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Can clozapine be used for treatment-refractory behavioral and psychological symptoms in dementia patients?

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1. Introduction

Behavioral and psychological symptoms of dementia (BPSD), including agitation, psychosis and aggression, sleep problems, wandering and various inappropriate behaviors, are universally experienced by people with dementia throughout the course of the illness (Gerlach and Kales, 2020; International Psychogeriatric Association, 2015). Agitation, aggression and psychosis in particular frequently lead to high levels of suffering for the patient and their family members and to hospitalization of the patient (Reus et al., 2016).

A network meta-analysis showed that non-pharmacological interventions such as multidisciplinary care, massage and touch therapy, and music combined with massage and touch therapy were more effective for aggression and agitation than medication (Watt et al., 2019). As regards antipsychotics, the Cochrane review concludes that there is some evidence that typical antipsychotics may decrease agitation and psychosis slightly in patients with dementia (Mühlbauer et al., 2021). For atypical antipsychotics the conclusion is even more cautious.

Practice guidelines generally recommend the use of antipsychotics only if non-pharmacological interventions have had insufficient effect and the symptoms are severe or dangerous, or are causing significant distress to the patient (Ma et al., 2022; Reus et al., 2016). The American Psychiatric Association (APA) guideline refers to the elevated risks of extrapyramidal side effects and cognitive worsening caused by antipsychotic medication in patients with Lewy Body dementia and Parkinson's disease dementia and the superior tolerability of quetiapine and clozapine, but questions the evidence of their efficacy, even though clozapine has been registered by the European Medicine Agency for Parkinson's disease psychosis on the basis of two positive randomized controlled trials (RCTs) (Friedman and Hershkowitz, 2022; Reus et al., 2016). Elsewhere in the APA guideline (as in other guidelines) quetiapine and clozapine are in fact noted as the most appropriate medications for individuals with BPSD and Lewy body dementia or Parkinson's disease dementia because of the risk of worsened motor symptoms with the other antipsychotic agents (Nederlandse Vereniging voor Klinische Geriatrie [Netherlands Clinical Geriatrics Society], 2014; Reus et al., 2016). However, there are also authors who advise against prescribing clozapine for elderly patients with dementia because of its side effects – in particular the dreaded agranulocytosis – or only recommend it as a last resort (Bullock and Saharan, 2002; Kumar and Brecher, 1999; Schneider et al., 2007).

The Dutch Clozapine Collaboration Group occasionally receives reports of patients with dementia and treatment-refractory BPSD who are being treated with clozapine (van Waalwijk et al., 2020). In Dutch guidelines clozapine is indicated for BPSD only in Parkinson's disease and Lewy body dementia. Our study of the extent of off-label clozapine use for dementia in a clinic specializing in the diagnosis and treatment of BPSD (Noorda et al., 2023) found among 124 patients admitted during the twelve-month research period four patients with vascular or Alzheimer dementia who were being treated with clozapine. This finding prompted us to conduct the narrative review presented here, which aims to explore the efficacy and tolerability of clozapine for treatment-refractory BPSD.

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2. Methods

We conducted systematic searches in Medline and Embase on the Ovid platform for publications about the treatment of BPSD with clozapine (see Supplementary Box 1). A systematic review with a meta-analysis of six RCTs conducted in China that compared clozapine and olanzapine used to treat BPSD (Wang et al., 2022) was excluded because it does not state that the patients were suffering from treatment-refractory BPSD, the original studies were in Chinese and moreover because it is extremely unlikely that the most aggressive patients with dementia who were eligible for clozapine treatment would have been included in an RCT.

3. Results

We found one open-label prospective study (Chacko et al., 1995), six retrospective consecutive case series (Frankenburg and Kalunian, 1994; Friedman and Hershkowitz, 2022; Lee et al., 2007; Noorda et al., 2023; Salzman et al., 1995; Teodorescu et al., 2018), five retrospective case series (Greene et al., 1993; Oberholzer et al., 1992; Pitner et al., 1995; Sauvaget et al., 2009; Srinivasan, 1999) and fourteen case reports (Archie et al., 2013; Bastiampillai et al., 2009; Bhamra et al., 2018; Burke et al., 1998; Geroldi et al., 1997; Gupta and Johnson, 2022; Jha et al., 2015; Kohen et al., 2009; Majic et al., 2010; Nacasch et al., 1998; Solla et al., 2006; Štuhec, 2013; Thomas et al., 2006; van Waalwijk et al., 2020); see Supplementary Table 1). These studies covered a total of 115 patients with BPSD, with a mean age of 73.1 years, who were being treated with clozapine (mean dose 72.0 mg, median dose 50.0 mg). A daily dose of clozapine higher than 100 mg was prescribed for 13 of 69 patients (18.8 %).

3.1. Response

In general, response or improvement was ascertained retrospectively on the basis of case notes; prospective studies using validated questionnaires were exceptions (Bhamra et al., 2018; Chacko et al., 1995; Oberholzer et al., 1992). The researchers classified 73 of 99 cases (73.7 %) as responders or improved (see Supplementary Table 1 under broad inclusion criteria). If all cases of Lewy Body dementia or Parkinson's disease, schizophrenia or some other psychotic disorder preceding the dementia and patients without explicit reference to treatment-refractory BPSD are excluded (narrow inclusion criteria), the result is 36 of 46 cases (78.30 %). To reduce the risk of publication bias, we also analyzed only the consecutive case series (Lee et al., 2007; Noorda et al., 2023; Salzman et al., 1995; Teodorescu et al., 2018). We then found that the percentage of successful clozapine treatments for treatment-refractory BPSD is 76.3 % (29 of 38 cases; mean age 70.4 years; mean clozapine dose 56.0 mg). A retrospective consecutive case series of 27 patients also reports a significant reduction of physical restraint after treatment with clozapine (Teodorescu et al., 2018).

3.2. Discontinuation and rechallenge

In four studies clozapine treatment was discontinued after good results had been attained previously (see Supplementary Table 1). This led to a relapse in all ten patients, including in one prospective study with seven patients. In three of these studies clozapine was subsequently reintroduced, again resulting in a response in eight of nine patients (see Supplementary Table 1).

3.3. Side effects

Twenty of the twentysix publications report side effects in a patient group with a total of 108 patients (see Supplementary Table 1). These are largely consistent with the known side effects in patients with schizophrenia such as orthostasis, sedation, sialorrhoea, urinary incontinence and constipation (Gurrera et al., 2022). However, there are also some details which may be related to the frailty of this patient group: delirium or confusion was reported in seven patients, which in five cases led to clozapine being discontinued, but resolved in two after about a week of continued clozapine treatment, syncope or falls in four patients, two of whom stopped clozapine, and movement disorders such as ataxia, extrapyramidal symptoms or tremor and motor restlessness in four patients. In three patients clozapine was discontinued because of mild leukopenia and in one patient because of agranulocytosis.

3.4. Acceptability

The acceptability, that is, whether and for how long clozapine treatment is continued, gives an idea of the assessment of clinical effect as regards efficacy and tolerability. Follow-up at a mean of 8.4 months later found that 12 of 54 patients (22.20 %) had stopped taking clozapine (see Supplementary Table 1). The study by Teodorescu et al. (2018) has been omitted here because the patients were treated with clozapine for a maximum of eight days, until discharge, and then mostly put on other antipsychotics because of reimbursement problems in the outpatient situation.

4. Discussion

4.1. Evidence of effectiveness and limitations

Our analysis of case reports and case studies finds that about three quarters of patients with treatment-refractory BPSD respond favorably to treatment with clozapine. This effect corresponds with the efficacy of clozapine for psychosis in Parkinson's disease and the unique position of clozapine in treatment-refractory schizophrenia.

We think it is unlikely that the beneficial effect of clozapine on treatment-resistant BPSD is solely the result of sedation, because none of the publications suggests this, whereas they do sometimes refer to sedation as a side effect and occasionally clozapine is discontinued because of it (see Supplementary Table 1). In schizophrenia the anti-aggressive effect is actually independent of both sedation and the anti-psychotic effect (Krakowski et al., 2006). In animal research the anti-aggressive effect of clozapine has also been found independently of sedation (Gallitano-Mendel et al., 2008). In humans, clozapine also has an anti-aggressive effect in non-psychotic disorders (Frogley et al., 2012).

Of course, case studies and case series have a significantly higher risk of bias than RCTs and RCTs are needed for better evidence. On the other hand it seems very unlikely that an RCT among the most difficult-to-treat patients with therapy-refractory BPSD, who are also often legally incompetent, will be conducted in the near future.

We therefore believe that in the absence of RCTs, the findings summarized here, namely the effectiveness of clozapine in a substantial proportion of patients with treatment-refractory BPSD, the deterioration in patients' condition after discontinuation of clozapine and the improvement in most patients after restarting clozapine, constitute the lowest level of evidence in medical research.

4.2. Weighing risks

This does not alter the fact that caution is essential in the elderly and often frail patient population specifically, because of side effects such as constipation and urine retention, orthostatic hypotension and excessive sedation which may lead to a fall or to delirium, especially if the dose is increased too quickly (Seppi et al., 2011). Nevertheless, in the absence of placebo-controlled trials with clozapine in BPSD the tolerability results of two RCTs ($N = 50$ and 60 respectively) with low-dose clozapine (maximum 50 mg) in elderly outpatients with psychosis in Parkinson's disease and mean MMSE scores in the demented range are reassuring (Parkinson Study Group, 1999; Pollak et al., 2004). The clozapine group

did not show more drooling, constipation, orthostatic hypotension or lightheadedness, confusion or syncope in comparison to placebo (see Supplementary Box 2).

Of course when clozapine treatment is being considered, as is the case with all antipsychotics for BPSD, it must be borne in mind that there is a US Food and Drug Administration (FDA) black-box warning regarding the use of antipsychotics including clozapine in dementia-related psychosis, citing increased mortality in elderly patients with dementia (Meeks and Jeste, 2008). The North American package insert states that most of the deaths are caused by either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) diseases. It is therefore essential to provide the patient if mentally competent or otherwise their legal representative with information about off-label use, the weak evidence of efficacy and the side effects and risks, and to document their consent. The absolute risk of death resulting from the use of antipsychotics in general for BPSD is 1.1 % within 3 to 16 weeks (Mühlbauer et al., 2021).

With clozapine, many prescribers are also worried about a fatal complication due to agranulocytosis. However, if the mandatory granulocyte monitoring is carried out, this clozapine-specific risk is 1.3 per 10,000 patients (Myles et al., 2018). Another much-feared complication with clozapine is myocarditis. The incidence is probably higher in proportion to the speed of titration and the absolute death rate is 4.0 per 10,000 patients (outside Australia and New Zealand) (Siskind et al., 2020; de Leon et al., 2022). Obviously these risks are negligible in comparison with the above-mentioned general mortality rate resulting from the use of antipsychotics in patients with BPSD — a mortality rate that clinicians evidently thought was acceptable when they first treated these patients with a non-clozapine antipsychotic. A large cohort study of 137,713 new users of individual antipsychotics aged 65 years or over found no higher risk of death in the 90 days after cohort entry in 1267 clozapine users than in patients on other antipsychotics, including for example haloperidol or risperidone. This finding also applies to the patient group with dementia (Schmedt et al., 2016).

4.3. Titration

After a decision has been made to trial clozapine for treatment-refractory BPSD, the next question is whether the clozapine titration should take place in a clinical setting. Reasons to opt for this might be that the patient cannot be managed safely at home, for example if there is a high risk of sudden complications (syncope, epilepsy), or if the caregiver does not have the skills required to work together with the clinician. Joseph Friedman, co-author of the above-mentioned trial in outpatients with psychosis in Parkinson's disease, recommends against hospitalization, because the sudden change in environment often exacerbates or aggravates agitation and psychosis (personal communication, April 2023).

The prescribing clinician should evaluate the patient weekly in their office, with the patient's caregiver attending, paying close attention to the clinical effect and side effects of clozapine. On day 3 or 4 of the same week the clinician should phone with the patient's caregiver. On either occasion the clinician may decide to increase, maintain or decrease the clozapine dose. It should be possible for the caregiver to contact the clinician between appointments if necessary.

For patients with dementia, we would like to see a cautious clozapine titration schedule similar to that used for psychosis in Parkinson's disease, starting with a daily dose of 6.25 mg before night, followed, if necessary, by progressive dose increments twice a week (daily doses of 12.5, 18.75, 25, and 37.5) up to 50 mg. If a 6.25 mg dose is not available, the 25 mg tablets may be quartered. If the 50 mg dose is not effective enough, it can be increased further by 12.5 mg twice a week, as dictated by the clinical presentation.

Sometimes a limiting factor when Parkinson's disease patients start with clozapine is somnolence (Pollak et al., 2004), which should lead to slower increases in dose. In schizophrenia patients on clozapine, epileptic fits and ileus resulting from undertreated constipation have been reported. These risks are dose-dependent and are less likely with the usually low dosages and slow titration for BPSD. Bowel movement should be monitored during titration and constipation treated rigorously. A further preventive measure in order to reduce the risk of sedation, delirium, aspiration, pneumonia, syncope, orthostatic hypotension and falls is to first taper off any psychotropic drugs with sedative or anticholinergic properties, which are often prescribed in patients with BPSD. This step is especially important in patients with a high risk of these complications.

For the management of the agranulocytosis risk the usual blood tests should be carried out. With respect to the risk of myocarditis the International Adult Guideline for Making Clozapine Titration Safer advises monitoring C-reactive protein (CRP) during the first four weeks as well (de Leon et al., 2022). According to this guideline, at the first sign of abnormal CRP during the titration, clinicians need to rule out a co-occurring inflammation, particularly an upper respiratory infection, and should also consider a clozapine-induced inflammation caused by a titration that has been too fast for that specific patient. In the event of abnormal CRP during clozapine titration, 1) clinicians should not increase the dose and the titration should be maintained and 2) where possible, consider daily monitoring of CRP and troponin. If the CRP and troponin do not normalize, clinicians need to decrease the clozapine dose or even stop it.

5. Conclusion

We believe that a trial treatment with clozapine under close observation and granulocyte monitoring is permissible for treatment-refractory BPSD that is causing serious suffering for patients and those around them. During a trial treatment the effect and tolerability can be observed and a decision can then be made to continue or discontinue the treatment.

Contributors

I am the only contributor to the invited commentary on "Can clozapine be used for treatment refractory neuropsychiatric symptoms in dementia patients?"

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.07.004.

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