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Commentary

The Dramatic Rise in Neuroleptic Use In Children: Why Do We Do It and What Does It Buy Us? Theories from Inpatient Data 1988–2010

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Introduction

In recent years, the increasingly greater use of atypical antipsychotics (AAPs) in children, especially compared with the rates of use of conventional antipsychotics two decades ago, has been the focus of research and public scrutiny. The most recent study by Olfson et al. (2012) uses data from office-based treatments to highlight that between 1993 and 1998 and between 2005 and 2009 there was a ninefold increase in antipsychotic use in children (2.4/1000–18.3/1000). Similar observations have been made in a variety of settings (Olfson et al. 2006), and whereas there is some regional variation (Patel et al. 2005), and international variation (Rani et al. 2008; Alessi-Severini et al. 2012), the trend has always been in the same direction: higher.

Picked up by the lay press in sensationalized terms, the take-home message is that these drugs are ''powerful,'' used to ''control'' little children with attention-deficit/hyperactivity disorder (ADHD), are used off-label, and that this is nothing short of reprehensible (Reinberg, 2012). Little time is spent examining rates of other healthcare changes over the same time period. We learn nothing of the circumstances of the children being treated. For example, rates are higher in foster care children than in children in their own families (Longhofer et al. 2011), higher in Medicaid samples than in managed care samples (Patel et al. 2005), and higher in children in group homes than in those in therapeutic foster homes (Breland-Nobel et al. 2004). This suggests that the populations being treated have a more severe condition than the comparison samples. Although the weight-gain propensity of these medications is well known, no time is spent on whether at least some of the children being treated are being maintained in a setting that otherwise would not tolerate them.

The common clinical features of the samples studied are that the children are prepubertal, male, white, being treated for ADHD and conduct disorder, and, where other treatments are examined, concomitant medications, usually stimulant medications, are common (Longhofer et al. 2011; Olfson et al. 2012).

Olfson et al. (2012) speculate that reasons for the increase include availability of AAPs because of clinical trials, practice guidelines supporting use in children, ease of use of the medications, proliferation of managed care limiting psychotherapy reimbursement, pharmaceutical marketing associated with off-label use, and, last but not least, ''some patients may respond but not remit to evidence based treatments'' leading to the use of AAPs as adjunctive treatment.

This commentary elaborates on several rationales suggested by Olfson et al. (2012), and adds information on comparable changes in other treatments over the same time frame, as well as examining the severity of the samples given medication.

Inpatient Experience

The 10-bed children's psychiatric inpatient unit at Stony Brook University Hospital, which opened in late 1986, treats children between the ages of 5 and 12. It began and kept a database for the years 1988–1993, at which point managed care inroads made it increasingly difficult to hospitalize children for the time necessary to significantly impact their problems and study treatment outcomes. Several publications describe the sample at length (Carlson and Kelly 2003; Carlson and Mick 2003; Carlson and Youngstrom 2003). In general, however, children were diagnosed using a combination of Schedule for Affective Disorders and Schizophrenia Epidemiological Version for School-Age Children (K-SADS E) (Orvaschel et al. 1982), admission information, and hospital course. Nurses and teachers on the unit rated the children weekly using several standardized rating scales. Children's ''time outs'' (sitting in a chair for 10 minutes as a consequence of a disruptive behavior) and use of seclusion (room isolation with door closed) was also systematically recorded as was medication treatment The major treatment modalities in addition to stimulant medication and tricyclic antidepressants were parent training and behavior modification.

Between 2002 and 2010, there were two occasions in which data were collected systematically. The first was a study between 2002 and 2004, ($n = 151$) of children's explosive outbursts, observed by staff trained to characterize outburst behaviors and their duration. Children were treated with liquid risperidone to determine if that decreased outburst frequency and duration (Carlson et al. 2009, 2010). Medications were recorded. Parent training and behavior modification remained the major nonmedical intervention. A best-estimate diagnosis was based on two psychiatrists' agreement.

The most recent study from 2010–2011 ($n = 82$) included consensus ratings by the research/treatment team of diagnosis and of specific symptoms of explosiveness, irritability, and ADHD and oppositional defiant disorder (ODD) severity (Margulies et al. 2012). Also recorded was the frequency of use of the ''quiet room'' (the seclusion room with the door open, which does not count as seclusion) and the frequency of p.r.n. medications used for agitation.

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The early sample (1988–1993) was compared with the combined two later samples for this discussion. Mean age (9.4 ± 2.1), gender (78% male), ethnicity (78% Caucasian), and overall rates of ADHD (66%) were similar.

The inpatient unit has experienced the same dramatic increase in use of neuroleptic medication, from 15.2% of patients receiving conventional antipsychotics in the early sample to 68.5% use of AAPs more recently. Simultaneously, however, the mean length of stay dropped from 10.4 ± 5.3 to 5.3 ± 4.1 weeks. The rate of rehospitalization increased from 17% to 42.2%. In the earlier sample, 30% of readmissions occurred within the first 6 months after discharge, compared with 58.4% in the later sample.

With the emphasis on decreasing seclusion, the mean number of seclusions per week dropped from 0.66 ± 1.47 (median 0.1) to 0.21 ± 0.48 (median of 0), a statistically significant drop in seclusion. However, if one includes the ''quiet room'' in the room isolation statistic, rates of children needing isolation have increased to 1.66 ± 1.9/week (median 0.95). Fewer children now return home to a biological parent (71.4% compared with 85.4% in the past, $p < 0.001$) and more children now go to residential treatment, although I do not have that statistic.

The impact of other changes is impossible to quantify. Residents used to have a rotation of 3 months, meaning that they got to know and treat their patients; their rotations are now 1 month. Primary nurses used to spend time with the children; now they are shackled to their computers inputting information into the electronic medical record. When children are admitted now, the first words out of the mouths of the managed care gatekeepers seems to be, ''what drug are you going to start,'' regardless of the six drugs the child was taking at admission.

ADHD, ODD and Neuroleptics

In the earlier data set, 15.6% of children, 62.5% of whom had ADHD, were treated with conventional antipsychotics. The rate of children being prescribed neuroleptics has increased, but the proportion of children who have ADHD (71.7%) is similar ($p = 0.257$).

Compared with the earlier sample, when only 17% of children with rage outbursts (vs. 15% without) received neuroleptics, now 80% of those with rages are treated with AAPs, significantly more often than those without outbursts (58.3%) (OR 20.03, 95%CI: 10.34, 38.79).

Across both time frames, ODD is the condition that encompasses the phenomenon of rage outbursts. Two thirds of children with ADHD and ODD had a rage outburst (65.1%) versus half of those with ADHD without ODD (49 %, OR 1.9 [95% CI: 1.12, 3.13]). The number of rage outbursts varied significantly by diagnosis (mean + standard deviation; median) with children with ADHD and ODD having the most outbursts by far: no ADHD = 1.3 ± 4.4; 0; ADHD = 3.8 ± 15.0; 1; ADHD and ODD = 8.4 ± 22.5; 2 $p < 0.0001$.

In the most recent data (2009–2010), where symptoms of explosiveness and irritability are rated, explosive children took AAPs twice as long as nonexplosive ones (26.9 ± 23.9 days vs. 13.4 ± 26.3 days [$t = 2.43$, df 78, $p = 0.018$]). The same was true for children with high irritability ratings (24.4 ± 27.1 vs. 12.6 ± 20.6 days [$t = 2.12$, df 61, $p = 0.038$]). This is further evidence that it is the behaviors that are directing treatment, and the ADHD/ODD diagnosis is simply the name the doctors use to ''code'' it.

Overall, the biggest change in this sample appears to be how children with ADHD and ODD are medicated (see Table 1). In the earlier sample, they were most likely to receive a stimulant alone (74.4%) and almost never received a neuroleptic alone (6.3%).

Table 1. Changes in Stimulant and Neuroleptic Use Over Time

	1988–1993	*2002–2010*
	ADHD + ODD	ADHD + ODD
Medication type	$n = 161$	$n = 92$
Neither	11.9%	4.3%
Neuroleptic only	6.3%	17.4%
Stimulant only	74.4%	16.3%
Both	7.5%	62.0%
	$X^2$110.96 df 3, $p < 0.0001$	

Currently, they rarely receive a stimulant alone (16.3%) and usually receive combined stimulant and AAP (62%). In other words, the children and their behaviors have not changed. We used to treat them with more extensive inpatient treatment, including parent training, behavior modification, and stimulant medication. Now, it appears that we get by with shorter lengths of stay and add AAPs.

Discussion

The answer to why doctors have gravitated to using AAPs in these patients seems simple. Even though there is no formal United States Food and Drug Administration (FDA) approval, there is an extensive database that has been quantified in meta-analyses (e.g., Connor et al. 2002; Pappadopulos et al. 2006) and treatment guidelines (e.g., Pliszka et al. 2006). Although there are no head-to-head studies, those meta-analyses suggest that despite their flaws, neuroleptics work better than lithium or anticonvulsants as adjunctive medications, especially when irritability, rage, or explosive behavior are the targets of the intervention. It is possible that the new formulations of the alpha agonists will impact the severity of rages, but this has yet to be studied.

Most clinicians are well aware of the ''down side'' of AAPs. Two things are perhaps not emphasized enough. The first is that clinicians sometimes give up too quickly on stimulant treatment (Blader et al. 2010). Explosive outbursts often occur just as doctors start medications to treat outbursts causing parents to insist ''the drug is making my child worse.'' This, of course, is not usually the case. When stimulants were the only alternative, we probably persisted longer with them. They certainly have their own drawbacks, but they are often effective in volatile children. Among the issues leading to adjunctive AAPs are that the appetite decrease/weight loss preclude effective stimulant dosing, or the afternoon cessation of effect and problems with sleep using stimulants may lead physicians to add an AAP.

The second underemphasized fact is that whereas the effect size (at least for risperidone) is decent (0.9) (Pappadopulos et al. 2006), it is not nearly good enough when compared with the severity and frequency of outbursts seen in some of the children being treated. Nor are other AAPs better. In mania trials, the impact on the ADHD rating scale of olanzapine (Tohen et al. 2007) or aripiprazole (Findling et al. 2009), although statistically significant, was clinically rather small. Contrary to the rhetoric about the AAPs being ''powerful,'' I find that the medications are not nearly as powerful as the rages they are trying to address. In addition, although there is evidence that combined with ADHD medications, parent training, and behavior modification our children are sometimes very much improved on discharge from our inpatient unit, the medications are not enough to maintain the treatment gains (Blader 2006) back in their environments, which accounts for more medications being added or, as noted earlier, relatively rapid readmission.

One final comment seems necessary. As we await publication of American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (DSM-V), there is still no way to code for or label explosive outbursts (regardless of diagnosis). The National Comorbidity Study-Adolescent Supplement (NCS-A) replication study recently reported that half of teens with serious ''anger attacks'' (i.e., 6.2%) do not meet intermittent explosive disorder criteria because of exclusionary criteria like ADHD and ODD (McLaughlin et al. 2012). Rates in children are likely to be even higher. Disruptive mood dysregulation disorder (DMDD), if it is included as a diagnosis option, is characterized by chronic irritability and outbursts occurring in more than one setting. Although incorporating outbursts into its definition, it, too, excludes many of the conditions in which the outbursts occur. Applying the DMDD definition to our inpatient children, we found only 30.5% of inpatient children met criteria for DMDD by parent report, and 15.9% by actual inpatient unit observation (Margulies et al. 2012). The name also disguises the fact that most of these children meet criteria for both ADHD and ODD (Carlson 2007) and if that is not acknowledged, the ADHD will not be treated.

It is ironic that the most noxious and impairing behavior, namely explosive outbursts in children, has no ''home'' in the DSM nosology. Recognizing that explosions can occur in many conditions (Connor et al. 2006), neither intermittent explosive disorder nor, if it is accepted into DSM-V, DMDD, allows the diagnosis if the explosions are ''better explained by'' another condition. There is not even a consistent way in which one can find information about rage outbursts. In PubMed, there are almost completely different databases for terms like rages, rage outbursts, anger outbursts, rage attacks, explosive outbursts, and meltdowns. Irritability, the term that seems increasingly to be adopted, like aggression, may subsume these behaviors, but is not synonymous. Therefore, we speculate that the behavior that most drives the most use of AAPs does not even have a label that can be consistently used, and will certainly, without a ''home,'' never be an indication for FDA approval.

Limitations in these analyses include changes in the diagnostic criteria, our interpretations of the criteria, and assessment of the children over the past 25 years. Enthusiasms for certain diagnoses for children with rages that provide both a diagnostic home and FDA approval (such as mania and autism with irritability) have also varied. Moreover, I have no illusions that data from a small, university-based children's inpatient service has great generalizability. I can, however, say that there has been a relationship between the decreasing time in treatment and increased use of AAPs. I am unable to say in the long run if that makes a long-term difference in the child's outcome. Both subjects should be addressed with more systematic research if anyone has treatment information with other modalities from the earlier time frame, as reported here.

In conclusion, the meteoric rise in the use of AAPs in children with ADHD and ODD reflects the fact that the traditional evidence-based treatments (stimulants and parent training/behavior modification) are either unsupported by providers and insurance (at least in terms of the intensity they require) or that these treatments are insufficient, because of the severity of the conditions being treated.

AAPs may be expensive, and clearly have important adverse effects. The question is whether society (and insurance companies) want to support the alternatives. If they do not, I feel that the rhetoric is disingenuous. I, for one, would be grateful if the AAPs could compensate for what we have lost in terms of other treatments, and were as powerful as the media imply.

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