Quetiapine for the treatment of behavioural and psychological symptoms of dementia (BPSD): a meta-analysis of randomised placebo-controlled trials

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Abstract

Aim This meta-analysis is aimed to determine the efficacy of quetiapine for the treatment of behavioural and psychological symptoms of dementia (BPSD).

Method Our electronic search included MEDLINE (1950-2009), Cochrane Central Register of Controlled Trials and PsychINFO. We also did a hand search of the International Psychogeriatric Association poster presentations and checked the National trial registry data bases from USA, UK, RSA, Holland, Australia and New Zealand. We included double-blinded randomised placebo-controlled trials studies that measured BPSD with the Neuropsychiatric Inventory (NPI). The Clinical Global Impression of Change scale (CGI-C) was our secondary outcome.

Results Six sets of data were included in this meta-analysis. Patients receiving quetiapine improved when compared to placebo with a weighted mean difference of -3.05 (95% CI: -6.10, -0.01) and -0.31 (95% CI: -0.54, -0.08) respectively on the NPI score and CGI-C score.

Conclusion This meta-analysis found that quetiapine is statistically more efficacious than placebo in the treatment of BPSD as measured by the NPI and CGI-C. However, improvement is of a small magnitude and observable clinical significance is questionable.

Dementia is a growing public health concern. The recently published Dementia Economic Impact Report by Alzheimers New Zealand estimated by 2050, 2.7% of the New Zealand population will have dementia or 146,699 people, and new cases will comprise 0.8% of the population (44,375 people) each year. In 2008, the total financial cost of dementia was estimated as $712.9 million and 27.449 years of healthy life were lost due to dementia across New Zealand. Similar findings were reported in Australia.

Behavioural and psychological symptoms of Dementia (BPSD) occur frequently (50-80%) in people with dementia at some point during their illness. These symptoms include anxiety, depression, irritability, delusions, hallucinations, insomnia, wandering, aggression and agitation. BPSD can result in premature institutionalisation, diminished quality of life for patients and caregivers, excess disability, caregiver stress and significant financial cost.

Non-pharmacological management should always be the first line treatment for BPSD and pharmacological treatment can be considered when non-pharmacological management fails or when there is a significant risk (for example, physical aggression; agitation; psychosis).
In New Zealand, risperidone is the only atypical antipsychotic listed on the Pharmaceutical Schedule for the treatment of BPSD including aggression, activity disturbance and psychotic symptoms. A number of non-randomised, non-placebo-controlled and non-blinded studies of quetiapine have shown some effectiveness for the treatment of BPSD.

Rainer et al have found quetiapine and risperidone were equally effective and generally well tolerated. Rocca et al reported that quetiapine, risperidone, and olanzapine produced similar significant improvements in behavioural disturbances. Quetiapine was also found to have a good efficacy in reducing behavioural symptoms, particularly delusions, agitation and aggression in three other open-label trials.

Ballard et al recently published an updated review on the management of agitation and aggression associated with Alzheimer’s disease. For the treatment of agitation/aggression the best evidence is for risperidone. There is also some evidence for aripiprazole but there is no clear evidence from published randomised controlled trials to indicate that other atypical antipsychotics are efficacious.

Despite the lack of evidence in published systematic reviews and meta-analyses, we have observed in our clinical practice that quetiapine is continued to be used off-label by psychiatrists, geriatricians and general practitioners for the treatment of BPSD, particular in residential care facilities.

The recently published clinical recommendations developed by the Royal Australian and New Zealand College of Psychiatrist Faculty of Psychiatry of Old Age (New Zealand) also listed quetiapine (up to 100mg) as one of the antipsychotics to treat psychotic symptoms in dementia. Bishara et al reported in an expert opinion paper where quetiapine was seen as the drug of choice for BPSD in the UK.

The perception that quetiapine is “safer” is most likely due to the report that risperidone was associated with a three-fold increased risk of serious cerebrovascular adverse events compared to placebo. There was a subsequent advisory note from the United States Food and Drug Administration warning of an increased mortality in patients with dementia who are treated with atypical antipsychotic medications.

Previous meta-analyses of double-blinded randomised placebo-controlled studies included a limited number of studies of quetiapine for the treatment of BPSD. For example, the Cochrane review by Ballard et al included only one study of quetiapine. Schneider et al included three studies of quetiapine in their meta-analysis of atypical antipsychotics for dementia. There was a lack of evidence for or against quetiapine because the three studies used different selection criteria and outcomes could not be statistically combined using a common rating scale.

We believe there have been new randomised placebo-controlled trials investigating the use of quetiapine for the treatment of BPSD and an updated meta-analysis is warranted to guide our clinical practice and to determine whether there is any evidence supporting the off-label use of quetiapine in dementia. The objective of this meta-analysis is to determine the efficacy of quetiapine for BPSD in elderly patients with dementia.
Method

Search strategies—Our search included MEDLINE (1950-2009), Cochrane Central Register of Controlled Trials and PsychINFO. Search terms were: quetiapine, behavioural and psychological symptoms of dementia, dementia and Alzheimer’s dementia. We did a hand search of the International Psychogeriatric Association poster presentations and checked the National trial registry data bases from USA, UK, RSA, Holland, Australia and New Zealand. The Medical Department of AstraZeneca New Zealand was also contacted for their database on clinical trials conducted for quetiapine in dementia.

Selection criteria—We only included double-blinded randomised controlled trials (RCTs) that used placebo as their control. As data was limited we included all trials of adequate design. We included studies that measured BPSD with the Neuropsychiatric Inventory (NPI) among patients with any stage and any subtypes of dementia living in any clinical setting. We decided to include different subtypes of dementia because medical practitioners working in primary care setting often do not have the specialist skill to diagnose subtypes of dementia. The Clinical Global Impression of Change scale (CGI-C) was our secondary outcome. We contacted the authors of three studies (Tariot et al, Kurlan et al and Paleacu et al) to obtain unpublished and/or missing data on NPI and CGI-C in order to complete this meta-analysis.

Neuropsychiatric Inventory (NPI)20—Neuropsychiatric Inventory is a tool for assessment of psychopathology in patients with dementia and other neuropsychiatric disorders. The NPI is based on a structured interview with a caregiver who is familiar with the patient. The following 10 neuropsychiatric domains are evaluated: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, aberrant motor activity, night-time behaviour disturbances. For each domain a screening question is asked to determine if the behavioural change is present or absent. If the answer is positive the domain is explored at greater depth with the sub-questions. If the sub-questions confirm the screening question, the severity and frequency of the behaviour are determined according to the criteria provided for each domain. Frequency is rated 1 to 4 and severity is scored 1 to 3. The product (severity x frequency) is calculated for each behavioural change present during the previous month or since the last evaluation (e.g. in order to evaluate treatment efficacy). A total NPI score can be calculated by adding the scores of the ten behavioural domain scores together.

Two versions of NPI are available: standard version and Nursing home version. The 10 behavioural domains and scoring system in the two versions are identical.

Clinical Global Impression of Change Scale (CGI-C)21—The CGI-C is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention. It is rated as: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; or 7=very much worse.

Data abstraction—The following data were obtained from each study: country, total number of randomised patients, baseline demographic data (age, gender), mean Mini-Mental Status Examination score (MMSE), diagnosis, setting, duration of study, quetiapine daily dose, concurrent use of cholerasterase inhibitors (CEIs), primary indication to enter the study, primary and other outcome measures, mean total NPI score, mean change from baseline of the total NPI score for both the quetiapine and placebo groups (and the level of significance for the mean difference in NPI between the two groups), mean CGI-C scores at the end of the study period for both the quetiapine and placebo groups (and the level of significance for the two groups).

Quantitative Data Analysis—We used Review Manager Software Version 5 (http://www.cc-imis.net/revman) to calculate the effect size and confidence interval (CI) of each individual study and the combined results. The average effect size across all studies is computed as a weight mean. We consulted a biostatistician from the Department of Population Health, University of Auckland, for the data analysis.

Results

Our search strategies yielded a total of six double-blinded RCT studies comparing quetiapine with placebo.22-27 One study (Ballard et al) was excluded because it did not have NPI or CGI-C as their outcome measures.
The study published by Zhong et al presented separate data for the two dosages of quetiapine (100mg daily and 200mg daily) used in the trial. An overall result for the two dosages was not published. We have therefore a total of six sets of data (from 5 studies) included in this meta-analysis (see Tables 1 and 2).

Table 1. Baseline variables of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Mean Age (Overall)</th>
<th>% Female (Overall)</th>
<th>Mean MMSE (Quetiapine Group)</th>
<th>Mean MMSE (Placebo Group)</th>
<th>Total NPI Score (Quetiapine Group)</th>
<th>Total NPI Score (Placebo Group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schnieder et al 2006</td>
<td>421</td>
<td>77.9</td>
<td>56</td>
<td>14.9</td>
<td>14.7</td>
<td>37.6</td>
<td>39.1</td>
</tr>
<tr>
<td>Tariot et al 2006</td>
<td>284</td>
<td>83.2</td>
<td>73</td>
<td>12.4</td>
<td>13.2</td>
<td>39.1</td>
<td>35.7</td>
</tr>
<tr>
<td>Kurlan et al 2007</td>
<td>40</td>
<td>73.8</td>
<td>37.5</td>
<td>19.2</td>
<td>17.2</td>
<td>25.1</td>
<td>25.9</td>
</tr>
<tr>
<td>Zhong et al 2007</td>
<td>333</td>
<td>83.2</td>
<td>74.2</td>
<td>100mg=4.8 200mg=5.6</td>
<td>5.5</td>
<td>38.5</td>
<td>35.7</td>
</tr>
<tr>
<td>Paleacu et al 2008</td>
<td>40</td>
<td>82.2</td>
<td>65</td>
<td>14.5</td>
<td>14.3</td>
<td>43.4</td>
<td>38.6</td>
</tr>
</tbody>
</table>

N=Total number of participants underwent randomisation; NR=Not reported

The included studies were conducted among of heterogenous group of participants with moderate to severe dementia (mean MMSE ranged from 5.5 to 17.2) from different settings (outpatient=1, residential=2, not reported =3). Three studies included only Alzheimer’s dementia, one study included both Alzheimer’s and vascular dementia and one study included dementia with Lewy bodies, Parkinson’s disease with dementia and Alzheimer’s dementia with parkinsonism.

The length of the studies ranged from 6 to 12 weeks. Various dosages of quetiapine were used in the five studies (daily dose of quetiapine ranged from 0 to 600mg). NPI was used as the primary outcome in one study (Paleacu et al). CGI-C was used as the primary outcome in two studies (Schnieder et al & Paleacu et al). The mean baseline NPI scores ranged from 25.1 to 43.4.

Participants who completed the entire duration of each study were included in the meta-analysis.

Figure 1 showed the effects of quetiapine on the total NPI among patients with moderate to severe dementia. Patients receiving quetiapine improved on the NPI score when compared to placebo with a weighted mean difference (WMD) of - 3.05 (95% CI: -6.10, -0.01).

Figure 2 showed the CGI-C scores in the quetiapine and placebo groups. Patients receiving quetiapine improved on the CGI-C score when compared to placebo with a weight mean difference (WMD) of -0.31 (95%CI: -0.54, -0.08).

There was no evidence of heterogeneity across the studies (NPI: p-value=0.78; CGI-C: p-value=0.37).
Table 2. Description of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Diagnosis</th>
<th>Setting</th>
<th>Duration</th>
<th>Quetiapine daily dose</th>
<th>Concurrent use of CEIs</th>
<th>Primary indication</th>
<th>Primary outcome</th>
<th>Other outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schnieder et al 2006</td>
<td>USA</td>
<td>AD</td>
<td>Outpatient</td>
<td>12 weeks</td>
<td>Mean=56.5mg Range=0-100mg</td>
<td>No</td>
<td>Psychosis, aggression or agitation</td>
<td>Time to discontinuation of treatment</td>
<td>CGI-C, NPI, BPRS</td>
</tr>
<tr>
<td>Tariot et al 2006</td>
<td>USA</td>
<td>AD</td>
<td>Residential</td>
<td>10 weeks</td>
<td>Medium=96.9mg Range=25-600mg</td>
<td>12.1% quetiapine group 10.1% Placebo group</td>
<td>BPRS, CGI-S</td>
<td>Psychosis</td>
<td>CGI-C, NPI-NH2</td>
</tr>
<tr>
<td>Kurlanl et al 2007</td>
<td>USA</td>
<td>DLB, PD with dementia, AD with Parkinsonism</td>
<td>NR</td>
<td>10 weeks</td>
<td>Mean=120mg Range=25-300mg</td>
<td>45% quetiapine group 70% Placebo group</td>
<td>BPRS</td>
<td>Psychosis or agitation</td>
<td>CGI-C, NPI, ADCS ADL</td>
</tr>
<tr>
<td>Zhong et al 2007</td>
<td>USA</td>
<td>AD, VD</td>
<td>Residential</td>
<td>10 weeks</td>
<td>Fixed dosing 100mg or 200mg</td>
<td>39% 100mg group 32% 200mg group 34% Placebo group</td>
<td>PANSS-EC</td>
<td>Agitation</td>
<td>CGI-C, CMAI, NPI-NH</td>
</tr>
<tr>
<td>Paleacu et al 2008</td>
<td>Israel</td>
<td>AD</td>
<td>NR</td>
<td>6 weeks</td>
<td>Medium=200mg Range=75-300mg</td>
<td>32% overall</td>
<td>A score &gt;6 on any NPI items</td>
<td>NPI, CGI-C</td>
<td></td>
</tr>
</tbody>
</table>

AD=Alzheimer’s disease; ADCS-ADL=Alzheimer’s Disease Cooperative Study Activity of Daily Living Questionnaire; BPRS=Brief Psychiatric Rating Scale; CEIs=Cholesterol inhibitors; CGI-C=Clinical Global Impression of Change; CGI-S=Clinical Global Impression-Severity of Illness; CMAI=Cohen-Mansfield Agitation Inventory; DLB=Dementia with Lewy Bodies; NPI=Neuropsychiatric Inventory; NPI-NH=Neuropsychiatric Inventory – Nursing Home version; NR=Not reported; PANSS-EC=Positive and Negative Syndrome Scale – Excitement Component; PD=Parkinson disease; SIB=Severe Impairment Battery; VD=Vascular dementia.
The study by Paleacu et al is a significant outlier in terms of the effectiveness (as measured by the NPI) in both of the placebo and quetiapine groups. This study had the highest baseline total NPI score for the quetiapine group (43.4) and the shortest trial period (6 weeks).

**Discussion**

This meta-analysis found that quetiapine is statistically more efficacious than placebo in the treatment of BPSD as measured by the NPI and CGI-C. However, the mean weight difference between the quetiapine and placebo groups was just over 3 points on the NPI. Previous authors have defined clinical response as a minimum change of 4 points (Mega et al) and 9 points (Kaufer et al) on the NPI. The improvement on CGI-C is also of a small magnitude (0.3 point).

Figure 3 showed the CGI-C scores in the quetiapine and placebo groups in the 5 studies. CGI-C is a 7-points scale with a one-point difference between each anchor.

**Figure 1. Neuropsychiatric Inventory (NPI)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Quetiapine Mean</th>
<th>SD</th>
<th>Total</th>
<th>Placebo Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurlan</td>
<td>-1.16</td>
<td>0.15</td>
<td>19</td>
<td>-1</td>
<td>0.15</td>
<td>19</td>
<td>0.00 [-1.12, 1.12]</td>
<td>6.5%</td>
</tr>
<tr>
<td>Paleacu</td>
<td>-2.58</td>
<td>0.21</td>
<td>16</td>
<td>-1.92</td>
<td>0.19</td>
<td>16</td>
<td>-0.66 [-2.76, 1.44]</td>
<td>5.7%</td>
</tr>
<tr>
<td>Schnieder</td>
<td>-1.66</td>
<td>0.19</td>
<td>31</td>
<td>-9</td>
<td>0.20</td>
<td>47</td>
<td>1.22 [-0.33, 2.77]</td>
<td>12.2%</td>
</tr>
<tr>
<td>Tariot</td>
<td>-1.24</td>
<td>0.19</td>
<td>86</td>
<td>-0.68</td>
<td>0.19</td>
<td>94</td>
<td>-0.56 [-1.20, 0.08]</td>
<td>29.2%</td>
</tr>
<tr>
<td>Zhong 100mg</td>
<td>-0.83</td>
<td>0.23</td>
<td>120</td>
<td>-0.8</td>
<td>0.23</td>
<td>92</td>
<td>-0.07 [-0.70, 0.55]</td>
<td>23.7%</td>
</tr>
<tr>
<td>Zhong 200mg</td>
<td>-0.7</td>
<td>0.23</td>
<td>114</td>
<td>-0.8</td>
<td>0.23</td>
<td>92</td>
<td>-0.15 [-0.78, 0.48]</td>
<td>22.8%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>389</td>
<td></td>
<td>362</td>
<td>100.0%</td>
<td></td>
<td>-3.05 [-6.10, 0.01]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2. Clinical Global Impression of Change Scale (CGI-C)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Quetiapine Mean</th>
<th>SD</th>
<th>Total</th>
<th>Placebo Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurlan</td>
<td>4.15</td>
<td>1.18</td>
<td>19</td>
<td>3.9</td>
<td>1.26</td>
<td>18</td>
<td>0.25 [-0.54, 1.04]</td>
<td>8.6%</td>
</tr>
<tr>
<td>Paleacu</td>
<td>2.89</td>
<td>1.2</td>
<td>19</td>
<td>3.32</td>
<td>1.25</td>
<td>19</td>
<td>-0.43 [-1.21, 0.35]</td>
<td>8.7%</td>
</tr>
<tr>
<td>Schnieder</td>
<td>2.7</td>
<td>1.1</td>
<td>31</td>
<td>3.3</td>
<td>1.5</td>
<td>48</td>
<td>-16.1% [-0.60, -0.03]</td>
<td>16.1%</td>
</tr>
<tr>
<td>Tariot</td>
<td>3.28</td>
<td>1.45</td>
<td>85</td>
<td>3.36</td>
<td>1.32</td>
<td>94</td>
<td>-31.9% [-0.08, -0.49]</td>
<td>31.9%</td>
</tr>
<tr>
<td>Zhong 100mg</td>
<td>3.2</td>
<td>2.19</td>
<td>120</td>
<td>3.6</td>
<td>1.91</td>
<td>92</td>
<td>-17.3% [-0.95, 0.15]</td>
<td>17.3%</td>
</tr>
<tr>
<td>Zhong 200mg</td>
<td>3.1</td>
<td>2.13</td>
<td>114</td>
<td>3.6</td>
<td>1.91</td>
<td>92</td>
<td>-17.4% [-0.60, -0.05]</td>
<td>17.4%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>388</td>
<td></td>
<td>363</td>
<td>100.0%</td>
<td></td>
<td>-0.31 [-0.54, -0.08]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
point. We believe it would be difficult to observe the 0.3 difference clinically. These results suggest that although there is a statistical evidence for quetiapine in the treatment of BPSD, observable clinical significance is questionable.

**Figure 3. CGI-C scores (at the end of the trials) in the quetiapine and placebo groups**

![Graph showing CGI-C scores](image)

CGI-C: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; or 7=very much worse.

This meta-analysis also suggested that placebo had a comparative clinical effect as quetiapine in the treatment of BPSD. This finding could be a result of the non-specific benefits obtained from the increased attention patients received during the trial. This in itself has an important clinical message that non-pharmacological management including increased attention should always be included in the overall management of BPSD.

In New Zealand, quetiapine and risperidone are the only two listed atypical antipsychotic medications which do not require special authority application from a specialist psychiatrist. Risperidone was the first atypical antipsychotic medication reported to have an increased mortality and morbidity with cerebrovascular events when it is prescribed for the treatment of BPSD.

There is a perception that other atypical antipsychotic medications are “safer”. However, we now have evidence to suggest that such risks are common to both typical and atypical antipsychotic medications. In a retrospective cohort study involving 22,890 patients 65 years of age or older, Wang et al have found typical antipsychotic medications were at least as likely as atypical agents to increase the risk of death.\(^{30}\)

Schneider et al reported a significant increase in mortality, but there was no difference between specific atypical agents in a meta-analysis of 16 studies of atypical antipsychotics for the treatment of BPSD.\(^{31}\) In addition, among the atypical
antipsychotic medications quetiapine was found to have the highest risk for overall mortality in a 11-year follow up cohort study of patients with schizophrenia in Finland.\textsuperscript{32}

Haloperidol has been compared to risperidone and quetiapine in the treatment of BPSD.\textsuperscript{24,33–35} Only one of the four trials found a significantly greater efficacy with the atypical than with the typical agent. However, in all four studies, haloperidol was associated with more extrapyramidal symptoms than the atypical agent. We believe that with the current knowledge of antipsychotic medications risperidone should be prescribed as the first-line treatment of BPSD in primary care setting and this is consistent with the guideline published by the Faculty of Old Age Psychiatry of the Royal Australian and New Zealand College of Psychiatrists.\textsuperscript{36}

The use of olanzapine and aripiprazole can also be considered. However, a risk-benefit analysis should be performed for each individual before an atypical antipsychotic medication is prescribed for the treatment of BPSD. Atypical antipsychotic medications should only be prescribed for people with dementia presenting with aggression, agitation or psychosis which is associated with severe distress or risk of physical harm to those living and/or working with the patient.

In addition to the treatment of cognitive deficits in dementia, cholesterase inhibitors (donepezil, galantamine, rivastigmine) have been used in the treatment of BPSD. Campbell et al recently published a meta-analysis to determine the efficacy of cholinesterase inhibitors in the treatment of BPSD in patients with mild to severe Alzheimer’s disease.\textsuperscript{37}

They found patients who were prescribed with cholesterase inhibitors improved by 1.38 point on the NPI as compared to the placebo group. Although the reduction in NPI was statistically significant, the authors concluded that the clinical relevance of this effect remains unclear.

Since 2010 donepezil has been fully subsidised by the prescription funding agency in New Zealand, Pharmac, for the treatment of Alzheimer’s disease. The use of cholesterase inhibitors can be considered as an alternative treatment for BPSD if there is significant risk involved in prescribing antipsychotic medications, for example, cerebrovascular events, falls and extrapyramidal side effects.

There is also some evidence for the use of citalopram in the treatment of BPSD.\textsuperscript{38–40} This medication is useful if there is a comorbid depression (which is not uncommon in dementia) and a rapid onset of action is not required. Other psychotropic medications can be considered for the treatment of BPSD includes memantine and carbamazepine.\textsuperscript{11}

Benzodiazepines are often prescribed by non-psychiatrists for the treatment of BPSD. Jeste et al identified two trials of benzodiazepines for BPSD in their literature search.\textsuperscript{41} Alprazolam was found to be as effective as low dose haloperidol in a randomised, double-blind crossover study.\textsuperscript{42}

Coccaro et al reported oxazepam, haloperidol and diphenhydramine appeared to have a similar efficacy for short-term management behaviour in severely demented patients.\textsuperscript{43} However, benzodiazepines should be cautiously used in older people.
because of their adverse side effects including sedation, drowsiness, confusion, falls and their long-term effects of tolerance and dependence.

Quetiapine has an advantage over other atypical antipsychotic medications (except clozapine) in terms of extrapyramidal side effects and has become a favourable choice for the treatment of psychosis in Parkinson’s disease and BPSD in Lewy Body Dementia and Parkinson’s disease with dementia. However, previous RCTs found quetiapine has no benefit in the treatment of psychosis in Parkinson’s disease.\textsuperscript{44-46}

The study by Kurlan et al (which was included in this meta-analysis) was specifically designed to determine the efficacy of quetiapine in the treatment of BPSD in Lewy Body Dementia, Parkinson’s disease with dementia and Alzheimer’s disease with parkinsonism. There is no evidence for quetiapine in the treatment of psychosis or agitation as measured by the Brief Psychiatric Rating Scale, CGI-C and NPI.

In contrast there have been two randomised placebo-controlled trials with clozapine in the treatment of psychosis in Parkinson’s disease and both studies showed significant improvements in psychopathology with no or minimal worsening in motor symptoms of Parkinson’s disease.\textsuperscript{47,48} The efficacy of rivastigmine on BPSD in Lewy Body Dementia has also been reported.\textsuperscript{49} McKeith et al found patients taking rivastigmine were significantly less apathetic and anxious, and had fewer delusions and hallucinations than controls.

In summary, the currently available literature does not support the use of quetiapine in the treatment of BPSD and more efficacious medication such as risperidone and medication with less risk such as cholesterase inhibitors, citalopram, memantine and carbamazepine are available.

Clozapine has the most evidence in the treatment of psychosis in Parkinson’s disease and rivastigmine can be considered for the treatment of BPSD in Lewy Body Dementia. With the exception of risperidone, general practitioners may not have the expertise prescribing the other medications mentioned here and guidance from the specialists will be required. In addition, clozapine can only be initiated by psychiatrists and there is a central registration programme for the monitoring of agranulocytosis. We like to highlight that the advice given in this article applies primarily in the New Zealand context, although the evidence is based on international research.

The main limitation of this study is that the individual domains of NPI were not analysed separately. Only the study by Tariot et al reported the data on the individual domains and they found no significant advantage with quetiapine in the NPI domain scores for agitation, hallucinations and delusions. All studies, except the one by Paleacu et al, included agitation and/or psychosis as their primary indications (Table 2).

It would be useful to obtain the original data from each of the study to perform further analysis on the NPI delusions, hallucinations and agitation/aggression domains. The failure to report the individual domains of NPI in the literature also raises issues of obscuring the effectiveness of some agents for specific targeting symptoms (e.g. agitation, aggression and psychosis) and masking the potential harms of some agents for other symptoms (such as apathy from antipsychotic medications).
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