

Clozaril® and neuroleptic malignant syndrome

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.

Background

The Summary of Product Characteristics (SmPC) for Clozaril® (clozapine) states that Neuroleptic Malignant Syndrome (NMS) is an uncommon (>1/1,000 but <1/100) side effect.^{1,2}

NMS is a serious and potentially fatal symptom complex that has been reported in association with antipsychotic drugs. The incidence of NMS reported with antipsychotics is in the region of 1% and the mortality rate for untreated NMS is in the region of 20%.^{3,5} The incidence of NMS reported in patients on clozapine is similar, or possibly slightly less, than that seen with other antipsychotics (due to its lower D2 affinity).^{4,7} Cases have been reported in patients using clozapine either as monotherapy or more commonly, in combination with lithium or other central nervous system (CNS) agents, e.g., other neuroleptics.^{4,5,8}

Risk factors

NMS can occur at any stage of clozapine treatment,⁸ although the average onset is 4 to 5 days.³ and it has also been reported following abrupt discontinuation of neuroleptics.⁹ In one review of NMS, it was reported that 90% of cases of NMS occurred within the first 10 days.³ There appears to be an association with dose, with an increased risk reported in patients who are started on high doses or who undergo rapid dose titration, or in patients who have had a significant dose alteration.^{3,4,11} Males appear to have twice the risk compared to females.^{3,11} The median age reported in the literature is between 20-50, which may correlate with peak neuroleptic use.^{3,4,11}

Other risk factors/precipitating factors for NMS include:^{3,4,10,11}

- History of NMS
- History of organic brain disease or alcoholism
- History of Parkinson's disease/ Huntington's Chorea
- Hyperthyroidism
- Catatonia
- Dehydration
- Agitation
- Elevated temperature
- Rechallenge with suspect medication
- Abrupt cessation of anticholinergics
- Concomitant use of predisposing drugs (e.g., lithium)
- Low serum iron concentrations
- High potency neuroleptics
- Depots/IM neuroleptic injections
- Extrapyramidal side-effect/tardive dyskinesia

Diagnosis

Diagnostic evaluation of patients with NMS is complicated and is based on the history, clinical presentation and laboratory findings. It is important to exclude other drug-induced, systemic or neuropsychiatric illness, but the diagnosis must be considered in any patient presenting with the clinical features of NMS, including those with high fever.

Clinical manifestations may include:^{3,5,10,11}

- Hyperthermia/fever
- Muscular rigidity (lead-pipe)
- Altered mental status: confusion, agitation, or altered consciousness
- Evidence of autonomic instability: tachycardia, fluctuating blood pressure with hypertension or hypotension, diaphoresis (sweating, which may be profuse), or tachypnoea
- Laboratory findings can include leucocytosis, metabolic acidosis, increased creatine phosphokinase (CPK) or increased urinary myoglobin

Due to clozapine's different pharmacologic profile NMS may present atypically in clozapine-treated patients.^{4,7,10} There may be fewer motor abnormalities and a milder fever.

As mentioned above, diagnosis of NMS can be difficult, especially as clozapine-induced NMS may not present with all the classical features. Many of the symptoms, signs and laboratory findings seen in NMS are known adverse reactions to clozapine (e.g., fever, rigidity, confusion, agitation, tachycardia, hypertension, hypotension, disturbances in sweating, hypersalivation, incontinence, tremor, leucocytosis and increased CPK) and occur in the absence of NMS. Marked increases of CPK (mostly asymptomatic or less commonly associated with myopathy or rhabdomyolysis) which were not associated with NMS have been reported in patients on clozapine.¹²⁻¹⁴

Differential diagnosis

A number of other differential diagnoses need to be considered, including CNS infections; lethal catatonia; malignant hyperthermia; heat stroke; Serotonin Syndrome; or other drug reactions (e.g., lithium toxicity) or drug withdrawal syndromes.^{3,11,14}

It is important to review the complete clinical picture of any patient who presents with features of NMS or in whom a diagnosis of NMS is suspected.

Management

If diagnosis of NMS is confirmed, Clozaril should be discontinued immediately and appropriate medical measures should be administered.^{1,2} Specialist care will be needed. The patient should be given general supportive medical care as an in-patient. Particular attention should be paid to cooling the patient (antipyretics, cooling blanket), adequate rehydration with intravenous fluids and correction of electrolyte abnormalities.¹¹ There is no proven effective treatment for NMS. Most patients recover from NMS in 2-14 days without any cognitive impairment¹¹ although mortality from untreated NMS has been reported to be as high as 20%.³

Clozapine rechallenge following NMS

Rechallenge of patients with a history of antipsychotic-induced NMS (including clozapine-induced NMS) is not contraindicated with clozapine. However, the decision to rechallenge must be made following a careful risk-benefit assessment of each individual case.

Clozapine has been used in patients with a history of NMS secondary to typical antipsychotics and, due to its different pharmacological structure, is the recommended choice of some authors.¹¹ However, there are reports of patients with a history of NMS due to other antipsychotics who developed a further episode of NMS following treatment with clozapine.^{5,6,14} Successful rechallenge after clozapine-induced NMS has also been reported.^{5,7,8,14,15} Rechallenge should only be considered after full recovery from the NMS. Low dose restart and slow titration must be used while monitoring the patient carefully for side-effects.

References

1. Clozaril (clozapine) Summary of Product Characteristics (online). Mylan Products Ltd. <http://www.medicines.org.uk/emc/> (Accessed on 08/04/2020).
2. Clozaril (clozapine) Summary of Product Characteristics (online). Mylan IRE Healthcare Limited. <http://www.medicines.ie/> (Accessed on 08/04/2020).
3. Heiman-Patterson T. Neuroleptic Malignant Syndrome and Malignant Hyperthermia: Important Issues for the Medical Consultant. *Med Clin N Am* 1993; **77**(2): 477-489.
4. Amore M *et al.* Atypical Neuroleptic Malignant Syndrome Associated with Clozapine Treatment. *Neuropsychobiology* 1997; **35**: 197-199.
5. Reddig S *et al.* Neuroleptic Malignant Syndrome and Clozapine. *Ann Clin Psych* 1993; **5**: 25-27.
6. Sachdev P *et al.* Clozapine-Induced Neuroleptic Malignant Syndrome: Review and Report of New Cases. *J Clin Psychopharmacology* 1995; **5**: 365-371.
7. Cohen S. Successful Clozapine Rechallenge Following Prior Intolerance to Clozapine. *J Clin Psych* 1994; **55**: 498-499.
8. D'Silva K and Quinn P. Successful Clozapine Rechallenge in Atypical NMS. *Progress in Neurol and Psych* 2001; **5**: 26-27.
9. Amore M and Zazzeri N. Neuroleptic Malignant Syndrome after Neuroleptic Discontinuation. *Prog Neuro-Psychopharmacol and Biol Psychiat* 1995; **19**: 1323-1334.
10. Taylor D *et al.* The Maudsley Prescribing Guidelines in Psychiatry 13th Edition. Wiley-Blackwell. 2015.
11. Pelonero A *et al.* Neuroleptic Malignant Syndrome – A Review. *Psychiatr Serv* 1998; **49**: 1163-72.
12. Scelsa SN *et al.* Clozapine-Induced Myotoxicity in Patients with Chronic Psychotic Disorders. *Neurology* 1996; **47**: 1518-23.
13. Keshavan MS, Stecker J and Kambhampati RK. Creatine Kinase Elevations with Clozapine. *Br J Psychiatry* 1994; **164**: 118-20.
14. Hasan S and Buckley P. Novel Antipsychotics and the Neuroleptic Malignant Syndrome: A Review and Critique. *Am J Psychiatry* 1998; **155**: 1113-6.
15. Manu P *et al.* When can Patients with Potentially Life-threatening Adverse Effects be Rechallenged with Clozapine? A Systematic review of the Published Literature. *Schizophr Res* 2012; **134**(2-3): 180-186.

PRESCRIBING INFORMATION**CLOZARIL 25 mg Tablets****CLOZARIL 100 mg Tablets**

Please see Summary of Product Characteristics (SmPC) for full information before prescribing Clozaril.

The use of Clozaril is restricted to patients, physicians and nominated pharmacists registered with the Clozaril Patient Monitoring Service (CPMS).

In the UK a white cell count with differential count must be monitored:

- At least weekly for the first 18 weeks of treatment
- At least at 2-week intervals between weeks 18 and 52
- After 1 year of treatment with stable neutrophil counts, patients may be monitored at least at 4 week intervals

Monitoring must continue throughout treatment and for at least 4 weeks after discontinuation.

Blood clozapine level monitoring is advised in situations such as a patient ceases smoking or switches to e-cigarettes, when concomitant medicines may interact to increase clozapine blood levels, where poor clozapine metabolism is suspected, when a patient has pneumonia or other serious infection and in the event of onset of symptoms suggestive of toxicity.

Clozaril is associated with an increased risk of myocarditis and cardiomyopathy. If suspected Clozaril must be stopped immediately and the patient referred to a cardiologist and not re-exposed to Clozaril.

Presentations

Clozaril 25 mg Tablets containing 25 mg clozapine. Clozaril 100 mg Tablets containing 100 mg clozapine.

Indications

Treatment-resistant schizophrenic patients and in schizophrenia patients with severe, untreatable neurological adverse reactions to other antipsychotic agents, including an atypical antipsychotic agent prescribed for adequate duration. Psychotic disorders occurring during the course of Parkinson's disease, where standard treatment has failed.

Dosage and AdministrationTreatment-resistant schizophrenic patients

12.5 mg once or twice on the first day, followed by 25 mg tablets once or twice on the second day. Increase dose slowly, by increments (see SmPC). In most patients, antipsychotic efficacy can be expected with 200 to 450 mg/day given in divided doses. If dose does not exceed 200 mg/day, it can be given as a single administration in the evening. Once control is achieved, a lower maintenance dose may be effective. Treatment should be maintained for at least 6 months. Doses up to 900 mg/day can be used but the possibility of increased adverse reactions (especially seizures) occurring at doses over 450 mg/day must be considered.

See SmPC for details on re-starting therapy, ending treatment or switching from another antipsychotic.

Psychotic disorders occurring during the course of Parkinson's disease in cases where standard treatment has failed

The starting dose must not exceed 12.5 mg/day taken in the evening. Increase dose by 12.5 mg increments, with a maximum of two increments a week up to a maximum of 50 mg, preferably given as a single dose in the evening. The mean effective dose is usually between 25 and 37.5 mg/day.

The maximum dose of 100 mg/day must never be exceeded. Dose increases should be limited or deferred if orthostatic hypotension, excessive sedation or confusion occurs. Blood pressure should be monitored during the first weeks of treatment. When there has been complete remission of psychotic symptoms for at least two weeks, an increase in anti-parkinsonian medication is possible on the basis of motor status. Cautious titration and a divided dosage schedule are necessary to minimise the risks of hypotension, seizure and sedation.

Method of administration Clozaril is administered orally.

Switching from a previous antipsychotic therapy to Clozaril

It is generally recommended that Clozaril should not be used in combination with other antipsychotics. When Clozaril therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that the other antipsychotic should first be discontinued by tapering the dosage downwards.

Special populations: Hepatic impairment Patients with hepatic impairment should receive Clozaril with caution along with regular monitoring of liver function tests (see section 4.4 of SmPC).

Paediatric population No paediatric studies have been performed. The safety and efficacy of Clozaril in children and adolescents under the age of 16 years have not yet been established. Clozaril should not be used in this group until further data becomes available.

Patients 60 years of age and older Initiation of treatment is recommended at a particularly low dose (12.5 mg given once on the first day), with subsequent dose increments restricted to 25 mg/day. See SmPC for information on ending therapy.

Contraindications

Hypersensitivity to the active substance or to any of the excipients. Patients unable to undergo regular blood tests. History of toxic or idiosyncratic granulocytopenia / agranulocytosis (with the exception of granulocytopenia / agranulocytosis from previous chemotherapy). History of Clozaril induced agranulocytosis. Concurrent treatment with substances known to have a substantial potential for causing agranulocytosis; concomitant use of depot antipsychotics is discouraged.

Impaired bone marrow function. Uncontrolled epilepsy. Alcoholic and other toxic psychoses, drug intoxication, comatose conditions. Circulatory collapse and/or CNS depression of any cause.

Severe renal or cardiac disorders (e.g. myocarditis). Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure. Paralytic ileus.

Warnings and Precautions

Agranulocytosis: Before initiating clozapine therapy, patients should have a blood test and a history and physical examination. Clozaril can cause agranulocytosis, so is restricted to patients who have initially normal leukocyte findings (White Blood Cell (WBC) count > 3.5x 10⁹/l and Absolute Neutrophil Count (ANC) > 2.0x 10⁹/l), and in whom regular WBC counts and ANC can be performed within 10 days prior to starting Clozaril, weekly for first 18 weeks, thereafter at 4 week intervals throughout treatment and for 4 weeks after complete discontinuation.

Patients with history of cardiac illness or abnormal cardiac findings on physical examination prior to treatment should be referred to a specialist for other examinations that might include an ECG, and the patient treated only if the expected benefits clearly outweigh the risks. The treating physician should consider performing a pre-treatment ECG.

QT interval prolongation: As with other antipsychotics, caution is advised in patients with known cardiovascular disease or family history of QT prolongation. As with other antipsychotics, caution should be exercised when clozapine is prescribed with medicines known to increase QTc interval.

Cerebrovascular adverse events: Clozapine should be used with caution in patients with risk factors for stroke. Risk of thromboembolism: Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. If the diagnosis of NMS is confirmed, Clozaril should be discontinued immediately and appropriate medical measures should be administered. **Metabolic changes:** Atypical antipsychotic drugs, including Clozaril, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. **Hyperglycaemia:** Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. **Hepatic impairment:** Patients with stable pre-existing liver disorders may receive Clozaril, but need regular liver function tests. Liver function tests should be performed in patients in whom symptoms of possible liver dysfunction, such as nausea, vomiting and/or anorexia, develop during Clozaril therapy.

Prior to treatment initiation, physicians must ensure that the patient has not experienced an adverse haematological reaction to clozapine that necessitated discontinuation.

Immediate discontinuation of Clozaril is mandatory if either the WBC count is less than 3.0x10⁹/l or the ANC is less than 1.5x10⁹/l at any time during Clozaril treatment. Patients in whom Clozaril has been discontinued as a result of either WBC or ANC deficiencies must not be re-exposed to Clozaril. Following discontinuation of Clozaril, haematological evaluation is required until haematological recovery has occurred. **If Clozaril has been withdrawn and either a further drop in the WBC count below 2.0x10⁹/l occurs or the ANC falls below 1.0x10⁹/l the management of this condition must be guided by an experienced haematologist.** The patient should be educated to contact the treating physician immediately if any kind of infection, fever, sore throat or other flu-like symptoms develop. WBC and differential blood counts must be performed immediately if any symptoms or signs of an infection occur.

Low WBC count/ANC: If, during Clozaril therapy, either the WBC count falls to between 3.5x10⁹/l and 3.0x10⁹/l or the ANC falls to between 2.0x10⁹/l and 1.5x10⁹/l, haematological evaluations must be performed at least twice weekly until the patient's WBC count and ANC stabilise within the range 3.0-3.5x10⁹/l and 1.5-2.0x10⁹/l respectively, or higher.

Eosinophilia: Discontinuation of Clozaril is recommended if the eosinophil count rises above $3.0 \times 10^9 / l$; therapy should be restarted only after the eosinophil count has fallen below $1.0 \times 10^9 / l$.
Discontinuation of Thrombocytopenia: Clozaril therapy is recommended if the platelet count falls below $50 \times 10^9 / l$.
Cardiovascular disorders: Orthostatic hypotension, with or without syncope, can occur during Clozaril treatment. Rarely, collapse can be profound and may be accompanied by cardiac and/or respiratory arrest which is more likely to occur with concurrent use of certain medications (See SPC for more details) and during initial titration with rapid dose escalation. Patients starting Clozaril treatment require close medical supervision. Clozaril is associated with an increased risk of myocarditis, pericarditis/pericardial effusion and cardiomyopathy; and if suspected, Clozaril treatment should be promptly stopped and the patient immediately referred to a cardiologist. Patients with clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to Clozaril. In patients who are diagnosed with cardiomyopathy while on Clozaril treatment, there is potential to develop mitral valve incompetence, including mild or moderate mitral regurgitation. Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first two months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure or symptoms mimicking myocardial infarction. Flu-like symptoms may also be present.
Myocardial infarction (MI): There have been post marketing reports of MI which include fatal cases.
Epilepsy: Patients with a history of epilepsy should be closely observed during Clozaril therapy since dose related convulsions have been reported.
Hepatic impairment: Patients with stable pre-existing liver disorders or liver dysfunction need regular liver function tests. If the LFTs are elevated, discontinue Clozaril and resume only if LFTs return to normal.
Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics, including Clozaril. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using clozapine, is recommended.
Anticholinergic effects: Use with care in patients with a history of colonic disease, a history of lower abdominal surgery, glaucoma, narrow angle glaucoma, prostatic enlargement and in patients receiving concomitant medications known to cause constipation, megacolon and intestinal infarction/ischaemia, paralytic ileus.
Pyrexia: High temperatures should be evaluated carefully to rule out underlying infection, agranulocytosis or Neuroleptic Malignant Syndrome (NMS). If NMS is confirmed, discontinue Clozaril immediately and administer appropriate medical measures. Patients with rare hereditary problems of galactose intolerance should not take Clozaril. Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. Falls: Clozaril may cause seizures, somnolence and other conditions that could lead to falls. Fall risk assessments should be performed on patients with exacerbating conditions.
Risk of thromboembolism: Immobilisation of patients should be avoided due to reports of thromboembolism. Increased mortality in elderly patients with dementia.
Caution when prescribing to pregnant women. Mothers receiving Clozaril should not breast-feed. Adequate contraceptive measures must be ensured in women of childbearing potential. Neonates exposed to antipsychotic drugs (including Clozaril), during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress or feeding disorder. Consequently, newborns should be monitored carefully. Activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment.

Interaction with other medicinal products and other forms of interaction

Clozaril must not be used concomitantly with substances having a well-known potential to suppress bone marrow function. (See Section 4.3 of the SmPC, Contraindications). Long-acting depot antipsychotics (with myelosuppressive potential) must not be used with Clozaril because these cannot be removed from the body in situations where they may be required e.g. neutropenia. Alcohol should not be used with Clozaril due to possible potentiation of sedation.

Caution is advised if Clozaril is used concomitantly with other CNS active agents such as, MAOIs, perazine, SSRIs especially fluvoxamine, caffeine, CNS depressants including narcotics, antihistamines and benzodiazepines, Clozaril is used concomitantly with antihypertensive agents, highly protein bound drugs (e.g. warfarin and digoxin), phenytoin, lithium, rifampicin, valproic acid, noradrenaline [norepinephrine], adrenaline [epinephrine] or omeprazole. Cases have been reported of an interaction between citalopram and clozapine, which may increase the risk of adverse events associated with clozapine. The nature of this interaction has not been fully elucidated. Hormonal contraceptives (including combinations of estrogen and progesterone or progesterone only) are CYP 1A2, CYP 3A4 and CYP 2C19 inhibitors. Therefore initiation or discontinuation of hormonal contraceptives, may require dose adjustment of clozapine according to the individual medical need. In cases of sudden cessation of smoking, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects. See SPC for more details.

Fertility, Pregnancy and Lactation

Pregnancy: Caution should be exercised when prescribing to pregnant women. Neonates exposed to antipsychotics (including Clozaril) during the third trimester are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Lactation: Animal studies suggest that clozapine is excreted in breast milk and has an effect in the nursing infant; therefore, mothers receiving Clozaril should not breast-feed.

Fertility: Limited data available on the effects of clozapine on human fertility are inconclusive.

Women of child-bearing potential: A return to normal menstruation may occur as a result of switching from other antipsychotics to Clozaril. Adequate contraceptive measures must therefore be ensured in women of childbearing potential.

Ability to Drive and Operate Machinery

Owing to the ability of Clozaril to cause sedation and lower the seizure threshold, activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment.

Undesirable effects

Adverse reactions are ranked under headings of frequency. Very common ($\geq 1/10$), common ($\geq 1/100, < 1/10$), uncommon ($\geq 1/1,000, < 1/100$), rare ($\geq 1/10,000, < 1/1,000$), very rare ($< 1/10,000$), including isolated reports.

The most serious adverse reactions experienced with clozapine are agranulocytosis, seizure, cardiovascular effects and fever.

Very common: Drowsiness/sedation, dizziness, tachycardia, constipation, hypersalivation.

Common: Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis, weight gain, blurred vision, headache, tremor, rigidity, akathisia, extrapyramidal symptoms, seizures, convulsions, myoclonic jerks, ECG changes, hypertension, postural hypotension, syncope, nausea, vomiting, anorexia, dry mouth, elevated liver enzymes, urinary incontinence, urinary retention, fatigue, fever, benign hyperthermia, disturbances in sweating/temperature regulation, dysarthria.

Uncommon: Agranulocytosis, neuroleptic malignant syndrome, dysphemia, falls.

For details of rare, very rare and not known undesirable effects please refer to SmPC."

Package Quantities and basic NHS price

28 x 25 mg tablets : £2.95 ; 84 x 25 mg tablets : £6.30; 100 x 25 mg tablets : £7.50

28 x 100 mg tablets : £11.76 ; 84 x 100 mg tablets : £25.21 ; 100 x 100 mg tablets : £30.01

Supply of Clozaril is restricted to hospital pharmacies registered with the CLOZARIL Patient Monitoring Service.

Marketing Authorisation Holder

Mylan Products Limited, 20 Station Close, Potters Bar, Herts, EN6 1TL, UK.

Product Authorisation Numbers

25 mg tablets: PL 46302/0054

100 mg tablets: PL 46302/0057

Legal Category: POM

Further information is available in the UK from: BGP Products Ltd., Building Q1, Quantum House, 60 Norden Road, Maidenhead, Berkshire, SL6 4AY, UK.

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Reporting of adverse reactions:

Please continue to report suspected adverse drug reactions with any medicine or vaccine to the MHRA through the Yellow Card Scheme.

It is easiest and quickest to report adverse drug reactions online via the Yellow Card website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Alternatively, you can report via some clinical IT systems (EMIS/SystemOne/Vision/MiDatabank) or by calling the Commission on Human Medicines (CHM) free phone line: 0800-731-6789. Adverse reactions/events should also be reported to Viatris via cpms@viatris.com

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