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The Evidence for Psychotropic Medication Management in Children and Adolescents

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The use of psychotropic medications in children as young as 2 years old is on the rise.[1] The following is a review of the available evidence regarding the use of psychotropic medications in preschool children (under 6 years old), children (6-12 years old) and adolescents (13-19 years old). The following definitions for level of evidence are used:

Good	large randomized controlled trials (RCT), quantitative systematic reviews & meta-analyses
Fair	small RCT's, uncontrolled or open label trials, cohort studies, case-control studies
Poor	case reports, retrospective chart reviews
Limited	not enough evidence to make a strong consensus statement.

Drugs to Treat ADHD

Multiple studies demonstrated significant short-term (days to weeks) efficacy of stimulants on target symptoms of attention deficit hyperactivity disorder (ADHD); specifically on the core symptoms of inattention, impulsivity, hyperactivity and observable social and classroom behaviors in preschoolers, children and adolescents.[2,3] Good evidence on functional and long-term outcomes is lacking. Evidence for comparative efficacy and adverse events of stimulants is limited by small sample sizes, short durations, and variations in measuring response. One large systematic review of ADHD drugs found fair quality evidence that methylphenidate (MPH) is superior to placebo, but did not find significant differences between the immediate release and long acting formulations.[3] Limited evidence suggests weight loss is greater with the amphetamine salts compared to MPH, atomoxetine may cause more vomiting and drowsiness than MPH or amphetamine salts, and MPH may cause more "abnormal thinking" than atomoxetine in children.[3] Concerns with cardiac effects have been identified leading to new black box warnings for all stimulants and a recommendation to assess children of all ages for heart conditions.[4]

Mood Stabilizers

While the evidence for mood stabilizer use in children and adolescents is fair quality (6 RCTs, 6 open-label), there is poor quality evidence for use in preschool children.[5] Trials show valproate is generally well-tolerated and effective in reducing aggression in children and adolescents with bipolar disorder (BPD) when given as monotherapy.[5] Lithium has demonstrated effectiveness in children and adolescents with mood disorder and conduct disorder in two short RCTs (4 weeks).[5] Oxcarbazepine and topiramate have not shown efficacy in this population.[7] National guidelines for treating BPD-I with or without psychotic features, recommend valproate alone, lithium alone, or either in combination with an atypical antipsychotic as a first line treatment option, though evidence supporting combination therapy is limited.[5]

Atypical Antipsychotics (AAPs)

AAPs have limited but growing evidence for use in conduct disorder (CD), oppositional defiant disorder (ODD), disruptive behavior disorder (DBD), BPD (specifically mania and/or psychotic symptoms), and autism spectrum disorders, however most evidence is from small, short-term trials, up to 6 weeks. Risperidone has fair quality evidence for effectiveness in autism (two 6 month RCTs, one 8 week open label trial), and has FDA approval for use in this disorder for age 5 years and older. A review on atypical antipsychotics found risperidone and olanzapine superior to placebo for improving behavioral symptoms in children with autism spectrum disorders, and found risperidone superior to placebo in children and adolescents with DBD.[8] In three larger studies (6 weeks duration) in children with DBD and one 6 month RCT in children and adolescents with ADHD and co morbid ODD and CD demonstrated significant improvement in behavioral symptoms with risperidone compared to placebo.[9-12] One open-label, 8 week trial evaluating the short-term safety and efficacy in 31 preschoolers (4-6 yrs) and found both risperidone (at 1 week) and olanzapine (at 2 weeks) reduced BPD mania symptoms; however, there were substantial adverse effects and the investigators concluded that benefits may not outweigh the risk in this population.[6] Long-term studies have not been completed in pediatric populations, but known side effects include: weight gain, sedation, metabolic and endocrine issues.

Antidepressants

Currently fluoxetine is the only second-generation antidepressant approved by the FDA for treating major depressive disorder (MDD) in pediatric populations. Published evidence is based on controlled trials in children 7 – 18 years old. Fluoxetine, fluvoxamine and sertraline are approved for the treatment of obsessive-compulsive disorder (OCD) in children and adolescents. Fluvoxamine and sertraline have not been approved for the treatment of MDD in children and adolescents. Systematic review data suggests that only fluoxetine has a favorable risk-benefit profile in pediatric populations, although placebo controlled evidence supports the efficacy of fluoxetine and citalopram in MDD.[13] Evidence is inconclusive about the efficacy of escitalopram, fluvoxamine, mirtazapine, venlafaxine, bupropion, and duloxetine for MDD in children and adolescents.[13] In 2007, the FDA added black box warnings for suicidal precautions in children, adolescents and young adults up to age 24 years taking all classes of antidepressants. From pooled analysis for short-term trials of nine different antidepressants (24 trials, more than 4,400 patients), the average risk of adverse suicidal reactions was 4%, twice the placebo risk of 2% in young people up to age 24.[14,15]

Polypharmacy

Most psychotropic combinations lack adequate evidence of effectiveness or safety in youth and are generalized from adult studies. Data reveal that children and adolescents differ from adults in adverse drug reactions to psychotropic medications.[16,17] In addition, pediatric research shows that increasing the number of concomitant medications increases the likelihood of adverse drug reactions.[16,17] The pediatric population is particularly vulnerable to the adverse effects of psychiatric polypharmacy. The American Academy of Child and Adolescent Psychiatry released the following statement "Little data exists to support advantageous efficacy for drug combinations keeping such use to clearly justifiable circumstances."[18]

The Texas Department of State Health Services provides the following guidance[19]:

- Monotherapy regimens for a given disorder or specific target symptoms should usually be tried before polypharmacy regimens.
- Before adding additional psychotropic medications to a regimen, the child should be assessed for adequate medication adherence, accuracy of the diagnosis, the occurrence of co morbid disorders, and the influence of psychosocial stressors.
- Polypharmacy is defined as the use of two or more medications for the same indication.

These guidelines also recommend a review of the patient's clinical status when the following issues of polypharmacy exist:

- Five (5) or more psychotropic medications prescribed concomitantly
- Two (2) or more concomitant antidepressants
- Two (2) or more concomitant antipsychotics
- Two (2) or more concomitant stimulants
- Three (3) or more concomitant mood stabilizer medications

Evidence Summary

Drug Class	3-5 yrs	6-18 yrs
Stimulants	Fair	Good for ADHD symptoms; long-term outcomes unknown
Mood Stabilizers	Poor	Fair for valproate and lithium
Atypical Antipsychotics	Poor	Fair for autism, CD, DBD
Antidepressants	Poor	Fair for fluoxetine, citalopram to treat MDD Fair for fluoxetine, fluvoxamine & sertraline to treat OCD
Polypharmacy (2 psychotropic drugs used concomitantly)	Poor	Fair for: 1. stimulants-short with long acting 2. ADHD or BPD plus co-occurring diagnosis 3. refractory BPD
Polypharmacy (3 or more psychotropic drugs used concomitantly)	None	Poor

In conclusion, the evidence to support the use of psychotropic drugs in pediatric populations is limited and typically based upon short-term studies. A review of available evidence, clinical experience and close monitoring can support clinical decision making. Adequate monotherapy treatments are recommended prior to the initiation of psychotropic polypharmacy.

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