

Actual Psychotropic Medication Use in Preschool Children

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Preschool children who receive psychotropic medications are a special and vulnerable group of children. They have a wide range of mental health and other medical diagnoses. Their families face challenges in parenting as well as social and mental health issues. These children receive a very large spectrum of psychotropic medications. The issue of safe and appropriate use of such medication is of concern within the context of increased diagnosis of mental health conditions, especially attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorders, and the increased use of psychotropic medications for all children and adults. Stimulants, risperidone, and clonidine are the few medications studied in this age group. A national registry or other large-scale organized approach is likely the best method to gather information related to indications and long-term management of psychotropic medications for preschool-aged children. An approach is suggested to allow treatment while specific guidance is formulated at the national level to address the urgent and serious problems presented by preschool children and their families.

Key words: *clonidine, mental health, methylphenidate, preschool, psychotropic medications, riperidone*

THE PREVALENCE OF PSYCHOTROPIC MEDICATION USE IN PRESCHOOLERS

The use of psychotropic medications in preschoolers is increasing when examined in general populations. It is extensive among children at particular risk, such as those with mental health conditions and developmental delays. This practice is remarkable for the wide variety of medications used and the use of concomitant psychotropic medications.

The use of four classes of psychotropic medications has increased among preschoolers, indicated by health services research in at least 8 states: stimulants, clonidine, selective serotonin re-uptake inhibitors (SSRIs), and atypical antipsychotics. An increase in prevalence of the use of methylphenidate for children aged 2 through 4 years in large

groups insured through managed care and Medicaid was found in 3 geographic regions, which ranged from 1.7- to 3.1-fold, with the highest prevalence in 1995 in the Midwest region (1.1% of preschoolers receiving methylphenidate). This study also found a large disparity between increases in the use of clonidine between these geographic regions, ranging from 6.8- to 28.2-fold increase, with the highest prevalence of clonidine use (0.2%) in 1995, again in the Midwest region (Zito et al., 2000). The prevalence of use of stimulants and SSRIs was examined in preschool children within a state Medicaid program from 1992 through 1998; the use of stimulants increased from 0.6% to 1.3%; the use of SSRIs increased from less than 0.01% to 0.1% (Rushton & Whitmire, 2001). Atypical antipsychotics were studied by examining first-time use in a state-wide managed care system. Over 5 years, a 61% increase was noted among children 2-5 years of age (Cooper, Hickson, Fuchs, Arbogast, & Ray, 2004). This trend was also examined by survey of day care centers in another Midwestern state, and 67% of 82 day care centers reported administering medication to preschoolers for ADHD (Sinkovits, Kelly, & Ernst, 2003).

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The prevalence of psychotropic medication use was found to be much higher in studies of children who are at risk, by virtue of underlying disorders. As early as 1976, in a study of preschool children in special education programs, psychotropic medications were received by 9% of children aged 3 years ($n = 31$) and by 25% of children aged 4 years ($n = 90$) (Gadow, 1976). In a state-wide, fee-for-service Medicaid program, 223 children aged 3 years and younger were diagnosed with ADHD; 57% of these children ($n = 127$) received 22 different psychotropic medications (Rappley et al., 1999). In a large managed care organization, services were described for children younger than 5 years of age with emotional and behavioral problems ($N = 743$). From 1993 through 1997, 16% of these children received psychotropic medications ($n = 120$) (DeBar, Lynch, Powell, & Gale, 2003).

The use of multiple psychotropic medications simultaneously is common among school-aged children and adolescents, and is well documented among preschoolers as well. Of the 223 children aged 1-3 years in the study described above, 35% ($n = 44$) received 2 to 4 psychotropic medications simultaneously (Rappley et al., 2002). The managed care study described above also noted preschool children treated with combinations of stimulants, alpha agonists, antidepressants, and neuroleptics (DeBar et al., 2003). In a retrospective chart review of medications for children with developmental delay, 26% ($n = 7$) of those receiving stimulants for ADHD were treated with more than one psychotropic medication (Ghuman et al., 2001). A thoughtful review notes that this practice continues in all ages despite very limited information to support rational choices for concomitant use of psychotropic medication (Safer, Zito, & DosReis, 2003).

DIAGNOSES ASSOCIATED WITH THE USE OF PSYCHOTROPIC MEDICATIONS IN PRESCHOOLERS

The most common mental health and behavioral disorders of childhood are also the

most common reasons for a preschool child to receive psychotropic medications. Identification of severe problems in early childhood predicts that these problems will persist as children grow older. The gender difference present among school-aged children is also seen in preschoolers, with boys consistently reported to more often receive psychotropic medications than do girls.

ADHD is the most common diagnosis among preschool-aged children that is associated with use of psychotropic medication (DeBar et al., 2003; Wilens et al., 2002). The *DSM IV* diagnostic criteria for ADHD are validated to 4 years of age (Lahey et al., 1998). Other diagnoses include oppositional defiant disorder, pervasive development disorder, mental retardation, depression, anxiety, and conduct disorder. ADHD is noted to have considerable morbidity and clinical significance for preschoolers and their families (DuPaul, McGoey, Eckert, & VanBrakle, 2001; Gadow, Sprafkin, & Nolan, 2001). It is also clear that ADHD and oppositional behavior are distinct and sometimes co-existing entities in the preschool-aged child (Gadow & Nolan, 2002).

Serious disruptive behaviors of preschoolers are shown to continue through at least the school years. Persistence of disruptive behavior and adaptive disability identified in 4-year-olds is described by Barkley et al. (2002) at 3-year follow-up. Severe problems persisted into school years, as noted in a review of outcomes associated with problems identified in the preschool age in 1987 and again in 1995 (Campbell, 1987, 1995). Persistence of symptoms as the child grows older was evident in the study of more than 11,000 individual twins with ADHD. Attention problems and overactivity persist as problems from age 3 through age 12 years; the stability of symptoms was moderate from age 3 to 7, and greater between age 7 and 12 years (Rietveld, Hudziak, Bartels, van Beijsterveldt, & Boomsma, 2004). More information about diagnostic issues in preschool children is provided in the article by Eggers et al. in this issue.

Preschool children with problems severe enough to prompt treatment with psychotropic medications often have multiple mental health disorders, chronic health conditions, and developmental delays. Parents are often dealing with their own mental health diagnoses and considerable disruption of their lives.

Two studies examined the range of mental health and chronic health conditions in preschoolers receiving psychotropic medications. The group of 223 children, 1- to 3-year-olds, described above was characterized as having more than one mental health condition and developmental delay (33%), chronic health conditions such as asthma (30%), and injury (43%). Both mental health and chronic health conditions predicted psychotropic medication use for these children (Rappley et al., 2002). Of the children described in the large managed care organization study, half had a diagnosis of ADHD, 11% had another mental health disorder, 37% had more than one mental health condition, 40% had speech and language delay, and 24% had developmental delay. In addition, 24% had been refused day care because of their behavior. In psychiatric referral clinics, the prevalence of more than one disorder is also high. Two hundred children 6 years or younger were described with a mean of 2 major psychiatric disorders per child (Wilens et al., 2002). In the retrospective chart review of children with developmental disorders, multiple medications were used for mood, anxiety, and obsessive compulsive disorder, in addition to ADHD (Ghuman et al., 2001).

Characteristics of families of children receiving psychotropic medications have also been examined. A higher proportion of children with emotional and behavioral problems cared for in the large managed care organization was insured through Medicaid, when compared to other children receiving services. In addition, 77% had documented instability in the home, 71% had parents with emotional problems or substance abuse disorder, 29% experienced some form of abuse, and 31% were removed from their home

(DeBar et al., 2003). Psychopathology and substance abuse among parents of young children with ADHD and co-existing conditions were studied with a control group matched for age, gender, ethnicity, and neighborhood of residence. Parents of children with ADHD and comorbid oppositional and conduct disorder were more likely to have mood, anxiety, childhood disruptive behavior, and substance abuse disorders (Chronis et al., 2003). Negative parenting styles and parental stress are also noted to predict persistence of serious problems from early childhood into later years (Campbell, 1995).

SPECIFIC PSYCHOTROPIC MEDICATIONS USED IN PRESCHOOLERS

Given the serious and persistent nature of severe disruptive behavior of early childhood, it is not surprising that the medications used successfully in older children and adults would be tried in preschoolers. However, very few have evidence to support their use in preschoolers.

Methylphenidate is the psychotropic medication most often used and most often studied in preschoolers. This is followed by dextroamphetamine, clonidine, antidepressants, and antipsychotics (DeBar et al., 2003; Rappley et al., 1999; Zito et al., 2000). Table 1 lists most of the psychotropic medications reported as used in preschool-aged children. The use of stimulants is discussed in more detail in the article by Kollins and Greenhill in this issue.

Clonidine is the second most common medication used for behavior management in preschool children, despite the fact that it is approved by the Food and Drug Administration for use in those 12 years and older. The literature regarding use in preschoolers is extensive, dating back to at least 1976. Close to half of this literature concerns toxicity and poisoning in the preschool years (Michael & Sztajnkrzyer, 2004). Two randomized controlled trials, 2 open trials, and several retrospective chart reviews include a very small number of children as young as

Table 1. Psychotropic medications recorded as used in preschool-aged children

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| Randomized placebo-controlled designed research in preschool-aged children: | |
| Methylphenidate | |
| Dextroamphetamine | |
| Case reports or other research designs: | |
| Clonidine | |
| Imipramine | |
| Risperidone | |
| Use reported in health services research or other records, most not studied in preschoolers | |
| Trazadone | Venlafaxine |
| Doxepin | Lithium |
| Nefazadone | Bupropion |
| Temazepam | Diazepam |
| Haloperidol | Thioridazine |
| Chlorpromazine | Trifluoperizine |
| Pemoline | Guanfacine |
| Nortriptyline | Amitriptyline |
| Desipramine | Fluoxetine |
| Sertraline | |

5 years old in the study populations. Indications described include ADHD, conduct disorder, tic disorders, Fragile X syndrome, post-traumatic stress disorder, sleep disturbance, HIV-associated encephalopathy, aggressive behavior, and hyperactivity in autism. The two randomized controlled double-blind placebo studies described modest improvement in hyperactive and impulsive behavior in 8 boys with autism, mean age 8 years, with sedation as a common side effect (Jaselskis, Cook, Fletcher, & Leventhal, 1992) and improvement in hyperarousal and social relationships in 9 men with autism, aged 5-33 years, again reporting sedation as a side effect (Fankhauser, Karumanchi, German, Yates, & Karumanchi, 1992). Clonidine is available as tablets and transdermal patches of 0.1 mg, 0.2 mg, and 0.3 mg. The tablets are very short acting, with effect lasting for 1/2 hour to 3 hours. Anecdotal clinical practice is to use one-quarter or one-half of the 0.1-mg tablet beginning at bedtime, and

adding doses titrated to the sedation effect. The patch may cause excessive sedation or skin irritation, or pose the safety hazard of ingestion by the preschool child. It is likely that the sedating quality of clonidine leads to its use for treating sleep problems and aggression in the preschooler with disruptive behaviors.

Selective serotonin re-uptake inhibitors are prescribed for preschoolers but the indications are unclear. In 2004, the Food and Drug Administration reconsidered approval of SSRIs in children and adolescents, and now approves only fluoxetine for the treatment of depression in children as young as 7 years. Fluoxetine is available as 10-, 20-, and 40-mg capsules, a 90-mg weekly capsule, a 10-mg tablet, and in a liquid preparation of 20 mg per 5 mL. The dosing of preschool children is not determined; the dose for children 7 years and older is 5 mg to 20 mg daily. Possible indications for the use of SSRIs in preschoolers might include depression, anxiety, and obsessive compulsive disorder. However, little information is available to guide this use.

Perhaps the best evidence for effectiveness and presence of adverse effects in preschoolers comes from research with risperidone, most often done in children with autism or pervasive developmental delay. However, risperidone is not approved for use in children. Children as young as 5 years of age were included in 3 randomized controlled trials conducted in 101, 79, and 110 subjects with autism or below average IQ (McCracken et al., 2002; Shea et al., 2004; Snyder et al., 2002). Additional research includes a naturalistic, 3-year study of 53 children aged 3-6 years with pervasive developmental delay (Masi, Cosenza, Mucci, & Brovedani, 2003); several open-label studies including children aged 3-5 years (Croonenberghs, Fegert, Findling, De Smedt, & Van Dongen, 2005; Findling, Aman, Eerdeken, Derivan, & Lyons, 2004; Gagliano et al., 2004; Masi, Cosenza, Mucci, & De Vito, 2001; Mukaddes, Abali, & Gurkan, 2004), as well as several case reports with children aged 2-6 years. All of these consistently report clinically significant improvement in

severe disruptive and irritable behavior for approximately 40% to 64% of children, with 20% to 70% experiencing side effects of sedation, somnolence, weight gain, and increase in serum prolactin levels (the later dose related and without clinical symptoms). Indications for use appear to be severely disruptive behavior, including severe aggression, especially in children with pervasive developmental delay, autism, mental retardation or other forms of central nervous system damage, and psychotic disorders of childhood. The most common effective dose was 0.5 mg per day, with a range from 0.25 mg to 3 mg per day. The initial dose is given at bedtime and additional doses added in the morning, and midday if needed. The dose is titrated to effect and sedation. The maximum dose for an adult is 6 mg per day. The maximum dose for a school-aged child or preschooler is not determined. Older studies more often used doses higher than 1 mg per day and report more side effects. Movement disorders are a possible serious side effect, seen in other studies, but these were not observed in the studies mentioned above, most likely due to their short duration. Risperidone comes in tablets of 0.25, 0.5, 1.0, 2.0, 3.0, and 4.0 mg, and a 1 mg/1 mL oral solution.

Atomoxetine is a newer medication studied in children as young as 6 years old; published studies are not yet available specifically regarding preschool children. Atomoxetine is a selective norepinephrine re-uptake inhibitor with a long half-life, making it possible to administer once daily and providing 24 hours coverage for inattention, hyperactivity, and impulsivity. The dose range for school-age children is 10 mg to 60 mg per day. As experience grows with this medication in school-age children, it seems apparent that the lower doses are less effective and higher doses can be given safely. It may be prudent, pending further evidence, to use smaller doses for the preschool child who has not tolerated stimulants. Atomoxetine might be preferred to the medications described above because the side effects are less serious. These include appetite suppression, nausea, headache, and for

some children sleep difficulty. Anecdotal reports include improved sleep for some children. Atomoxetine is available as a tablet (10, 18, 25, 40, and 60 mg).

Imipramine, a tricyclic antidepressant, has a long history of use for enuresis and was previously considered the second-line medication for ADHD (Fritz & Rockney, 2004). Tricyclic antidepressants are effective for anxiety as well as attention problems, and studies that included preschool-age children demonstrated effectiveness in post-traumatic stress disorder, anxiety associated with treatment of severe burns, and other anxiety (Robert, Blakeney, Villarreal, Rosenberg, & Meyer, 1999). Few randomized controlled studies included preschool children. Use of tricyclic antidepressants is now limited by concerns for adverse cardiac effects (Wilens et al., 1996).

AN APPROACH TO TREATMENT OF PRESCHOOL CHILDREN WITH PSYCHOTROPIC MEDICATIONS

In all but the most extreme circumstances, psychotropic medications will not be the first treatment for behavioral and mental health problems of preschool children. Parent training programs effectively improve problem behaviors of preschoolers (Borr, Sanders, & Markie-Dadds, 2002; Sonuga-Barke, Daley, Thompson, Laver-Bradbury, & Weeks, 2001). Detailed discussion of the evidence for behavioral interventions is provided by Sonuga et al. in this issue. The degree of effectiveness for these programs is greater than that achieved with stimulant medications. Therefore, the use of psychotropic medications is always carefully considered. Table 2 describes reasons to avoid and reasons to resort to the use of these medications for severe behavior problems of early childhood.

Existing evidence does not yet allow guidelines to be established for treating preschool children with psychotropic medications. However, because severe problems of preschoolers and their families continue to be presented to physicians, an approach

Table 2. Considering the role of psychotropic medications for preschoolers

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| <p>Reasons to avoid psychotropic medications</p> <ul style="list-style-type: none"> ● Best evidence supports parent training interventions ● Evidence to guide treatment is limited by small number of preschool children included in randomized, controlled designs ● Information about the effect of medications on the developing brain is limited ● Developmental differences in metabolism, including distribution and clearance of medications, are not well known and cannot guide dosing decisions ● Side effects may be more likely to occur, but short term appear to be mild ● Long-term side effects are not known <p>Reasons to consider psychotropic medications</p> <ul style="list-style-type: none"> ● Serious mental health conditions exist in very young children ● Parent training or other psychological treatment may not be possible <ul style="list-style-type: none"> ○ Such interventions were tried and not successful ○ Such interventions are not accessible to the child and family ● Risk may be incurred in not treating the child <ul style="list-style-type: none"> ○ Physical harm to child or others ○ Disruption of the family, adoption, or foster placement ○ Potential for abuse directed toward the child in reaction to problem behaviors ● Stimulants are well studied, shown to be effective, and safe in school-aged children |
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is offered in Table 3 that might allow careful consideration of symptoms and treatment options. The severity of symptoms as well as diagnostic entities must be considered. A condition that meets diagnostic criteria for ADHD, for example, may not necessarily warrant the use of psychotropic medication in a 3-year-old child. Conversely, symptoms such as aggression may be of high severity, while the whole set of diagnostic criteria for any one condition is not met. The later situation may warrant intervention with psychotropic medication due to safety issues. The physician must make it clear to parents that the diagnostic process is ongoing, especially in preschool children, whose symptoms evolve as the child matures. It is possible to continue a diagnostic process while treating target behaviors of high severity. Physicians must also take care not to create an impression that a child with a complicated condition has a simple case of ADHD. For example, children with genetic syndromes associated with extreme hyperactivity and children with autism may improve with the use of psychotropic medications, but the underlying condition will remain with special needs that must be addressed.

A decision that a preschool child's problems are severe enough to warrant psychotropic medication will almost always involve other child specialists, such as staff of early intervention programs and child psychologists. The most difficult dilemma facing the clinician is likely to be access to such specialists and to training programs for parents. Access may be limited because of insurance coverage, family inability to organize and utilize services, or lack of such services within a community. Similar access problems are encountered with referrals to child psychiatry and developmental and behavioral pediatricians.

Once a decision is made to use medication management, the choice of medication is determined by the available evidence that methylphenidate and dextroamphetamine are effective and associated with primarily mild short-term side effects. Atomoxetine may be a useful alternative; however, the current concern for possible liver dysfunction may make this medication more difficult to use with young children. It is prudent to begin treatment with a low dose of stimulant and increase the dose gradually in the young child.

Table 3. Suggested approach to treating preschool-aged children with psychotropic medication

- Refer to Early Intervention Program of city, county, or region if activated and in place
- Parents complete parent training program
- Gather diagnostic information from more than one source, over time
- Consider severity of symptoms and symptom complexes as well as diagnostic entities
- Inform parents about risks of condition and risk and benefit expected with medication
 - Serious behavioral problems of very young children are often associated with other mental health and health conditions
 - Severe problems in preschoolers are not likely to be uncomplicated attention-deficit/hyperactivity disorder as we know it in school-aged children
 - If the child's safety or placement in the home is at risk, this must be weighed with the risk of medication
 - Long-term risks are unknown
- Establish target behaviors and outcomes with parents and others
 - Establish level of function and status of target behaviors at baseline
- Consider stimulants as current research provides evidence for effective treatment
 - Treatment is initiated with lowest dose and titrated to effective level or occurrence of side effects
 - Short-acting preparations may allow use of lowest dose and maximum flexibility over the course of a day
 - Long-acting preparations may be difficult for child to swallow, but if accepted may obviate struggles over administering medication several times a day
- Monitor with follow-up visits every 1- 3 months; more frequent as initial dose is established
 - Monitor effectiveness according to target behaviors and outcomes
 - Monitor side effects: weight, height, pulse, blood pressure, mood, sleep
 - Weight may need close attention and specific intervention to prevent prolonged periods of time without adequate gain
 - Failure to gain weight, and failure of family to organize around need for child to have increased calories, may limit use
 - Review input from day care, preschool, other family members regarding effectiveness and side effects
 - Seek more global parameters of effect
 - Relationships with others: family members, teachers, peers
 - Participation and achievement of age-appropriate activities of daily living: dressing self, bedtime routines, day care or preschool routines
 - Monitor safety of child and family
 - Supervision of child and arrangements for care
 - Daily issues: seat belt use, remaining with parent or supervising adult
- Inquiry specifically made regarding parents' health, mental health, and social well-being, with referral as needed, at baseline and with each follow-up
- Remain alert over time to need for referral to other services: speech and language, physical and occupational therapy, medical specialists, social work, child protective services
- Remain alert over time to need for referral of parent for mental health services

Problems with failure to gain weight may limit ability to treat, especially for the family that is not organized in providing meals for young children. Short-acting medications may provide flexibility both in addressing the

most problematic times of day for the child and family, and in taking advantage of a better appetite when the effect of medication wears off. Other medications are distant second choices due to the frequency of serious

side effects associated with clonidine and risperidone. These might be considered for the very aggressive or extremely hyperactive child who did not respond to or tolerate stimulants or atomoxetine. Risperidone may be especially helpful in the child who has pervasive developmental disorders, autism, or mental retardation. The lack of clear indication for use of SSRIs in this age group limits their use.

Close monitoring is essential for the preschool child taking psychotropic medications. A recommendation for visits every 1 to 3 months is empirical but prudent. The nature of symptoms evolves rapidly in the young child; new problems may become obvious that warrant specific intervention, such as language delays or fine and gross motor problems. Such problems may not be new but may have gone unnoticed in the very aggressive and hyperactive preschooler. Side effects of medications may present at any time in the course of treatment. Information gathered from multiple sources over time, perhaps over years in this age group, is essential to accurate diagnosis and formulation of effective treatment plans. Positive relationships with family members and obtaining history of age-appropriate developmental and social milestones are critical to optimal development of the young child. Safety issues that prompt a family to seek treatment will likely continue to need careful attention over time. Parents may have the energy and resources to address their own health and mental health needs as treatment is underway for the child; the physician is in a key position to provide appropriate referrals. Close monitoring allows the physician to continually assess the role of medication in achieving these goals for the child and family.

Primary care physicians are often faced with the dilemma of being the only available provider for the family and preschool child with severe disruptive behavior. The physician should not underestimate the importance of continued engagement with the child and family, whether or not medication treatment is undertaken.

RECOMMENDATIONS FOR IMPROVING SERVICES FOR THE PRESCHOOL CHILD AND FAMILY

Current practice in the use of psychotropic medications for preschoolers is marked by inconsistent and idiosyncratic patterns of prescribing. It is likely that this results from a combination of urgent problems, an expectation that such problems will be addressed by the physician with medication, and lack of information to guide such decisions.

It is not likely that traditional research designs will provide the information needed to treat families and preschool children with severe disruptive behavior and mental health issues. The number of such cases is too small for the kind of large-scale studies needed to account for the wide range of normal variation in development and the incidence of rare or long-term side effects of medications. The children, however, and their urgent problems are presented in primary care and specialty offices with increasing frequency.

One solution may be national registries organized to allow incorporation of data from practice networks around the country. This is an efficient and timely model that has resulted in vast improvement in quality of life and standardization of effective treatment in childhood cancer, for example. This approach could be coupled with more intensive randomized controlled studies, similar to the Multimodal Treatment Study of ADHD. The result might be guidance and eventually guidelines for physicians and families dealing with these issues.

Serious mental health disorders of preschool children are well documented. The evidence of studies examining the persistence of problems indicates that rates may be similar to school-aged children for serious disruptive disorders. The strongest evidence for treatment supports parent training programs. A small number of children and families may be unsuccessful or may be unable to access such programs and will seek management with psychotropic medications. In an effort

to bring more consistency and informed decision making to bear on these problems, an approach to such treatment is described, culled from available reports, and formulated with best available evidence. Ultimately,

guidelines and a standard of care will emerge, as both practice and research communities join in national organized efforts to bring the best of care to these vulnerable children and their families.

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