OBJECTIVES
The atypical antipsychotic drugs are rapidly replacing the older typical therapies for the treatment of schizophrenia. The two most widely prescribed atypicals, olanzapine and risperidone, now account for $US4.9 billion in global health care sales per annum (2001) and hence analyses on their respective efficacies and safeties are important. This study was undertaken to examine the discrepancies of short term versus longer term efficacy and safety in trials where olanzapine is compared to risperidone in the treatment of schizophrenia.

METHODS
Efficacy
Several randomised controlled trials have compared these two drugs directly, but there is some inconsistency in the reported relative efficacy. The eight week study by Conley and Mahmoud (2001) suggested that risperidone is more effective than olanzapine. By contrast, the 28 week trial by Tran et al. (1997) suggested that olanzapine is more effective than risperidone. Two smaller, medium to long-term trials also showed significant improvements in a variety of efficacy rating scales for patients treated with olanzapine compared with those receiving risperidone (Purdon et al., 2000; Gureje et al., 2003). These trials ran for 52 and 30 weeks, respectively.

In order to explore why there was a difference in the findings of the four trials, we examined the mean change in PANSS (positive and negative syndrome) total score over time with olanzapine and with risperidone in the Tran et al. (1997) study. The original trial dataset was provided by the trial sponsor (El Lilly) and the mean change in PANSS total score was plotted for both study arms over the duration of the study.

RESULTS
Efficacy
Figure 1 shows the mean change in PANSS total score in the Tran et al. (1997) study, in which 10–20 mg/day olanzapine was compared with 4–12 mg/day risperidone over a 28-week period. The efficacy of both treatments is seen to be similar until week 20. After that, olanzapine treated patients required a significantly lower change in PANSS total score than those taking risperidone. These results suggest that olanzapine and risperidone have similar efficacy in the short term (up to about eight weeks), after which time olanzapine offers superior effectiveness to risperidone. This is an important finding, which may explain the different outcomes in the four comparative trials.

Figure 1 Olanzapine versus risperidone – mean change in PANSS total score (random-effects method) Tran et al. 1997 (HGBQ trial)

Safety
Table 1 shows that in the short term evaluation (6–8 weeks), there was no difference in the mean percentage of patients dropping out for any reason (mean p = 0.2). However, in the longer term (28–30 weeks), the total number of patient dropouts for any reason was significantly lower for those treated with olanzapine compared to those taking risperidone (mean p = 0.008). Although Gureje et al. (2003) was a longer term trial of 30 weeks duration, short term results of 6–8 weeks were not reported in this study.

Table 1 Olanzapine versus risperidone – patient dropout (for any reason)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Percentage (%) of patients dropping out of the trial (for any reason)</th>
<th>Short term (6–8 weeks)</th>
<th>Longer term (28–30 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conley</td>
<td>Olanzapine 22.8</td>
<td>Risperidone 28.2</td>
<td>p = 0.2 Not reported</td>
</tr>
<tr>
<td>Gureje</td>
<td>Olanzapine 4.8</td>
<td>Risperidone 63.6</td>
<td>p = 0.008 Not reported</td>
</tr>
<tr>
<td>Purdon</td>
<td>Olanzapine 4.8</td>
<td>Risperidone 42.4</td>
<td>p = 0.008 Not reported</td>
</tr>
<tr>
<td>Tran</td>
<td>Olanzapine 26.2</td>
<td>Risperidone 28.7</td>
<td>p = 0.008 Risperidone 52.7</td>
</tr>
<tr>
<td>Mean total</td>
<td>Olanzapine 23.3</td>
<td>Risperidone 27.1</td>
<td>p = 0.008 Risperidone 55.7</td>
</tr>
</tbody>
</table>

Figure 2 shows more patients taking risperidone required anticholinergic rescue medication after 6–8 weeks than those taking olanzapine (mean p = 0.02). Of the four trials, only the Tran et al. (1997), Purdon et al. (2000) and Gureje et al. (2003) trials had longer term extension phases of 28–30 weeks. Figure 3 shows that in both trials patients in the risperidone treatment group required significantly more anticholinergic rescue medication than those treated with olanzapine.

Figure 2 Percentage of patients requiring anticholinergic rescue medication in the short term (6–8 weeks)

Figure 3 Percentage of patients requiring anticholinergic rescue medication in the longer term (28–30 weeks)

CONCLUSIONS
Since schizophrenia is a chronic condition, understanding the longer-term differences between antipsychotic treatments is critical both to the selection of appropriate therapy and to the allocation of antipsychotic drug budgets. Whilst the results of these analyses suggest that olanzapine is more effective and safer than risperidone, over the longer term, it is proposed that additional longer-term trials are needed to confirm this.

There is no doubt that conducting long-term clinical trials in schizophrenia is complicated. Many patients with schizophrenia discontinue their antipsychotic medication for various reasons. Others are simply lost to follow up. In addition, it is unethical to continue patients on treatment over the long term if they are not responding to a sufficient level. All these factors contribute to the preference for shorter-term trials. However, a true indication of long-term effectiveness and safety cannot be evaluated in such trials.

In order to address the limitations of existing studies in this patient population, a number of naturalistic prospective studies, such as the Schizophrenia Outpatient Health Outcomes (SCHHO) and Schizophrenia Care Assessment Program (SCAP), funded by Eli Lilly, are currently underway.