New York State Office of Mental Health

Quality Concerns in Psychotropic Prescribing: Reducing Psychotropic Prescribing Risk for Youth

Reference Guide

PSYKES

Quality Concerns in Psychotropic Prescribing: Reducing Psychotropic Prescribing Risk for Youth

- ***Client focus:*** Children and adolescents on higher-risk regimens of psychotropic medications
- ***Project goal:*** Medication change to a lower-risk regimen if clinically feasible following clinical evaluation, for each youth identified on a higher-risk medication regimen
- ***Medication concerns:*** 3 or more psychotropic medications in youth under eighteen years of age; doses over the recommended maximums; psychotropic medication prescribed to children under 6.

Brief Description

PSYCKES Youth Indicators	
Very young children on psychotropics [<6yrs]	Very young children (5 years and younger) on a psychotropic, among all youth on a psychotropic in the past 35 days
Youth on higher than recommended dose of psychotropic [Dose(Y)]	Youth on any psychotropic in the past 35 days with evidence of a dose higher than the recommended maximum for that psychotropic
Psychotropic polypharmacy in youth (three or more) [3PP(Y)]	The percentage of consumers younger than eighteen years old on three or more psychotropics for longer than 90 days, among those on at least 1 psychotropic for longer than 90 days
Youth summary	The percentage of consumers meeting criteria for any of the youth indicators, among consumers under 18 on any psychotropic

Scope of the Problem

Psychotropic medications offer both the promise of effective treatment for psychiatric disorders in youth and the risk for development of significant health concerns. The PSYCKES Youth indicator set focuses on children and adolescents prescribed higher than recommended doses of psychotropics, on psychotropic polypharmacy, or who are receiving psychotropics and less than 6 years old. In the past ten years there has been an increase in the number of new psychotropic medications which are being prescribed to children and adolescents. These include new and long-acting medications to treat attention deficit hyperactivity disorder (ADHD), several new antipsychotic medications, and new antidepressants. However, the growth of the scientific evidence regarding best practices for use of these medications in youth has been slow, with few randomized, controlled studies to guide use and document adverse effects. Despite this lack of evidence, the rates of psychotropic prescribing are increasing [1]. More children are being prescribed multiple psychotropic medications, driven in large part by a preferential increase in antipsychotic prescribing for children under 10 years old [1,2]. Doses are increasingly higher than the recommended maximums. More preschoolers are being prescribed psychotropic medications, particularly stimulants and antipsychotics [3]. Issues of

psychotropic prescribing in youth are often referred to as problems of “too much, too many, too young.”

National trends are reflected in New York State (NYS) Medicaid claims data, which shows that 44,600 youths who were given a mental health service or diagnosis in 2010 received psychotropic medications. More than 2,000 of these are children under the age of 6. 78.5 % of youth receive medications prescribed by non-mental health practitioners. 63% of youths receive psychotropic medication for behavioral symptoms often associated with ADHD and autism; 10% have mood disorders and only 1.5% has psychotic disorders. Nearly 5,000 youths are prescribed higher than recommended doses; the majority of these high dose prescriptions are for antipsychotics and stimulants. The PSYCKES Scientific Advisory Committee identified areas of concern for children and adolescents including: 1) polypharmacy of 3 or more medications, 2) high doses above the recommended maximum recommended dose, and 3) psychotropic medication prescribing to children under 6 years old [4].

Prescribers consider many factors when determining what medications may benefit a particular child or adolescent. Accurate diagnosis of the primary disorder and any comorbid conditions determines the starting point in psychotropic prescribing. The FDA and other national organizations have published guidelines for psychotropic medication indications and dosing in the pediatric population, based on existing scientific data. The most effective regimen and the safest dose of medication varies for each individual based on a number of factors including age, genetics, rate of metabolism, and types and severity of symptoms. For some children, higher doses may be needed to achieve the remission of symptoms needed to maximize function. There is some evidence from small short-term clinical trials that antipsychotics and mood stabilizers can reduce behavioral symptoms in children with ADHD or autism [5-9]. Adding a second medication in the setting of a careful and comprehensive psychiatric evaluation may be helpful for children with complex or comorbid illnesses, such as ADHD with depression or bipolar disorder [10-12]. Given the growing scientific literature describing safety concerns, these prescribing practices should be carefully balanced with potential risks, particularly for long term use.

Quality Concerns in Psychotropic Prescribing for Youth: Polypharmacy

Although there is little empirical evidence to support its use, polypharmacy is becoming an increasingly frequent practice in the mental health treatment of youth. Studies in several states of various payer groups—Medicaid, private insurance, SCHIP—note rates of polypharmacy in children and adolescents of up to 70% in children taking any psychotropic medication [13,14]. The NYS Medicaid claims data rates of polypharmacy in youth seen at OMH-licensed clinics and taking any psychotropic are as high as 57% in some areas. Rates of polypharmacy for children and youth in foster care have been shown to be dramatically higher, without any report of therapeutic advantage [15,16]. Risks of polypharmacy in comparison to monotherapy have not been systematically investigated; existing evidence appears largely in case reports, and includes increased risk of serious drug interactions, delirium, serious behavioral changes, cardiac arrhythmias, and death [13]. Public concern about the prescription of multiple powerful medications to small children has been growing. *The New York Times* reported on a child prescribed 5 psychotropic medications by the age of 3, with consequent obesity, sedation, drooling and cognitive impairment [17]. In this compelling story the child and family did not receive any psychosocial treatment.

Youth are at least as vulnerable as adults to the increased cardiometabolic risk associated with even brief atypical antipsychotic treatment. Excessive weight gain is prominent, particularly with

olanzapine [18,19]. Given the association between obesity and cardiovascular disease in adults, along with the understanding that obesity in children rarely resolves in adulthood, the possible long term morbidity and mortality from this side effect is concerning [20,21]. Atypical antipsychotics have also been associated with elevated lipids and high glucose levels leading to Type 2 diabetes in some children. First time prescriptions of atypical antipsychotics appear to have the most pronounced effect [18]. In one group of children, 25% had developed a cardiometabolic disorder in addition to their psychiatric disorder by the end of a 3 month antipsychotic course [22]. Only a small percentage of youth receive adequate screening for cardiometabolic risks during treatment with antipsychotics. This evidence of short-term risk suggests that long-term usage may have serious lifelong medical consequences.

Treating behavioral symptoms, particularly impulsivity and aggression, is a major driver of polypharmacy in children and adolescents. The American Academy of Child and Adolescent Psychiatry, in its practice guideline on polypharmacy, stresses the importance of determining the primary psychiatric diagnosis through a comprehensive evaluation prior to initiating pharmacotherapy. Pharmacotherapy should then be directed toward treatment of the primary diagnosis, with the goal of remission of symptoms. In studies of impulsive aggression in children with ADHD [4,5] increasing the dose of the stimulant medication until symptoms of ADHD resolved, also resulted in the resolution of behavioral symptoms in 50% of the children. For most children the dose needed to treat ADHD and the behavioral problems will remain below the recommended maximum dose. The effects on behavior of environmental stressors at home and school should be well-understood, and treated with appropriate psychosocial interventions [23]. These evidence-based nonpharmacologic therapies include contingency management programs (token economies), behavior report cards, social skills training, problem solving therapy, anger management, parenting skills training, and cognitive behavioral treatments for trauma-related difficulties [9].

Sleep difficulties in young children and youth often increase the polypharmacy burden. Childhood insomnia is common in children and youth with psychiatric disorders, and is associated with hyperactivity, irritability, restlessness, poor concentration, impulsivity, mood swings, suicide risk, and decreased memory. Over 50% of children with ADHD have difficulty sleeping. Up to 75% of youths with neurodevelopmental disorders have disordered sleep. The first step in managing childhood insomnia begins with accurate diagnosis of the primary disorder and other contributors to poor sleep [24]. First-line treatments for ADHD and depression can worsen insomnia. Treatment side effects, including akathisia from antipsychotic agents, restless leg syndrome from antidepressants, obstructive sleep apnea due to weight gain, and undertreated anxiety or depression can impair sleep. Children with vulnerable brains may be especially sensitive to environmental factors of light, noise, smell, and activity. There is very little scientific evidence regarding pharmacologic treatments for insomnia in children and youth, and no FDA-approved drugs for this indication. There is clear evidence of benefit from nonpharmacologic treatment of insomnia in young children including extinction and graduated extinction strategies, positive routines, scheduled awakenings, and parent education interventions. Cognitive behavioral techniques for managing insomnia and anxiety, education about sleep-wake cycles, developing consistent patterns of sleep hours, and reduction of stimuli, particularly electronic and social activities, can be helpful for youth. Adequate treatment of the primary diagnosis, use of psychotherapeutic strategies, and environmental adjustment often can eliminate the need for medication for insomnia.

Quality Concerns in Psychotropic Prescribing for Youth: Psychotropic Prescribing to Children Younger than 6

During the past decade rates of prescription of psychotropic medications to preschool children have risen for both Medicaid and privately insured groups. In a national study of Medicaid claims, 50% of children under the age of 6 with autism spectrum disorders were prescribed medication. In this group, antipsychotics were prescribed as frequently as stimulants [25]. These rates are considerably higher than those reported a decade earlier [26]. The rate of antipsychotic use in privately insured preschoolers more than doubled from 1999 to 2007. Rates of psychotherapy, the safest and most effective treatment for behavioral symptoms in this age group, declined during the same period [3].

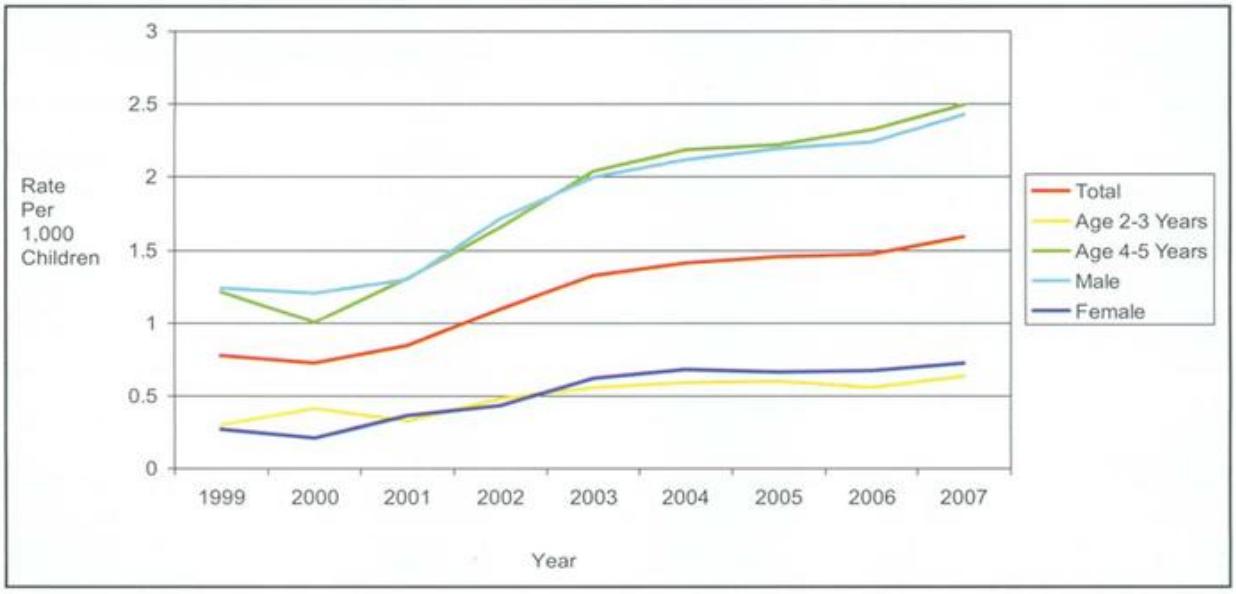

Figure 1. Rates of Antipsychotic Use among Preschoolers, 1999-2007 (Olfson et al., 2010)

The effectiveness, safety, and appropriate dosing of second generation antipsychotics in preschool children remain unknown. Worrisome adverse effects have been documented even at low doses, including excessive weight gain resulting in obesity, large increases in prolactin, and higher risk of extrapyramidal side effects including tardive dyskinesia. The effects of antipsychotics on neurodevelopment of young children are unknown; animal research has demonstrated permanent alteration in receptor distribution after exposure to antipsychotics [27]. Use of antipsychotics should be limited in young children to those with serious psychiatric disorders with intractable symptoms and high risk behaviors, as a part of a comprehensive treatment plan for the child and the family.

Quality Concerns in Psychotropic Prescribing for Youth: Higher than Recommended Doses of Psychotropics

Little scientific evidence regarding high doses of medications exists for children and adolescents outside the FDA approval process; therefore, caution is needed when prescribing for this population. Few studies involve large numbers of youth in controlled trials; most studies are open label designs and case series. In the existing evidence, high doses do not improve symptom control. Studies of second generation antipsychotics in youth have demonstrated equal or worsening response when higher doses are compared to lower doses [28,29]. Studies of stimulants have shown that for some children, attention and hyperactivity symptoms remain

well controlled at lower doses; for children with ADHD-related behavioral problems, higher doses may be helpful. Higher doses of psychotropic medications often do lead to an increase in serious side effects [28,30] and problems with adherence. Dosing parameters in this PSYCKES quality improvement project have been taken from the FDA approvals for individual medications, the Texas guidelines for Foster Children, the PDR, and standard texts on pediatric psychopharmacology.

Clinical Recommendations for Reducing Psychotropic Medication Risk in Youth

1. Psychiatric medications are one part of a **multimodal, multidisciplinary treatment** plan and cannot replace the need for therapeutic support, behavioral strategies, problem solving, parent training, and other interventions.
2. Determination of the **primary diagnosis** and any comorbidity is the first step in treatment prior to initiation of any medications (except in emergent circumstances). Every youth deserves a **multidisciplinary comprehensive evaluation,** including a medical history and evaluation if warranted. **Treat the primary diagnosis** first. Treatment planning with children and their families and teachers should include **psychosocial interventions as well as medication** prescription.
3. A plan for **monitoring symptoms and side effects** during a medication trial in both the short term and long term is essential and should include the **use of rating scales.** Prescribers should be cautious when implementing a treatment plan that cannot be appropriately monitored. **Regular monitoring for cardiometabolic side effects** is essential when prescribing atypical antipsychotic medications and requires close collaboration with pediatricians.
4. **Education of the child and family** regarding diagnosis, recommended treatment, and monitoring plan should be part of every child's treatment plan. This should include a discussion of risks and benefits of both proposed and alternate treatments, as well as collaborative planning for adherence. Children and families should be aware of what medications can and cannot do.
5. **Prescribers should prescribe medication at an adequate dose for an adequate duration of time**, with close monitoring of dose and response. Medication doses should be returned to the lowest possible therapeutic dose. Whenever possible, use medications supported by double-blind randomized controlled trials for the age group and diagnosis. (e.g. TADS, CAMS, PATS, MTA, TEOSS, POTS, RUPP).
6. **Start low and go slow with dose increases or tapers.**
7. When changing medications, make **only one medication change at a time** and monitor results. Always **consider environmental strategies** as an alternative to or augmentation of medication.
8. **Evaluate the iatrogenic effects** of multiple medications. When effects and side effects are unclear, consider tapering or discontinuing the most worrisome medication or the one with the least amount of high quality scientific evidence.
9. **Alternate non-antipsychotic treatments should be considered for children and adolescents** with cardiometabolic risk. If an antipsychotic medication is indicated, a low risk medication is the first-line choice.
10. **Reassessment and diagnostic review** is indicated if a child does not respond to the initial medication trial as expected.
11. Use of **medication combinations (polypharmacy) requires a clear rationale and target symptoms**—monotherapy is recommended if possible.

12. Medication discontinuation requires a specific plan. After a period of stability for 6 months, tapering of psychotropic medication used for aggression and sleep should be considered. Most **medications should be tapered gradually** to avoid withdrawal or rebound side effects.
13. Avoid any pharmacotherapy in children under 6 if at all possible. Focus on behavioral management of behavioral symptoms, and include the family in treatment planning.
14. **Child psychiatry consultation** if available is advised for children with complex disorders or prior to initiation of polypharmacy.

Annotated Bibliography for Reducing Psychotropic Medication Risk in Youth

These papers have been selected and briefly summarized to provide clinicians and CQI teams with key evidence from the scientific literature which may be helpful in informing clinical practice and working with clients to reduce their health risks from psychotropic medications. The scientific summaries located on the PSYCKES website provide more in-depth information and critical review of important scientific articles.

Polypharmacy in Children and Adolescents

1. **McIntyre RS, Jerrell JM: Metabolic and cardiovascular adverse events associated with antipsychotic treatment in children and adolescents.** *Archives of Pediatric and Adolescent Medicine* 162(10):929-935, 2008

This informative study highlights the increased effects of both antipsychotic polypharmacy as well as polypharmacy involving antipsychotic plus another class of medication on cardiovascular and metabolic illness in youth under 18. It is designed as a retrospective cohort study using Medicaid data in a single state (SC), and compares the incidence/prevalence of metabolic, cardiovascular, and cerebrovascular events in a group of youths treated with antipsychotics (n=4140) to a random sample of youth (n=4500) without antipsychotic exposure over a 10 year period. The study compared risks between the exposed and unexposed groups, and then looked at which factors increased the risk of cardiometabolic health problems in both groups. Potential factors examined included gender, ethnicity, age, antipsychotic polypharmacy, and other drug classes prescribed concomitantly with the antipsychotic. Preexisting cardiovascular, cerebrovascular, and metabolic disorders were factored out.

- 42% of youth received antipsychotic polypharmacy.
- The antipsychotic-treated cohort had higher prevalence of obesity (OR 2.13), type 2 diabetes (OR 3.23), and cardiovascular conditions (OR 2.70). The control sample, interestingly, had a higher prevalence of dyslipidemia (OR 3.01) and hypertension (OR 2.35)
- Odds of obesity and/or weight gain were greatest for youth receiving antipsychotic polypharmacy (OR 2.28), polypharmacy including mood stabilizers (OR 1.78), polypharmacy including high risk antidepressants (amitriptyline, nortriptyline, mirtazapine, and paroxetine) (OR 1.66). Female gender (OR 1.75) and age ≥13 (OR 1.34) were also significant.
- The odds of developing Type 2 diabetes were higher for youth on antipsychotic polypharmacy (OR 2.36), for girls (OR 1.79), and youth ≥ 13 (OR 1.52).
- The mean age of initiation of antipsychotic treatment was 11.4; the mean age of onset of incident type 2 diabetes was 13.8. Youth taking aripiprazole (Abilify), compared to other psychotropics had significantly longer time to diagnosis of DM (OR 35.92).

- Odds of dyslipidemia were higher for antipsychotic polypharmacy (OR 5.26), girls (OR 2.08) and youth ≥ 13.
- Hypertension was unrelated to which antipsychotic was used.
- Incident cardiovascular conditions were more likely with the use of haloperidol (Haldol) (OR 4.34) and multiple antipsychotics (OR 1.57).

2. **Blader JC, Schooler NR, Jensen PR, Pliszka SR, Kafantaris V. Adjunctive Divalproex Versus Placebo for Children With ADHD and Aggression Refractory to Stimulant Monotherapy.** *American Journal of Psychiatry* 2009; vol 166, p1392-1401

This interesting study provides evidence regarding polypharmacy in youth with ADHD who have aggressive behaviors. The study demonstrates that aggression resolves in a substantial proportion of youth with ADHD when the stimulant dose is titrated to maximum benefit, thus avoiding polypharmacy to treat potentially dangerous symptoms. It also proposes that divalproex (Depakote) may be helpful for aggressive symptoms which do not respond to stimulant optimization. 82 children from 6-13 years with ADHD and comorbid conduct or oppositional-defiant disorder and behaviors were at least moderate in severity. Children with MDD, Bipolar, Tourette's, PDD and mental retardation were excluded. The stimulant optimization lead-in phase involved use of triphasic methylphenidate (Concerta) to 90 mg, biphasic methylphenidate (Metadate) to 60 mg, or Adderall SR to 35 mg titrated to resolution of both ADHD and behavioral symptoms. All children had concurrent behaviorally-oriented psychosocial treatment during this phase. Children who continued to have aggressive behaviors after stimulant optimization proceeded on to the divalproex vs. placebo phase of the trial.

- 50% (n=31) of children had clinically significant resolution of aggression with stimulant titration. 30 children continued to the divalproex phase.
- 57% of the children (n=8 of 14) taking an average dose of 567 mg (68 mg/liter blood level) of divalproex reached remission vs. 15% (n=2/13)of children on placebo. Note that the low numbers of children in this phase of the study limit generalization.

Higher Than Recommended Doses in Children and Adolescents

Kumra S, Kranzler H, Gerbino-Rosen G et al. Clozapine and "High-Dose" Olanzapine in Refractory Early-Onset Schizophrenia: A 12-Week Randomized and Double-Blind Comparison. *Biological Psychiatry* 2008; 63: 524-529.

The CATIE trial in adults allowed olanzapine doses up to 30 mg, a dose classified as over the recommended maximum in the PSYCKES project. Some clinicians have felt that the results of the CATIE trial which favored olanzapine may be attributed to this dosing. Case reports of high doses of olanzapine in youth have been associated with improved response and lack of adverse effects. This clinical trial studied 18 children 10-18 years old with schizophrenia who had been resistant or intolerant to at least 2 antipsychotic medications. The youth were randomized in double blind fashion to either olanzapine or clozapine groups. Each medication was flexibly dosed to a maximum of 30 mg of olanzapine (Zyprexa) or clozapine (Clozaril 900 mg). Response criteria were a 30% reduction in the total BPRS score as well as a CGI of "1" (very much improved) or "2" (much improved). The results, though the n is small, suggest that moving to clozapine is more effective than using high dose olanzapine in this population and does not cause more serious metabolic effects.

- Mean olanzapine (Zyprexa) dose was 26 mg in youth who completed the study. Mean clozapine (Clozaril) dose was 478 mg.
- Response rate to clozapine was 66%; response rate to "high dose" olanzapine was 33%.

- There were no differences between the two drugs in metabolic or other side effects.
- 70% of the high dose olanzapine non-responders subsequently responded to clozapine.

Reducing Psychotropic Prescribing to Children Under 6 Years of Age

1. **Greenhill L, Rollins S, Abikoff H et al. Efficacy and Safety of Immediate-Release Methylphenidate Treatment for Preschoolers with ADHD.** *Journal of the American Academy of Child and Adolescent Psychiatry* 2006, 45:11, p1284-1295.

This paper is the only double blind placebo-controlled randomized clinical trial of pharmacology in this age group. This complex multiphase study looks at methylphenidate (MPH) immediate release safety and efficacy in preschool children with ADHD. The study enrolled 165 children ages 3 to 5.5 years old who were stimulant-naïve. The first phase of the study was an open-label safety lead-in for one week during which methyphenidate doses were titrated on a fixed schedule to a max of 7.5 mg tid. Children who tolerated MPH in the first phase went on to a 5 week optimal dose-finding phase with randomization to different doses of medication. The final phase included 114 children randomized to receive their best dose MPH or placebo.

- In the crossover phase dose-response rates were: 1.25 mg tid: 15%, 2.5 mg tid: 16%, 5 mg tid: 18%, 7.5 mg tid: 22%, 10 mg tid: 4%. 4 children were non-responders and 8% responded to placebo.
- 22% of children taking medication and 13% of those on placebo met "excellent" response criteria. Dose efficacy effect sizes for each dose were: 1.25 mg: 0.22 (not different from placebo), 2.5 mg: 0.48, 5.0 mg: 0.52, 7.5 mg: 0.87. The three higher doses were all statistically significant in improvement of symptoms.
- This study demonstrated substantially lower response rates in this age group when compared with school aged children trials.
- Effective doses were lower than in school aged children.
- Higher rates of emotional lability were noted in this younger population.

2. **Safer D, Zito JM. Treatment-Emergent Effects from Selective Serotonin Reuptake Inhibitors by Age Group: Children vs. Adolescents.** *Journal of Child and Adolescent Psychopharmacology* 2006. Vol 16; no 1/2, p 159-169.

This study reviews all clinical trials of SSRIs which included both children and adolescents and separated adverse effects by age group (<12 vs. ≥ 12 years old). AEs were grouped into 5 categories: activation, somnolence, insomnia, nausea, and vomiting. Doses were on average 25% higher in the adolescent group of children.

- Rates of activation and nausea were significantly higher in the younger group of children in comparison to the older group of children and to all ages taking placebo.

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