

# **Psychotropic Medication Guidelines for Youth in Care with the Indiana Department of Child Services**

**Approved 1/21/16**

**Developed by the Indiana Psychotropic Medication Advisory  
Committee (PMAC), Psychotropic Advisory Subcommittee**

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## **About the Indiana Psychotropic Medication Advisory Committee (PMAC)**

The Indiana Psychotropic Medication Advisory Committee (PMAC) was launched in January, 2013 to review the psychiatric treatment of DCS-involved youth, with a specific focus on psychotropic medication utilization patterns. This committee includes representatives from IUSM Department of Psychiatry, DCS, OMPP, DMHA, pediatricians, social workers, psychologists, pharmacists, child advocates and other identified stakeholders (see 2014 members below; see current, 2016 members below). The PMAC monitors Federal legislation, reviews best-practice guidelines for psychotropic medication use, monitors Indiana prescription patterns, reviews formularies and makes policy recommendations to DCS. Specific responsibilities of the committee include the following:

- Review the literature on psychotropic medication best practice (e.g., AACAP) and provide guidance to DCS, OMPP, IUSM and prescribing providers;
- Provide assistance to DCS in establishing a consultation program for youth in state care who are prescribed psychotropic medications;
- Publish guidelines for the utilization of psychotropic medications among DCS-involved youth, with revisions made on a semi-annual basis, as needed;
- Review DCS policies for requesting and obtaining consent to treat DCS-involved youth with psychotropic medications and make recommendations for change to DCS Permanency and Practice Support Division; and
- Identify non-pharmacologic, evidence-based mental health treatments for DCS-involved youth.

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- II. Mary Margaret Gleason, Helen Link Egger, Graham J. Emslie, Laurence L. Greenhill, Robert A. Kowatch, Alicia F. Lieberman, Joan L. Luby, Judith Owens, Lawrence D. Scahill, Michael S. Scheeringa, Brian Stafford, Brian Wise, Charles H. Zeanah. (2007) Psychopharmacological Treatment for Very Young Children: Contexts and Guidelines. *Journal of the American Academy of Child and Adolescent Psychiatry*, volume 46, issue 12, Pages 1532-1572.

**Introduction:**

In an attempt to provide improved utilization of psychotropic medications and therefore overall mental health care to Indiana's children in the placement and care of the Department of Child Services (DCS), DCS convened a work group in 2013 to lead this effort. To guide Indiana's prescribers, this work group, the Indiana Psychotropic Medication Advisory Committee (PMAC) agreed to adopt the September 2013 version of the *Psychotropic Medication Utilization Parameters for Children and Youth in Foster Care* ("Texas parameters;" TP) developed by the Texas Department of Family and Protective Services and The University of Texas at Austin College of Pharmacy (see Appendix I). To consider the applicability of the Texas parameters, the PMAC tasked its Psychotropic Advisory Subcommittee with a review of the Texas parameters. As a result of this review, the Subcommittee recommended adoption of the Texas parameters with the following modifications/clarifications and additions.

In February, 2015, upon the recommendation of the Indiana Medicaid Mental Health Quality Advisory Committee (MHQAC), the Indiana Medicaid Drug Utilization Review (DUR) Board approved exempting drug therapy regimens, based upon recommendations from the IUSM Department of Psychiatry, from prior authorization (PA). Subsequently, managed care entities (MCEs) administering pharmacy benefits for affected youth agreed to participate in this program and adopted the PA exemption process.

A revision was completed January 2016.

**I. Modifications/Clarifications:****General Principles:**

1. In the state of Indiana, a comprehensive evaluation prior to the use of medications should be performed by a licensed professional *or a qualified professional under the supervision of a licensed professional*.
2. To clarify, a physical examination is not typically completed by a child psychiatrist or necessarily required for the use/start of psychotropic medications (excluding evaluation for extrapyramidal or other movement side effects). If warranted, it is the responsibility of the evaluating mental health professional to refer the child for a physical examination.
3. A standardized trauma assessment (e.g., CANS, Trauma Symptom Checklist) is preferred for clinical assessment of exposure of trauma and maltreatment. For youth with more extensive trauma histories, a comprehensive trauma assessment may be recommended by DCS. The service standard for comprehensive trauma assessments can be found at <http://www.in.gov/dcs/3159.htm>.
4. In addition to the need to identify DSM-5 diagnoses to direct treatment, diagnoses outlined in the relevant version of the International Classification of Diagnoses (e.g., ICD-10) are also appropriate.

5. In addition to diagnoses, benefits/risk, lab findings, adverse events, alternatives, and risks of no treatment, informed consent should also include a discussion of possible medication interactions.
6. If a non-child psychiatrist is treating a child and they are not improving TP recommend referral to be initiated. We would like to clarify that the window for expected improvement for most childhood psychiatric disorders is 3 months.
7. When treating youth with medication for aggression, TP recommend a slow taper with discontinuation every 6 months. To clarify, youth with aggression resulting from any of the following disorders should be given an opportunity for a taper: oppositional defiant disorder, conduct disorder, disruptive mood dysregulation disorder, developmental disabilities and autism spectrum disorder. We would like to further note that such tapers may not be routine in current clinical practice, but they are now highly recommended.

### **Medication-Specific Recommendations**

1. Although short acting alpha agonists for use in the treatment of ADHD and tics are not FDA approved, they remain the recommended first line agents.
2. Tapering antipsychotics in children may require longer than a 4 week period.
3. See Tables for additions
4. Routine lipid screening is recommended to be every year, rather than every 6 months, as outlined in the TP. If abnormal values are detected, more regular monitoring (every 3-6 months) are recommended.
5. Fasting lipids and glucose are recommended to be checked on every pediatric patient prior to starting (or at first contact if medication has already been started) medications known to impact these labs (e.g., antipsychotics).
6. Evaluation of blood pressure, heart rate, weight and height is recommended for every medication monitoring visit and initial evaluation.
7. Clomipramine is only recommended for obsessive compulsive disorder if the child or adolescent has failed two complete trials of serotonin reuptake inhibitors.
8. Due to concerns about the potential for cardiac conduction abnormalities, citalopram should not be prescribed at doses greater than 40 mg daily.
9. Orap should only be used for the treatment of tics if Haldol use was a failure or intolerable.

### **II. Additions:**

#### **General:**

1. Rating scales used to identify response to treatment can be identified in numerous sources. A large number of evidence-based assessment tools are available free of charge for provider use in the DSM-5 ([www.psychiatry.org/practice/dsm/dsm5/online-assessment-measures](http://www.psychiatry.org/practice/dsm/dsm5/online-assessment-measures)).
2. We would like to call special attention to best practices for care of very young children, particularly those laid out in Gleason et al, 2007 (see Appendix II).

3. Given problematic weight gain among youth on psychotropic agents, diet and exercise counseling with referrals to primary care physicians, dieticians and specialized pediatricians are recommended for any child with weight changes, ideally early in the treatment course.
4. Conversely, youth on stimulants who are unable to gain weight at a rate appropriate for age should be assessed for stimulant dosage reduction or discontinuation. Dietary counseling is recommended.

### **Criteria Indicating Need for Further Review of a Child's Clinical Status**

The following situations indicate a need for review of a patient's clinical care. These parameters differ from those set out in the TP and are intended to fully replace page 8 of the 2013 TP. These parameters do not necessarily indicate that treatment is inappropriate, but they do indicate a need for further review.

#### **For a child being prescribed a psychotropic medication, any of the following suggests the need for additional review of a patient's clinical status:**

1. Absence of a complete DSM-V (or comparable ICD-10) diagnosis in the youth's medical record
2. Four (4) or more psychotropic medications prescribed concomitantly
3. Any psychotropic medication prescribed to a child less than one (1) year of age
4. Prescribing of:
  - Stimulants to a child less than three (3) years of age
  - Antipsychotics to a child less than four (4) years of age
  - Antidepressants to a child less than four (4) years of age
  - Mood stabilizers to a child less than four (4) years of age
5. The psychotropic medication dose exceeds usual recommended doses (FDA and/or literature based maximum dosages).
6. The prescribed psychotropic medication is not consistent with the appropriate care for the patient's diagnosed mental disorder or with documented target symptoms usually associated with a therapeutic response to the medication prescribed.
7. Psychotropic polypharmacy (2 or more medications) for a given mental disorder is prescribed before utilizing psychotropic monotherapy.
8. Prescribing of:
  - Two (2) or more concomitant stimulants\*
  - Two (2) or more alpha-2 agonists, including the combination of short- and long-acting agents (i.e. clonidine ER plus clonidine immediate release)
  - Two (2) or more concomitant antidepressants
  - Two (2) or more lithium-based agents
  - Three (3) or more concomitant lithium-based mood stabilizers or other mood stabilizers (e.g., anticonvulsants)

- Two (2) or more antipsychotics
- Three (3) or more sedative-hypnotics
- Two (2) or more benzodiazepines
- Any long acting injectable antipsychotic
- Excessive (2 weeks of 4 or more days with PRN use) or inappropriate (3 or more at once; high dose) PRN medication use

\*The prescription of a long-acting stimulant and an immediate release stimulant of the same chemical entity (e.g., methylphenidate) does not constitute concomitant prescribing.

9. Use medications (in a particular age range, when specified) when no evidence exists to support their use for psychiatric indications:

Stimulants and alternatives

amphetamine aspartate/amphetamine sulfate/dextroamphetamine (< 3 yrs)  
nortriptyline

Antidepressants

isocarboxazid (< 16 yrs)  
phenelzine sulfate (< 13 yrs)  
tranylcypromine sulfate (< 13 yrs)

Antidepressants, SSRIs

paroxetine HCl/mesylate

Antidepressants, TCAs

amitriptyline HCl (< 13 yrs)  
amoxapine (< 16 yrs)  
nortriptyline (< 13 yrs)

Antipsychotics, Typical

thioridazine HCl (< 2 yrs)

Barbiturates

Butisol

Benzodiazepines

chlordiazepoxide HCl (< 6 yrs)

Mood Stabilizers

divalproex sodium (< 10 yrs)  
valproic acid (< 2 yrs)  
valproate sodium (< 2 yrs)  
lamotrigine (< 2 yrs)

### III. Tables:

To address new medications or additional information, the following tables have been added, in order to supplement the tables provided in the TPs. [Abbreviations used in tables: Insufficient evidence=IE; Food and Drug Administration=FDA; NA= Not FDA approved for children or adolescents (i.e., safety and effectiveness in pediatric patients has not been established); milligram = mg]

**Table 1. Newly Approved Antidepressant Agents**

Drug (generic)	Drug (brand)	Initial Dosage	Literature Based Maximum Dosage	FDA Approved Maximum Dosage for Children & Adolescents	Schedule	Black Box Warning(s)	Warnings and Precautions
Vilazidone	Viibryd®	IE	IE	NA	--	--	--
Levomilnacipran	Fetzima®	IE	IE	NA	--	--	--
Vortioxetine	Brintellix®	IE	IE	NA	--	--	--

**Table 2. Long-Acting Injectable Psychotropic Medications**

Drug (generic)	Drug (brand)	Initial Dosage	Literature Based Maximum Dosage	FDA Approved Maximum Dosage for Children and Adolescents	Schedule
Haloperidol decanoate	Haldol® decanoate	50mg <sup>1</sup>	100mg <sup>1</sup>	NA	Monthly
Fluphenazine decanoate	--	IE	IE	NA	IE
Risperidone long-acting injection	Risperdal® Consta®	--	25mg <sup>2</sup>	NA	Every 2 weeks
Paliperidone palmitate	Invega® Sustenna®	--	39mg <sup>3</sup>	NA	Monthly
Olanzapine for extended release injectable suspension	Zyprexa® Relprevv™	IE	IE	NA	IE
Aripiprazole for extended release injectable suspension	Abilify Maintena™	IE	IE	NA	IE
Aripiprazole lauroxil extended-release injectable suspension	Aristada™	IE	IE	NA	IE
Naltrexone for extended release injectable suspension	Vivitrol® (opiate/alcohol use disorders) (see Table 6)	IE	IE	NA	IE

References:

1. Alessi N, Alkhoury I, Fluent T, et al. Haloperidol decanoate in children. *J Am Acad Child Adolesc Psychiatry*. 2001 Aug; 40: 865-6.
2. Fu-I L, Boarati M, Stravogiannis, et al. Use of risperidone long-acting injection to support treatment adherence and mood stabilization in pediatric bipolar patients: a case series. *J Clin Psychiatry*. 2009 Apr; 70: 604-6.
3. Kowalski J, Wink L, Blakenship K. Paliperidone palmitate in a child with autistic disorder. *J Child Adolesc Psychopharmacol*. 2011 Oct; 21: 491-3

Warnings and precautions, including black box warnings are the same as the oral preparations except for a delirium/sedation syndrome (including agitation, anxiety, confusion, disorientation) that has been observed following use of Zyprexa Relprevv.

**Table 3. Sedative-Hypnotics Agents**

Drug (generic)	Drug (brand)	Initial Dosage	Literature Based Max Dosage	FDA Approved Maximum Dosage for Children and Adolescents	Schedule	Black Box
Zolpidem	Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist	≤ 17 years: 0.25mg/kg at bedtime <sup>1</sup>	0.5mg/kg OR 20mg <sup>1</sup>	NA	Nightly	--
Eszopiclone	Lunesta	IE	IE	NA. Failed to demonstrate efficacy in controlled clinical studies of pediatric patients with ADHD associated insomnia.	--	--
Zaleplon	Sonata	IE	IE	NA	--	--
Ramelteon	Rozerem	4mg <sup>1</sup>	8mg <sup>1</sup>	NA	Nightly	--

Warnings and Precautions:

**Adverse Psychiatric Events:** Abnormal thinking and behavioral changes (e.g., aggressiveness, uncharacteristic extroversion, bizarre behavior, agitation, hallucinations, depersonalization, amnesia) may occur unpredictably. Possible worsening of depression (including suicidal thinking) with sedative or hypnotic use in patients with depression. Immediately evaluate any new behavioral sign or symptom.

**Complex Sleep-related Behaviors:** Complex behaviors such as sleep-driving (i.e., driving while not fully awake after ingesting a sedative and hypnotic drug, with no memory of the event), preparing and eating food, making phone calls, or having sex while not fully awake after taking a sedative and hypnotic drug, and usually with no memory of the event, reported.

**Withdrawal Effects:** Rapid dosage reduction or abrupt discontinuance of sedatives or hypnotics has resulted in signs and symptoms of withdrawal.

**Abuse Potential:** Abuse potential similar to that of benzodiazepines and related hypnotics.

**Sensitivity Reactions:** Angioedema involving the tongue, glottis, or larynx reported rarely following initial or subsequent doses of sedative and hypnotic drugs, including zolpidem. Some patients experienced additional symptoms (e.g., dyspnea, closing of the throat, nausea and vomiting [suggestive of anaphylaxis]). Some individuals required medical treatment in an emergency department. Angioedema reported during post-marketing surveillance.

**Endocrine:** Ramelteon has been associated with an effect on reproductive hormones in adults, e.g., decreased testosterone levels and increased prolactin levels. It is not known what effect chronic or even chronic intermittent use of ramelteon may have on the reproductive axis in developing humans. The same concerns may apply to melatonin, given but little research in humans is available at this time.

References:

1. Zolpidem monograph. Lexi-Comp™, Pediatric & Neonatal Lexi-Drugs Online™, Hudson, Ohio: Lexi-Comp, Inc.; December 30, 2013.
2. Stigler K, Posey D, McDougle C. Ramelteon for insomnia in two youths with autistic disorder. *J Child Adolesc Psychopharmacol.* 2006 Oct; 16: 631-6.

**Table 4. Other Antipsychotics.**

Generic name	Trade name	Initial dosage	Maximum dosage	FDA max	Schedule	Black Box	Warnings and Precautions
<b>Brexpiprazole</b>	Rexulti	IE	IE	IE	NA	Suicidal thinking/behavior in ≤24 years of age Mortality in Elderly Patients with dementia	same
<b>Cariprazine</b>	Vraylar	IE	IE	IE	NA	Mortality in Elderly Patients with dementia	same
<b>Chlorpromazine</b>	Thorazine	2 mg/kg/d	500 mg/d	500 mg/d	Q 6-8 hr	Mortality in Elderly Patients with dementia	Anticholinergic Hypotension Tardive dyskinesia NMS Leukopenia QT changes
<b>Thioridazine</b>	Mellaril	0.5 mg/kg/d	3mg/kg/d	800 mg	TID	QT changes Mortality in Elderly Patients with dementia	Tardive Dyskinesia NMS Leukopenia
<b>Haloperidol</b>	Haldol	0.05 mg/kg/d	0.15 mg/kg/d	6 mg	B-Tid	Mortality in Elderly Patients with dementia	QT changes Tardive Dyskinesia NMS Leukopenia
<b>Trifluoperazine</b>	Stelazine	1 mg	15 mg		Q-BID	same	same

Loxapine	Loxitane	10 mg	250 mg/d			same	same
Pimozide	Orap	0.05 mg/kg/d	10 mg	10 mg	QDay		same

Notes:

- Haloperidol label states “Pediatric Use- Safety and effectiveness in pediatric patients have not been established” but goes on to give recommendations for children from 3-12 years.
- Trifluoperazine is labeled for “Children, ages 6 to 12, who are hospitalized or under close supervision.”
- Loxapine-Very limited data on use in children; Label has no information on children. An OVID search of “loxapine & children” found only one positive case report 5 mg tid is positive in a child who had dystonia on Haldol, elevated AST on risperidone & olanzapine, no effect of quietapine by history( J Child Adolesc Psychopharm V16 2006, pp 639-634) and one letter to the editor about an 8 year old boy who overdosed on 15 ml when prescribed 0.6 ml. Dose listed above is from table on p 233 of Wolraich et al. Developmental-Behavioral Pediatrics: Evidence and Practice, 2008.
- Pimozide dosage in children based on a 24 week open label study of 36 children ages 2-12 with Tourette disorder. Pimozide prolongs QTc significantly. Pimozide blood levels are increased by dapoxetine, vilazodone, vortioxetine, and the SSRIs, as well as non-psychotropic medications such as mycin antibiotics (i.e. Zpak) and ketoconazole.
- Clinical Pharmacology: “Thioridazine has not been evaluated for use in children under the age of 2 years. Thioridazine should not be used to treat conditions in children for which specific pediatric dosages have not been established. There is no known indication for use of thioridazine in infants or neonates.”
- Older antipsychotics are no longer used commonly in children. Extrapyramidal movement disorders, QT changes and the increasing evidence base for newer “atypical antipsychotics” have much diminished their use. None are labeled for use in children. Newer textbooks frequently do not list them in in tables of treatment of children with disabilities. FDA labeling is often old without consideration of more recent standards.

**Table 5. Tricyclic Antidepressants**

Drug (generic)	Drug (brand)	Initial Dose	Lit. based max. dosage	FDA- Approved Max Dosage for Children and Adoles.	Schedule	Patient Monitoring	Black Box Warning	Warnings and Precautions
Amitriptyline (for depression)	Elavil	10 mg TID	IE	150mg daily (for 12 and above; not recommended in <12)	Three times daily	Pulse ECG	Suicidality	<ul style="list-style-type: none"> <li>•Use in combination with MAOIs</li> <li>•Suicidal ideation</li> <li>•Activation of mania/</li> </ul>

								<ul style="list-style-type: none"> <li>hypomania</li> <li>•Lowers seizure threshold</li> <li>•Discontinuation syndrome</li> <li>•Caution with cardiac disease</li> </ul>
Clomipramine (for OCD) 10 and older	Anafranil	25 mg daily	IE	3 mg/kg/day or 200 mg, whichever is smaller	May give as single qHS dose once tolerated	Pulse ECG	See amitriptyline	See amitriptyline
Protriptyline (for depression)	Vivactil	5 mg TID		60 mg daily (for 12 and above?)	Three to four times daily	Pulse ECG	See amitriptyline	See amitriptyline
Imipramine (in children, efficacy established for nocturnal enuresis only)	Tofranil	30 mg daily for teens	IE	2.5 mg/kg/day in children; doses above 100 mg daily in teens "generally not necessary"	Divided doses	Pulse ECG	See amitriptyline	<ul style="list-style-type: none"> <li>See amitriptyline</li> <li>•Methylphenidate raises blood level</li> <li>•Imipramine may block clonidine effect</li> </ul>
Desipramine	Norpramine	25 mg	IE	Usual maximum 100 mg daily; up to 150 mg in more severely ill	Daily dose	Pulse ECG	See amitriptyline	See amitriptyline and imipramine

**Table 6. Medications used to treat substance use disorders**

Drug (generic)	Drug (brand)	Initial Dose	Lit. based max. dosage	FDA-Approved Max Dosage for Children and Adoles.	Schedule	Patient Monitoring	Black Box Warning	Warnings and Precautions
Naltrexone	Vivitrol (IM) Or orally dosed naltrexone (PO; revia)	380 mg (IM) or 25 mg (PO)	IE	None (FDA approved in adults for treatment of alcohol and opioid use disorders)	Once monthly (IM) and once-twice daily (PO)	Urine drug screen (must be abstinent for 7 days) Liver functions	None	<ul style="list-style-type: none"> <li>•can precipitate severe opioid withdrawal</li> <li>•Dose related hepatotoxicity</li> </ul>
Buprenorphine/naloxone	Suboxone; Subutex; Zubsolv; Bunavail	2mg/.5	IE	24mg/6mg (FDA approved for treatment of opioid use disorder in 16 and older)	Complex induction protocol; See package insert	W/drawal signs Liver functions	None	<ul style="list-style-type: none"> <li>•Requires waiver from DEA to prescribe</li> <li>•Risk of diversion and misuse</li> <li>•Lethal in overdose</li> </ul>

<b>N-acetyl cysteine</b>	none	600 mg	IE	None	Twice daily	None	None	Can cause hypersensitivity reaction, nausea, wheezing
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While no medication is FDA approved to treat substance use disorders in adolescents younger than 16, there is a pressing clinical need to judiciously use such medications, at times. A small number of case reports and clinical trials suggest that each of these medications can be efficacious when used appropriately in adolescents, while no research supports their use in children.

**Table 7. New Stimulant Preparations**

<b>Drug (generic)</b>	<b>Drug (brand)</b>	<b>Initial Dose</b>	<b>Lit. based max. dosage *</b>	<b>FDA- Approved Max Dosage for Children and Adoles.</b>	<b>Schedule</b>	<b>Patient Monitoring</b>	<b>Black Box Warning</b>	<b>Warnings/Precautions &amp; Additional Info</b>
<b>Methylphenidate</b>	Aptensio XR (approved 04/17/2015)	10mg daily	60mg daily	60mg daily	Once daily	Same as other methylphenidate preparations	High potential for abuse and dependence	Approved for children 6 years and older May sprinkle capsules on applesauce or swallow whole
<b>Methylphenidate</b>	Quillivant XR	20mg daily	60mg daily	60mg daily	Once daily	Same as other methylphenidate preparations	High potential for abuse and dependence	Approved for children 6 years and older Oral suspension
<b>Methylphenidate</b>	QuilliChew ER (approved 12/04/2015)	20mg daily	60mg daily	60mg daily	Once daily	Same as other methylphenidate preparations	High potential for abuse and dependence	Approved for children 6 years and older Cherry flavored chewable tablets
<b>Dextroamphetamine sulfate</b>	Zenzedi	Age 3-5: 2.5mg/day Age ≥6: 5mg once or twice daily		Age 3-5: 40mg/day Age ≥6: 40mg/day	Once or twice daily; 2 <sup>nd</sup> dose should be administered at 4-6 hours interval	Same as other dextroamphetamine products	High potential for abuse and dependence	Immediate release tablets

\*As these are simply new preparations of long established medications, the literature based maximum dose is specific for the product itself, and not the compound.

**Table 8. Literature-based ADHD Medication Dosage by Weight**

<b>Medication</b>	<b>Mg/kg/day</b>
<b><i>Stimulants</i></b>	
Dexmethylphenidate	0.5-1.0
Dextroamphetamine	0.3-1.0
Mixed amphetamine salts	0.5-1.5
Methylphenidate	1.0-2.0
<b><i>Non-stimulants</i></b>	
Atomoxetine	0.5-1.4
Clonidine	0.003-0.010
Guanfacine	0.015-0.05

Reference

Spencer TJ, Biederman J, Wilens TE. Medications used for Attention-Deficit/Hyperactivity Disorder. In Dulcan's Textbook of Child and Adolescent Psychiatry, Second Edition, ed. Mina K. Dulcan. American Psychiatric Association Publishing, 2016: 711-726.

# Psychotropic Medication Utilization Parameters for Children and Youth in Foster Care



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- ❖ *Texas Medical Association*

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*September 2013*

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# Psychotropic Medication Utilization Parameters for Children and Youth in Foster Care

## Introduction and General Principles

The use of psychotropic medications by children and youth is an issue confronting parents, other caregivers, and health care professionals across the United States. Children and youth in foster care, in particular, have multiple needs, including those related to emotional or psychological stress. They typically have experienced abusive, neglectful, serial or chaotic caretaking environments. Birth family history is often not available. These children often present with a fluidity of different symptoms over time reflective of past traumatic events that may mimic many psychiatric disorders and result in difficulties with attachment, mood regulation, behavioral control, and other areas of functioning. Establishment of rapport may be difficult. These multiple factors serve to complicate diagnosis. Foster children may reside in areas of the state where mental health professionals such as child psychiatrists are not readily available. Similarly, caregivers and health providers may be faced with critical situations that require immediate decisions about the care to be delivered. For these and other reasons, a need exists for treatment guidelines and parameters regarding the appropriate use of psychotropic medications for children and youth in foster care.

*Because of the complex issues involved in the lives of foster children, it is important that a comprehensive evaluation be performed before beginning treatment for a mental or behavioral disorder. Except in the case of an emergency, a child should receive a thorough health history, psychosocial assessment, mental status exam, and physical exam before prescribing a psychotropic medication.* The physical assessment should be performed by a physician or another healthcare professional qualified to perform such an assessment. It is recog-

nized that in some emergency situations, it may be in the best interest of the child to prescribe psychotropic medications before a physical exam can actually be performed. In these situations, a thorough health history should be performed to assess for significant medical disorders and past response to medications, and a physical evaluation should be performed as soon as possible. A thorough psychosocial assessment should be performed by an appropriately qualified mental health clinician (masters or doctoral level), a psychiatrist/child psychiatrist, or a primary care physician with experience in providing mental health care to children and youth. The child's symptoms and functioning should be assessed across multiple domains, and the assessment should be developmentally age appropriate. It is very important that information about the child's history, including history of trauma and current functioning be made available to the treating physician in a timely manner, either through an adult who is well-informed about the child or through a comprehensive medical record. It is critical to meet the individual needs of patients and their families in a culturally competent manner. This indicates a need to address communication issues as well as differences in perspective on issues such as behavior and mental functioning. Interpretation of clinical symptoms and decisions concerning treatment should, whenever possible, be informed by the child's developmental history of trauma, neglect or abuse and the timing of these stressors. At present there are no biomarkers to assist with the diagnosis of mental disorders, and imaging (e.g., MRI) and other tests (e.g., EEG) are not generally helpful in making a clinical diagnosis of a mental disorder.

*The role of non-pharmacological interven-*

*tions should be considered before beginning a psychotropic medication, except in urgent situations such as suicidal ideation, psychosis, self-injurious behavior, physical aggression that is acutely dangerous to others, or severe impulsivity endangering the child or others; when there is marked disturbance of psychophysiological functioning (such as profound sleep disturbance), or when the child shows marked anxiety, isolation, or withdrawal.*

Given the history of trauma, unusual stress and change in environmental circumstances associated with being a child in foster care, psychotherapy should generally begin before or concurrent with prescription of a psychotropic medication. Referral for trauma-informed, evidence based psychotherapy should be considered when available and appropriate. Patient and caregiver education should be provided about the condition to be treated, treatment options (non-pharmacological and pharmacological), treatment expectations, and potential side effects that may occur during the prescription of psychotropic medications.

It is recognized that many psychotropic medications do not have Food and Drug Administration (FDA) approved labeling for use in children. The FDA has a statutory mandate to determine whether pharmaceutical company sponsored research indicates that a medication is safe and effective for those indications that are listed in the approved product labeling. The FDA assures that information in the approved product labeling is accurate, and limits the manufacturer's marketing to the information contained in the approved labeling.

*The FDA does not regulate physician and other health provider practice. In fact, the FDA has stated that it does "not limit the manner in which a practitioner may*

*prescribe an approved drug.” Studies and expert clinical experience often support the use of a medication for an “off-label” use.* Physicians should utilize the available evidence, expert opinion, their own clinical experience, and exercise their clinical judgment in prescribing what is best for each individual patient.

### **Role of Primary Care Providers**

Primary care providers play a valuable role in the care of youth with mental disorders. Not only are they the clinicians most likely to initially interact with children who are in distress due to an emotional or psychiatric disorder, inadequate numbers of child psychiatrists are available to meet all children’s mental health needs. Primary care clinicians are in an excellent position to perform screenings of children for potential mental disorders, and they should be able to diagnose and treat relatively straightforward situations such as uncomplicated ADHD, anxiety, or depression. Primary care providers should provide advice to youth in foster care and their care givers about handling feelings and behaviors, recognizing the need for help, making decisions regarding healthy life styles, and the available treatments for childhood mental disorders. As always, consideration should be given regarding the need for referral for counseling, psychotherapy, or behavioral therapy. Primary care providers vary in their training, clinical experience, and confidence to address mental disorders in children. Short courses and intensive skills oriented seminars may be beneficial in assisting primary clinicians in caring for children with mental disorders. Active liaisons with child psychiatrists who are available for phone consultation or referral can be beneficial in assisting primary care clinicians to meet the mental health needs of children. A useful toolkit (American Academy of Pediatrics Task Force on Mental Health Addressing Mental Health Care in Primary Care: A Clinicians Toolkit) can be found at: [www.aap.org/pcorss/demos/mht.html](http://www.aap.org/pcorss/demos/mht.html)

### **General principles regarding the use of psychotropic medications in children include:**

- A DSM-5 psychiatric diagnosis should be made before the prescribing of psychotropic medications.
- Clearly defined target symptoms and treatment goals for the use of psychotropic medications should be identified and documented in the medical record at the time of or before beginning treatment with a psychotropic medication. These target symptoms and treatment goals should be assessed at each clinic visit with the child and caregiver in a culturally and linguistically appropriate manner. Whenever possible, standardized clinical rating scales (clinician, patient, primary caregiver, teachers, and other care providers) or other measures should be used to quantify the response of the child’s target symptoms to treatment and the progress made toward treatment goals.
- In making a decision regarding whether to prescribe a psychotropic medication in a specific child, the clinician should carefully consider potential side effects, including those that are uncommon but potentially severe, and evaluate the overall benefit to risk ratio of pharmacotherapy.
- Except in the case of an emergency, informed consent should be obtained from the appropriate party(s) before beginning psychotropic medication. Informed consent to treatment with psychotropic medication entails diagnosis, expected benefits and risks of treatment, including common side effects, discussion of laboratory findings, and uncommon but potentially severe adverse events. Alternative treatments, the risks associated with no treatment, and the overall potential benefit to risk ratio of treatment should be discussed.
- Youth, as well as caregivers, should be involved in decision-making about treatment, in accordance with their developmental level.
- During the prescription of psychotropic medication, the presence or absence of medication side effects should be documented in the child’s medical record at each visit.
- Appropriate monitoring of indices such as height, weight, blood pressure, or other laboratory findings should be documented.
- Monotherapy regimens for a given disorder or specific target symptoms should usually be tried before polypharmacy regimens. While the goal is to use as few psychotropic medications as can be used to appropriately address the child’s clinical status, it is recognized that the presence of psychiatric comorbidities may affect the number of psychotropic medications that are prescribed. When polypharmacy regimens are needed, it should occur in a systematic orderly process, accompanied by on-going monitoring, evaluation, and documentation. The treatment goal is to minimize polypharmacy while maximizing therapeutic outcomes.
- Medications should be initiated at the lower end of the recommended dose range and titrated carefully as needed.
- Only one medication should be changed at a time, unless a clinically appropriate reason to do otherwise is documented in the medical record. (Note: starting a new medication and beginning the dose taper of a current medication is considered one medication change).
- The use of “prn” or as needed prescriptions is discouraged. If they are used, the situation indicating need for the administration of a prn medication should be clearly indicated as well as the maximum number of prn doses in a day and a week. The frequency of administration should be monitored to assure that these do not become regularly scheduled medications.
- The frequency of clinician follow-up

with the patient should be appropriate for the severity of the child's condition and adequate to monitor response to treatment, including: symptoms, behavior, function, and potential medication side effects. At a minimum, a child receiving psychotropic medication should be seen by the clinician at least once every ninety days.

- The potential for emergent suicidality should be carefully evaluated and monitored, particularly in depressed children and adolescents as well as those initiating antidepressants, those having a history of suicidal behavior or deliberate self-harm and those with a history of anxiety or substance abuse disorders.
- If the prescribing clinician is not a child psychiatrist, referral to or consultation with a child psychiatrist, or a general psychiatrist with significant experience in treating children, should occur if the child's clinical status has not experienced meaningful improvement within a timeframe that is appropriate for the child's clinical response and the medication regimen being used.
- Before adding additional psychotropic medications to a regimen, the child should be assessed for adequate medication adherence, accuracy of the diagnosis, the occurrence of comorbid disorders (including substance abuse and general medical disorders), and the influence of psychosocial stressors.
- If a medication has not resulted in improvement in a child's target symptoms (or rating scale score), discontinue that medication rather than adding a second medication to it.
- If a medication is being used in a child for a primary target symptom of aggression associated with a DSM-5 nonpsychotic diagnosis (e.g., conduct disorder, oppositional defiant disorder, intermittent explosive disorder), and the behavior disturbance has been in remission for six months, then seri-

ous consideration should be given to slow tapering and discontinuation of the medication. If the medication is continued in this situation, the necessity for continued treatment should be evaluated and documented in the medical record at a minimum of every six months.

- The clinician should clearly document care provided in the child's medical record, including history, mental status assessment, physical findings (when relevant), impressions, adequate laboratory monitoring specific to the drug(s) prescribed at intervals required specific to the prescribed drug and potential known risks, medication response, presence or absence of side effects, treatment plan, and intended use of prescribed medications.

### *Use of Psychotropic Medication in Preschool Age Children*

The use of psychotropic medication in young children of preschool ages is a practice that is limited by the lack of evidence available for use of these agents in this age group. The Preschool Psychopharmacology Working Group (PPWG) published guidelines (Gleason 2007) summarizing available evidence for use of psychotropic medications in this age group. The PPWG was established in response to the clinical needs of preschoolers being treated with psychopharmacological agents and the absence of systematic practice guidelines for this age group, with its central purpose to attempt to promote an evidence-based, informed, and clinically sound approach when considering medications in preschool-aged children.

The PPWG guidelines emphasize consideration of multiple different factors when deciding on whether to prescribe psychotropic medications to preschool-aged children. Such factors include the assessment and diagnostic methods utilized in evaluating the child for psychiatric symptoms/illness, the current state of knowledge regarding the impact of psychotropic medication use on

childhood neurodevelopmental processes, the regulatory and ethical contexts of use of psychotropic medications in small children (including available safety information and FDA status), and the existing evidence base for use of psychotropic medication in preschool aged children.

The publication includes specific guidelines and algorithm schematics developed by the PPWG to help guide treatment decisions for a number of psychiatric disorders that may present in preschool-aged children, including Attention-Deficit Hyperactivity Disorder, Disruptive Behavioral Disorders, Major Depressive Disorder, Bipolar Disorder, Anxiety Disorders, Post-Traumatic Stress Disorder, Obsessive-Compulsive Disorder, Pervasive Developmental Disorders, and Primary Sleep Disorders.

The working group's key points and guidelines are similar to the general principles regarding the use of psychotropic medication in children already detailed in this paper. However, the working group's algorithms put more emphasis on treating preschool-aged children with non-psychopharmacological interventions (for up to 12 weeks) before starting psychopharmacological treatment, in an effort to be very cautious in introducing psychopharmacological interventions to rapidly developing preschoolers. The working group also emphasizes the need to assess parent functioning and mental health needs, in addition to training parents in evidence-based behavior management, since parent behavior and functioning can have a large impact on behavior and symptoms in preschool-aged children.

### *Therapeutic Controversies*

#### *Antipsychotic selection*

Significant controversy exists regarding the use of 2nd generation versus 1st generation antipsychotics. Most of the data supporting no difference in efficacy between these two groups of antipsychotics comes from studies conducted in chronically ill adults with schizophrenia. Most of the controlled studies of the use of antipsychotics to treat

behavioral disorders in children have been performed with 2nd generation antipsychotics, with the most evidence for risperidone. The only study comparing a 1st generation antipsychotic versus 2nd generation antipsychotics in youth was conducted in individuals with early onset schizophrenia. The 1st generation agent used in this study was molindone, an antipsychotic, no longer on the market, that is known to be weight neutral or cause weight loss in adults. It is unknown how the results of this study can be extrapolated to the treatment of children with other first generation antipsychotics.

Antipsychotics vary with regard to their side effect profiles, and side effects are the primary basis for individual medication choice. Second generation antipsychotics are prone to cause significant weight gain in many children, but the risk for the development of weight gain in youth varies significantly among the 2nd generation agents. In a systematic review (De Hert 2011) of 31 short-term randomized controlled trials including 3595 youth, the average weight gain was olanzapine (3.78 kg, 3.4 weeks), risperidone (2.37 kg, 7.5 weeks) quetiapine (2.15 kg, 4.5 weeks), aripiprazole (1.04 kg, 6.1 weeks), and ziprasidone (0.49 kg, 5.3 weeks). Significant weight gain was more common in children with autistic disorder who were younger and more likely first-time antipsychotic users. In addition, the most significant effects on glucose and lipids are associated with the 2nd generation antipsychotics known to cause the largest weight gain. Because of the risk of obesity and metabolic dysfunction associated with some of the 2nd generation antipsychotics, particularly olanzapine, clinicians should consider being proactive and implement diet counseling and exercise programs at the same time that antipsychotics are initiated.

First generation antipsychotics are prone to causing extrapyramidal side effects. In particular, youth are especially susceptible to developing acute dystonic reactions from 1st generation antipsychotics. Similarly, 1st generation antipsychotics pose a higher risk for the development of tardive dyskinesia in chronically treated individuals. If antipsy-

chotics are indicated, the clinician should carefully evaluate the individual needs of the child, actively engage the family in decision-making, evaluate overall benefit to risk ratio, and when indicated, choose the antipsychotic that the clinician thinks will be best tolerated by that child.

#### *Psychotropic medication choice in acute mania*

Traditionally, because of a lack of research, clinicians have used the same medications to treat mania associated with bipolar disorder in children and adolescents as are used in adults. Recently studies addressing the treatment of mania and mixed mania in children and adolescents have been conducted. The Treatment of Early Age Mania (TEAM) study (Geller 2012) evaluated the relative efficacy and tolerability of risperidone, lithium, and divalproex in 279 medication naïve children and adolescents with either mania or mixed mania. Risperidone was superior in efficacy to either lithium or divalproex. The discontinuation rate was higher with lithium, suggesting better tolerability with risperidone. However, risperidone did have significant adverse effects including weight gain, BMI increase, and hyperprolactinemia.

#### *Depression, Suicidality, and Antidepressants*

In October 2003, the FDA released a public health advisory alerting health care professionals to reports of suicidality (suicidal verbalizations and suicidal behaviors) in clinical trials of antidepressants in pediatric populations. These reports provided the impetus for a FDA meta-analytic review of short-term clinical trials of antidepressants in children and adolescents. These analyses involved review, assessment, and reclassification of over 400 case descriptions. This review ultimately resulted in findings of an increased risk of suicidality during the first few weeks of antidepressant treatment. The FDA responded by issuing a black box warning in October 2004. The black box warning describes 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 analyses was about 4% for those youth receiving antidepressants compared with 2% on placebo. It is important to note that no completed suicides (i.e., deaths) were reported in any of these trials.

The mortality risk of depression is from suicide. Other major suicide risk factors that should be assessed include: anxiety, substance abuse, and conduct disorders, life stressors (such as legal or disciplinary/school problems), interpersonal losses, 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, hopelessness and cognitive distortions. All youth with depression should be monitored carefully for the potential presence of suicidal thoughts or behaviors. This should occur at the time of initial clinical assessment and upon each visit follow-up until depression is no longer present. Assessment of suicidality should include asking questions about ideation and frequency, plans, intention, means, and potential dangerousness. More frequent visits, combined with follow-up calls as necessary, should be considered along with appropriate review of safety plans. It is noteworthy that in one study, the concomitant use of cognitive behavioral therapy was shown to decrease the incidence of suicidality associated with SSRI use.

#### *Stimulants and growth*

Parents and caregivers are often concerned about the possibility that stimulants may adversely affect growth. This is largely related to the fact that, at least short term, stimulants decrease appetite. Although data from different studies are mixed, results from the Multimodal Treatment of ADHD (MTA) study, indicate that weight loss occurred during the first 3-4 months of treatment, but this was followed by a resumption of weight increase. The rate of growth in height decreased by about 1-3 cm/year over the first 1-3 years of medication treatment. These decreases in height were only seen in the youth who were adherent with their stimulant medications. Although both advantages and disadvantages

es are associated with medication holidays or vacations, this has been suggested as one mechanism to minimize potential effects on growth. It is questionable whether the use of stimulants has any effect on ultimate adult height (Swanson 2008; Vitello 2008)

#### *Stimulants and cardiovascular side effects*

Both stimulants and atomoxetine cause small but statistically significant increases in blood pressure and pulse rate. However, it is unclear whether these changes are clinically significant. Although case reports of sudden death in children taking stimulants have been reported, a causal link has not been proven. A large cohort study using data from a 5-state Medicaid database [1999-2003] and the 14-state HealthCore Integrated Research Database [2001-2006] with 241,417 incident users found no statistically significant difference between incident users and nonusers in the rate of sudden death, ventricular arrhythmia, or death from any cause. One theory is that underlying cardiac disorders such as serious structural abnormalities, cardiomyopathies, serious heart rhythm disturbances, or other serious cardiac problems may place children at increased risk of sudden death when stimulants are administered. The clinician should conduct a careful history of the child and the family regarding potential heart problems. A thorough physical exam should also be conducted. If the history and physical provide suspicion of a cardiac problem, then an electrocardiogram should be considered before beginning a stimulant. Although not routinely required, if the child has a known history of a cardiac problem, then a cardiology consult should be considered before beginning a stimulant. (Cooper 2011, Correll 2011, Perrin 2008, Skelleman 2011).

### ***Distinguishing between Levels of Warnings Associated with Medication Adverse Effects***

Psychotropic medications have the potential for adverse effects, some that are treatment-limiting. Some adverse effects are detected prior to marketing, and are included in

product labeling provided by the manufacturers. When looking at product labeling, these adverse effects will be listed in the "Warnings and Precautions" section. As well, the "Adverse Reactions" section of the product labeling will outline those adverse effects reported during clinical trials, as well as those discovered during post-marketing evaluation. Many tertiary drug information resources also report information regarding common adverse effects and precautions for use with psychotropic medications.

At times, post-marketing evaluation may detect critical adverse effects associated with significant morbidity and mortality. The Food and Drug Administration (FDA) may require manufacturers to revise product labeling to indicate these critical adverse effects. If found to be particularly significant, these effects are demarcated by a black box outlining the information at the very beginning of the product labeling, and have, in turn, been named black box warnings. Black box warnings are the strongest warning required by the FDA. It is important for clinicians to be familiar with all medication adverse effects, including black box warnings, in order to appropriately monitor patients and minimize the risk of their occurrence.

The FDA has in recent years taken additional measures to try and help patients avoid serious adverse events. New guides called Medication Guides have been developed, and are specific to particular drugs and drug classes. Medication Guides advise patients and caregivers regarding possible adverse effects associated with classes of medications, and include precautions that they or healthcare providers may take while taking/prescribing certain classes of medications. FDA requires that Medication Guides be issued with certain prescribed drugs and biological products when the Agency determines that certain information is necessary to prevent serious adverse effects, that patient decision-making should be informed by information about a known serious side effect with a product, or when patient adherence to directions for the use of a product are essential to its effectiveness. During the drug distribution process, if a Medication Guide has been developed for a

certain class of medications, then one must be provided with every new prescription and refill of that medication.

Copies of the Medication Guides for psychotropic medications can be accessed on the FDA website at:

<http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm>

### ***Usual Recommended Doses of Common Psychotropic Medications***

The attached medication charts are intended to reflect usual doses and brief medication information for commonly used psychotropic medications. The preferred drug list of medications potentially prescribed for foster children is the same as for all other Texas Medicaid recipients.

These are intended to serve as a guide for clinicians. The tables are not intended to serve as comprehensive drug information references or a substitute for sound clinical judgment in the care of individual patients, and individual patient circumstances may dictate the need for the use of higher doses in specific patients. In these cases, careful documentation of the rationale for the higher dose should occur, and careful monitoring and documentation of response to treatment should be observed.

Not all medications prescribed by clinicians for psychiatric diagnoses in children and adolescents are included below. However, in general, medications not listed do not have adequate efficacy and safety information available to support a usual maximum dose recommendation.

**See Psychotropic Medication Tables beginning on page 14.**

## Criteria Indicating Need for Further Review of a Child's Clinical Status

The following situations indicate a need for review of a patient's clinical care. These parameters do not necessarily indicate that treatment is inappropriate, but they do indicate a need for further review.

For a child being prescribed a psychotropic medication, any of the following suggests the need for additional review of a patient's clinical status:

1. Absence of a thorough assessment for the DSM-5 diagnosis(es) in the child's medical record
  2. Four (4) or more psychotropic medications prescribed concomitantly (side effect medications are not included in this count)
  3. Prescribing of:
    - Two (2) or more concomitant stimulants \*
    - Two (2) or more concomitant alpha agonists
    - Two (2) or more concomitant antidepressants
    - Two (2) or more concomitant antipsychotics
    - Three (3) or more concomitant mood stabilizers
- \* The prescription of a long-acting stimulant and an immediate release stimulant of the same chemical entity (e.g., methylphenidate) does not constitute concomitant prescribing.
- Note: When switching psychotropics, medication overlaps and cross taper should occur in a timely fashion, generally within 4 weeks.
4. The prescribed psychotropic medication is not consistent with appropriate care for the patient's diagnosed mental disorder or with documented target symptoms usually associated with a therapeutic response to the medication prescribed.
  5. Psychotropic polypharmacy (2 or more medications) for a given mental disorder is prescribed before utilizing psychotropic monotherapy.
  6. The psychotropic medication dose exceeds usual recommended doses (FDA and/or literature based maximum dosages).
  7. Psychotropic medications are prescribed for children of very young age, including children receiving the following medications with an age of:
    - Stimulants: Less than three (3) years of age
    - Alpha Agonists: Less than four (4) years of age
    - Antidepressants: Less than four (4) years of age
    - Antipsychotics: Less than four (4) years of age
    - Mood Stabilizers: Less than four (4) years of age
  8. Prescribing by a primary care provider who has not documented previous specialty training for a diagnosis other than the following (unless recommended by a psychiatrist consultant):
    - Attention Deficit Hyperactive Disorder (ADHD)
    - Uncomplicated anxiety disorders
    - Uncomplicated depression
  9. Antipsychotic medication(s) prescribed continuously without appropriate monitoring of glucose and lipids at least every 6 months.

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**Committee Members Disclosures:** Since September 1, 2007, the authors below disclose the following financial relationships:

Dr. Allison has served as a member of the speakers' bureaus for Watson Pharmaceuticals, Novartis, and Abbott Pharmaceuticals, and he has received grant support through his employer institution from BIPi, Bristol Myers Squibb, Forest, Glaxo Smith Kline, Juergen, Novartis, Orexigen, and Pfizer Pharmaceuticals.

Dr. Crismon has received grant support through his employer institution from Shire Pharmaceuticals. He has served as an expert witness for the U.S. Department of Justice.

Dr. Kratochvil has received royalties from Oxford Press, and through his employer institution he has received support for serving as a consultant for AstraZeneca, Abbott, Lilly, Pfizer, Quintiles, and Theravance. He has received grant support through his employer institution from Abbott, AstraZeneca, Forest, Lilly, Pfizer, Seaside, and Shire Pharmaceuticals, and through his employer institution he has received support for serving on the Data Safety Monitoring Boards for Otsuka, Pfizer and Seaside Pharmaceuticals.

Dr. Lopez holds stock in Lilly, Merck, Proctor & Gamble, and Pfizer Pharmaceuticals.

Dr. Pliszka has received speaking honoraria from Janssen/Ortho McNeil, he has served as a consultant for Shire Pharmaceuticals, and he has served as an expert witness for Eli Lilly Pharmaceuticals. He has received research grants through his employer institution from Janssen/Ortho McNeil and Shire Pharmaceuticals.

The other members of the working group do not have any financial relationships to disclose.

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## Stimulants (for treatment of ADHD)

Drug (generic)	Drug (brand)+	Initial Dosage	Literature Based Maximum Dosage	FDA Approved Maximum Dosage for Children and Adolescents	Schedule	Black Box Warning**	Warnings and Precautions
Amphetamine mixed salts*	Adderall®	• Age 3-5 years: 2.5 mg/day • Age ≥ 6 years: 5-10 mg/day	>50 kg: 60 mg/day	Approved for children 3 years and older: 40 mg/day	One to three times daily	<ul style="list-style-type: none"> <li>• Abuse potential</li> <li>• Sudden death and serious cardiovascular events</li> </ul>	<ul style="list-style-type: none"> <li>• Sudden death in those with pre-existing structural cardiac abnormalities or other serious heart problems</li> <li>• Hypertension</li> <li>• Psychiatric adverse event</li> <li>• Long-term suppression of growth</li> <li>• Tics</li> <li>• Decreased appetite</li> <li>• Sleep disturbance</li> </ul>
	Adderall®XR	• Age 6-12 years: 5-10 mg/day • Age ≥ 13 years: 10 mg/day		Approved for children 6 years and older: 30 mg/day	Once daily		
Dextroamphetamine*	Dexedrine®	• Age 3-5 years: 2.5 mg/day • Age ≥ 6 years: 5 mg twice daily	>50 kg: 60 mg/day	Approved for children 6 years and older: 40 mg/day	Once or twice daily		
	Dexedrine Spansule®	• Age ≥ 6 years: 5 mg/day					
Lisdexamfetamine	Vyvanse®	30 mg/day	70 mg/day	Approved for children 6 years and older: 70 mg/day	Once daily		
Methylphenidate*	Ritalin®	• Age 3-5 years: 2.5 mg twice daily • Age ≥ 6 years: 5 mg twice daily	<ul style="list-style-type: none"> <li>• Age 3-5 years: 22.5 mg/day</li> <li>• &gt;50 kg: 100 mg/day</li> </ul>	Approved for children 6 years and older: 60 mg/day	One to three times daily		
	Ritalin®SR	20 mg/day			1-2 X daily		
	Ritalin®LA	20 mg/day			Once daily		
	Metadate®ER	10 mg/day			2-3 X daily		
	Metadate®CD	10 mg/day	Once daily				
	Methylin®	5 mg twice daily	Approved for children 6 years and older: 60 mg/day	One to three times daily			
	Methylin®ER	10 mg/day		2-3 X daily			
	Concerta®	18 mg/day	108 mg/day	Approved for children 6 years and older: • Age 6-12 years: 54 mg/day • Age 13-17 years: lesser of 72 mg/day or 2 mg/kg/day	Once daily		
Daytrana®TD	10 mg/day	30 mg/day	Approved for children 6 years and older: 30 mg/day (largest patch)	Once daily			
Dexmethylphenidate*	Focalin®	2.5 mg twice daily	50 mg/day	Approved for children 6 years and older: 20 mg/day	Twice daily		
	Focalin®XR	5 mg/day		Approved for children 6 years and older: 30 mg/day	Once daily		

\* Generic available

\*\* See the FDA approved product labeling for each medication for the full black box warnings.

+ IR, immediate release; SR, sustained-release formulation; CD, combined immediate release and extended release; ER and XR, extended-release; LA, long-acting; TD, transdermal

## Other ADHD Treatments

Drug (generic)	Drug (brand)+	Initial Dosage	Literature Based Maximum Dosage	FDA Approved Maximum Dosage for Children and Adolescents	Schedule	Baseline/Monitoring	Black Box Warning	Warnings and Precautions
Atomoxetine	Strattera®	<ul style="list-style-type: none"> <li>• Weight ≤70 kg: 0.5 mg/kg/day</li> <li>• Weight &gt;70 kg: 40 mg/day</li> </ul>	Lesser of 1.8 mg/kg or 100 mg/day	Approved for treatment of ADHD (age 6-17 years): Lesser of 1.4 mg/kg/day or 100 mg/day	Once or twice daily	None	Suicidal thinking in children and adolescents being treated for ADHD	<ul style="list-style-type: none"> <li>• Severe liver injury</li> <li>• Serious cardiovascular events, including sudden death, particularly in those with pre-existing structural abnormalities or other serious heart problems</li> <li>• Increased blood pressure and heart rate</li> <li>• Psychiatric adverse events</li> <li>• Allergic Events</li> <li>• Priapism</li> <li>• Long-term suppression of growth</li> <li>• Weight gain</li> </ul>
Clonidine*	Catapres® (IR)	<ul style="list-style-type: none"> <li>• Weight &lt;45 kg: 0.05 mg/day</li> <li>• Weight &gt;45 kg: 0.1 mg/day</li> </ul>	<ul style="list-style-type: none"> <li>• Weight 27-40.5 kg: 0.2 mg/day</li> <li>• Weight 40.5-45 kg: 0.3 mg/day</li> <li>• Weight &gt;45 kg: 0.4 mg/day</li> </ul>	Not approved for treatment of ADHD in children and adolescents	One to four times daily	Personal and family cardiovascular history	None	<ul style="list-style-type: none"> <li>• Hypotension</li> <li>• Bradycardia</li> <li>• Syncope</li> <li>• Sedation/Somnolence</li> <li>• Do not discontinue abruptly</li> </ul>
	Kapvay® (ER)	0.1 mg/day	0.4 mg/day	Approved for treatment of ADHD (age 6-17 years): 0.4 mg/day	Once or twice daily			
Guanfacine*	Tenex® (IR)	<ul style="list-style-type: none"> <li>• Weight &lt;45 kg: 0.5 mg/day</li> <li>• Weight &gt;45 kg: 1 mg/day</li> </ul>	<ul style="list-style-type: none"> <li>• Weight 27-40.5 kg: 2 mg/day</li> <li>• Weight 40.5-45 kg: 3 mg/day</li> <li>• Weight &gt;45 kg: 4 mg/day</li> </ul>	Not approved for children and adolescents	One to four times daily	Personal and family cardiovascular history	None	<b>CAUTION IF USED WITH ANTIPSYCHOTICS (↓ BP)</b>
	Intuniv® (ER)	1 mg/day	4 mg/day	Approved for treatment of ADHD (age 6-17 years): 4 mg/day	Once daily			
Bupropion*	Wellbutrin®	Lesser of 3 mg/kg/day or 150 mg/day	Lesser of 6 mg/kg/day or 300 mg/day with no single dose >150 mg	Not approved for children and adolescents	One to three times daily	None	Increased risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders	<ul style="list-style-type: none"> <li>• Use in combination with MAOIs</li> <li>• Suicidal ideation</li> <li>• Activation of mania/hypomania</li> <li>• Lowers seizure threshold</li> <li>• Discontinuation syndrome</li> <li>• Caution with cardiac disease</li> </ul>
	Wellbutrin®SR	Same as above	400 mg/day		Once or twice daily			
	Wellbutrin®XL	Same as above	450 mg/day		Once daily			
Imipramine*	Tofranil®	Lesser of 1 mg/kg/day or 25 mg/day	Lesser of 4 mg/kg/day or 200 mg/day	Approved for treatment of enuresis in children Age 6-12 years: lesser of 2.5 mg/kg/day or 50 mg/day Age ≥ 12 years: lesser of 2.5 mg/kg/day or 75 mg/day Approved treatment of depression ≥ 12 years: 100 mg/day	Twice daily	<ul style="list-style-type: none"> <li>• Pulse</li> <li>• ECG</li> </ul>		
Nortriptyline*	Aventyl®	0.5 mg/kg/day	Lesser of 2 mg/kg/day or 100 mg/day	Not approved for children and adolescents	Twice daily	<ul style="list-style-type: none"> <li>• Pulse</li> <li>• ECG</li> </ul>		
	Pamelor®							
	Nortrilen®							

\* Generic available

+ IR, immediate release; SR, sustained-release formulation; ER, extended-release; XL, extended-length

## Antidepressants, SSRIs

Drug (generic)	Drug (brand)+	Initial Dosage	Literature Based Maximum Dosage	FDA Approved Maximum Dosage for Children and Adolescents	Schedule	Patient Monitoring Parameters	Black Box Warning	Warnings and Precautions
Citalopram*	Celexa®	• Children: 10 mg/day • Adolescents: 20 mg/day	40 mg/day	Not approved for children and adolescents	Once daily	<ul style="list-style-type: none"> <li>• Pregnancy test – as clinically indicated</li> <li>• Monitor for emergence of suicidal ideation or behavior</li> <li>• Monitor weight and growth</li> </ul>	Increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders	<ul style="list-style-type: none"> <li>• Use in combination with MAOIs</li> <li>• Suicidal ideation</li> <li>• Activation of mania/hypomania</li> <li>• Discontinuation syndrome</li> <li>• Abnormal bleeding</li> <li>• Weight loss</li> <li>• Serotonin Syndrome or Neuroleptic Malignant Syndrome</li> <li>• Interference with cognitive and motor performance</li> <li>• Lowers seizure threshold</li> <li>• Hyponatremia</li> </ul>
Escitalopram*	Lexapro®	• Age 6-17 years (autism): 2.5 mg/day • Adolescents (MDD): 10 mg/day	<ul style="list-style-type: none"> <li>• Age 6-12 years: 20mg/day</li> <li>• Age ≥ 12 years: 30 mg/day</li> </ul>	<ul style="list-style-type: none"> <li>• Not approved for children</li> <li>• Approved for treatment of MDD in adolescents (age 12-17 years): 20 mg/day</li> </ul>				
Fluoxetine*	Prozac®	• Children: 5-10 mg/day • Adolescents: 10 mg/day	60/day	<ul style="list-style-type: none"> <li>• Approved for treatment of MDD (age 8-18 years): 20 mg/day</li> <li>• Approved for treatment of OCD (age 7-17 years): 60 mg/day</li> </ul>				
Paroxetine*	Paxil®	• Children: Not recommended • Adolescents: 10 mg	• Children: Not recommended • Adolescents: 40 mg	Not approved for children and adolescents	Daily doses >50 mg should be divided			
	Paxil®CR	• Children: Not recommended • Adolescents: 25 mg	• Children: Not recommended • Adolescents: 50 mg					
Fluvoxamine*	Luvox®	25 mg/day	• Age 8-11 years: 200 mg/day	Approved for treatment of OCD (age 8-17 years); • Ages 8-11 years: 200 mg/day • Ages 12-17 years: 300 mg/day				
	Luvox®CR	100 mg/day	• Age 12-17 years: 300 mg/day					
Sertraline*	Zoloft®	Age 6-12 years: 12.5-25 mg/day Age 13-17 years: 25-50 mg/day	200 mg/day	Approved for treatment of OCD (age 6-17 years): 200 mg/day	Once daily			

\* Generic available

+ CR, controlled-release

From Black Box Warning in product labeling: Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Both patients and families should be encouraged to contact the clinician if depression worsens, the patient demonstrates suicidal behavior or verbalizations, or if medication side effects occur. The appropriate utilization of non-physician clinical personnel who are knowledgeable of the patient population can aid in increasing the frequency of contact between the clinic and the patient/parent.

## Antidepressants, SNRIs

Drug (generic)	Drug (brand)+	Initial Dosage	Literature Based Maximum Dosage	FDA Approved Maximum Dosage for Children and Adolescents	Schedule	Patient Monitoring Parameters	Black Box Warning	Warnings and Precautions
Venlafaxine*	Effexor	Age 7-17 years: 37.5 mg/day	<ul style="list-style-type: none"> <li>Children: 150 mg/day</li> <li>Adolescents: 375 mg/day</li> </ul>	Not approved for children and adolescents	IR: Two to three times daily XR: Once daily	<ul style="list-style-type: none"> <li>Pregnancy test – as clinically indicated</li> <li>Monitor for emergence of suicidal ideation or behavior</li> <li>Blood pressure during dosage titration and as clinically indicated</li> <li>Monitor weight and growth</li> <li>Serum cholesterol levels</li> </ul>	Increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders	<ul style="list-style-type: none"> <li>Use in combination with MAOIs</li> <li>Suicidal ideation</li> <li>Abnormal bleeding</li> <li>Severe skin reactions</li> <li>Discontinuation syndrome</li> <li>Activation of mania/hypomania</li> <li>Hepatotoxicity</li> <li>Orthostatic hypotension and syncope</li> <li>Serotonin Syndrome or Neuroleptic Malignant Syndrome</li> <li>Seizures</li> <li>Elevated blood pressure</li> <li>Hyponatremia</li> </ul>
	Effexor®XR							
Duloxetine	Cymbalta®	<ul style="list-style-type: none"> <li>Children: Insufficient Evidence</li> <li>Adolescents: 40 mg/day</li> </ul>	<ul style="list-style-type: none"> <li>Children: Insufficient Evidence</li> <li>Adolescents: 60 mg/day</li> </ul>	Not approved for children and adolescents	Once or twice daily	<ul style="list-style-type: none"> <li>Pregnancy test – as clinically indicated</li> <li>Monitor for emergence of suicidal ideation or behavior</li> <li>Blood pressure prior to initiating treatment, during dosage titration and as clinically indicated</li> <li>Hepatic function testing – baseline and as clinically indicated</li> </ul>		
Desvenlafaxine	Pristiq®	<ul style="list-style-type: none"> <li>Children: Insufficient Evidence</li> <li>Adolescents: 50 mg/day</li> </ul>	<ul style="list-style-type: none"> <li>Children: Insufficient Evidence</li> <li>Adolescents: 100 mg/day</li> </ul>	Not approved for children and adolescents	Once daily	<ul style="list-style-type: none"> <li>Pregnancy test – as clinically indicated</li> <li>Monitor for emergence of suicidal ideation or behavior</li> <li>Blood pressure prior to initiating treatment, during dosage titration and as clinically indicated</li> <li>Hepatic function testing – baseline and as clinically indicated</li> <li>Serum cholesterol and triglyceride levels</li> </ul>		

\* Generic Available

+ XR, extended-release

From Black Box Warning on package inserts: Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Both patients and families should be encouraged to contact the clinician if depression worsens, the patient demonstrates suicidal behavior or verbalizations, or if medication side effects occur. The appropriate utilization of non-physician clinical personnel who are knowledgeable of the patient population can aid in increasing the frequency of contact between the clinic and the patient/parent.

# Antipsychotics: Second Generation (Atypical)

Drug (generic)	Drug (brand)+	Initial Dosage	Literature Based Maximum Dosage	FDA Approved Maximum Dosage for Children and Adolescents	Schedule	Patient Monitoring Parameters	Black Box Warning	Warnings and Precautions
Aripiprazole	Ablify®	2 mg/day	<ul style="list-style-type: none"> <li>Children: 15 mg/day</li> <li>Adolescents: 30 mg/day</li> </ul>	<ul style="list-style-type: none"> <li>Approved for treatment of Bipolar Mania or Mixed Episodes (age 10-17 years) and Schizophrenia (13-17 years): 30 mg/day</li> <li>Approved for treatment of irritability associated with Autistic Disorder (age 6-17 years): 15 mg/day</li> </ul>	Once daily	<ul style="list-style-type: none"> <li>Fasting plasma glucose level or hemoglobin A1c – at baseline, at 3 months, then every 6 months.</li> <li>Lipid screening [total cholesterol, low-and high-density lipoprotein (LDL and HDL) cholesterol, and triglycerides]-at baseline, at 3 months, then every 6 months.</li> <li>CBC as indicated by guidelines approved by the FDA in the product labeling.</li> </ul>	Not approved for depression in under age 18. Increased the risk of suicidal thinking and behavior in short-term studies in children and adolescents with major depressive disorder and other psychiatric disorders	
Quetiapine*	Seroquel® Seroquel®XR (brand only)	<ul style="list-style-type: none"> <li>Age ≤ 9 years: 12.5-25 mg/day</li> <li>Age 10-17 years: 50 mg/day</li> </ul>	<ul style="list-style-type: none"> <li>Age ≤ 9 years: 400 mg/day</li> <li>Age 10-17 years: 800 mg/day</li> </ul>	<ul style="list-style-type: none"> <li>Approved for treatment of Bipolar Mania (age 10-17 years): 600 mg/day</li> <li>Approved for treatment of Schizophrenia (13-17 years): 800 mg/day</li> </ul>	Two to three times daily	<ul style="list-style-type: none"> <li>Pregnancy test – as clinically indicated</li> <li>Blood pressure, pulse rate, height, weight and BMI measurement – when a new antipsychotic is initiated and at every visit</li> </ul>	None related to youth	<ul style="list-style-type: none"> <li>Neuroleptic Malignant Syndrome</li> </ul>
Olanzapine*	Zyprexa®	<ul style="list-style-type: none"> <li>Age &lt; 6 years: 1.25 mg/day</li> <li>Age 6-12 years: 2.5 mg/day</li> <li>Age ≥ 13 years: 2.5-5 mg/day</li> </ul>	<ul style="list-style-type: none"> <li>Children: 12.5 mg/day</li> <li>Adolescents: 20 mg/day</li> </ul>	Approved for treatment of Bipolar Mania or Mixed Episodes and Schizophrenia (age 13-17 years): 20 mg/day	Once daily	<ul style="list-style-type: none"> <li>Sexual function inquiry – inquire yearly for evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory disturbances in males (Priapism has been reported with loperidone, Risperidone and Ziprasidone). This inquiry should be done at each visit (quarterly for inpatients) for the first 12 months after starting an antipsychotic or until the medication dose is stable and then yearly.</li> </ul>	None related to youth	<ul style="list-style-type: none"> <li>Tardive Dyskinesia</li> <li>Hyperglycemia and Diabetes Mellitus</li> <li>Weight gain</li> <li>Dyslipidemia</li> <li>Orthostatic Hypotension</li> </ul>
Risperidone*	Risperdal®	<ul style="list-style-type: none"> <li>Children                             <ul style="list-style-type: none"> <li>&lt;20 kg: 0.25 mg/day</li> <li>&gt;20 kg: 0.5 mg/day</li> </ul> </li> <li>Adolescents: 0.5 mg/day</li> </ul>	<ul style="list-style-type: none"> <li>Children: 3 mg/day</li> <li>Adolescents: 6 mg/day</li> </ul>	<ul style="list-style-type: none"> <li>Approved for treatment of Schizophrenia (age 13-17 years) and Bipolar Mania or Mixed Episodes (age 10-17 years): 6 mg/day</li> <li>Approved for treatment of irritability associated with autistic disorder (age 5-16 years): 3 mg/day</li> </ul>	Once or twice daily	<ul style="list-style-type: none"> <li>EPS evaluation (examination for rigidity, tremor, akathisia) – before initiation of any antipsychotic medication, then weekly for the first 2 weeks after initiating treatment with a new antipsychotic or until the dose has been stabilized and weekly for 2 weeks after a dose increase.</li> </ul>	None related to youth	<ul style="list-style-type: none"> <li>Leukopenia, neutropenia, and agranulocytosis</li> <li>Lowers seizure threshold</li> <li>Cognitive and motor impairment</li> <li>Hyperthermia</li> </ul>
Clozapine*	Clozaril® Fazaclo® (oral disintegrating tablet)	<ul style="list-style-type: none"> <li>Children: 6.25-12.5 mg/day</li> <li>Adolescents: 6.25-25 mg/day</li> </ul>	<ul style="list-style-type: none"> <li>Children: 150-300 mg/day</li> <li>Adolescents: 600 mg/day</li> </ul> <p>Target serum clozapine level of 350 ng/mL for optimal efficacy</p>	Not approved for children and adolescents	Once or twice daily	<ul style="list-style-type: none"> <li>None related to youth</li> </ul>	None related to youth	<ul style="list-style-type: none"> <li>Dysphagia</li> <li>Hyperprolactinemia (Except not reported with Aripiprazole, Clozapine, and Asenapine)</li> <li>Extrapyramidal side effects</li> </ul>
Asenapine (sublingual)	Saphris®	Insufficient evidence	Insufficient evidence	Not approved for children and adolescents	Insufficient evidence; nothing by mouth for 10 minutes after sublingual administration	None related to youth	None related to youth	
lloperidone	Fanapt®	Insufficient Evidence	Insufficient evidence	Not approved for children and adolescents	Insufficient Evidence	None related to youth	None related to youth	
Paliperidone	Invega®	<ul style="list-style-type: none"> <li>Children: Insufficient evidence</li> <li>Adolescents: 3 mg/day</li> </ul>	<ul style="list-style-type: none"> <li>Children: Insufficient evidence</li> <li>Adolescents:                             <ul style="list-style-type: none"> <li>Weight &lt; 51 kg: 6 mg/day</li> <li>Weight ≥ 51 kg: 12 mg/day</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Approved for treatment of Schizophrenia (age 12-17 years):                             <ul style="list-style-type: none"> <li>Weight &lt; 51 kg: 6 mg/day</li> <li>Weight ≥ 51 kg: 12 mg/day</li> </ul> </li> </ul>	Once daily	<ul style="list-style-type: none"> <li>Tardive Dyskinesia evaluation – every 12 months. For high risk patients (including the elderly), every 6 months..</li> <li>Vision questionnaire – ask whether the patient has experienced a change in vision and should specifically ask about distance vision and blurry vision-yearly. (Cataracts have been reported for Quetiapine)</li> </ul>	None related to youth	
Ziprasidone*	Geodon®	<ul style="list-style-type: none"> <li>Bipolar Disorder (age 10-17 years): 20 mg/day</li> <li>Tourette's Disorder: 5 mg/day</li> </ul>	<ul style="list-style-type: none"> <li>Bipolar Disorder                             <ul style="list-style-type: none"> <li>Weight ≤ 45 kg: 80 mg/day</li> <li>Weight &gt; 45 kg: 160 mg/day</li> </ul> </li> <li>Tourette's Disorder: 40 mg/day</li> </ul>	Not approved for children and adolescents	Insufficient evidence; take with ≥500 calorie meal	None related to youth	None related to youth	
Lurasidone	Latuda®	Insufficient Evidence	Insufficient evidence	Not approved for children and adolescents	Insufficient evidence; take with >350 calorie meal	<ul style="list-style-type: none"> <li>EKG - Baseline and as clinically indicated (QTc prolongation reported for Asenapine, Clozapine, lloperidone, Paliperidone, Quetiapine and Ziprasidone)</li> </ul>	None related to youth	

\* Generic available  
+ XR, extended-release

## Antipsychotics: First Generation (Typical)

Drug (generic)	Drug (brand)	Initial Dosage	Literature Based Maximum Dosage	FDA Approved Maximum Dosage for Children and Adolescents	Schedule	Black Box Warning	Warnings and Precautions
Chlorpromazine*	Thorazine®	<ul style="list-style-type: none"> <li>Age &gt; 6 months: 0.25 mg/lb every 4-6 hours, as needed</li> <li>Adolescents: 10-25 mg/dose every 4-6 hours</li> </ul>	<ul style="list-style-type: none"> <li>Age &lt; 5 years: 40 mg/day</li> <li>Age 5-12 years: 75 mg/day</li> <li>Age &gt; 12 years: 800 mg/day</li> </ul>	Approved for treatment of severe behavioral problems (age 6 months-12 years) <ul style="list-style-type: none"> <li>Outpatient Children: 0.55 mg/kg every 4-6 hours, as needed</li> <li>Inpatient Children: 500 mg/day</li> </ul> Approved for the management of manifestations of Psychotic Disorders (age > 12 years): 1 g/day	One to six times daily	None related to youth	<ul style="list-style-type: none"> <li>Tardive Dyskinesia</li> <li>Neuroleptic Malignant Syndrome</li> <li>Leukopenia, neutropenia, and agranulocytosis</li> </ul>
Haloperidol*	Haldol®	<ul style="list-style-type: none"> <li>Age 3-12 years, (15 – 40 kg): 0.025-0.05 mg/kg/day</li> <li>Age ≥13 years: 1 mg/day</li> </ul>	<ul style="list-style-type: none"> <li>Children: 0.15 mg/kg/day</li> <li>Adolescents                             <ul style="list-style-type: none"> <li>Acute agitation: 15 mg/dose</li> <li>Psychosis: 15 mg/day</li> <li>Tourette's Disorder: 15 mg/day</li> </ul> </li> </ul>	Approved for treatment of Psychotic Disorders, Tourette's Disorder, and severe behavioral problems (age ≥3 years): <ul style="list-style-type: none"> <li>Psychosis: 0.15 mg/kg/day</li> <li>Tourette's Disorder and severe behavioral problems: 0.075 mg/kg/day</li> <li>Severely disturbed children: 6 mg/day</li> </ul>	One to three times daily	None related to youth	<ul style="list-style-type: none"> <li>Drowsiness</li> <li>Orthostatic hypotension</li> <li>EKG changes</li> <li>Extrapyramidal symptoms</li> </ul>
Perphenazine*	Trilafon®	<ul style="list-style-type: none"> <li>Children: insufficient evidence</li> <li>Adolescents:                             <ul style="list-style-type: none"> <li>Outpatient: 4-8 mg three times daily</li> <li>Inpatient: 8-16 mg twice to four times daily</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Children: insufficient evidence</li> <li>Adolescents: 64 mg/day</li> </ul>	Approved for treatment of psychotic disorders (age ≥12 years): <ul style="list-style-type: none"> <li>Outpatient: 24 mg/day</li> <li>Inpatient: 64 mg/day</li> </ul>	Two to four times daily	None related to youth	<ul style="list-style-type: none"> <li>Ocular changes</li> <li>Hyperprolactinemia</li> <li>Anticholinergic effects (constipation, dry mouth, blurred vision, urinary retention)</li> </ul>
Pimozide	Orap®	Age ≥7 years: 0.05 mg/kg	<ul style="list-style-type: none"> <li>Age 7-12 years: lesser of 6 mg/day or 0.2 mg/kg/day</li> <li>Age ≥ 12 years: Lesser of 10 mg/day or 0.2 mg/kg/day</li> </ul>	Approved for treatment of Tourette's Disorder (age ≥12 years): Lesser of 10 mg/day or 0.2 mg/kg/day	Once or twice daily	None related to youth	<ul style="list-style-type: none"> <li>Antiemetic effect (Reported in Chlorpromazine and Perphenazine)</li> </ul>

\* Generic available

# Mood Stabilizers

Drug (generic)	Drug (brand)+	Initial Dosage	Target Dosage Range	Literature Based Maximum Dosage	FDA Approved Maximum Dosage for Children and Adolescents	Schedule	Baseline Monitoring	Black Box Warning	Warnings and Precautions
Carbamazepine*	Carbato®(ER)	• Age < 6 years: 10-20 mg/kg/day	• Age <6 years: 35 mg/kg/day	• Age <6 years: 35 mg/kg/day	Approved for treatment of Seizure Disorders in all ages: • Age < 6 years: 35 mg/kg/day • Age 6-15 years: 1000 mg/day • Age >15 years: 1200 mg/day	Twice daily	• HLA-B*1502 Allele (risk of SJS) • Pregnancy test • CBC • Electrolytes	• Stevens-Johnson Syndrome • Aplastic Anemia/granulocytosis	• Stevens-Johnson Syndrome • Aplastic anemia • Suicidal ideation • Teratogenicity • Neutropenia • Hyponatremia • Induces metabolism of itself and some other drugs • Decreased efficacy of oral contraceptives • Withdrawal seizures
	Tegretol®	• Age 6-12 years: 10 mg/kg/day or 200 mg/day	• Ages 6-12 years: 400-800 mg/day	• Ages 6-12 years: 800 mg/day		Two to four times daily			
	Tegretol®XR	• Age >12 years: 400 mg/day	• Age >12 years: 800-1200 mg/day	• Age >15 years: 1200 mg/day		Twice daily			
Divalproex Sodium*	Depakote®	10-15 mg/kg/day	30-60 mg/kg/day	Serum level: 125 µg/mL, or 60 mg/kg/day	Approved for treatment of Seizure Disorders (age ≥ 10 years)  Maximum dose based upon serum level: 50-100 µg/mL, or 60 mg/kg/day	One to three times daily	• Chemistry Panel • CBC (with platelets) • LFTs • Pregnancy test	• Hepatotoxicity • Teratogenicity • Pancreatitis	• Hepatotoxicity • Pancreatitis • Urea cycle disorders • Teratogenicity • Suicidal ideation • Thrombocytopenia • Hyperammonemia • Multi-organ hypersensitivity reaction • Withdrawal seizures • Polycystic ovaries • Neutropenia
Lithium*	Eskalith®	• Children: Lesser of 15-20 mg/kg/day or 150mg twice per day  • Adolescents: Lesser of 15-20 mg/kg/day or 300 mg twice per day	Dose adjustment based upon serum level  Serum level: 0.6-1.2 mEq/L	Serum level: 1.2 mEq/L, or 1800 mg	Approved for treatment of manic episodes and maintenance of Bipolar Disorder (age ≥ 12 years)  Maximum dose based upon serum level: 1.2 mEq/L	One to four times daily	• Chemistry Panel • CBC (with platelets) • Serum Creatinine • LFTs • Pregnancy test • ECG • Blood for lithium serum levels should be drawn 10-12 hours after the last dose.	Toxicity above therapeutic serum levels	• Toxicity above therapeutic serum levels • Chronic renal function impairment • Special risk patients: those with significant renal or cardiovascular disease, severe debilitation, dehydration, or sodium depletion • Polyuria • Tremor • Diarrhea • Nausea • Hypothyroidism • Teratogenicity
	Eskalith®CR								
	Lithobid®(ER)								
Lamotrigine*	Lamictal®	• Children: 2-5 mg/day  • Adolescents: 25 mg/day (increase by 25 mg every 2 weeks)	Children • Monotherapy: 4.5-7.5 mg/kg/day • With Valproate: 1-3 mg/kg/day • With Valproate and EIAEDs +: 1-5 mg/kg/day • With EIAEDs: 5-15 mg/kg/day  Adolescents • Monotherapy: 225-375 mg/day • With Valproate: 100-200 mg/day • With Valproate and EIAEDs +: 100-400 mg/day • With EIAEDs +: 300-500 mg/day	Approved for adjunctive therapy for Seizure Disorders: Age 2-12: 400 mg/day Age >12: 500 mg/day  Safety and effectiveness for treatment of Bipolar Disorder in patients younger than 18 years had not been established	Once or twice daily	• Serious rashes including Stevens-Johnson syndrome	• Dermatological reactions • Potential Stevens-Johnson Syndrome • Multi-organ hypersensitivity reactions and organ failure • Blood dyscrasias • Suicidal ideation • Aseptic meningitis • Concomitant use with oral contraceptives increases lamotrigine clearance • Withdrawal seizures		
Oxcarbazepine*	Trileptal®	8-10 mg/kg/day	Monotherapy (based on weight): • 20-24.9 kg: 600-800 mg/day • 25-34.9 kg: 900-1200 mg/day • 35-44.9 kg: 900-1500 mg/day • 45-49.9 kg: 1200-1500 mg/day • 50-59.9 kg: 1200-1800 mg/day • 60-69.9 kg: 1200-2100 mg/day • ≥70 kg: 1500-2100 mg/day	• Children: 60 mg/kg/day or 1500 mg/day  • Adolescents: 60 mg/kg/day or 2100 mg/day	Approved for treatment of Seizure Disorders as monotherapy (age ≥ 4 years), or as adjunctive therapy in (age ≥ 2 years): 60 mg/kg/day or 1800 mg/day	Twice daily	• CBC • Electrolytes • Pregnancy test	• Hyponatremia • Anaphylactic reactions and angioedema • Patients with a past history of hypersensitivity reaction to carbamazepine • Serious dermatological reactions • Withdrawal seizures • Cognitive/neuropsychiatric adverse events • Multi-organ hypersensitivity • Hematologic events	

\* Generic Available

+EIAED's - Enzyme Inducing Anti-Epileptic Drugs (e.g. Carbamazepine, Phenobarbital, Phenytoin, Primidone)

+ ER and XR, extended-release; CR, controlled release

## Sedatives/Hypnotics

Drug (generic)	Drug (brand)	Initial Dosage	Literature Based Maximum Dosage	FDA Approved Maximum Dosage for Children and Adolescents	Schedule	Black Box Warning**	Warnings and Precautions
Diphenhydramine*	Benadryl®	<ul style="list-style-type: none"> <li>• Age 3-5 years: 6.25-12.5 mg (1mg/kg max)</li> <li>• Age 5-12 years: 12.5-25 mg</li> <li>• Age ≥12 years: 25-50 mg</li> </ul>	<ul style="list-style-type: none"> <li>• 25-37 lbs: 12.5 mg</li> <li>• 38-49 lbs: 19 mg</li> <li>• 50-99 lbs: 25 mg</li> <li>• ≥100 lbs: 50 mg</li> </ul>	Approved for treatment of insomnia (age ≥12 years): 50 mg at bedtime	Once at bedtime		<ul style="list-style-type: none"> <li>• Drowsiness</li> <li>• Dizziness</li> <li>• Dry mouth</li> <li>• Nausea</li> <li>• Nervousness</li> <li>• Blurred vision</li> <li>• Diminished mental alertness</li> <li>• Paradoxical excitation</li> <li>• Respiratory disease</li> <li>• Hypersensitivity reactions</li> </ul>
Trazodone*	Dasyrel®	<ul style="list-style-type: none"> <li>• Children: Insufficient Evidence</li> <li>• Adolescents: 25 mg</li> </ul>	<ul style="list-style-type: none"> <li>• Children: Insufficient Evidence</li> <li>• Adolescents: 100 mg/day</li> </ul>	Not approved for children or adolescents	Once at bedtime	Increased the risk compared to placebo of suicidal thinking and behavior (Suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders	<ul style="list-style-type: none"> <li>• Serotonin Syndrome</li> <li>• Neuroleptic Malignant Syndrome</li> <li>• Use in combination with MAOIs</li> <li>• Suicidal ideation</li> <li>• Activation of mania/hypomania</li> <li>• Discontinuation syndrome</li> <li>• Abnormal bleeding</li> <li>• QT prolongation and risk of sudden death</li> <li>• Orthostatic hypotension and syncope</li> <li>• Abnormal bleeding</li> <li>• Priapism</li> <li>• Hyponatremia</li> <li>• Cognitive and motor impairment</li> </ul>
Eszopiclone	Lunesta®	Insufficient Evidence	Insufficient evidence	Not approved for children or adolescents	Once at bedtime		<ul style="list-style-type: none"> <li>• Psychiatric/physical disorder</li> <li>• Abnormal thinking and behavior changes</li> <li>• Withdrawal effects</li> <li>• Drug abuse and dependence</li> <li>• Tolerance</li> </ul>
Melatonin		<ul style="list-style-type: none"> <li>• Age 3-6 years: 0.5mg</li> <li>• Age ≥6 years: 1mg</li> </ul>	<ul style="list-style-type: none"> <li>• Age 3-6 years: Lesser of 0.15 mg/kg or 3 mg</li> <li>• Age ≥6 years: Lesser of 0.15mg/kg or 6mg</li> </ul>	Not FDA approved	Once at bedtime		<ul style="list-style-type: none"> <li>• Sedation</li> <li>• May adversely affect gonadal development</li> </ul>
Ramelteon	Rozerem®	Insufficient Evidence	Insufficient evidence	Not approved for children or adolescents	Insufficient Evidence		<ul style="list-style-type: none"> <li>• Hypersensitivity reactions</li> <li>• Need to evaluate for co-morbid diagnoses</li> <li>• Abnormal thinking and behavioral changes</li> <li>• CNS depression</li> <li>• Decreased testosterone</li> <li>• Hyperprolactinemia</li> </ul>
Hydroxyzine*	Vistaril®	<ul style="list-style-type: none"> <li>• Age 3-6 years: 25 mg</li> <li>• Age ≥6 years: 50mg</li> </ul>	<ul style="list-style-type: none"> <li>• Age 3-6 years: 25 mg/day</li> <li>• Age 6-12 years: 50 mg</li> <li>• Age &gt; 12 years: 100 mg</li> </ul>	<ul style="list-style-type: none"> <li>• Approved for treatment of anxiety and tension:</li> <li>• Age &lt;6 years: 50 mg/day</li> <li>• Age ≥ 6 years: 50-100 mg/day</li> </ul> <p>Approved as a sedative when used as a premedication and following general anesthesia: 0.6 mg/kg</p>	Once at bedtime		<ul style="list-style-type: none"> <li>• Drowsiness</li> <li>• Dry mouth</li> <li>• Involuntary motor activity</li> <li>• Blurred vision, dizziness, diminished mental alertness</li> <li>• Paradoxical excitation</li> </ul>

\* Generic Available

\*\* Maximum doses for the sedative/hypnotics are based upon night time doses to induce sleep in a child with severe insomnia.

Use of zolpidem in pediatric patients: Safety and effectiveness of zolpidem have not been established in pediatric patients. In an 8-week study in pediatric patients (aged 6-17 years) with insomnia associated with ADHD, zolpidem did not decrease sleep latency compared to placebo. Hallucinations were reported in 7.4% of the pediatric patients who received zolpidem; none of the pediatric patients who received placebo reported hallucinations

## *Glossary*

**BMI** = Body Mass Index. A measure of body fat based upon height and weight.

**CBC** = Complete blood count. Lab test used to monitor for abnormalities in blood cells, e.g., for anemia.

**Serum creatinine** = A lab test used to calculate an estimate of kidney function.

**ECG** = Electrocardiogram

**EEG** = Electroencephalogram

**EPS** = Extrapyrimal side effects. These are adverse effects upon movement, including stiffness, tremor, and severe muscle spasm

**FDA** = U.S. Food and Drug Administration

**Hemoglobin A1c** = A laboratory measurement of the amount of glucose in the hemoglobin of the red blood cells. Provides a measure of average glucose over the previous 3 months.

**LFTs** = Liver function tests

**MAOIs** = Monoamine Oxidase Inhibitors

**MRI** = Magnetic resonance imaging

**PRN** = as needed

**Prolactin** = A hormone produced by the pituitary gland

**TFTs** = Thyroid Function Tests

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## *Acknowledgements*

**Dara Teibel, Pharm.D.** (at the time a University of Texas Pharm.D. Candidate) assisted with the literature search and updating of the medication tables.

**Richard Steinberg** (Texas Department of Assistive and Rehabilitative Services) provided final editing and design.

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Web Reference for the *September 2013 Psychotropic Medication Utilization Parameters for Children and Youth in Foster Care*

[http://www.dfps.state.tx.us/Child\\_Protection/Medical\\_Services/guide-psychotropic.asp](http://www.dfps.state.tx.us/Child_Protection/Medical_Services/guide-psychotropic.asp)

## Psychopharmacological Treatment for Very Young Children: Contexts and Guidelines

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### ABSTRACT

Systematic research and practice guidelines addressing preschool psychopharmacological treatment in very young children are limited, despite evidence of increasing clinical use of medications in this population. The Preschool Psychopharmacology Working Group (PPWG) was developed to review existing literature relevant to preschool psychopharmacology treatment and to develop treatment recommendations to guide clinicians considering psychopharmacological treatment in very young children. This article reviews the developmental considerations related to preschool psychopharmacological treatment, presents current evidence bases for specific disorders in early childhood, and describes the recommended algorithms for medication use. The purpose of this effort is to promote responsible treatment of young children, recognizing that this will sometimes involve the use of medications. *J. Am. Acad. Child Adolesc. Psychiatry*, 2007;46(12):1532–1572. **Key Words:** preschool, treatment, psychopharmacology.

In 2000 the American Academy of Child and Adolescent Psychiatry's Research Forum highlighted the developmental, logistical, and ethical challenges

related to preschool psychopharmacological research (Greenhill et al., 2003). The group recommended the development of guidelines for the pharmacological treatment of preschoolers with psychiatric disorders. Where randomized controlled data were not available, the group recommended that guidelines be derived from clinical experience and community standards. To date, our field lacks these guidelines. Thus, clinicians and families face a delicate balancing process, weighing the risks of medications with the risks of not intervening in complex clinical situations that are resistant to nonpharmacological interventions. The risks associated with psychiatric disorders are not insignificant; preschool psychiatric disorders can be associated with child care expulsion, inability to participate in family activities, impaired peer relationships, high-risk behaviors (Byrne et al., 2003; Egger and Angold, 2006; Gilliam, 2005), and future mental health problems (e.g., Lavigne et al., 1998).

Accepted July 10, 2007.

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This project was supported by a grant from the AACAP Abramson Fund.

The authors would like to acknowledge the important contributions of the young children and families with whom we work, and the valuable feedback received from the Early Childhood Clinical Research team at Bradley Hospital.

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0890-8567/07/4612-1532©2007 by the American Academy of Child and Adolescent Psychiatry.

DOI: 10.1097/chi.0b013e3181570d9e

### WORKING GROUP METHODS

The Preschool Psychopharmacology Working Group (PPWG) was established in response to the

clinical needs of preschoolers being treated with psychopharmacological agents and the absence of systematic practice guidelines for this age group. The central aim of this working group is to develop best practice algorithms for the use of psychopharmacological agents in preschool children based upon literature review, clinical experience, and expert consensus. This discussion of psychopharmacological treatment of severely impaired young children is provided as an attempt to promote an evidence-informed, clinically sound approach to considering medications in this age group. It is not intended to promote the use of medications. We anticipate that application of these algorithms will result in a reduction in the use of psychopharmacological agents for young children. The working group includes professionals with expertise in early childhood psychiatric disorders, psychopharmacology, general and behavioral pediatrics, clinical psychology, and neurodevelopmental processes.

The working group has met in person and reviewed material via multiple conference calls and e-mail communication. Articles were identified through PubMed and PsycINFO searches for the period 1990–2007 using the search terms “preschool,” “psychopharmacology,” “medications,” “childhood,” “stimulants,” “anti-depressants,” “SSRI,” “neuroleptic,” “antipsychotic,” “mood stabilizer,” “ADHD,” “depression,” “anxiety,” “OCD,” “PTSD,” “sleep disorder,” “insomnia,” “aggression,” “DBD,” “conduct disorder,” “oppositional defiant disorder,” “bipolar disorder,” “safety,” and “prescribing.” We reviewed all of the identified preschool psychopharmacology publications as were relevant. Because of the important influence of older child and adolescent data on prescribing for preschool children, we also reviewed the highest level of evidence in older children.

The group developed treatment algorithms to guide psychopharmacological treatment of preschool psychiatric disorders using the systematic literature review, survey responses from practicing clinicians (unpublished PPWG survey), and the research and clinical expertise of the working group. The algorithms are not intended to suggest certainty where none exists. Each step of the algorithm is labeled with the level of evidence that supports the step to allow clinicians to consider systematic approaches to treatment, to be aware of data as well as extant gaps in evidence base, and to understand the basis for recommendations. The algorithms that were developed represent the group’s

best attempt to integrate data and clinical experience; however, clinicians may determine that an alternative approach is indicated in a particular clinical situation.

Algorithms can facilitate clinical decisions by explicitly identifying clinical decision points, defining strategic (what to do) and tactical (how to do it) processes (Emslie et al., 2004b). They are intended to be user-friendly and reduce unnecessary variance in clinical practice patterns. Algorithm implementation, study of clinical outcomes, and a growing research base will guide future changes in treatment recommendations (Gilbert et al., 1998).

### OVERVIEW OF PRESCRIBING PRACTICES

Of preschoolers with psychiatric disorders, only a small proportion are referred for mental health treatment, and the primary treatment modality for most very young children is psychotherapeutic rather than psychopharmacological (AACAP, 1997b; Egger and Angold, 2006; Lavigne et al., 1993). Studies using varied methods yielded estimates that 3 to 9/1,000 U.S. preschoolers received prescriptions for psychotropic medications in the 1990s (DeBar et al., 2003; Zito et al., 2000). Rates of stimulants and  $\alpha$ -agonist prescriptions increased dramatically between 1991 and 1995 in Medicaid populations (Zito et al., 2000). From 1991–1995, prescription rates for Medicaid-enrolled preschoolers approximately doubled, with the most notable increases in atypical antipsychotic and antidepressant use, with stable rates of stimulant prescriptions (Cooper et al., 2004; Patel et al., 2005; Zito et al., 2007; Zuvekas et al., 2006). These population-based studies do not link the prescription with clinical information, and it is possible that some prescriptions written for infants or very young children may, in fact, be intended to treat uninsured parents.

In addition, these studies do not examine complementary and alternative medication (CAM) use. In a survey of parents in an emergency room (mean age 5.3 years;  $n = 103$ ), 16% of parents reported giving their child a CAM agent for relaxation (Lanski et al., 2003). Although the details of the use of CAM in preschoolers are beyond the scope of this article, CAM is a factor in preschoolers’ exposure to psychotropic agents (Chan, 2002).

A few studies have examined patterns of prescriptions for children with psychiatric diagnoses. Across a variety of populations including community, HMO, and

Medicaid, the majority of prescriptions written for preschoolers are for stimulants (DeBar et al., 2003; Luby et al., 2007; Zito et al., 2007). In an HMO population including 743 preschoolers with emotional or behavioral problems, 16% ( $n = 120$ ) of diagnosed children received psychopharmacological treatment, most commonly monotherapy with a stimulant (DeBar et al., 2003). In this study, stimulant use was clearly linked to attention-deficit/hyperactivity disorder (ADHD) and  $\alpha$ -agonists to sleep and aggression. The authors could not discern an association between antidepressant use and diagnoses or symptoms. In a community sample, Luby et al. (2007) reported that 12% (17/123) of preschoolers with a *DSM-IV* diagnosis had received medication for at least 1 month. In both studies, slightly less than 80% of preschoolers who received psychopharmacological treatment also received psychotherapy. A total of 33% of the community sample and 74% of the HMO sample received their prescription from a primary care provider. In higher risk populations, such as medically complex toddlers with ADHD and psychiatrically hospitalized young children, reports describe higher rates of psychopharmacological treatment (57%–79%) and more prevalent use of more than one medication (Pathak et al., 2004; Rappley et al., 1999; Rappley et al., 2002).

Taken together, these early studies of preschool psychopharmacological practice suggest that the majority of preschoolers with mental health problems do not receive psychopharmacological treatment. Access to other mental health services appears variable. Prescription patterns support the value of clearly defined treatment recommendations for rational use of medications.

### SPECIAL CONTEXTS OF PRESCHOOL PSYCHOPHARMACOLOGY

Treatment decisions involving young children include consideration of developmentally specific assessments and diagnosis, attention to neurodevelopmental and ethical factors, and the existing evidence base.

#### Assessment

Although a comprehensive discussion of assessment in preschool children is beyond the scope of this article, a comprehensive, developmentally sensitive, and contextually relevant assessment is a prerequisite to consideration of treatment. A number of resources

can be used to guide this process (AACAP, 1997b; Carter et al., 2004; DelCarmen-Wiggins and Carter, 2004; Zeanah et al., 2000). An assessment of a preschooler includes multiple appointments, uses multiple informants, and usually occurs within the context of a multidisciplinary team. A preschool psychiatric evaluation should address a child's emotional and behavioral symptoms, relationship patterns, medical history, developmental history and status, as well as parental and other environmental stressors and supports (e.g., Egger et al., 2006a). In addition, early childhood development is particularly sensitive to the quality of the caregiver-child relationship, as well as family, child care, community, and cultural contexts, which may influence the clinical presentation, case formulation, and treatment plan (e.g., Seifer et al., 2001; Zeanah et al., 1997).

Structured, validated approaches to preschool psychiatric assessments can enhance the information obtained in an assessment. These approaches include brief parent report questionnaires focused on child symptomatology, such as the Infant-Toddler Social Emotional Assessment (Briggs-Gowan, 1998) or the Child Behavior Checklist 1½–5 (Achenbach and Rescorla, 2000), diagnostic interviews including the Preschool Age Psychiatric Assessment (Egger et al., 2006b), and structured observations of parent-child interactions, such as the Clinical Problem Solving Procedure (Crowell and Fleischmann, 2000).

A comprehensive preschool psychiatric assessment is impractical in a primary care setting, where many children receive their prescriptions (DeBar et al., 2003; Goodwin et al., 2001). In any setting, a rational preschool treatment plan must be founded upon an adequate history and mental status examination that allow a reasonable biopsychosocial formulation. For a primary care prescriber, multiple appointments, collection of collateral information from other caregivers, and consultation with the child's mental health specialist provide the foundation for treatment decisions while allowing a primary care provider to practice within the scope of his or her knowledge.

#### Diagnosis

In clinical practice psychiatric diagnosis generally drives treatment planning. Applying diagnoses can facilitate the clinical application of research findings focused on that diagnosis and can provide a common

language to describe complex clinical syndromes. In clinical practice, most but not all impaired preschoolers will meet full criteria for a diagnosis (Keenan et al., 1997). For those who do not, applying standard nosologies and recognizing subthreshold disorders can focus treatment planning.

Two diagnostically sensitive nosologies have been developed to address concerns about the *DSM-IV*'s lack of attention to young children: the Research Diagnostic Criteria: Preschool Age (AACAP Task Force on Research Diagnostic Criteria: Infancy Preschool Age, 2003) and the Diagnostic Criteria: 0-3R (Zero to Three Diagnostic Classification Task Force, 2005). The Research Diagnostic Criteria: Preschool Age are developmentally sensitive, evidence-informed modifications of the *DSM-IV* criteria intended to introduce reliability into the assignment of diagnoses to preschoolers, particularly in the research setting. The recently revised Diagnostic Criteria: 0-3R also address developmentally specific clinical presentations of mental health problems, focused primarily on infants and toddlers and their relationships with caregivers.

Overall, using developmentally sensitive criteria, psychiatric disorders can be reliably assessed in children as young as 2 years old (Egger et al., 2006b). Empirical support for specific preschool diagnoses is somewhat variable. Some disorders, including major depressive disorder (Luby et al., 2003a; Luby et al., 2003b; Luby et al., 2003c; Luby et al., 2004b), posttraumatic stress disorder (PTSD; Scheeringa et al., 2001; Scheeringa et al., 1995; Scheeringa et al., 2004; Scheeringa et al., 2005), disruptive behavior disorders (Keenan and Wakschlag, 2002; Keenan and Wakschlag, 2004), ADHD (Lahey et al., 2004; Lahey et al., 1998), and autism (Lord et al., 2006) have empirical evidence that supports convergent and predictive validity. Other disorders, including many anxiety disorders, have not been empirically tested in preschoolers. Reliable and valid diagnostic criteria are necessary to develop empirically supported treatments for preschool disorders.

#### Nonpharmacological Treatment

Clinical decision making includes consideration of alternative therapies. Thus, prescribers should be aware of the growing (but still limited) evidence base for psychotherapeutic interventions in preschoolers. Evidence-supported models of treatment are effective in decreasing aggression and behavioral problems in young

children with disruptive behavior disorders (Eyberg, 1988; Hood and Eyberg, 2003; Webster-Stratton et al., 2004), reducing child traumatic stress disorder symptoms (Cohen and Mannarino, 1997; Lieberman et al., 2005; Lieberman et al., 2006). Psychotherapeutic interventions for preschoolers with PTSD (Scheeringa et al., in press) and mania-like symptoms (Luby et al., in press) have also shown promising preliminary outcomes, although randomized controlled trials have not yet been published. In our experience, access to these evidence-based psychotherapeutic interventions can be variable and may be limited by a number of variables including provider training, third-party payer restrictions, and parental motivation to participate.

#### Neurodevelopmental Processes

Biology also influences consideration of psychopharmacological treatment in young children. The impact of early and/or prolonged exposure to psychotropic medications in the preschool period has not been systematically studied, but research highlights the sensitivity of the developing brain. Synaptic density, dopamine receptor density, and cerebral metabolic rates peak in the first 3 years of life and decline over subsequent decades (reviewed in Shonkoff and Phillips, 2000; Vitiello, 1998). In animal models early exposure either to psychotropic agents or stressors can permanently affect distribution of the neurotransmitter receptors (e.g., Maciag et al., 2005; Matthews, 2002; Yannielli et al., 1999). Similarly, abnormal infant psychophysiological processes are associated with fetal exposure to maternal psychopathology (Engel et al., 2005; Lundy et al., 1999; Yehuda et al., 2005). These findings highlight the potential central nervous system sensitivity to exogenous factors including medications as well as endogenous stress responses.

Longitudinal studies of children's early exposure to psychotropic medications are limited to fetal and neonatal exposure from maternal antidepressant treatment, which provide mixed results. Although prenatal antidepressant exposure is associated with measurable changes in infant pain responsivity and toddler motor skills (Casper et al., 2003; Oberlander et al., 2005; Oberlander et al., 2006), no cognitive differences or increased rates of internalizing or externalizing symptoms have been observed in preschool follow-up (Misri et al., 2006; Nulman et al., 1997; Oberlander et al.,

2007). These results highlight the need for future investigations examining longitudinal studies of preschoolers exposed to psychotropic medications, about whom no neurodevelopmental findings have been published.

Other organ systems also develop during the first years of life. In preschoolers, medication absorption, distribution, and metabolic processes can have a significant impact on the pharmacokinetics of medications, generally meaning that children need higher doses to achieve comparable plasma levels (Coté, 2005; Crom, 1994). In practice, this pattern must be balanced with our knowledge that preschoolers also experience more side effects than older children and adults (e.g., Greenhill et al., 2006; Wigal et al., 2006). Taken together, developmental pharmacokinetic issues and sensitivity to adverse effects make dosing medications in young children a delicate balance.

#### Regulatory and Ethical Context

Finally, and not insignificantly, regulatory and ethical considerations in preschool psychopharmacological treatment must be considered. A Food and Drug Administration (FDA) indication reflects empirical support, although the lack of an indication does not necessarily reflect a lack of evidence (AAP Committee on Drugs, 2002). In the United States, only a small proportion of medications are approved for use in pediatrics and medications are commonly used "off-label" (AAP Committee on Drugs, 2002; Shah et al., 2007). Four psychiatric medications—haloperidol, dextroamphetamines, chlorpromazine, and risperidone—are approved for children under age 6 years (Greenhill, 1998). The FDA has developed incentives to encourage the development and testing of medications for children, but to date progress is limited for children under 6 (Balakrishnan et al., 2006; FDA, 2002; Grieve et al., 2005). Recently, concerns about the safety of medications in children have resulted in further regulatory actions including black box warnings on selective serotonin reuptake inhibitors (SSRIs) in the United States and temporary suspension of mixed amphetamine salts because of concerns of possible adverse cardiovascular effects in Canada in 2005 (FDA, 2005a; FDA, 2005b).

In this context, although off-label use of medications is acceptable, informed consent requires clear, thorough discussions with parents about the FDA status of a

medication and the level of evidence supporting the recommendation, potential risks, benefits, and alternatives to its use (Jensen, 1998). In the context of a preschooler's psychiatric disorder, parental distress related to the child's disorder or other pressures may affect a parent's participation in the informed consent process (Spetie and Arnold, 2007). Thus, in preschool treatment planning, the ethical principles of autonomy, justice, and beneficence are worthy of special attention (Spetie and Arnold, 2007).

#### CONSIDERING PSYCHOPHARMACOLOGICAL TREATMENT

The contextual factors reviewed here render rational prescribing considerably more challenging for preschool children compared to older children. Jensen has argued, however, that these diagnostic, neurodevelopmental, metabolic, and regulatory considerations do not "comprise a universal proscription against the use of medication in young children" (Jensen, 1998, p. 588). A child with moderate to severe symptoms and functional impairment that persist despite appropriate psychotherapeutic interventions may be better served by a carefully monitored medication trial than by continuing other ineffective treatments. For some children, the safety concerns and developmental risks related to the psychiatric disorder may outweigh safety concerns related to planful psychopharmacological treatments. Our group recommends that trial of evidence-supported psychosocial treatments precede psychopharmacological treatments. In the authors' view, psychopharmacological treatment is not indicated for preschoolers with only mild or single-context symptomatology or impairment.

#### Evidence Base

The algorithm section of this article describes the details of diagnosis-specific treatment reports, which include one multisite, randomized placebo-controlled trial (Greenhill et al., 2006), as well as case reports and open trials (see Table 1). Although these studies provide the foundation for further studies of preschool psychopathology and treatment, there is not yet a broad evidence base for the use of most psychotropic medications in children under 6 years of age. In the current context clinicians must also consider studies using older populations and their own clinical experiences

**TABLE 1**  
Published Preschool Psychopharmacology Studies (Mean Age <6 Years)

Disorder	Authors	Medication	Method	Ages, y	N	Dose	Outcome	AE
ADHD (DISC diagnosis)	Greenhill et al., 2006; Wigal et al., 2006	MPH	Multi-site, double-blind, randomized controlled trial	3-5.5	165	7.5-22.5 mg divided t.i.d.	Remission rate: 21% on MPH vs. 13% placebo ( $P \leq 0.001$ ) Lower effect sizes than older children (0.2-0.7 SD)	11% discontinued MPH because of AE (including irritability, emotionality, social withdrawal, decreased appetite) Greater decrease in growth velocity than in older children Risk of side effects associated with genetic polymorphisms
	Kratochvíl et al., 2007	Atomoxetine	8-wk prospective open trial	5-6.11	22	0.5 mg/kg titrated to max 1.8 mg/kg (mean 1.25 mg/kg)	72.7% response rate (CGI-I very much or much improved) Mean decrease on ADHD IV-RS 20.68 (SD 12.8)	No discontinuations associated with AE 54.5% (12/22) mood lability Mean decrease in weight 1.4 kg No clinically significant changes in vital signs
ADHD	Short et al., 2004	MAS (n = 6) and MPH (n = 22)	Prospective open trial; 3- to 4-wk placebo-controlled forced titration	4.0-5.9	28	MAS: 5-15 mg MPH; 10-30 mg/day divided b.i.d.	For 22/28 of children, best dose either 5 or 10 mg MPH b.i.d. Significant difference between placebo and best dose T-scores on ADHD-RS (parent: 71.5 vs. 52.5 and teacher: 62.2 vs. 50.1), AQS, and HSQ	Most commonly reported AE on best dose = decreased appetite (7/25), irritability (6/25), same rate on pcb), crying (6/25), and rebound effects (5/14)
DBD: Aggression	Cesena et al., 2002	Risperidone (concomitant with other medications)	Retrospective chart review	4-6.11 (mean 4.9)	8	0.25 mg titrated to effect or side effects (range 1.0-1.5 mg q.d.)	Mean CGI-S decrease 5.5-3.5	6/8: weight gain (5.5 ± 4.9 kg) Normal glucose, CBC, LFTs Hyperprolactinemia (n = 1)

(Continued on next page)

TABLE 1. (Continued)

Disorder	Authors	Medication	Method	Age, y	N	Dose	Outcome	AE
Bipolar: aggression, mood instability, manic symptoms + bipolar family history	Hugno et al., 1995	Li	Retrospective chart review of AE	4-6	20	With AE: 37.2 mg/kg No AE: 31.5 mg/kg	60% had at least 1 AE (50% CNS, 25% GI, 10% GU) 20% had serious AE Higher Li level associated with higher rates of AE Higher rates of AE associated with diagnosis of bipolar disorder	
Bipolar	Biederman et al., 2005b	Olanzapine and risperidone	Open trial	4-6	31 (16 risperidone, 15 olanzapine)	Risperidone: 0.25 mg q.d. titrated to max 2.0 mg q.d. Olanzapine: 1.25 mg q.d. titrated to max 10 mg q.d.	Risperidone: decrease 18.3 ± 11.9 points on YMRS Olanzapine 12.1 ± 10.4 points on YMRS	Weight gain: risperidone: 2.2 + 0.4 kg; olanzapine: 3.2 + 0.7 kg over 8 wk Increase in prolactin levels: risperidone: 12.0 ± 10.4; olanzapine: 7.6 ± 4.1 Not presented
Bipolar	Scheffer et al., 2004	AED, stimulants, atypical antipsychotic agents, (17 DYP mono-therapy, others polypharmacy)	Retrospective chart review	2-5	31	Not presented	Significant decrease in YMRS at 2 mo (34.7-13.8; n = 22), nonsignificant decrease on CGI-S (5.0-3.3) No change in YMRS from 2 mo to extended follow-up of 1-2 y; n = 11 "not hitting... more cooperative"; "sleeps all night without arguing... slowed down"; "stable"; "aggression ceased"; "less aggressive... not defying or bossing adults"; "insufficient follow-up" (n = 2) Parent refused Li (n = 1) Required addition of CBZ; "stable"; "successfully treated" (n = 2) "Mood lability decrease" Full remission at 5 wk; recurrence after discontinuation	Not presented
Bipolar: mania	Mora-Castillo et al., 2001	Valproate	Retrospective chart review	21 mo-5 y	9	250-500 mg q.d. Levels: 72-86 µg/L		
Bipolar: mania	Tumuluru et al., 2003	Li (n = 5) + CBZ (n = 1)	Retrospective chart review	3-5.11 (mean 4.6)	6	Not addressed		Not addressed
Bipolar	Tuzun et al., 2002	CBZ	Case report	5.2	1	300 mg q.d. (6.7 µg/mL)		Mild sedation Normal biochemical analyses

Bipolar: mania (PAPA diagnosis)	Pavuluri et al., 2002	Topiramate and risperidone	Case report	4.5	1	Risperidone: 0.25 mg b.i.d. Topiramate 25 mg b.i.d.	Risperidone monotherapy: reduction in irritability Topiramate: mood more stable, sleep improved, weight loss 2.7 kg/week x 4 wks, overall loss 18.1 kg	Weight gain on risperidone monotherapy: 15.4 kg in 2 mo Other concomitant meds: Li (polyuria)
Anxiety disorders (specific phobia, social anxiety, and feeding anxiety)	Hanna et al., 2005	Bupropion	Case report	4	1	12.5 mg b.i.d.	Decreased social anxiety, feeding anxiety, and specific phobia symptoms	Relapse with discontinuation, remission with reinitiation of treatment
Anxiety: selective mutism	Wright et al., 1995	Fluoxetine	Case study	4.10	1	4-8 mg q.d.	Talking freely in all settings, decreased CBCL internalizing scores (68-60)	Not addressed
Anxiety: specific phobia and panic attacks	Avci et al., 1988	Fluoxetine	Case report	2.5	1	5 mg q.d. (0.25 mg/kg/day)	Decreased anxiety symptoms and resolution of panic attacks	Not addressed
Anxiety: trauma related	Harmon and Riggs, 1996	Clonidine	Open trial	3-6	7	0.05 mg titrated to 0.15 mg q.d.	Decreased teacher-rated symptoms in at least >5/7 children	Contact dermatitis with patch, inability to tolerate patch, 1 child developed acute HTN with poststreptococcal glomerulonephritis (HTN thought to be exacerbated by abrupt decline of clonidine)
PDD	Masi et al., 2003	Risperidone	Open trial	36-71 mo	53	0.25 mg titrated up; mean optimal dose 0.55 mg	47% improved or very much improved	22% withdrew because of AE Mean weight gain 2.4 (0.9-9.5 kg) over mean of 9 mo

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TABLE 1. (Continued)

Disorder	Authors	Medication	Method	Age, y	N	Dose	Outcome	AE
PDD (autism or PDD NOS)	Luby et al., 2006	Risperidone	RCT × 6 mo	2.5-6.0	24	0.5-1.5 mg (mean dose 1.38 mg)	8% decrease in CARS score in risperidone group vs. 3% in pcb group CARS score decreased from "severely autistic" to mild-moderate in risperidone groups; no change in pcb group	Weight gain: 2.96 kg in risperidone group vs. 0.61 in pcb group Higher increase in prolactin level and trend toward higher increase in leptin levels in risperidone group Transient sedation ( <i>n</i> = 5); increased appetite ( <i>n</i> = 6); hypersalivation ( <i>n</i> = 2) in risperidone group 2.8 kg increase vs. 1.7 (ns) on pcb; transient ( $<3$ wk) sedation ( <i>n</i> = 4); transient dyskinesia ( <i>n</i> = 3)
PDD	Nagaraj et al., 2006	Risperidone	RCT × 6 mo	2-9 (mean 58-63 mo)	39	0.5-1.0 mg	63% response rate on CARS on risperidone (20% decrease in score) vs. 0% on pcb  94% improved on CGI-I vs. 30% on pcb	

*Note:* Unless otherwise noted, clinical diagnoses were used and insufficient information is provided to confirm standardized diagnosis. ADHD = attention deficit/hyperactivity disorder; AQS = Abbreviated Symptom Questionnaire; ADHD IV-RS = ADHD Rating Scale-IV; AE = adverse effects; AED = antiepileptic drug; b.i.d. = twice per day; CARS = Child Autism Rating Scale; CBC = complete blood count; CBCL = Child Behavior Checklist; CBZ = carbamazepine; CGI-I = Clinical Global Impressions-Improvement; CGI-S = Clinical Global Impressions Scale-Severity; CNS = central nervous system; DBD = disruptive behavior disorder; DISC = Diagnostic Interview Schedule for Children; DVP = divalproex; GI = gastrointestinal; GU = genitourinary; HSQ = Home Situations Questionnaire; HTN = hypertension; LFTs = liver function tests; Li = lithium; MAS = Mixed amphetamine salts; MPH = methylphenidate; NOS = not otherwise specified; PAPA = Preschool Age Psychiatric Assessment; pcb = placebo; PDD = pervasive developmental disorder; q.d. = every day; RCT = randomized controlled trial; t.i.d. = three times per day; VPA = valproate; YMRS = Youth Mania Rating Scale.

as they weigh potential risks, benefits, and alternatives in treating preschoolers with medication.

#### ALGORITHMS

The algorithms share five common factors. Assessment and diagnosis are important components in any clinical practice. These steps are included in the algorithm to highlight the importance in young children for whom the diagnostic process can be more complex than for older children. At every treatment initiation point, we recommend reassessment of the diagnosis and clinical formulation in recognition of young children's rapid development. Second, psychotherapeutic intervention steps are included as an integral part of the algorithms because a decision to use medication includes consideration of alternative treatments options. For some diagnoses, the weight of evidence supporting the psychotherapeutic intervention is stronger than for medications, making it an empirically driven recommendation. In other disorders the risks associated with the medication may be greater than the risks of a trial of psychotherapeutic intervention. In areas in which evidence-based therapies are not available, clinicians may choose to advance to the subsequent step in the algorithm, recognizing that this decision is driven by necessity rather than evidence. Third, each algorithm step is marked with the level of evidence supporting the step, allowing clinicians to consider the body of evidence and apply it to the individual clinical context. Fourth, each algorithm includes recommendations for a discontinuation trial after successful psychopharmacological treatment in recognition of the importance of reassessing the need for medication in rapidly developing preschoolers. Fifth, our group recognizes that patients may arrive at the end of the algorithm with ongoing impairment and distress. At this point, clinical consultation, ideally with a colleague experienced in early childhood psychiatry, is recommended. Although the algorithms address individual diagnoses, a number of universal guidelines are provided to encourage careful and planful clinical practice:

- Avoid medications when therapy is likely to produce good results.
- Generally, an adequate trial of psychotherapy precedes consideration of medication, and psychotherapy continues if medications are used.

- Medications should be considered in the context of a clinical diagnosis and substantial functional impairment.
- A system should be developed to track symptoms and impairment before initiating treatment.
- Parent referral or treatment for psychopathology may optimize their ability to participate in treatment as well as family mental health.
- Informed consent includes explicit information about FDA approval and level of evidence supporting recommendations.
- The "N of 1" trial approach should be considered when initiating medication treatment.
- Medication discontinuation trials are encouraged to reduce unnecessary medication treatment.
- The use of medications primarily to address side effects of other medications is not recommended.

#### ADHD ALGORITHM

##### Stage 0: Diagnostic Assessment and Psychotherapeutic Trial

Hyperactivity in the preschool period has a broad differential diagnosis. The diagnosis of ADHD, therefore, should include assessment and consideration of other causes of behavioral dysregulation including family contextual patterns, anxiety processes, and medical problems (see Fig. 1). Reports from child care providers or teachers allow a clinician to assess the symptoms in more than one setting. Structured baseline assessments of symptoms and level of functioning can guide treatment and monitor treatment response. Commonly used tools for monitoring symptoms include the Conners Rating Scale (Conners et al., 1998), the Child Behavior Checklist 1½-5 (Achenbach and Rescorla, 2000), and the Swanson, Nolan, and Pelham (Swanson, 1992; reviewed in AACAP, 2002). Although studies in older children suggest that psychosocial treatments alone are not as effective as methylphenidate alone (MTA Cooperative Group, 1999), clinical consensus suggests that parent management training is a first-line intervention in preschool ADHD (Kollins et al., 2006; Kratochvil et al., 2004; unpublished PPWG survey 2006, available from M.M.G.). Parent management training is more effective in decreasing preschoolers' attentional problems than parent support or waitlist controls (Sonuga-Barke et al., 2001). If parent management training is

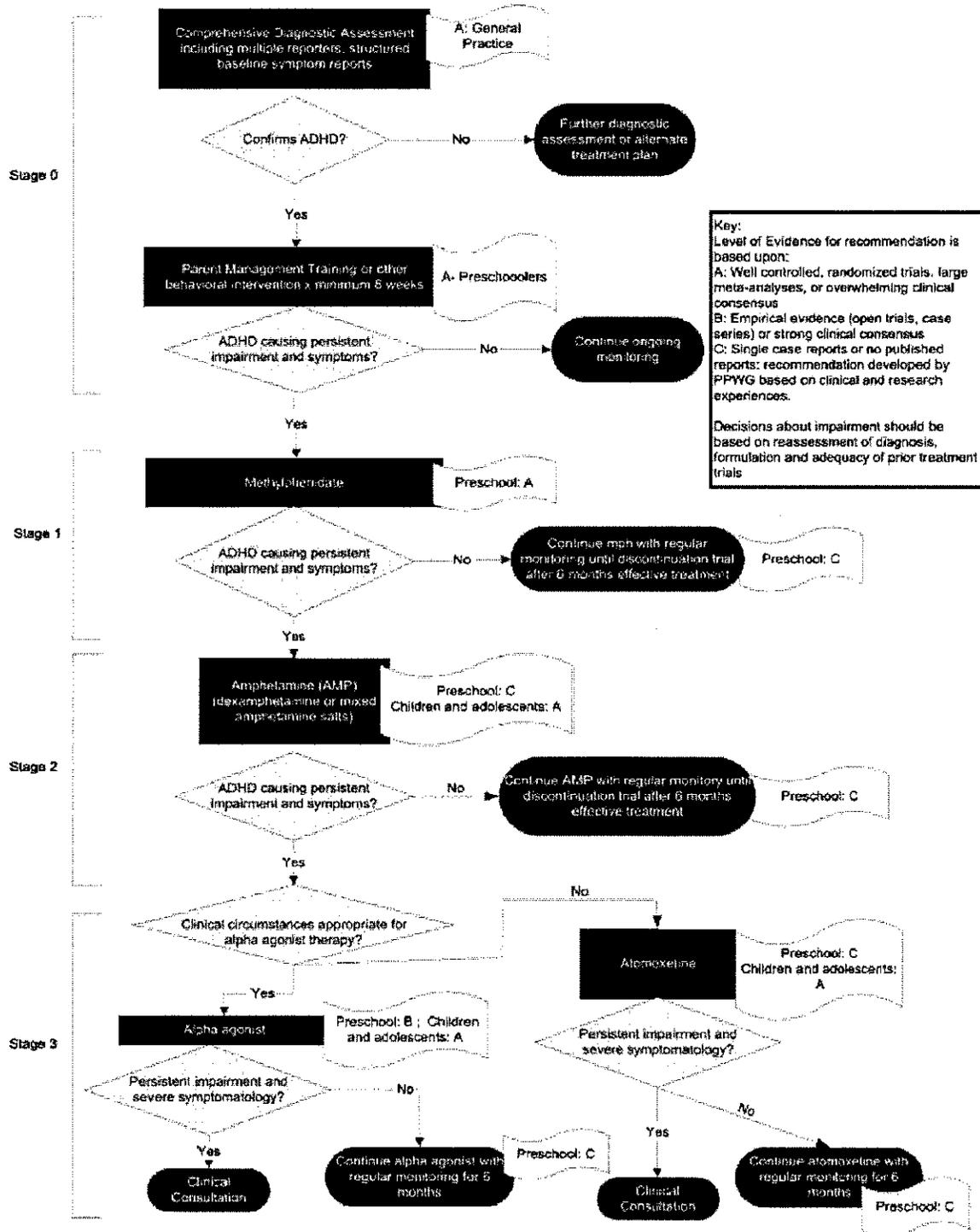


Fig. 1 ADHD algorithm.

effective, then a clinician will continue to monitor the child's symptoms.

#### Stage 1: Psychopharmacological Trial (Methylphenidate)

Methylphenidate is the first-line psychopharmacological treatment for preschool ADHD in the PPWG algorithm. A large, multisite randomized controlled trial in preschoolers and 10 other smaller studies on methylphenidate provide empirical support for its use in preschool ADHD (Greenhill et al., 2006). In the Preschool ADHD Treatment Study (PATS), methylphenidate was significantly more effective than placebo in treating ADHD and was generally tolerated. The PATS found that optimal daily doses ranged from 7.5 to 30 mg/day, divided in three daily doses of immediate-release methylphenidate. Clinicians should recognize that the effect size (0.4–0.8) in the PATS was smaller than that seen in older children (0.5–1.3), and that preschoolers also had higher rates of emotional lability compared with published rates for older children (Wigal et al., 2006). ADHD response and side effects will guide titration of methylphenidate doses.

Although no data exist to support extended-release stimulants in preschoolers, clinical experience highlights the challenges of three times per day dosing. Thus, the algorithm includes use of extended-release methylphenidate formulations to address compliance considerations. These formulations limit dosing flexibility in the lowest dose ranges and therefore may be contraindicated in children whose optimal tolerated dose is lower than the extended release dose.

If methylphenidate is effective in treating ADHD, then the algorithm recommends a discontinuation trial after 6 months of treatment to reassess the underlying psychopathology. Although ADHD has significant diagnostic stability, a proportion of children diagnosed with ADHD will not meet criteria in the future and may not require ongoing psychopharmacological treatment (Lahey et al., 2004). Symptoms should be assessed in all of the appropriate settings using structured adult report measures and clinical observation, if possible. In the AACAP survey, 60% ( $n = 62$ ) of respondents described using natural experiments (e.g., when parents did not give the medication as prescribed) as discontinuation trials. Although these events provide useful information, unplanned discontinuations usually occur because of disruptions in routines and may not

represent an optimal discontinuation trial because of the context, limited structured reports, and short duration. The recommendation for a discontinuation trial after 6 months applies to all of the medications in the ADHD algorithm.

#### Stage 2: Psychopharmacological Intervention (Amphetamine Formulations)

If the methylphenidate trial is unsuccessful, then psychopharmacological treatment should be switched to an amphetamine formulation (D-amphetamine or mixed amphetamine salts). Amphetamines are less commonly used in preschool ADHD treatment than methylphenidate (Zito et al., 2000). Only one prospective study and no randomized controlled trials have examined the efficacy of mixed amphetamine salts in preschoolers (Short et al., 2004). In older children amphetamine is equivalent to and possibly slightly more effective than methylphenidate for treating ADHD (Faraone et al., 2002) and is recommended as an appropriate first-line medication for ADHD (Plizska et al., 2006). In the absence of preschool amphetamine dosing data, appropriate doses may be extrapolated from the PATS data, with the recognition that amphetamines are roughly twice as potent as methylphenidate (Pelham et al., 1999). Considerations of extended release formulations of amphetamines are similar to those of methylphenidate.

#### Stage 3: Psychopharmacological Intervention ( $\alpha$ -Agonist or Atomoxetine)

When stimulants are ineffective or have unacceptable adverse effects, other medications may be considered after careful reassessment of the need for psychopharmacological intervention, based on diagnosis (including severe symptoms and impairment), clinical case formulation, and adequacy of intervention trials. Two other classes of medication,  $\alpha$ -agonists and atomoxetine, are commonly used for treatment of ADHD. In older children atomoxetine is recommended as the medication choice after stimulants and it has documented effectiveness for treating ADHD in children and adolescents (Kelsey et al., 2004; Michelson et al., 2002). It does not have abuse potential and produces less insomnia or anorexia compared with stimulants (Sangal et al., 2006). A recent prospective open trial including twenty-two 5- and 6-year-olds (mean age 6.06 years) reported a mean 20-point decrease in ADHD

symptoms on the ADHD Rating Scale after 8 weeks of atomoxetine at a mean dose of 1.25 mg/kg (Kratovich et al., 2007). Of note, 54% of the children experienced mood lability, although none discontinued the medication because of this event.  $\alpha$ -Agonists are more commonly used to treat preschoolers with ADHD (Rappley et al., 1999; Zito et al., 2000). In older children  $\alpha$ -agonists have smaller effect sizes than stimulants in treating ADHD, although they are more effective than placebo (Connor et al., 2003; Connor et al., 1999; Hazell and Stuart, 2003; Scahill et al., 2001; Tourette Syndrome Study Group, 2002). No trials of  $\alpha$ -agonists have focused exclusively on preschoolers, although open trials and retrospective chart reviews included children as young as 4 years old (Hunt et al., 1995; Prince et al., 1996).  $\alpha$ -Agonists can be associated with adverse effects including sedation, irritability, bradycardia, and hypotension (Connor et al., 1999; Scahill et al., 2001), and require regular monitoring of blood pressure and heart rate (Plizska et al., 2006). In overdose  $\alpha$ -agonists can result in sedation, hypotension, or death (e.g., Klein-Schwartz, 2002). Thus, a family's inability to administer and store the medication safely may be a contraindication to using the medications. The algorithm allows clinicians to use individual clinical factors to choose between atomoxetine and  $\alpha$ -agonists at stage 3 because the existing evidence does not suggest one is superior to the other. At this stage, clinicians should recognize the limited level of evidence associated with these medications in preschoolers, and weigh the risks and benefits of using these medications against alternative treatment approaches.

#### DISRUPTIVE BEHAVIOR DISORDERS ALGORITHM

##### Stage 0: Diagnostic Assessment

Although the validity of the *DSM-IV* diagnoses of oppositional defiant disorder (ODD) and conduct disorder have been the focus of some debate, a growing body of evidence demonstrates the existence of a group of preschoolers with severe and sustained impairment associated with the symptoms of *DSM-IV* disruptive behavior disorders (DBD; Egger and Angold, 2006; Keenan and Wakschlag, 2002). Because of the prevalence of behavioral dysregulation in preschoolers with psychopathology, careful assessment must differentiate

DBDs from other primary disorders, including ADHD, mood disorders, anxiety disorders, or developmental delays (as described in Fig. 2). In addition, co-occurring disorders may be the primary cause of a child's impairment and should be treated first.

Assessment of DBDs in preschoolers should include a complete history from caregivers and structured and unstructured observations. The disruptive behavior diagnostic observation schedule provides a structured approach to observation and diagnosis of these disorders (Wakschlag et al., 2005). For these disorders in particular, the potential for relationship-specific or context-specific behavioral symptoms makes information from additional sources, such as child care providers or other caregivers, immensely valuable. Structured tools to obtain this information, such as the Conners Rating Scale, can provide baseline information and assist with careful monitoring.

##### Stage 1: Nonpsychopharmacological Interventions

The balance between the relatively strong evidence base for psychotherapeutic intervention and complete lack of evidence for medication use in typically developing children guides our strong recommendation for psychotherapeutic intervention involving parents as the first-line intervention (Burke et al., 2002; Dozier et al., in press; Farmer et al., 2002; Hood and Eyberg, 2003; Webster-Stratton et al., 2004). Evidence-supported treatment models, such as the Incredible Years Series (Webster-Stratton and Hammond, 1997) or Parent-Child Interaction Therapy (Eyberg, 1988) focus on increasing parent skills to support positive interactions with their children and increasing consistent consequences for aggressive or unacceptable behaviors. The availability of these evidence-based interventions can be limited. Other therapies including behavioral therapy with parent involvement, positive parenting interventions, or social skills groups that include the parent may be appropriate alternatives. The evidence-based psychotherapeutic interventions for preschoolers with disruptive behaviors have a treatment duration of 10 to 20 weeks, which should be considered a minimum treatment trial duration. Families may benefit from additional community resources, case management, child care, or school interventions as supplements to therapy as the clinical picture warrants (AACAP, 1997a). As with other disorders, parental psychopathology may influence parents' experience and description of a preschooler's

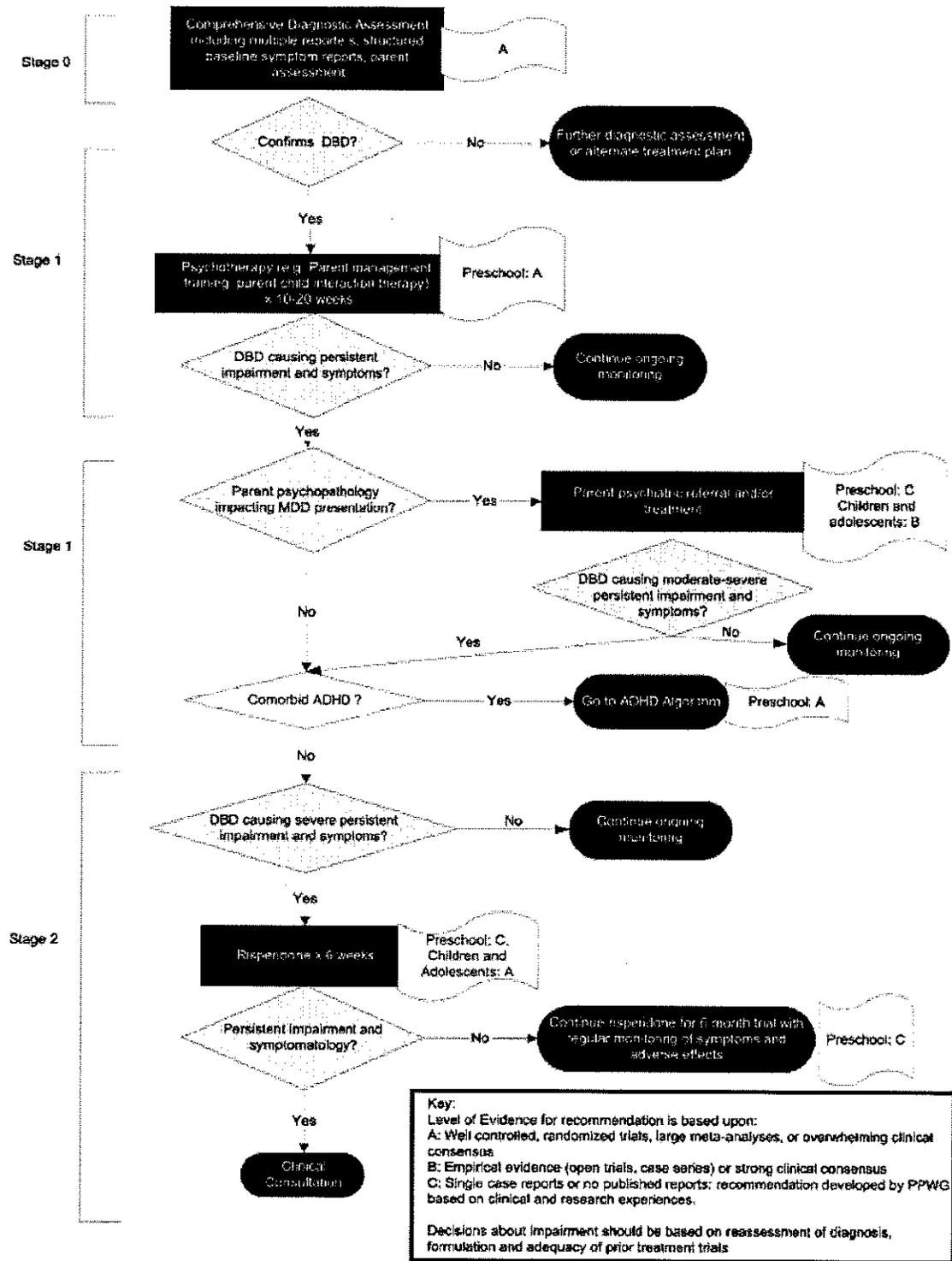


Fig. 2 Disruptive behavior disorder (DBD) algorithm. MDD = major depressive disorder.

behaviors (Biederman et al., 1998; Chilcoat and Breslau, 1997; Ingersoll and Eist, 1998). Parental mental health should be assessed and addressed if parental symptomatology appears to be affecting child symptoms. If the trial of therapy is ineffective, then the diagnoses and formulation should be reassessed before moving to the psychopharmacological treatment step.

#### Stage 2: Psychopharmacological Intervention (Risperidone)

There are no controlled trials of psychopharmacological interventions for preschoolers with ODD or conduct disorder who do not have comorbid mental retardation or pervasive developmental disorder (PDD). One retrospective case series of children taking risperidone for aggressive behavior associated with various diagnoses described a mean decrease of 36% of severity of symptoms associated with the risperidone treatment (Cesena et al., 2002). With limited evidence, medications should be considered only after a trial of psychotherapy and in the case of safety concerns or extreme impairment in multiple settings and relationships. If a child has co-occurring ADHD, the ADHD algorithm should be followed because that treatment is guided by a higher level of preschool data (Connor et al., 2002). Psychotherapy should continue throughout treatment, because therapy will affect parent-child interactions and thus have a broader focus than medications, which target only children's symptoms.

Before initiating medication, structured measures should be used to identify baseline symptomatology and these should be administered at least monthly during treatment. In older children and adolescents, most studies target aggression rather than a specific diagnosis. In a meta-analysis of 20 published studies of treatment of aggression, Connor and colleagues described moderate to large effect sizes for stimulants (treating co-occurring aggression and ADHD), antipsychotic agents including risperidone, and valproate and lithium (Connor et al., 2003; Connor et al., 2002). More recently published randomized controlled trials have demonstrated decreases in ODD symptoms and associated improvement in functioning in children with comorbid ADHD and ODD on Adderall XR (Spencer et al., 2006). Thus, for children with ADHD, the ADHD algorithm should be followed because the evidence base for methylphenidate exceeds that of other medications that are effective in treating aggression (Greenhill et al., 2006).

Risperidone is recommended as the first medication choice for treating children with DBD with severe aggression without co-occurring ADHD (Aman et al., 2002; Connor et al., 2003; Connor et al., 2002; Gerardin et al., 2002; Reyes et al., 2006). Compared with other agents with efficacy in treating aggression, risperidone has a wider therapeutic window than mood stabilizers and the most data regarding tolerability, although primarily in developmentally delayed children (Cesena et al., 2002; Masi et al., 2003; Mukaddes et al., 2004). In fact, in children with autism, there is sufficient evidence for an FDA indication for aggression and irritability (Janssen, 2006). Dosing can be informed by reports of tolerated use of risperidone in preschoolers with bipolar disorder (BPD) and PDD that have used doses as low as 0.25 mg and increased to 1.5 to 2 mg/day (Biederman et al., 2005b; Cesena et al., 2002; Luby et al., 2006). Although risperidone has more tolerability data than other medications, it is not without potential adverse effects. Weight gain (up to 3 kg in 6 months), hyperprolactinemia of unclear clinical relevance, and transient sedation have been associated with risperidone treatment in young children (Anderson et al., 2007; Biederman et al., 2005b; Luby et al., 2006; Masi et al., 2003). Drooling and nocturnal enuresis have also been described in older children with PDD (Aman, 2005; RUPP Autism Network, 2002). Use of atypical antipsychotic agents should follow the AACAP practice parameter on atypical antipsychotic agents (AAAs; AACAP, in preparation). This practice parameter describes the minimum standards for monitoring vital signs, body mass index, fasting blood glucose, extrapyramidal symptoms, lipid profiles, and electrocardiography. The practice parameter suggests that a recommendation for routine prolactin monitoring is not supported by the existing evidence. However, a recently published study adds to the data documenting significant (up to fourfold) elevations of prolactin in children and adolescents taking risperidone (Anderson et al., 2007). In the spirit of caution, but without evidence about the potential developmental impact of this elevation, monitoring of prolactin in preschoolers taking AAAs could be considered. Treatment effects may progress during the course of a 6-week trial (Findling et al., 2000). Risperidone should be discontinued after 6 months to reassess underlying symptoms.

If a trial of risperidone is ineffective, then the diagnosis, formulation, co-occurring diagnoses, and

level of psychotherapeutic intervention should be reassessed to determine whether the clinical picture continues to warrant aggressive treatment because of extreme impairment and distress across settings and relationships. The existing level of evidence does not provide clear guidance regarding a second-line medication for severe DBDs in preschoolers, although AAAs, mood stabilizers, or stimulants have been used in older children (Farmer et al., 2002; Pappadopulos et al., 2003; Spencer et al., 2006; Steiner et al., 2003).

*Not-Endorsed Practice.* Psychopharmacological intervention for behavior problems without psychotherapy is not recommended because of the stronger evidence base for psychotherapy in preschoolers with DBDs and the potential for longer lasting and broader targets of the psychotherapeutic interventions. Similarly, the use of medications as chemical restraints is not recommended, nor is the use of medication on an as-needed basis generally recommended. Medications with narrow therapeutic windows and risk of lethality if misused warrant caution and attention to the family's ability to safely maintain and administer medications.

#### MAJOR DEPRESSIVE DISORDER ALGORITHM

##### Stage 0: Diagnostic Assessment

Preschool major depressive disorder (MDD) is a serious and impairing disorder. In preschoolers MDD can be validly diagnosed using slight modifications to the *DSM-IV* criteria, including a change in the duration criteria to reflect developmental variability in mood presentation and inclusion of play-specific observations (Luby et al., 2002; Luby et al., 2003b; Luby et al., 2003c). A review of the current state of preschool MDD diagnosis and assessment provides a comprehensive approach to this diagnosis in preschoolers (Stalets and Luby, 2006). Assessment includes taking a history as well as observations with attention to the quality of play, which can differentiate depressed preschoolers from those who are not depressed (Fig. 3; Luby et al., 2003b; Mol Lous et al., 2002). Symptoms can be monitored throughout treatment with the Preschool Feelings Checklist, a highly sensitive screen for preschool depression, although its validity as a treatment monitor has not been tested (Luby et al., 2004a).

##### Stage 1: Nonpharmacological Treatment

Although no psychotherapeutic interventions have been specifically studied for the treatment of MDD in preschoolers, this algorithm recommends psychotherapy as the first-line intervention for this disorder. This recommendation is based on the equal lack of evidence in both psychotherapy and psychopharmacology for preschool MDD, the potential for sustained psychotherapy treatment effects demonstrated in other disorders (The POTS Team, 2004), the potential risks of psychopharmacological exposure, and the importance of the parent-child relationship and family context in young children's mood and emotional regulation. Treatment modalities that target the dyadic relationship have been shown to be effective in reducing emotional symptoms (not specifically MDD) in preschoolers (Choate et al., 2005; Hood and Eyberg, 2003; Lieberman et al., 2005) and may be useful in treating preschool MDD. Members of the PPWG had varying recommendations for recommended length of treatment, with most in the 3- to 6-month period, based primarily on clinical experience. When a psychotherapeutic intervention is ineffective, the authors recommend reassessing the diagnosis, formulation, and appropriateness of the psychotherapeutic intervention. Using clinical approaches similar to those described here, experienced specialists in preschool MDD and early childhood psychiatry generally report that they have needed to proceed to medications for preschool MDD only a few times in their careers. This is in contrast to PPWG survey respondents, two thirds of whom reported they would use medications to treat preschool MDD. The discrepancy in practice patterns may reflect differential access to therapy modalities in different practice settings.

Assessment should also include attention to parental psychopathology, with referral for treatment as appropriate (Byrne et al., 2006). Successful parental treatment would be an optimal goal because it may be associated with a reduction in child symptoms (Byrne et al., 2006; Weissman et al., 2006) and may enhance a parent's ability to participate fully in psychotherapeutic interventions. However, because this goal is not always possible, this step should not delay a child's access to treatment if a parent does not obtain treatment or if treatment is not successful.

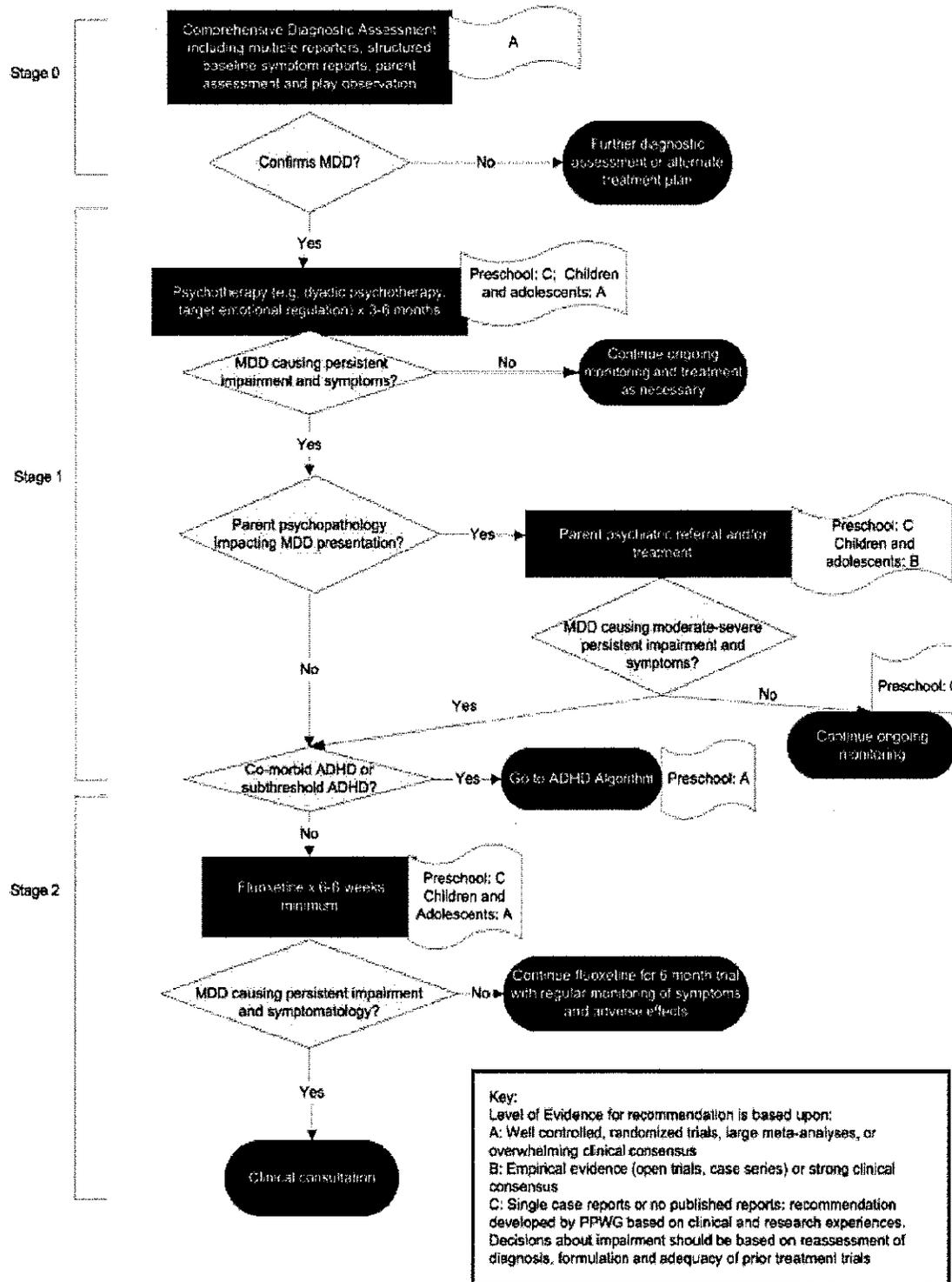


Fig. 3 Major depressive disorder algorithm.

### Stage 2: Psychopharmacological Treatment

If the clinical picture continues to warrant medication because of extreme impairment and distress, then psychopharmacological treatment can be considered, although psychotherapy should be continued. Because of the absence of an empirical base for treating preschool MDD, the algorithm recommends that clinicians follow the algorithm for co-occurring conditions for which more treatment evidence exists (e.g., ADHD) before considering psychopharmacological treatment for preschoolers.

Recommendations for psychopharmacological treatment of preschool MDD are based on the data and recommendation regarding older children (Hughes et al., 2007). Randomized clinical trials have demonstrated the efficacy of fluoxetine, citalopram, sertraline, and the combination of fluoxetine and cognitive-behavioral therapy (CBT; Emslie et al., 2004a; Emslie et al., 2002; TADS Study Team, 2004; Wagner et al., 2003; Wagner et al., 2004b). Of these, only the efficacy of fluoxetine has been demonstrated in more than one study (Emslie et al., 2002; Emslie et al., 1997; TADS Study Team, 2004). In addition, only fluoxetine had a favorable efficacy-safety profile based on review of published and nonpublished studies (Whittington et al., 2004) and, in a recent meta-analysis, only fluoxetine showed benefit over placebo for children under 12 years old (Bridge et al., 2007). Thus, fluoxetine is recommended as the first-line medication for preschoolers with MDD. If fluoxetine is effective in treating depressive disorder, then a cessation trial can be considered after 6 to 8 months of treatment to reassess the child's baseline mood symptoms and need for medication. If a 6- to an 8-week trial of medication is ineffective (CMAP, 2006), then the diagnosis, formulation, level of psychotherapeutic intervention should be reassessed.

SSRIs have received high levels of attention because of concerns about risk of suicidality in children and adolescents who are taking these medications. These concerns have resulted in a black box warning on these medications for children (FDA, 2004). Epidemiological analyses suggest an association between decreased rates of completed suicide and higher rates of SSRI use in U.S. youth (Gibbons et al., 2006). Although this issue is beyond the scope of this article, clinicians should be aware of FDA warnings and follow expert

recommendations for monitoring children who are taking SSRIs (APA and AACAP, 2004).

*Not-Endorsed Practice.* A small proportion of PPWG survey respondents reported using tricyclic antidepressants to treat preschool MDD (5.8%). This class of medications is not recommended for use in preschoolers with MDD because it has no proven efficacy in children and adolescents with MDD. In addition, bupropion is not recommended to treat preschool MDD because of the limited evidence in youth with MDD and the theoretical risk of seizures in a population with developing central nervous systems.

### BIPOLAR DISORDER ALGORITHM

#### Stage 0: Diagnostic Assessment

The diagnosis of BPD in preschoolers has not been the focus of significant empirical research. The limited literature may be related to the ongoing controversy about the diagnosis and its definition in older school-age children and adolescents, a phenomenon that only adds to skepticism about the application of the diagnosis to younger children (AACAP, 2007). In fact, there is no clear consensus that young children with severe emotional dysregulation have a bipolar disorder. Within the PPWG, consensus about this diagnosis in preschoolers was not achieved; however, attention to the diagnosis is warranted because this diagnosis tends to be associated with the use of aggressive psychopharmacological interventions, often without psychotherapeutic or psychosocial interventions in community settings (Danielyan et al., 2007). Our group agreed that discussion of extreme mood and behavior dysregulation in preschoolers deserves attention.

Until recently, the literature describing preschoolers diagnosed with BPD was limited to case reports and retrospective analyses (Biederman et al., 2005b; Scheffer et al., 2004; Tumuluru et al., 2003). In 2006 Luby and Belden published a controlled exploratory investigation of age-adjusted mania symptoms, demonstrating that a mania-like syndrome was identifiable in preschool-age children when age-adjusted mania manifestations were assessed. The key specific characteristics of mania in this age group included elation, grandiosity, and hypersexuality. This syndrome was distinguishable from normative developmental extremes as well as other Axis I disruptive behavioral disorders. Perhaps most

suggestive of the need for clinical attention to this early-onset symptom constellation was the finding of significant impairment in functioning, even greater impairment than those with other Axis I disruptive disorders.

Structured assessment approaches, including several systematic interviews and observations, are recommended for diagnosis, with attention to the presence of symptoms that are unique to bipolar disorder (Fig. 4). A comprehensive assessment, focused on developmental level, psychosocial stressors, parent-child relationship difficulties, and temperament is considered a "minimal standard" in the 2007 AACAP practice parameter for BPD (AACAP, 2007).

#### Stage 1: Nonpharmacological Interventions

Empirical evidence for psychotherapeutic interventions is limited; however, given the need to implement the safest possible interventions, it is important to also explore age-appropriate forms of psychotherapy as first treatment stages. A well-tested and known efficacious early intervention for disruptive behaviors in preschoolers, parent-child interaction therapy (PCIT; Eyberg, 1988) has been adapted for testing in preschool BPD and has been described elsewhere (Luby et al., in press). A pilot study of PCIT in preschoolers is underway. The efficacy of PCIT remains to be tested in larger, controlled investigations. Interventions focused on parent psychoeducation and support, behavioral interventions, affect regulation, symptom monitoring, medication adherence, and treatment of parental psychopathology may be useful components in treating children with extreme dysregulation (Fristad, 2006; Milkowitz et al., 2006). There are no data to guide recommendations for the duration of such treatment, although most behavioral interventions include 8 to 12 sessions. If therapy does not appear to be effective, then the diagnosis, formulation, and appropriateness of the intervention should be reassessed. As recommended in the AACAP practice parameters, ongoing psychotherapeutic treatment is indicated throughout treatment for children with extreme behavioral dysregulation (AACAP, 2007). In addition, attention to co-occurring disorders such as ADHD, ODD, generalized anxiety disorder (GAD), and parental psychopathology is recommended before continuing along the algorithm.

#### Stage 2: Psychopharmacological Intervention

If psychotherapeutic efforts fail to improve the child's mood and behavior, then pharmacological interventions may be considered in cases of significant impairment and distress associated with signs of serious mood and behavioral dysregulation. The available literature on the psychopharmacological treatment of preschool mania consists of case studies, open trials, and retrospective chart reviews (Biederman et al., 2005b; Mota-Castillo et al., 2001; Pavuluri et al., 2002; Scheffer et al., 2004; Tuzun et al., 2002).

The tolerability of lithium in preschoolers has been examined in a small case series (Hagino et al., 1995). This group found that 20% ( $n = 4$ ) preschoolers had serious central nervous system side effects (confusion, slurred speech, ataxia) and an additional 40% ( $n = 8$ ) had "nuisance" side effects that included polyuria. When preschoolers are learning to achieve bladder control, polyuria and nocturnal enuresis may constitute significant adverse effects.

There have been three reports about the use of AAAs in preschoolers with mania (Biederman et al., 2005b; Pavuluri et al., 2002; Scheffer et al., 2004). Biederman and colleagues reported the results of an open trial of olanzapine or risperidone in 31 children, ages 4 to 6 years, diagnosed clinically with BPD (I, II, or NOS) with a manic or mixed episode (Biederman et al., 2005b). Both treatment groups showed a significant reduction in their manic symptoms on the Young Mania Rating Scale (YMRS). Response rates, defined as a 30% decrease in symptoms from baseline, were 69% for risperidone and 53% for olanzapine. In a retrospective chart review, Scheffer et al. described a significant decrease in mania symptoms in 31 children 2 to 5 years old treated primarily with valproate. Pavuluri et al. described a case report of a 4½-year-old girl who was clinically diagnosed with BPD, who showed improvement in irritability but ongoing moodiness and significant weight gain on risperidone. The addition of lithium was associated with intolerable polyuria in this patient. The addition of topiramate was associated with improved mood stability, sleep, and weight loss.

Pavuluri and associates reported the results of an open, long-term, prospective trial that examined the safety and efficacy of risperidone augmentation of lithium in preschool-onset BPD among youth who

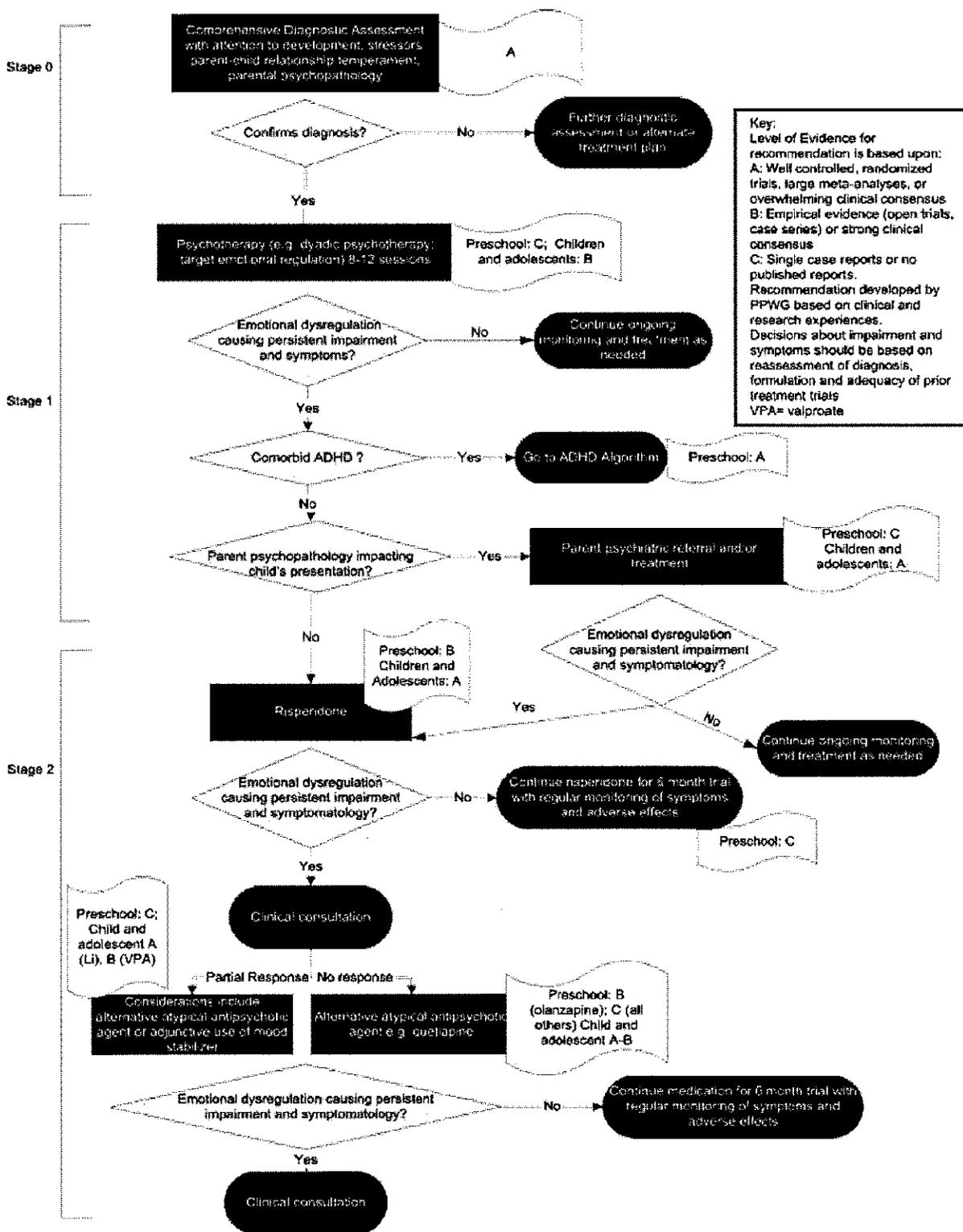


Fig. 4 Bipolar disorder algorithm. Li = lithium.

insufficiently responded to lithium monotherapy (Pavuluri et al., 2006). Of 38 patients with preschool-onset BPD ages of 4 and 17 years (mean age  $11.37 \pm 3.8$  years), 21 failed to respond to 8 weeks of lithium monotherapy or relapsed during the 12-month trial. These patients received augmentation with risperidone. Response rate in the youths treated with lithium augmented with risperidone was 85.7% ( $n = 18/21$ ). The authors concluded that a substantial proportion of youth with a history of preschool-onset BPD were either nonresponders or partial responders to lithium and that subsequent augmentation of lithium with risperidone in these cases was well tolerated and efficacious.

In a prospective placebo-controlled investigation of lithium in children and adolescents with BPDs, Geller et al. reported that subjects treated with lithium showed a significant improvement in global assessment of functioning (Geller et al., 1998). In addition, four older crossover trials with lithium showed response rates from 33% to 80% (Annell, 1969; Brumback and Weinberg, 1977; Dyson and Barcai, 1970; Gram and Rafaelsen, 1972). In four open, prospective trials of valproate, response rates varied from 53% to 80% (Kowatch et al., 2000; Pavuluri et al., 2005; Scheffer et al., 2005; Wagner et al., 2002). There have been no controlled studies of carbamazepine for the treatment of children and adolescents with BPD. Negative randomized controlled trials of oxcarbazepine and topiramate have been published (DelBello et al., 2005; Wagner et al., 2006).

There are two controlled studies of atypical antipsychotic agents to treat mania in children and adolescents. Tohen et al. (2005) conducted a multicenter, randomized, double-blind, parallel trial of olanzapine in adolescents with BPD. The olanzapine-treated patients experienced a significantly greater mean decrease from baseline to endpoint in YMRS total score relative to placebo, and a greater proportion of patients treated with olanzapine met response and remission criteria (45% vs. 18%). Although olanzapine was more effective than placebo in the treatment of acute mania in adolescent patients, the olanzapine-treated patients had significantly greater weight gain. A recent double-blind placebo-controlled trial compared monotherapy with divalproex to monotherapy with quetiapine (DelBello et al., 2006). Although a repeated measures analysis of variance using the last-observation-carried-

forward data indicated no statistically significant group difference in YMRS, a comparison of slopes revealed that improvement in YMRS scores occurred more rapidly in the quetiapine group than in the divalproex group.

The efficacy and tolerability of quetiapine in combination with valproate for acute mania in adolescents with BPD was assessed in a randomized, double-blind placebo-controlled study (DelBello et al., 2002). The results of this study demonstrated that quetiapine in combination with valproate was more effective at reducing manic symptoms associated with BPD than valproate monotherapy and that quetiapine is tolerated when used in combination with valproate.

Ziprasidone and aripiprazole have the advantage of being associated with the least amount of weight gain among the atypical antipsychotics in adults (Newcomer, 2007). In a recently completed dose-finding 3-week open-label study of ziprasidone for adolescents with psychosis ( $N = 46/63$  with bipolar disorder), patients were randomized to receive 40 mg b.i.d. (low-dose group,  $n = 23$ ) or 80 mg b.i.d. (high-dose group,  $n = 40$ ) of ziprasidone titrated over approximately 10 days. In the patients with BPD, there was a mean reduction in YMRS score of 17.2 (8.2) for completers in the low-dose group and 13.1 (8.9) for completers in the high-dose group (Versavel et al., 2005). Aripiprazole is the newest atypical antipsychotic and two retrospective case series reported similar results, suggesting that approximately 70% of children and adolescents with BPDs may respond to aripiprazole (Barzman et al., 2004; Biederman et al., 2005a). One study reported, however, that approximately one fourth of patients treated with aripiprazole experience akathisia (Barzman et al., 2004).

#### Recommendations for Treatment

If psychotherapeutic efforts fail and pharmacological interventions are needed, risperidone is the option with the most available data on effectiveness and tolerability in preschool-age children (Biederman et al., 2005b) and the only atypical antipsychotic with an FDA indication for irritability and aggression in children older than age 6 with autism. In making this recommendation, we prioritized efficacy and safety and considered that a primary target of medication in children with manic symptoms would often be their aggressive behaviors and irritability, symptoms for which risperidone has a preschool indication in autistic children (Janssen,

2006). The open trials discussed above suggest that initial doses of 0.25 to 2.0 mg/day may be appropriate (Biederman et al., 2005b), with 0.25 mg b.i.d. often effective. The adverse effect profile for use of risperidone is described in the section on DBD.

Some patients may not fully respond to, not tolerate, or worsen with risperidone after a 3- to 4-week trial. If this is the case, then clinical consultation with an expert in pediatric psychopharmacology or child psychiatry with experience treating preschoolers is recommended. The traditional mood stabilizing agents lithium, valproate, and carbamazepine remain largely untested in controlled studies in this age group and their tolerability and efficacy remain unclear. When a child demonstrates a partial response to risperidone and still has significant mood or behavioral symptoms, some clinicians may consider the addition of a traditional mood stabilizer like lithium or valproate. However, these agents require frequent blood draws and are sometimes less feasible in young children given their relative difficulty tolerating blood draws. Either of these agents should be considered only under conditions in which parents are highly reliable and can monitor the child carefully for side effects.

If there is no response or a negative response to risperidone, then a trial of an alternative atypical antipsychotic may be considered. Quetiapine has the advantage of a low rate of extrapyramidal side effects and no elevation of serum prolactin (AACAP, in preparation; Weiden, 2007). Olanzapine may also be considered, based on data in older children with BPDs (Tohen et al., 2005); however, controlled studies of the tolerability and efficacy of these agents are needed in all age groups of patients with BPD.

The longitudinal course of preschoolers identified as having BPD is not yet known. Thus, a discontinuation trial of medication is warranted after 6 months of treatment to reassess symptoms and the need for continued treatment.

#### Not Recommended

Although BPD in older children is often treated solely with psychopharmacological agents, the use of medication without psychotherapeutic intervention is not recommended in preschoolers. The challenges and controversy surrounding the diagnosis, the value of supporting preschoolers' development in the areas of emotional and behavioral self-regulation, and the

known impact of preschool dysregulation on the family guide this recommendation. We recognize that empirically supported psychotherapy for preschoolers with BPD have not yet been identified, however, a common-sense approach requires that nonbiological interventions will be necessary to support families with an extremely dysregulated preschooler.

In addition, 20% of physicians surveyed in the PPWG survey endorsed using more than one medication concomitantly for preschool BPD. This practice, which is likely a reflection of the extreme impairment associated with these symptoms, is not supported by empirical studies and may have adverse effects on the developing child. Thus, combination therapy should be used only after clinical consultation, with extreme caution, and in patients who have not responded to monotherapy.

#### ANXIETY DISORDERS ALGORITHM

##### Stage 0: Diagnostic Assessment

This section reviews the treatment of a group of anxiety disorders: separation anxiety disorder (SAD), GAD, selective mutism (SM), and specific phobia (SP; Fig. 5). These disorders are addressed together because the psychopharmacological approaches for these disorders are similar in older children with SAD, GAD, SM, and SP (e.g., RUPP Anxiety Study, 2001). Panic disorder is not included because there is insufficient evidence that this disorder presents in the preschool age (AACAP Task Force on Research Diagnostic Criteria: Infancy Preschool Age, 2003). PTSD and obsessive compulsive disorder (OCD) are addressed separately because evidence suggests they may require different treatment approaches. Anxiety disorders can be distinguished from typical preschool fears and worries by the intensity of the symptoms and by the presence of functional impairment. Parental accommodation to the symptoms can sometimes appear to reduce functional impairment and warrant explicit exploration during the assessment.

Assessment of preschool anxiety disorders should include parent report history, child report of symptoms if verbal skills are sufficient, observations of child and parent-child interactions, and structured measures. Co-occurring conditions, including other anxiety disorders, depression, and DBDs are common and should be explored (Egger et al., 2006a). When an anxiety

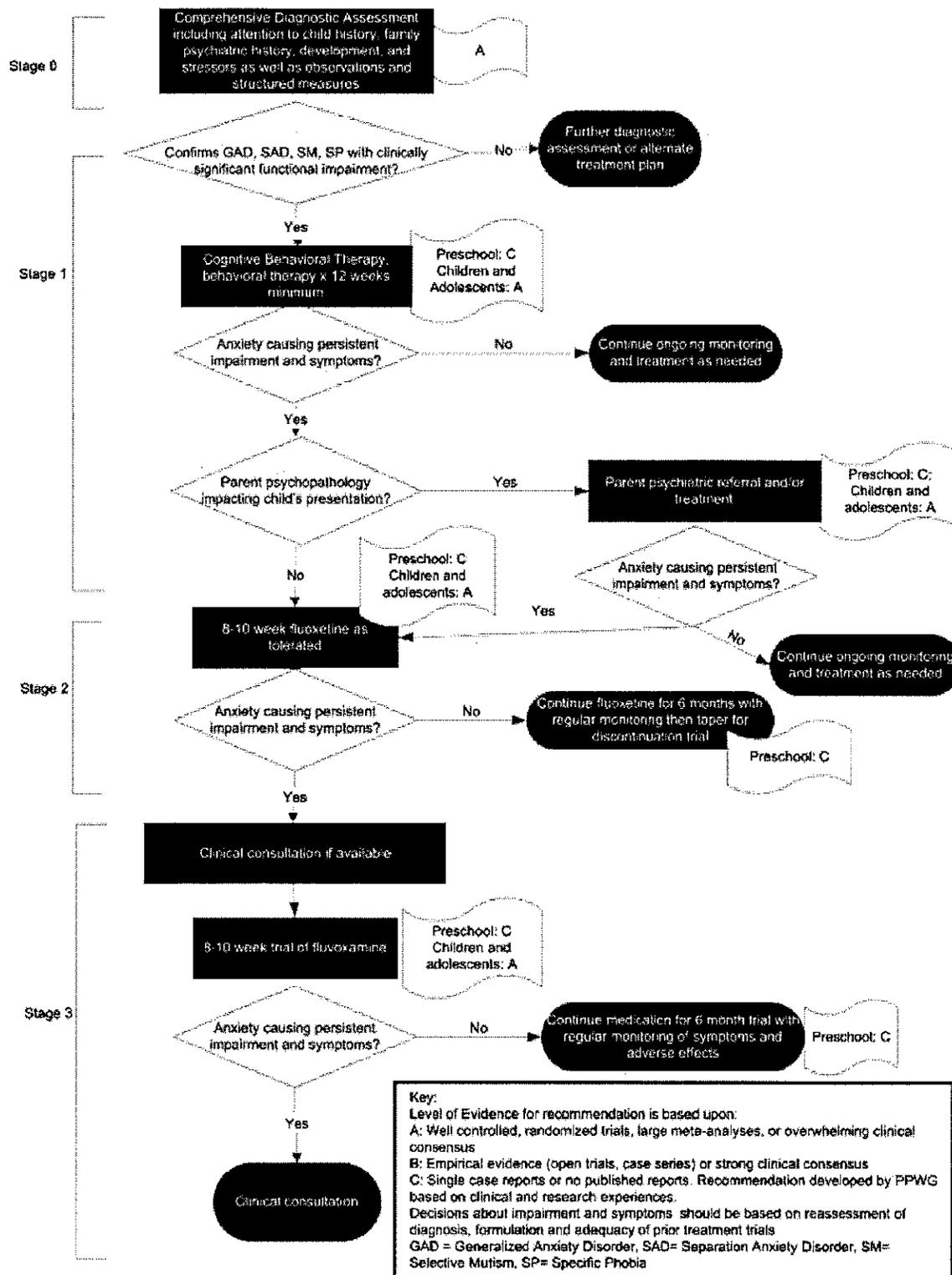


Fig. 5 Anxiety disorders algorithm (GAD, SAD, SM, and SP).

disorder is diagnosed, symptom severity can be monitored with a structured measure. Although no measure has specifically been validated for measuring preschool anxiety, subsets of the Child Behavior Checklist 1½–5 Anxiety scale (Achenbach and Rescorla, 2000) or the Infant-Toddler Social Emotional Assessment (Briggs-Gowan, 1998), or developmentally modified anxiety scales for older children such as the Screen for Child Anxiety Related to Emotional Disorders (Birmaher et al., 1999) may be appropriate. Use of the measure at regular intervals over the course of treatment can inform additional treatment.

#### Stage 1: Nonpsychopharmacological Interventions

Although the published empirical support for psychotherapeutic interventions for preschoolers with non-PTSD, non-OCD anxiety disorders is limited, case reports and open trial data suggest that behavioral therapy techniques and CBT interventions can be valuable in treating preschoolers with anxiety disorders (King et al., 2005). Widely used psychotherapeutic interventions can be modified to address the child's specific clinical presentation, developmental level and language abilities, and access to therapy resources in the community (Compton et al., 2002; James et al., 2005; Kendall et al., 1997). A comprehensive review of interventions for anxiety disorders in children and adolescents may serve to guide these choices (Compton et al., 2002). The existing treatment data suggest that a minimum duration for psychotherapy intervention trial is 12 weeks. Consistent with this recommendation, most PPWG survey respondents reported treating preschoolers psychotherapeutically for at least 3 months before considering medication treatment. Because of the strong probability of a family history of anxiety in children with anxiety disorders, parental psychiatric assessment or referral should be considered, particularly if the parental symptomatology appears to be affecting the child's presentation (Byrne et al., 2006; Cobham et al., 1998).

#### Stage 2: Psychopharmacological Intervention (Fluoxetine)

In rare cases a preschooler may have intolerable ongoing symptoms, even after sufficient psychotherapeutic interventions. In these cases it is critical to reassess the diagnosis, case formulation, and assessment of the adequacy of the psychotherapy trial. If the clinical presentation continues to reflect that an anxiety

disorder is the primary source of impairment, the child exhibits extreme impairment in at least one setting, and the psychotherapy trial was adequate, then psychopharmacological intervention may be considered.

Data related to psychopharmacological treatment of anxiety disorders in preschoolers are scant. There are no randomized controlled studies of psychopharmacological interventions with preschoolers with anxiety disorders. Most reports on psychopharmacological anxiolytic agents in preschoolers focus on premedication for medical and dental procedures or toxic ingestions of benzodiazepines (e.g., Wiley and Wiley, 1998). Three case reports represent the published preschool non-PTSD, non-OCD anxiety disorder literature (Avci et al., 1988; Hanna et al., 2005; Wright et al., 1995). In these individual case reports fluoxetine and buspirone are described as part of the effective treatment approaches. Ineffective trials of alprazolam and hydroxyzine are also described within one case report (Avci et al., 1988). Although these cases provide the important first steps toward developing a literature focused on clinical treatment of preschoolers with anxiety, diagnostic uncertainty, coadministration of various therapeutic modalities, and unclear rationale for medication choices limit their generalizability.

In randomized controlled trials in older children, fluoxetine and fluvoxamine have been shown to be superior to placebo in treating children with anxiety disorders including SAD, GAD, and SP (Birmaher et al., 2003; RUPP Anxiety Study, 2001). Randomized clinical trials also support the efficacy of paroxetine for SAD and sertraline for GAD (Rynn et al., 2001; Wagner et al., 2003). No SSRIs are approved for use in children or adolescents for non-OCD anxiety disorders. It is worth noting that negative reports for pediatric anxiety disorders have included clonazepam (Graae et al., 1994), alprazolam (Simeon et al., 1992), imipramine (Klein et al., 1992), and buspirone (Bristol-Myers Squibb, 2000).

Based on the efficacy and safety literature in preschoolers, children, and adolescents, fluoxetine is the first-choice medication for preschool anxiety (Avci et al., 1988; Birmaher et al., 2003; Black and Uhde, 1994). It has been used most extensively in children and adolescents and has the strongest safety profile at least in studies of depression (Whittington et al., 2004). Although Wagner and colleagues demonstrated the

efficacy of paroxetine in the largest randomized controlled anxiety study in children and adolescents (Wagner et al., 2004a), this drug is not recommended as a first line medication because of safety concerns that have been raised about it. The existence of two negative studies of buspirone in older children suggests that it may not be an effective antianxiety agent in children and adolescents (Bristol-Myers Squibb, 2000), in spite of the case report suggestion of effectiveness.

Consideration of safety and monitoring of SSRIs in young children with anxiety are similar to those with depression. Based on case reports, doses as low as 5 to 8 mg/day of fluoxetine may be effective for treating anxiety, although it may be necessary to increase the dose to achieve optimal dose (Avci et al., 1988; Wright et al., 1995). When a dose is stabilized, symptoms should be monitored at least monthly with a validated measure. An adequate trial of medication is 8 to 10 weeks long, if tolerated (Birmaher et al., 2003; RUPP Anxiety Study, 2001). As with all successful psychopharmacological interventions in preschoolers, treatment initiation should include a discussion of planned discontinuation trial after 6 to 9 months of treatment. This treatment duration is shorter than recommended for older children because of the rapid development occurring in preschoolers, and the recognition that some fears may decrease after the preschool period (Muris et al., 2000).

#### Stage 3: Psychopharmacological Intervention (Fluvoxamine)

If the psychopharmacological intervention is ineffective, then the clinician should reassess the diagnosis, formulation, and intensity level of the psychotherapeutic intervention. Before a second psychopharmacological psychotherapeutic trial is initiated, the algorithm recommends that clinicians consult with a child psychiatrist with expertise in early childhood psychiatry. If the consultant and clinician concur that the clinical presentation continues to warrant medication because of extreme impairment and distress in multiple settings, then a trial of a second SSRI may be considered. For example, after an unsuccessful trial of fluoxetine, switching to fluvoxamine could be justified because these are the best studied SSRIs in children (RUPP Anxiety Study, 2001).

*Not-Endorsed Practices.* Benzodiazepines are not recommended for ongoing use in preschool anxiety

disorders because of the lack of evidence supporting benzodiazepines in preschool anxiety disorders, as well as the potential dangers associated with unintentional ingestion of these medications in preschoolers. These medications may be appropriate for medical or dental procedures in children with extreme anxiety reactions to procedures. In the PPWG survey, approximately 25% of physicians who prescribe medications for preschoolers with anxiety disorders reported using  $\alpha$ -agonists and 10% reported using tricyclic antidepressants. These medications have narrow therapeutic windows and are not recommended as anxiety treatments for preschoolers.

### POSTTRAUMATIC STRESS DISORDER ALGORITHM

#### Stage 0: Diagnostic Assessment

Assessment of PTSD is a more complicated task compared to most other disorders. Whereas much of the symptomatology of other common disorders of childhood are easy to understand and directly observable, identifying the key symptomatology of PTSD requires that the clinician recognize the link between a child's observable behaviors and a traumatic experience. It is not uncommon for children to respond to triggers that adults do not identify as reminders of the trauma. In the early childhood period, children may have limited verbal skills to talk about traumatic experiences and concurrently are at the highest risk of child abuse (U.S. Children's Bureau, 2004). Thus, it is particularly important for clinicians to consider the possibility of trauma exposure in preschoolers presenting with psychiatric symptoms. The assessment of preschool PTSD requires developmentally sensitive application of the *DSM-IV* criteria, thus a clinician with experience in working with young children and in assessment of PTSD is the optimal evaluator. Baseline symptoms should be assessed systematically and the clinician should develop a plan for regular monitoring with a structured measure such as the Child Behavior Checklist-PTSD (Fig. 6; Dehon and Scheeringa, 2006).

#### Stage 1: Nonpsychopharmacological Interventions

PTSD is unique among preschool anxiety disorders because of the strength of empirical evidence supporting psychotherapeutic interventions. The two best studied modalities, child-parent psychotherapy (CPP) and preschool CBT, have not been compared to each other, but both are related to sustained decreases in rates

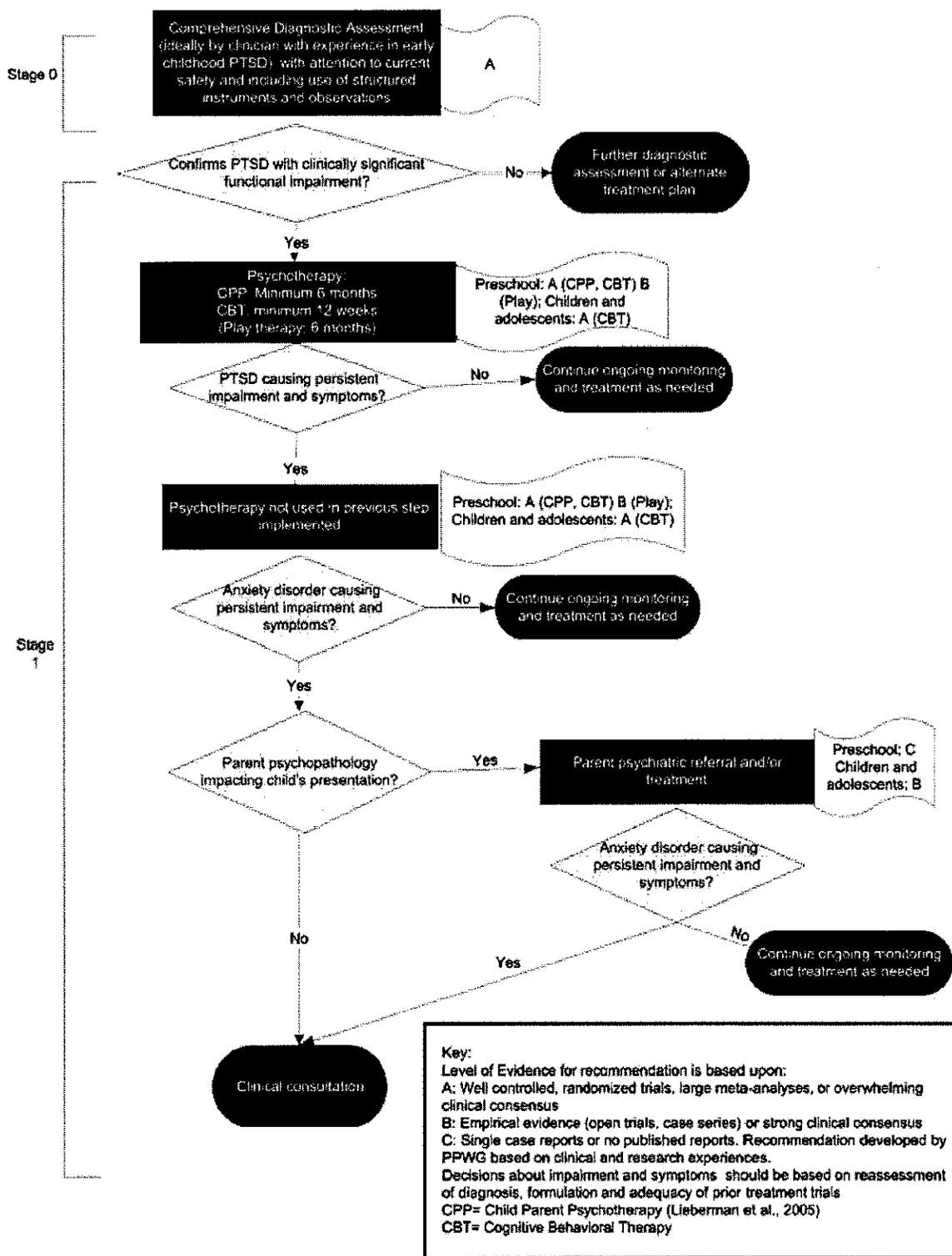


Fig. 6 Posttraumatic stress disorder algorithm. CBT = cognitive-behavioral therapy.

of diagnosis and symptoms in preschoolers exposed to traumatic events in controlled trials (Cohen and Mannarino, 1996; Cohen and Mannarino, 1997; Lieberman et al., 2006; Lieberman et al., 2005). Either may be used as a first-line therapeutic intervention, depending on therapist skills and local resources. Consistent with this recommendation, in the PPWG survey, more than 50% of respondents reported that both dyadic therapy and CBT were necessary before considering psychopharmacological treatment. A trial of preschool-specific CBT, which should include parents, should be implemented for a minimum of 12 weeks, the duration of published preschool CBT interventions (Cohen et al., 2004; Cohen and Mannarino, 1996). Although CPP has only been studied as a year-long treatment and for one type of traumatic experience (domestic violence), this working group felt that a year-long trial is impractical in most practice settings, especially if the treatment did not seem effective. There are no known published data to guide recommendations of a shorter trial, but the group agreed that a 6-month trial may be appropriate for CPP before determining whether different treatment is warranted. This recommendation is only slightly longer than the most common response for recommended psychotherapy duration on the PPWG survey.

If neither CPP nor CBT is available, the algorithm recommends a 6-month trial of play therapy, which has been used extensively in treating trauma-exposed preschoolers (Gaensbauer, 2000; Gaensbauer, 2004). This therapy, which is not supported by randomized controlled trials, is recommended preferentially to medications because psychopharmacological intervention would require extrapolation from adult data because there are no randomized controlled trials of medications for PTSD in children. If the first trial of a psychotherapeutic intervention is ineffective, the working group recommends that the child's safety, diagnosis, case formulation, and adequacy of intervention be re-evaluated and a second psychotherapeutic approach be applied if available.

In a number of circumstances, children and parents experience traumatic experiences together, the interplay of symptoms within the dyad can have important and lasting implications for the child's presentation and treatment outcome (Cohen and Mannarino, 1998; Scheeringa and Zeanah, 2001). When parental symp-

toms have a negative impact on dyadic or individual functioning, parents should be referred for treatment; however, preliminary findings in preschoolers do suggest that children can respond to PTSD treatment before their parents show improvement (Scheeringa et al., in press). Thus, parental symptomatic improvement should not delay preschool psychotherapeutic intervention.

#### Stage 2: Psychopharmacological Intervention

Because the only randomized controlled trials for psychopharmacological treatment in adults and because of a relatively strong literature supporting psychotherapeutic interventions for PTSD, the working group cannot recommend the use of psychopharmacological intervention for PTSD in preschoolers in this algorithm. It should be noted that in the PPWG survey, only 11% of providers reported that they do not use medications to treat preschool PTSD, and more than half reported using SSRIs for preschool PTSD. Although we recognize our recommendation may not reflect current practices in the community for preschoolers with trauma exposure, and our group recognizes the potential for symptom severity and limited access to psychotherapeutic modalities, we are reluctant to make recommendations for psychopharmacological treatment in the context of the current literature. Clinicians may choose to follow other algorithms for children with co-occurring disorders, such as ADHD.

*Not-Endorsed Practices.* A striking proportion of the PPWG survey respondents reported using tricyclic antidepressants (9.2%) and benzodiazepines (9.2% lorazepam, 5.8% clonazepam) to treat preschool PTSD. This algorithm does not recommend regular use of these medications to treat PTSD because of the narrow therapeutic windows of these agents and the lack of empirical support for their use.

### OBSESSIVE-COMPULSIVE DISORDER ALGORITHM

#### Stage 0: Diagnostic Assessment

Like PTSD, OCD has a unique evidence base warranting individual attention. OCD in preschoolers has received little attention in the literature, in spite of the attention on developmental processes in OCD (Freeman et al., 2003; Geller et al., 1998; Scabill et al., 2003; Tobias and Walitza, 2006). The differential diagnosis of OCD includes SAD or other anxiety

disorders, tic disorders, PDD, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, or movement disorders (Fig. 7; Freeman et al., 2003; Rapoport and Inoff-Germain, 2000). Although magical thinking and some rigidity are not uncommon in the preschool years, repetitive checking or other common compulsions are rare in typically developing preschoolers (Evans et al., 2002; Spence et al., 2001). In clinical practice, preschoolers with OCD can present with extremely rigid behavior patterns, which can cause significant family and personal functional distress and impairment. Baseline symptoms should be assessed with a systematic measure, such as the Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS; Scahill et al., 1997).

#### Stage 1: Nonpharmacological Intervention

Psychoeducation related to OCD may help to reduce stigma, blame, and guilt that is related to the disorder (Freeman et al., 2003; Piacentini and Langley, 2004) and consequently reduce the impact of OCD symptoms on a child and family. This is particularly important because negative responses to OCD behaviors such as punishments have been shown to be counterproductive in pediatric OCD (March et al., 2001).

CBT using exposure and response prevention techniques and involving parents is recommended for treatment of preschool OCD. Only two known case reports describe the successful treatment of preschool OCD. In one case, family CBT resulted in symptom improvement (Tolin, 2001). Inpatient behavioral treatment, for which limited details are available, was effective in the second case (Tobias and Walitza, 2006). The OCD literature provides compelling data comparing psychopharmacological treatment and psychotherapeutic treatment in older children. CBT in combination with medication (sertraline) has been shown to be more effective than CBT alone, which in turn had a larger effect size than sertraline alone (The POTS Team, 2004). Compared with sertraline, CBT is also associated with a lower relapse rate 9 months after treatment (Asbahr et al., 2005). CBT alone has been suggested as the first-line treatment in prepubertal OCD (March, 1995). The literature provides solid support for the use of CBT and its components in OCD, but not for insight-oriented therapies, play therapy, and non-CBT-based family therapy (as

reviewed in King et al., 1998; Piacentini and Langley, 2004; Turner, 2006). Parental psychopathology, especially OCD, can interfere with a child's OCD presentation and should be addressed if parental symptoms affect a child's symptoms or a parent's ability to participate in therapy.

#### Stage 2: Psychopharmacological Treatment (Fluoxetine, Fluvoxamine, Sertraline)

The psychopharmacological treatment literature for preschool OCD is limited. There are no studies or reports of psychopharmacological treatment for preschoolers with OCD. In school-age children and adolescents, there is a more extensive literature, which is focused on psychopharmacology and comparisons of medication with psychotherapy. In a meta-analysis of 12 studies including 1,044 children, the SSRIs (fluoxetine, fluvoxamine, sertraline, and paroxetine) were equally efficacious and were more effective than placebo, although the benefit over placebo is small (Geller et al., 2003). Increasing the dose to achieve larger effects is likely to be unsuccessful and be associated with adverse effects. Consensus in the field supports the use of newer SSRIs over clomipramine because of tolerability, monitoring issues, and safety, with particular attention paid to the prolongation of the QT interval on clomipramine (AACAP, 1998; Geller et al., 2004; The POTS Team, 2004).

Preschool psychopharmacological treatment should be considered only if the symptoms continue to cause significant distress or severe impairment in a child's relationships, daily routine at home, or in the child care setting. Although the CYBOCS does not have reliability and validity data for preschoolers (Scahill et al., 1997), a child with a CYBOCS score <10 or a Global Assessment of Functioning Score <50 is not likely to meet these severity and impairment criteria. Psychopharmacological treatment should always occur in the context of ongoing cognitive and/or behavioral interventions (AACAP, 1998). SSRIs provide the best safety profile in school-age children and are the most commonly used; these medications should be used only in the context of the current AACAP and FDA recommendations. Among fluoxetine, fluvoxamine, and sertraline, there is insufficient evidence to suggest that one medication is more likely to be efficacious than the others in older children with OCD (Geller et al., 2003). As described in the section on MDD, the dose of

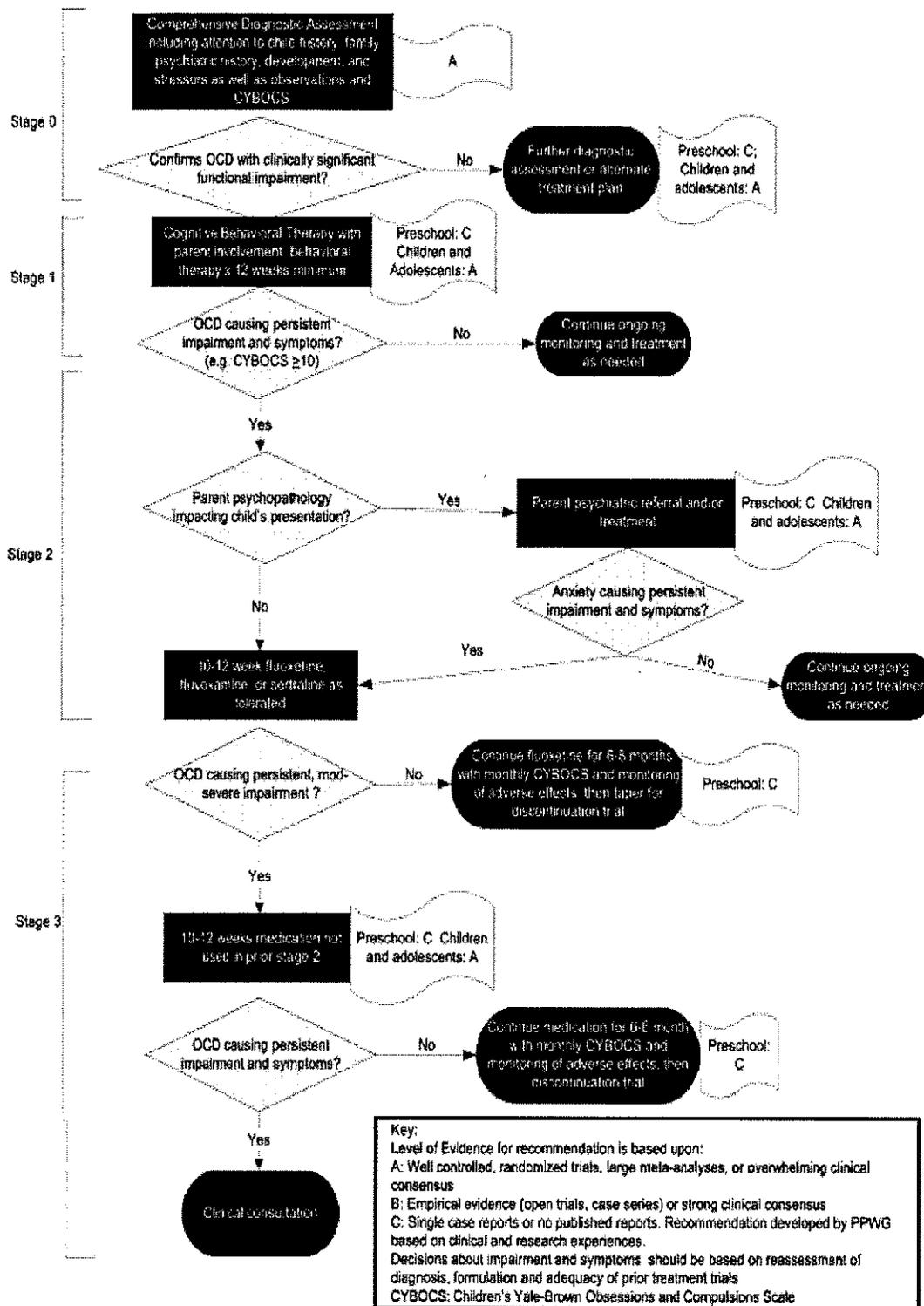


Fig. 7 Obsessive-compulsive disorder algorithm.

fluoxetine may be as low as 5 mg. Doses of sertraline or fluvoxamine should initially be targeted at similarly low doses. The liquid formulations of sertraline and fluoxetine allow gradual upward adjustment of doses from low starting doses. Medication trials in OCD should be at least 10 to 12 weeks with careful monitoring of adverse effects and treatment response with monthly CYBOCS administration (AACAP, 1998; Geller et al., 2003). If a preschooler with OCD responds to an SSRI, then a discontinuation trial is recommended after 6 to 8 months of successful treatment, with appropriate taper of medication and psychoeducation for the child and family.

#### Stage 3: Psychopharmacological Intervention (Fluoxetine, Fluvoxamine, Sertraline)

If a first medication trial fails, reassessment of clinical symptoms, case formulation, and appropriateness of the psychotherapeutic intervention are recommended. If a clinical need for medication is determined because of severe impairment limiting the child's functioning, then a second SSRI may be considered, used in the same manner as the first. Because of documented EKG changes in children on clomipramine, it should be considered only for severe, treatment-resistant OCD and would require close monitoring of EKG changes as well as clinical symptoms (Leonard et al., 1995).

*Not-Endorsed Practices.* A number of experimental biological treatments for OCD, including plasmapheresis and intravenous immunoglobulin, have been tested in small samples of older children with severe, treatment-resistant disease (Perlmutter et al., 1999). Because of the limited data, risk for hemodynamic instability, and risk for exposure to blood products, these treatments are not endorsed for use in the preschool age group.

### PERVASIVE DEVELOPMENTAL DISORDERS ALGORITHM

#### Stage 0: Diagnostic Assessment

By the *DSM-IV* definition, autism must present before age 3 years, and other PDDs are typically recognized by parents in the first 3 years of life (reviewed in Chawarska and Volkmar, 2005). These disorders presents with severe delay in socialization, as well as delayed and deviant language and/or repetitive behaviors. Minimum assessment of children with PDD

includes testing IQ and adaptive behavior, language and hearing, structured, categorical and dimensional validated measures of symptoms of PDD (e.g., the Child Autism Rating Scale [Shopler et al., 1988] and the Aberrant Behavior Checklist [Aman et al., 1985]), and review of medical and family history, and psychiatric history (Fig. 8; reviewed in Scahill, 2005). In addition to the core symptoms of autism, a substantial number of affected children have behavioral problems including hyperactivity, aggression, tantrums, and self-injury, and they may be at risk for other disorders including anxiety (Leyfer et al., 2006; RUPP Autism Network, 2002; RUPP Autism Network, 2005b).

#### Stage 1: Nonpharmacological Treatment

Comprehensive treatment of children with PDD is multimodal and multidisciplinary, focused on promoting language, social development, and adaptive functioning and reducing repetitive behavior, aggression, tantrums, self-injury, and hyperactivity (AACAP, 1999; Aman, 2005). Psychoeducation for parents is essential to allow parents to align their expectations with the child's disability (Bodfish, 2004). Consensus in the field strongly supports early intervention to promote optimal development. Depending on a child's developmental and language levels, children with co-occurring psychiatric disorders may be able to participate in psychosocial treatments developed for typically developing children.

#### Stage 2: Psychopharmacological Treatment

One study has focused solely on preschoolers with autism or PDD-NOS (Luby et al., 2006). The severity of autism as measured on the Child Autism Rating Scale decreased more in a group randomly assigned to risperidone compared to the placebo group, although the difference was modest (8% change in risperidone group vs. 3% change in placebo group). The authors note that baseline differences between the groups complicate the interpretation of the study results. A second randomized placebo-controlled risperidone study of 40 children ages 2 to 9 years old, with a mean age of 58 to 63 months, showed a 63% response rate of core symptoms in the risperidone group compared with 0% in the placebo group (Nagaraj et al., 2006). Improvements in irritability and hyperactivity were also observed. Open trials of risperidone in young children have also shown decreases in overall symptoms and core symptoms of PDD (Masi et al., 2003;

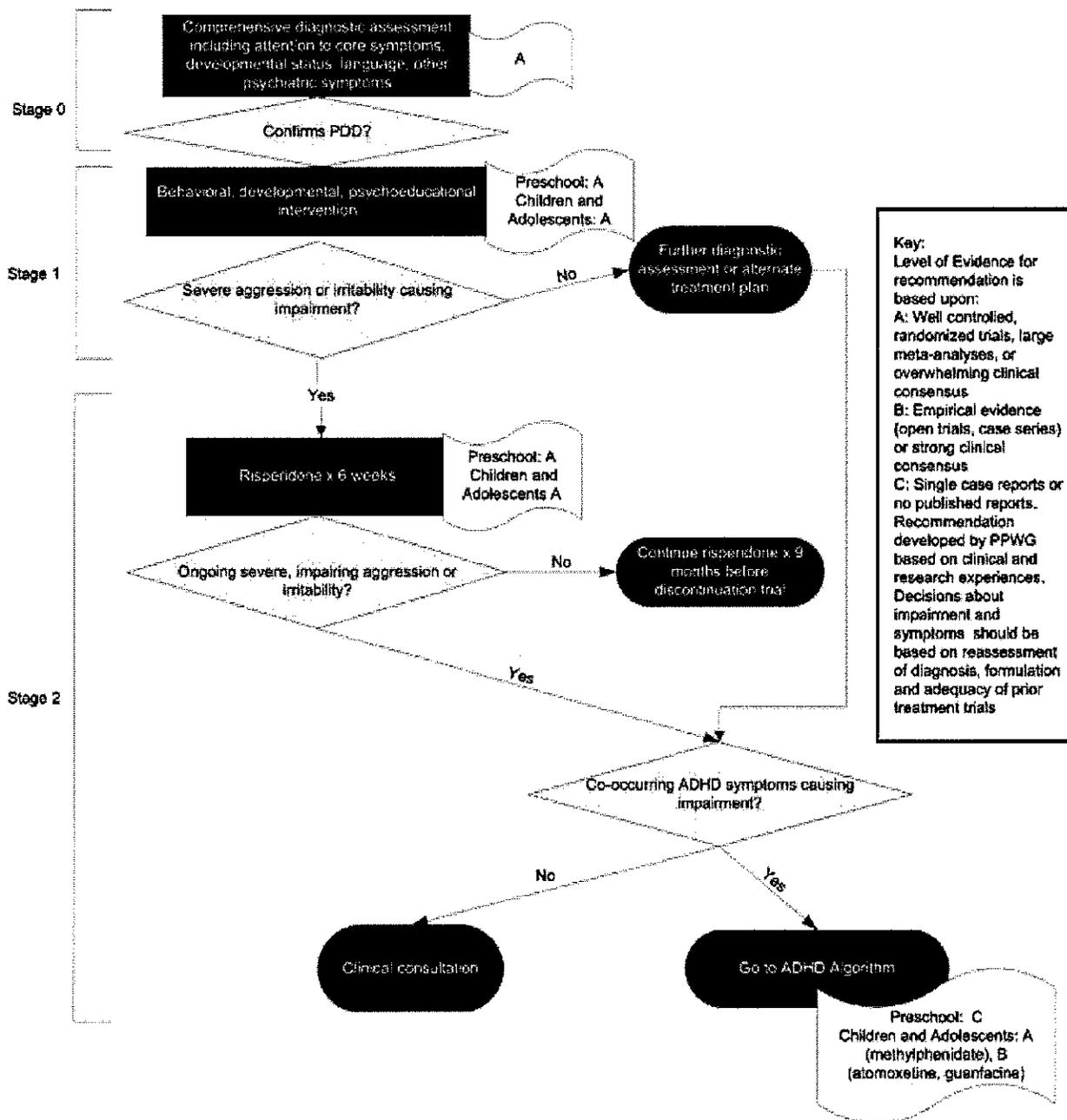


Fig. 8 Pervasive developmental disorders algorithm.

Mukaddes et al., 2004), but methodological weaknesses limit the generalizability of these findings.

Risperidone is now FDA approved for use in treating 5- to 17-year-olds with autism and severe aggression and irritability. In an 8-week, randomized placebo-controlled trial of 101 children ages 5 to 17 years,

risperidone (mean dose 1.8 mg/day) was associated with a significant decrease in aggression, tantrums, and self-injury, as well as stereotypies and other repetitive behaviors (McDougle et al., 2005). These gains were stable over time, and there was a high probability of symptomatic relapse when the medication

was discontinued. The likelihood of return of tantrums, aggression, and self-injury upon discontinuation of risperidone has been replicated in a separate sample (Troost et al., 2005).

**Hyperactivity.** Two randomized placebo-controlled studies have evaluated medications for ADHD symptoms in the context of PDD. The Research Units of Pediatric Psychopharmacology Autism Network examined the efficacy of methylphenidate in treating hyperactivity in children with PDD ages 5 to 13 (RUPP Autism Network, 2005a). They found a 20% to 30% improvement in teacher and parent ratings compared to placebo. This level of improvement, although significant, is clearly smaller in magnitude than seen in typically developing children with ADHD. Atomoxetine was superior to placebo in treating ADHD symptoms in a small study of 12 children, although its use was associated with high rates of adverse effects (Troost et al., 2006). In an open trial of 25 children with PDD, guanfacine treatment was associated with decreased hyperactivity using 1 to 3 mg/day (Scahill et al., 2006).

**Repetitive Behavior.** Although commonly used in children with PDD for the treatment of repetitive behavior, the SSRIs have not been well studied even in school-age children with PDD. In a study of 39 children, fluoxetine at a mean daily dose of 10 mg was superior to placebo, but the magnitude of effect was small (Hollander et al., 2005). The state of the literature of SSRIs in children with PDD does not support the use of these medications in preschoolers with PDD.

Close monitoring of adverse effects is warranted for all medications used in young children with PDD. Risperidone appears to have a relatively low risk of neurological side effects (RUPP Autism Network, 2005b). However, risperidone is associated with weight gain, with preschoolers demonstrating a mean weight gain of 2.96 kg over 6 months (Luby et al., 2006). In children with PDD risperidone is also associated with hyperprolactinemia (Hellings et al., 2005; Luby et al., 2006; Masi et al., 2003), although there is uncertainty about the relative clinical importance of this observation. Methylphenidate is also associated with higher rates of adverse events causing discontinuation of the medication (18%) in children with PDD than expected in typically developing children (RUPP Autism Network, 2005a). Similarly,

5 of the 12 children in the atomoxetine trial exited the study due to adverse events (Troost et al., 2005). Children with PDD also appear to be especially vulnerable to behavioral activation on SSRIs (reviewed in Kolevson et al., 2006).

There is substantial evidence that risperidone is effective for the treatment of tantrums, aggression, and self-injury in children with PDD as young as 5 years of age. The collateral benefits in socialization and repetitive behavior are not sufficient to warrant use of a drug such as risperidone for children with PDD. Thus, the PPWG recommends using risperidone only for children with severe behavioral problems that interfere with a child's functioning. Reported risperidone doses range from 0.7 mg (Masi et al., 2003) to 1.5 mg/day (Luby et al., 2006) for preschoolers with PDD. Vigilant monitoring for adverse events is warranted in children with PDD.

Behavioral treatments focused on the core symptoms of PDD should be administered in conjunction any medication treatment. If treatment is successful, our group recommends continuing risperidone for 6 months before a discontinuation trial. For children with severe hyperactivity, methylphenidate may be considered, following the ADHD algorithm, and parents should be informed of the higher risk for adverse effects.

#### PRIMARY SLEEP DISORDERS ALGORITHM

##### Stage 0: Diagnostic Assessment

The sleep algorithm was derived primarily from recently published young children's sleep practice guidelines developed by the American Academy of Sleep Medicine (Morgenthaler et al., 2006; Owens et al., 2006). The diagnostic assessment of a child presenting with a sleep disturbance includes three components: thorough evaluation for primary sleep disorders that may present with neurobehavioral and mood impairments, inventory of possible contributing/exacerbating factors, and detailed assessment of sleep patterns and behaviors including the impact of the sleep disturbance on daytime functioning of both the child and caregivers (Fig. 9). The differential diagnosis of preschool sleep problems is broad and clinicians should consider obstructive sleep apnea, restless leg syndrome/periodic leg movement disorder, as well as the contributions of environmental factors, sleep hygiene, psychiatric disorders, and medications. Careful

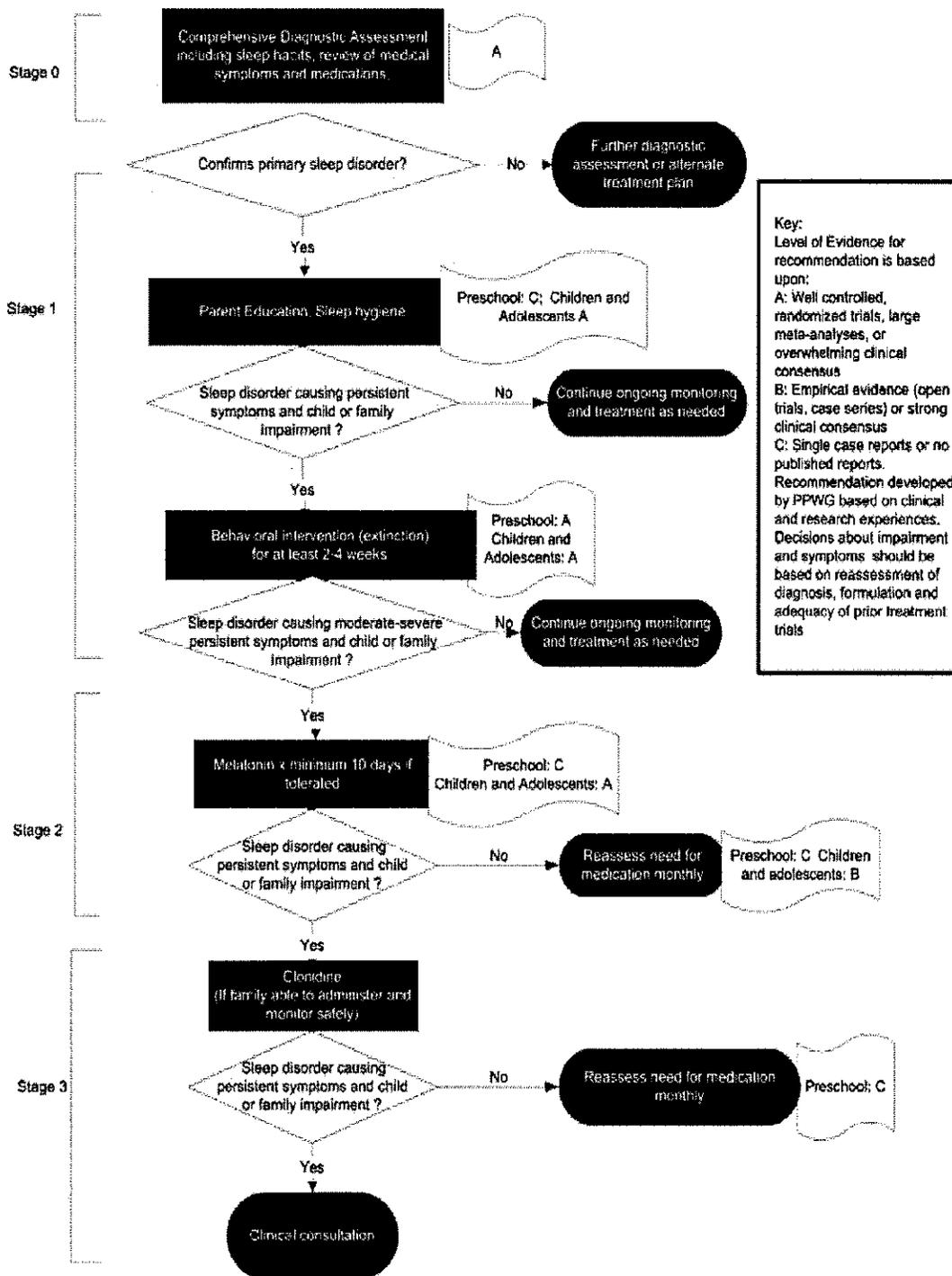


Fig. 9 Primary sleep disorder algorithm.

assessment will guide further evaluations including the need for polysomnography (see Owens et al., 2006).

#### Stage 1: Nonpharmacological Interventions

Parent education is the first step in addressing parental concerns about sleep, with particular attention to developmental sleep patterns as well as the potential risks of over-the-counter medications. Although it has only been evaluated as a component of treatment strategies, sleep hygiene should be reviewed and encouraged (Mindell et al., 2006). Behavioral interventions for bedtime resistance and night wakings (e.g., extinction or graduated extinction) have sound empirical support and should be implemented as the first-line treatment for behaviorally based sleep disorders. An adequate trial of behavioral intervention, assuming parent compliance, is 2 to 4 weeks.

#### Stage 2: Pharmacological Intervention (Melatonin)

Pharmacological intervention should be reserved for situations in which well-being and daytime functioning of the child and/or caregiver is compromised by the sleep disturbance, behavioral treatment has failed, or caregivers are unable to fully implement the behavioral interventions after reasonable attempts. Medication should be given for as short a duration as possible (not longer than 1 month at a time without reassessment) and should always be combined with ongoing behavioral interventions (Owens et al., 2006). In school-age children with and without ADHD, melatonin has demonstrated reductions in sleep latency when given at bedtime (Smits et al., 2003; Van der Heijden et al., 2007; Weiss et al., 2006). It is worth noting that although melatonin was associated with clinically significant gains, children in the ADHD group continued to have sleep onset latency near 1 hour (Weiss et al., 2006). Doses in school-age children range from 3 to 6 mg, with the lower dose used for lower weight children (Smits et al., 2003; Van der Heijden et al., 2007). Recommendations for preschool dosing range from 1 to 3 mg. Administration of melatonin earlier in the day (e.g., 5–7 hours before bedtime to optimize its chronobiotic properties), and the effects of melatonin agonists (e.g., ramelteon) have not been studied in children (see Touitou and Bogdan, 2007). In short-term use, melatonin seems to have few side effects, although it is not recommended for use in patients with immune disorders (reviewed in Pelayo

et al., 2004). Melatonin's over-the-counter status may reassure parents, although clinicians should keep in mind that supplements such as melatonin are not regulated or monitored by the FDA. A trial of melatonin should be at least 10 to 14 days (Weiss et al., 2006).

#### Stage 3: Pharmacological Intervention (Clonidine)

If melatonin is ineffective and the sleep disorder continues to functionally impair a child, then a clinician may consider a short trial of clonidine. In a retrospective chart review of 62 school-age children with ADHD and sleep disturbances, 53% of children who were prescribed clonidine were much improved or very much improved while taking the medication (mean daily dose 0.0245 mg; Prince et al., 1996). Side effects were described as mild, with 24% ( $n = 15$ ) children endorsing morning sedation and 11% ( $n = 7$ ) with fatigue. Although this series did not find cardiovascular side effects, reports of clonidine toxicity after ingestion describe a range of adverse effects including respiratory depression and hypotension (Klein-Schwartz, 2002; Rachmiel et al., 2006; Spiller et al., 2005). Thus, clinicians should educate parents about safely administering and monitoring of the medication (Klein-Schwartz, 2002) and consider the family's ability to safely follow these recommendations. Recommended doses may range from 0.025 to 0.05 mg in preschoolers 30 minutes before bedtime (Hunt et al., 1995; Prince et al., 1996). As with melatonin, the administration of clonidine to treat sleep disorders should be short term.

#### CONCLUSIONS

It is encouraging to see that young children have more access to mental health care than in the past, but studies showing a rise in use of medication, including multiple medications in the preschool age group raise some concerns, especially given the limited body of evidence (e.g. DeBar et al., 2003; Rappley et al., 2002; Zito et al., 2000). The PPWG has responded to the gap between practice and evidence by clearly defining the current state of preschool psychopharmacological treatment, advocating caution in practice, and using the existing evidence and clinical consensus to provide treatment algorithms for preschool psychopharmacological treatment. We aim to inspire more clinical

research to better inform the many questions remaining and to emphasize the limitations of applying findings from older individuals to children in this age range. Preschool psychopathology and treatment must be considered in its unique developmental, clinical, regulatory, and ethical contexts.

Treatment algorithms based on preschool data, extrapolation from older children, and expert opinion will provide a first step in standardizing treatment approaches; however, the need for strengthening the evidence base is urgent. Large-scale, randomized controlled trials are the gold standard and are needed in this population. In addition, individual physicians and groups of physicians can also provide much needed data to the field through reports of single or pooled "N of 1" studies, which include reports of systematic assessment and monitoring of symptoms, adverse effects, and discontinuation trials and by reporting carefully documented case reports.

Preschool psychiatry is an important public health issue. Clinicians who work with very young children and parents have the opportunity to advocate for increased access to (and study of) nonpharmacological treatment options, increased funding for research, increased support for training clinicians with expertise in childhood mental health, and adequate third party payer reimbursement for specialized assessments and treatments necessary in early childhood psychiatry.

*Disclosure: Dr. Emslie receives research support from Eli Lilly, Organon, and Forest Laboratories; is a consultant to Eli Lilly, GlaxoSmithKline, Wyeth-Ayerst, and Biobehavioral Diagnostics Inc.; and serves on the speakers' bureau of McNeil. Dr. Greenhill receives support from Eli Lilly, Novartis, Forest, Pfizer, and Otsuka. Dr. Kowatch receives research support from Bristol-Myers Squibb, serves as a consultant to Creative Educational Concepts and Abbott, is the editor of Current Psychiatry, and is on the speakers' bureau of Astra-Zeneca and Abbott. Dr. Owens receives research support from Lilly, Shire, Sepracor and serves as a consultant to Cephalon, Shire, Lilly, Sanofi-Aventis, and Boehringer-Ingelheim. Dr. Scabill is a consultant for Janssen, Supernus, Bristol-Myers Squibb, and Neutropharm and serves on the speakers' bureau of Janssen. The other authors have no financial relationships to disclose.*

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**Mental Health and Social Competencies of 10- to 12-Year-Old Children Born at 23 to 25 Weeks of Gestation in the 1990s: A Swedish National Prospective Follow-up Study** Aijaz Farooqi, MD, PhD, Bruno Hägglöf, MD, PhD, Gunnar Sedin, MD, PhD, Leif Gothefors, MD, PhD, Fredrik Serenius, MD, PhD

**Objective:** We investigated a national cohort of extremely immature children with respect to behavioral and emotional problems and social competencies, from the perspectives of parents, teachers, and children themselves. **Methods:** We examined 11-year-old children who were born before 26 completed weeks of gestation in Sweden between 1990 and 1992. All had been evaluated at a corrected age of 36 months. At 11 years of age, 86 of 89 survivors were studied and compared with an equal number of control subjects, matched with respect to age and gender. Behavioral and emotional problems, social competencies, and adaptive functioning at school were evaluated with standardized, well-validated instruments, including parent and teacher report questionnaires and a child self-report, administered by mail. **Results:** Compared with control subjects, parents of extremely immature children reported significantly more problems with internalizing behaviors (anxiety/depression, withdrawn, and somatic problems) and attention, thought, and social problems. Teachers reported a similar pattern. Reports from children showed a trend toward increased depression symptoms compared with control subjects. Multivariate analysis of covariance of parent-reported behavioral problems revealed no interactions, but significant main effects emerged for group status (extremely immature versus control), family function, social risk, and presence of a chronic medical condition, with all effect sizes being medium and accounting for 8% to 12% of the variance. Multivariate analysis of covariance of teacher-reported behavioral problems showed significant effects for group status and gender but not for the covariates mentioned above. According to the teachers' ratings, extremely immature children were less well adjusted to the school environment than were control subjects. However, a majority of extremely immature children (85%) were functioning in mainstream schools without major adjustment problems. **Conclusions:** Despite favorable outcomes for many children born at the limit of viability, these children are at risk for mental health problems, with poorer school results. *Pediatrics* 2007;120:118-133.