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Guidelines for Adolescent Depression in Primary Care (GLAD-PC): Part II. Treatment and Ongoing Management

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abstract

OBJECTIVES: To update clinical practice guidelines to assist primary care (PC) in the screening and assessment of depression. In this second part of the updated guidelines, we address treatment and ongoing management of adolescent depression in the PC setting.

METHODS: By using a combination of evidence- and consensus-based methodologies, the guidelines were updated in 2 phases as informed by (1) current scientific evidence (published and unpublished) and (2) revision and iteration among the steering committee, including youth and families with lived experience.

RESULTS: These updated guidelines are targeted for youth aged 10 to 21 years and offer recommendations for the management of adolescent depression in PC, including (1) active monitoring of mildly depressed youth, (2) treatment with evidence-based medication and psychotherapeutic approaches in cases of moderate and/or severe depression, (3) close monitoring of side effects, (4) consultation and comanagement of care with mental health specialists, (5) ongoing tracking of outcomes, and (6) specific steps to be taken in instances of partial or no improvement after an initial treatment has begun. The strength of each recommendation and the grade of its evidence base are summarized.

CONCLUSIONS: The Guidelines for Adolescent Depression in Primary Care cannot replace clinical judgment, and they should not be the sole source of guidance for adolescent depression management. Nonetheless, the guidelines may assist PC clinicians in the management of depressed adolescents in an era of great clinical need and a shortage of mental health specialists. Additional research concerning the management of depressed youth in PC is needed, including the usability, feasibility, and sustainability of guidelines, and determination of the extent to which the guidelines actually improve outcomes of depressed youth.

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BACKGROUND

Studies have revealed that up to 9% of teenagers meet criteria for depression at any one time, with as many as 1 in 5 teenagers having a history of depression at some point during adolescence.[1–7] In primary care (PC) settings, point prevalence rates are likely higher, with rates up to 28%.[8–12] Taken together, in epidemiologic and PC-specific studies it is suggested that despite relatively high rates, major depressive disorder (MDD) in youth is underidentified and undertreated in PC settings.[13,14]

Because adolescents face barriers to receive specialty mental health services, only a small percentage of depressed adolescents are treated by mental health professionals.[15] As a result, PC settings have become the de facto mental health clinics for this population, although most PC clinicians feel inadequately trained, supported, or reimbursed for the management of depression.[14–21] Although MDD management guidelines have been developed for specialty care settings (eg, the American Academy of Child and Adolescent Psychiatry[22]) or related problems such as suicidal ideation or attempts,[23] it is clear that significant practice and clinician differences exist between the primary and specialty care settings that do not allow a simple transfer of guidelines from one setting to another.

Recognizing this gap in clinical guidance for PC providers, in 2007, a group of researchers and clinical experts from the United States and Canada established Guidelines for Adolescent Depression in Primary Care (GLAD-PC), a North American collaborative, to develop guidelines for the management of adolescent depression in the PC setting. The development process of GLAD-PC is described in detail in Part I of the original GLAD-PC articles.[24,25] In this article, we describe the updated recommendations regarding treatment, ongoing management, and follow-up, along with the supporting empirical evidence for these recommendations. In our companion article, we provide a detailed description of the update process as well as the corresponding updated recommendations for GLAD-PC regarding practice preparation, depression identification, assessment, and diagnosis, and initial management before formal treatment.

METHODS

A full description of the methodology used for the update of GLAD-PC is included in our companion article. In brief, the expert collaborative used a mix of qualitative (expert consensus) and quantitative (literature reviews) methods to inform the update of GLAD-PC. In view of space limitations, only the methods and results of the updated literature reviews regarding available evidence for treatment and ongoing management are presented in this article.

The following 3 literature reviews were conducted for the updated GLAD-PC recommendations: (1) nonspecific psychosocial interventions in pediatric PC, including studies pertaining to integrated behavioral health and collaborative care models; (2) antidepressant treatment; and (3) psychotherapy interventions.

For the first review, we searched the literature (PubMed, PsycInfo, and the Cochrane Database) for articles published from 2005 to the present in which researchers examined evidence for psychosocial interventions delivered in the PC setting to update the previous review conducted by Stein et al.[26] The "related articles" function was used to search for articles similar to Asarnow et al[14] and Richardson et al.[27] In addition, reference lists of all relevant articles were also examined for other relevant studies.

In the second updated review, we examined the efficacy and safety of antidepressant medications in the pediatric population (under the age of 18 years). This review was used to update the findings from the US Food and Drug Administration (FDA) safety report[28] and the previously published GLAD-PC review on antidepressants in youth depression.[29] Studies in which researchers examined the management of depression with the use of antidepressants as both monotherapy and combination therapy were included.

In the third review, we searched the literature for depression trials in which researchers examined the efficacy of psychotherapy for the management of depression in children and adolescents. The search included all forms of psychotherapy, including both individual and group-based therapies. We not only identified both individual studies but also high-quality systematic reviews, given the extensive empirical literature in this area. In both the second and third reviews, the literature searches were conducted by using Medline and PsycInfo to find studies published between 2005 to the present. To ensure additional articles were not missed, reference lists of included articles were hand-searched for other relevant studies. A full description of the 3 reviews is available on request.

RESULTS

Organizational Adoption of Integrative Care

Within the past decade, there has been a shift in medicine and in mental health away from the "traditional" model of autonomous individual providers and toward delivering empirically supported interventions in a team-based manner. This followed a growing recognition that complex chronic conditions, such as depression,

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are more successfully managed with proactive, multidisciplinary patient-centered care teams. Ongoing changes in the health care landscape helped to solidify support for this revolution. Systems are enacting top-down changes designed to make the entire delivery system (organizations, clinics, and providers) more effective, efficient, safe, and satisfying to both patients and providers.

Proposed integrated care models include "chronic care management," "integrated behavioral health care," "collaborative care," and "medical home." Here, the term "integrative care" will be used to collectively refer to models such as these. These complex care models share multiple features, such as an emphasis on systematically identifying and tracking target populations, multidisciplinary patient care, structured protocols for symptom management, regular follow-ups, decreasing fragmentation across the care team, and enhancing the patient's ability to self-manage their condition.[30] The following list represents many of the components described in 1 or more of these health care models:

1. a treatment team that includes the patient, the family, and access to mental health expertise;
2. education (including decision tools) for PC providers, patients, and family;
3. tools and/or procedures to systematically identify, assess, and diagnose patients who are at risk or are currently experiencing depressive symptoms;
4. a care plan for target patients (which may involve the family when possible and includes resources at other agencies or in the community);
5. improved communication and coordination of care across providers and/or between patient, family, and provider;
6. case management and/or patient and family support;
7. routine tracking of patient progress, with appropriate follow-up action as needed;
8. routine evaluation of staff performance metrics to inform ongoing quality improvement efforts; and
9. increased patient and family motivation and capacity to self-manage symptoms, including education, feedback, etc.

A variety of integrative care models have been proposed or discussed in the literature,[31,32] but few studies have actually been conducted to examine whether they ultimately improve care for children and adolescents with mental health disorders, broadly speaking, or depression, specifically. In the present review, only 3 randomized clinical trials were identified. In the first, Asarnow et al[14] found that adolescents treated for depression at PC clinics engaging in a quality improvement initiative received higher rates of mental health care and psychosocial therapy, endorsed fewer depressive symptoms, reported a greater quality of life, and expressed greater satisfaction with their care than comparison adolescents in a usual care condition. In a second study, researchers examined the additive benefits of providing brief (4-session) cognitive behavioral therapy (CBT) for depression in conjunction with antidepressant medication compared with medication alone in a collaborative care practice with embedded care managers and found a weak but positive benefit for adjunctive CBT.[33] Finally, Richardson et al[27] randomly assigned adolescents to either an integrative care condition, in which patients chose from a treatment menu of antidepressant medication alone, brief CBT alone, or a combination of the 2, versus usual care. Results revealed that integrative care was associated with significant decreases in depression scores and improved response and remission rates at 12 months compared with treatment as usual.[27] The results of a cost-effectiveness analysis of this trial revealed that the integrative care condition was more effective at reducing depression symptoms for adolescents, resulting in incremental cost savings given the quality of life years gained from improved functioning.[34]

Although research studies offer support for the impact of integrative or collaborative health care delivery models as a whole,[35] multiple changes to the practice setting are being evaluated simultaneously. The components of integrative health care models have largely been identified through practice-based research[36] or "best ideas" about how to solve identified problems, without a clear theoretical or empirical basis for these components individually or in combination. Thus, it is unknown what "active ingredients" account for the greatest proportion of variance in patient improvement because no dismantling studies have been conducted in which the relative impact of the individual components was examined. Given that integrated health care approaches are resource-intensive to implement and maintain, it may not be feasible for many PC practices to fully adopt such a model. Some states and communities have attempted to implement "wraparound services" under the "systems of care model"; however, unfortunately, these services are usually restricted to severely impaired children with chronic mental health problems. Nonetheless, such services are available if PC providers are interested.[37,38] Unfortunately, there is relatively little information to help guide prioritization and decision-making for PC clinics that wish to improve patient care within the constraints

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of highly limited human and/or financial resources.

Antidepressant Treatment

The updated treatment review for antidepressant safety and efficacy included randomized controlled trials (RCTs) of antidepressants in youth with depression. In this GLAD-PC review, we identified 27 peer-reviewed articles in this area, including trials with fluoxetine, sertraline, citalopram, paroxetine, duloxetine, and venlafaxine. In addition, in several studies, the switch from a selective serotonin reuptake inhibitor (SSRI) to venlafaxine, a serotonin norepinephrine reuptake inhibitor, was explored.[39–41] Older antidepressants (ie, monoamine oxidase inhibitors, tricyclic antidepressants) were not included in our updated review because of several reasons. First, the 2004 FDA review that was used for the development of the guidelines only involved newer classes of antidepressants. Second, older antidepressants are not used because of the lack of efficacy demonstrated in clinical trials data for other classes of older antidepressants.[42]

Overall, both individual clinical trial evidence and evidence from systematic reviews still support the use of antidepressants in adolescents with MDD. Bridge et al[43] conducted a meta-analysis of the clinical trials data and calculated the numbers needed to treat and numbers needed to harm. They concluded that 6 times more teenagers would benefit from treatment with antidepressants than would be harmed.[43] In reviewing the individual studies, the percentage of subjects who responded to antidepressants ranged from 47% to 69% and from 33% to 57% for those on placebo (see Table 1). The majority of these studies revealed a significant difference between those on medication versus those on placebo. Similarly, on the basis of the updated review, fluoxetine still has the most evidence to support its use in the adolescent population.[44]

TABLE 1 Response Rates in RCTs of Antidepressants Based on Clinical Global Impression

Medication	Drug, %	Placebo, %	*P*
Fluoxetine[45,a]	56	33	.02
Fluoxetine[46]	52	37	.03
Fluoxetine[47]	61	35	.001
Paroxetine[48,b]	66	48	.02
Paroxetine[49]	69	57	NS
Paroxetine[49]	65	46	.005
Citalopram[50]	47	45	NS
Citalopram[51]	51	53	NS
Sertraline[52]	63	53	.05
Escitalopram[53]	63	52	.14
Escitalopram[54]	64	53	.03

NS, not significant.
[a] Fluoxetine alone compared with placebo.
[b] Paroxetine compared with placebo.

The largest study, the Treatment of Adolescent Depression Study, involved subjects who were randomly assigned to receive placebo, CBT alone, fluoxetine alone, or a combination treatment of CBT with fluoxetine.[45] Subjects assigned to receive combination treatment or fluoxetine alone showed significantly greater improvement in their depressive symptoms compared with those on placebo or those treated with CBT alone (also see subsection "CBT"). There is also a more rapid initial response when medication is initiated first or in combination with therapy.[55] The superiority of combination therapy is also demonstrated in adolescents with anxiety.[56,57] However, a few trials have revealed little extra benefit to combination therapy, but these findings might be confounded by the control therapy intervention (ie, routine specialist care).[58–60]

Combination therapy has also been evaluated in adolescents with treatment-resistant depression. In the Treatment of SSRI-resistant Depression in Adolescents study, researchers examined treatment options for adolescents aged 12 to 18 whose depression had not improved after 1 adequate trial of an SSRI.[39–41,49,61–63] Subjects were randomly assigned to 4 possible interventions: (1) switch to a different SSRI (citalopram, fluoxetine, paroxetine), (2) switch to a second SSRI in combination with CBT, (3) switch to venlafaxine, or (4) switch to venlafaxine in combination with CBT. Patients who received CBT and changed their medication to a second SSRI or venlafaxine had a higher response rate (54.8%; 95% confidence interval [CI]: 47%–62%) than changing the medication alone (40.5%; 95% CI: 33%–48%; $P = .009$). Additionally, there was no difference in response rate between venlafaxine and a second SSRI (48.2%; 95% CI: 41%–56%; and 47%; 95% CI: 40%–55%; $P = .83$) as well as no significant differences among Children's Depression Rating Scale–Revised improvements between treatment options.

Finally, with available evidence from RCTs, it is suggested that adverse effects do emerge in depressed youth who are treated with antidepressants.[45] Adverse effects (ie, nausea, headaches, behavioral activation, etc) were found to occur in most adolescents treated with antidepressants, with duloxetine, venlafaxine, and paroxetine as the most intolerable.[45] Therefore, routine monitoring of the development of adverse events is critical for depressed youth treated with antidepressants.

The most significant adverse effect of antidepressants is the emergence of

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new onset or worsening suicidality, which was demonstrated in the FDA review in 2004.[29] The estimated risk of suicidality is 4% in those on medication versus 2% in those on placebo. However, further analyses of clinical trials data revealed that there is overall improvement in suicidality in subjects treated with antidepressants, with only a few subjects reporting worsening or new onset suicidality.[49] In the FDA review, it was also suggested that paroxetine and venlafaxine have a significantly higher risk for suicidality compared with other serotonergic antidepressants.

The doubling of risk of suicidality was also confirmed in population level studies.[63] However, studies have also revealed that almost all adolescents who die by suicide do not test positive for antidepressants in postmortem toxicology tests despite being prescribed these drugs.[64] Furthermore, Olfson et al[65] found an inverse relationship between rates of SSRI prescriptions and rates of suicide in adolescent populations.

Psychotherapy

In the third review conducted, we examined the efficacy of psychotherapy, such as CBT, interpersonal psychotherapy for adolescents (IPT-A), as well as nonspecific interventions such as counseling and support. Through our search, we were able to identify both individual studies as well as several high-quality meta-analyses and/or reviews that were recently conducted to examine the efficacy of psychotherapy in adolescent depression.

CBT

Numerous meta-analyses and reviews have been conducted on CBT in the treatment of adolescent depression and showed improved outcomes for subjects treated with CBT.[66–68] There are also several ongoing studies in which researchers are evaluating CBT in youth up to age 21.[69]

The effectiveness of CBT for adolescents with moderate to moderately severe depression was also evaluated in Treatment of Adolescent Depression Study, in which researchers randomly assigned 439 12- to 17-year-olds who were depressed to treatment with CBT, fluoxetine, CBT plus fluoxetine, or placebo.[45,70] According to Clinical Global Impressions severity scores, the posttreatment response rate to 15 sessions of CBT over 12 weeks (43.2%; 95% CI: 34%–52%) was not significantly different ($P = .40$) from placebo (34.8%; 95% CI: 26%–44%). The authors attributed this relatively low response rate, in part, to the fact that the study population suffered from more severe and chronic depression than participants in previous studies and to a high rate of psychiatric comorbidity in their study participants. Along with the fairly robust placebo-response rate, it is also possible that the nonspecific therapeutic aspects of the medication management could have successfully competed with the specific effects of the CBT intervention. As a consequence, one cannot and should not conclude that CBT is ineffective.

In another study with adolescents with depression, Fleming et al[71] evaluated the effectiveness of a computerized cognitive behavioral therapy (CCBT) intervention called SPARX in treating adolescents aged 13 to 16 years excluded from mainstream education ($n = 20$). After randomly assigning them to CCBT or the waitlist control, it was found that there were significantly greater reductions in Children's Depression Rating Scale and Reynolds Adolescent Depression Scale scores from baseline to week 5 for the intervention group compared with those who waited. In addition, the SPARX group was significantly more likely to be in remission or have a significant reduction in symptoms.

In several other studies, researchers have evaluated CCBT interventions and have also found similar results, with 1 study conducted in the PC setting.[72,73]

IPT-A

In terms of IPT-A, only a handful of studies have been conducted. First, Tang et al[74] randomly assigned 347 adolescents who were depressed to receive IPT-A in schools or treatment as usual. IPT-A was found to have significantly higher effects on reducing severity of depression, suicidal ideation, and hopelessness compared with treatment as usual. In Gunlicks-Stoessel et al's[75] study, 63 adolescents who were depressed were randomly assigned to IPT-A or treatment as usual. Adolescents who were depressed who reported higher baseline levels of interpersonal difficulties showed a greater and more rapid reduction in depressive symptoms if treated with IPT-A compared with treatment as usual. In the most recent study,[76] 57 adolescents with depressive symptoms were randomly assigned to receive either 8 weeks of interpersonal therapy–adolescent skills training or supportive school counseling. Adolescents who were treated with interpersonal therapy–adolescent skills training showed significantly greater rates of change compared with adolescents who received school counseling on the Center for Epidemiologic Studies Depression Scale ($t[215] = -2.56$, $P = .01$), Children's Depression Rating Scale-Revised ($t[169] = -3.09$, $P < .01$), and the Children's Global Assessment Scale ($t[168] = 3.24$, $P < .01$).

GUIDELINES

Each of the recommendations below was graded on the basis of the level of supporting research evidence from the literature and the extent to which experts agreed that it is highly appropriate in PC. The level

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of supporting evidence for each recommendation is based on the Oxford Centre for Evidence-Based Medicine grades of evidence[1–5] system, with 1 to 5 corresponding to strongest to weakest evidence (see http://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf/).

Recommendation strength based on expert consensus was rated in 4 categories: very strong (>90% agreement), strong (>70% agreement), fair (>50% agreement), and weak (<50% agreement). The recommendations in the guidelines were developed only in areas of management that had at least a "strong agreement" among experts (see Fig 1 for the treatment algorithm).

Treatment

Recommendation 1: PC clinicians should work with administration to organize their clinical settings to reflect best practices in integrated and/or collaborative care models (eg, facilitating contact with psychiatrists, case managers, embedded therapists). (grade of evidence: 4; strength of recommendation: very strong).

There is a growing recognition that complex chronic conditions, such as depression, are most successfully managed with proactive, multidisciplinary, patient-centered care teams.[77,78] Proposed integrated care models include chronic care management, integrated behavioral health care, collaborative care, and medical home. These complex care models have been shown to be more effective in improving outcomes and share multiple features, such as an emphasis on systematically identifying and tracking target populations, decreasing fragmentation across the care team, and enhancing the patient's ability to self-manage their condition.

Recommendation 2: After initial diagnosis, in cases of mild depression, clinicians should consider a period of active support and monitoring before starting evidence-based treatment (grade of evidence: 3; strength of recommendation: very strong).

After a preliminary diagnostic assessment, in cases of mild depression, clinicians should consider a period of active support and monitoring before recommending treatment (from 6 to 8 weeks of weekly or biweekly visits for active monitoring). Evidence from RCTs with antidepressants and CBT show that a sizable percentage of patients respond to nondirective supportive therapy and regular symptom monitoring.[42,43,45,48,50,70,79] However, if symptoms persist, treatment with antidepressants or psychotherapy should be offered, whether provided by PC or mental health. Active support and monitoring is also essential in cases in which depressed patients and/or their families and/or caregivers refuse other treatments. Active support and counseling for adolescents by pediatric PC clinicians have been evaluated for several different disorders, including substance abuse and sleep disorders.[22]

Furthermore, expert opinion based on extensive clinical experience and qualitative research with families, patients, and clinicians indicates that these strategies are a crucial component of management by PC clinicians. For further guidance on how to provide active support, please refer to the GLAD-PC toolkit (http://www.gladpc.org).

For moderate or severe cases, the clinician should recommend treatment; crisis intervention; patient and family support services, such as in-home or skill-building services (as indicated); and mental health consultation immediately, without a period of active monitoring.

Recommendation 3: If a PC clinician identifies an adolescent with moderate or severe depression or complicating factors and/or conditions such as coexisting substance abuse or psychosis, consultation with a mental health specialist should be considered (grade of evidence: 5; strength of recommendation: strong). Appropriate roles and responsibilities for ongoing comanagement by the PC clinician and mental health clinician(s) should be communicated and agreed on (grade of evidence: 5; strength of recommendation: strong). The patient and family should be active team members and approve the roles of the PC and mental health clinicians (grade of evidence: 5; strength of recommendation: strong).

In adolescents with severe depression or comorbidities, such as substance abuse, clinicians should consider consultation with mental health professionals and refer to such professionals when deemed necessary. In cases of moderate depression with or without comorbid anxiety, clinicians should consider consultation by mental health and/or treatment in the PC setting. Although the access barriers to mental health services need to be addressed by policy makers to make mental health consultations more feasible, available, and affordable in underserviced areas, clinical judgment should prevail in the meantime; thus, the need for consultation should be based on the clinician's judgment. PC providers should also take into consideration the treatment preferences of patients and/or families, the severity and urgency of the case presentation, and the PC provider's level of training and experience.

Active support and treatment should also be started in cases in which there is a lengthy waiting list for mental health services. Once a

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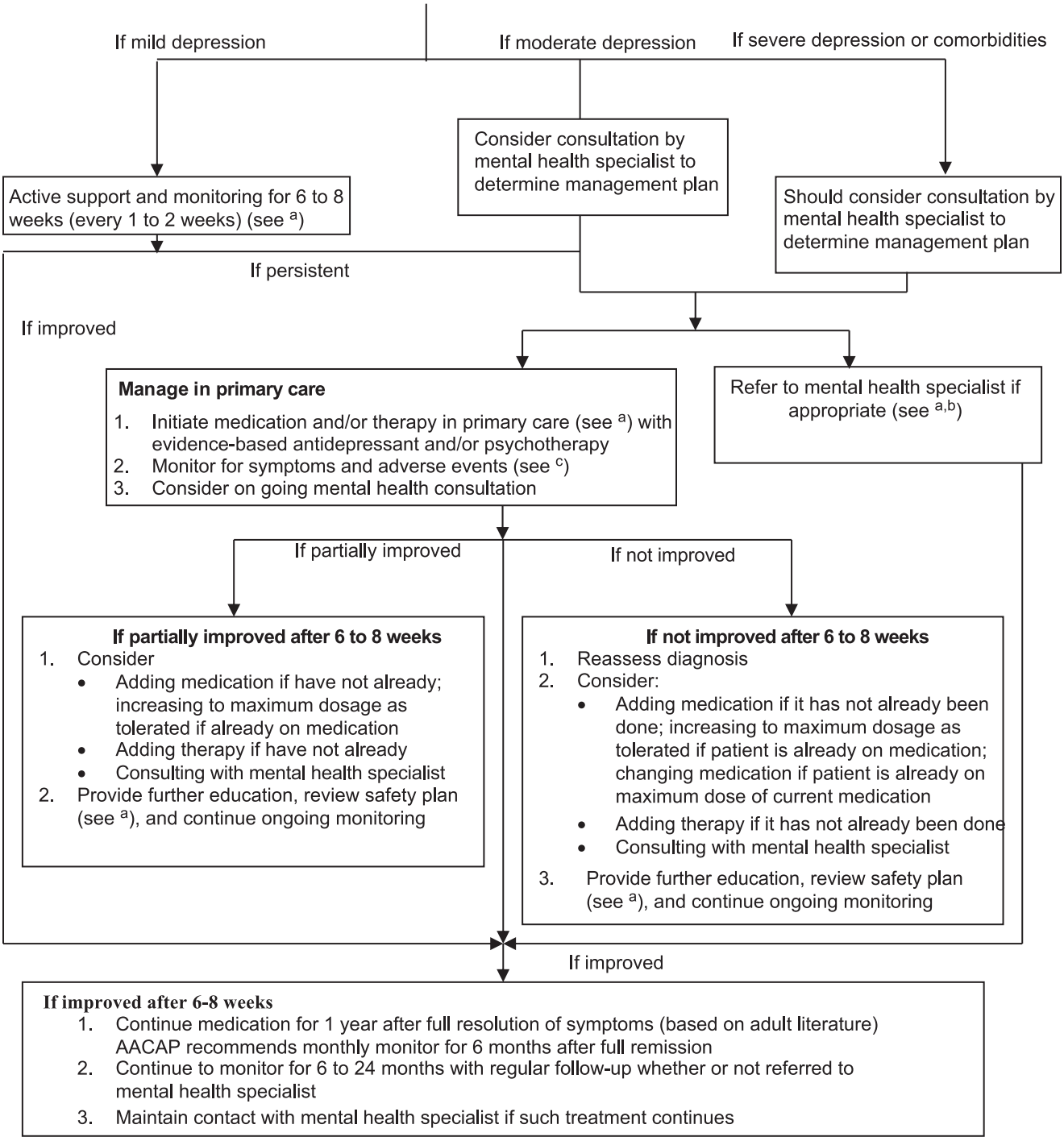

FIGURE 1

Clinical management flowchart. [a]Psychoeducation, supportive counseling, facilitate parental and patient self-management, refer for peer support, and regular monitoring of depressive symptoms and suicidality. [b]Negotiate roles and/or responsibilities between PC and mental health and designate case coordination responsibilities. Continue to monitor in PC after referral and maintain contact with mental health. [c]Clinicians should monitor for changes in symptoms and emergence of adverse events, such as increased suicidal ideation, agitation, or induction of mania. For monitoring guidelines, please refer to the guidelines and/or toolkit. AACAP, American Academy of Child and Adolescent Psychiatry.

referral is made, comanagement of treatment should take place with the PC clinician remaining involved in follow-up. In particular, roles and responsibilities should be agreed on between the PC clinician and mental health clinician(s), including the designation of case coordination responsibilities.[48,50,77,78,80,81] It is critical for PC clinicians to make linkages with their closest crisis support and hospital services so that

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they are supported in crisis situations when caring for depressed youth.

Recommendation 4: PC clinicians should recommend scientifically tested and proven treatments (ie, psychotherapies, such as CBT or IPT-A, and/or antidepressant treatment, such as SSRIs) whenever possible and appropriate to achieve the goals of the treatment plan[82] (grade of evidence: 1; strength of recommendation: very strong).

After providing education and support to the patient and family, the range of effective treatment options, including medications, psychotherapies, and family support should be considered. The patient and family should be assisted to arrive at a treatment plan that is both acceptable and implementable, taking into account their preferences and the availability of treatment services. The treatment plan should be customized according to the severity of disease, risk of suicide, and the existence of comorbid conditions. The GLAD-PC toolkit (www.gladpc.org) provides more detailed guidance around the factors that may influence treatment choices (ie, a patient with psychomotor retardation may not be able to actively engage in psychotherapy). A "common factors" approach is focused on evidence-based practices, which are common across therapies. Common factors include better communication skills, to be supportive, to take advantage of therapeutic alliance, and to engage in shared decision-making.[83] Common sense approaches such as the prescription of physical exercise, sleep hygiene, and adequate nutrition should also be used in the management of these patients.

As an aside, the majority of CBT and IPT-A studies in which researchers included patients with MDD also included patients with depression not otherwise specified, subthreshold depressive symptoms, or dysthymic disorder. In contrast, medication RCTs for depression in adolescents generally only included subjects with MDD. Thus, although the general treatment of depression is addressed in these guidelines, medication-specific guidelines apply only to fully expressed MDD.

TABLE 2 Components of CBT and IPT-A

Therapy	Key Components
CBT	Thoughts influence behaviors and feelings and vice versa. Treatment targets patient's thoughts and behaviors to improve his or her mood. Essential elements of CBT include increasing pleasurable activities (behavioral activation), reducing negative thoughts (cognitive restructuring), and improving assertiveness and problem-solving skills to reduce feelings of hopelessness. CBT for adolescents may include sessions with parents and/or caregivers to review progress and to increase compliance with CBT-related tasks.
IPT-A	Interpersonal problems may cause or exacerbate depression, and that depression, in turn, may exacerbate interpersonal problems. Treatment targets patient's interpersonal problems to improve both interpersonal functioning and his or her mood. Essential elements of interpersonal therapy include identifying an interpersonal problem area, improving interpersonal problem-solving skills, and modifying communication patterns. Parents and/or caregivers are involved in sessions during specific phases of the therapy.

Psychotherapies

Both CBT and IPT-A have been adapted to address depression in adolescents and have been shown to be effective in treating adolescents with MDD in tertiary care as well as community settings.[57,84] CBT has been used in the PC setting with preliminary positive results.[33,35] Also suggested in emerging evidence is the superior efficacy of combination therapy (medication and CBT) versus CBT alone.[43] For a brief description of the 2 therapies, see Table 2.

Antidepressant Treatment

Previous research has shown that up to 25% of pediatric PC clinicians and 42% of family physicians in the United States had recently prescribed SSRIs for more than 1 adolescent under the age of 18.[15] When indicated by clinical presentation (ie, clear diagnosis of MDD with no comorbid conditions) and patient and/or family preference, an SSRI should be used. The selection of the specific SSRI should be based on the optimum combination of safety and efficacy data. Deliberate self-harm and/or suicide risk is more likely to occur if the SSRI is started at higher doses (rather than normal starting doses).[85] The patient and family should be informed about the possible adverse effects (clinicians may use checklist), including possible switch to mania or the development of behavioral activation or suicide-related events. Once the antidepressant is started, and if tolerated, the clinician should support an adequate trial up to the maximum dose and duration.

In Table 3, recommended antidepressants and dosages for use in adolescents with depression are listed. These recommendations are based on the updated literature review and reviewed by the GLAD-PC Steering Committee. Generally, the effective dosages for antidepressants in adolescents are lower than would be found in adult guidelines. Note that only fluoxetine has been approved by the FDA for use in children and adolescents with depression, and only escitalopram has been approved for use in adolescents aged 12 years and older. Clinicians should know the potential drug interactions with SSRIs. Further information on the use of antidepressants is described in the GLAD-PC toolkit (www.gladpc.org). In addition, all SSRIs should be slowly tapered when discontinued because of risk of withdrawal effects. Details regarding the initial selection of a specific SSRI and possible reasons for initial drug choice can be found in the GLAD-PC toolkit.

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TABLE 3 SSRI Titration Schedule

Medication	Starting Dose (qd/od), mg	Increments, mg	Effective Dose, mg	Maximum Dosage, mg	Contraindicated
Citalopram	10	10	20	60	MAOIs
Fluoxetine	10	10–20	20	60	MAOIs
Fluvoxamine	50	50	150	300	MAOIs
Paroxetine[a]	10	10	20	60	MAOIs
Sertraline	25	12.5–25	50	200	MAOIs
Escitalopram	10	5	10	20	MAOIs

MAOI, monoamine oxidase inhibitor; qd/od, every day once daily.
[a] Not recommended to be started in PC.

Contact (either in person or by telephone with either the clinician or member of the clinical staff) should take place after the initiation of treatment to review the patient's and family's understanding of and adherence to the treatment plan. Issues such as the current status of the patient and the patient and/or family's access to educational materials regarding depression should be discussed during follow-up conversations. For relevant educational resources for patients and/or families, please refer to the GLAD-PC toolkit (www.gladpc.org).

Recommendation 5: PC clinicians should monitor for the emergence of adverse events during antidepressant treatment (SSRIs) (grade of evidence: 3; strength of recommendation: very strong).[82]

Re-analysis of safety data from clinical trials of antidepressants led to a black-box warning from the FDA regarding the use of these medications in children and adolescents in 2004 and a recommendation for close monitoring. The exact wording of the FDA recommendation is:

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

It should be noted, however, that there is no empirical evidence to support the requirement of face-to-face meetings per se. In fact, evidence from large population-based surveys reveals high reliability of telephone interviews with adolescent subjects for the diagnosis of depression.[86,87] Although obtaining a diagnosis is not the same as the elicitation of adverse events while in treatment, with this evidence, it is suggested that telephone contact may be just as effective in monitoring for adverse events. More importantly, a regular and frequent monitoring schedule should be developed, taking care to obtain input from the adolescents and families to ensure compliance with the monitoring strategy.[88,89] This may include monitoring of depressive symptoms, risky behaviors, and also functioning in the school setting, especially if an individualized education program is in place. Working closely with the family will ensure appropriate monitoring and help-seeking by caregivers.

Ongoing Management

The strength of evidence on which each recommendation is based has been rated 1 (strongest) through 5 (weakest), according to the Oxford Centre for Evidence-Based Medicine levels of evidence, and paired with the strength of recommendation (Very strong [>90% agreement]), Strong [>70% agreement], Fair [>50% agreement], Weak [<50% agreement]).

Recommendation 1: Systematic and regular tracking of goals and outcomes from treatment should be performed, including assessment of depressive symptoms and functioning in several key domains. These include home, school, and peer settings (grade of evidence: 4; strength of recommendation: very strong).

Goals should include both improvement in functioning and resolution of depressive symptoms. Tracking of goals and outcomes from treatment should include function in several important domains (ie, home, school, peers). Evidence from large RCTs reveals that depressive symptoms and functional impairments may not improve at the same rate with treatment.[28,70] Therefore, symptoms and functioning should be tracked regularly during the course of treatment with information gathered from both the patients and their families when possible.

According to expert consensus, it is ideal that patients are assessed in person within 1 week of the initiation of treatment. At every assessment, clinicians should inquire about each of the following: (1) ongoing depressive symptoms, (2) risk of suicide, (3) possible adverse effects from treatment (including the use of specific adverse-effect scales), (4) adherence to treatment, and (5) new or ongoing environmental stressors. In several studies, researchers have examined medication maintenance after response.[90–93] Emslie et al[93] randomly assigned pediatric patients who had responded to fluoxetine by 19 weeks to placebo or to medication continuation for an additional 32 weeks. Of the 20 subjects randomly assigned to the 32-week medication relapse-prevention arm, 10 were exposed to fluoxetine for 51 weeks. Significantly fewer relapses occurred in the group randomly assigned to medication maintenance, which suggests that longer medication continuation periods, possibly 1 year, may be necessary for relapse prevention. In addition, Emslie et al[93] found the greatest risk of relapse to be in the first 8 to 12 weeks

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after discontinuing medication, which suggests that after stopping an antidepressant, close follow-up should be encouraged for at least 2 to 3 months. Other studies have revealed similar benefits of prolonged treatment after acute response.[90–93]

With the limited evidence in children and adolescents and the emerging evidence in the adult literature in which it is suggested that antidepressant medication should be continued for 1 year after remission, both GLAD-PC and the American Academy of Child and Adolescent Psychiatry concluded that medication be maintained for 6 to 12 months after the full resolution of depressive symptoms.[22,90–93]

However, regardless of the length of treatment, all patients should be monitored on a monthly basis for 6 to 12 months after the full resolution of symptoms.[22,93,94] If the depressive episode is a recurrence, clinicians are encouraged to monitor patients for up to 2 years given the high rates of recurrence as demonstrated in the adult literature in which maintenance treatment in those with recurrent depression continues for up to 2 years after the full resolution of symptoms. Clinicians should obtain consultation from mental health professionals if a teenager develops psychosis, suicidal or homicidal ideation, and new or worsening of comorbid conditions.

Recommendation 2: Diagnosis and initial treatment should be reassessed if no improvement is noted after 6 to 8 weeks of treatment (grade of evidence: 4; strength of recommendation: very strong). Mental health consultation should be considered (grade of evidence: 4; strength of recommendation: very strong).

If improvement is not seen within 6 to 8 weeks of treatment, mental health consultation should be considered. Evidence of improvement may include reduction in the number of depressive symptoms, improved functioning in social or school settings, or improvement spontaneously reported by the adolescent and/or parent or caregiver. The clinician should also reassess the initial diagnosis, choice and adequacy of initial treatment, adherence to treatment plan, presence of comorbid conditions (eg, substance abuse) or bipolar symptoms that may influence treatment effectiveness, and new external stressors. If a patient has no response to a maximum therapeutic dose of an antidepressant medication, the clinician should consider changing the medication. Alternatively, if the patient has failed to improve on antidepressant medication or therapy alone, the addition of or switch to the other modality should be considered.

Recommendation 3: For patients achieving only partial improvement after PC diagnostic and therapeutic approaches have been exhausted (including exploration of poor adherence, comorbid disorders, and ongoing conflicts or abuse), a mental health consultation should be considered (grade of evidence: 4; strength of recommendation: very strong).

If a patient only partially improves with treatment, mental health consultation should be considered. The clinician should also review the diagnosis and explore possible causes of partial response, such as poor adherence to treatment, comorbid disorders, or ongoing conflicts and/or abuse. These causes may need to be managed first before changes to the treatment plan are made.

If a patient has been treated with a SSRI (maximum tolerated dosage) and has shown only partial improvement, the addition of an evidence-based psychotherapy should be considered, if not previously initiated. Other considerations may include the addition of another medication, an increase of the dosage above FDA-approved ranges, or a switch to another medication as suggested in the Treatment of SSRI-resistant Depression in Adolescents study,[39] preferably done in consultation with a mental health professional. Likewise, if a patient's condition fails to improve after a trial of either CBT or IPT-A and has not yet begun medication, the clinician should consider a trial of SSRI antidepressant treatment. Strong consideration should also be given to a referral to mental health services.

Recommendation 4: PC clinicians should actively support depressed adolescents referred to mental health services to ensure adequate management (grade of evidence: 5; strength of recommendation: very strong). PC clinicians may also consider sharing care with mental health agencies and/or professionals where possible (grade of evidence: 1; strength of recommendation: very strong). Appropriate roles and responsibilities regarding the provision and comanagement of care should be communicated and agreed on by the PC clinician and the mental health clinician(s) (grade of evidence: 4; strength of recommendation: very strong).

PC clinicians should continue follow-up with adolescents with depression who have been referred to mental health services for assessment and/or management.[95] Where possible, PC clinicians may consider sharing management of depressed adolescents with mental health agencies and/or professionals. There is emerging evidence from the literature about the greater effectiveness of "shared-care" models for the management of depression in the PC setting.[27,31,95–97] There is also increasing evidence to support that quality improvement strategies and techniques can change PC

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practitioner behavior both in mental health and in other arenas.[98,99]

DISCUSSION

The recommendations regarding treatment and ongoing management highlight the need for PC providers to become familiar with the use of empirically tested treatments for adolescent depression, including both antidepressants and psychotherapy. In particular, antidepressant treatments can be useful in certain clinical situations in the PC setting. In many of these clinical scenarios, PC providers should schedule systematic and routine follow-up, including mental health support when appropriate. The need for systematic follow-up, whether by PC provider or by mental health provider, is especially important in light of the FDA black-box warnings regarding the emergence of adverse events with antidepressant treatment.

Psychotherapy is also recommended as first-line treatment of adolescents who are depressed in the PC setting. Although the provision of psychotherapy may be less feasible and practical within the constraints (ie, time, availability of trained staff) of PC settings, there is some evidence to support that quality improvement projects involving psychotherapy can improve the care of adolescents who are depressed.[35]

GLAD-PC was developed and now updated on the basis of the needs of PC clinicians who are faced with the challenge of caring for depressed adolescents as well as many barriers, including the shortage of mental health resources in most community settings. Although it is clear that more evidence and research in this area are needed, these updated guidelines represent a necessary step toward improving the care of depressed adolescents in the PC setting. Similar guidelines have also been produced for other health care contexts, such as in the United Kingdom (https://www.nice.org.uk/guidance/cg28). The updated GLAD-PC guidelines and the toolkit (www.gladpc.org) reflect the coming together of available evidence and the consensus of experts representing a broad spectrum of specialties and advocacy organizations within the North American health care context. However, no improvements in care will be achieved if changes do not occur in the health care systems that would allow for increased training in mental health for PC clinicians and in collaborative models for both primary and specialty care clinicians. Therefore, it is critical that training programs for PC providers increase their focus on mental health issues and that trainees in both PC and specialty care areas be helped to hone their skills in working in collaborative care models[89] (see http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/implementing_mental_health_priorities_in_practice.aspx). For providers who are currently practicing, continuing education should strengthen skills in collaborative work, and specifically, for PC providers, increase skills and knowledge in the management of depression.

LIMITATIONS

Although the guidelines covered a range of issues regarding the management of adolescent depression in the PC setting, there were other controversial areas that were not addressed in these recommendations. These included such issues as the use of augmenting agents and treatment of subthreshold symptoms. New emerging evidence may impact on the inclusion of such areas in future iterations of the guidelines and the toolkit (available for download at www.gladpc.org). Many of these recommendations are made in the face of an absence of evidence or at lower levels of evidence.

FUTURE DIRECTIONS

Ample evidence exists to support the notion that guidelines alone are insufficient in closing the gaps between recommended versus actual practices.[100,101] Thus, it will be necessary to identify effective methods for disseminating information and provide assistance to PC clinicians in changing practice. Researchers should build on this work by piloting and evaluating methods, tools, and strategies to facilitate the adoption of these guidelines for the management of adolescent depression in PC settings. Researchers should also explore optimal methods for helping clinicians and their clinical settings address the range of obstacles that may interfere with the adoption of necessary practices to yield sustainable management of adolescent depression in PC settings.

Many jurisdictions have recognized the need to increase collaborative care to address the care of adolescents with mental illness. In Canada and the United States, models of care involving mental health and PC are being implemented (National Network of Child Psychiatry Access Programs: www.nncpap.org; Massachusetts Child Psychiatry Access Program: https://www.mcpap.com/; Partnership Access Line; Training and Education for the Advancement of Children's Health).[102–106] However, the empirical support for these models is modest internationally; therefore, additional research is urgently needed.

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ABBREVIATIONS

CBT: cognitive behavioral therapy
CCBT: computerized cognitive behavioral therapy
CI: confidence interval
FDA: Food and Drug Administration
GLAD-PC: Guidelines for Adolescent Depression in Primary Care
IPT-A: interpersonal psychotherapy for adolescents
MDD: major depressive disorder
PC: primary care
RCT: randomized controlled trial
SSRI: selective serotonin reuptake inhibitor

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