Antipsychotic Discontinuation in Patients with Dementia: A Systematic Review and Meta-Analysis of Published Randomized Controlled Studies

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Key Words
Antipsychotics · Discontinuation · Dementia · Behavioral and psychological symptoms of dementia · Meta-analysis

Abstract
Background: There is a lack of clarity in the literature on the impact of antipsychotic discontinuation in dementia. Method: We conducted a systematic review and meta-analysis of published randomized controlled studies comparing the effects of antipsychotic discontinuation versus continuation in dementia. MEDLINE, EMBASE, PsycInfo, Cochrane Library and CINAHL were searched. Severity change of behavioral and psychological symptoms of dementia (BPSD) was the primary outcome. Results: Ten studies were included in the systematic review and 9 studies in the meta-analysis. The results showed that the antipsychotic discontinuation group had no statistically significant difference in BPSD severity change compared to the continuation group (n = 214, standardized mean difference: 0.19, 95% CI: –0.20 to 0.58). Secondary outcome analyses revealed that the discontinuation group included a statistically significantly higher proportion of subjects whose BPSD severity worsened (n = 366, risk ratio: 1.78, 95% CI: 1.31–2.41). Although not statistically significant, the discontinuation group appeared...
to have higher early study termination rates and a lower mortality during follow-up. **Conclusions:** This meta-analysis showed that antipsychotic discontinuation resulted in no statistically significant difference in BPSD severity change, early study terminations and mortality. However, a statistically significantly higher proportion of subjects with BPSD worsened in this group compared to the continuation group. Further studies are needed to explore the effects of antipsychotic discontinuation on BPSD.

**Introduction**

Dementia is a syndrome of progressive deterioration in memory, other cognitive abilities, and functional impairment. Besides amnesia and functional impairment, there may also be behavioral and psychological symptoms of dementia (BPSD) such as delusions, disturbed behaviors and agitation. The prevalence of such symptoms can reach 50% in subjects with dementia [1]. BPSD causes distress in individuals with dementia and their caregivers and constitutes a major burden to the family and society [2–4]. It is also a leading factor for hospitalization or institutionalization in patients with dementia [5].

Antipsychotic medication is often used to manage BPSD, with the recommendation that it should be used when nonpharmacological approaches are ineffective [6]. Rates of antipsychotic prescription are up to 30–60% in some groups with dementia [7, 8]. However, the effect size of antipsychotics in BPSD appears to be only small to moderate [9]. Furthermore, studies have shown that both conventional and atypical antipsychotics increase the risk of mortality [10–12] and cerebrovascular adverse events [13–15] in dementia. Safety concerns about the use of these medications in dementia have increased [16]. Therefore, experts emphasize that the high antipsychotic prescription rates are an urgent safety issue for health systems and that the prescription of antipsychotics should be reduced [17]. This means that the question of the effect of discontinuation of antipsychotic medication in dementia has high clinical relevance.

Previous research has suggested that patients with dementia can benefit from antipsychotic discontinuation including mortality risk reduction [18], improvement in cognitive function [19] and affect [20]. It has also been suggested that two thirds of patients can stop antipsychotic medications without exacerbating BPSD [21, 22]. However, other studies have reported that antipsychotic discontinuation causes statistically significant worsening of BPSD [23, 24]. The literature suggests that factors predicting a poor outcome of antipsychotic discontinuation may include: higher baseline antipsychotic dosage, higher baseline BPSD scores and use of benzodiazepines at baseline [19, 21, 25–27]. In view of the inconsistent results from different study populations and methodologies, we conducted a systematic review and meta-analysis to summarize all related findings to evaluate the risks and benefits of antipsychotic discontinuation in dementia.

**Methods**

*Inclusion Criteria*

**Types of Studies and Language**

Randomized, parallel-group, clinical controlled studies of any antipsychotic used in dementia were included. A double-blind or assessor-blind study design was permitted, but no open-label studies. The language was limited to English.
Types of Participants

Patients from both genders who were aged 50 years or older were included if they met one of the following criteria for dementia: DSM-IV or ICD-10 or probable/possible dementia according to the National Institute of Neurological Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA). Another criterion was the use of antipsychotics for BPSD.

Types of Interventions

Intervention Target

Studies involved patients with dementia who were treated with antipsychotics and aimed to evaluate the impact of the cessation of antipsychotic medication. Studies were excluded if interventions focused on psychotropic medications other than antipsychotics. Another reason for exclusion from the meta-analysis was discontinuation of combinations of antipsychotics and other psychotropic medications, and if the studies did not report the discontinuation effects separately. Moreover, interventions focusing only on staff education or administrative strategies to reduce the percentage of antipsychotic treatment were also excluded.

Definition of Antipsychotics

Both first-generation antipsychotics and second-generation antipsychotics were included. The classification of antipsychotics (N05A) was done according to the ATC (anatomical therapeutic chemical) index of the WHO. However, not all N05A medications were included, since some of the N05A medications are not used as antipsychotics in clinical practice, such as lithium for example (N05AN). The antipsychotics included in this review are presented in Appendix 1.

Intervention Type

The intervention group was defined as the study subjects whose antipsychotic agents were discontinued. Antipsychotic discontinuation could be achieved by abrupt cessation or tapering over weeks. The control group was defined as the study subjects whose antipsychotic agents and dosage were kept the same as in the prestudy period.

Types of Outcome Measures

All outcome measures were tested for the differences between the intervention group and control group. The primary outcome was change in BPSD severity score from study baseline to endpoint. The planned secondary outcomes included the proportion of subjects with BPSD worsening, death, new cerebrovascular adverse events, early study terminations, and changes in scores of cognitive function, quality of life, limitation of function and caregiver burden from study baseline to endpoint.

Search Methods for Study Identification

Electronic databases including MEDLINE, EMBASE, PsycInfo, Cochrane Library and CINAHL were searched. The related search terms used in this review included randomized controlled studies [random and the truncation symbol (random*) or control* or placebo], dementia [dement* or Alzheimer*], antipsychotics [antipsychotic* or neuroleptic* or tranquilizer* or individual name of all antipsychotics, see list in Appendix 1], and discontinuation or tapering [discontinue* or cessa* or withdr* or stop* or end* or taper* or reduc* or decreas*]. The search included both the medical subject heading (MeSH) terms and the free text. We did not search for unpublished studies because of concerns regarding study quality. All the references of the related studies were manually searched to find additional articles.

Data Collection and Analysis

Selection of Studies

In the first stage, two reviewers (H.-Y.C. and Y.-J.P.) independently reviewed the title and abstract of all identified articles. The studies which were recognized by both reviewers as relevant were obtained in full text. In the second stage, all full text articles were assessed independently by the two reviewers to decide whether they fulfilled the criteria. In case of disagreement, the articles were discussed by the two reviewers to achieve consensus. If no agreement could be achieved, a third reviewer (C.-S.W.) joined the discussion to make the final decision.
Data Extraction and Management

The two reviewers (H.-Y.C. and Y.-J.P.) independently extracted data from all included articles using a data extraction form. The following items were extracted: the name of the first author and the year of publication, number of study subjects, gender and age distribution, study setting, previous antipsychotics, methods of tapering antipsychotics, duration of follow-up, methods of randomization and allocation concealment, blinding methods, primary and secondary outcomes and their measurements, data analysis methods, and the data to evaluate the risk of bias. The methods of dealing with disagreement of data extraction were the same as for study selection.

Assessment of the Risk of Bias

The internal validity of the included studies was assessed independently by the two reviewers. They used the Cochrane collaboration’s tool to assess the risk of bias in randomized trials and items included random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data and selective reporting [28]. The process of disagreement management was the same as for study selection.

Statistical Methods

We used the risk ratio (RR) with 95% confidence interval (CI) to calculate the relative risk of the intervention group compared to the control group if the outcome measure was binary. Therefore, we could extract the risk rate from both intervention and control groups in a randomized clinical trial (RCT). We calculated the mean differences with 95% CIs between intervention group and control group for continuous outcome measures. In the meta-analysis, mean differences with 95% CIs were used to calculate the outcome which was measured by the same scales. Standardized mean differences (SMD) [29] with 95% CIs were used to standardize the different scales in the different studies.

We checked for statistical heterogeneity by visually examining the statistics and 95% CIs of all studies (forest plots). Then, we performed the I² test and χ² tests to determine the percentage of effect variability because of heterogeneity and its statistical significance. Criteria for statistical heterogeneity were a value of more than 50% in the I² test (substantial) and statistical significance in the χ² test [30, 31]. If statistical heterogeneity was found, we inspected the heterogeneity by subgroup analysis and/or meta-regression.

We used funnel plots to detect publication bias when there were more than 10 primary studies [32]. Begg’s rank correlation test and Egger’s linear regression test were used to test the statistical significance of reporting bias [33, 34]. If more than 2 studies provided relevant data for a specific outcome, a meta-analysis was performed. Random-effect models were used for all analyses because statistical heterogeneity existed among different studies. We summarized the results of these studies and discussed the sources of heterogeneity and other related issues. The data were analyzed using Review Manager Version 5.0 (http://www.cochrane.org/revman) and STATA Version 8.2 (StataCorp, College Station, Tex., USA). The level of statistical significance was two-sided and set at p < 0.05.

Results

Search Flow

The search strategy initially identified 3,402 publications from five electronic databases (MEDLINE: 1,265, EMBASE: 622, PsycInfo: 919, CINAHL: 622, Cochrane trial: 286). After identification of duplicate references and completion of the initial title and abstract screening, 47 studies were rated as potentially relevant and reviewed in full text. From these 47 studies, 29 were excluded because they were part of an educational program to reduce antipsychotic prescription, 7 were excluded because of the observational study design and 1 was excluded because 2 studies [18, 25] were the same study with a different follow-up period and outcomes reporting. Therefore, 10 studies [18, 19, 21–24, 26, 35–37] were entered into the qualitative data synthesis. Among the studies in the qualitative data synthesis, 1 study [35] was excluded from the meta-analysis because the medication discontinuation combined antipsychotics and other psychotropic medications and did not report the results separately. Finally, 9 studies
[18, 19, 21–24, 26, 36, 37] were entered into a meta-analysis. Each of the 9 studies can only provide some, but not all, data for different outcome variables. Therefore, different sets of studies were used for each outcome variable. The Quality of Reporting of Meta-analyses (QUOROM) flow diagram is presented in figure 1.

**Fig. 1.** The Quality of Reporting of Meta-analyses (QUOROM) flow diagram.

Characteristics of Included Studies for Qualitative Data Synthesis

The characteristics of included studies for qualitative data synthesis are presented in table 1. All studies were double-blind in design. The year of publication was from 1989 to 2012. All studies were done in North America or Western Europe, and they were all funded by governmental or nonprofit sectors. There were 663 patients in the 10 included studies. The average age of the participants was 75 years (standard deviation, SD 8) in 1 study [26].
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Setting</th>
<th>Previous AP before study, n</th>
<th>Follow-up period</th>
<th>Primary outcome measure</th>
<th>AP continuation group vs. AP withdrawal group, n</th>
<th>Tapering speed</th>
<th>Primary results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devanand et al., 2012</td>
<td>Outpatients or residents of assisted-living facilities or nursing homes</td>
<td>Risperidone (110)</td>
<td>16 weeks (for primary outcome)</td>
<td>Psychotic symptoms relapse: (1) NPI core score increased ≥30% or (2) NPI core score increased ≥5 or (3) CGI-C score 6 or 7</td>
<td>Risperidone (70), placebo (40)</td>
<td>≥3 mg/day at baseline: 2 mg/day in the first week and then 1 mg/day in the second week; 2 mg/day at baseline: 1 mg/day in the first week and then placebo; &lt;2 mg/day at baseline: discontinued directly</td>
<td>Relapse rate was significantly higher in the placebo group than in the risperidone group (60 vs. 33%, p = 0.004) hazard ratio for relapse was significantly higher in the placebo group than in the risperidone group (hazard ratio: 1.94, p = 0.02)</td>
</tr>
<tr>
<td>Devanand et al., 2011</td>
<td>Outpatients</td>
<td>Haloperidol (20)</td>
<td>24 weeks</td>
<td>Psychotic and agitated symptoms worsening: the sum score of 3 BPRS items</td>
<td>Haloperidol (10), placebo (10)</td>
<td>4 mg/day at baseline: 2 mg/day in the first week and then 1 mg/day in the second week; 2–3 mg/day at baseline: 1 mg/day for 2 weeks, 0.5–1 mg/day at baseline: discontinued directly</td>
<td>Proportion of subjects with more than 50% psychotic symptoms worsening: 49% in the haloperidol group vs. 80% in the placebo group</td>
</tr>
<tr>
<td>Ballard et al., 2008, 2009</td>
<td>Residents of long-term care facilities</td>
<td>Traditional AP or risperidone (165)</td>
<td>6 months’ outcomes</td>
<td>BPSD severity change</td>
<td>Traditional AP or risperidone (83), placebo (82)</td>
<td>Direct discontinuation</td>
<td>NPI score change: 1.3 points increase in the AP continuation group and 4.5 points increase in the placebo group; no significant group difference noted</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 months’ outcomes</td>
<td>(1) Mortality</td>
<td>Traditional AP or risperidone (83), placebo (82)</td>
<td>Survival rate: 74.7% in the AP group and 79.3% in the placebo group; no statistically significant difference noted</td>
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<td>(2) BPSD severity change</td>
<td>Traditional AP or risperidone (28), placebo (31) (only data of study completers were analyzed)</td>
<td>NPI score change: 1.4 points increase in the AP group and 11.4 points increase in the placebo group; significant group difference noted</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Extended outcomes (up to 54 months)</td>
<td>Mortality</td>
<td>Traditional AP or risperidone (83), placebo (82)</td>
<td>The placebo group had a significantly higher mortality rate than the AP group [log rank test: p = 0.02, hazard ratio: 0.58 (0.36–0.92)]</td>
<td></td>
</tr>
<tr>
<td>Ruths et al., 2008</td>
<td>Residents of nursing homes</td>
<td>Haloperidol or risperidone or olanzapine (55)</td>
<td>4 weeks</td>
<td>NPI score change</td>
<td>Haloperidol or risperidone or olanzapine (28), placebo (27)</td>
<td>Direct discontinuation</td>
<td>Proportion of subjects with NPI score remained the same or decreased: 86% in the AP group and 66% in the placebo group; no significant difference noted</td>
</tr>
<tr>
<td>Author, year</td>
<td>Setting</td>
<td>Previous AP before study, n</td>
<td>Follow-up period</td>
<td>Primary outcome measure</td>
<td>AP continuation group vs. AP withdrawal group, n</td>
<td>Tapering speed</td>
<td>Primary results</td>
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</tr>
<tr>
<td>Ruths et al., 2004</td>
<td>Nursing homes</td>
<td>Risperidone (22), olanzapine (4), haloperidol (4)</td>
<td>4 weeks</td>
<td>NPI-Q sum score change</td>
<td>Risperidone or olanzapine or haloperidol (15), placebo (15)</td>
<td>Direct discontinuation</td>
<td>Proportion of subjects with NPI-Q sum score remained stable or decreased: 87% in the AP group and 73% in the placebo group; no significant difference noted</td>
</tr>
<tr>
<td>Ballard et al., 2004</td>
<td>Residents of long-term care facilities</td>
<td>Traditional AP or risperidone (100)</td>
<td>3 months</td>
<td>NPI score change</td>
<td>Traditional AP (54) or risperidone, placebo (46)</td>
<td>Direct discontinuation</td>
<td>Proportion of subjects with NPI score remained the same or decreased: 91% in the AP group and 87% in the placebo group; no significant difference noted</td>
</tr>
<tr>
<td>Van Reekum et al., 2002</td>
<td>Residents of long-term care facilities</td>
<td>Risperidone (12), olanzapine (3), traditional AP (18)</td>
<td>6 months</td>
<td>BEHAVE-AD score change</td>
<td>Traditional AP or risperidone (16) or olanzapine, placebo (17)</td>
<td>Discontinuation after 2 weeks of tapering</td>
<td>Proportion of subjects without early withdrawal due to behavioral worsening: 81.2% in the AP group and 76.5% in the placebo group; no significant difference noted</td>
</tr>
<tr>
<td>Cohen-Mansfield et al., 1999</td>
<td>Residents of nursing homes</td>
<td>Traditional AP (58)</td>
<td>6 weeks</td>
<td>BPRS score and CMAI score at study endpoint</td>
<td>Traditional AP or lorazepam (29), placebo (29). A crossover trial</td>
<td>Discontinuation after 3 weeks of tapering</td>
<td>BPRS score at study endpoint: 2.32 in the AP group and 2.12 in the placebo group; no significant difference noted; CMAI score at study endpoint: 1.72 in the AP group and 1.77 in the placebo group; no significant difference noted</td>
</tr>
<tr>
<td>Bridges-Parlet et al., 1997</td>
<td>Residents of a long-term care institute</td>
<td>Haloperidol (21), thioridazine (9), thiothixene (3), other traditional AP (3)</td>
<td>4 weeks</td>
<td>Early study withdrawal due to agitation or aggression</td>
<td>Traditional AP (14), placebo (22)</td>
<td>Direct discontinuation</td>
<td>Proportion of subjects who can complete study without agitation: 100% in the AP group and 91% in the placebo group; no significant difference noted</td>
</tr>
<tr>
<td>Findlay et al., 1989</td>
<td>Long-stay psychogeriatric ward of a hospital</td>
<td>Thioridazine (36)</td>
<td>4 weeks</td>
<td>CAS for cognitive function; SCAGS and LPRS for behavioral features</td>
<td>Thioridazine (18), placebo (18)</td>
<td>Discontinuation after 1 week of tapering</td>
<td>Total score changes from baseline to study endpoint: CAS: 1.7 points increase in the placebo group and no change in the AP group; SCAGS: 1.1 points increase in the placebo group and 1.7 points increase in the AP group; LPRS: 1.1 points increase in the placebo group and 0.9 points decrease in the AP group (no statistically significant between-group differences in all outcome measures)</td>
</tr>
</tbody>
</table>

AP = Antipsychotics; BEHAVE-AD = Behavioral Pathology in Alzheimer’s Disease Rating Scale; BPRS = Brief Psychiatric Rating Scale; CAS = Cognitive Assessment Scale; CMAI = Cohen Mansfield Agitation Inventory; CGI-C = Clinical Global Impression-Change; LPRS = London Psychogeriatric Rating Scale; NPI-Q = Neuropsychiatric Inventory Questionnaire; SCAGS = Sandoz Clinical Assessment Geriatric Scale.
and 80 years or older in the other 9 studies. Most studies had a higher proportion of female participants than male ones. The majority of studies were conducted in nursing homes or other long-term care facilities, and only 1 study focused on outpatients. The follow-up period of 4 studies was 4 weeks, and only 1 study lasted 1 year. The sample size of 5 studies was less than 40 participants, and only 3 studies had more than 100 participants. Most studies investigated the effects of discontinuation of first-generation antipsychotics or risperidone. Five studies discontinued antipsychotics abruptly at baseline, and 5 studies tapered down antipsychotics over 1–3 weeks.

**Outcome Results of the Meta-Analysis**

**Primary Outcome**

Figure 2 shows the forest plot of the BPSD severity change from baseline to study endpoint. Only 3 studies provided the primary outcome data (mean and SD of the BPSD severity change from baseline to study endpoint). One of the 3 studies only presented BPSD severity change data of study completers. The average age of the participants was 80 years or older, and there were more females than males in all 3 studies. All 3 studies recruited patients from nursing homes or other long-term care facilities, and their follow-up periods were 4 weeks, 3 months and 1 year, respectively.

Since the rating scales used to assess BPSD severity were different among these 3 studies, we used SMD to estimate the effect size. The compiled SMD of BPSD severity change showed that the BPSD scores in the antipsychotic discontinuation group increased more than in the continuation group, but that difference did not reach statistical significance (total number of patients: 214, SMD: 0.19, 95% CI: −0.20 to 0.58).

**Secondary Outcomes**

Proportion of Study Participants with BPSD Worsening

Figure 3 shows the forest plot of the proportion of study participants with BPSD worsening. Seven studies provided the proportion of study participants with BPSD worsening from baseline to study endpoint. In 1 study, the average age of the participants was 75 years [26], in the others it was 80 years or older. Six studies had a higher proportion of female participants than male ones. Five studies recruited patients from nursing homes or other
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long-term care facilities, 1 study recruited outpatients, and another one recruited both outpatients and patients from long-term care facilities. The follow-up periods of 3 studies were 4 weeks and in 4 studies between 1 month and 1 year.

The compiled results showed that the antipsychotic discontinuation group had a statistically significantly higher proportion of participants with BPSD worsening than the antipsychotic continuation group (total number of patients: 366, Mantel-Haenszel (M-H) test for RR: 1.78, 95% CI: 1.31–2.41).

Proportion of Study Participants with Early Study Termination
Figure 4 shows the forest plot of the proportion of participants with early study terminations. Six studies provided the proportion of study participants with early terminations from

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antipsychotic withdrawal events total</th>
<th>Antipsychotic continuation events total</th>
<th>Weight, %</th>
<th>Risk ratio M-H, random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ballard, 2004</td>
<td>14 46</td>
<td>14 54</td>
<td>15.1</td>
<td>1.17 [0.63, 2.20]</td>
<td></td>
</tr>
<tr>
<td>Ballard, 2009</td>
<td>37 64</td>
<td>36 64</td>
<td>65.9</td>
<td>1.03 [0.76, 1.39]</td>
<td></td>
</tr>
<tr>
<td>Bridges-Parlet, 1997</td>
<td>2 22</td>
<td>0 14</td>
<td>0.7</td>
<td>3.26 [0.17, 63.30]</td>
<td></td>
</tr>
<tr>
<td>Devanand, 2012</td>
<td>4 40</td>
<td>8 70</td>
<td>4.6</td>
<td>0.88 [0.28, 2.72]</td>
<td></td>
</tr>
<tr>
<td>Ruths, 2008</td>
<td>4 27</td>
<td>3 28</td>
<td>3.0</td>
<td>1.38 [0.34, 5.61]</td>
<td></td>
</tr>
<tr>
<td>van Reekum, 2002</td>
<td>10 17</td>
<td>6 16</td>
<td>10.7</td>
<td>1.57 [0.74, 3.31]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>216 246</td>
<td>100</td>
<td>1.11 [0.87, 1.41]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>71 67</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 1.91$, d.f. = 5 (p = 0.86), $I^2 = 0\%$
Test for overall effect: $Z = 0.82$ (p = 0.41)

Fig. 3. Forest plot of the proportion of study participants with BPSD worsening.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Discontinuation events total</th>
<th>Continuation events total</th>
<th>Weight, %</th>
<th>Risk ratio M-H, random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bridges-Parlet, 1997</td>
<td>2 22</td>
<td>0 14</td>
<td>1.1</td>
<td>3.26 [0.17, 63.30]</td>
<td>1997</td>
</tr>
<tr>
<td>van Reekum, 2002</td>
<td>4 17</td>
<td>3 16</td>
<td>5.2</td>
<td>1.25 [0.33, 4.76]</td>
<td>2002</td>
</tr>
<tr>
<td>Ruths, 2004</td>
<td>4 15</td>
<td>2 15</td>
<td>3.9</td>
<td>2.00 [0.43, 9.32]</td>
<td>2004</td>
</tr>
<tr>
<td>Ballard, 2004</td>
<td>12 36</td>
<td>11 46</td>
<td>19.3</td>
<td>1.39 [0.70, 2.79]</td>
<td>2004</td>
</tr>
<tr>
<td>Ruths, 2008</td>
<td>9 27</td>
<td>4 28</td>
<td>8.3</td>
<td>2.33 [0.81, 6.68]</td>
<td>2008</td>
</tr>
<tr>
<td>Devanand, 2011</td>
<td>8 10</td>
<td>4 10</td>
<td>13.7</td>
<td>2.00 [0.88, 4.54]</td>
<td>2011</td>
</tr>
<tr>
<td>Devanand, 2012</td>
<td>23 40</td>
<td>22 70</td>
<td>48.5</td>
<td>1.83 [1.18, 2.83]</td>
<td>2012</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>167 199</td>
<td>100</td>
<td>1.78 [1.31, 2.41]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>62 46</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 1.27$, d.f. = 6 (p = 0.97), $I^2 = 0\%$
Test for overall effect: $Z = 3.70$ (p = 0.0002)
The average age of the participants was 80 years or older in all 6 studies. Five studies had a higher proportion of female participants than male ones. Five studies recruited patients from nursing homes or other long-term care facilities, and 1 study recruited both outpatients and patients from long-term care facilities. The follow-up periods of 2 studies were 4 weeks, 3 studies had follow-up periods between 1 month and 1 year, and 1 study had a 1-year follow-up period.

The compiled results showed that the antipsychotic discontinuation group had a higher proportion of participants with early study terminations than the antipsychotic continuation group, but there was no statistically significant difference (total number of patients: 462, M-H test for RR: 1.11, 95% CI: 0.87–1.41).

Mortality of Study Participants

Figure 5 shows the forest plot of mortality in study participants. Five studies provided the proportion of study participants who died during the study period. The average age of the participants was 80 years or older in all 5 studies. Four studies had a higher proportion of female participants than male ones. Four studies recruited patients from nursing homes or other long-term care facilities, and 1 study recruited both outpatients and patients from long-term care facilities. The follow-up period of 1 study was 4 weeks, 3 studies had follow-up periods between 1 month and 1 year, and only 1 study had a 1-year follow-up period.

The compiled results showed that the antipsychotic discontinuation group had a lower proportion of participants dying during the study period than the antipsychotic continuation group, but this difference did not reach statistical significance (total number of patients: 407, M-H test for RR: 0.83, 95% CI: 0.49–1.39).

**Heterogeneity and Risk of Bias Assessment**

The primary outcome and all secondary outcomes did not show significant statistical heterogeneity in Cochrane’s Q statistic and I statistic (fig 2–5). Figure 6 shows how to use the risk of bias tool to assess study quality. We found out that allocation concealment was the least well-reported item, followed by random sequence generation, and then incomplete...
outcome data. Many studies had been classified as double-blind but did not report the details of sequence generation and allocation concealment. Some studies only reported some of the symptom domains or side effect domains but not both of them (potential selective reporting). In addition, some studies had other risks of bias such as baseline imbalance between groups that might have been caused by the small numbers of cases in these studies.

**Subgroup and Sensitivity Analysis**

Since there were no significant statistical heterogeneities among the primary and secondary outcomes, we did not perform the subgroup analysis. In the sensitivity analysis, we deleted each study one at a time to determine their influence on the overall effect. The results showed that the overall effects in the primary and secondary outcomes did not vary substantially after excluding each study.
Publication Bias

The primary outcome and all secondary outcomes were available only from 7 studies or less. In this situation, we did not perform the funnel plot test or other statistical methods to detect publication bias.

Discussion

Since BPSD constitutes a major burden for individuals with dementia and their caregivers, change in severity and worsening of BPSD after antipsychotic discontinuation are clinically important issues. The results of this study demonstrate that although the proportion of patients with BPSD severity worsening was significantly higher in the antipsychotic discontinuation group compared to the continuation group, there was no statistically significant between-group difference in BPSD severity change. The finding that taking antipsychotics in dementia is associated with an increased mortality is a major public health issue [10–12]. Therefore, clinicians want to find out if antipsychotic discontinuation can reduce the mortality rate. The meta-analysis reported here showed that the mortality rate was lower in the antipsychotic discontinuation group compared to the continuation group; however, there was no statistically significant difference. Larger numbers may be needed to investigate this relatively rare effect. Early study termination is related to the global judgment of clinicians, patients and caregivers on the appropriateness of patients continuing participation in a study. It is determined by multiple factors including severity change of BPSD, tolerability of antipsychotic discontinuation and the decreased side effects of antipsychotic discontinuation. Our results showed that the proportion of patients with early termination was higher in the antipsychotic discontinuation group compared to the continuation group, but there was no statistically significant difference. This review provides a summary of the existing literature on antipsychotic discontinuation in patients with dementia.

There are limitations in the populations and antipsychotic interventions of previous antipsychotic discontinuation RCTs. First, most of these studies focused on typical antipsychotics or risperidone rather than other atypical antipsychotics. Therefore, we do not know the discontinuation effect of other atypical antipsychotics. Second, most previous studies focused on patients with dementia in care homes or other residential facilities, not outpatients, so the generalizability of these studies is limited to the residents of the long-term care facilities. Third, many antipsychotic discontinuation studies assess the combined effects of several antipsychotic medications. Thus, it is difficult to assess the unique discontinuation effects of a specified antipsychotic medication or to make a comparison between different antipsychotics. There is a need for studies that resolve the continuing limitations in the evidence base. This would allow us to better understand the consequences of antipsychotic discontinuation in dementia.

Furthermore, there are limitations in the sample size, outcome measures and reporting in the previous antipsychotic discontinuation studies. Half of the studies in the meta-analysis had less than 40 study participants, and only 3 studies had 100 or more participants. Many studies had limited outcome measures or only reported part of their results. In addition, even for the primary outcome, only 3 studies with 214 participants in total provided the mean and SD of the BPSD severity change from baseline to study endpoint in both antipsychotic discontinuation and continuation groups. Although there were more studies and study participants with which to consider the secondary outcomes, the probability of type II error exists and impairs the value of the meta-analysis and clinical extrapolation. Furthermore, the different follow-up periods of the studies also influence the results. Change in BPSD severity, the
proportion of BPSD worsening, early study termination and mortality were all influenced by study duration. Each outcome has its own optimum follow-up period with mortality needing the longest follow-up. Realistically, the study duration of several studies was too short (4 weeks) to provide meaningful data for the majority of outcomes.

Due to the above-mentioned limitations and the inconsistent results, it is difficult to draw definite conclusions from the current published studies about the effects of antipsychotic discontinuation in dementia. Therefore, it is difficult to use these data to formulate better treatment guidelines because of insufficient evidence.

The results of the meta-analysis showed that a higher proportion of BPSD worsening did not parallel the severity of BPSD change. Several factors could have contributed to this discrepancy. Firstly, the studies which contributed to the results of the change of BPSD severity are different from the proportion of BPSD worsening. Therefore, this difference may result in their inconsistency. Secondly, the worsening of BPSD severity in the study participants of the antipsychotic discontinuation group may be only mild and not clinically relevant. For instance, the study by Ruths et al. [21] showed that after a 6-month follow-up, the neuropsychiatric inventory score changes of the antipsychotic discontinuation group and the continuation group were -0.19 (SD 5.3) and -1.79 (SD 4.9), respectively. Thus, the higher proportion of worsening only contributed to a small amount of BPSD severity change.

The RR of death was lower in the antipsychotic discontinuation group compared to the continuation group, but it did not reach statistical significance. This may be because the follow-up periods of most studies did not last more than 6 months, and the case numbers in this meta-analysis did not have enough statistical power to detect the difference. To investigate mortality fully, there is a need for sufficient person time in the studies. Therefore, more than 10,000 dementia cases may be needed to analyze the difference in the between-group mortality rate with sufficient statistical power [11, 38]. There is a need for studies that monitor death rates after antipsychotic discontinuation in dementia.

There were limitations to this review. First, we only reviewed peer-reviewed published studies and there may be unpublished literature. Therefore, the possibility of publication bias exists. Second, our included studies were limited to the English language, and thus there may be language bias. Third, we only included studies focusing on antipsychotic discontinuation but not on other psychotropic medications. Consequently, the results of this study cannot be applied to other psychotropic medications. Finally, educational programs and other nonpharmacological interventions to reduce the usage of antipsychotics were excluded from this review. Thus, the result of this study can only apply to pharmacological interventions of antipsychotics discontinuation.

Although this study has the above-mentioned limitations, it also has several strengths. First, we searched the related electronic database comprehensively, and we manually checked the references of the included published articles. Therefore, the probability of missing the related published studies is low. Second, we used standard methods (two independent reviewers) to screen the title and abstract of the electronic screening, to judge which study met all inclusion and exclusion criteria, to perform data extraction and to assess the quality of the recruited studies. Therefore, the quality of this review is high and trustworthy.

This study provides a synthesis of the available evidence on the impact of antipsychotic discontinuation in dementia. The main problem is the low number of RCTs available to provide data for meta-analysis. It is striking that all RCTs in this review were funded by governmental or nonprofit sectors. This kind of studies are not likely to secure funding from pharmaceutical companies, and this will contribute to the relative scarcity of antipsychotic discontinuation studies. Governmental nonprofit sectors should provide adequate funding to widen the field of antipsychotic discontinuation studies in dementia. There is a need for definitive randomized, double-blind, placebo-controlled studies to compare the differences in
outcomes between discontinuation and continuation groups of the specific antipsychotics that are most commonly used. For example, a limitation of the evidence base is that there are no discontinuation studies of quetiapine despite its popularity in BPSD.

Although the impact of antipsychotic discontinuation in dementia is an important clinical issue, this systematic review showed that there were only 10, mostly small, published RCTs scattered over the last 3 decades, with only 9 RCTs contributing data for meta-analysis. Treatment guidelines suggest that, where necessary, antipsychotics should be used only in the short term (less than 3 months) for psychotic or agitated symptoms of BPSD. Moreover, physicians need to closely monitor the effectiveness and side effects of these medications during the treatment period. Treatment guidelines state that after 3 months of treatment, physicians should try to taper, and then discontinue antipsychotics. The equivocal nature of the evidence and the small number of RCTs indicate that more studies are needed to investigate the effect of dose and type of antipsychotics and the method of discontinuation.

**Acknowledgements**

This work was supported by a scholarship to Dr. Hung-Yu Chan funded by the Department of Health, Taiwan.

**Disclosure Statement**

The authors report no financial relationships relevant to the subjects of this article.

**Appendix 1**

*Included Antipsychotics in This Review Classified by the ATC Classification*

<table>
<thead>
<tr>
<th>ATC Code</th>
<th>Antipsychotics</th>
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<tbody>
<tr>
<td>N05A</td>
<td>N05AA Phenothiazines with aliphatic side chain&lt;br&gt;Chlorpromazine (N05AA01)</td>
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<tr>
<td></td>
<td>N05AB Phenothiazines with piperazine structure&lt;br&gt;Fluphenazine (N05AB02), perphenazine (N05AB03), trifluoperazine (N05AB06)</td>
</tr>
<tr>
<td></td>
<td>N05AC Phenothiazines with piperidine structure&lt;br&gt;Thioridazine (N05AC02), mesoridazine (N05AC03), pipotiazine (N05AC04)</td>
</tr>
<tr>
<td></td>
<td>N05AD Butyrophenone derivatives&lt;br&gt;Haloperidol (N05AD01), trifluperidol (N05AD02)</td>
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<tr>
<td></td>
<td>N05AE Indole derivatives&lt;br&gt;Molindone (N05AE02), sertindole (N05AE03), ziprasidone (N05AE04)</td>
</tr>
<tr>
<td></td>
<td>N05AF Thioxanthenes derivatives&lt;br&gt;Flupentixol (N05AF01), clopentixol (N05AF02), chlorprothixene (N05AF03), zuclopentixol (N05AF05)</td>
</tr>
<tr>
<td></td>
<td>N05AG Diphenylbutylpiperidine derivatives&lt;br&gt;Pimozide (N05AG02)</td>
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<td></td>
<td>N05AH Diazepines, oxazepines, thiazepines and oxepines&lt;br&gt;Loxapine (N05AH01), clozapine (N05AH02), olanzapine (N05AH03), quetiapine (N05AH04), sarsenapine (N05AH05), cloiapine (N05AH06)</td>
</tr>
<tr>
<td></td>
<td>N05AL Benzamides&lt;br&gt;Sulpiride (N05AL01), remoxipride (N05AL04), amisulpride (N05AL05)</td>
</tr>
<tr>
<td></td>
<td>N05AX Other antipsychotics&lt;br&gt;Risperidone (N05AX08), zotepine (N05AX11), aripiprazole (N05AX12), paliperidone (N05AX13) and iloperidone (N05AX14)</td>
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References


