# The Texas Children's Medication Algorithm Project: Revision of the Algorithm for Pharmacotherapy of Attention-Deficit/Hyperactivity Disorder

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**ABSTRACT**

**Objective:** In 1998, the Texas Department of Mental Health and Mental Retardation developed algorithms for medication treatment of attention-deficit/hyperactivity disorder (ADHD). Advances in the psychopharmacology of ADHD and results of a feasibility study of algorithm use in community mental health centers caused the algorithm to be modified and updated. **Method:** We convened a consensus conference of academic clinicians and researchers, practicing clinicians, administrators, consumers, and families to revise the algorithms for the pharmacotherapy of ADHD itself as well as ADHD with specific comorbid disorders. New research was reviewed by national experts, and rationales were provided for proposed changes and additions to the algorithms. The changes to the algorithms were discussed and approved both by the national experts and experienced clinicians from the Texas public mental health system. **Results:** The panel developed consensually agreed-upon algorithms for ADHD with and without comorbid disorders. The major changes included elimination of pemoline as a treatment option, adding atomoxetine to the algorithm, and refining guidelines for treating ADHD with comorbid depression, aggressive behaviors, and tic disorders. **Conclusions:** Medication algorithms for ADHD can be modified to keep abreast of developments in the field. Although these evidence- and consensus-based treatment recommendations may be a useful approach to guide the treatment of ADHD in children, additional research is needed to determine how these algorithms can be used to maximally benefit child outcomes. *J. Am. Acad. Child Adolesc. Psychiatry,* 2006;45(6):642–657. **Key Words:** attention-deficit/hyperactivity disorder, algorithm, psychopharmacology, practice parameters.

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In 1998, the Texas Department of Mental Health and Mental Retardation (now the Texas Department of State Health Services [DSHS]) convened a consensus conference to develop algorithms for the medication treatment of attention-deficit/hyperactivity disorder (ADHD) with or without comorbid disorders (Pliszka et al., 2000a). Briefly, this algorithm recommended a stimulant (methylphenidate [MPH] or amphetamine [AMP]) as the first stage of treatment. If this stimulant did not produce a satisfactory result, then stage 2 would be the stimulant not used in stage 1. Stage 3 was a trial of pemoline, and stage 4 was a trial of either bupropion or a tricyclic antidepressant. Stage 5 was the agent not

used in stage 4, whereas stage 6 was treatment with an alpha agonist.

Subsequently, an open trial of the feasibility of the algorithm for the treatment of primary ADHD was undertaken (Pliszka et al., 2003). Child and adolescent psychiatrists in DSHS community mental health centers were trained in the use of the algorithms, and then 50 children with ADHD were treated by these physicians using the algorithm. Children were studied for 4 months of treatment. The algorithm was generally well received by the physicians, with good adherence to the first two treatment stages. No physician used pemoline because of the reports of hepatoxicity and the stringent laboratory monitoring of liver function that became mandatory shortly after the 1998 consensus conference. Physician adherence to the algorithm was lower when treating the small number of children who required treatment beyond stage 2. Children who failed both MPH and AMP often failed to move to stage 4 in part because of family and physician desires to return to a stimulant tried in stage 1 and in part because of issues raised with methods for handling comorbid oppositional and aggressive behavior, which varied widely. When aggressive behaviors did not respond to stage 1 or 2 stimulant treatment, clinicians frequently used nonalgorithm medications (principally risperidone and clonidine) with the rationale that the children met criteria for bipolar not otherwise specified (NOS) or mood disorder NOS. Nonetheless, children treated via the algorithm were exposed to significantly less polypharmacy and had better clinical outcome than historical controls (Pliszka et al., 2003). The feasibility study suggested that methods for dealing with severe oppositional and aggressive behavior in children with ADHD needed to be added to the algorithm. DSHS also sought to modify the algorithm in light of this experience, and to reflect new research evidence for the treatment of ADHD. Additional developments that dictated the need to revise the algorithms were as follows: (1) new agents for the treatment of ADHD, including atomoxetine, modafinil, and long-acting stimulants, (2) the emergence of consensus statements for the treatment of aggression (Pappadopulos et al., 2003; Schur et al., 2003); and (3) controversy over antidepressant treatment of children and adolescents with major depressive disorder (MDD), which influenced the algorithm for the treatment of ADHD with comorbid depression.

In September 2004, a consensus conference was reconvened, using methodology that was identical to that of the original conference (Hughes et al., 1999) to carry out these revisions. Although psychosocial interventions are an important component of the treatment of ADHD (particularly for children with ADHD with comorbid disorders), the algorithms presently address the pharmacological treatment of ADHD. The members of the consensus panel and their roles are listed in the Appendix. External experts presented data on the first morning of the conference and a discussion period followed each presentation. On the first afternoon, internal experts commented on how the original algorithms fit into clinical practice in the community mental health centers and made suggestions based on their clinical experience. Family members then discussed their experience with the medication treatment of their child's ADHD and offered advice to panel members. Finally, the external and internal experts convened on the second day of the conference to revise the algorithms in light of all of the data and experiences presented. Decisions were made by consensus, with all experts members having equal input. No major areas of disagreement remained at the end of the conference. Table 1 summarizes the major changes to the algorithms that are described in more detail below.

## EVALUATION OF ADHD

### Stage 0: Assessment and Inclusion/Exclusion Criteria

Entry into the ADHD algorithm is predicated on a well-established diagnosis of ADHD. In the DSHS system, each child receives a psychiatric assessment. Exclusionary criteria for entry into the algorithm include: meets criteria for a manic episode, any psychotic disorder (schizophrenia, psychosis NOS), or a pervasive developmental disorder (e.g., autism, Asperger's, Rett's disorder). Children with ADHD and other comorbid conditions may enter the algorithm. These comorbid conditions include depressive disorders, oppositional defiant disorder, conduct disorder, anxiety disorders, and tic disorders. The original algorithm discussed the treatment of ADHD with comorbid intermittent explosive disorder. During the feasibility trial, this diagnosis was rarely used by child psychiatrists in the community mental health centers.

**TABLE 1**
Summary of Changes in Revised Texas CMAP Algorithm

| Algorithm | Stage | 1998–2004 Algorithm | 2005 Algorithm |
|---|---|---|---|
| ADHD | 1 | Stimulant (MPH or AMP) | Same, but additional long-acting formulations and dextro-MPH |
| | 2 | Alternative Stimulant | Same, but may attempt different formulations of stimulant within stage |
| | 3 | Pemoline | Atomoxetine (pemoline eliminated) |
| | 4 | Bupropion or tricyclic antidepressant | Same |
| | 5 | Alternative not used in stage 4 | Same |
| | 6 | Alpha Agonist | Same |
| ADHD and Depression | 1 | Use stimulant to treat ADHD first, then add an SSRI if depressive symptoms do not remit with successful treatment of ADHD | Treat whichever disorder is most severe first, then add treatment for the second disorder if monotherapy does not result in remission of both disorders |
| ADHD and Anxiety | 1 | Use stimulant to treat ADHD first, then add an SSRI if anxiety symptoms do not remit with successful treatment of ADHD | Use atomoxetine to treat both ADHD and anxiety, or first treat ADHD with stimulant, then add an SSRI for treatment of anxiety |
| | 2 | None | Use alternative strategy from above |
| ADHD and Tic Disorders | 1 | Stimulant monotherapy | Same |
| | 2 | Stimulant required for ADHD, but if tics continue to impair, add alpha agonists | Same |
| | 3 | Add risperidone | Add an atypical antipsychotic |
| | 4 | Add pimozide | Add pimozide or haloperidol only after failure of several atypical antipsychotics |
| ADHD and Aggression | 1 | Treat ADHD, determine whether aggression resolves | Same |
| | 2 | Add a mood stabilizer (lithium or divalproex sodium) or alpha agonist to ADHD agent | Add behavioral intervention to stimulant |
| | 3 | Use alternative class from stage 2 | Add an atypical antipsychotic to stimulant |
| | 4 | Add an atypical antipsychotic | Add lithium or divalproex sodium to stimulant |
| | 5 | None | Add agent not used in stage 4 |

*Note*: ADHD = attention-deficit/hyperactivity disorder; MPH = methylphenidate; AMP = amphetamine; SSRI = selective serotonin reuptake inhibitor.

Although clinicians in the feasibility trial were not formally interviewed regarding this fact, a variety of reasons exist for this phenomenon: general unfamiliarly with the intermittent explosive disorder diagnosis and a sense that it was a "diagnosis of exclusion," a tendency to perceive all aggressive behavior as stemming from some other comorbidity (particularly bipolar disorder, thus excluding the child from the algorithm), and a sense that aggression occurred more along a spectrum rather than as a categorical diagnosis. The consensus panel was strongly influenced by the Treatment Recommendations for the use of Antipsychotics for Aggressive Youth (TRAAY; Pappadopulos et al., 2003). Thus, the consensus conference panel deemed that it is more clinically useful to define aggression dimensionally. The algorithm now refers to the treatment of ADHD with comorbid aggression.

## ALGORITHM FOR ADHD WITHOUT COMORBID PSYCHIATRIC DISORDER

### Stage 1: Stimulant Treatment

Figure 1 shows the algorithm for the psychopharmacological treatment of ADHD alone. The conference reaffirmed that the stimulant medications (MPH and AMP) have the most evidence for efficacy and safety in the treatment of ADHD, and they remain the first stage of medication intervention. No clinical predictors exist as to which child will respond to which stimulant, thus the choice of MPH versus AMP is left to the physician and the parent.

Since the consensus conference in 2000, d-MPH, the pure dextro isomer of MPH, has been approved for the treatment of ADHD (Focalin). d-MPH is superior to placebo and comparable to MPH in reducing symptoms of ADHD and may have an average duration of 6 hours as compared with 4 hours with MPH (Arnold et al., 2004; Wigal et al., 2004b). In the last 5 years, extensive trials have been carried out with newer long-acting forms of MPH (Concerta, Metadate, Focalin XR, Ritalin LA) and AMP (Adderall XR; Biederman et al., 2002; Greenhill et al., 2002; McCracken et al., 2003a; Pelham et al., 2001; Swanson et al., 1998, 2003; Wolraich, 2000; Wolraich et al., 2001). These long-acting formulations are equally efficacious as the matched multiple doses of the immediate-release forms and can be used initially, barring no immediate obstacles to the family such as cost or availability. The long-acting mechanism makes diversion of the stimulant for substance abuse far less likely. In addition, naturalistic data suggest that treatment persistence is greater and reduced stimulant switching occurs with the newer long-acting formulations (Lage and Hwang, 2004; Sanchez et al., 2005). Clinical consensus suggests that compliance is better with these formulations, and they eliminate the need for in-school dosing. Short-acting stimulants are often used as initial treatment in small children (weight <16 kg) for whom no long-acting dosage form is available in a sufficiently low dose, or in children whom the physician feels are vulnerable to side effects.

Laboratory-based pharmacodynamics/pharmacokinetics modeling studies of stimulants indicate a positive relationship between stimulant serum concentration (either MPH or AMP) and a 10-minute math test as well as positive teacher-rated attention and deportment. Modeling comparisons of different MPH formulations indicate that during a 12-hour interval, the formulation producing the highest MPH serum concentration at a point in time is also associated with the most improvement in pharmacodynamic performance (Swanson et al., 2002, 2004). When equated for the initial immediate release component, Concerta and Metadate have the same drug delivery profile and the same effects during the first 6 hours, but different targets were chosen in development for matching twice-per-day dosing for Metadate (Wigal et al., 2003) or three-times-per-day dosing for Concerta (Swanson et al., 2003) schedule of immediate release MPH. However, when the total daily dose is matched, these formulation produce different pharmacodynamic patterns of effect over time that are related to the serum concentration profiles Because the various MPH stimulant formulations may not produce identical clinical responses in individual patients, clinicians may elect to perform a trial of different MPH formulations within a given stage of the algorithm, but it is not mandatory to try all of the different formulations of MPH before moving to the next stage of the algorithm.

Data emerging from the Multimodality Treatment of ADHD study has confirmed that a linear relationship exists between stimulant dose and clinical response. In any group of ADHD subjects, more

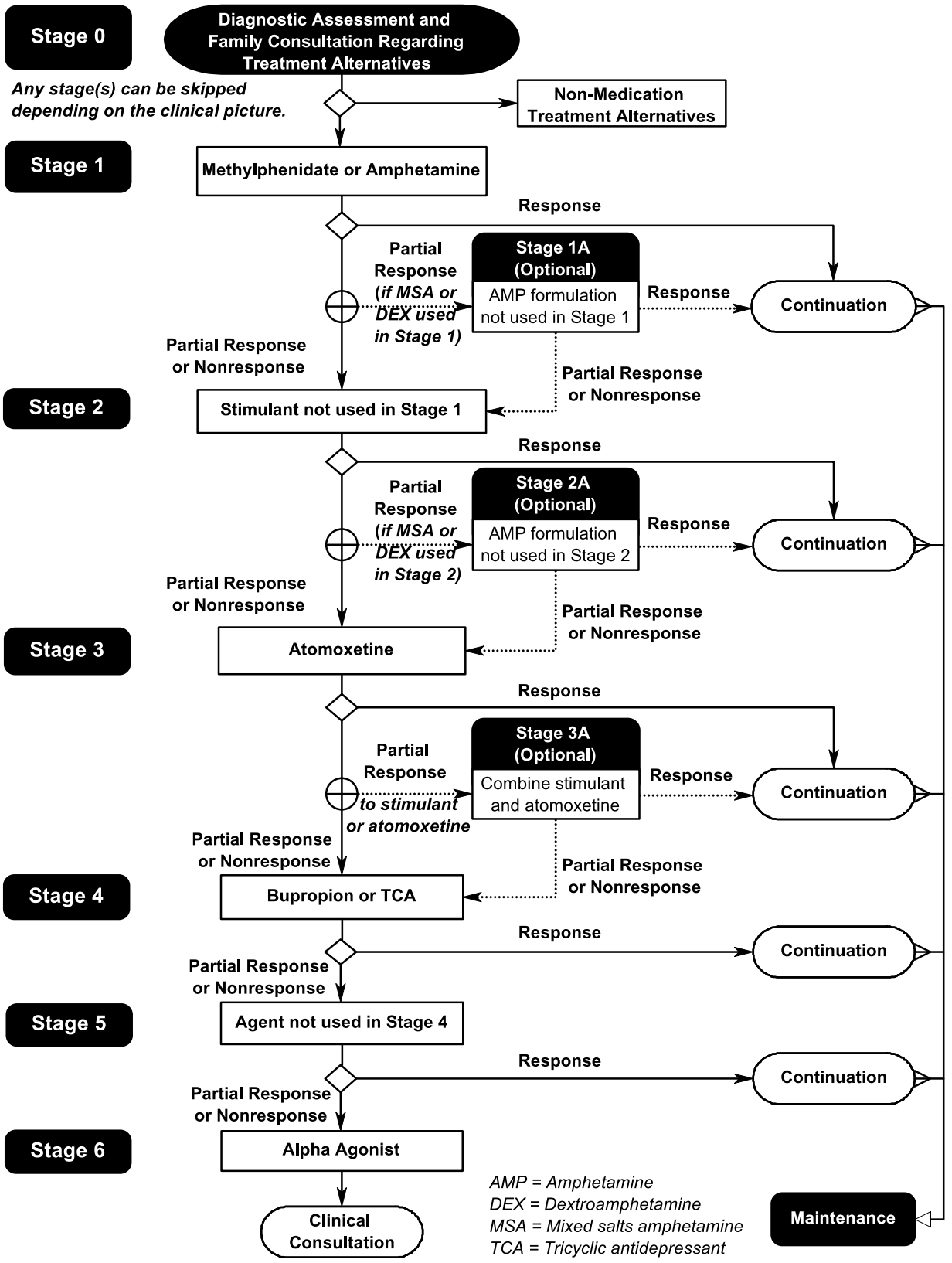


**Fig. 1** Algorithm for the psychopharmacological treatment of ADHD.

subjects will be classified as responders and a greater reduction in symptoms occurs with higher stimulant doses. No evidence supports a global "therapeutic" window in ADHD patients. Each patient, however, has a unique dose-response curve. If a full range of MPH doses are used, then roughly one third of patients will have an optimal response on a low (<15 mg/day), a medium (16–34 mg/day), or a high (>34 mg/day) daily dose (Vitiello et al., 2001). Thus, the conference reaffirmed the use of a milligram-based titration scheme for either MPH or AMP rather than a weight-adjusted milligram-per-kilogram-per-day dose formula. As described in the original CMAP ADHD tactics paper, physicians should use a full range of doses of the respective stimulant (Pliszka et al., 2000b). Long-acting stimulants should be used in equivalent daily doses to the short-acting ones.

After the consensus conference, Health Canada suspended the sales of Adderall XR because of reports of several cases of sudden death (Health Canada, 2005a). In contrast, the U.S. Food and Drug Administration (FDA; Food and Drug Administration, 2005a) recommended changes in Adderall XR labeling that the drug should be used with caution in patients with preexisting structural heart disease. After an extensive review, Health Canada lifted the suspension of Adderall XR on August 24, 2005 (Health Canada, 2005b). The consensus conference did not believe that these events should change any current practice of clinical monitoring of patients on mixed salts amphetamine or any other stimulant.

### Stage 2: Alternative Stimulant

If ADHD symptoms do not adequately improve with the first stimulant tried, or if side effects occur that make long-term use inappropriate, pharmacotherapy should be switched to a stimulant that was not used in stage 1. Switching between different formulations of MPH is not regarded as a stage change. The physician may proceed to stage 3 after one MPH formulation and one AMP product have been used. Although no evidence exists to support a differential response of dextroamphetamine versus mixed salts amphetamine, this substaging was added because physicians in the feasibility study clearly viewed the two AMP compounds as separate agents, each of which may deserve a trial in individual patients before moving to stage 3. The algorithm does not make a trial of different AMP agents mandatory, however.

### Stage 3: Atomoxetine

Since the initial consensus conference, atomoxetine has been approved for the treatment of ADHD. Atomoxetine is a noradrenergic reuptake inhibitor that is superior to placebo in the treatment of ADHD in children, adolescents, and adults (Michelson et al., 2001, 2002, 2003; Swensen et al., 2001). Its effect size has been calculated to be 0.7 in one study (Michelson et al., 2002). Direct comparisons of the efficacy of atomoxetine to MPH (Michelson, 2004) and AMP (Wigal et al., 2004a) have shown a greater treatment effect of the stimulants, and in a meta-analysis of atomoxetine and stimulant studies, the effect size for atomoxetine was 0.62 as compared with 0.91 and 0.95 for immediate-release and long-acting stimulants, respectively (Faraone et al., 2003). Atomoxetine may be considered as the first medication for ADHD in individuals with an active substance abuse problem or after one stimulant trial, if the child experienced severe side effects such as mood lability or severe tics. Potential family opposition to the use of stimulants is also an important factor in medication selection; patient and caregiver education is critical with regard to the role of medications in the treatment of ADHD (Lopez et al., 2005).

Atomoxetine can be given in the late afternoon or evening, whereas stimulants generally cannot; atomoxetine may have less pronounced effects on appetite and sleep than stimulants, although it may produce relatively more nausea or sedation. Gastrointestinal distress can be minimized by taking the medication after a meal. In children and young adolescents, atomoxetine is initiated at a dose of 0.3 $mg \cdot kg^{-1} \cdot day^{-1}$ and titrated over 1 to 3 weeks to a maximum dose of 1.2 to 1.8 $mg \cdot kg^{-1} \cdot day^{-1}$ (Kratochvil et al., 2003) Adults or adult-size adolescents should be started on atomoxetine 40 mg daily and titrated to 80 to 100 mg/day of atomoxetine over 1 to 3 weeks, if needed (Kratochvil et al., 2003). The labeling for atomoxetine recommends both once-daily and twice-daily dosing, although its elimination half-life of 5 hours as well as clinical experience suggest twice-daily dosing (early morning and early evening) is more effective and less prone to side effects. Michelson et al. (2002) showed that although atomoxetine was superior to placebo at week 1 of the trial, its greatest effects

were observed at week 6, suggesting that patients should be maintained at the full therapeutic dose for at least several weeks to observe the full effects of the drug. Side effects of atomoxetine, which occurred more often than placebo in clinical trials, included gastrointestinal distress, sedation, and decreased appetite. These can generally be managed by dose adjustment and often attenuate with time. On December 17, 2004, the FDA required that a warning be added to atomoxetine as a result of reports of two patients (an adult and a child) who developed severe liver disease (Food and Drug Administration, 2005b). Both patients recovered. In the clinical trials of 6,000 patients, no evidence of hepatoxicity was found. Patients who develop jaundice or dark urine or other symptoms of hepatic disease should discontinue atomoxetine. The consensus panel did not believe that baseline or routine laboratory monitoring of liver function is necessary for atomoxetine treatment. In September 2005 (after the consensus conference), the FDA also issued an alert regarding suicidal ideation with atomoxetine in children and adolescents (Food and Drug Administration, 2005c). In 12 controlled trials involving 1,357 patients taking atomoxetine and 851 taking placebo, the average risk of suicidal thinking was 4/1,000 in the atomoxetine-treated group versus 0 in the group taking placebo. There was one suicide attempt in the atomoxetine group but no completed suicides. A boxed warning was added to the atomoxetine labeling. The panel did not feel these data should affect atomoxetine's position in the algorithm, but this risk should be discussed with patients and family and children should be monitored for the onset of suicidal ideation, particularly in the first few months of treatment.

Clinicians at the consensus conference noted that they frequently use low doses ($0.5–1.0\ mg \cdot kg^{-1} \cdot day^{-1}$) of atomoxetine in combination with stimulants. This was done most often when atomoxetine failed to adequately improve ADHD symptoms in school settings as well as stimulants, but stimulants did not cover symptoms occurring in the evening, even with long-acting forms. Atomoxetine was typically given in the afternoon to assist with evening behavior or to reduce rebound-type symptoms. Although no controlled data exist on this practice, the conference elected to include it as a substage of stage 3. The consensus panel cautioned that such a substage should be entered only after full monotherapy trials of two stimulants and atomoxetine have shown partial but not fully adequate improvement of the child's ADHD symptoms. The consensus panel further emphasized that minimal data are available regarding possible side effects of a stimulant–atomoxetine combination, thus this substage is optional. The clinician may instead move directly to stage 4. Given its lack of use in the CMAP feasibility study and amid growing concerns over liver toxicity (Adcock et al., 1998; Rosh et al., 1998), pemoline was deleted from the algorithm.

Cephalon, Inc. (2004) issued a press release on August 19, 2004 announcing its intent to seek an indication for modafinil for the treatment of ADHD in children and adolescents ages 6 to 17 years. The company reported that three 9-week, double-blind, placebo-controlled trials involving 600 subjects showed that modafinil was superior to placebo in reducing symptoms ratings on the teacher ADHD Rating Scale-IV (DuPaul et al., 1998). The most common side effects observed in these studies were insomnia, headache, and loss of appetite. These data were not available at the time of the consensus conference; therefore, participants elected to wait for FDA approval of modafinil for the treatment of ADHD (expected in spring 2006) before placing it in the algorithm.

### Stage 4: Antidepressant Treatment

Stage 4 remains unchanged from the original algorithm. The physician may select either bupropion or a tricyclic antidepressant (imipramine or nortriptyline). The panel continued to exclude desipramine from the algorithm because of concerns regarding case reports of sudden death (Biederman et al., 1995). When a child is placed on a tricyclic, electrocardiogram monitoring should be done at baseline and after the child is taking a stable dose of the medication. Bupropion is contraindicated in a child with a seizure disorder. Data on the pharmacokinetics of the slow release form of bupropion show that the half-life of bupropion and its metabolites are significantly shorter in children and adolescents than adults (Daviss et al., 2005). Thus, the slow-release formulation should always be dosed twice a day. Pharmacokinetic data from children and adolescents on the once-a-day (XL) form of bupropion are not available, but clinical experience suggests it can be used successfully in older adolescents. However, clinicians should consider the possibility that those in the pediatric age group may metabolize bupropion sufficiently rapidly to make once-daily dosing of the XL formulation inadequate.

The tactics for using these medications remain largely unchanged (Pliszka et al., 2000b).

### Stage 5: Alternative Antidepressant

If a child's ADHD symptoms do not improve or significant side effects are encountered with the antidepressant used in stage 4, then the physician should switch the child to an alternate antidepressant.

### Stage 6: Alpha Agonists

Alpha agonists remain the last stage in the algorithm for treatment of primary ADHD. The physician may choose either clonidine (Connor et al., 1999) or guanfacine (Scahill et al., 2001). Again, tactics for the use of these medications are unchanged from the previous report (Pliszka et al., 2000b). Of note, no further reports of serious cardiovascular side effects or sudden death in children treated with alpha agonists have been published since the last consensus conference. Monitoring of pulse and blood pressure should be performed periodically.

## CO-OCCURRING DEPRESSIVE/ANXIETY DISORDERS

In the feasibility study of the CMAP MDD algorithm, 15 patients were enrolled who had both ADHD and MDD, dysthymia or depression NOS (Emslie et al., 2004). Following the original algorithm, most of these patients ($n$ = 9) were prescribed a stimulant first; only two of these patients required the subsequent addition of a selective serotonin reuptake inhibitor (SSRI) for treatment of their depressive symptoms. Six of these patients were treated with a combination of a stimulant and an SSRI, and two were treated only with an SSRI. Thus, although most

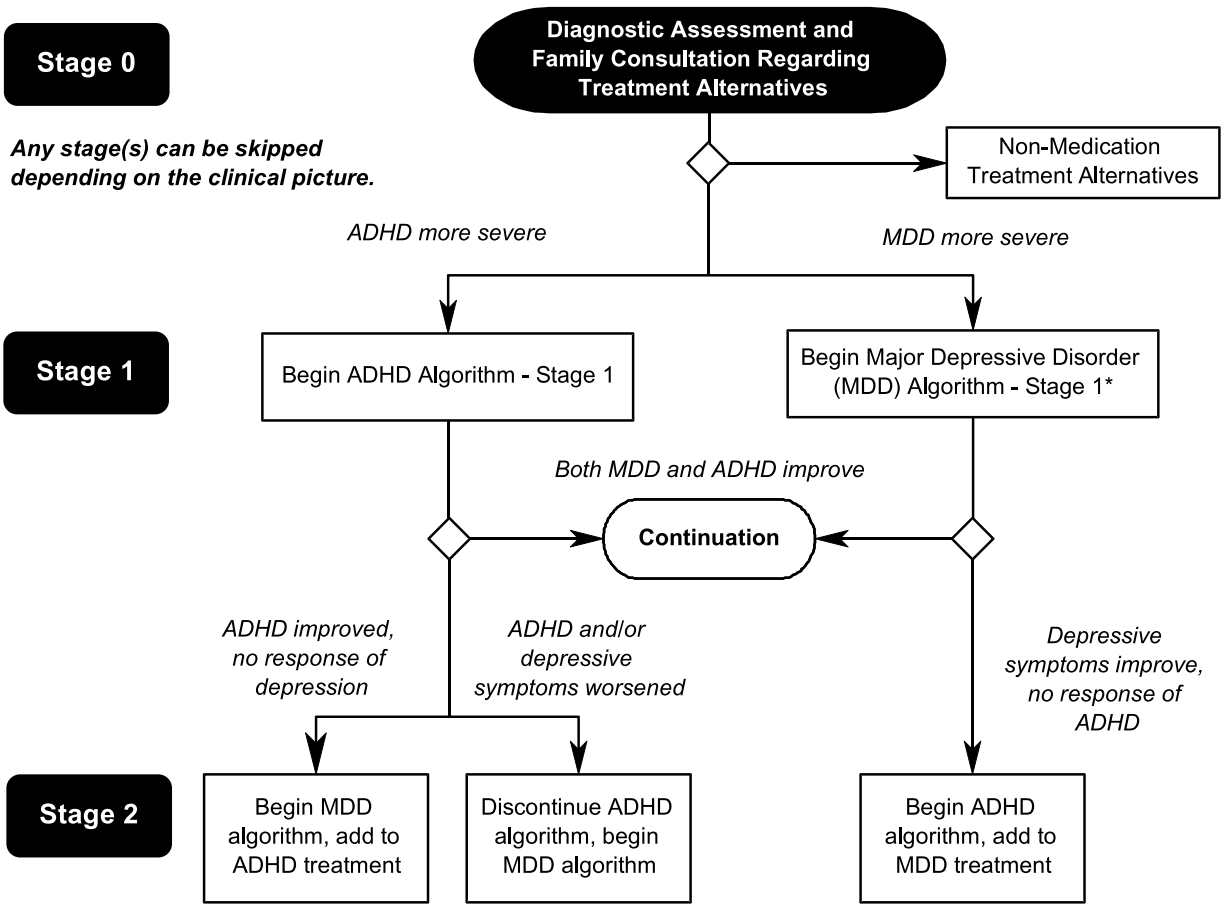


**Fig. 2** Algorithm for the psychopharmacological treatment of ADHD and comorbid depressive disorder. (*See Hughes et al., unpublished, 2005.)

patients with comorbidity responded to the algorithm approach (treat ADHD first), Emslie et al. believed that a few patients had depressive symptoms severe enough to require that the affective disorder be treated first.

The issue of the treatment of comorbid MDD and ADHD is vastly complicated by the emergence of controversy over whether antidepressants increase suicidal ideation in a small number of patients treated with SSRIs (Jick et al., 2004). In a pooled analysis of 24 short-term, double-blind, placebo-controlled trials of children and adolescents with depression or select anxiety disorders, 4% of subjects exposed to SSRIs and other newer antidepressants demonstrated suicidal ideation or showed evidence of self-harm, compared with 2% of those taking placebo (Food and Drug Administration, 2004). However, no suicides occurred in these studies. On this basis, the FDA required a black box warning be placed on the labeling of all antidepressants, alerting patients to an increased risk of suicide and suggesting precautionary methods for physicians to take when prescribing antidepressants to children and adolescents (Food and Drug Administration, 2005d). At the CMAP consensus conference on pharmacotherapy for depression in children and adolescents held in January 2005 (Hughes et al., unpublished data, 2005), several recommendations were made regarding pharmacotherapy for depression co-occurring with ADHD. Clinicians should use structured instruments such as the Children's Depression Rating Scale (Poznanski and Mokros, 1996) or the Reynolds Adolescent Depression Scale (Reynolds, 1992) to assess the severity of the respective disorders. In general, the clinician should focus initially on the treatment of the disorder that is the most severe and which produces the most impairment for the child (see Fig. 2). Because the treatment of one disorder often results in the improvement of symptoms associated with the other disorder, it is recommended that pharmacotherapy be initiated for only one disorder, the one that is judged to be the most severe. Only

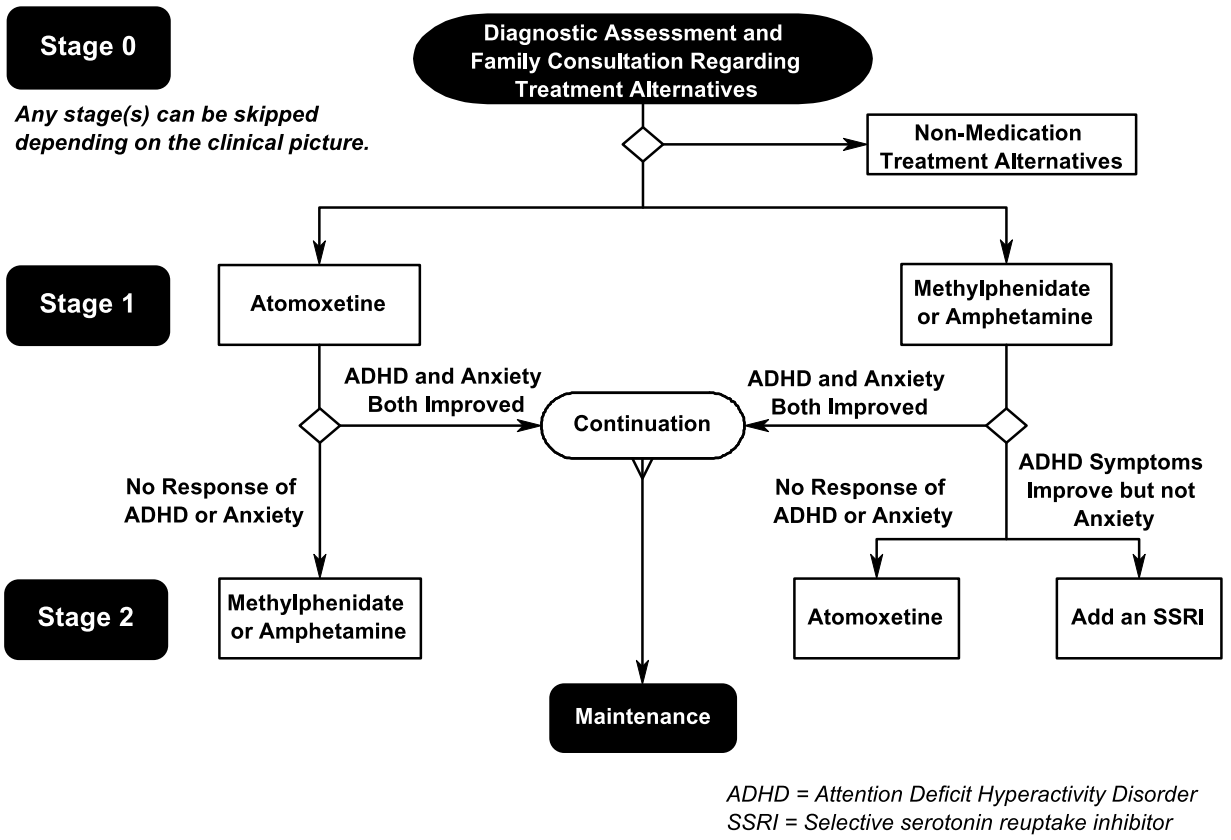


**Fig. 3** Algorithm for the psychopharmacological treatment of ADHD and comorbid anxiety disorder.

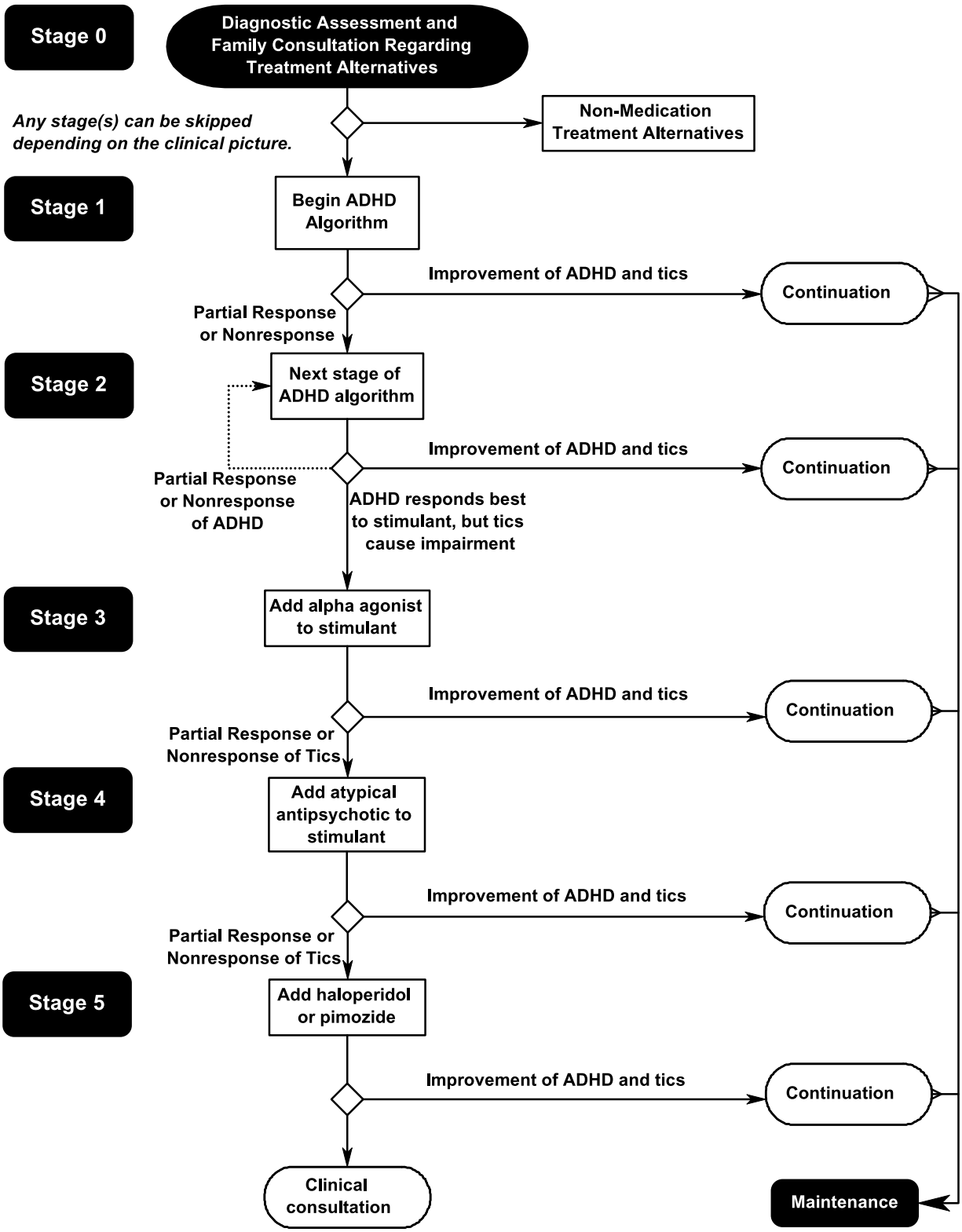


**Fig. 4** Algorithm for the psychopharmacological treatment of ADHD and comorbid tic disorder.

children with ADHD and adolescents with unequivocal MDD should be treated first with an SSRI; that is, the patient should experience a several-hours-long depressed mood associated with significant neurovegetative signs nearly every day. Based on the CMAP depression feasibility study (Emslie et al., 2004), it is likely that the majority of patients with comorbid ADHD/MDD can be managed with a stimulant. However, a strong consensus was voiced by both the ADHD and MDD conference panels that initial treatment with an SSRI should exist as an option for treating children and adolescents presenting with more severe depression. Once pharmacotherapy is initiated and optimized for the most severe disorder, then symptomatology of the co-occurring disorder can be assessed for need for pharmacotherapy. The consensus panel strongly recommended that, whenever possible, only one change in pharmacotherapy be made at a time. These recommendations are based on expert consensus because minimal research data exist to support pharmacotherapy recommendations for co-occurring MDD and ADHD.

The use of atomoxetine in the treatment of patients with ADHD and comorbid anxiety has been studied (Sumner et al., 2005). Patients with ADHD or an anxiety disorder (generalized anxiety, separation anxiety, or social phobia) were randomized to either atomoxetine ($n = 87$) or placebo ($n = 89$) in a double-blind, placebo-controlled manner for 12 weeks of treatment. At the end of the treatment period, atomoxetine led to a significant reduction in ratings of symptoms of both ADHD and anxiety relative to placebo, suggesting that the drug is efficacious in the treatment of both conditions. This study is of interest because treatment algorithms for ADHD with comorbid anxiety have recommended that ADHD be treated first with stimulants and then an SSRI added for the treatment of persistent anxiety (Pliszka et al., 2000a). Recently, however, the SSRI fluvoxamine was not found to be superior to placebo for the treatment of anxiety when added to a stimulant in a small sample ($n = 25$) of children with ADHD and comorbid anxiety (Abikoff et al., 2005). This small study does not invalidate this practice, but the above results of Sumner et al. (2005) suggest that the use of atomoxetine for the treatment of ADHD with comorbid anxiety is a viable, alternative approach. However, no evidence exists that atomoxetine is effective for the treatment of MDD (Bangs et al., 2005). The consensus panel recommended that either approach is acceptable as a stage 1 intervention for the treatment of ADHD and comorbid anxiety, and that the alternative approach should be used as stage 2 (see Fig. 3).

## TIC DISORDERS

Figure 4 shows the algorithm for the treatment of ADHD with comorbid tic disorders. The conference reaffirmed that stimulants are an appropriate treatment for patients with ADHD and comorbid tic disorder, given that on average, most ADHD/tic disorder patients will not experience an exacerbation of their tics with stimulants (Castellanos, 1999; Law and Schachar, 1999). Nevertheless, if tics worsen with stimulant use, a patient's physician should progress through the algorithm stages in an attempt to find an agent that is effective in treating the ADHD while not worsening the tics. Despite isolated case reports that atomoxetine may exacerbate tics (Lee et al., 2004), preliminary analyses of a controlled trial of atomoxetine in children with ADHD and tics did not show that atomoxetine worsened tics relative to placebo (McCracken et al., 2003b). In some cases, however, ADHD is best treated with a stimulant. If this stimulant worsens the tics, then an alpha agonist should be added to the stimulant. The efficacy of combining MPH and clonidine was recently validated in a double-blind, placebo-controlled trial of these agents (Tourette's Syndrome Study Group, 2002). Children with ADHD and tic disorder did better on the combination of the two medications than on either agent alone, both in terms of ADHD and tic symptom control.

If an alpha agonist in combination with a stimulant does not adequately improve the tics, then an atypical antipsychotic can be used in conjunction with the stimulant. Controlled trials have shown that atypical antipsychotics are superior to placebo and compare favorably to typical antipsychotics for tic control (Bruggeman et al., 2001; Sallee et al., 2000; Scahill et al., 2003). Only if several atypical antipsychotics fail to control tics should treatment with a typical antipsychotic such as haloperidol or pimozide be considered.

## AGGRESSION

Severe aggressive outbursts are seen in some ADHD children, particularly those with comorbid conduct disorder. The consensus panel recommended that such behavior be quantified using a behavior rating scale with

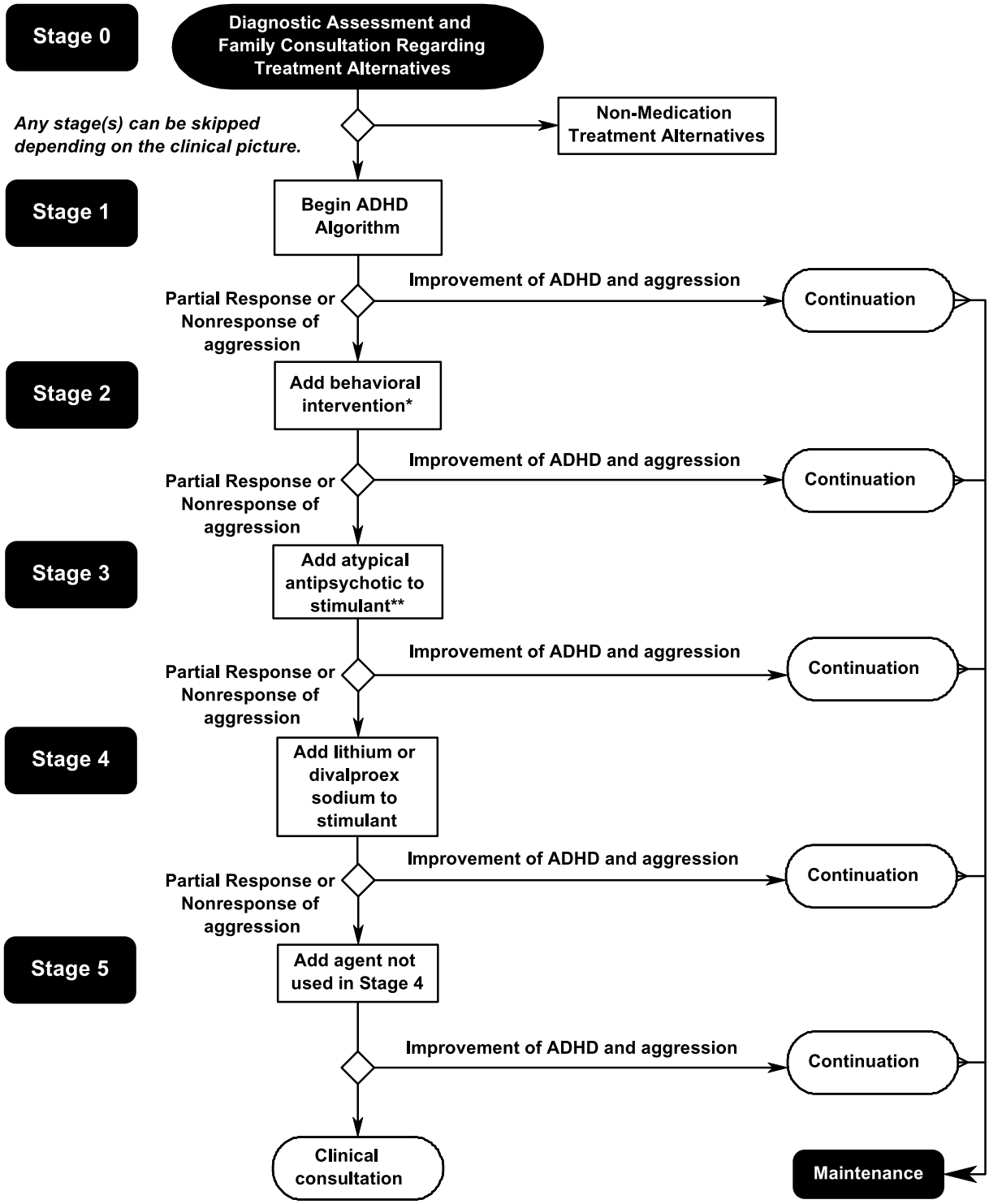


**Fig. 5** Algorithm for the psychopharmacological treatment of ADHD and comorbid aggression.

defined norms for aggressive behavior (Jensen et al., in press; Pappadopulos et al., 2003). The TRAAY consensus panel listed nine published rating scales for assessing aggression in children and adolescents. These scales consisted of both caretaker and clinician-rated instruments (Pappadopulos et al., 2003). Thus, aggression in patients with ADHD may be a target for treatment regardless of a specific diagnosis. A recent meta-analysis showed that antisocial behaviors such as stealing and fighting can be reduced by treatment with stimulants (Connor et al., 2002). The treating physician should assess the effectiveness of the stimulant in reducing any comorbid antisocial behavior. The consensus panel recommended that if aggressive outbursts remain problematic despite the attenuation of ADHD symptoms, a behavioral intervention targeting the aggressive behavior (and any contributing family or community factors) be initiated. If the behavioral treatment produces inadequate improvement, or the aggressive behavior is so extreme that it poses a danger to the patient or others, then psychopharmacological treatment should be initiated (see Fig. 5). Consistent with TRAAY, an atypical antipsychotic should be added to the stimulant (Pappadopulos et al., 2003). Although most randomized controlled trials of the pharmacotherapy of aggressive behavior have used risperidone (Aman et al., 2002; Snyder et al., 2002), clinicians may select any of the atypical antipsychotics based on the individual clinical situation. Physicians must be aware of the risks of excessive weight gain, type 2 diabetes mellitus, and dyslipidemia, and must follow established guidelines for minimizing these risks (Marder et al., 2004). If aggression does not adequately diminish with the use of the atypical antipsychotic, then a trial of lithium (Campbell et al., 1995) or divalproex sodium (Donovan et al., 2000) is appropriate. The consensus panel agreed that evidence for the antiaggressive effect of alpha agonists is minimal and elected not to include them in the algorithm for the treatment of aggression.

## LIMITATIONS

Although much more controlled data on the pharmacotherapy of ADHD was available to consensus conferees relative to the first conference, clinical experience and uncontrolled open trials remain key sources for the development of the algorithm. To date, no randomized controlled study of the algorithm itself has been performed to confirm that algorithm-based treatment yields a superior outcome for ADHD as compared with treatment as usual. Discussions are under way among CMAP consensus panel members to plan such trials, and in particular, to examine how clinician adherence to the algorithms can be enhanced.

## CLINICAL IMPLICATIONS

The new algorithm presents a wider range of treatment options for the clinician involved in the treatment of ADHD and its common comorbid disorders. The new algorithm demonstrates that evidence-based guidelines can keep pace with new developments in the field. Although preliminary evidence suggests that ADHD treatment guidelines may result in improved patient outcomes (Pliszka et al., 2003), additional studies will be needed to test the benefits of this modified algorithm and to develop optimal methods to encourage child and adolescent psychiatrists and other practitioners in their actual application. The consensus panel members will continue to consult via teleconference and e-mail as developments in the field emerge. The rapid expansion of knowledge in child and adolescent psychopharmacology is a major challenge to the process of developing algorithms.

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## APPENDIX

### Members of the Texas Consensus Conference Panel on Pharmacotherapy of Childhood Attention Deficit Hyperactivity Disorder: External Experts and Role

C. Keith Conners, Ph.D., overall discussant for presentations

M. Lynn Crismon, Pharm.D. (co-chair), presented on principles of algorithm development and the use of α-agonists in the treatment of ADHD

Graham J. Emslie, M.D., expert with regard to ADHD and depressive/anxiety disorders

Carroll W. Hughes, Ph.D., overall discussant; principal representative from CMAP Major Depressive Disorder consensus panel

Peter S. Jensen, M.D., presented on the treatment of aggressive behavior in children and adolescents

James T. McCracken, M.D., presented studies on the use of long-acting stimulants

Steven R. Pliszka, M.D. (chair), presented on the use of nonstimulants in the treatment of ADHD and CMAP feasibility study; principal author of the consensus guidelines

James Swanson, Ph.D., presented on pharmacodynamics/pharmacokinetics of different stimulant formulations and the use of psychosocial treatments for ADHD

### Texas State Department of Health Services (Mental Health): Internal Experts

Molly Lopez, Ph.D., Texas Department of State Health Services, Austin

Robin Mallett, M.D., Gulf Coast MHMR Center, League City, TX

Sylvia Musquiz, M.D., Mental Health and Mental Retardation Authority of Harris County, Houston

Steven P. Shon, M.D., Medical Director for Behavioral Health Services, Texas Department of State Health Services, Austin

Sylvia Turner, M.D., Terrell State Hospital, Terrell, TX

Linda Logan, family member, Austin

Susan Rogers, family member, Dallas

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**Factors Associated With Age of Diagnosis Among Children With Autism Spectrum Disorders** David S. Mandell, ScD, Maytali M. Novak, MA, Cynthia D. Zubritsky, PhD

*Objective:* Early diagnosis of children with autism spectrum disorders (ASD) is critical but often delayed until school age. Few studies have identified factors that may delay diagnosis. This study attempted to identify these factors among a community sample of children with ASD. *Methods:* Survey data were collected in Pennsylvania from 969 caregivers of children who had ASD and were younger than 21 years regarding their service experiences. Linear regression was used to identify clinical and demographic characteristics associated with age of diagnosis. *Results:* The average age of diagnosis was 3.1 years for children with autistic disorder, 3.9 years for pervasive developmental disorder not otherwise specified, and 7.2 years for Asperger's disorder. The average age of diagnosis increased 0.2 years for each year of age. Rural children received a diagnosis 0.4 years later than urban children. Near-poor children received a diagnosis 0.9 years later than those with incomes >100% above the poverty level. Children with severe language deficits received a diagnosis an average of 1.2 years earlier than other children. Hand flapping, toe walking, and sustained odd play were associated with a decrease in the age of diagnosis, whereas oversensitivity to pain and hearing impairment were associated with an increase. Children who had 4 or more primary care physicians before diagnosis received a diagnosis 0.5 years later than other children, whereas those whose pediatricians referred them to a specialist received a diagnosis 0.3 years sooner. *Conclusion:* These findings suggest improvements over time in decreasing the age at which children with ASD, especially higher functioning children, receive a diagnosis. They also suggest a lack of resources in rural areas and for near-poor families and the importance of continuous pediatric care and specialty referrals. That only certain ASD-related behaviors, some of which are not required to satisfy diagnostic criteria, decreased the age of diagnosis suggests the importance of continued physician education. **Pediatrics** 2005;116:1480–1486.