Antipsychotic treatment of schizophrenia and schizophrenia-like illnesses is associated with reduced psychotic symptoms, an increased time to recurrence of psychotic symptoms, and reduced rates of hospital admissions. However, people diagnosed with schizophrenia often do not fully adhere to oral medication regimens. In an effort to improve adherence, physicians often recommend long-acting intramuscular antipsychotic injections. Pharmaceutical manufacturers typically prepare long-acting intramuscular formulations of antipsychotics as esters, suspended in oil. These formulations are absorbed and eliminated by the body at a slower rate than oral preparations. When it produced the long-acting formulation of risperidone, the manufacturer did not esterify the drug. They instead produced an aqueous suspension of risperidone microspheres. As a result, long-acting injections of risperidone must be refrigerated, reconstituted with a diluent supplied by the manufacturer, and administered within 6 hours of reconstitution. In addition, clinicians need to administer the risperidone long-acting formulation bi-weekly to maintain a therapeutic concentration.

Paliperidone Paliperidone is the active metabolite of risperidone. Cytochrome P450 enzymes 2D6 and 3A4 metabolise risperidone to 9-hydroxyrisperidone, marketed orally as paliperidone. We previously reviewed its efficacy and safety for treatment of schizophrenia and related psychotic disorders. To make a long-acting injectable formulation of paliperidone, its hydroxyl group is esterified. Paliperidone palmitate is an aqueous suspension with low water solubility that is absorbed and eliminated slowly. It is supplied in pre-filled syringes of 39, 78, 117, 156 or 234 mg. Clinicians reconstitute it with vigorous shaking before administration. Paliperidone palmitate does not require refrigeration and can be administered monthly. After intramuscular administration, the drug slowly dissolves. After hydrolysis to paliperidone, it becomes available in the systemic circulation. The drug is measured in plasma as early as the first day of administration and lasts as long as 126 days, reaching maximum plasma concentration at 13 days. We have previously reviewed its efficacy and safety for treatment of schizophrenia.

Method

Search methods We searched the Cochrane Schizophrenia Group Specialised Register for randomised controlled trials (RCTs) comparing paliperidone palmitate with any other treatment for schizophrenia. We inspected references of identified studies.
for further trials and contacted the manufacturers of paliperidone palmitate, the US Food and Drug Administration and authors of relevant reports for additional material. We used RevMan version 5.1 software on Windows to conduct the analyses. All relevant RCTs were included.

Data collection and analysis
Data were analysed on an intention-to-treat basis. When appropriate, we calculated risk ratios (RR) and 95% confidence intervals with the number needed to benefit/harm statistic (NNB/NNH). We calculated weighted mean differences (WMD) for continuous data.

Results
We included five studies\(^9\)–\(^13\) with 2215 participants that compared paliperidone palmitate with placebo. Fewer people randomised to paliperidone palmitate left studies early (\(n = 2183\), 5 RCTs: RR = 0.76, 95% CI 0.70–0.84; NNB 9, 95% CI 7–14). People receiving any dose of paliperidone palmitate were less likely to show no improvement in global state (\(n = 1696\), 4 RCTs: RR = 0.79, 95% CI 0.74–0.85; NNB 7, 95% CI 5–9). In a single trial designed to study recurrence of psychosis, people randomised to paliperidone palmitate were less likely to experience a recurrence than those randomised to placebo (\(n = 312\): RR = 0.28, 95% CI 0.17–0.48; NNB 5, 95% CI 4–6). People who received paliperidone palmitate were also less likely to experience a recurrence of psychotic symptoms in studies that recorded recurrence as an adverse event (\(n = 1837\), 4 RCTs: RR = 0.55, 95% CI 0.44–0.68; NNB 10, 95% CI 8–14). Paliperidone palmitate was associated with less use of anxiolytics (\(n = 2170\), 5 RCTs: RR = 0.89, 95% CI 0.83–0.96; NNB 16, 95% CI 11–44) and with fewer reports of agitation or aggression (\(n = 2180\), 5 RCTs: RR = 0.65, 95% CI 0.46–0.91; NNB 39, 95% CI 25–150). Both men and women who received paliperidone palmitate experienced significant elevation in serum prolactin (ng/mL), but the data were too heterogeneous for us to analyse. We found no evidence of sexual dysfunction associated with paliperidone palmitate in these short-term trials, but people receiving paliperidone palmitate gained more weight than those who received placebo (\(n = 2052\), 5 RCTs: WMD 1.34, 95% CI 0.97–1.70).

Paliperidone palmitate v. depot risperidone
Two additional studies\(^14\)–\(^15\) compared paliperidone palmitate with depot risperidone (\(n = 1969\)). In these flexibly dosed trials, the mean doses of paliperidone palmitate were 73.3 mg and 104.6 mg every 4 weeks compared with depot risperidone at mean doses of 35.3 mg and 31.7 mg every 2 weeks. There was no difference for leaving these studies early for any reason between paliperidone palmitate and depot risperidone (\(n = 1969\), 2 RCTs: RR = 1.12, 95% CI 1.00–1.25). Those receiving paliperidone palmitate were no more likely to have a recurrence of psychotic symptoms (\(n = 1961\), 2 RCTs: RR = 1.23, 95% CI 0.98–1.53). There were a total of six deaths in these two trials, with five in the paliperidone palmitate groups. Although this difference was not significant (\(n = 1967\), 2 RCTs: RR = 3.62, 95% CI 0.60–21.89), the small number of these events and wide confidence interval makes it unclear whether this finding is meaningful. Patients randomised to paliperidone palmitate were significantly less likely to use anticholinergic medications (\(n = 1587\), 2 RCTs: RR = 0.67, 95% CI 0.55–0.82; NNB 13, 95% CI 10–24).

We found no data regarding service use, quality of life, patient satisfaction or cost. Similarly, we found no randomised studies that compared paliperidone palmitate with any other treatments for schizophrenia or schizophrenia-like illnesses.

Discussion
In short-term studies, paliperidone palmitate is an efficacious antipsychotic drug. Its adverse effects are similar to oral paliperidone, oral risperidone and depot risperidone. Extrapyramidal side-effects, weight gain and tachycardia are more common with paliperidone palmitate than placebo. Paliperidone palmitate is associated with substantial increases in serum prolactin. Used at mean doses of approximately 70–110 mg every 4 weeks, it appears comparable in efficacy and tolerability with depot risperidone used at mean doses of approximately 35 mg every 2 weeks.\(^8\) People who received paliperidone palmitate were significantly less likely to receive anticholinergic medications. Paliperidone palmitate has two practical advantages over depot risperidone in that it does not need to be refrigerated and can be administered monthly rather than bi-weekly, but we found no clear benefit of paliperidone palmitate over depot risperidone.

This study confirms our suspicion that paliperidone palmitate will affect people with schizophrenia similarly to depot risperidone. For individual clinicians to select paliperidone palmitate over other long-acting injectable antipsychotics on the basis of appropriate evidence, researchers will need to conduct longer-term pragmatic studies that more closely resemble the lived experience of patients with schizophrenia. Appropriate comparators include fluphenazine decanoate, haloperidol decanoate, depot olanzapine and depot risperidone. Clinicians would also benefit from studies that assess the efficacy, adverse effects and safety of long-term use of paliperidone palmitate, including behaviour, mortality, satisfaction with treatment and cost-effectiveness in comparison with oral antipsychotics.

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