BJPsych Advances (2023), vol. 29, 3–7 doi: 10.1192/bja.2022.34

ROUND THE CORNER

Should antipsychotics be used for the management of agitation and psychosis in dementia?†

Hannah Glatzel

SUMMARY

Agitation and psychosis are two common distressing symptoms of dementia. The results of this issue's Cochrane Corner review suggest that, if a pharmacological approach is required, the use of risperidone and other atypical antipsychotics for the purpose of managing these symptoms seems questionable. Furthermore, typical antipsychotics, haloperidol in particular, might have a greater impact on agitation and psychosis than already recognised. This commentary critically appraises the evidence on the efficacy of typical and atypical antipsychotics for agitation and psychosis in dementia.

KEYWORDS

Alzheimer's disease; vascular dementia; agitation; psychosis; behavioural and psychological symptoms of dementia.

In 2015, 47 million people worldwide suffered from dementia (Livingston 2017), including 5% of the population over 60 years old (Prince 2015: p. 24). As the disease progresses, approximately 90% of individuals will develop behavioural and psychological symptoms of dementia (BPSD) (Borsje 2018). BPSD include apathy, depression, agitation and psychosis (Kales 2015); two of these, agitation and psychosis, are particularly difficult to manage (Aalten 2003). This is of clinical importance, as BPSD are distressing to both patients and carers (Cohen-Mansfield 2016).

Do non-pharmacological interventions work?

Non-pharmacological interventions are the first-line of treatment for those experiencing BPSD (National Institute for Health and Care 2018: section 1.4) and they include aromatherapy, dance and music therapy. Research supports the efficacy of music therapy in reducing agitation in people with dementia (Abraha 2017), with effects continuing beyond the end of treatment (Livingston 2014). Significantly, one paper suggested that non-pharmacological measures could reduce the severity of BPSD with the same efficacy as pharmacological interventions (Brodaty 2012).

Despite this supportive evidence for non-pharmacological interventions, antipsychotics are routinely prescribed to treat agitation and psychosis in dementia (Yohanna 2017).

Antipsychotics – friend or foe?

Research has highlighted the potential side-effects antipsychotics can have in those with dementia exhibiting BPSD. These included extrapyramidal side-effects, somnolence, further cognitive decline and serious adverse events (Lonergan 2002; Ballard 2005).

The Halting Antipsychotic Use in Long-Term care (HALT) study, which focused on the deprescribing of antipsychotics, identified that increased agitation was the most common reason for restarting or remaining on antipsychotics. The majority of these requests came from the nursing team (63.2%) and family members (Aerts 2019).

Interestingly, it has been proposed that carers deem the benefits of antipsychotics 'more perceptible than their side-effects' (Almutairi 2018), potentially increasing their prescription (Kerns 2018). It is also noteworthy that, despite the perceived benefits on BPSD, one small study proposed that antipsychotics might also reduce positive emotions such as delight (Fujii 2019).

The aim of the review in this month's Cochrane Corner (Mühlbauer 2021) was to provide an updated analysis of these issues incorporating two previous papers reviewing the effect of typical and atypical antipsychotics on people with dementia (Lonergan 2002; Ballard 2006).

The Cochrane Review

Summary

The review authors included only randomised, placebo-controlled trials that involved people with Alzheimer's disease, vascular dementia or both, with significant agitation or psychosis, regardless of their age or severity of disease. Trials were

Hannah Glatzel, MBChB, BSc, is currently working as a Foundation Doctor with Oxford University Hospitals NHS Foundation Trust, Oxford, UK. Her research interests include mental health and emergency medicine.

Correspondence Hannah Glatzel. Email: hannahglatzel@outlook.com

First received 18 Apr 2022
Final revision 9 May 2022
Accepted 11 May 2022

†Commentary on… Antipsychotics for agitation and psychosis in people with Alzheimer's disease and vascular dementia (Cochrane Corner). See this issue.

https://doi.org/10.1192/bja.2022.34 Published online by Cambridge University Press

excluded if the majority of participants had other types of dementia or if they included delirium specifically. For this critical appraisal, I will focus on the primary outcomes, which were: efficacy of antipsychotics for both agitation and psychosis, and adverse events associated with antipsychotics (somnolence, extrapyramidal side-effects, any adverse event or death). Efficacy in treating agitation and psychosis was most commonly assessed using the Cohen–Mansfield Agitation Inventory (CMAI) (Cohen-Mansfield 1996) and the psychosis subscale of the Neuropsychiatric Inventory Nursing Home version (NPI-NH) (Cummings 2009) respectively.

The authors searched the ALOIS database (Box 1) on 7 January 2021. ALOIS advised that the database was not up-to-date because of the COVID-19 pandemic (https://alois.medsci.ox.ac.uk/about-alois) and therefore the authors also ran independent searches in the major databases, clinical trial registers and grey literature. Two authors independently assessed the eligibility of the identified studies and subsequently extracted the data. Any discrepancies were reviewed by a third author and resolved by consensus.

For continuous outcomes (e.g. changes on the CMAI), data were expressed as standardised mean differences (s.m.d.) with 95% confidence intervals (95% CI). For dichotomous variables, data were analysed using risk ratios (RRs) with 95% CIs. Heterogeneity was assessed by the χ^2 statistic; a fixed-effects model was used if the I^2 statistic was under 40% and a random-effects model was used if it was over 40%. However, the Cochrane Handbook recommends caution against using the χ^2 statistic to decide between different statistical analyses (Deeks 2022: section 10.10.2). This is important as the presence of heterogeneity in a fixed-effects model will generate a smaller confidence interval than in a random-effects model.

At the time of this review, risperidone and haloperidol were the first-choice antipsychotics in many countries and were thus subject to subgroup analyses. A *post hoc* analysis of quetiapine was added following peer review.

The bias of each paper was analysed using the Cochrane Risk of Bias tool (Higgins 2019) and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Schünemann 2020) was used to analyse the quality of the evidence. As per Cochrane guidelines, the review authors used funnel plots to assess publication bias when over 10 studies were available in the analyses.

BOX 1 What is the ALOIS database?

ALOIS, named after Alois Alzheimer, is a database maintained by the Cochrane Dementia and Cognitive Improvement Group (https://alois.medsci.ox.ac.uk). Researchers conduct monthly searches identifying new randomised/quasi-randomised trials involving people with all types of dementia (not just Alzheimer's disease), cognitive impairment or 'for the improvement of, or prevention of decline in, cognitive function in healthy people' and adds these studies to the database (https://alois.medsci.ox.ac.uk/about-alois).

Results

A total of 8233 records were initially identified, with 1196 duplicates excluded; 7005 of the remaining papers were deemed ineligible, leaving 24 studies for qualitative synthesis and 23 for meta-analysis. The distribution of these studies is shown in Fig. 1.

Most studies included individuals with moderate or severe dementia, which is consistent with the notion of increasing BPSD with disease progression (Stern 1987). Notably, the review authors highlighted that often they were unable to ascertain whether the participants recruited had responded to non-pharmacological interventions. As mentioned earlier, in the community, patients are treated with non-pharmacological interventions first, followed by antipsychotics if this is ineffective. Therefore, if study participants had not received non-pharmacological interventions before recruitment to the pharmacological trials, then the participants included in this review might not be representative of those treated with antipsychotics in the community.

It is uncertain whether typical antipsychotics reduce agitation (s.m.d. = −0.36, 95% CI −0.57 to −0.15), owing to pronounced heterogeneity and imprecision of the confidence interval. Haloperidol might decrease agitation (s.m.d. = −0.29, 95% CI −0.51 to −0.07), although notably the confidence interval is close to 0. Haloperidol might also improve psychosis slightly (s.m.d. = −0.29, 95% CI −0.55 to −0.03), but the confidence interval suggests an effect of no clinical relevance. Moreover, each paper analysing the efficacy of typical antipsychotics had a high risk of bias in at least one domain.

Haloperidol probably increases the risk of somnolence (RR = 2.62, 95% CI 1.51–4.56); despite a confidence interval above 1, there is pronounced heterogeneity. Haloperidol potentially increases the risk of extrapyramidal side-effects (RR = 2.33, 95% CI 0.9–6.01), but only one study analysed this. Unfortunately, despite the thorough literature search there was a lack of data regarding the number of serious adverse events, which appears to be a common problem (Parsons 2019). The authors proposed that typical antipsychotics, and specifically haloperidol, might increase the risk of mortality even though these confidence intervals (RR = 1.46, 95% CI 0.54–4.00 and RR = 1.88,

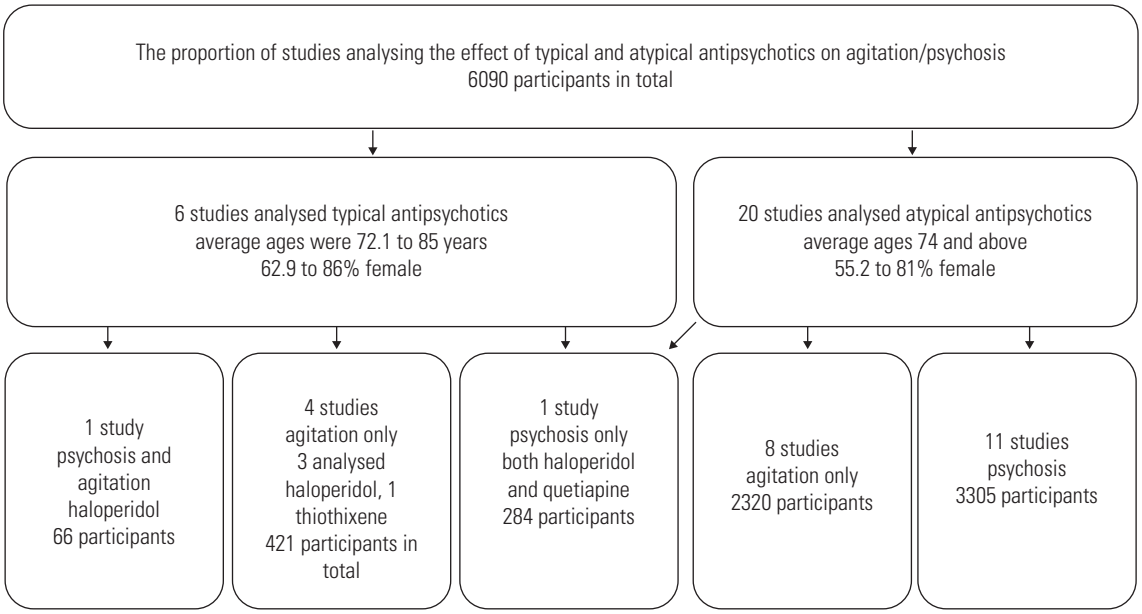

FIG 1 Proportion of studies analysing typical and atypical antipsychotics for behavioural and psychological symptoms of dementia (Mühlbauer 2021).

95% CI 0.65–5.48 respectively) encompass an important harmful effect as well as a protective one.

The authors propose that atypical antipsychotics reduce agitation (s.m.d. = −0.21, 95% CI −0.30 to −0.12), but the clinical significance is questionable owing to the small effect size (Page 2014). Furthermore, they probably have little to no effect on psychosis (s.m.d. = −0.11, 95% CI −0.18 to −0.03), reflected in the marginal effect size. Risperidone potentially reduces agitation (s.m.d. = −0.26, 95% CI −0.44 to −0.09), although with pronounced heterogeneity, and probably has a negligible effect on psychosis (s.m.d. = −0.11, 95% CI −0.23 to 0.01) owing to a confidence interval that indicates no clinical relevance.

The authors found that atypical antipsychotics increase the risk of somnolence (RR = 1.93, 95% CI 1.57–2.39) and probably the risk of extrapyramidal side-effects (RR = 1.39, 95% CI 1.14–1.68). In particular, risperidone probably increases the risk of somnolence (RR = 3.35, 95% CI 1.99–5.65) and may increase the risk of extrapyramidal side-effects (RR = 1.75, 95% CI 1.32–2.33). Analyses regarding adverse events and atypical antipsychotics had a high risk of bias in at least one domain. Meta-analysis suggested that both atypical antipsychotics and risperidone might increase the risk of mortality (RR = 1.36, 95% CI 0.90–2.05 and RR = 1.29, 95% CI 0.64–2.60 respectively). However, the confidence intervals in both analyses encompass a harmful as well as a protective effect.

Discussion

Despite haloperidol being available for over 50 years, there are few high-quality studies examining its effectiveness in managing BPSD, making it difficult to draw a definitive conclusion regarding its efficacy in people with dementia. There is some evidence that haloperidol reduces psychosis, but owing to the small number of studies, the review authors were unable to assess its effects on agitation with any degree of certainty. The lack of trials of typical antipsychotics for BPSD means that there is no current evidence for their use, but some research has suggested that typical antipsychotics are more frequently prescribed than atypical antipsychotics in dementia (Allers 2017).

Interestingly, higher doses of haloperidol were prescribed in all of these studies than is currently recommended. BNF guidance regarding persistent aggression and psychotic symptoms in elderly people with dementia is to prescribe 0.5 mg daily for a maximum of 6 weeks (Joint Formulary Committee 2022). However, the maximum dose used in these studies was 12 mg. This is significant given that it is 24 times higher than current BNF guidance, meaning adverse events might have been much greater, with or without a significant improvement in the patient's agitation and/or psychosis.

The authors cite the large amount of data to justify their confident conclusion that atypical antipsychotics have only a small effect on agitation and little to no effect on psychosis. The disparity between the sizes of clinical trials is significant, with just 12% of the participants in this meta-analysis enrolled in a study with typical antipsychotics. Although there are no papers to support this, one could argue that there is more funding for trials of newer antipsychotics owing to more interest from pharmaceutical companies, which could explain this disparity.

BOX 2 What is a wash-out period and why does this affect the results of a study?

The wash-out period is a set amount of time that researchers decide on to ensure prohibited medication (e.g. if the person is already on the treatment drug) or other medications are washed out of the body prior to commencing the active treatment. This aims at reducing confounding variables. However, it can also mean that patients who are eligible at the start of the wash-out period might not be eligible when the intervention starts (Hulshof 2015). This could be exacerbated by the length of time involved in a wash-out period.

Interestingly and perhaps very significantly, all 23 papers included in the meta-analysis had a high risk of bias in at least one domain, most commonly 'other bias'. The majority – 18 out of 23 – included a wash-out period. In one paper in particular, there was a 6 week wash-out period (Grossberg 2020), which risks biasing the results (Box 2).

One must consider the average age of participants when assessing the applicability of these findings. Significant differences between the average ages of the researched group and the affected population can undermine the validity of extrapolations to wider populations. Although the review authors did not conduct a statistical analysis to assess whether there is a significant difference between these average ages, the average age for all included participants is 80 years. In comparison, the average age for those in society with dementia is 80–84 for men and 85–89 for women (Prince 2014). Thus, the average age of 80 in this review makes this sample different from the average affected population, which is likely to be over 85 years old owing to the female majority (>50%). This disparity in demographics is important to consider when applying findings to the clinical setting. Furthermore, as BPSD symptoms tend to arise later during the dementia course (Stern 1987), one could argue that the symptoms experienced in the researched population could be quite different and potentially milder than in the population treated for BPSD clinically.

Conclusions

Overall, current guidance to manage primarily psychosocial symptoms in dementia and to minimise the use of antipsychotics as a treatment for dementia appears more in keeping with the evidence provided by this Cochrane Review: in other words, non-pharmacological interventions should always be prioritised. However, this is not always practical, owing to the perceived stress that patients are in and the associated impact on both their families and carers. Nonetheless, if a pharmacological approach is required, the use of risperidone and other atypical antipsychotics to manage agitation and psychosis seems questionable owing to a lack of supportive evidence, compounded by their significant side-effect profiles. Despite the low certainty of supportive evidence, there is the potential that typical antipsychotics, haloperidol in particular, might have a greater impact on agitation and psychosis than already recognised. More high-quality studies should be conducted to establish whether such conclusions can be drawn with greater certainty.

Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

Acknowledgement

I thank Dr Alvaro Barrera for his advice and support in writing this commentary.

Funding

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Declaration of interest

None.

References

Aalten P, de Vugt ME, Lousberg R, et al (2003) Behavioral problems in dementia: a factor analysis of the neuropsychiatric inventory. *Dementia and Geriatric Cognitive Disorders*, **15**: 99–105.

Abraha I, Rimland JM, Trotta FM, et al (2017) Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia: the SENATOR-OnTop series. *BMJ Open*, **7**(3): e012759.

Aerts L, Cations M, Harrison F, et al (2019) Why deprescribing antipsychotics in older people with dementia in long-term care is not always successful: insights from the HALT study. *International Journal of Geriatric Psychiatry*, **34**: 1572–81.

Allers K, Dörks M, Schmiemann G, et al (2017) Antipsychotic drug use in nursing home residents with and without dementia: keep an eye on the pro re nata medication. *International Clinical Psychopharmacology*, **32**: 213–8.

Almutairi S, Masters K, Donyai P (2018) The health professional experience of using antipsychotic medication for dementia in care homes: a study using grounded theory and focussing on inappropriate prescribing. *Journal of Psychiatric and Mental Health Nursing*, **25**: 307–8.

Ballard C, Margallo-Lana M, Juszczak E, et al (2005) Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. *BMJ*, **330**: 874.

Ballard C, Waite J (2006) The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. *Cochrane Database of Systematic Reviews*, **1**: CD003476.

Borsje P, Lucassen PLBJ, Wetzels RB, et al (2018) Neuropsychiatric symptoms and psychotropic drug use in patients with dementia in general practices. *Family Practice*, **35**: 22–8.

Brodaty H, Arasaratnam C (2012) Meta-analysis of nonpharmacological interventions for neuropsychiatric symptoms of dementia. *American Journal of Psychiatry*, **169**: 946–53.

Cohen-Mansfield J (1996) Conceptualization of agitation: results based on the Cohen-Mansfield Agitation Inventory and the Agitation Behavior Mapping Instrument. *International Psychogeriatrics*, **8**(suppl 3): 309–15.

Cohen-Mansfield J, Cohen R, Golander H, et al (2016) The impact of psychotic symptoms on the persons with dementia experiencing them. *American Journal of Geriatric Psychiatry*, **24**: 213–20.

Cummings J (2009) *Neuropsychiatric Inventory Nursing Home Version (NPI-NH): Comprehensive Assessment of Psychopathology in Patients with Dementia Residing in Nursing Homes*. UCLA (http://dementiamanagement-strategy.com/File.axd?id=c9f7405f-3596-4f5f-9f8d-f322e5188678).

Deeks J, Higgins J, Altman D (2022) Analysing data and undertaking meta-analyses. In *Cochrane Handbook for Systematic Reviews of Interventions, Version 6.3* (eds J Higgins, J Thomas): Ch 10: Section 10.2. Cochrane Collaboration (https://training.cochrane.org/handbook/current/chapter-10).

Fujii M, Butler JP, Sasaki H (2019) Antipsychotic drug use and favourable natures of emotional functions in patients with dementia. *Psychogeriatrics*, **19**: 320–4.

Grossberg GT, Kohegyi E, Mergel V, et al (2020) Efficacy and safety of brexpiprazole for the treatment of agitation in Alzheimer's dementia: two 12-week, randomized, double-blind, placebo-controlled trials. *American Journal of Geriatric Psychiatry*, **28**: 383–400.

Higgins JPT, Savović J, Page MJ, et al (2019) Assessing risk of bias in a randomized trial. In *Cochrane Handbook for Systematic Reviews of Interventions, Version 6.0* (updated July 2019) (eds J Higgins, J Thomas, J Chandler, et al): 205–28. Cochrane Collaboration.

Hulshof TA, Zuidema SU, Ostelo RW, et al (2015) The mortality risk of conventional antipsychotics in elderly patients: a systematic review and meta-analysis of randomized placebo-controlled trials. *Journal of the American Medical Directors Association*, **16**: 817–24.

Joint Formulary Committee (2022) Haloperidol. In *British National Formulary (BNF)*. BMJ Publishing Group/Royal Pharmaceutical Society (https://bnf.nice.org.uk/drug/haloperidol.html). Accessed 17 May 2022.

Kales HC, Gitlin LN, Lyketsos CG (2015) Assessment and management of behavioral and psychological symptoms of dementia. *BMJ*, **350**: h369.

Kerns JW, Winter JD, Winter KM, et al (2018) Caregiver perspectives about using antipsychotics and other medications for symptoms of dementia. *Gerontologist*, **58**: e35–e45.

Livingston G, Kelly L, Lewis-Holmes E, et al (2014) Non-pharmacological interventions for agitation in dementia: systematic review of randomised controlled trials. *British Journal of Psychiatry*, **205**: 436–42.

Livingston G, Sommerlad A, Orgeta V, et al (2017) Dementia prevention, intervention, and care. *Lancet*, **390**: 2673–734.

Lonergan E, Luxenberg J, Colford J (2002) Haloperidol for agitation in dementia. *Cochrane Database of Systematic Reviews*, **2**: CD002852.

Mühlbauer V, Möhler R, Dichter MN, et al (2021) Antipsychotics for agitation and psychosis in people with Alzheimer's disease and vascular dementia. *Cochrane Database of Systematic Reviews*, **12**: CD013304. Available from: https://doi.org/10.1002/14651858.CD013304.pub2.

National Institute for Health and Care Excellence (2018) *Dementia: Assessment, Management and Support for People Living with Dementia and their Carers (NICE Guideline NG97)*. Accessed 12 Apr 2022.

Page P (2014) Beyond statistical significance: clinical interpretation of rehabilitation research literature. *International Journal of Sports Physical Therapy*, **9**: 726–36.

Parsons R, Golder S, Watt I (2019) More than one-third of systematic reviews did not fully report the adverse events outcome. *Journal of Clinical Epidemiology*, **108**: 95–101.

Prince M, Knapp M, Guerchet M, et al (2014) *Dementia UK: Update 2nd ed. Alzheimer's Society* (https://www.alzheimers.org.uk/sites/default/files/migrate/downloads/dementia_uk_update.pdf).

Prince M, Wimo A, Guerchet M, et al (2015) *World Alzheimer Report 2015: The Global Impact of Dementia. An Analysis of Prevalence, Incidence, Cost and Trends*. Alzheimer's Disease International.

Schünemann H, Higgins JPT, Vist GE, et al (2020) Interpreting results and drawing conclusions. In *Cochrane Handbook for Systematic Reviews of Interventions, version 6.1* (updated September 2020) (eds J Higgins, J Thomas, J Chandler, et al): Ch 15. Cochrane.

Stern Y, Mayeux R, Sano M, et al (1987) Predictors of disease course in patients with probable Alzheimer's disease. *Neurology*, **37**: 1649–9.

Yohanna D, Cifu AS (2017) Antipsychotics to treat agitation or psychosis in patients with dementia. *JAMA*, **318**: 1057–8.