Texas Children’s Medication Algorithm Project: Update From Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder

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ABSTRACT

Objective: To revise and update consensus guidelines for medication treatment algorithms for childhood major depressive disorder based on new scientific evidence and expert clinical consensus when evidence is lacking. Method: A consensus conference was held January 13-14, 2005, that included academic clinicians and researchers, practicing clinicians, administrators, consumers, and families. The focus was to review, update, and incorporate the most current data to inform and recommend specific pharmacological approaches and clinical guidance for treatment of major depressive disorder in children and adolescents. Results: Consensually agreed on medication algorithms for major depression (with and without psychosis) and comorbid attention-deficit disorders were updated. These revised algorithms also incorporated approaches to address issues of suicidality, aggression, and irritability. Stages 1, 2, and 3 of the algorithm consist of selective serotonin reuptake inhibitor and norepinephrine serotonin reuptake inhibitor medications whose use is supported by controlled, acute clinical trials and clinical experience. Recent studies provide support that selective serotonin reuptake inhibitors in addition to fluoxetine are still encouraged as first-line interventions. The need for additional assessments, precautions, and monitoring is emphasized, as well as continuation and maintenance treatment. Conclusions: Evidence and expert clinical consensus support the use of selected antidepressants in the treatment of depression in youths. The use of the recommended antidepressant medications requires appropriate monitoring of suicidality and potential adverse effects and consideration of other evidence-based treatment alternatives such as cognitive behavioral therapies.


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A second consensus conference for childhood major depressive disorder (MDD) was held January 13–14, 2005, in Dallas, TX, to revise and update the medication algorithms for childhood depression (Hughes et al., 1999). It was deemed important to incorporate new research findings, address recent controversial issues regarding the use of antidepressants in the pediatric population, U.S. Food and Drug Administration (FDA) warnings about possible increased suicidality with antidepressant use in children and adolescents, and data from a recent feasibility trial for the childhood MDD algorithm. The latter study indicated clear improvement in clinical symptoms, functioning, and global response when the guidelines were implemented in Texas community mental health settings in comparison to a historical cohort (Emser et al., 2004b). Treatment algorithms for adults as a component of disease management have been successfully completed in a large-scale comparative trial in adults with MDD in the public sector (Rush et al., 2006; Trivedi et al., 2004). The rationale and methods for developing algorithms to guide clinical practice and their importance for improving clinical outcomes have been reviewed elsewhere (Crismon et al., 1999; Gilbert et al., 1997; Rush and Kupfer, 1995; Rush et al., 1999).

Recent reviews of the efficacy and safety of antidepressants in depressed youths summarize the findings for all of the recent pediatric antidepressant studies including both published and unpublished data (Cheung et al., 2005; Hammad et al., 2006; Mann et al., 2006). The reviews focus on the results of double-blind, randomized, placebo-controlled, acute clinical trials included in the recent FDA analyses (autumn 2004) of the efficacy (Cheung et al., 2005; Mann et al., 2006) and safety (Hammad et al., 2006) of selective serotonin reuptake inhibitors (SSRIs) and non-SSRI antidepressants (nefazodone, venlafaxine, and mirtazapine) for major depression in youths. Lengthy reanalyses of all of the suicide-related data from randomized, controlled acute trials (RCTs) including a re-examination of the rating scales that had been used, resulted in the FDA issuing a box warning in October 2004 (Cheung et al., 2005; Hammad et al., 2006). The warning described an increased risk of suicidality (suicidal behavior and ideation) for all antidepressants used in individuals under the age of 18. The incidence of suicidal ideations and behaviors in these pooled reanalyses of all RCTs of antidepressants in children was about 4% for those youths receiving antidepressants compared with 2% on placebo (Hammad et al., 2006).

It is important to note that no completed suicides were reported in any of these RCTs. Furthermore, methodological limitations of the suicidality data based on post hoc reviews from these RCT's question the strength of the conclusion regarding the causal relationship between suicidality and antidepressant treatment in youths. No systematic assessment of suicidality was performed during the RCTs (Posner et al., 2007a). Only a few prospective treatment studies of adolescent suicidal behavior have been conducted, all underpowered, and none used medication in a standard fashion, despite its administration to most depressed suicidal youths in clinical practice. The first multisite pilot treatment study of adolescents who have recently attempted suicide is in progress (National Institute of Mental [NIMH] Treatment of Adolescent Suicide Attempters [TASA]).

Contrary to the FDA’s conclusions on childhood suicidality, epidemiological studies have found an inverse relationship between suicides in the community and prescription rates of SSRI antidepressants for both youths and adults (Gibbons et al., 2005, 2006; Olfson et al., 2003, 2005). Other pharmacological studies have found no association between SSRIs and suicide after controlling for factors that increase the risk of suicide (Ludwig and Marcotte, 2005; Valuck et al., 2004). Other analyses of large medical claim databases have found higher rate of suicide among antidepressant users (Olfson et al., 2006). However, it is important to keep in mind that risk of suicide has been shown to be greatest in the month before commencing antidepressant treatment and continues to decrease after initiating treatment (Simon et al., 2006). A recent FDA meta-analysis of placebo-controlled clinical trials indicated that the risk for suicidality during antidepressant treatment is higher than on placebo until age 25 but that past that age the risk for suicidality for those taking antidepressants becomes less than when taking placebo declines afterward to become actually favorable to antidepressant in older age (Food and Drug Administration, 2006; Stone, 2006). Toxicology studies of completed suicides have found that most teenagers, even those who had been prescribed an antidepressant, did not take antidepressants before the suicide (Gray et al., 2003; Isacsson et al., 2005; Isacsson and Rich, 2005; Leon et al., 2004).
Disconcertingly, since the introduction of FDA’s warnings, SSRI prescription rates have declined by 25% (Nemeroff, 2007; Rosack, 2005). Given the well-documented inverse relationship between suicide and antidepressant prescription rates, there has been increasing concern that these recent effects on prescribing practices would negatively affect completed suicide rates in youths. Recent Centers for Disease Control and Prevention data revealed a 14% increase in suicide rates among 5- to 19-year-olds between 2003 (the introduction of FDA warnings) and 2004 (Centers for Disease Control and Prevention, 2006). This represents by far the largest increase in youth completed suicide rates since the Centers for Disease Control and Prevention began documenting rates in 1979 (R. Gibbons, Ph.D., personal communication, 2007). In addition to reductions in prescription rates, rates of MDD diagnoses in the general pediatric population have also declined significantly since the FDA initiated warnings (Valuck, 2006).

Medication algorithms for childhood MDD have been incorporated as pharmacotherapy guidelines for a number of ongoing NIMH-sponsored trials in both children and adolescents (e.g., TASA; Vitiello, 2006) and adults (Fava et al., 2003; Rush et al., 2006; Trivedi et al., 2004, 2006; Yates et al., 2004). Clinicians, administrators, and patients and families have endorsed the use of these treatment algorithms recently. Initial concerns regarding the applicability of the algorithms, concern that treatment algorithms would limit clinical judgment and professional identity as well as concerns about liability have not been borne out (Emslie et al., 2004b). Algorithm recommendations meld available research evidence with expert academic opinion and that of practicing clinicians.

When the first childhood MDD algorithm was published (Hughes et al., 1999), placebo-controlled trials of SSRIs in youths were limited to one positive acute study with fluoxetine (Emslie et al., 1997a). The initial double-blind study finding fluoxetine superior to placebo in children and adolescents with MDD (Emslie et al., 1997a) has been replicated in one multisite RCT and supported by the results from the Treatment for Adolescents With Depression Study (TADS; Emslie et al., 2002; Treatment for Adolescents With Depression Study [TADS] Team, 2004). A number of additional RCTs in more than 2,500 child and adolescent patients have been conducted since the original study. A number of issues related to the treatment of depression in youths, including FDA hearings on antidepressants and suicidality, have arisen. The revised childhood MDD algorithm incorporates the new research findings and addresses FDA warnings about possible increased suicidality with antidepressant use in children and adolescents.

**METHOD**

**2005 Consensus Conference Update**

The Children’s Medication Algorithm Project (CMAP) Depression Consensus Conference Update, sponsored by the Texas Department of State Health Services (DHS) was held in Dallas, TX, in January 2005. An expert panel consisted of the authors and also included practicing child and adolescent psychiatrists in DHS facilities and contracted community mental health centers, administrators, and parents/caregivers of depressed youths.

The format consisted of a series of presentations of current research evidence and panel discussions, including practitioners within DHS and parents/caregivers of youths with depression. The consensus panel used previously established rules for evaluating and classifying available evidence (i.e., level A data consist of randomized, double-blind, placebo-controlled studies; level B data consist of open-label and large epidemiological studies; and level C data consist of case series and expert consensus; Crismon et al., 1999; Hughes et al., 1999). The panel (see participant list) critically discussed the available data and drafted the revisions to the treatment algorithms, strategies, and tactics (Hughes et al., 1999). This was followed by multiple postmeeting reviews and revisions to produce the algorithms reported here.

**General Principles**

The 10 general principles underlying the algorithm are as follows:

1. Treatment recommendations are based on both empirical science and expert clinical consensus.
2. Careful and accurate diagnosis with careful evaluation of potential comorbid diagnoses is a precursor to treatment.
3. The algorithm is driven by the developmentally unique aspects of depression in children and adolescents.
4. Child- and adolescent-specific assessments and outcome measures are important.
5. Psychoeducation for both caregivers and youths is a critical element of medication treatment, independent of a lack of empirical data.
6. Nonmedication treatment alternatives should be considered and discussed with parents and children.
7. Patient/caregiver preference is important in treatment decisions and the decision about whether to treat with medication, psychotherapy, or both is left to clinician judgment with discussion and consent/assent from the family and patient.
8. The presence of depression in family members as well as family conflict must be addressed and treated (Birmaher et al., 2000; Brent et al., 1998).
9. The role of schools in providing input about a patient’s symptoms and functioning is recognized.
10. Complicated, partial, or nonresponsive cases, whenever possible, should be referred to a child and adolescent psychiatrists.
The algorithm strategies are subdivided into three major phases of treatment: acute, continuation, and maintenance. For acute phase, initial strategies involve implementation of single medications with favorable side effect profiles and level A data. Treatment may progress to the next stage either because of inadequate symptom improvement or medication intolerance. A clinician may choose to begin treatment at any of the stages with a documented rationale (e.g., patient history, family preference). As one progresses down the algorithm sequence, evidence becomes less rigorous, strategies become more complicated, risk of adverse effects may be greater, and closer monitoring by and attention from clinicians are required (Crismon et al., 1999; Rush et al., 1998).

**RESULTS**

**Updated Algorithm for MDD**

The updated algorithm focuses on youths 6 to 17 years of age who meet DSM-IV criteria for MDD and whose depression is deemed to be of sufficient severity to warrant medication (e.g., significant psychosocial impairment in family and peer functioning or school performance and/or at risk of harm to self or others). Insufficient data exist to make guideline recommendations for children younger than 6 years of age (Thomas et al., 1997) and for childhood adjustment disorders with depressed mood.

**Treatment Strategies**

Treatment strategies are divided into a series of stages (Fig. 1) with multiple options within each stage. In addition to the strategies for acute treatment, recommendations are provided for continuation and maintenance treatment.

**Stage 0: Diagnostic Assessment and Monitoring.** The consensus panel identified unique and important aspects of children and adolescents with MDD involving treatment and assessment issues (Vitiello et al., 2003). Therefore, stage 0 summarizes and emphasizes the following areas that need to be addressed before initiating medication treatment in children and adolescents with MDD. These are often addressed over multiple visits before initiating medication.

Assessment and monitoring issues. The diagnostic criteria are essentially the same for child or adult MDD, except for the inclusion of either depressed or irritable mood as a key qualifying symptom along with anhedonia. However, the diagnostic process is different and requires synthesizing information from both parents and children separately and evaluation of school performance instead of work. The panel noted that the irritable mood symptom can be mistaken as a symptom of an externalizing disorder or bipolar disorder, and careful assessment is required.

Nonspecific treatment intervention. Indirect evidence suggests that depression in children and adolescents is influenced by psychosocial variables such as peers and family as well as environmental events (see Hammen, 1999), and children in particular appear more responsive to nonspecific treatment (e.g., higher placebo response rate in some acute RCT’s than in adult trials). This is reflected in the Cheung et al. (2005) review in which the placebo response rates vary from around 35% in the fluoxetine trials to 50% to 60% in other studies. In contrast to earlier reports for children versus adolescents in smaller studies, Mayes et al. (2007) reported in a large study of combined fluoxetine trials that the drug-placebo difference was greater in children compared with adolescents. Although the panel did not specifically recommend a minimum time between initial evaluation and initiating medication (stage 1), the clinician and parent/child should consider this developmental difference in deciding whether to initiate medication at the initial assessment. “Watchful waiting” (alternatively called “active monitoring” in Guidelines for Adolescent Depression in Primary Care, Cheung et al., in press) with ongoing assessment of clinical status for a few weeks is encouraged when this can be safely done, particularly for preadolescents. Psychoeducation and lifestyle management training may be helpful adjuncts during this period (Cheung et al., 2005; Lopez et al., 2005).

Assessment of suicidality. The panel strongly emphasizes not only the importance of initial assessment for suicidality (both present and past) in children and adolescents but also the continued need for monitoring for emerging suicidality and suicide attempts during treatment. For example, history of attempts (e.g., type, lethality) and suicidal ideation are reviewed. Because cognition and energy often improve with pharmacotherapy more rapidly than mood, patients may be at increased risk to act on suicidal ideation during the first few weeks of treatment. Therefore,
careful monitoring and systematic assessment of suicidal thoughts and behavior during medication initiation and dose changes are essential. A helpful tool to track suicidal events throughout any treatment is the Columbia Suicide Severity Rating Scale (available from posnerk@childpsych.columbia.edu).

Medication versus alternative treatment interventions. The decision to initiate medication versus specific psychotherapy is made jointly by the clinician and adequately informed parents (guardians) with assent from the child. Evidence suggests that specific therapies, such as cognitive-behavioral therapy (CBT; Brent et al., 1997; Clarke et al., 1999) and interpersonal therapy (Mufson et al., 2004) are effective treatments, at least for mild to moderate depression. Specific psychotherapies have shown efficacy with diagnosed depressed adolescents, and CBT significantly reduces depressive symptoms in prepubertal children (Curry, 2001). CBT has yielded response rates similar to those of medication and appears superior to supportive psychotherapy and systemic behavioral family therapy (Birmaher et al., 2000; Brent et al., 1997; Compton et al., 2004). However, in the recent TADS (Treatment for Adolescents With Depression Study [TADS] Team, 2004) of
439 adolescents, CBT did not produce significantly better results than placebo. On the primary categorical outcome measure (responder status based on a final Clinical Global Impressions-Improvement score of 1 or 2), the response rate for combination treatment was the most effective with 71% response, followed by fluoxetine alone (61%), CBT (43%), and placebo (35%). The response rates with combination or fluoxetine were superior to placebo, whereas CBT was not (Treatment for Adolescents With Depression Study [TADS] Team, 2004). Recent additional analyses indicated that at the end of acute TADS treatment (week 12), clinical response was moderated by family income, severity of depression, and cognitive distortions (Curry et al., 2006). CBT alone was as effective as combination treatment for adolescents from higher income/higher parental education families (fluoxetine did not add anything). Conversely, medication alone was as effective as combination treatment for severely depressed adolescents (CBT did not add anything). Teenagers with higher levels of cognitive distortions benefited from adding CBT to medication (combination treatment), whereas those with low levels of cognitive distortion did not benefit (CBT did not add anything).

Elements to consider when deciding on medication versus psychotherapy include the severity of the depression, suicidality, how other family members have responded to medication or therapy, recurrence of a depression or its chronicity, lack of response to psychotherapy, family preferences, and consideration of psychosocial stressors. It is important to note that nonspecific therapies (e.g., supportive, psychodynamic, family therapy, psychoeducation) may be appropriate in addition to medication as part of an individualized treatment plan, although no empirical evidence exists to guide the selection of these interventions. No specific recommendations were made about when to use combination therapies versus medication management alone because the focus of the algorithm is medication management.

**Therapeutic alliance.** Stage 0 emphasizes the necessity of a therapeutic relationship between the clinician and the patient and family. A clinician unfamiliar with interviewing children and adolescents cannot conduct medication management. Antidepressant trials in youths often fail because of medication nonadherence (Lloyd et al., 1998), inadequate dosing, or inadequate duration of antidepressant treatment. It is important that the health care delivery system allow for continuity of care by the same clinician whenever possible.

**Stage 1: SSRIs (Monotherapy).** Because medications may differ in their potential benefit and risk profiles and given recent FDA box warnings applying to all antidepressants, parents or guardians should provide informed consent for each separate medication initiated. Entering into stage 1 is based on the clinician and family agreeing that medication is indicated. A patient entering stage 1 is either treatment naïve for the current episode or received an inadequate trial (e.g., inadequate dose or duration, nonalgorithm medication). The recommended monotherapy antidepressants for stage 1 are the SSRIs fluoxetine, sertraline, or citalopram.

Three SSRIs have at least one RCT demonstrating efficacy compared with placebo on the a priori determined primary outcome: fluoxetine (Emslie et al., 1997a, 2002; Treatment for Adolescents With Depression Study [TADS] Team, 2004), sertraline (Wagner et al., 2003), and citalopram (Wagner et al., 2004b). One acute trial of citalopram showed greater symptom response compared with placebo (Wagner et al., 2004b). A second study, which was conducted in Europe beginning in 1996, was negative (i.e., unable to distinguish between citalopram and placebo). In the latter study, both inpatients and outpatients were included and more than two thirds of patients were also receiving concurrent psychotherapy (von Knorring et al., 2006). Two identically designed RCTs of sertraline versus placebo were prospectively pooled to gain greater statistical power, and the results were positive for sertraline (Wagner et al., 2003). These two RCTs were reported separately to the FDA to satisfy requirements for a 6-month patent extension, and individually were negative. The FDA requires two positive acute trials for approval of an indication, and the FDA concluded that these studies individually did not support efficacy for sertraline. Because it was prospectively determined that efficacy analyses would be performed on the total sample, the consensus panel accepted this as a positive acute study for sertraline.

One acute study of paroxetine failed to demonstrate efficacy on the a priori identified primary outcome, but found efficacy on several secondary outcome measures (Keller et al., 2001). Two other unpublished studies with paroxetine in youths were negative (Berard et al.,
Thus, the available evidence provides the greatest support for the efficacy of fluoxetine in treating depression in children and adolescents, and fluoxetine is the only antidepressant to show positive efficacy in more than one acute trial. It is the only antidepressant with FDA-approved labeling for treatment of depression in this population and remains a first-line choice based on a preponderance of evidence (Emslie et al., 1997a,b, 2002, 2006a; Kratochvil et al., 2006; Treatment for Adolescents With Depression Study [TADS] Team, 2004). Several other antidepressants (citalopram, sertraline, paroxetine) show some evidence of efficacy, but results are inconsistent and have not been replicated in other trials.

Fluoxetine, as in the original algorithm, remains the antidepressant of choice, unless reasons exist in an individual patient to choose a different SSRI (e.g., potential drug interactions, past poor response, family resistance, prior lack of response with an adequate dose and trial). However, sertraline and citalopram are also alternatives in stage 1 because both have demonstrated efficacy. The pros and cons of selecting the particular SSRI should be reviewed with the family and joint decisions should be made.

When comparing the SSRIs recommended in stage 1, all of them have relative advantages and disadvantages. The FDA box warning is included in the labeling for all antidepressants. The consensus panel held that adverse effects are not clearly different among SSRIs, and prescribing clinicians should remain sensitive to family preferences. SSRIs should usually be initiated with low doses (e.g., fluoxetine 10 mg/day), titrated upward, and backed down if side effects emerge.

Other antidepressants are not recommended for stage 1, given the lack of supporting randomized, placebo-controlled studies of these medications demonstrating efficacy in childhood and adolescent depression.

**Stage 2: Switching to Alternate SSRI (Mono therapy) (SSRIs—Fluoxetine, Sertraline, Citalopram, Escitalopram, or Paroxetine [Adolescents Only If Paroxetine]).** Stage 2 is recommended for children who did not experience adequate clinical improvement during stage 1 due to unsatisfactory symptom response or medication intolerance. If depressive symptoms did not adequately improve with the SSRI used in stage 1, then an alternate SSRI is recommended.

If the patient is not switching from fluoxetine, then the new antidepressant should usually be cross-tapered with the initial antidepressant. If the patient experienced intolerable side effects (e.g., nausea, excessive restlessness, agitation) on the SSRI chosen in stage 1, then initiation of an alternate SSRI at a lower dose should be considered.

All SSRIs, including escitalopram and paroxetine, are included in stage 2. These two medications were not included in stage 1 because they do not have level A data. However, they are included as additional SSRI options. A recent double-blind study of escitalopram versus placebo in 6- to 17-year-olds did not show a significantly improved Children’s Depression Rating Scale-Revised (CDRS-R) score at endpoint with last observation carried forward analysis (Wagner et al., 2006). However, a post hoc analysis of adolescents only did find a better response to escitalopram than placebo. Efficacy data are mixed with paroxetine. The adolescent study was positive on some secondary outcome variables (Keller et al., 2001); however, two other trials did not demonstrate positive efficacy, even in the adolescent age group (Berard et al., 2006; Emslie et al., 2006b). Level A data do not support the use of paroxetine in preadolescent children (Emslie et al., 2006b), although level B data (open studies) have shown positive efficacy of paroxetine in preadolescents (Rey-Sanchez and Gutierrez-Casares, 1997). In addition, paroxetine appears to be associated with more dropouts caused by adverse effects in prepubertal children (Emslie et al., 2006b), and it may cause more agitation/hostility than other SSRIs (Cheung et al., 2005). It has been suggested that this may be associated with the shorter half-life of paroxetine in children. Therefore, paroxetine is not recommended for prepubertal children. Although paroxetine had a higher mean risk ratio for suicidality in the FDA-supervised analyses of the SSRI RCTs, the 95% confidence interval from its analyses overlapped with those of other antidepressants (Hammad et al., 2006). The panel did not deem the evidence adequate to prove causality and elected to keep paroxetine at stage 2 in the algorithm for adolescents until stronger data exist to make a different recommendation.

**Stage 2A: SSRI + Augmentation.** For children and adolescents showing a partial response to SSRI treatment, stage 2A provides the option of adding an augmenting agent. In children and adolescents only limited data exist to support the efficacy of augmenting agents (Ryan et al., 1988; Strober et al., 1992). No recent double-blind studies of SSRI augmentation in
children and adolescents have been conducted. Augmentation is typically used when a partial response occurs with antidepressant monotherapy or when remission is not achieved despite significant clinical improvement. The potential advantages of augmentation versus switching to another antidepressant monotherapy include no need for discontinuation of initial antidepressant, less lag time for response, partial responders continue to receive treatment without interruption, and treatment of breakthrough symptoms is possible. Most augmentation recommendations are extrapolated from available adult data (Trivedi et al., 2006). Recent RCTs have shown mirtazapine and sustained-release bupropion to be effective augmenting agents in adults who have experienced inadequate improvement with an SSRI, but this has not been studied in children (Carpenter et al., 2002; Trivedi et al., 2006). The best augmenting agent for children and adolescents who fail to respond to SSRIs or are partial responders remains to be determined.

Based on adult data and clinical opinion, augmentation may be a useful strategy for youths who have shown initial response with optimal dosing, but who have not achieved remission.

**Stage 3: Switching to Alternate Antidepressant Monotherapy (Bupropion, Venlafaxine, Mirtazapine, Duloxetine).** To move to stage 3, the child should have experienced at least two failed trials of SSRI antidepressants. It is critical to readdress the accuracy of diagnosis, comorbidity, and contributing factors. The adequacy of psychotherapeutic interventions should also be addressed and modified as needed. An alternate antidepressant monotherapy is recommended at stage 3 (bupropion, venlafaxine, mirtazapine, duloxetine). Quitkin et al. (2005) demonstrated in adults that 85% of patients would achieve therapeutic response and about two thirds would achieve remission after three sequential antidepressant trials of adequate dose and duration. Based on adult data, the panel recommends switching to a different class of medication.

In contrast to major depression in adults, studies of other newer antidepressants show little evidence of efficacy for the pediatric population. Two acute venlafaxine trials (Emslie et al., 2007) and two acute mirtazapine trials in children and adolescents with MDD have been negative (Cheung et al., 2005, although the pooled data from the venlafaxine trials indicate some efficacy for adolescents, but not for children. (See Cheung et al., 2005, and Mann et al., 2005, 2006 for a thorough discussion of these studies.) A small open-label trial of bupropion in children and adolescents with depression (MDD or dysthymia) and attention-deficit/hyperactivity disorder (ADHD) was conducted (Daviss et al., 2001) that found that 87.5% of subjects met criteria for depression response with bupropion. However, a large trial specific to MDD has not been conducted with bupropion. It should be noted that controlled studies in youths completed on mirtazapine and venlafaxine did not establish efficacy over placebo.

One acute trial of nefazodone in adolescents with MDD demonstrated a positive effect of medication over placebo, but only on secondary outcomes. Another acute nefazodone trial was negative. Nefazodone was not included for stage 3 because of a lack of data and potential side effects including hepatotoxicity. No pediatric trials with duloxetine have been performed; however, adult data suggest that it is an effective treatment for depression (Mallinckrodt et al., 2006). No reports are available from controlled studies in youths who have failed to respond to an SSRI, although such a study is nearing completion (Treatment of Resistant Depression in Adolescents [TORDIA], NIMH, David Brent, PI).

Meta-analyses of tricyclic antidepressant studies show no statistically significant efficacy in depressed children and adolescents (Hazell et al., 2002; Maneeton and Srisurapanont, 2000) and have unfavorable side effect profiles, including cardiotoxicity. However, the meta-analysis relies heavily on trials with small sample sizes.

Overall, the recommended medications for stage 3 are generally well tolerated by youths. Venlafaxine is the only antidepressant for which a statistically significant increased risk of suicidal behavior over placebo has been shown, although this was attributable primarily to ideation, not to attempts. Although these medications are not recommended for initial treatment stages, it is possible that they may be considered for patients who have failed to respond with two previous trials of SSRIs based on adult studies (Trivedi et al., 2006). This is an area where additional data are critically needed.

**Stage 4: General Treatment Guidance.** The panel deemed that inadequate data are available to make specific algorithm recommendations beyond the recommendations above. This does not negate the fact that the clinician must keep working to treat...
the child’s/adolescent’s depression. Thus, one should not infer that clinicians are expected to give up after multiple medication trials, but rather that inadequate research evidence exists to provide specific guideline recommendations. This being said, general recommendations are provided for options that clinicians may consider.

First, assessment of medication adherence as well as the adequacy of the medication trials (dose and duration) should occur. A thorough diagnostic reassessment should occur with close re-examination of the primary diagnosis as well as co-occurring diagnoses (including substance abuse). Reassessment of the family situation, including the child’s/youth’s perspectives on the causes of his or her difficulties and attempts to address such should occur as well as the need for any family-based therapies.

Considerations for treatment options include:

- If the child has been in psychotherapy, then the adequacy of the psychotherapy should be assessed. If a psychotherapy technique other than CBT or interpersonal therapy has been used, then one of these is recommended. If psychotherapy has not been used, then it should be recommended to the child and family.
- Although minimal research evidence is available to support antidepressant augmentation (Trivedi et al., 2006) or antidepressant combinations in youths, these strategies may be considered if the clinicians judge that the potential clinical benefits outweigh any potential adverse effects of the chosen regimen.
- Consider other pharmacotherapy treatment options based on data from the adult literature (Rush et al., 2006). However, in applying this information to the treatment of children and adolescents, one should be diligent about the challenges in doing this. In particular, interventions showing efficacy in adults have not consistently been done so in youths, particularly in preadolescents. Side effect risks may also be different in children and adolescents than in adults.
- If the depression is severe and nonresponsive, then electroconvulsive therapy (ECT) should be considered at some point. Good efficacy data exist for adults (Abrams, 1992; Buchan et al., 1992; Fink and Foley, 1999; Prudic et al., 1996) (level A) and level B and C literature exists for children and adolescents (AACAP, 2004; Bertagnolli and Borchart, 1990; Kucher and Robertson, 1995; Scheekloth et al., 1993; Strober et al., 1988). ECT is recommended with the awareness that state and institutional guidelines must be followed, and, at least in Texas, state statutes do not permit ECT for patients under the age of 16 years. Recent ECT practice guidelines have been developed for adolescents (AACAP, 2004).

It is anticipated that most children and adolescents will benefit from the early stages of the algorithm that are best supported by efficacy data; however, more treatment-resistant depressions may benefit from additional interventions. The actual response rates are not known because the algorithmic hierarchy has not been empirically tested, although a current study of treatment resistance in adolescents is ongoing (TORDIA, NIMH, David Brent, PI).

**Approach for MDD With Psychotic Features**

The treatment of MDD with psychotic features remains unchanged at this time and is approached the same as nonpsychotic MDD with the addition of the clinician’s choice of antipsychotic medication at each stage. The panel recognized the lack of data to support the choice of antipsychotic medication, but did prefer one of the newer atypicals because of the lower risk of neurological side effects. Clinicians are referred to recent reviews (Patel et al., 2005; Schur et al., 2003) for additional information on the use of antipsychotics in children and adolescents. Emphasis is placed on education to provide families and children with various nonpharmacological options (Pappadopulos et al., 2003), with the additional warning of the potential hazards of not actively treating the psychosis as well as the MDD. It is important in the assessment phase to evaluate the possible role of substance abuse as part of the diagnosis, and if there is no response by end of stage 3, further evaluation for possible bipolar disorder is needed. Again, “watchful waiting” with ongoing assessment of clinical status for a few weeks is an option when this can be safely done, particularly for preadolescents.

If an antidepressant is used in conjunction with antipsychotic medication, then the clinician should continue as previously recommended in the algorithm for MDD without psychotic features. Alternatively, the physician may choose to use an antipsychotic alone as initial treatment with the addition of an antidepressant if improvement is not seen. It is important to begin...
tapering the antipsychotic after remission of psychotic symptoms. One needs to be aware of weight gain and metabolic abnormalities associated with at least some atypical antipsychotics and of potential drug interactions between SSRIs and most antipsychotics (Crismon and Buckley, 2005). Prolonged use of an antipsychotic is associated with a risk of tardive dyskinesia, with atypical antipsychotics possessing a lower relative risk.

MDD plus psychosis is an indicator of possible development of bipolar disorder (Akiskal et al., 1995; Strober and Carlson, 1982), and clinicians should be alert to this possibility, particularly if antidepressants are prescribed.

### Treatment of MDD With Anxiety Disorders

A specific medication algorithm to address childhood anxiety disorders comorbid with MDD remains to be developed, although one is available for obsessive-compulsive disorder (March et al., 1998). Anxiety disorders or anxiety symptoms are frequently associated with depressive disorders, and treatment with SSRIs tends to address both sets of symptoms. A number of double-blind, placebo-controlled studies in youths have been completed in recent years demonstrating SSRIs to be superior to placebo in treating general anxiety disorder (Birmaher et al., 2003; Rynn et al., 2001; Walkup et al., 2002), social anxiety disorder (Wagner et al., 2004a), and obsessive-compulsive disorder (Riddle et al., 1992, 2001). In sum, the pharmacotherapy studies of childhood anxiety disorders with SSRIs have been encouraging without the prior concerns of abuse associated with the benzodiazepines (Hughes and Emslie, 1998). As with depression alone, consideration should be given to the use of nonpharmacological interventions (Compton et al., 2004; Manassis and Monga, 2001) because some of these disorders can be addressed with CBT (Cartwright-Hatton et al., 2004).

**Posttraumatic Stress Disorder (PTSD).** The panel emphasized that the possibility of co-occurring PTSD needs to be addressed in the assessment of depressed youths (AACAP, 1998). It is critical that a thorough history is conducted for potential trauma, and that PTSD be recognized and treated if present. Trauma-focused CBT has demonstrated efficacy (Cohen et al., 2005). Although only minimal research has been conducted addressing pharmacotherapy in youths with PTSD, adult studies support the use of SSRIs.

### Algorithm for MDD With ADHD

In the original algorithm the panel recommended treating ADHD first unless the child had suicidal thoughts or behaviors. However, for the updated algorithm (Fig. 2, the panel recommended that clinicians assess the severity of the respective disorders and treat the most severe disorder first.

Only children and adolescents with ADHD and unequivocal MDD that is clearly more severe than the ADHD should be treated first with an SSRI. The patient should have depressed mood nearly every day, lasting several hours, and it should be associated with significant neurovegetative signs. Patients with a comorbid diagnosis of ADHD and MDD whose ADHD has responded to a stimulant and are already stable can continue taking it and antidepressant therapy begun. The algorithm was revised in part because of the results from the feasibility study (Emslie et al., 2004b) in which a small number of patients presented with both MDD and ADHD and the depression was the more severe disorder. The treating clinicians chose to treat the depression first in those cases. As such, in the update of CMAP, the panel elected to allow the clinician to make the determination of which disorder to treat first, recognizing that the ADHD is known to respond more quickly and is a safer treatment.

Once a treatment algorithm is initiated, symptoms should be reassessed after a few weeks of treatment. If the symptoms begin to remit (e.g., MDD) and if the other disorder’s symptoms remain (e.g., ADHD), then the clinician should begin the appropriate algorithm in conjunction with the first. Because treatment of one disorder often results in improvement of symptoms associated with the other disorder, it is recommended that pharmacotherapy be initiated for only one disorder at a time—the disorder judged to be more severe. Once pharmacotherapy is initiated and optimized for the first disorder treated, then symptomatology of the co-occurring disorder can be assessed for the possible need of additional pharmacotherapy (Fig. 2). If a child is started on a stimulant and then develops increased irritability, then the stimulant should be stopped. The clinician should switch to treating the depression and then, if necessary, retrying the stimulants.

**Treatment Recommendations for Stage 0.** Recommendations for stage 0 are as above for MDD.
Treatment Recommendations If ADHD Is Treated First.

**Stage 1.** Begin treatment with stage 1 of the ADHD algorithm, either methylphenidate or amphetamine (Pliszka et al., 2006). If both depressive and ADHD symptoms adequately improve, then continuation treatment with the agent used in stage 1 is maintained (Fig. 2).

**Stage 2.**

- **Decision possibility 1:** If the patient’s ADHD symptoms respond but the patient’s depressive symptoms remain, then the clinician should begin the MDD algorithm and add a stage 1 SSRI to the stimulant.

- **Decision possibility 2:** If neither the patient’s ADHD symptoms nor depressive symptoms respond to a stimulant, then the clinician should discontinue the stimulant and treat according to the MDD algorithm. If partial improvement has occurred and the clinician deems that inadequate response may be due to the ADHD symptoms, then the clinician may consider adding an

For MDD; therefore, initial treatment with an SSRI for the depression, with the possibility of the addition of a stimulant for the ADHD, is preferred over initiating a noradrenergic antidepressant.

Treatment Recommendations If Depression Is Treated First.

**Stage 1.** Begin treatment with an SSRI from stage 1 of the depression algorithm. If both depressive and ADHD symptoms adequately improve, then continuation treatment with the agent used in stage 1 is maintained.

**Stage 2.**

- **Decision possibility 1:** If the patient’s depressive symptoms adequately improve but the ADHD symptoms remain, then the clinician should begin the ADHD algorithm and add a stage 1 stimulant to the regimen.

- **Decision possibility 2:** If the patient’s depressive symptoms do not improve, the clinician should continue with stage 2 of the depression algorithm. If partial improvement has occurred and the clinician deems that inadequate response may be due to the ADHD symptoms, then the clinician may consider adding an
ADHD algorithm stage 1 stimulant. However, it is important that only one medication change (e.g., dose change, switch to another medication) be made at a time so that the effectiveness and tolerance of the change can be evaluated.

Comorbid Mood Disorder With Aggression and Other Disruptive Behavior Disorders

A need exists to address individuals who present with mood and disruptive behavior disorders and when SSRI monotherapy is insufficient to address these disruptive behaviors (Jensen et al., 2007). The recommended first step in these cases is careful assessment to rule out bipolar disorder, and if bipolar disorder is diagnosed, then the clinician should consider implementing a recent algorithm developed specifically for childhood bipolar disorder (Kowatch et al., 2005).

A mood disorder with irritable and aggressive mood often necessitates additional measures to quickly ensure safety and efficacy (Pliszka et al., 2006). Guidelines have been published to address this important need, with 14 specific treatment recommendations for the use of atypical antipsychotics for youths with aggressive behavior that is comorbid with other psychiatric disorders (Pappadopulos et al., 2003; Schur et al., 2003). For situations in which mood disorders co-occur with aggression, the application of these guidelines is recommended.

Treatment Tactics

Although strategies define which treatment to provide and the recommended order (stage) to implement, tactics address how to optimally implement a chosen treatment regimen (i.e., a strategy; Crismon et al., 1999; Rush et al., 1998, 1999). Table 1 outlines proposed tactics with the emphasis that the goal of treatment is to achieve remission of symptoms.

For patients showing minimal or no improvement, a change in treatment stage may be considered at 4 to 8 weeks. However, recent studies in adults have shown that many nonresponders at 4 to 6 weeks will actually have symptom remission by 12 weeks of continued treatment (Quitkin et al., 2005). For patients with a partial response, the pharmacotherapy trial may last up to 12 weeks because decisions to increase the dose or augment with lithium may reasonably postpone the critical point at which it would be decided to change stages. Serious consideration should be given to changing treatment stages in patients who are only partial responders at 12 weeks because patients with residual depressive symptoms are at risk of relapse. It should be noted that this includes individuals who demonstrate robust improvement, but who still have not achieved remission.

Visit Frequency. The consensus group agreed that patients should be seen more often early in treatment (e.g., every 1–2 weeks). Seeing patients often allows the clinician to detect potential worsening of depression, emergence of suicidality, and onset of bothersome adverse effects, and to adjust dose; this likely increases patient adherence to treatment. In addition, more frequent contact enhances the engagement of the child and family in treatment and provides additional opportunities for education (Crismon et al., 1999; Depression Guideline Panel, 1993; Lopez et al., 2005; Rush and Kupfer, 1995). The 2004 FDA box warning recommends that patients treated with antidepressants be observed closely, and that “such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then visits every other week for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks.” However, visit frequency for specific patients may vary based on multiple factors (e.g., presence of suicidal behaviors, severity of illness, severity of psychosocial stressors, development of therapeutic alliance, level of family support, progress in treatment). Both patients and families should be encouraged to contact the clinician if depression worsens, the patient demonstrates suicidal behavior or verbalizations, or medication side effects occur. The appropriate use of nonphysician personnel who are knowledgeable about the patient population can aid in increasing the frequency of contact between the clinic and the patient/parent.

Measurement of Outcome. It is recommended that improvement in depressive symptoms be systematically and objectively monitored (e.g., when treating someone for high blood pressure, physicians measure ongoing changes in blood pressure to determine whether the treatment is effective). Similarly, severity of depression, rather than simply overall functioning, needs to be monitored. Various depressive rating scales are available in both clinician-rated and self-report
Further refinement of measures that would be easier for clinicians to use is needed.

**Dosing and Side Effects.** Although dosing should usually start low to minimize side effects, dose titration should occur in children and adolescents who do not achieve a robust improvement in symptoms (e.g., at 4–6 weeks of treatment). In patients achieving less than a robust response and with minimal or no side effects, further dose adjustments should be considered (e.g., at 8–10 weeks of treatment) before declaring a therapeutic or stage failure. Children should be monitored carefully for the emergence of side effects, including over-activation, during dose titration. If such side effects occur, then the dose should be lowered or an alternate treatment stage should be considered.

**TABLE 1**

<table>
<thead>
<tr>
<th>Assessment Point</th>
<th>Clinical Status</th>
<th>Plan</th>
</tr>
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<tbody>
<tr>
<td>Before pharmacotherapy</td>
<td>Symptomatic</td>
<td>Watchful waiting, particularly for preadolescents. Consider psychoeducation and lifestyle management.</td>
</tr>
<tr>
<td>Weeks 1–3 (critical point 1)</td>
<td>Symptomatic</td>
<td>Initiate medicine: adjust dose to lower end of therapeutic dose range or serum level if useful. If patient shows rapid remission in first 2–3 wk, then this may be a placebo response; continue to offer treatment and encouragement.</td>
</tr>
<tr>
<td>Week 4 (critical point 2)</td>
<td>Response or remission Partial response*</td>
<td>Go to continuation phase. Satisfactory rate of improvement: observe. Rate too slow, tolerating well: increase dose.</td>
</tr>
<tr>
<td></td>
<td>Minimal or no response; patient intolerant of lowest therapeutic dose</td>
<td>Discontinue, proceed to next stage.</td>
</tr>
<tr>
<td></td>
<td>Minimal or no response; patient tolerating medicine</td>
<td>Increase dose*.</td>
</tr>
<tr>
<td>Week 6 (critical point 3)</td>
<td>Response or remission Partial response</td>
<td>Go to continuation phase. Satisfactory rate of improvement if previously increased dose: observe. Rate too slow, tolerating well: increase dose; if dose already increased to maximum, then consider augmentation (stage 2 or later).</td>
</tr>
<tr>
<td></td>
<td>Minimal response; patient intolerant of higher dose</td>
<td>Discontinue, proceed to next stage.</td>
</tr>
<tr>
<td></td>
<td>Minimal response; patient tolerating medicine</td>
<td>Consider augmentation (stage 2 or later).</td>
</tr>
<tr>
<td>Week 8 (critical point 4)</td>
<td>Response or remission Partial response</td>
<td>Go to continuation phase. If tolerating regimen, then consider augmentation with lithium (or alternative as above) if not previously done (stage 2 and later). If not tolerating regimen, then go to next stage.</td>
</tr>
<tr>
<td></td>
<td>Minimal response to lithium augmentation for 2–3 wk</td>
<td>Discontinue, switch to next level in plan.</td>
</tr>
<tr>
<td>Week 10 (critical point 5)</td>
<td>Response or remission Partial response</td>
<td>Go to continuation phase. Increase lithium dose if not previously done (stage 2 and later). If on higher lithium dose, then go to next stage.</td>
</tr>
<tr>
<td>Week 12 (critical point 6)</td>
<td>No or minimal response</td>
<td>Go to next stage.</td>
</tr>
<tr>
<td></td>
<td>Remains partial responder</td>
<td>Go to continuation phase.</td>
</tr>
</tbody>
</table>

* Partial response: Patient is showing some evidence of improvement based on rating scales to the extent that it is unlikely that the clinician would choose to switch to a different medication. However, some change in treatment may be warranted to enhance response.

* Minimal response: Patient is showing virtually no change, although 1–2 symptoms may be showing slight improvement. Some change in treatment, whether dose change, switching, or augmenting, are definitely warranted.
The half-lives of the SSRIs and other newer antidepressants are shorter in children (Axelson et al., 2002; Daviss et al., 2005). At least theoretically, based on these data, children and adolescents could experience withdrawal side effects 8 to 12 hours after the last medication dose (except with fluoxetine), and these symptoms could be confused with lack of response or medication side effects.

SSRIs are associated with several side effects such as headache, gastrointestinal distress, sexual dysfunction, increased sweating, disruptive sleep, and, rarely, bleeding and serotonergic syndrome (Cassano and Fava, 2004; Masand and Gupta, 2002). Throughout each stage of the algorithm, the treatment of medication-related side effects should be addressed through the lowering of doses where possible, and if no improvement results, changing medications. In particular, although not common, patients should be monitored for the emergence of behavioral symptoms such as aggression, hostility, mania, behavioral activation, or motor restlessness, as well as for suicidal thoughts and behaviors (Cheung et al., 2005). No level A or B data exist to support the addition of another medication as a means of treating or reducing the severity of a side effect in children and adolescents.

Drug interactions can result in either increased side effects or decreased therapeutic effectiveness (DeVane and Nemeroff, 2002), and clinicians should be knowledgeable about and vigilant regarding potential interactions when patients are receiving multiple medications.

Assessment of Suicidality. The panel also recommends that suicidality be assessed at every visit to include behavior and ideation, including frequency, plans, intention, and potential dangerousness (Posner et al., 2007a). More frequent visits, combined with follow-up calls as necessary, should be considered along with appropriate review of safety plans and contracts with patient and family. A challenge to adequate assessment has been the clinical myth that asking about suicidality will cause increases in suicidal feelings when in fact recent research has shown this not to be the case (Gould et al., 2005). Other major suicide risk factors that should be assessed include substance abuse and conduct disorder (because there are even higher rates of substance abuse in male victims [Shaffer et al., 1996]), life stressors such as legal or disciplinary/school problems and interpersonal losses (Brent, 1993; Gould et al., 1996), family and peer discord, abuse, lack of support, poor interpersonal problem-solving ability, the tendency to respond with hostility or overt aggression to frustration or stress, and hopelessness and cognitive distortions (Beautrais, 2000; Brent et al., 2002; Fergusson et al., 2000; Gould et al., 2003; Molnar et al., 2001; Shaffer et al., 1996). Finally, assessment should include parental depression and substance abuse (Gould et al., 1996).

Reassessment of Treatment Nonresponders. See stages 0 and 4, “inadequate response,” above.

Continuation Phase Treatment for MDD

Recommendations for continuation phase treatment for children and adolescents are based on available studies of childhood and adolescent depression (Emslie et al., 2004a; Keller et al., 1998; Pine, 2002) as well as adult guidelines.

At baseline and throughout treatment, patients should receive an assessment of their psychosocial needs, including the utility of psychotherapy or other rehabilitative interventions. Continuation of medication(s) for 6 to 12 months is recommended after symptom remission (i.e., after end of successful acute phase treatment) at the full therapeutic dose used in the acute phase (Crismon et al., 1999; Emslie et al., 2004a; Depression Guideline Panel, 1993; Fava and Rosenbaum, 1995; Pine, 2002; Rush and Kupfer, 1995). After reaching remission of depression, patients should be seen by clinicians at least once every 3 months (preferably every 1–2 months) during continuation treatment to monitor for relapse of symptoms or suicidal ideation. Because bipolar disorder may present with depression as the initial episode, monitoring for the potential occurrence of a manic episode should occur. If this was the first major depressive episode, then the patient should be evaluated for tapering and medication discontinuation at the end of continuation phase treatment. If previous depressive episodes have occurred, then the patient should be evaluated for maintenance treatment. Determining the duration of continuation treatment, frequency of visits, and need for maintenance treatment is based on several factors, including severity of the index episode, ongoing residual symptoms, history of multiple episodes, patient and family preference, and side effects of continued treatment. Clinicians, patients, and families...
collaboratively evaluate the patient’s need for and intensity of ongoing treatment.

The multisite fluoxetine trial (Emslie et al., 2002, 2004a) reports on the pharmacological maintenance treatment of 40 children and adolescents who had responded to 20 to 60 mg fluoxetine during a 19-week, double-blind, placebo-controlled study of fluoxetine. Patients were rerandomized to either continue fluoxetine or switch to placebo for an additional 36 weeks (Emslie et al., 2004a). Relapse was defined as a CDRS-R score >40 with a history of 2 weeks of clinical deterioration or patients who had, in the opinion or the physician, experienced a relapse. Fewer fluoxetine subjects (34%) than placebo subjects (60%) met the criteria for relapse. Furthermore, time to relapse was shorter for placebo subjects than fluoxetine subjects (71.2 ± 9.5 days versus 180.7 ± 17.0 days, respectively; p = .046). Using the strict CDRS score >40 criterion (excluding physician decision to terminate), 21% fluoxetine versus 47% placebo relapsed, and time to relapse was 37.2 ± 2.1 days versus 203.0 ± 13.0 days (p = .032).

When discontinuing the antidepressant, the dose should be tapered no more rapidly than 25%/week (or as slow as practical with available dose forms). Tapering and discontinuation usually occur over a 2- to 3-month period (Crismon et al., 1999; Depression Guideline Panel, 1993; Pine, 2002; Rush and Kupfer, 1995). Although fluoxetine has a long elimination half-life, it is likely best to taper it as well, if for no other reason than it reinforces the need for the family to observe the patient for possible reemergence of depression with tapering and discontinuation. The time to begin a taper and the tapering schedule should be discussed with and agreed to by the patient and family. Patients and their primary caretaker should be taught to monitor for recurrence of depressive symptoms. Because a new depressive episode is most likely to occur within the first 8 months after medication discontinuation, patients should be seen every 2 to 4 months during this period (Emslie et al., 1997b). If depression recurs, then prompt treatment with the previously effective medication should be reinitiated (i.e., initiate algorithm stage and tactic that previously resulted in remission of depressive symptoms).

For patients with MDD with psychotic features treated with an antipsychotic medication, the acute phase antipsychotic dose should be continued for 2 to 3 months following remission of psychotic symptoms and then slowly tapered (Schur et al., 2003). The duration of antipsychotic treatment should be limited as the patient’s clinical situation permits to reduce the risk of neurological side effects.

For patients with comorbid ADHD who are stabilized on only a stimulant medication, recommendations for continuation phase treatment follows those suggested by the CMAP Consensus Conference Panel on ADHD (Pliszka et al., 2006).

Maintenance Phase Treatment

In adults with an initial episode of MDD, at least 50% are at risk of a second episode, and by the third episode, the recurrence risk is 90% (Depression Guideline Panel, 1993). Similarly, up to 70% of youths experiencing MDD will experience a recurrence (Birmaher et al., 2002). Therefore, all patients, including children and adolescents, experiencing their third depressive episode, and depending on risk factors (e.g., family history, severity of episode, suicidality during the episode) some patients with a second episode, should be considered for maintenance treatment (Crismon et al., 1999; Depression Guideline Panel, 1993; Fava and Rosenbaum, 1995; Rush and Kupfer, 1995). Data suggest that continuity of major depression exists between childhood and adulthood, with recurrence rates of another depressive episode estimated to be approximately 60% to 70% (Harrington et al., 1990; Rao et al., 1995).

Maintenance medication should continue at full therapeutic doses, and, as in the continuation phase, the regimen associated with symptom remission is recommended. The optimal duration of maintenance medication has not been established in adults or children and adolescents, but depending on risk factors, is generally believed to be between 3 years and lifetime.

Active discussions regarding the initiation and duration of maintenance treatment are an important element in the clinician–patient–family collaboration. The patient and family’s personal preference as well as the risk factors for recurrence must be considered in the decision process.

No published maintenance studies of antidepressant use in children are available, and these recommendations are borrowed from the adult MDD literature, which may or may not be applicable to children and adolescents.
CONCLUSIONS

A consensus panel of experts, clinicians, administrators, and consumer family members revised and updated the Texas medication treatment algorithm for MDD in children and adolescents. The final product resulted in revised recommendations for antidepressant treatment, with an emphasis on adverse event monitoring and specialized assessment for suicidality and comorbid disorders.

The implementation of a treatment algorithm as a component of disease management for children with depression was superior to a historical treatment as usual cohort of children and adolescents (Emslie et al., 2004a) as well as in a large-scale comparative trial in adults with MDD in the public sector (Trivedi et al., 2004, 2006). Medication algorithms for childhood MDD have been incorporated as pharmacotherapy guidelines for a number of ongoing NIMH-sponsored trials in both children and adolescents (e.g., NIMH Treatment of Adolescent Suicide Attempters; Vitiello, 2006) and adults (Fava et al., 2003; Rush et al., 2006; Trivedi et al., 2004; Yates et al., 2004). Clinicians, administrators, patients, and families have recently endorsed the use of these treatment algorithms. Initial concerns regarding the applicability of the algorithms, concern that treatment algorithms would limit clinical judgment and professional identity, and concerns about liability have not been borne out.

Medication algorithms do not limit clinicians’ ability to use their clinical judgment; rather they provide a framework for decision making. The medication algorithms include simplified initial treatment interventions for straightforward cases with an emphasis placed on initial monotherapy trials. Algorithms do not reduce the need for experienced clinicians to use their clinical acumen in diagnosis, assessment of severity, ongoing monitoring, decision making, and ability to establish a therapeutic relationship. In fact, a consistent clinician–patient relationship is mandatory in the treatment of a disorder frequently requiring long-term treatment and adherence to medication regimens and close monitoring of initial and emerging side effects.

Both parents and adolescents continue to be supportive of the use of the algorithms. They want accurate and understandable information about mental disorders and their appropriate treatment. Family advocates participated in the development of a psychoeducational program as a critical component of the algorithm disease management program during the CMAP feasibility trial. They strongly endorsed the need for adequate parent/child education and the need to be involved in treatment decisions (Lopez et al., 2005).

The major limitation to developing MDD algorithms for children and adolescents continues to be the lack of empirical double-blind, placebo-controlled studies of various medications that demonstrate efficacy and safety (only five published in the past 6 years). Similarly, almost no research regarding antidepressant combinations or augmentation is available in children or for treating individuals who are treatment resistant. A strength of the Texas algorithmic approach is that it synthesizes available empirical data with expert opinion, clinical experience, and consumer perspectives. It is designed to adjust and incorporate new information on an ongoing basis.

A CMAP Web site link (Texas Department of State Health Services, 2005) provides a source for all of the CMAP- and Texas Medication Algorithm Project–related documents including downloadable psychoeducational material that has been developed to support the algorithm approach.

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