Second-generation antipsychotics in older people: risk of hospitalisation for acute kidney injury and other adverse events

An observational study reinforces existing safety concerns about the use of antipsychotics in adults aged 65 years and older. It found that the risk of hospitalisation within 90 days for acute kidney injury, hypotension, acute urinary retention, pneumonia, acute myocardial infarction and ventricular arrhythmia was increased in new-users of second-generation antipsychotics, compared with non-users. All-cause mortality was also increased in new-users compared with non-users. More than half of the patients had dementia and prescribers should continue to follow existing advice on the use of antipsychotics in people with behavioural and psychological symptoms of dementia.

Overview and current advice

The harms and limited benefits of using first- and second-generation antipsychotics for treating dementia in people who exhibit challenging behaviours are well recognised. In a Drug Safety Update, the MHRA advised that no antipsychotic (with the exception of risperidone in some circumstances) is licensed in the UK for treating behavioural and psychological symptoms of dementia and offered advice to prescribers on using antipsychotics in people with these symptoms.

The NICE/SCIE guideline Dementia: supporting people with dementia and their carers in health and social care (NICE Clinical guideline 42) gives recommendations on the care of people with all types of dementia, including managing behavioural and psychological symptoms of dementia. The guideline advises against the use of any antipsychotics 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. Any use of antipsychotics should include a full discussion with the person and carers about the possible benefits and risks of treatment.

A NICE Pathway on dementia brings together all related NICE guidance and associated products on dementia in a set of interactive topic-based diagrams. Non-cognitive symptoms and behaviour that challenges are included in the NICE Quality standard on dementia. In addition, a NICE Key therapeutic topic summarises the evidence-base on low-dose antipsychotics in people with dementia and highlights various resources. See the NICE Clinical knowledge summary on dementia for a general overview of the condition.
New evidence

Little information is available on the risk of acute kidney injury with second-generation antipsychotics. Therefore, a Canadian observational study investigated whether new use of oral second-generation antipsychotics in a non-hospital setting was associated with hospitalisation for acute kidney injury within 90 days (the primary outcome) in adults aged 65 years and older without end-stage renal disease. Various linked healthcare databases in Ontario were used to ascertain information including patient demographics and characteristics, prescription drug use and hospitalisations.

A total of 97,777 people with a new outpatient prescription for an oral second-generation antipsychotic between June 2003 and December 2011 were matched 1:1 with people with similar baseline characteristics who did not receive a second-generation antipsychotic. Their mean age was 80.7 years, 23.8% resided in a long-term care facility, and 53.8% had dementia. The most frequently prescribed second-generation antipsychotic was risperidone (45.7%: median dose 0.5 mg daily), followed by quetiapine (35.3%; median dose 25 mg daily) and olanzapine (19.0%; median dose 2.5 mg daily).

After 90 days' follow-up, second-generation antipsychotic use was associated with a statistically significantly higher risk of hospitalisation for acute kidney injury compared with no antipsychotic use (1.02% compared with 0.62% respectively; relative risk [RR] adjusted for geographical area 1.73, 95% confidence interval [CI] 1.55 to 1.92). Subgroup analyses found that the results were similar independent of antipsychotic dose or type, and the presence of chronic kidney disease.

Compared with non-use, second-generation antipsychotic use was also associated with a statistically significantly higher 90-day risk of all-cause mortality (6.8% compared with 3.1%; adjusted RR 2.39, 95% CI 2.28 to 2.50), and hospitalisation for hypotension (adjusted RR 1.91, 95% CI 1.60 to 2.28), acute urinary retention (RR 1.98, 95% CI 1.63 to 2.40), pneumonia (RR 1.50, 95% CI, 1.39 to 1.62), acute myocardial infarction (RR 1.36, 95% CI 1.20 to 1.53) and ventricular arrhythmia (RR 1.47, 95% CI 1.18 to 1.82). There was no statistically significant difference between the groups in the risk of neuroleptic malignant syndrome or rhabdomyolysis.

This study is an observational study and, therefore, it is prone to confounding and bias, and can only show that antipsychotic use is associated with hospital admissions for acute kidney injury, not that the drugs caused the acute kidney injury. Results of case-control studies should be expressed as odds ratios not relative risks. However, because the incidence of the outcomes was low in the study the use of relative risks is acceptable (see MeReC Briefing 30 for more information). The study included adults aged 65 years and older and is not applicable to younger people. Only risperidone, quetiapine and olanzapine were studied and the results may not be generalisable to other oral second-generation antipsychotics such as aripiprazole, ziprasidone and paliperidone.

Commentary

Commentary provided by the Medicines and Prescribing Centre

The study found that new use of an oral second-generation antipsychotic was associated with a higher 90-day risk of hospitalisation for acute kidney injury and other conditions that are known to cause or co-occur with acute kidney injury. However, it has limitations. Primarily, there may have been differences between users and non-users of antipsychotics: although cases and controls were matched for clinical conditions such as mental health problems, Parkinson’s disease and chronic kidney disease, no adjustment was made for other physical health conditions. For example, people with behavioural and psychological symptoms of dementia – which might well be the indication for starting an antipsychotic drug – may not drink enough and become dehydrated. Dehydration is a risk factor for acute kidney injury. Similarly, although many drugs commonly associated with acute kidney injury were assessed and well-balanced between the groups, others such as over-the-counter non-steroidal anti-inflammatory drugs were not considered. Nevertheless, the study reinforces existing safety concerns about the use of antipsychotics in adults aged 65 years and older.
The NICE guideline on acute kidney injury (NICE Clinical guideline 169) stresses the importance of risk assessment and prevention, early recognition and treatment. It recommends investigating for acute kidney injury in adults with acute illness in the presence of certain other risk factors, including age 65 years and over, and includes recommendations around the use of nephrotoxic drugs (although not specifically antipsychotics).

The condition the antipsychotics were prescribed to treat is not reported. Around 54% of people in the study were recorded as having dementia, 8% had schizophrenia or another psychotic disorder, and 6% had bipolar disorder. However, the low doses used and the age of the participants (mean 81 years) suggest that most people in the study were probably prescribed antipsychotics for behavioural and psychological symptoms of dementia.

The authors of the study state that current available evidence calls for a careful re-evaluation of prescribing second-generation antipsychotics in older adults, especially for the unapproved indication of managing behavioural symptoms of dementia. They advise that drugs should be used only after other approaches have been exhausted and, when prescribed, patients must be warned about potential adverse effects. Their renal function should also be monitored and, if deterioration occurs, second-generation antipsychotics should be considered a potential cause and consideration be given to prompt discontinuation.

The results of the study support recommendations in the NICE/SCIE guideline on dementia, MHRA advice on prescribing antipsychotics for behavioural and psychological symptoms of dementia, and the NICE Key therapeutic topic on low-dose antipsychotics in people with dementia. This advises that prescribing of low-dose antipsychotics in people with dementia should be reviewed and, if appropriate, revised, in accordance with the NICE/SCIE guideline and the NICE quality standard on dementia, and the Alzheimer’s Society best practice guide.

NICE guidelines on psychosis and schizophrenia (NICE Clinical guideline 178) and bipolar disorder (NICE Clinical guideline 38) make recommendations around monitoring service-users’ physical health and treatment with antipsychotics.

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References

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