

Safe use of clozapine in an aging population

Clozapine is arguably the gold standard antipsychotic and is the only one with proven effectiveness for people with treatment resistant schizophrenia. It has transformed the lives of many patients. However it is associated with a well-known range of challenging side effects.

In NHS GGC we have just under 1200 people receiving treatment with clozapine. Of that cohort 91 are currently between the ages of 66 & 80. The majority of these 91 individuals started clozapine treatment as adults. The number of people treated with clozapine graduating into older age is increasing. The purpose of this article is to remind prescribers of the challenges this may bring in maintaining good control of their mental health at a period in their lives where they are at greater risk of adverse effects from drug treatment.

Factors to consider

1. Pharmacokinetics and pharmacodynamics

As we age the way our bodies handle medicines may alter. Receptors may become more sensitive which may contribute to an increased incidence and severity of side effects.

Pharmacokinetics can be affected across all aspects i.e. absorption, distribution, metabolism and elimination. Increased volume of distribution combined with reduced hepatic metabolism may cause clozapine to be less well metabolised in older people in comparison to younger adults and this may lead to higher plasma levels and increased side effect burden.

Consequently there is a need to keep clozapine doses under review for elderly people and to consider more frequent plasma level monitoring.

2. Polypharmacy

With the increased incidence of physical illness in older people and consequent increased prescribing, polypharmacy and the risk of drug interactions increases. This will be true for clozapine patients too. Research suggests more than 45% of adults over the age of 75 attending A&E are taking 5 or more medicines regularly and 11% take 10 or more. Drugs that may increase hypotensive effects, worsen the risk of constipation or affect clozapine metabolism are of particular concern.

Reviewing the overall drug burden and seeking advice from pharmacy to support polypharmacy reviews is worth considering.

3. Side effects

Agranulocytosis/neutropenia

Agranulocytosis may occur more frequently in older people perhaps due to changes in clozapine clearance and influenced by polypharmacy. There is some contradictory evidence about the impact of age on neutropenia. Outcomes for older patients may be more severe. Effects on white blood cells are independent of dose and therefore dose reduction will not be protective.

The clozapine monitoring services however do not recommend altering the standard blood monitoring frequencies for older people.

Cardiac effects

Orthostatic (Postural) hypotension is commonly reported with clozapine and may impact older people more severely due to an increased risk of dizziness and falls. This may be compounded by polypharmacy. BP (sitting & standing) should be monitored more frequently for older people at least every time they attend for routine full blood counts and more often if they experience postural effects. This is a dose related side effect and therefore dose reduction may be necessary.

Tachycardia is very common in people prescribed clozapine. In most instances it is benign and not of concern however over prolonged periods it may result in further cardiac issues. If problematic cessation of clozapine treatment might be necessary.

Clozapine induced myocarditis may be more likely in older patients. Periodic monitoring of CRP and troponin is worthwhile in older patients.

Anticholinergic effects

Clozapine is a drug with significant anticholinergic effects and these effects may have significant impact on older people. Dry mouth, blurred vision, constipation, urinary retention and cognitive effects are of particular concern. The risk of cognitive decline and delirium should be considered in older people. Close monitoring is essential and review of clozapine treatment may be necessary.

Constipation

Constipation is a very common dose related side effect of clozapine that can have potentially fatal consequences. Older people are already at increased risk of constipation due to lower intestinal motility and the effects of polypharmacy.

Therefore higher vigilance for bowel issues is essential and proactive use of prophylactic laxatives is appropriate if dietary modification alone proves ineffective in resolving constipation. Ensuring they are maintained on the lowest effective clozapine dose is important too. Further advice is available via this link [Clozapine and Constipation | Right Decisions \(scot.nhs.uk\)](#)

Sedation

Persistent sedation is often seen in older people prescribed clozapine and often leads to clozapine discontinuation. It may lead to reduced alertness, confusion and an increased risk of falls.

Dose decreases or weighting doses to bedtime may help prevent daytime sedation.

Hypersalivation

Excessive salivation is seen across all ages prescribed clozapine and is dose dependent. In older people it may lead to an increased risk of aspiration pneumonia. Dose reduction may help. Use of anticholinergic agents in an attempt to dry up saliva is best avoided because of the adverse impact on cognition.

Metabolic side effects

Weight gain, impaired glucose tolerance, risk of developing type 2 diabetes and altered triglycerides are common risks associated with clozapine therapy. Continuing to monitor metabolic parameters throughout clozapine treatment remains important in older age. [Physical Health Monitoring \(Clozapine\) | Right Decisions \(scot.nhs.uk\)](#)

Management

Clozapine is as effective a treatment in older people as it is in others. The average dose seen across the 91 patients between the ages of 66 – 80 was 300mg per day (range 75 – 662.5mg). Ideally dosing should be minimised as people reach older age to help mitigate the adverse effects listed above.

If initiating clozapine in an older person a slow titration and reduced target dose (< 300mg) is appropriate.

For people prescribed clozapine graduating into old age the challenge is maintaining their mental health while minimising the issues described above. Reviewing their dose in light of potentially emerging side effects is important. Cautious planned dose reductions may be possible until the minimum safe and effective dose is established.

Doses above 200mg should be split as this may reduce the risk of orthostatic hypotension.

Clozapine plasma assay monitoring

With all the factors that may alter clozapine pharmacokinetics in older people assay monitoring for this patient group may be more important especially if concerns about dose related side effects emerge. Guidance on clozapine therapeutic drug monitoring may be found here [Therapeutic Drug Monitoring \(Clozapine\) | Right Decisions \(scot.nhs.uk\)](#)

MH Prescribing Management Group

October 2024