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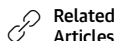
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Antipsychotics, Excess Deaths, and Paradoxes of Child Psychiatry

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Diagnostic Paradox

Before commenting on the Ray et al article¹ that reports an increased risk of unexpected deaths in patients 6 to 24 years old who received antipsychotics, it might be useful to consider the findings vis-à-vis diagnostic and treatment paradoxes of child psychiatry. Intuitively, many consider child psychiatry as a subspecialty that deals with little patients and little problems, but the reality is that psychiatrically ill children are not adult "lite." Rather, they have the same disorders as adults, including those that have pediatric US Food and Drug Administration indications for antipsychotic use (eg, schizophrenia, bipolar disorder). Notably, 50% of psychiatry disorders begin by age 14 years,² and childhood age at onset is a risk factor for a more severe longitudinal course in mood and other disorders. Suicide occurs across the child and adolescent spectrum, including in children 5 to 11 years old, who use similar methods to their adult counterparts (eg, hanging, firearms).³ Although the gravity of childhood-onset psychosis is similar to adult diagnoses, some manifestations, such as delusional content, vary developmentally (eg, children believe that school personnel rather than the Federal Bureau of Investigation are plotting to kill them). Given that serious psychopathology occurs in childhood, it is not surprising that major psychotropics are a therapeutic option.

Treatment Paradox

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Instinctively, it might seem that children and adolescents who are physically healthy would sustain fewer and less serious adversities from antipsychotic medications than their adult counterparts. However, the opposite is true for certain metabolic and endocrine effects, such as relatively greater weight gain and prolactin level elevation than adults and the onset of type 2 diabetes within the first year of treatment.⁴ While obesity is associated with long-term cardiovascular and neurological diseases, recent preclinical data support acute brain changes in mice with obesity, including decreased cognition associated with phagocytosis of synapses in the hippocampus.⁵ Possible short-term effects of obesity raise the question of whether the effect will be greater during child and adolescent brain maturation, if similar changes occur in humans. Another question is whether elevated prolactin levels during pubertal development might influence later development of breast cancer, a proposed long-term outcome of antipsychotic use. Increases in lipids and decrements in glucose metabolism are important considerations during the childhood years, because many of the disorders for which antipsychotics are prescribed, such as schizophrenia, are lifelong and thus may require decades of antipsychotic exposure. Notably, antipsychotics, such as aripiprazole, that cause less weight gain and do not elevate prolactin levels are associated with gambling and impulse-control disorders,⁶ which could result in more severe symptoms in children and adolescents because of their developmentally immature prefrontal cortices.

Excess Deaths With Antipsychotics

Against this background of serious adversity with antipsychotic use in childhood, the study by Ray et al¹ adds that the risk of death associated with antipsychotic use in patients 6 to 24 years old who are receiving chlorpromazine equivalents doses of more than 50 mg was 3.5 times higher than in patients who were not receiving antipsychotics. This study is a childhood version of their methodologically rigorous study of deaths in adults who received antipsychotics based on death certificates and Tennessee Medicaid data, with a few methodological differences. In the adult study, the rationale for excluding deaths in those diagnosed with schizophrenia was to avoid confounding by indication. By contrast, in the childhood research, the reason for excluding schizophrenia and Tourette syndrome was that antipsychotics are the only medication option for these diagnoses, and other disorders with FDA pediatric indications for antipsychotics have alternative treatment possibilities. However, there are child and adolescent patients with bipolar disorders in whom nonantipsychotic choices are ineffective or clinically inadvisable. For example, some patients with mood disorders are unresponsive to lithium for possible genetic and epigenetic reasons,⁷ and female patients may not want to risk developing polycystic ovarian syndrome from valproate medications. Nevertheless, given the inclusion and exclusion criteria in the Ray et al study,¹ the authors considered the research to be focused on off-label prescriptions. Another viewpoint on excluding schizophrenia and Tourette syndrome is that studying these diagnoses is most important just because of limited nonantipsychotic medication options.

Patients in Ray et al¹ were similar to those in other studies of antipsychotic use in children and adolescents⁸ with respect to the circumstance that most prescriptions were for off-label use. Specifically, among patients receiving higher antipsychotic doses, relatively few had diagnoses for which there is an FDA-approved indication (21.9% had bipolar disorder and 6.2% had



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common in patients receiving high-dose antipsychotics (45.1% received medications for attention-deficit/hyperactivity disorder and 42.2% were taking antidepressants).

One question about the Ray et al¹ findings is whether some deaths were undetected suicides, because individuals receiving high doses of antipsychotics had high rates of mood disorders (71.2%) and a category called attention-deficit/hyperactivity disorder/conduct disorders/impulsivity (64.1%), which are risk factors for childhood suicide in psychological autopsies.⁹ Notably, suicidality rates in those receiving higher antipsychotic doses in Ray et al¹ (8% suicidal ideation and 3.8% self-harm) were lower than those reported in eighth-grade and 12th-grade students (19.6% ideation and 8.2% attempts),¹⁰ who would be expected to have less suicidality than a population with serious psychiatric disorders.

Regardless of the relatively low level of suicidality, could some of the excessive deaths be from undetected suicides by overdoses with one of the coprescribed drugs or with designer illicit drugs that are not routinely assayed? The hazard ratio was 4.29 (95% CI, 1.33-13.89) for cardiovascular deaths in the high antipsychotic group compared with the nonantipsychotic group. This increased risk for cardiovascular deaths could plausibly be associated with overdose deaths from prescribed antidepressants or illicit drugs.

Future Considerations

To optimize detection of suicide, future investigations should include both physical and psychological autopsies and assays for prescribed and illicit drugs. Research to confirm the excess deaths reported in Ray et al¹ should also include cases from across the diagnostic spectrum and have large enough sample sizes to discern specific types and doses of antipsychotics and distinct drug combinations that might increase the risk for excess deaths. Investigations will be more informative if they examine outcomes within child, adolescent, and young adult age subgroups, as opposed to combining all youth 6 to 24 years old.

Results in the study by Ray et al¹ heighten the already increased caution about prescribing antipsychotics to children and adolescents and emphasize the need to consider situational triggers of psychopathology to avoid medicating the environment. Concerns about excess deaths are likely to increase because the prevalence of some disorders for which antipsychotics are prescribed off-label (eg, attention-deficit/hyperactivity disorder) and the number of prescriptions for indicated and off-label use are rising.⁸

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