Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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The risk of myocardial infarction with antipsychotics

A systematic review and meta-analysis of 9 observational studies found that taking antipsychotic medicines almost doubled the risk of having a myocardial infarction (MI). The risk was greatest within the first 30 days of exposure to an antipsychotic medicine. Despite its limitations, the review highlights the importance of continuing to follow current advice that these medicines should be used with caution in people with cardiovascular disease. The NICE guideline on psychosis and schizophrenia in adults, recommends that various cardiovascular assessments should be carried out before starting an antipsychotic medicine and that ongoing monitoring should continue during treatment. The guideline on dementia, produced jointly by NICE and the Social Care Institute for Excellence (SCIE), advises against using antipsychotic medicines for non-cognitive symptoms or challenging behaviour of dementia unless the person is severely distressed or there is an immediate risk of harm to them or others.

Overview and current advice

Antipsychotic medicines should be used with caution in people with cardiovascular (CV) disease. They have been associated with CV side effects such as tachycardia, arrhythmias, hypotension and QT-interval prolongation; and cases of sudden death have occurred. The NICE guideline on psychosis and schizophrenia in adults recommends that the likely benefits and possible side effects of each antipsychotic medicine should be discussed with the person. This includes discussing CV history, possible CV side effects and carrying out baseline investigations, such as weight, waist circumference, pulse, blood pressure, blood glucose, blood lipids and an electrocardiogram (ECG) if required. Side effects should be monitored and recorded, as should various parameters such as pulse, blood pressure, lipids, weight, waist circumference and blood glucose.

A previous NICE medicines evidence commentary reported on an observational study¹ that reinforced existing safety concerns about the use of antipsychotic medicines in adults aged 65 years and older (more than half of whom had dementia). It found that the risk of hospitalisation within 90 days for acute kidney injury, hypotension, acute urinary retention, pneumonia, acute myocardial infarction (MI) and ventricular arrhythmia was increased with new use of second-generation antipsychotic medicines, compared with no use. All-cause mortality was also increased with new use compared with no use¹. However, the evidence on whether antipsychotic medicines increase the risk of MI has been inconclusive.

The NICE Pathway on psychosis and schizophrenia brings together all related NICE guidance and associated products on these conditions in a set of interactive topic-based diagrams. The Clinical
Knowledge Summaries information on psychosis and schizophrenia gives a general overview of prescribing considerations.

New evidence
A systematic review and meta-analysis of 9 observational studies was carried out to estimate the risk of MI in adults from use of antipsychotic medicines. It included 3 case-control studies, 2 cohort studies, 2 case-crossover studies, 1 study that used a self-controlled case-series and cohort study design, and 1 study that used a self-controlled case-series and case-control study design. Data were taken from medical records for 2 studies and from databases for the other 7. People with schizophrenia, mood disorder or dementia were included in 4 studies, people only with dementia in 1 study and those with any diagnosis in the other 4. The earliest study began in 1992 and the most recent ended in 2015. Only 2 of the studies were conducted in the UK.

Meta-analysis of all 9 studies found that antipsychotic medicines were associated with a statistically significant increase in the risk of MI (odds ratio [OR] 1.88, 95% CI 1.39 to 2.54, \( p<0.001 \)); but there were differences between the included studies. However, the authors conducted a sensitivity analysis and did not find an important change in this pooled risk estimate when individual studies were excluded, or when certain results were included.

When several subgroup analyses were carried out, an increase in the risk of MI, which was statistically significant, was found with typical antipsychotic medicines (OR 2.19, 95% CI 1.46 to 3.28; 7 studies). The authors reported that the increase in the risk of MI was also statistically significant with atypical antipsychotic medicines (OR 1.72, 95% CI 0.96 to 3.07; 5 studies), but no \( p \) value was given to confirm this. In 2 studies, the increase in risk of MI appeared to be dose-dependent, but this was not the case in another study. Few studies reported on the effects of individual medicines, but 1 study reported a 5 to 6 fold increase in the risk of MI with amisulpride, although the confidence intervals were wide (OR 5.65, 95% CI 2.97 to 10.76). The association between antipsychotic medicine use and the risk of MI appeared to weaken over time. The OR at 30 days was 2.64 (95% CI 2.48 to 2.81; 3 studies), whereas after 60 days it was 1.59 (95% CI 1.17 to 2.18; 2 studies) and after 90 days it was 1.35 (95% CI 1.09 to 1.67; 3 studies).

The strongest association between antipsychotic medicine use and risk of MI was seen in people who had a diagnosis of schizophrenia (OR 2.48, 95% CI 1.66 to 3.69; 3 studies) and dementia (OR 1.82, 95% CI 1.16 to 2.84; 3 studies). No association was seen in people with mood disorders (OR 1.66, 95% CI 0.86 to 3.22; 2 studies). Although the authors did not identify any statistical evidence of publication bias, they highlighted that asymmetry of the funnel plot suggested that there was the potential for some publication bias. Of the different study types, when grouped by study design, the 3 cohort studies did not show an increase in the risk of MI with antipsychotic medicine use that was statistically significant.

Commentary
Commentary provided by NICE
This systematic review and meta-analysis suggests that taking antipsychotic medicines almost doubles the risk of having an MI, although the authors describe the increased risk as being ‘modest’. The authors discussed several possible explanations for this, but the mechanisms are largely speculative. The risk appears to be greatest within the first 30 days of taking the medicine and in people who have a diagnosis of schizophrenia. The study has strengths in that it included a large number of people who were taking antipsychotic medicines in a real-life setting. However, it also has several limitations, which should be taken into account when interpreting these results. In particular randomised controlled trials (RCTs) looking at the risk of MI when taking antipsychotic medicines are
lacking\(^2\) and so it only included observational studies, which are subject to many confounding factors. For example, the authors were unable to look at other medicines that study participants were taking (some of which may affect CV risk, such as antidepressants) and they were unable to evaluate the risks of individual antipsychotic medicines (some of which may impact on a person’s CV risk differently). In addition, it is not clear from the paper whether the authors made any adjustments for participants’ baseline CV risk.

Another limitation of this systematic review is that there were several differences between the included studies. For example, the definition of antipsychotic exposure was different in the studies. Also, the authors found evidence of heterogeneity for the association between antipsychotic medicine use and MI risk. It should also be noted that only 2 of the 9 studies were carried out in people from the UK and so it is not known if the results will translate to UK clinical practice. In addition, the included studies were in adults and, therefore, the effect of antipsychotic medicines on younger people is unclear.

Despite the limitations of this study, it highlights the importance of continuing to follow current advice that antipsychotic medicines should be used with caution in people with CV disease. The NICE guideline on psychosis and schizophrenia in adults, recommends that various cardiovascular assessments should be carried out before starting an antipsychotic medicine and that ongoing monitoring should continue during treatment. For people who have dementia, the NICE/SCIE guideline on dementia advises against using antipsychotic medicines for non-cognitive symptoms or challenging behaviour of dementia unless the person is severely distressed or there is an immediate risk of harm to them or others. See the NICE key therapeutic topic on low-dose antipsychotics in people with dementia for further details.

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References


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