Schizophrenia: long-acting injectable antipsychotics no better than oral antipsychotics for relapse prevention in adults

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A systematic review and meta-analysis found long-acting injectable antipsychotics were no more effective than oral antipsychotics for relapse prevention in adults with schizophrenia. This is consistent with NICE guidance which recommends the use of oral antipsychotics in all phases of schizophrenia treatment in adults. Depot or long-acting injectable antipsychotics can be considered to promote recovery if patients would prefer these after an acute episode, or if avoiding non-adherence to treatment is a clinical priority.

Overview and current advice:

The NICE clinical guideline on the management of schizophrenia in adults (currently being partially updated) recommends that people with newly diagnosed schizophrenia should be offered oral antipsychotic medication. For people with an acute exacerbation or recurrence of schizophrenia, oral antipsychotics are also recommended. The guideline advises that depot or long-acting antipsychotics may be given after an acute episode of schizophrenia in people who would prefer such treatment, or where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority within the treatment plan.

The choice of drug should be made by the service user and healthcare professional together. The relative potential of individual antipsychotic drugs to cause extrapyramidal side effects (including akathisia), metabolic side effects (including weight gain) and other side effects (including unpleasant subjective experiences) should be taken into account, together with the clinical response and side effects to any current or previous medication.

See the NICE Evidence topic page on schizophrenia for a general overview of the condition.
New evidence:

Kishimoto et al carried out a systematic review and meta-analysis comparing the efficacy of long-acting injectable antipsychotics with oral antipsychotics for relapse prevention in schizophrenia or related disorders. The review included 21 head-to-head randomised controlled trials (RCTs; n=5176, range per study 31–921) of relapse prevention or maintenance treatment lasting at least 24 weeks (range 24–130 weeks) in inpatients or outpatients. Ten of the included RCTs were of first-generation (typical) long-acting injectable antipsychotics, and 11 were of second-generation (atypical) long-acting antipsychotics. The primary outcome was study-defined relapse at the latest point of follow-up, based on the ‘safety and/or efficacy’ population (which included patients who took at least 1 dose of study drug and had at least 1 post-baseline assessment).

Across all 21 RCTs (n=4950), long-acting injectable antipsychotics were no more effective than oral antipsychotics for relapse prevention at the longest time point (relative risk [RR] 0.93, 95% confidence interval [CI] 0.80 to 1.08, p=0.35). There was also no difference between long-acting injectable antipsychotics and oral antipsychotics in all-cause discontinuation (21 RCTs, n=4882; RR 1.00, 95% CI 0.89 to 1.13, p=0.99), discontinuation due to adverse events (19 RCTs, n=4662; RR 1.10, 95% CI 0.74 to 1.64, p=0.65) or non-adherence (10 RCTs, n=2018, RR=0.77, 95% CI 0.49 to 1.22, p=0.22), although it was not clear how adherence was measured.

Long-acting injectable antipsychotics were no more effective than oral antipsychotics in any clinically relevant subpopulation or treatment group, including in outpatient studies lasting at least 1 year, or when the intention-to-treat population was used. Studies using first-generation long-acting injectable antipsychotics (10 RCTs, n=897, RR 0.82, 95% CI 0.69 to 0.97, p=0.02) and those published until 1991 (8 RCTs [consisting exclusively of all-fluphenazine studies], n=826, RR 0.79, 95% CI 0.65 to 0.96, p=0.02) showed a statistically significant improvement in relapse prevention with long-acting injectable antipsychotics over oral antipsychotics. However, the authors acknowledged that these findings could be due to a cohort effect. There was no difference between first-generation and second-generation injectable antipsychotics (p=0.14 for effect size), and head-to-head RCTs would be needed to investigate this finding further.

There were several limitations with this systematic review and meta-analysis; most notably, the quality and heterogeneity of the included studies. Not all of the studies had a double-blind design, and relapse definitions varied. In 9 of the included studies, relapse was not defined and hospitalisation rates or study-defined symptomatic worsening was used. The included studies also differed in patient populations, treatment settings (inpatient and outpatient), study duration and treatment allocation (half of the included studies used different medications in the long-acting injectable antipsychotic and oral antipsychotic arms), making interpretation of the results difficult.

Commentary provided by Medicines and Prescribing Centre

The findings of this systematic review and meta-analysis are consistent with those from recent RCTs (see MeReC Rapid Review No. 2735) that long-acting injectable antipsychotics are no more effective than oral antipsychotics for relapse prevention. This is in contrast to a previous meta-analysis of RCTs (which did not include these newer studies) and observational studies which suggested that long-acting injectable antipsychotics did have advantages in relapse prevention. One of the perceived advantages of long-acting injectable antipsychotics is improved adherence. However, this was only assessed directly in 2 of the RCTs included by Kishimoto et al, and crude measures of adherence showed no difference between long-acting injectable antipsychotics and oral antipsychotics. The authors suggest that larger and longer-term pragmatic trials, which better resemble clinical practice, are needed to further understand the real-world effectiveness of long-acting injectable antipsychotics.

Despite the limitations of this systematic review and meta-analysis, the findings of Kishimoto et al are consistent with the NICE clinical guideline on the management of schizophrenia in adults. This
recommends the use of oral antipsychotics in all phases of treatment, with depot or long-acting injectable antipsychotics being considered to promote recovery if patients would prefer these after an acute episode, or if avoiding non-adherence to treatment is a clinical priority.

Study sponsorship

National Institute of Mental Health Advanced Center for Services and Intervention Research: the Zucker Hillside Hospital.

References

3. About this Medicines Evidence Commentary

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