

# Drugs for kids: Good or bad?

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In recent years there has been an increase in the number of drugs approved for use in children and adolescents to treat emerging mental illness. These drugs were approved on the basis of short-term efficacy studies, and little is known about their long-term effects. However, animal studies indicate that drug treatment during postnatal periods equivalent to childhood or adolescence can lead to long-term alterations in brain function and behaviour. Here, 2 types of drugs used in children are discussed: psychostimulants and second-generation antipsychotics. Although diagnosis of attention-deficit/hyperactivity disorder (ADHD) and appropriate prescription and use of psychostimulants has been established over many years, relatively little is known about their long-term effects. Results from animal studies suggest possible long-term effects on addiction and reward, although this does not appear to be the case in the short-term for patients with ADHD. With respect to antipsychotics, the challenges of diagnosing schizophrenia and bipolar disorder in children make it difficult to assess the effectiveness of antipsychotics to treat them. Weight gain and associated pathology have been reported with the use of these drugs in children. While early treatment of emerging psychopathology can be beneficial, human and animal studies of the long-term effects of these treatments on the developing brain are needed to better define what is good or bad.

## Psychotropic drugs approved for use in children

Psychostimulants, such as methylphenidate and amphetamine, have been approved for many years for the treatment of ADHD in children as young as 6 years old. These drugs are mechanistically related to drugs of abuse, such as cocaine or methamphetamine, all of which increase dopaminergic neurotransmission. Although infrequent, off-label use of high-dose methylphenidate (54 mg/d) has been reported for treatment in 5 year-old children.<sup>1</sup> These drugs are also used off-label to treat ADHD symptoms in children with comorbid autism and behavioural disorders. In the United States, it is estimated that 5% of children aged 6–17 years are prescribed stimulants.<sup>2</sup> The steady increase in the use of psychostimulants in children, especially adolescents,<sup>3</sup> is because of their effectiveness in improving the hyperactivity, cognitive and be-

havioural symptoms of ADHD. Management of these symptoms improves social interaction and intellectual performance. In a school environment, this treatment can change disruptive behaviour in a child in a cycle of punishment to receptive behaviour in a child who benefits further from positive feedback and reinforcement from teachers and peers.<sup>4</sup>

More recently, the second-generation antipsychotic aripiprazole has been approved in Canada for adolescents aged 15–17 years for the treatment of emergent symptoms of schizophrenia<sup>5</sup> and in those aged 13–17 years to treat bipolar disorder I. In the United States, aripiprazole is approved for treatment of schizophrenia in adolescents aged 13–17 years, manic or mixed episodes associated with bipolar disorder I in children aged 10–17 years and for irritability in autistic disorder in children aged 6–17 years. It is postulated that bipolar disorder can be diagnosed in 13-year-olds, but diagnosis in younger children is unclear and has limited resemblance to adult-onset bipolar disorder.<sup>6</sup> In children at high risk for bipolar disorder, hypomania or mania has not been diagnosed before age 13 years, making bipolar disorder difficult to differentiate from unipolar depression. Diagnosis of schizophrenia and bipolar disorder at an early age may have been driven by financial interests rather than evidence-based criteria.<sup>7</sup> Given that the current diagnostic criteria of schizophrenia and bipolar disorder have not been thoroughly validated in children, it can be argued that the approval of these drugs for these 2 conditions in children is not as rigorous as for approval of these medications for adults. On the other hand, early pharmacological treatment of individuals at high risk for schizophrenia may be associated with reduced emergence or severity of psychotic symptoms.<sup>8,9</sup> As an alternative, nonpharmacological treatments that are often as effective could be considered for high-risk individuals,<sup>8,9</sup> noting that guidelines differ from those for diagnosed conditions.

## Animal studies

Despite the potential benefits of using drugs to treat psychopathology in children, animal models raise concerns regarding their use during development. There is increasing evidence that early-life alterations in neurotransmitter systems by drug treatment in animal models can have lifelong effects. For example,

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treatment with drugs that modify the serotonin system, such as selective serotonin reuptake inhibitors or serotonin-1A receptor agonists, during the early postnatal period (P4–P21) can lead to a lifelong increase in anxiety-related behaviour in mice.<sup>10–12</sup> There have been few studies investigating mechanisms by which drugs can produce such long-term effects on adult brain function. However, studies examining long-term effects of early-life stress on adult behaviour suggest that persistent changes in DNA methylation could be a candidate mechanism.<sup>13–15</sup> In mice, the period of early adolescence (P15–P30) appears to correspond to a distinct behavioural phenotype in which responses to conditioned fear are temporarily reduced, but recovered later in life.<sup>16</sup> In humans, this period of adolescence may correspond to increased susceptibility to psychostimulant addiction during adolescence.<sup>17</sup> Consistent with early adolescence as a period of increased brain plasticity in humans are the profound changes in gene expression that occur in the prefrontal cortex between the ages of 10 and 20 years.<sup>18</sup> It remains unclear at what age during child development pharmacological intervention will produce persistent effects. It appears likely that drug-induced persistent alterations will be both age- and brain region-specific, as suggested by a study of the effect of early-life sexual abuse in humans on brain structures.<sup>19</sup>

The long-term effects of methylphenidate have been examined in animal models. Evidence in rodent models using clinically relevant treatment dose ( $\geq 2$  wk; equivalent to 2–4 yr of human adolescence) indicates several long-term effects that persist in adulthood.<sup>20,21</sup> These include alterations in the dopamine (DA) system with reduced DA transporters, reduced DA activity after withdrawal, a desensitized response to acute methylphenidate, increased cocaine addiction<sup>22</sup> and refractory cocaine-induced reward.<sup>23</sup> In addition, there is evidence of reduced hippocampal neurogenesis, an anxiety- or depression-like phenotype and impaired spatial memory,<sup>24,25</sup> perhaps due to a persistent impairment in prefrontal cortical activity.<sup>26</sup> However, in these studies drugs were administered by injection, which is believed to be more highly addictive than oral or slow-release formulations used in clinic,<sup>20</sup> although one study suggests that both routes may be equivalent.<sup>27</sup> Further studies using clinically relevant routes of administration and animal models of ADHD need to be conducted to clarify the long-term effects of these drugs.

## Human studies

In contrast to animal models, there is a paucity of studies of the developmental effects of pharmacological intervention with these compounds in human childhood or early adolescence. Most studies are only 3–6 months in duration and have not addressed long-term changes in behaviour or addiction that persist to adulthood. To date, long-term studies of psychostimulant treatment for ADHD in late adolescence have found protective effects against later psychopathology<sup>28</sup> and indicate that psychostimulant treatment may even reduce substance abuse.<sup>29–31</sup> However, these studies were limited by relatively small samples and the early period of adulthood used as the end point. In one study, 173 patients with ADHD were followed until the age of 25 years;<sup>31</sup> the other study followed

112 patients with ADHD until the age of 22 years.<sup>29</sup> Epidemiological studies following large numbers of patients with ADHD over an extended period of time need to be conducted to more extensively address the long-term effects of stimulants. For second-generation antipsychotics, little is known about long-term effects on behaviour. A major concern is the problem of drug-induced weight gain that has been well documented in adults and adolescents,<sup>32,33</sup> although aripiprazole appears less problematic than other drugs in its class. Early and long-term treatment with second-generation antipsychotics is likely to exacerbate a problem that has severe long-term consequences, including heart disease and diabetes.<sup>34</sup>

With regard to long-term effects of psychostimulants, a recent epidemiological study indicates that long-term treatment with stimulants leads to increased heart rate and is associated with a 2-fold increase in ventricular arrhythmia or sudden cardiac death, equivalent to an incidence rate of 1 case per 1000 patient-years.<sup>35</sup> This remains controversial, as another study did not find an increase in serious cardiovascular events in children taking stimulants and found a very low frequency of these events.<sup>36</sup> It is also of note that these drugs can be used as cognitive enhancers in individuals who are not affected by ADHD. In young adults, illicit use of methylphenidate or amphetamine is linked to the reputed cognitive enhancing ability at a low dose.<sup>37</sup> However, the potential for abuse and disabling adverse events can lead to persistent problems, such as addiction and depression, particularly with nonmedical and nonoral administration of these compounds.<sup>38,39</sup> Interestingly, the proportion of college students who abuse psychostimulants is similar to those using them for treatment of ADHD. In contrast to youth illicitly using methylphenidate or amphetamine, for youth who are prescribed these compounds for management of ADHD, available evidence indicates that there is no increased susceptibility for later substance abuse. The mechanistic basis for the difference between response to treatment with versus addiction to stimulants is unclear, but may relate to different routes of administration during treatment with versus abuse of psychostimulants.<sup>40</sup>

## Conclusion

There are a number of issues that need to be considered regarding the use of drugs in children. Psychostimulants have been used for many years and are often very beneficial to children with ADHD. However, like cocaine, methylphenidate and amphetamine are listed as class 2 controlled substances in the United States because of their addictive properties. Stimulants and drugs of abuse act by the same mechanisms, and treatment with stimulants in early life can induce long-term behavioural changes in animal models. Although there is no evidence of stimulant-induced substance abuse in the short term in patients with ADHD, the long-term effects of medically prescribed stimulants need to be addressed in a large population over a longer time. For antipsychotics, their use depends on the accurate diagnosis of bipolar disorder or schizophrenia, which is not always possible in young children. Second-generation antipsychotics lead to rapid weight gain in children as well as hyperprolactinemia, which could

have lifelong risks for metabolic syndrome and infertility.<sup>33</sup> The increased use of drugs approved in adults for the treatment of children represents a huge naturalistic trial that is currently being undertaken. It remains unclear whether anyone is monitoring the results that will unfold 10–20 years after initiation of treatment. The question becomes how much and how long before we know whether the beneficial effects outweigh potentially serious (e.g., sudden cardiac death) or lifelong adverse events. A systematic method to track adverse events in children receiving these drugs over the long term needs to be put in place. Given the limited extent of current long-term studies, it would be wise to at least follow medically treated patients over the course of adult development.

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