Therapeutic Equivalence of Generic Concerta

Children and adolescents with ADHD experienced significant symptom improvement when they were switched from a non-OROS to the OROS generic formulation of extended-release methylphenidate (Concerta).¹ This observation supports the FDA’s concerns about the therapeutic inequivalence of generic Concerta formulations.

Background: Concerta’s osmotic controlled-release oral delivery system (OROS) is a delivery technology designed to release methylphenidate from the capsule over 10–12 hours, consistent with the effect of 3-times-a-day dosing of immediate-release methylphenidate. Of 3 Concerta generics now on the market, only 1 uses OROS technology. This formulation is manufactured by Janssen, the manufacturer of brand-name Concerta, and marketed by Actavis under a licensing agreement. Two other extended-release generics, manufactured by Kremers and Mallinckrodt, are FDA-approved as pharmaceutical equivalents of Concerta, with the same dosage and route of administration. However, following reports from consumers of waning efficacy during the day, the FDA lowered the equivalence rating of these 2 generics in November 2014.² They are still approved but no longer recommended as automatically substitutable for Concerta.

Methods: Outcomes were compared among extended-release methylphenidate formulations in children and adolescents referred to an outpatient clinic at an academic medical center. All treatment decisions were made as part of routine clinical care. Following a diagnosis of ADHD (DSM-IV-TR), the patients were given a prescription for and were taking Concerta, but they were experiencing symptoms during the day, despite dosage titration. After contacting the pharmacies, it was discovered that non-OROS generics had been substituted. Patients’ caregivers and pharmacists were then instructed to fill the prescriptions only with the OROS generic. Treatment efficacy was assessed using the Conners-Third Edition: Parent Rating Scale, Short Form [Conners 3-P(S)] at the time of diagnosis, following treatment with non-OROS generics, and again following treatment with the OROS generic.
Results: The sample consisted of 14 patients, with an average age of 11 years (range 8–16 years). All patients had clinically significant scores on the Connors 3-P(S) Inattention subscale at baseline. Overall scores on the Connors 3-P(S) did not improve after treatment with the non-OROS generics, but they improved significantly when patients were switched to the OROS generic (p=0.0004 vs. baseline). Compared with scores during non-OROS treatment, after switching, Inattention scores were significantly reduced (p=0.014 for patients with inattentive-type ADHD and p=0.0015 for those with combined type). In patients with the combined type, scores on the Hyperactivity scale were also reduced (p=0.0048). Average scores on both subscales were below the clinically significant threshold when patients were receiving the OROS generic.

Discussion: The authors note that these observations are preliminary. The FDA is now conducting or concluding bioequivalence and pharmacokinetic/pharmacodynamic studies in healthy adults and in children with ADHD.

1 Lally M, Kral M, Boan A: Not all generic Concerta is created equal: comparison of OROS versus non-OROS for the treatment of ADHD. Clinical Pediatrics 2015; doi 10.1177/0009922815611647. From the Medical University of South Carolina, Charleston. This study was conducted without funding. The authors declared no potential conflicts of interest.


Depression Prevention in At-Risk Adolescents

Adolescents at familial risk of depression who completed a cognitive-behavioral prevention (CBP) program in a multi-center controlled trial continued to maintain lower rates of new-onset depression than a control group after 6 years of follow-up.1

Background: Previously reported results for this study sample indicate efficacy of CBP for acute treatment as well as shorter-term follow-up.2,3 The present long-term follow-up study was designed to evaluate the extent and duration of those positive effects during the transition from adolescence to young adulthood.

Methods: Participants were 316 adolescents, aged 13–17 years at study entry, who had ≥1 parent with major depression or dysthymia either occurring in the past 3 years, with ≥3 years’ duration, or with ≥3 recurrences. Adolescents themselves were not experiencing a depressive episode at study entry but had either a past depressive episode now in remission or current subsyndromal depressive symptoms. Participants were randomly assigned to a usual-care comparison group or to CBP, a modified version of the Coping with Depression for Adolescents program that emphasizes cognitive restructuring and problem solving. CBP consisted of 8 weekly 90-minute group sessions, 6 monthly booster sessions, and 2 informational sessions for the parents. Outcomes for the present analysis were measured at 75 months and included time to depression onset (the primary outcome), depression-free days, functioning (Global Assessment Scales), and developmental competence in emerging adulthood (Status Questionnaire).

Results: At 6 years, 88% of the original participants were available for follow-up. Their mean age was 21 years (range, 18–25 years). Depression onset was significantly less likely in the group that received CBP (hazard ratio,* 0.76; p=0.05). The groups did not differ statistically in the overall number of depressive episodes or depression-free days during follow-up. Further analysis indicated that CBP was effective prevention only in adolescents whose parents had not been experiencing a depressive episode at baseline.

The overall between-group differences were driven by lower depression onset in the CBP group early after treatment. Depression incidence was significantly lower during the first 9 months of follow-up in patients who received CBP (hazard ratio, 0.64; p=0.05), but not thereafter. Thus, gains were maintained but did not increase over the following years. CBP was not associated
with differences in use of mental health services, global functioning, or developmental competence. As with depression onset, the benefits in developmental competence were limited to adolescents whose parent was not experiencing a depressive episode at baseline.

**Discussion:** The acute and long-term effects of the CBP intervention in this study suggest it is beneficial. It is possible that the program might be made even more effective by treating parental depression either before or at the start of child treatment. Rather than focusing strictly on the adolescent, CBP programs could also work on improving parenting and the quality of the parent-child relationship. Additional booster sessions could potentially extend the early benefits of CBP over a longer time.

1^Brent D, Brunwasser S, Hollon S, Weersing V, et al: Effects of a cognitive-behavioral prevention program on depression 6 years after implementation among at-risk adolescents: a randomized clinical trial. *JAMA Psychiatry* 2015; doi 10.1001/jamapsychiatry.2015.1559. From the University of Pittsburgh, PA; and other institutions. Funded by the NIMH; and other sources. One study author disclosed potentially relevant financial relationships; the remaining 11 authors declared no competing interests.


*See Reference Guide.

### Aripiprazole Monotherapy for Resistant OCD

According to results of a preliminary study, aripiprazole monotherapy is effective in children with treatment-resistant obsessive-compulsive disorder.

**Methods:** Study subjects were 16 consecutively-treated children (mean age, 11 years) who had received aripiprazole monotherapy after showing no improvement with trials of cognitive behavioral therapy with ≥2 types of SSRI or clomipramine. Patients with schizophrenia or bipolar disorder were excluded from the retrospective analysis, but those with other psychiatric comorbidity were included. All patients received flexibly-dosed, open-label aripiprazole for 12 weeks and were evaluated for response and adverse effects monthly. The mean aripiprazole dosage was 4.75 mg/day (range, 2–7.5 mg/day).

**Results:** At baseline, patients were rated at least "markedly ill" according to scores on the Clinical Global Impression–Severity (CGI-S) scale. More than 80% of patients had comorbid disorders, most commonly ADHD, but also tics, major depression, conduct disorder, and/or oppositional defiant disorder.

After 3 months of treatment, patients showed substantial improvement in OCD symptoms and overall illness severity. (See table.) In addition, improvement in each of the 10 symptom domains of the Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS) was highly significant (p=0.002 or better). Only 1 patient experienced an adverse event, increased appetite.

<table>
<thead>
<tr>
<th>Baseline and Follow-Up Evaluations</th>
<th>CY-BOCS, mean</th>
<th>Baseline</th>
<th>3 months</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obsession score</td>
<td>14.1</td>
<td>7.2</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Compulsion score</td>
<td>16.4</td>
<td>7.6</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>30.6</td>
<td>15.3</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CGI–Improvement, Number (Percent)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No change or minimally improved</td>
<td>3 (19%)</td>
</tr>
<tr>
<td>Significantly improved</td>
<td>5 (31%)</td>
</tr>
<tr>
<td>Nearly or completely cured</td>
<td>8 (50%)</td>
</tr>
</tbody>
</table>
Discussion: Aripiprazole augmentation has been shown to be effective in refractory OCD in several clinical trials, but there is less evidence of its efficacy as monotherapy. Its pharmacological profile, with a partial agonistic effect on D2 receptors and 5-HT1a agonistic properties, may underlie its efficacy as single-agent therapy for OCD.

Erçan E, Ardic U, Erçan E, Yuce D, et al: A promising preliminary study of aripiprazole for treatment-resistant childhood obsessive-compulsive disorder. *Journal of Child and Adolescent Psychopharmacology* 2015;25 (September):580–584. From Ege University School of Medicine, Izmir, Turkey. The study was conducted without funding. One author disclosed relationships with commercial sources; the remaining 4 authors declared no conflicts of interest.

Common Drug Trade Names: aripiprazole—Abilify; clomipramine—Anafranil

### Methylphenidate/Acetaminophen Hallucinations

A 6-year-old boy with ADHD had been receiving 18 mg/day OROS methylphenidate (Concerta) for 2 months with significant improvement in behavior. The only reported adverse effect was appetite suppression. He presented with a 1-week history of anxiety, fearfulness, and refusal to leave his parents. After he started 120 mg/day acetaminophen suspension following a flu-like illness, the patient reported visual hallucinations, during which he was oriented to time and place. Because hallucinations had not occurred with methylphenidate monotherapy, it was presumed not to be the cause. The acetaminophen was discontinued, and the hallucinations resolved. They did not recur during 6 months of follow-up with continued methylphenidate monotherapy.

Methylphenidate is generally safe and well tolerated but has reportedly caused psychotic symptoms in a small number of young patients. Because the patient was not rechallenged with the methylphenidate–acetaminophen combination, it is unclear whether the acetaminophen alone or the combination of the drugs precipitated the hallucinations. However, it was speculated that concomitant use of acetaminophen and methylphenidate led to excessive brain levels of dopamine that then resulted in the hallucinations. It is also possible that acetaminophen elevated the patient’s serum methylphenidate concentrations, increasing the risk of adverse effects.

Herguner S, Ozyayhan H: Visual hallucinations with methylphenidate and acetaminophen in combination. *Journal of Child and Adolescent Psychopharmacology* 2015;25 (September):598–599. From Necmettin Erbakan University, Konya; and Konya Training and Research Hospital, Turkey. The authors declared no competing interests.

### Cardiovascular Safety of Atypicals with Stimulants

Concomitant use of atypical antipsychotics did not increase the cardiovascular risks of long-acting stimulants in children and adolescents with ADHD, according to a population-based study.

**Background:** Clinical trials have shown that stimulants lead to increases in heart rate and blood pressure, but recent observational studies and a meta-analysis have not shown increased risk of disease events. Antipsychotics, used increasingly to manage behavioral symptoms of ADHD and comorbid disorders, are associated with orthostatic hypotension, QT interval prolongation, transient ischemic attack, stroke, and myocardial infarction (MI).

**Methods:** Claims data were collected for a 4-year period from the IMS LifeLink database, which contains information about commercially insured patients in the U.S. The study cohort consisted of nearly 38,000 young patients, aged 6–16 years, with a diagnosis of ADHD who received a new prescription for a long-acting stimulant between July 2004 and December 2006. Medications of interest included 5 long-acting stimulants (i.e., methylphenidate, dexmethylphenidate, amphetamine–dextroamphetamine, pemoline, lisdexamfetamine) and 6 second-generation antipsychotics (i.e., clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole). Concomitant use was defined as receiving both types of medication at the same time for ≥14 days. Patients’ records were examined for up to 1 year from the first
stimulant prescription or until they switched to a shorter-acting stimulant class. The primary outcome was a cardiovascular disease event—e.g., acute MI, stroke, hypertension, angina, aneurysm, arrhythmia, syncope, tachycardia, or palpitation.

Results: Of the nearly 38,000 patients who received treatment with a long-acting stimulant, 538 (2%) also received an atypical antipsychotic. Those who used both classes of medication were predominantly male (71%), aged ≤12 years (64%), and privately insured (94%). There was no difference in risk for a cardiovascular event between users and nonusers of atypical antipsychotics (adjusted hazard ratio,* 1.19). Cardiovascular risk was increased in boys, patients aged ≤12 years, and those with comorbid tic disorders, asthma, diabetes, and obesity, but the association was independent of combined use of the 2 medication classes. Risk was also increased in patients taking mood stabilizers and/or anxiolytics at baseline.

Discussion: Although both classes of medication have been associated with cardiac risk, their opposing pharmacological actions may cause them to counteract each other's adverse-event profile, thus not increasing cardiac risk. Until additional evidence is produced, cardiovascular-risk screening should be undertaken every 3 months if a long-acting stimulant and an atypical antipsychotic are used concurrently.

Bali V, Kamble P, Aparasu R: Cardiovascular safety of concomitant use of atypical antipsychotics and long-acting stimulants in children and adolescents with ADHD. Journal of Attention Disorders 2015; doi: 10.1177/1087054715608443. From Westlake Village, CA (independent practice); and other organizations. This research was conducted without funding. The authors declared no competing interests.

Common Drug Trade Names: aripiprazole—Abilify; clozapine—Clozaril; dexamethasone—Focalin; lisdexamfetamine—Vyvanse; methylphenidate, long acting—Concerta; amphetamine—dextroamphetamine—Adderall; olanzapine—Zyprexa; pemoline (not available in the U.S.)—Cylert; quetiapine—Seroquel; risperidone—Risperdal; ziprasidone—Geodon

*See Reference Guide.

Paliperidone ER: Long-Term Safety

Treatment with extended-release paliperidone was generally well tolerated over 2 years in adolescents participating in a large open-label extension study.

Methods: This study was conducted to assess the safety and tolerability of paliperidone and, as a secondary objective, to measure efficacy. Participants were aged 12–17 years at enrollment and had a confirmed DSM-IV diagnosis of schizophrenia. The 400 study patients were enrolled either directly (n=243) or after participating in a 6-week placebo-controlled trial of paliperidone (n=157). Open-label paliperidone was initiated at 6 mg/day and could be adjusted to dosages between 1.5 and 12 mg/day based on efficacy and tolerability.

Results: A total of 220 participants completed the 2-year study, and the average duration of paliperidone exposure was >15 months. The most common paliperidone-associated adverse events were somnolence and weight gain (18% each). Severe treatment-emergent adverse events occurring in ≥3 patients were schizophrenia exacerbation (n=19), suicidal ideation (n=8), dystonia (n=4), weight gain (n=4), akathisia (n=3), and anxiety (n=3). A total of 25 patients (6%) discontinued treatment because of adverse events.

There were no clinically significant changes in pulse rate, blood pressure, or electrocardiogram parameters. Nearly half of patients gained >7% of their initial body weight, but z scores* indicated that the weight gain was usually age-appropriate. About 17% had a clinically meaningful weight gain in relation to their z score. Most patients were post-pubertal at study entry, but those who started treatment at age 12 or 13 years experienced normal sexual maturation.

Lipid levels remained stable over time, but 14 patients (4%) demonstrated a shift from low or normal to high levels of glucose. Serum prolactin increased with treatment, reaching above-normal values in 60% of boys and 48% of girls. Prolactin-related adverse effects (mainly
amenorrhea and galactorrhea in girls) occurred in 9% of patients, including 4 who discontinued paliperidone as a result. Treatment-related extrapyramidal symptoms affected 37% of patients and included akathisia (13%), tremor (11%), muscle rigidity (6.5%), and dystonia (5%). No cases of tardive dyskinesia were reported.

Treatment efficacy was measured using the Positive and Negative Syndrome Scale (PANSS). Total PANSS scores improved during the first 3 months of treatment and remained stable thereafter. A total of 67% were considered treatment responders, and 42% achieved remission.

Discussion: Although atypical antipsychotics have similar efficacy, their adverse-effect profiles differ. This study suggests paliperidone is associated with less weight gain than risperidone or olanzapine and a low risk of hyperglycemia, similar to risperidone. Extrapyramidal symptoms were more common in this patient population than in adults taking paliperidone, an observation common to other antipsychotics. Similar to risperidone, paliperidone increases prolactin levels, but this does not appear to affect Tanner stage progression.


Common Drug Trade Names: olanzapine—Zyprexa; paliperidone—Invega; risperidone—Risperdal

*See Reference Guide.

Reference Guide

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Z Score: A statistical measurement of a score’s relationship to the mean in a group of scores. A Z-score of 0 means the score is the same as the mean.

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