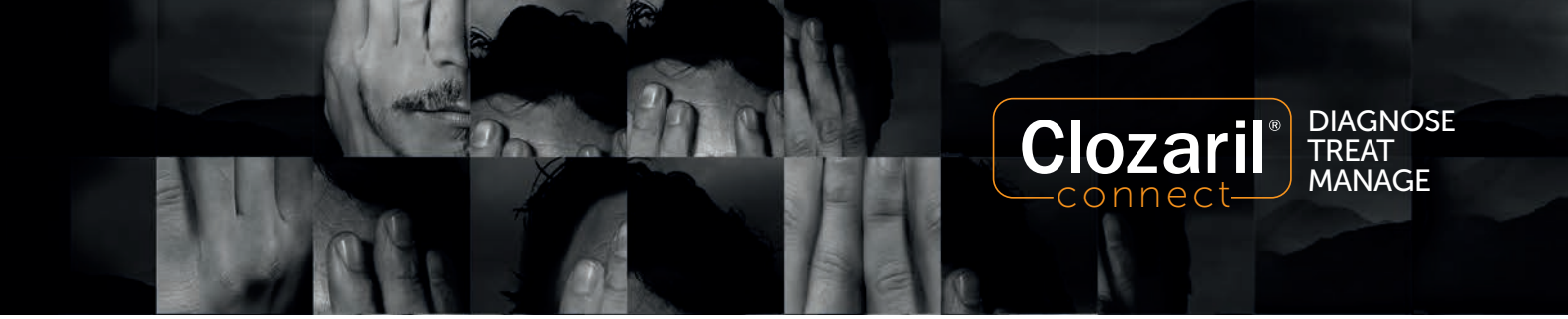


Use of clozapine in patients aged 60 years and older

The information in this document is not intended as a definitive treatment strategy, but as a suggested approach for clinicians. It is based on previous successful experience. Each case should, of course, be considered individually.

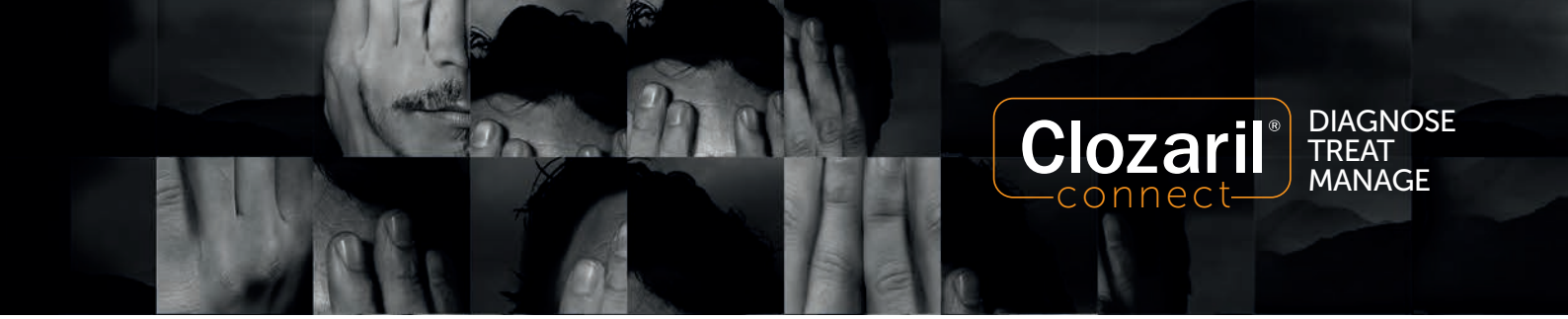
This information is provided for healthcare professionals and should not be used as a patient information leaflet.

The Summary of Product Characteristics (SPC) for Clozaril® (clozapine) states that Clozaril® is licensed for psychotic disorders of Parkinson's disease in cases where standard treatment has failed.[1,2]

Clozapine has been shown to be effective in treating elderly patients with schizophrenia.[3,4] However, patients aged 60 years and older are generally at more risk of adverse effects from medications due to the normal effects of ageing and the fact that they are much more likely to have medical problems. 80% of elderly patients have at least one chronic disease[5] and drug interactions are also more likely due to concomitant use of other medications.[5]

The ageing process can affect absorption, distribution, metabolism and clearance of drugs.[5] Drug absorption may be modified by reductions in both gastric acidity and splanchnic blood flow. Lean body mass and total body size decrease with ageing which means that there is a wider distribution of antipsychotics, and other fat-soluble drugs, which may take longer to clear.[5] A decline in liver and kidney function due to ageing may slow the elimination of drugs.[5]

Patients aged 60 years and older are particularly susceptible to extrapyramidal symptoms and tardive dyskinesia secondary to antipsychotics.[5] Given the low incidence of these adverse events with clozapine versus the typical antipsychotics, this is less likely to be a major issue. One small study evaluating clozapine usage in the elderly by Frankenburg *et al* (1994) demonstrated that pre-existing extrapyramidal symptoms and tardive dyskinesia improved after starting clozapine.[6] Another study evaluating patients with Parkinson's disease demonstrated improvements in parkinsonian tremor.[7]



Key side effects of clozapine to note in patients aged 60 years and older

Orthostatic hypotension: Patients aged 60 years and older may be more susceptible to clozapine-induced orthostatic hypotension and particularly if they have compromised cardiovascular function.[1,2] The risk of orthostatic hypotension is higher in patients who are taking other drugs which may cause this and these include antihypertensives, nitrates, antiparkinsonian medications and antidepressants. Cases of orthostatic hypotension are well documented in the literature. It often occurs very early on in treatment, including after the first dose and may be severe.[8,9] Concomitant use of additional medications, including benzodiazepines which impair balance,[10] may increase the risk of falls.

Agranulocytosis: Drug-induced blood disorders are more common in elderly patients[10] and increased age has been documented to be a higher risk for clozapine-induced agranulocytosis.[11,12] Munro *et al* (1999) suggested that in elderly patients, different pathways may be involved in clozapine metabolism and that these may cause increased haemopoietic toxicity, although in their study they found a decreased risk of neutropenia with age.[12]

Other side effects: Patients aged 60 years and older may be particularly susceptible to the anticholinergic effects of clozapine, such as urinary retention and constipation.[1,2] Confusion and drowsiness/sedation with clozapine may also be more likely in elderly patients.[13] Frankenburg *et al* (1994) reviewed the use of clozapine in eight patients over 65 years with treatment-resistant psychoses. Of these patients, six showed at least moderate improvement and two stopped treatment due to confusion and excessive sedation.[6]

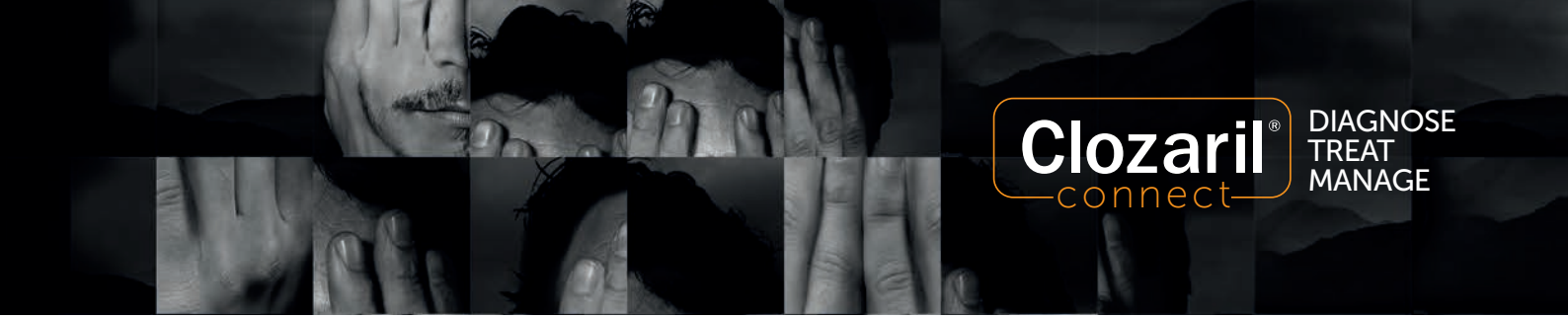
Management

In patients aged 60 years and older it is particularly important to consider any concomitant medical conditions prior to starting clozapine and review other medications if appropriate. Clozapine should be used with caution in patients with prostatic enlargement and narrow angle glaucoma due to its anticholinergic effects.[1,2]

The recommended dose for clozapine in patients aged 60 years and older is 12.5mg given once on the first day, with subsequent dose increments restricted to 25mg/day. However, one author noted that a starting dose of 6.25mg of clozapine may be more suitable for some elderly patients and close observation for the first 24 hours may be necessary especially in those patients with concurrent cardiovascular or cognitive impairment.[8] Slow titration of clozapine dose is recommended and, if side effects occur, it may be necessary to reduce the dose and/or speed of titration. Close monitoring of elderly patients is advisable and outpatient initiation may not be suitable for patients aged 60 years and older.

Chengappa *et al* (1995) reviewed the records of 12 female patients with psychoses all over 60 years of age, who had received clozapine.[9] Their findings confirmed the need for low dose initiation and slow titration. Patients who were titrated slowly tolerated the drug relatively well and remained on it, with clinical improvement over time whereas four of the six patients on standard titration experienced problems with postural hypotension and discontinued the drug.

In another review paper, Barak *et al* (1999) noted that elderly patients were managed on much lower maintenance doses than the average, with a mean dose in their review of 134mg/day and that most adverse events occurred in the first 90 days of treatment.[4]



In patients with Parkinson's disease monitoring of standing and supine blood pressure is necessary during the first weeks of treatment.[1,2]

As the dose of clozapine is increased, consideration should be given to the fact that patients aged 60 years and older, especially female ones, may have higher plasma levels than younger ones.[14]

In summary

Treatment with clozapine has been shown to be effective in patients aged 60 years and older in treatment resistant schizophrenia and psychosis occurring in Parkinson's disease. For each patient it is important to undertake a risk-benefit analysis to assess suitability. Careful management of dose and titration rates with monitoring for adverse effects, particularly in the early stages of treatment, may reduce the incidence and severity of side-effects.

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