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Can antipsychotic medication administered for paediatric emotional and behavioural disorders lead to brain atrophy?

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In recent years, there has been considerable debate in adult psychiatry as to whether antipsychotic medication can cause cerebral atrophy, based on the findings of animal and human studies. However, the possibility that antipsychotics might have long-lasting effects on the structure and function of the developing brain has been less widely discussed in child psychiatry, despite the rising prescription rates of antipsychotics among Australian children and adolescents. A recent survey of Australian paediatricians found that psychotropics were the most commonly prescribed class of medication in paediatric practice. Although stimulants were the most prescribed psychotropic medication, antipsychotics were prescribed to 5.6% of children with developmental-behavioural and mental health diagnoses (Efron et al., 2017).

It is well recognised that children are more sensitive than adults to the side effects of second-generation antipsychotics (SGAs), such as obesity, diabetes and sedation. However, there are no published studies on the possible effects of antipsychotic exposure on the brain volumes of children and adolescents treated for non-psychotic disorders. At present, our only guides are studies of adult patients with psychotic disorders, and animal studies that indicate cerebral atrophy can occur in the brains of normal juvenile animals exposed to antipsychotics (Vernon et al., 2011).

Evidence from animal studies indicates that antipsychotic induced cerebral atrophy might occur in adult and juvenile animals in the absence of any neurological disease process like schizophrenia. For example, macaque monkeys demonstrated significant total brain weight loss of approximately 10% after 17–27 months of exposure to haloperidol or olanzapine, compared to macaque monkeys receiving sham medication (Dorph-Peterson et al., 2005). All major brain regions were affected, but the most significant changes were noted in the frontal and parietal lobes.

A juvenile rat study replicated these findings with significant decreases in whole brain volume loss of between 6–8% following just 8 weeks of exposure to either haloperidol or olanzapine, compared to sham medication (Vernon et al., 2011). Most of the volume loss was identified in the frontal cerebral cortex. Of note, the effect was of similar magnitude for both the first-generation antipsychotic, haloperidol and the SGA, olanzapine.

It is well known that patients with schizophrenia experience progressive brain volume loss. These findings reinforced the hypothesis that schizophrenia is potentially a neurodegenerative illness. However, based on animal studies, it has also been postulated that some of the progressive brain volume loss seen in schizophrenia might be a direct effect of antipsychotic medication.

In a landmark study, Ho et al. (2011) specifically investigated the potential for antipsychotic associated brain volume loss. This cohort study followed up 211 patients with first episode schizophrenia using sequential high-resolution magnetic resonance imaging (MRI) scanning (average of three scans) over an average of 7.2 years. The study found that greater intensity of antipsychotic treatment (doses and treatment length) was associated with a small but significant loss of total brain volume. This effect remained, even after controlling for illness duration, illness severity and substance abuse. In fact, illness severity had only a modest correlation with total brain volume loss. The authors commented that these

> *findings may lead to heightened concerns regarding potential brain volume changes associated with the sharp rise in atypical antipsychotic use in non-schizophrenia psychiatric disorders. Even though no studies have assessed the long-term effects of antipsychotics on brain volumes in nonschizophrenia patients, our results suggest that antipsychotics should still be used with caution in these*

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patient groups after careful risk-benefit assessment. (p. 135)

Nevertheless, SGAs are being prescribed for large numbers of children and adolescents with non-schizophrenic disorders, despite limited study of their safety and efficacy. The practice began over a decade ago in the United States, and according to industry data from Intercontinental Marketing Services (IMS) Health, antipsychotics were being widely prescribed for US children and adolescents by 2006 (42,459 children aged 1–6 years; 220,305 aged 7–12 years and 305,165 aged 13–18 years: Olfson et al., 2015). Rates for the youngest cohort were roughly 15% higher in 2008 before falling by around 25% by 2010, following new pre-authority prescribing laws. Adolescent rates continued to climb.

The leading diagnostic groups, for which SGAs were prescribed in the United States, were boys with autistic spectrum disorder or disruptive behaviour disorders including attention-deficit hyperactivity disorder, oppositional defiant disorder and conduct disorder. SGA prescription rates had also risen for 'paediatric bipolar disorder', a controversial diagnosis, distinct from classical bipolar disorder, and diagnosed on the basis of affective lability or irritability. In the IMS Health data, 8% of scripts for 1–6 year olds were for bipolar disorder, as were 13% of scripts for children aged 7–12% and 20% of scripts for adolescents aged 13–18 (Olfson et al., 2015). Prescriptions for paediatric bipolar disorder included multiple psychotropics over many years, sometimes with more than one SGA concurrently.

While there was a rise in SGA prescription rates for non-psychotic child and adolescent mental health diagnoses in the United States, Olfson and colleagues noted that *most young people treated with antipsychotics did not have any diagnosis recorded in their health care claims data* (p. 872). SGAs were often used as a stand-alone treatment behavioural problem with less than a quarter of the children and adolescents prescribed SGAs receiving any form of psychosocial therapy.

With recent evidence that antipsychotics are now being more widely prescribed for Australian children and adolescents (Efron et al., 2017), there is an urgent need for human studies on the possible effects of SGAs on the structure and function of the developing brain, including whether SGAs might be neurotoxic, leading to cerebral atrophy, as found in studies of juvenile animals. Pending this research, psychiatrists and paediatricians should be even more cautious about prescribing SGAs for non-psychotic disorders (Ho et al., 2011). If SGAs are being considered as part of a comprehensive treatment plan for a severe developmental-behavioural or mental health disorder, doctors need to inform parents and young people about the recognised side effect profile, including the risk of substantial weight gain. In addition, the recent findings on brain volume loss following antipsychotic administration in the juvenile animal studies indicate that doctors should also discuss with parents and young people whether there might be any potential risks for the developing brain.

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