Algorithm for the Psychopharmacological Management of Attention Deficit Hyperactivity Disorder (ADHD)

Revised May 2009

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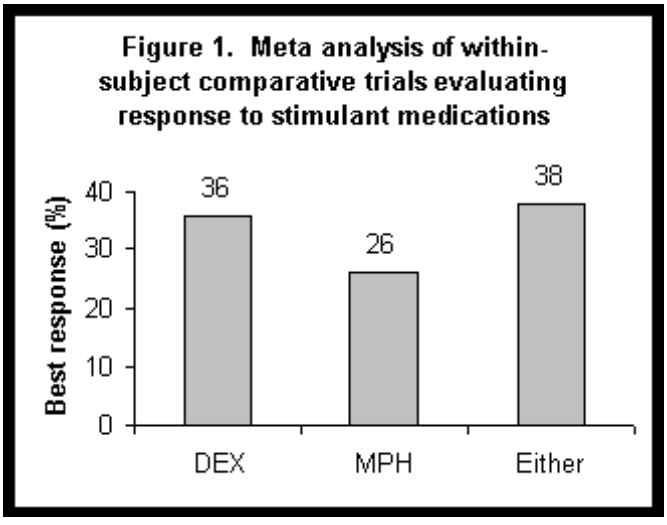
Stimulants

Stimulants have consistently shown robust behavioral efficacy in hundreds of randomized controlled trials conducted since the 1960's. By 1993, Swanson's "Review of reviews" reported over 3,000 citations and 250 reviews of stimulant treatment (Swanson et al., 1993). Robust short-term stimulant-related improvements in ADHD symptoms were found in 161 studies encompassing 5 preschool, 140 school age, 7 adolescent and 9 adult RCTs (Spencer et al., 1996). Improvement was noted for 65-75% of the 5,899 patients assigned to stimulant treatment versus only 4-30% of those assigned to placebo for methylphenidate (MPH) (n=133 trials), dextroamphetamine (DEX) (n=22 trials), and pemoline (n=6 trials). This body of data has continued to grow since then with the introduction of the short acting mixed salts of amphetamine (MSA) (Pliszka et al., 2000). MPH has both a dextro (d) and levo (l) isomer; the d-MPH isomer alone shows efficacy equal to that of the d, 1-MPH form, with some evidence that the d-isomer administered alone has a slightly longer duration of action than d,l.-MPH (Weiss et al., 2004). Short acting stimulants rarely have duration of action longer than six hours, requiring multiple doses per day. Long acting forms have been developed for d,l MPH (Concerta®, Daytrana® Transdermal System, Metadate® CD, Ritalin® LA), MSA (Adderall®) and d-MPH (Focalin® XR). Results have shown that long-acting agents have a response rate similar to that shown by short-acting stimulants in the earlier studies.

Pemoline (Cylert®) was taken off the market in 2006 and short-acting dextro-amphentamine was removed from the UHS formulary early in 2009. Recently, lisdexamfetamine dimeyslate (Vyvanse®) has been shown to be superior to placebo and equivalent to Adderall® in the treatment of both childhood and adult ADHD (Adler et al., 2008; Biederman et al., 2007; Faraone, 2008; Findling et al., 2008). It may have less abuse potential than short acting stimulants (Jasinski and Krishnan, 2009).



As noted in figure 1, when methylphenidate and dextroamphetamine are compared head to head, only about 38% of children with ADHD respond equally well to both classes of stimulant medication (Arnold, 2000) with the other subjects being selective responders. Thus having more than one stimulant medication on the

subsidized formulary is important – since up to 30% of children with ADHD will be non-responders to any one drug. Since mixed salts amphetamine contains levo-amphetamine as well as dextroamphetamine, there may be children who respond to it rather than dextroamphetamine (Arnold et al., 1976). Thus all three types of formulary stimulants (short acting MSA, lisdexamfetamine & a formulation of MPH) may be tried before moving on to non stimulant treatment.

Stimulants have now been widely used in the treatment of ADHD in adults (Adler et al., 2007; Biederman et al., 2005; Biederman et al., 2006; Spencer et al., 2005). The effective doses for methylphenidate are 60-80 mg a day and 50-60 mg a day of amphetamine.

Atomoxetine

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; Michelson et al., 2002; Michelson et al., 2003; Swensen et al., 2001). Given its pharmacokinetic half-life of 5 hours, it is generally dosed twice a day. Atomoxetine may also reduce tics (Allen et al., 2005) and be effective in children with ADHD who have comorbid anxiety (Sumner et al., 2005). The FDA has issued warnings regarding rare side effects of hepatotoxicity and suicidal ideation(Food and Drug Administration, 2005).

Bupropion

Bupropion is an antidepressant with effects primarily on the norepinephrine and dopamine systems, it is superior to placebo in the treatment of ADHD (Conners et al., 1996). It has far fewer controlled trials documenting its effectiveness than atomoxetine. It should not be used in patients with a seizure disorder.

Clonidine

Clonidine has been shown to be superior to placebo in reducing ADHD symptoms in a number of controlled trials (Connor et al., 1999), though these trials were not as methodologically sound as those for stimulants or antidepressants. Blood pressure and pulse should be monitored at follow up visits. Sedation is the most common side effect. Clonidine should be used for children who have failed stimulants *and* atomoxetine for treatment of their ADHD. However, it may be used in combination with stimulants in ADHD children with comorbid Tic disorder or severe aggressive outbursts. (Hazell and Stuart, 2003; Tourette's Syndrome Study Group,2002).

The algorithm on page 6 illustrates a summary of the stages described here and shows the following medications recommended in the management of ADHD: mixed salts amphetamine (Adderall®) lisdexamfetamine (Vyvanse®), methylphenidate, atomoxetine (Strattera®), bupropion, and clonidine.

Stage 1: Stimulant Treatment

Since effectiveness of stimulants in the treatment of ADHD is without dispute, the first stage of *medication* intervention inevitably involves their use. No clinical predictors exist as to which child will respond to which stimulant, thus the choice of methylphenidate vs. mixed salts amphetamine vs. lisdexamfetamine is left to the physician and the parent. Dosing guidelines of the stimulants are shown in the “A” tables.

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Stage 2: Alternative Stimulant-1

If a patient fails to respond to the first stimulant tried or has side effects which make its long-term use inappropriate, the patient should be switched to an alternative stimulant. Dosing guidelines of the stimulants are shown in the "A" tables.

Stage 3: Atomoxetine

If a patient fails 2-3 stimulant medications, atomoxetine should be given a trial in stage 3. Dosing guidelines are shown in table B.

Stage 4: Bupropion

If atomoxetine fails, consider a trial of bupropion. Dosing guidelines for bupropion are shown in table C. A generic sustained release form of bupropion is available.

Stage 5: Clonidine

Clonidine would be the final step in the algorithm. Dosing guidelines for clonidine and laboratory tests are noted in table D.

Dosing Guidelines Tables:

A. Stimulants - (Stage 1 and 2)

Methylphenidate immediate-release or IR (Ritalin®)

	35-50 lbs	**51-70 lbs**	**70lbs- 90**	**> 90 lbs**
Week 1-2	2.5 am/noon	5 mg am/noon	10 mg am/noon	10 mg am/noon
Week 2-4	5 mg am/noon	10 mg am/ noon	15 mg am/noon	20 mg am/12 noon
Week 3-6	10 mg am/ noon	15 mg am/noon	20 mg am/ noon	20 mg bid
Week 7	*15 mg bid*	*20 mg bid*	*20 mg bid/tid*	*20 mg bid/tid*

For doses in italics -- monitor for side effects carefully. Add third dose after school if necessary

Methylphenidate extended-release or ER (8 hours)

	35-50 lbs	**51-70 lbs**	**70lbs- 90**	**> 90 lbs**
Week 1-2	Use IR first	20 mg q am	20 mg q am	20 mg q am
Week 2-4	20 mg q am	40 mg q am	40 mg q am	40 mg q am
Week 3-6				*60 mg q am*

Would need to supplemented with p.m. methylphenidate IR if after school dose needed

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Methylphenidate-OROS (Concerta®)

	40-50 lbs	**51-70 lbs**	**70lbs- 90**	**> 90 lbs**
Week 1-2	18 mg q am	18 mg q am	27mg q am	36 mg q am
Week 2-4	27 mg q am	36 mg q am	36 mg q am	54 mg q am
Week 3-6	36 mg q am	54 mg q am	72 mg q am	72-108* mg q am

* adults

Mixed Salts Amphetamine (Adderall®)

	35-50 lbs	**51-70 lbs**	**70lbs- 90**	**> 90 lbs**
Week 1-2	2.5 am	5 mg am	10 mg q m	10 mg q am
Week 2-4	5 mg am	10 mg q am	15 mg q am	20 mg q am
Week 3-6	10 mg q am	15 mg q am	20 mg q am	20 mg q am/ 10 mg q noon
Week 7	*15 mg q am*	*20 mg q am*	*20 mg q am/ 10 mg q noon*	*20 mg q am & 12 noon, max 30 mg bid*

For doses in italics -- monitor for side effects carefully. Split doses if it is wearing off in early afternoon or for am side effects. If dose of >0.4 mg/kg/dose is needed in am, split dose bid

Lisdexamfetamine dimeyslate (Vyvanse®)

	35-50 lbs	**51-70 lbs**	**70lbs- 90**	**> 90 lbs & adults**
Week 1-2	10 mg q am	30 mg am	30 mg q m	30-50 mg q am
Week 2-4	20 mg am	40 mg q am	50 mg q am	70 mg q am
Week 3-6	30 mg q am	60 mg q am	70 mg q am	100 mg q am

B. Atomoxetine (Strattera®)

Children and adolescents < 125 lbs (divide bid)

Weight Range	**Starting Dose (3-7 days)**	**Target Dose**
40-62 lbs	18 mg	25 mg
63-93 lbs	25 mg	40 mg
94-126 lbs	40 mg	60 mg

Adults and adolescents >125 mg (Divide bid)
Day 1: 40 mg Day 3 - 7: 80 mg Maximum dose: 100 mg/day

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C. Bupropion (Wellbutrin®)

Children and Adolescents < 125 lbs

Starting dose: 3 mg/kg/day. Titrate to 6 mg/kg/day or 300 mg/day, whichever is smaller. No single dose should be greater than 150 mg

Adolescents > 125 lbs and adults

Starting dose 100 mg bid, titrate to a maximum of 400 mg/day, divided bid or tid. No single dose should be greater than 150 mg

D. Alpha-agonist (clonidine)

Preadolescent (< 100 lbs	**Clonidine**
Day 1-4	.05 q hs
Day 5-9	.05 q am & hs
Day 10-14	0.5 tid
Day 14 and up	0.5 mg qid

Adolescent (>100 lbs)	**Clonidine**
Day 1-4	.05 q hs
Day 5-9	.1 q hs
Day 10-14	.1 bid
Day 14 and up	.1 tid/qid

Need baseline BP and pulse (standing, lying); repeat at each visit. Reduce dose if patient complains of dizziness, chest pain, palpitations, sedation > 48 Hours.

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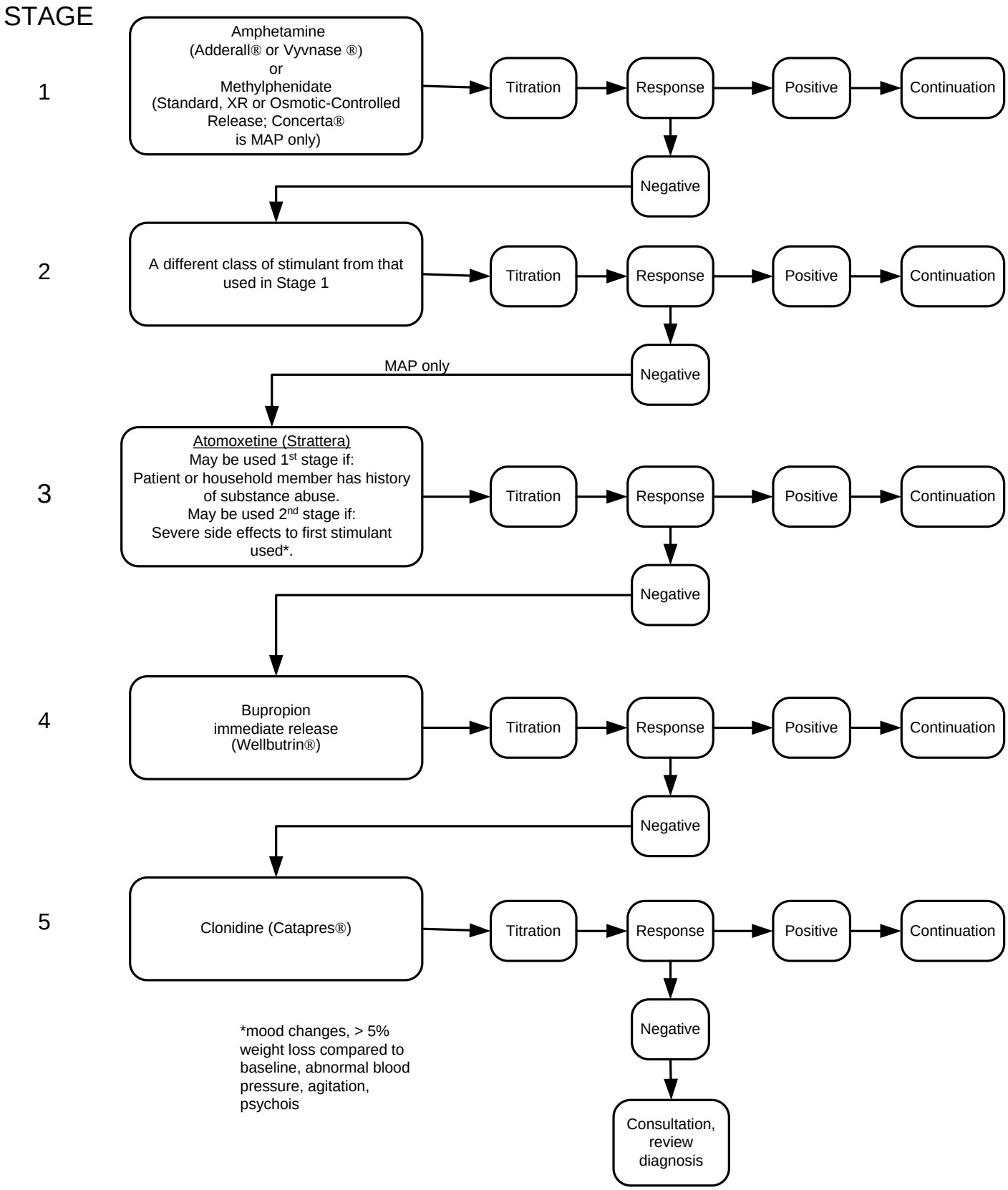

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Special Note on Prescription writing:

The stimulants are Class II controlled substances and require special Texas Department of Public Safety prescription forms. To maximize cost-effectiveness, the University Health System Pharmacies will carry only certain strengths of these drugs. To avoid verbal changes and rewritten prescriptions, it is best to call the pharmacy where the patient will be filling the prescription to determine what they have available. However, unlike the old triplicate prescriptions, pharmacists may now take verbal order changes for the amounts (1/4 or ½) of the tablets. Verbal modifications must be made within 21 days of the date the prescription was written.

Special Alerts from the FDA:

Medications for ADHD: AHA Clarification of Cardiovascular Screening Recommendation - May 2008

In an effort to reduce the rate of sudden cardiac death especially in pediatric patients receiving stimulant medications for the treatment of attention-deficit/hyperactivity disorder (ADHD), the American Heart Association (AHA) has issued a statement in April 2008 recommending that all patients diagnosed with ADHD who may be candidates for stimulant medications have a thorough cardiovascular assessment prior to initiation of drug therapy. The AHA scientific statement was issued by the Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. On May 16, 2008, the AHA issued a clarification of the recommendations due to the language regarding ECG recommendations and subsequent interpretations.

These recommendations are based on the Food and Drug Administration (FDA) reports of serious cardiovascular adverse events (including sudden death) in patients (both children and adults) taking usual doses of stimulant medications. Most of these patients were found to have underlying structural heart disease (eg, hypertrophic obstructive cardiomyopathy). In 2006, these reports prompted the FDA to recommend labeling changes of these medications to include warnings about cardiovascular events and to develop patient medication guides to be distributed with each prescription.

Stimulant medications theoretically increase cardiovascular risk due to potential effects on blood pressure elevation and increased heart rate. These effects have generally been considered clinically insignificant in most children, however, may be detrimental in certain patients with underlying cardiovascular disease. None of the medications have been shown to cause heart conditions or proven to have caused sudden cardiac death.

The committee suggests that patients needing the following ADHD medications receive a thorough cardiovascular assessment: methylphenidate, amphetamine, dextroamphetamine, lisdexamfetamine, atomoxetine, clonidine, guanfacine, desipramine, imipramine, bupropion, and modafinil.

According to the clarified AHA recommendations, this assessment should include a combination of thorough medical history, family history, and physical examination with the intent to identify risk factors for sudden death. Although not mandatory, physicians should consider obtaining an ECG.

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Patients already maintained on ADHD medications should not stop taking their medication. Instead, patients or their caregivers should contact their healthcare provider. It is reasonable that these patients undergo a similar cardiovascular assessment without interruption of therapy.

Press releases and clarified recommendations from the AHA note that the intent of this statement is not to reduce appropriate use of these medications, but to provide physicians with useful tools to identify heart conditions in children with ADHD in order to make more informed prescribing decisions. ECG testing is recommended as one option to be used as part of a combination screening process. They do suggest that a lack of ECG testing should not necessarily mean that treatment not be initiated.

The clarified statement has been endorsed by the American Academy of Patient and Adolescent Psychiatry, the American College of Cardiology, Children and Adults with Attention-Deficit/Hyperactivity Disorder, and the National Initiative for Children's Healthcare Quality.

For more information, refer to:

http://americanheart.mediaroom.com/index.php?s=43&item=422

http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.189473/DC1

http://americanheart.mediaroom.com/index.php?s=43&item=398

http://www.fda.gov/medwatch/safety/2007/safety07.htm

http://www.fda.gov/bbs/topics/NEWS/2007/NEW01568.html

FDA Alerts Reference List

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