



Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Antipsychotic treatment: risk of unexpected death in children and young people

A large US retrospective cohort study suggests that the prescribing of high dose antipsychotics in children and young people who do not have schizophrenia or related psychosis is associated with an increased risk of unexpected death. There was an increased risk in deaths from cardiovascular and metabolic causes but not from suicide and injury compared with the control group. Despite some limitations with this study, it reinforces NICE recommendations for safe prescribing of antipsychotics in this age group.

Overview and current advice

Antipsychotics are associated with potentially life-threatening, cardiovascular (CV), metabolic and other adverse effects ([Ray et al, 2019](#)). Guidelines for mental health conditions other than psychosis and schizophrenia in children and young people do not generally recommend that antipsychotics are prescribed. (For example, see NICE guidelines on [ADHD](#), [antisocial behaviour and conduct disorders in children and young people](#), [social anxiety](#), and [learning disabilities](#)). Antipsychotics are [recommended as an option to treat mania or hypomania in children and young people with bipolar disorder](#).

The MHRA has issued several important safety warnings for this class of drugs. These include an [increased risk of venous thromboembolic events](#), [reducing prescribing of antipsychotics to older people with dementia](#) because they are associated with an increased risk of cerebrovascular adverse events and greater mortality in this population and a [reminder to monitor and manage weight, glucose, and lipid levels with atypical \(second-generation\) antipsychotics](#). NICE has also published various medicines evidence commentaries considering the safety of these drugs, including reports on [taking antipsychotics increases the risk of myocardial infarction \(MI\)](#) and [risk of hospitalisation for acute kidney injury and other adverse events](#) associated with their use in older people. Most of the safety data on antipsychotics relates to their use in adults and older people, whereas the risks of mortality in children and young adults who take antipsychotics is less well documented. The NICE key therapeutic topic (KTT) on [Psychotropic medicines in people with learning disabilities whose behaviour challenges](#) summarises the evidence base on psychotropic medicines in this specific group.

New evidence

A large US retrospective [cohort study](#) of 247,858 children and young people (aged 5 to 24 years) used Medicaid (US government health insurance) data to examine unexpected deaths in those who had begun treatment with oral antipsychotics or other medicines ([Ray et al, 2019](#)). Participants had a mental health condition (diagnosed in the previous 12 months) and 70.6% were recorded as having

behavioural symptoms, such as attention deficit hyperactivity disorder (ADHD). A small number of participants had learning disabilities (5.3 to 7.0% in each group). Children and young people with life-threatening physical illnesses, a diagnosis of schizophrenia or related psychoses, or a neurologic indication for an antipsychotic were excluded. Participants entered the cohort when their first prescription for an oral antipsychotic or control drug had been filled.

The cohort was split into a low-dose antipsychotic group (n=18,729; 32.3% female, mean age 11.7 years) who received initial doses of 50 mg or less chlorpromazine equivalents (most commonly risperidone 66.0%) and a high-dose antipsychotic group (n=30,120, 39.2% female, mean age 14.5 years) who received initial doses higher than 50 mg chlorpromazine equivalents (most commonly quetiapine 34.3%, aripiprazole 23.4% and olanzapine 16.6%).

The control group included 189,361 children and young people with the same exclusion criteria as the cohort (43.4% female, mean age 12.0 years) who had been newly prescribed medicines commonly used for the same indications as antipsychotics such as ADHD medications, antidepressants and mood stabilisers.

Deaths were [statistically significantly](#) higher in the high-dose antipsychotic group than in the control group (146.2, 95% [confidence interval](#) [CI] 107.3 to 199.4 per 100,000 person-years [40 deaths] compared with 54.5, 95% CI 42.9 to 69.2 per 100,000 person-years [67 deaths]; $p < 0.001$), 52.5% were unexpected deaths. There was no significant difference between deaths in the low-dose antipsychotic group (49.5, 95% CI 24.8 to 99.0 per 100,000 person-years [8 deaths]; $p = 0.80$) and the control group.

After adjusting for [confounding](#), children and young people in the high-dose antipsychotic group had a relative increase of 80% in the risk of death overall compared with the control group (adjusted [hazard ratio](#) [HR] 1.80, 95% CI 1.06 to 3.07). This was attributed to a 3.5-fold increased risk in unexpected deaths (adjusted HR 3.51, 95% CI 1.54 to 7.96), whereas no increase in death from injury or suicide was found with high-dose antipsychotics compared with the control group (adjusted HR 1.03, 95% CI 0.53 to 2.01). Further analysis identified that the high-dose antipsychotic group had an increased risk of unexpected deaths other than from intentional drug overdose (adjusted HR 3.50, 95% CI 1.35 to 9.11), including an increased risk of death from CV or metabolic causes (adjusted HR 4.29, 95% CI 1.33 to 13.89). There was also no significant increase in risk of death in the high-dose antipsychotic group from unintentional overdose.

The authors report that the study has some limitations such as potential bias due to confounding. For example, important participant factors, such as body mass index, family history and undiagnosed CV abnormalities were missing from study data. The number of deaths from CV or metabolic abnormalities was small although the authors report that, as an end-point, this is less likely to be subject to confounding factors. The number of participants was too small to assess the association of individual antipsychotics, dose and potential drug interactions. The study did not review the relative safety of higher doses of antipsychotic in the high-dose group or consider the impact of co-prescribing of drugs such as benzodiazepines, opioids and antidepressants that may be associated with an increased risk of death with antipsychotics.

Commentary

Commentary provided by NICE

The study by Ray et al suggests that children and young people who are newly prescribed high doses of antipsychotics for mental health conditions other than schizophrenia, have an increased risk of unexpected death, other than from suicide and injury. This included an increased risk of death from CV or metabolic causes.

This study was based on a US population, where prescribing practices may differ from the UK. Participants were all eligible for government health insurance and may not be representative of a more affluent population. Children and young people with severe somatic illness, schizophrenia or related psychoses, or Tourette syndrome or chronic tic disorder, major chronic diseases or other severe conditions were also excluded.

Despite the limitations of this study, and the points above about the generalisability of the result to children and young people in the UK, it reinforces NICE recommendations for safe prescribing of antipsychotics in this age group. Guidelines for mental health conditions other than psychosis and schizophrenia in children and young people, also do not generally recommend that antipsychotics are prescribed. (For example, see NICE guidelines on [ADHD](#), [antisocial behaviour and conduct disorders in children and young people](#), [social anxiety](#), and [learning disabilities](#)). In the guideline on [psychosis and schizophrenia in children and young people](#), NICE recommends specialist assessment before starting antipsychotics and regular monitoring throughout treatment, to ensure that they are used safely and effectively. Antipsychotics are [recommended as an option to treat mania or hypomania in children and young people with bipolar disorder](#) and this group were not excluded from this study.

A large proportion of people in this study had ADHD. In the guideline on [ADHD](#) NICE recommends that for children aged 5 years and over and young people with ADHD, methylphenidate is offered as the first line pharmacological treatment. Atypical antipsychotics in addition to stimulants should not be offered without advice from a tertiary ADHD service for people with ADHD and coexisting pervasive aggression, rages or irritability.

A small number of people with learning disabilities were included in the study and this is a group where it is particularly important to prevent inappropriate use of antipsychotics, in line with national recommendations. See the NICE key therapeutic topic (KTT) [Psychotropic medicines in people with learning disabilities whose behaviour challenges](#) for more detail.

Study sponsorship

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References

Ray WA, Stein M, Murray KT et al. (2019) [Association of antipsychotic treatment with risk of unexpected death among children and youths](#). JAMA Psychiatry 76: 162–171

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