antidepressant treatment was not found to increase suicidal ideation or intentional self-injury.[57,78] Taken altogether, presently available evidence indicates that the benefit of antidepressant use with adolescent major depression is much greater than any potential risk.[51,69,71,73,79]

Systematic monitoring of pharmacotherapy variables

Medication management requires knowing how patients actually have been taking their medicines,[39] in addition to determining whether or not progressive clinical improvement

is taking place, or clinical remission has been achieved, or treatment is failing and there is risk of discontinuation.[80] The occurrence of unacceptable adverse effects must be promptly detected.[12,22,81,82] These clinical variables need to be systematically monitored, preferably weekly, until remission of acute illness episodes has been achieved.

The feedback process must be practical and clinically useful for clinicians;[80,83] it must be sufficiently brief, straightforward, and relevant to insure parent/caretaker completion;[83] it should enhance patient and caretaker tracking of relevant symptoms;[84] and it should reflect consensus observations of several informants, where possible. Use of a brief standardized depression rating scale would provide an objective measure of clinical status at each evaluation point. Feedback can be obtained by employing some combination of: (1) frequently scheduled clinician appointments, (2) clinician-office initiated telephone evaluations and adherence support,[85,86] and (3) strongly encouraged, systematic caretaker reporting.

Assessing adherence in outpatient clinical settings is problematic. Reports regarding adherence often will be inaccurate, even after caretakers have been forewarned that adolescent compliance cannot be trusted and must be closely monitored. Velligan et al[1,2] review evaluation options. In selected circumstances, adherence might be monitored by periodic medication plasma concentration determinations, which might or might not encourage adolescent cooperation. Interpretation of results will be difficult, however, because of considerable interindividual pharmacokinetic variability in rates of drug absorption, first-pass metabolism, and subsequent drug elimination. Age, gender, genetic phenotype, stress, and physical activity all influence plasma concentrations and bioavailability.[87] Clinicians will be unable to distinguish low plasma concentrations caused by poor adherence from low concentrations caused by pharmacokinetic factors, unless investigation by parents/caregivers reveals an adherence problem.

The pharmacotherapy process

Selection of a selective serotonin reuptake inhibitor (SSRI) other than paroxetine is generally preferred, because of minimal elicitation of side effects, ease of use, greater likelihood of compliance, and safety.[38,88–90] Once-daily dosing significantly improves medication adherence.[22,91,92] Medication dosing schedules should be integrated into adolescents' daily routines. *Treatment must proceed as rapidly as can be accomplished and must be significantly effective.* Inadequate response to an antidepressant agent, or absence of perceived improvement, is a common cause of unsanctioned medication discontinuation.[22–25] Slow recovery is associated with occurrence of suicidal events.[93]

Major depression is commonly undertreated.[94,95] In the Treatment for Adolescents with Depression Study (TADS), for example, flexible doses of a single agent (fluoxetine) were slowly increased and limited to a maximum 40 mg/day throughout the first 12 weeks of study.[96–98] Clinicians were permitted to maintain doses below this maximum in the presence of persisting mild-to-moderate depressive illness.[98] At 12 weeks, 16.5% of the TADS fluoxetine-randomized subjects had withdrawn from the study,[97] residual symptoms were commonly present in the remaining subjects,[67,99] and 11.9% of the fluoxetine-randomized subjects had received antidepressant medication outside of the TADS protocol.[96] At 12 weeks, fluoxetine-condition response and remission rates were only 62% and 23%, respectively.[67,97,99] The use of nonaggressive dosing with a single antidepressant agent for 12 weeks clearly reflects suboptimal psychopharmacologic practice.

Although the TADS fluoxetine dose could have been increased to a maximum of 60 mg/day during the succeeding 6 weeks,[96] at 18 weeks the fluoxetine-condition response and remission rates had risen only to 69% and 37%, respectively.[96,97] By 36 weeks, only 50% of the TADS fluoxetine monotherapy-randomized subjects remained in this treatment arm.[97] At this evaluation point, the response and remission rates are reported to have risen to 81% and 55%, respectively, in spite of there having been no TADS-protocol medication adjustments during weeks 19–36.[96,97] The TADS team attributed these week 36 results to a remarkable delay in medication response, without providing week 12 and week 18 average fluoxetine dose information, or otherwise explaining how insufficient benefit at 12 weeks would have become more impressive over time, in the presence of residual symptoms, high risk for relapse,[96,97,99] and marked increase in emergency room use and psychiatric hospitalization during weeks 13–36.[100]

The pharmacotherapy protocols of the Adolescent Depression Antidepressant and Psychotherapy Trial (ADAPT) and Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) studies were marred, like that of the TADS trial, by nonaggressive dosing of antidepressant medication: 30 mg/day mean fluoxetine dose at 12 weeks in the ADAPT trial,[57] and 33.8 mg/day mean dose for fluoxetine and citalopram and 205.4 mg/day mean dose for venlafaxine at 12 weeks in the TORDIA trial,[78] in spite of

monotherapy response rates of only 40%–45% after 3 months of treatment.[78,101]

Patients of any age with major depression should be administered doses of antidepressant medicine that are steadily increased until full remission is achieved or such dosing is limited by the emergence of unacceptable adverse effects. Antidepressant dosing should not otherwise be limited, given the severe potential consequences of major depression undertreatment. Doses must be sufficiently high to achieve clinically effective plasma concentrations. Given the marked pharmacokinetic variation that exists among pediatric patients, and the possibility that greater severity of pathology might require higher plasma concentrations, doses sufficient to bring about full remission cannot be predetermined.

Decisions to step up the intensity of treatment should take place every 1–2 weeks, based upon weekly systematic feedback. When further dose increase is unacceptable, but full remission has not been achieved, use of an alternative antidepressant medication, or addition of a second antidepressant to the initially prescribed agent, are potentially effective strategies. When an adolescent has a past history of treatment resistance, combining an antidepressant medication and an augmenting agent, including a second antidepressant, from the initiation of treatment may be advisable.[102] Thase et al[103] provide information relevant for clinicians coping with treatment-resistant adolescents.

Management of adverse effects
Antidepressant adverse effects can include both physiologic symptoms and exacerbation of the symptoms of underlying illnesses (eg, induction of panic symptoms,[104] or the emergence of manic symptoms or rapid bipolar cycling). The latter may assist clinician identification of comorbid, or underlying, illness. Adverse physiologic symptoms encountered early in treatment tend to become nonproblematic in succeeding weeks; usually these can be managed with education and support. Symptoms of panic exacerbation can be managed with short-term benzodiazepine coverage. Acutely emergent hypomanic or manic symptoms are best treated with an antipsychotic agent; no preferred treatment has been established for rapid bipolar cycling.[105] An antidepressant medication should not be prematurely discontinued unless this is clearly necessary (eg, following the occurrence of rapid, unmanageable weight gain).

Episodes of nonadherence
Episodes of treatment nonadherence, when these occur, should be gracefully forgiven and treated as opportunities to examine whether or not the prescribed treatment had been effective – ie, whether or not the subsequent nonadherence has been associated with clinical deterioration. Confirmation of treatment efficacy should be used to augment insight regarding the importance of adherence.

Effective treatment: psychotherapy
Patient preference for treatment modality
Major depression is most often treated with individual psychotherapy,[106] pharmacotherapy, or a combination of both modalities. Cognitive-behavioral therapy (CBT) appears to be more effective for the treatment of depression than other individual psychotherapies,[60,107] eg, primary care psychosocial support.[108] Because adolescents tend to attribute their problems to external factors, eg, family dysfunction,[29] they are likely to prefer psychotherapy.[65,109]

A majority of adults prefer psychotherapeutic treatment for depression,[20,94] especially when life events or family dysfunction are perceived as causative.[20] Even when symptoms of depression are perceived as arising from biologic mental illness, adults believe psychotherapy and pharmacotherapy to be comparably appropriate.[20] Preference for psychotherapy probably reflects predominantly nonmedical understanding of the cause of major depression,[20] misunderstanding about the mechanism of action of psychiatric medication (eg, treating symptoms but covering underlying problems),[20] and apprehension about adverse effects of medication,[12] exacerbated by media reports of alleged problematic outcomes.[110] Patient and caretaker education will be particularly challenging if adolescents' family members, or social-network peers, have overtly negative attitudes about psychiatric medication.

Psychotherapy
CBT of adolescent (and adult) depression, when administered by CBT-trained clinicians using research-based protocols, can be effective,[111,112] although not strongly so.[55,97,107] Many clinical psychologists and other psychotherapeutic clinicians, however, perhaps the majority, tend not to use optimal, evidence-based interventions.[111] Considerable evidence indicates that they give more value to their intuition, personal clinical experiences, and informal problem solving.[111] Thus, depressed adolescents and their families seeking community psychotherapeutic services cannot assume that treatment obtained will be informed by scientific evidence of efficacy.[111] Moreover, regardless of psychotherapist competence, the probability of beneficial acute response to CBT

is markedly lowered by the presence of moderately severe or severe major depressive symptoms, economic adversity, and probably also by comorbid conditions.[107,113]

Beneficial response of depression to CBT monotherapy typically occurs 12 or more weeks after initiation of treatment.[97] At week 12 of the TADS trial, the CBT treatment-condition results did not differ from those of the placebo condition on any of the 16 TADS endpoint measures[113] and nearly 60% of the CBT-treated adolescents were nonresponders.[67,113] This delay of CBT monotherapy response is unacceptable for moderately or severely depressed adolescents: *the earliest achievable response and remission are the goals of treatment.* From week 18, or week 24 depending upon TADS endpoint measure, through week 36, the CBT and fluoxetine monotherapy-treatment response rates are reported to have been comparable,[97] although 29.7% of the CBT-monotherapy-randomized subjects received antidepressant medication during weeks 13–18 and 38.7% received antidepressant medication during weeks 19–36.[96]

There are additional concerns about referral of adolescent major depression for individual psychotherapy. First, to be successful, psychotherapy requires adolescent willingness and capacity to fully cooperate with intensive hour-long, weekly therapy sessions for at least 4 months. This will be problematic with many depressed adolescents.[50,114] Of 111 adolescents randomized to CBT monotherapy in the TADS trial, only 80 (72%) remained in this treatment condition at week 12 and only 55 (49.5%) remained at week 36.[97] Second, approximately 35%–40% of psychotherapy patients derive no benefit from this treatment and 5%–10% deteriorate.[80] Third, when administered following incidents of self-harm, psychotherapy does not appear to reduce the likelihood of subsequent suicide.[115]

Combination treatment

The TADS Team strongly endorses combination therapy as the treatment of choice for adolescent major depression.[97,116] This recommendation is problematic for many reasons: (1) the TADS antidepressant monotherapy treatment was inadequate (as discussed above), (2) adding CBT to pharmacotherapy is unlikely to improve remission rates with adolescents whose major depressions are moderately severe or severe, or associated with low levels of cognitive distortion,[117] (3) the ADAPT trial found no difference in treatment effectiveness between SSRI monotherapy and SSRI + CBT combination therapy, and no protection from combination treatment against the emergence of suicidal ideation and self-injury[57] (the TORDIA trial also detected

no additional combination-treatment protection against suicidal ideation or self-injury[78]), and (4) even when competent, evidence-based individual psychotherapy is available, combination treatment is more expensive than medication monotherapy and likely often to be unaffordable.[57] The TADS medication plus medication management costs were less than half the average cost of CBT.[100] The ADAPT trial found combination therapy to be more expensive and no more cost-effective than antidepressant monotherapy, whether or not the hospital costs of 2 combination-treated subjects were included.[57] Domino et al[100] inflated their estimate of total antidepressant monotherapy costs by including disproportionately greater emergency room and psychiatric hospitalization expenses incurred in this treatment arm during weeks 13–36. Had the TADS subjects in this treatment arm been managed more aggressively, including use of a full range of medication treatment options, hospital expenses should have been negligible. Addition of individual psychotherapy to pharmacotherapy may,[118–120] or may not,[57,121] be the most effective treatment.

Other predictors of poor treatment adherence

Successful medical treatment of adolescent illnesses requires management of predictors of poor adherence, particularly those that effective education can modify, and also those related to the presence of comorbid disorders, which can be concurrently treated. Table 1 contains a list of predictors of poor treatment adherence among adolescent (and adult) clinical populations, grouped into categories of related items. Research studies emphasize both predictors of poor treatment compliance and predictors of better, or good, compliance. The latter are included in Table 1 in their opposite form, as predictors of poor adherence.

Many predictors of poor treatment adherence can be ameliorated by effective patient and caretaker education. These predictors are readily identifiable in Table 1. Other predictors of poor adherence cannot be modified by treating clinicians. Examples of the latter include low level of education[81] and/or poor English-language proficiency,[23] psychosocial immaturity,[122,123] and disadvantaged economic[23,82,124] and/or family functioning[123–125] circumstances. Although clinicians always should communicate in a clear, easily understood manner,[47,53] this is especially necessary in situations where the latter adverse predictors are prominent. Their presence should be borne in mind.

The comorbid presence of attention-deficit hyperactivity disorder (ADHD), and/or significant anxiety, and/or

Table 1 Predictors of poor treatment adherence

Predictors
Doctor–patient relationship
Inadequate doctor–patient relationship[15,17–19,27,28,31,32]
Patient knowledge
Inadequate information/insight, or erroneous beliefs or fears, about the health condition or its treatment (eg, about antidepressant medication); uncertainty about the treatment selection[12,25,31,81,126,163]
Low level of education; poor English-language proficiency[23,81]
Comorbidity and maturity
Presence of ADHD/disruptive behavior, significant anxiety, and/or alcohol/substance abuse[9,82,86,126,127,129,148]
High level of reckless, risk-taking behaviors[129]
Low level of maturity (regardless of age); younger age; poor coping strategies[122,123,127]
Denial of illness[49]
Caregiver/social network
Low level of caregiver and/or social-network support for the selected treatment; embarrassment or concern about social stigma[23,54,126,143]
Low level of caregiver collaborative involvement[43]
Aspects of treatment
Occurrence of unpleasant/unacceptable aspects of treatment[12,22–25,28,81,82]
Absence of sufficient improvement[22–25,28]
Life circumstances
Disadvantaged economic circumstances, including inadequate insurance[23,82,90,124]
Stressful family environment; inadequate caregiver discipline of adolescent[123–125]
Stressful life events[125]

Abbreviation: ADHD, attention-deficit hyperactivity disorder.

substance abuse, in adolescents with major depression, predicts worsened treatment adherence.[9,82,86,126,127] Prominent symptoms of adolescent ADHD include disorganization and forgetfulness (the latter symptom is reported to be the most common cause of medication nonadherence in adults[18,26,128]). Adolescents with ADHD also may exhibit risk-taking behaviors that are associated with poor treatment outcomes.[129] Significant anxiety in adolescents with major depression may signal the presence of fears of taking medication or attending clinic appointments, which otherwise might not be detected. Comorbidity with ADHD and/or an anxiety disorder is treatable and may need to be concurrently addressed. The presence of substance abuse, especially alcohol abuse, in adolescents with major depression, is an obstacle to effective treatment that requires confrontation and separate therapy. Court-ordered intervention may be necessary. The major depression should be simultaneously treated.

Excessive anger has been identified as a correlate of medication noncompliance during treatment of pediatric illness.[130] Problematic anger responds to a variety of pharmacologic treatments.[131]

Insuring safety
Assessment for risk of harm to self or others
Adolescents with major depression must be assessed for risk of harm. As many as 15% of adolescents in the general population experience significant risk of suicide[132] and approximately 4% attempt killing themselves.[133,134] Table 2 contains a combined list of risk factors for adolescent suicide and suicidal homicide. Unfortunately, the presence of many risk factors does not accurately predict danger, nor does their absence insure safety.[135] Clinical judgments of risk are uncertain.

Relevance of treatment adherence
Most adolescent suicide attempts are probably impulsive (over 40% of adult suicide attempts, aged 18 years and older, are reported to be unplanned[136]). Because suicide attempts cannot be accurately anticipated, when an evaluation raises concern about the possibility of an attempt, the ensuing treatment plan must emphasize close monitoring of clinical status and compliance with the prescribed treatment. Insufficient treatment response is associated with worsened adherence[23,25] and suicide attempt[137] and must be quickly detected. Adherence is critically important because (1) antidepressant discontinuation is associated with significant risk of subsequent suicide attempt[5,138] and (2) a majority of treated adolescent suicide victims are reported to have been poorly or noncompliant prior to death.[139]

Those adolescents with a previous history of suicide attempt are at greater risk for subsequent attempts and completed suicide.[140–142] They typically will have been poorly compliant

Table 2 Predictors of adolescent risk of harm to self or others

Predictors
Symptoms
Current major depression[93,134,135,137,151–153]
Suicidal ideation[93,137,151,152,154]
Excessive anger[135,146,155]
Trait of impulsive aggressivity[135,151,152,156,157]
Violent fantasies[146,153]
Use of alcohol and/or drugs[134,135,142,151–153,158,159]
Past history
Suicide attempt[93,135,136,139,142,152,160]
Family history
Suicide or attempts[135,142,152,156,161]
Assaultive behavior[135,158,162]
Stressor
Interpersonal discord or loss[135,137,146,152,153]
Victim of bullying[144–146,153]
Means
Access to lethal agents[135,151,158,159]

with treatment after past attempts.[140] When potentially suicidal adolescents also have comorbid ADHD, significant anxiety, and/or a substance use disorder, they are even less likely to be compliant with treatment.[143] Adherence and response to treatment must be especially closely monitored with these patients.

Risk of homicide

A very small percentage of depressed adolescents, typically boys who have been bullied, murder peers or family members.[144–146] Risk of homicide can arise when there has been bullying by a peer group[146] or by a family member; and the bullied adolescent is suicidally depressed, expresses vengeful anger,[146] and has violent fantasies associated with use of media that portrays violent solutions to threatening circumstances.[146] Angry, depressed adolescent males require close monitoring.

Treatment protocols
Low risk of suicide or assault

When risk of harm to self or others appears low, an abbreviated treatment protocol, as outlined in Table 3, should suffice to achieve satisfactory compliance with prescribed treatment. Patient and family education are provided and effective therapeutic alliances are established. Caregivers are recruited for support. Pharmacotherapy is prescribed and adherence, adverse effects, and clinical response are monitored, optimizing medication dose as quickly as feasible, while maintaining awareness that adolescents are likely to be poorly compliant. Even when this appears not to be the case, adherence tends to decrease during a course of treatment[147] and should be evaluated periodically during long-term maintenance therapy.

Moderate risk of suicide or assault

When an assessment indicates moderate risk of harm, or other considerations prompt special concern, use of a comprehensive treatment plan is indicated (Table 4). In addition to the components of the abbreviated protocol, comorbid disorders should be identified and simultaneously treated,[148] if present. Other predictors of poor treatment adherence, listed in Table 1, should be comprehensively evaluated and addressed.[22,26,149] Medication management should be accompanied by active psychosocial care,[55] when indicated.

Depressed adolescents with previous histories of serious suicide attempts should receive comprehensive treatment. Optimizing treatment adherence and efficacy is critically important for these individuals, because community treatment-as-usual does not reduce suicide mortality.[141]

Noncompliance with treatment for serious nonpsychiatric diseases, eg, HIV infection, type I diabetes, or cystic fibrosis, results in morbidity and premature death. The comprehensive strategy (Table 4) is most appropriate for managing the adherence of adolescents who have any potentially fatal pediatric disease.

Apparent high risk of suicide or assault

When risk of harm appears high, eg, when plans to commit suicide, excessive anger, history of impulsive aggressivity, hopelessness, and substance abuse, are identified, depressed adolescents should be hospitalized, unless caregiver support can insure safety and treatment adherence. Hospitalization will be necessary when a high-risk suicidal adolescent is aggressively hostile towards his caregivers; or is refusing treatment, or appears unlikely to cooperate with close supervision; or if the caregivers appear insufficiently stable, supportive, or responsible to insure safety and treatment adherence.[150] If safe supervision is assured, the comprehensive treatment protocol outlined in Table 4 should be followed.

Conclusion

When treatments are ordered for major depression or other serious illnesses in adolescents, adherence to these treatments and

Table 3 Enhancing treatment adherence with adolescents not at risk of suicide or assault

Assessment	Goals		Strategies
Confirm the presence of major depression and the apparent low risk of harm	Establish effective therapeutic alliances	⟹	Communicate with warmth, interest, and nonjudgmental acceptance; encourage patient and caretaker collaboration
	Provide effective patient and caregiver education	⟹	Explain the logic for, and the value of, use of the recommended treatment; alleviate misconceptions and fears
	Establish long-term treatment adherence and illness remission	⟹	Establish family/caregiver support Prescribe acceptable and rapidly effective treatment Monitor adherence, adverse effects, and treatment response

Table 4 Comprehensive strategy for optimizing treatment adherence with potentially suicidal or assaultive adolescents

Assessment	Goals		Strategies
Confirm the presence of major depression and the apparent moderate-high risk of harm	Establish effective therapeutic alliances	⟹	Communicate with warmth, interest, and nonjudgmental acceptance; encourage patient and caretaker collaboration
Identify misconceptions and fears about the illness or medication	Provide effective patient and caregiver education	⟹	Explain the logic for, and the value of, use of the recommended treatment; alleviate misconceptions and fears
Identify ADHD, anxiety, substance use disorders, excessive anger. impulsive aggressivity	Ameliorate symptoms of comorbid conditions	⟹	Prescribe indicated treatments for comorbid conditions or problematic symptoms
Identify family psychosocial problems Identify other predictors of poor treatment adherence	Ensure safety and establish long-term treatment adherence and illness remission	⟹	Establish family/caregiver support that ensures adherence and safety Prescribe acceptable (including adverse effects) and rapidly effective treatment Closely monitor adherence, adverse effects, treatment response, and safety Attend to relevant predictors of poor adherence

Abbreviation: ADHD, attention-deficit hyperactivity disorder.

clinical outcomes are likely to be unsatisfactory unless patient and caregiver education is effective, therapeutic alliances are established, and specific predictors of poor adherence are managed as indicated. When risk of harm to self or others appears significant, likelihood of successful outcomes will be optimized by use of treatment plans that comprehensively address these basic principles of the medical treatment of adolescent illnesses.

The goals of treatment are to achieve the earliest possible response and remission.[79] Accordingly, treatment must proceed as rapidly and aggressively as can be accomplished and must be significantly effective.

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Disclosure

The author reports no conflicts of interest in this work.

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