According to a review from the NIMH, irritability has become a major focus of neuroscience and translational research but remains a challenge in clinical practice. Recognizing irritability as a mood problem, rather than simply a behavioral issue, along with consideration of it in the context of common comorbidities, could improve patient outcomes while reducing unsupported use of antipsychotics.

Irritability is defined, somewhat imprecisely, as an increased proneness to anger relative to peers at the same developmental level. It is recognized in the DSM-5 as a dimensional construct, as a subgroup of oppositional defiant disorder, and as the main characteristic of disruptive mood dysregulation disorder (DMDD). The underlying mechanism is believed to be aberrant responding to frustrative nonreward and threat processing, resulting in anger and, ultimately, downstream problems within the family.

Irritability is a transdiagnostic entity, and regardless of the pathophysiological context, it can be measured in the same way. Instruments for assessing irritability include questionnaires such as the Affective Reactivity Index or the Modified Overt Aggression Scale; semi-structured interviews such as the DMDD Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children; structured interviews such as the DMDD module of the Development and Wellbeing Assessment; and change measures such as the Clinical Global Impression scale for irritability, currently the primary outcome measure in many clinical trials.

For children with irritability, treatment should first address comorbid conditions, using evidence-based therapies such as stimulants for ADHD, as irritability often improves when the underlying disorder is controlled. In parallel with this approach or as a next step, psychological treatments should be considered; parenting interventions for younger children and cognitive behavioral therapy for adolescents have well-supported efficacy. Newer psychological treatment approaches include exposure techniques to increase tolerance for frustration and computer-based interventions such as interpretation bias training. Medications for irritability should be reserved for later stages in many cases.
Several clinical trials of medications for irritability are underway. The only completed trial, of lithium, found no benefit. SSRIs can curb anger attacks in adults but are less effective in younger patients, and there are concerns about activation, suicidality, and inducing mania. Two atypical antipsychotics, aripiprazole and risperidone, have FDA approval to treat disruptive behaviors in children with autism spectrum disorder, and olanzapine may also be effective. However, because of the adverse effects of these drugs, use should be limited to brief periods only in children who have not experienced response to a series of other treatments.


Common Drug Trade Names: aripiprazole—Abilify; olanzapine—Zyprexa; risperidone—Risperdal

Generic ER Methylphenidate: Therapeutic Failure

Approved generic formulations of extended-release (ER) methylphenidate in Canada were associated with a 10-fold higher rate of reported therapeutic failure, compared with branded OROS methylphenidate (Concerta). Inequivalence of generic extended-release methylphenidate is also under investigation by the U.S. FDA, which has recommended withdrawal of previously approved generics. The present study examined adverse events reported to Health Canada, primarily, but also analyzed events reported to the FDA.

Methods: Adverse-event reports of therapeutic failure were identified in Health Canada’s online reporting system for the 1-year period beginning 8 months following the market approval of branded OROS methylphenidate and generic extended-release methylphenidate. The 8-month lag was intended to reduce the influence of inflated early reports for a new drug. Exposure was quantified as the total number of tablets dispensed, assuming once-daily dosing. Narratives of individual cases were reviewed to characterize the features of therapeutic failure. The authors also conducted a similar analysis of U.S. FDA adverse-events reports involving the authorized generic of OROS methylphenidate (the branded product that is distributed as a generic and that is identical to Canadian branded OROS methylphenidate), comparing it to a generic that was the subject of the FDA investigation.

Results: In both the Canadian and U.S. data, reports of therapeutic failure were about 10 times more frequent with generic than OROS methylphenidate. In the Canadian data, the rates of therapeutic failure per 100,000 patient-years of exposure were 412 with generic ER methylphenidate and 38 with branded OROS methylphenidate (rate ratio,* 10.99). Corresponding numbers from the U.S. data were 69 and 7 per 100,000 patient-years of exposure, respectively (rate ratio, 9.51).

Of the 230 Canadian reports that were individually reviewed, 26% were assessed as probably related and 74% as possibly related to the generic medication, based on recognized causality criteria. No cases were determined to be unrelated. Nearly all patients reported being switched to the generic from branded OROS methylphenidate. The generic was reported as not being effective throughout the day in half of patients, mainly with loss of efficacy in the afternoon. Nearly 14% of reports concerned symptoms of excessive drug exposure, occurring primarily in the morning. Adverse effects on social functioning were reported in 22% of cases. Findings in the U.S. data were similar; however, 29% of reports involved loss of efficacy and 40% involved excessive exposure.

Discussion: In Canada, clinical deterioration after a medication switch is a reportable adverse effect. In both countries, approval of generics is based on the assumption that pharmacokinetic bioequivalence predicts therapeutic equivalence. Adverse-event reports in the U.S.
have led the FDA to revise its bioequivalence standards and to withdraw its designation of 2 extended-release generics as bioequivalent to OROS methylphenidate. The observed adverse effects of generic ER methylphenidate are consistent with pharmacokinetic data indicating an earlier peak and decline of the generic product.


*See Reference Guide.

Pharmacokinetics of Evening-Dosed Methylphenidate

HLD200 is an investigational formulation of methylphenidate designed to provide symptom control beginning in the early morning and lasting throughout the day, following evening administration. Current extended-release methylphenidate formulations leave an important unmet need for coverage in the hours after awakening. The single-dose pharmacokinetics and tolerability of HLD200 were evaluated in a pair of studies, 1 in healthy adults and 1 in children and adolescents.

HLD200 uses a proprietary delivery platform, DELEXIS®, consisting of microbeads with 2 layered coatings surrounding a methylphenidate core. The outer coating is designed to delay release until the drug reaches the ileocolon, based on several aspects of gastrointestinal physiology. The inner coating provides extended release of drug in the colon. Both layers utilize multiple mechanisms to control drug release, minimizing inter- and intra-patient variability.

Participants in the adult study were 12 healthy individuals (6 men) who received 54 mg HLD200 at 9 PM or a morning dose of immediate-release methylphenidate in a randomized crossover fashion. The child/adolescent study included 11 children, aged 6–12 years, and 18 adolescents, aged 13–17 years. After a ≥5-day washout of their ongoing ADHD medication, pediatric patients received a 54-mg capsule of HLD200 at about 9 PM. In both studies, the last follow-up was 48 hours after administration.

Pharmacokinetics were similar in adults, adolescents, and children. Because the dosage was not weight-adjusted, peak concentrations and area under the time-concentration curve were higher in children and adolescents than in adults. In all age groups, average drug exposure was <3% during the 10 hours following administration, from 9 PM to 7 AM. The median time to achieve peak concentrations was about 18 hours post dose in children and 16 hours post dose in adolescents and adults. Inter-patient variability in pharmacokinetics was low, and the drug absorption profile was similar in all age groups. Following administration, after about an 8-hour delay in drug release, plasma methylphenidate concentrations increased rapidly, peaked at 16–18 hours post-dose, and then declined slowly, demonstrating extended-release characteristics. The methylphenidate was eliminated by 48 hours. In children, there were no adverse events judged to be medication related. In adolescents, 5 adverse events were probably or possibly related to medication; most were mild. Sleep-related adverse effects did not occur.


**Hormonal Contraceptives and Suicide Risk**

Risk of a suicide attempt was increased 2-fold in young women using hormonal contraceptives in a Danish nationwide cohort. The risk increase was particularly large in adolescents.

**Methods:** The study cohort consisted of women living in Denmark who turned age 15 years between 1996 and 2013 and who had no prior history of hormonal contraceptive use, suicide attempts, antidepressant use, or psychiatric diagnoses. Contraceptive use was defined as current or recent (within the past 6 months), and former use was defined as discontinuation ≥6 months in the past. Study outcomes were a first suicide attempt and completed suicide.

**Results:** The study population comprised nearly 500,000 women aged 15–33 years. The average follow-up was >8 years, and the mean age during follow-up was 21 years. About half of all women (54%) were current or recent users of hormonal contraceptives.

Compared with never-users, current/recent users of hormonal contraception had a nearly 2-fold elevation in risk for a first suicide attempt and a 3-fold increase in suicide. (See table). Risk was highest in adolescents and increased rapidly after the initiation of hormonal contraceptives. Risk remained at least doubled until 1 year after initiation, and subsequently subsided to levels that were still 30% higher than in non-users after >7 years of use. Former users of hormonal contraceptives were also found to have increased risk of a first suicide attempt or of completed suicide. Risks were elevated for all types of hormonal contraceptives. Patch, vaginal ring, and progestin-only contraceptives were associated with higher risk than oral combined products.

**Discussion:** Most previous studies have failed to show an association between hormonal contraceptive use and suicide risk, perhaps because they included women several years after they started using the agents, resulting in selection bias favoring women who can tolerate hormonal contraception. In the present study, the decrease in suicide risk after 1 year of contraceptive use was probably the result of discontinuation by women sensitive to the adverse mood effects of these drugs.

Skovlund C, Morch L, Kessing L, Lange T, et al: Association of hormonal contraception with suicide attempts and suicides. *American Journal of Psychiatry* 2017; doi 10.1176/appi.ajp.2017.17060616. From the University of Copenhagen, Denmark; and Peking University, China. *Funded by the Lundbeck Foundation; and Rigshospitalet, University of Copenhagen.* Three of 5 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.

![Adjusted risk of a first suicide attempt and completed suicide](https://example.com/adjusted_risk_table.png)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio*</th>
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</thead>
<tbody>
<tr>
<td>Suicide attempt</td>
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<tr>
<td>All current/recent</td>
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</tr>
<tr>
<td>15–19 years</td>
<td>2.06</td>
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<tr>
<td>20–24 years</td>
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<tr>
<td>25–33 years</td>
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<tr>
<td>Former users</td>
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<td>Current/recent users</td>
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<tr>
<td>Former users</td>
<td>4.82</td>
</tr>
</tbody>
</table>

*Adjusted for age, calendar year, education, polycystic ovary syndrome, and endometriosis

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**Aripiprazole for Tourette's Disorder**

In a manufacturer-sponsored, multinational controlled trial, aripiprazole (*Abilify*) was a safe and effective treatment for tics in children and adolescents with Tourette's disorder.

**Methods:** Participants received treatment at multiple sites in North America and Europe, were aged 7–17 years, and had a diagnosis of DSM-IV-TR Tourette’s disorder. Tics were required to be of at least moderate severity, with baseline Yale Global Tic Severity Scale (YGTSS) scores of ≥20 and causing impairment in normal routines. After a washout of previous medications, patients were randomly assigned to double-blind treatment with low- or high-dose aripiprazole...
or placebo. In patients weighing <110 lbs, target aripiprazole dosages were 5 mg/day (low) and 10 mg/day (high). Target dosages for those weighing >110 lbs were 10 and 20 mg/day, respectively. The primary efficacy outcome was change from baseline in YGTSS score at week 8. The key secondary efficacy endpoint was the Clinical Global Impression–Tourette’s Syndrome (CGI-TS) Improvement score.

**Results:** Of 133 patients randomized to treatment, 119 (90%) completed the study. The average baseline YGTSS score overall was about 62. At the 8-week endpoint, YGTSS scores were decreased by 13 and 17 points with low- and high-dose aripiprazole, respectively, compared with a 7-point decrease in the placebo group (p<0.002). High-dose aripiprazole was significantly superior to placebo in all study weeks, and low dose in all evaluations except week 2. High-dose was superior to low-dose aripiprazole in weeks 4–8. Superiority of aripiprazole was demonstrated in subgroup analyses based on age (children vs adolescents), initial YGTSS severity, and geographic location; and on YGTSS subscales for vocal tics, motor tics, and impairment. Findings were similar for CGI-TS ratings; 69% and 74% of the low- and high-dose aripiprazole groups were rated as much or very much improved, compared with 38% of the placebo group.

Aripiprazole was associated with higher rates of response than placebo according to the study’s a priori definition of response (i.e., >25% improvement in YGTSS-TTS score or a CGI-TS improvement rating of much improved or better): 74% and 89% of the low- and high-dose groups, respectively, compared with 55% of the placebo group. A more stringent definition of response (i.e., >50% improvement in YGTSS–TTS score) was applied later because of the high response rate in the placebo group. The more stringent response rates were 41% and 57% with low- and high-dose aripiprazole, compared with 17% in the placebo group (p<0.02 and p<0.0001, respectively).

Aripiprazole adverse effects were similar to those observed in other pediatric clinical trials and included sedation, somnolence, and fatigue. No serious adverse events occurred. Study discontinuation for adverse effects occurred most often in smaller children. A total of 14 patients discontinued drug or placebo treatment because of adverse events; 11 of these children weighed <110 lbs and received aripiprazole (2 low-dose, 9 high-dose). Clinically relevant weight gain occurred in 18% of the low-dose aripiprazole group and in 9% of both the high-dose and placebo groups.

**Study Rating**—17 (100%): This study met all criteria for a randomized controlled trial.

Sallee F, Kohegyi E, Zhao J, McQuade R, et al: Randomized, double-blind, placebo-controlled trial demonstrates the efficacy and safety of oral aripiprazole for the treatment of Tourette’s disorder in children and adolescents. *Journal of Child and Adolescent Psychopharmacology* 2017;27 (November):771–781. From the University of Cincinnati, OH; and other institutions including Otsuka Pharmaceutical Development & Commercialization, Inc. **Funded by Otsuka.** Nine of 10 study authors disclosed financial relationships with commercial sources including Otsuka; the remaining author declared no competing interests.

*See Reference Guide.*

### Prenatal Acetaminophen and ADHD Risk

According to the results of a population-based study, long-term maternal use of acetaminophen during pregnancy is associated with a >2-fold increase in risk of ADHD in offspring. The increased risk appears to be independent of maternal indications for acetaminophen use and familial ADHD risk.

**Methods:** The study, conducted by the Norwegian Institute of Public Health, began with an invitation to all pregnant women in the country to complete a mailed questionnaire at about 18 weeks of gestation. About 40% of invited women agreed to participate. The cohort consisted of
nearly 115,000 children born in 1999 and 2009, about 95,000 mothers, and about 75,000 fathers. Both mothers and fathers completed questionnaires about their acetaminophen use during the 6 months before the pregnancy, indications for use, ADHD symptoms, and other factors. Mothers completed additional questionnaires at the 30th gestational week and again 6, 18, and 36 months after delivery. The study outcome was an ICD-10 diagnosis of hyperkinetic disorder, which requires the presence of both inattentive and hyperactive symptoms, in the offspring between 2008 and 2014.

Results: Nearly half of the women (47%) reported acetaminophen use during pregnancy, and about 2200 children received a diagnosis of hyperkinetic disorder. Preconception acetaminophen use by fathers was associated with a small increase in ADHD risk, but preconception maternal use was not. However, compared with children with no prenatal acetaminophen exposure, those whose mothers reported acetaminophen use during pregnancy had increased risk of developing ADHD (based on unadjusted hazard ratios*) of 17–46%, depending on the number of trimesters exposed. These risks were not diminished after adjusting for pre-pregnancy use by either parent and were reduced slightly after adjustment for parental ADHD symptoms and other potential confounders including indication for use. Risk increased with increasing exposure. Hazard ratios for exposure during 1, 2, or all 3 trimesters ranged from 1.07 to 1.27, and the greatest increase was observed with ≥29 days of prenatal use (hazard ratio, 2.20).

Discussion: A possible explanation for the association between ADHD and paternal acetaminophen use is endocrine disruption in the testis, leading to germ line epigenetic effects. ADHD is highly familial; however, the present observations suggest that the association of acetaminophen with ADHD in the offspring occurs regardless of parental ADHD symptoms. In addition, fever and infection, common indications for acetaminophen, may adversely affect neurodevelopment, but these results suggest the indications for maternal use are not a major factor in the association. Finally, the lack of an association with pre-pregnancy maternal use indicates that there is a specific gestational effect, which is consistent with but not proof of causality.


*See Reference Guide.

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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.

Rate Ratio: A comparison of the rates of a disease/event in 2 groups that differ by demographic characteristics or exposure history. The rate for the group of primary interest is divided by the rate for a comparison group.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.