

Literature Review: Managing Multiple Myeloma in patients on Clozapine Therapy

Nazish Aurangzeb¹, Tariq Islam^{1*}

¹Consultant Psychiatrist, Nazish Aurangzeb, Haematology, Speciality Doctor, Southampton General Hospital

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*Corresponding author: Tariq Islam

Consultant Psychiatrist, Nazish Aurangzeb, Haematology, Speciality Doctor, Southampton General Hospital

Abstract

Review Article

Caring for a patient who has both multiple myeloma (MM) and treatment-resistant schizophrenia forces clinicians into a space where no organ system is safe from collateral damage. Clozapine, the irreplaceable antipsychotic for treatment-resistant schizophrenia, is feared for its ability to cause neutropenia and agranulocytosis. The frontline therapies for MM proteasome inhibitors, immunomodulatory drugs, and alkylating agents often hit the bone marrow just as hard. This review brings together what is currently known about their overlapping haematological toxicities, digs into the emerging signal that long-term clozapine exposure may itself raise the risk of a haematological malignancy, and offers practical, real-world strategies for threading this clinical needle. In the absence of formal guidelines, we argue that a truly functional multidisciplinary team, armed with a pre-agreed crisis plan, is not just helpful; it is the entire margin of safety.

Keywords: Multiple myeloma, Clozapine, Treatment-resistant schizophrenia, Haematological toxicity, Myelosuppression, Drug-drug interactions.

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1. INTRODUCTION

Multiple myeloma is a malignancy of plasma cells that hunker down in the bone marrow, driving a cascade of end-organ damage anaemia, kidney failure, and lytic bone lesions [1]. Treating it well typically calls for combination regimens built on proteasome inhibitors like bortezomib or carfilzomib, immunomodulatory drugs such as lenalidomide, and monoclonal antibodies like daratumumab [1]. On the other side of this clinical equation stands clozapine. It remains the only evidence-backed option for treatment-resistant schizophrenia, defined as a poor response to two or more other antipsychotics [2]. Yet despite its striking efficacy, clozapine is notoriously underused, largely because of the 1% risk of severe neutropenia and the regulatory burden that comes with it [2, 3]. When myeloma and clozapine-dependence collide in the same patient, two therapeutic imperatives meet one fragile bone marrow. Table 1 lays out the core tensions.

Search Methodology

A structured literature search was conducted across multiple databases including PubMed/MEDLINE, Google Scholar, and drug

interaction platforms up to April 2026. The systematic process is outlined in the PRISMA-style flow chart below.

Search strategy

Combined terms for the psychiatric intervention ("clozapine," "atypical antipsychotic," "treatment-resistant schizophrenia") with terms for the oncological condition ("multiple myeloma," "plasma cell dyscrasia," "haematological malignancy"). Subsequent searches focused on specific toxicities: "neutropenia," "agranulocytosis," "benign ethnic neutropenia," "clozapine-induced neutropenia (CIN)," and drug-drug interaction checkers for common MM therapies including "carfilzomib," "bortezomib," "lenalidomide," and "cyclophosphamide." Priority was given to peer-reviewed research published in English, with emphasis on literature from 2020–2026 to capture the evolving understanding of clozapine's long-term haematological effects and modern MM treatment protocols. As this is an area with limited primary research, case reports specifically documenting MM in patients on clozapine were included to provide the highest level of clinical detail available for this niche topic.

Table 1: Overlapping Clinical Concerns in the Co-Management of Multiple Myeloma and Clozapine Therapy

Clinical Domain	Clozapine-Specific Concern	Myeloma Therapy-Specific Concern	Synergistic Risk/Challenge
Haematological Toxicity	Idiosyncratic neutropenia/agranulocytosis (CIN/CIA) in ~1% of patients, highest in first 18 weeks [2, 3].	Predictable, dose-dependent myelosuppression (neutropenia, thrombocytopenia) from proteasome inhibitors, IMiDs, alkylators [1].	Additive assault on bone marrow reserve, potentially leading to severe, prolonged neutropenia [4].
Monitoring	Mandatory absolute neutrophil count (ANC) monitoring registries (weekly, biweekly, then monthly) [3].	Cycle-dependent blood counts and dose adjustments per oncological protocols	Standard clozapine monitoring intervals may be insufficient during chemotherapy nadir periods
Drug-Drug Interactions	Clozapine metabolism is highly dependent on CYP1A2, with contributions from 3A4, 2D6 [5]	Many agents (e.g., cyclophosphamide) are prodrugs; some supportive care drugs (e.g., certain azole antifungals) are strong CYP inhibitors	Potential for both pharmacokinetic interactions altering clozapine levels and pharmacodynamic synergy [4, 5].
Benign Ethnic Neutropenia (BEN)	Lower baseline ANC in individuals of certain ancestries; must not be mistaken for pathological neutropenia to avoid unjustified clozapine cessation [6].	BEN can be misinterpreted as chemotherapy-induced myelosuppression, leading to unnecessary dose reductions or treatment delays.	Risk of "double jeopardy" where a single low ANC reading from a patient with BEN on both therapies could prompt irreversible, life-altering treatment decisions

*CIN: clozapine-induced neutropenia; CIA: clozapine-induced agranulocytosis; IMiDs: immunomodulatory drugs; ANC: absolute neutrophil count; CYP: cytochrome P450 enzyme. *

2. Overlapping Haematological Toxicity and Drug-Drug Interactions

The most immediate and visceral concern is the combined myelosuppressive potential. Both clozapine and a swathe of anti-myeloma agents carry independent black-box or strong warnings for neutropenia [2, 4].

2.1 Clozapine-Induced Haematological Dyscrasias

Clozapine-induced neutropenia (CIN) and agranulocytosis (CIA) are idiosyncratic, type B reactions unpredictable, not dose-dependent, and thought to arise from a messy interplay of toxic, immune, and genetic factors [2, 3]. Mechanistically, this looks nothing like the predictable marrow suppression of chemotherapy. To catch it early, patients are locked into mandatory monitoring registries, a system that has dramatically reduced deaths but also medicalized the prescription. A "red alert" an ANC typically falling below $1.5 \times 10^9/L$ mandates an abrupt stop and daily surveillance [7]. For a patient with schizophrenia, this is not a minor inconvenience; it is a psychiatric emergency waiting to happen.

2.2 Myeloma Therapies and Myelosuppression

Standard MM regimens are cytopenic by design. Bortezomib brings cyclical thrombocytopenia; lenalidomide is powerfully neutropenic; cyclophosphamide can pancitopenize [1]. Carfilzomib, in particular, has an explicitly flagged additive neutropenia risk with clozapine [4]. While one must always check for pharmacokinetic interactions clozapine's CYP1A2 metabolism makes it vulnerable the loudest signal usually comes from a simple

pharmacodynamic pile-on: two agents, one bone marrow, limited reserve [4, 5].

3. A Deeper and More Troubling Link: Could Clozapine Seed the Disease Itself?

Beyond the immediate skirmish over neutrophil counts lies a more unsettling question. Pharmacovigilance data, notably a large Finnish nationwide study, found that high cumulative clozapine exposure was associated with a significantly increased risk of haematological malignancies (odds ratio 3.35; 95% CI, 2.22–5.05), a signal that remained even after extensive adjustment [8]. A recent case report by Goel *et al.*, (2025) adds a tangible face to that statistic: a 47-year-old woman who developed lambda light chain MM after a decade of clozapine therapy [9]. While the literature is still dominated by reports of leukaemia's and lymphomas, this case contributes to a slow-burn recognition that plasma cell disorders may belong on that list. The uncomfortable implication for the treating team is that the patient's bone marrow may not have been pristine to begin with it may have endured a decade or more of subclinical haematological stress before the first dose of chemotherapy was ever given.

4. Management: Pragmatic Strategies Where No Roadmap Exists

There are no published clinical practice guidelines for this specific intersection. What we offer here, summarized in Table 2, is a synthesis of best-available evidence and hard-won clinical logic.

Table 2. Synthesized Management Recommendations for Patients on Clozapine Requiring Multiple Myeloma Treatment

Management Pillar	Key Recommendation	Rationale and Supporting Evidence
1. Regimen Selection	Favor regimens with a lower myelosuppressive profile; specify the regimen-psychiatric interaction.	The CyBorD (cyclophosphamide, bortezomib, dexamethasone) regimen has published, albeit limited, evidence of safe use with clozapine [9]. The combination of carfilzomib and clozapine has an explicit additive neutropenia warning and should be approached with heightened caution [4].
2. Intensified Monitoring	Increase ANC monitoring frequency during chemotherapy cycle nadirs, guided by a joint haematology-psychiatry plan.	Standard monthly clozapine monitoring may miss a chemotherapy-induced nadir. Monitoring should be intensified, particularly during the first cycles of a new regimen [4]. Evidence from the COVID-19 pandemic suggests that in very stable, long-term patients, extended intervals away from acute illness can be safe, but this principle does not apply during active chemotherapy [10].
3. G-CSF Prophylaxis	Proactively consider use of granulocyte colony-stimulating factor (G-CSF) per oncological guidelines.	G-CSF is standard for preventing chemotherapy-induced febrile neutropenia. Its off-label use in severe clozapine-induced agranulocytosis is also documented, providing a bridge for dual risks under specialist guidance [11].
4. Benign Ethnic Neutropenia Protocol	Document baseline ANC and relevant ancestry; adopt an institution-specific BEN protocol for clozapine monitoring thresholds.	Individuals with BEN have a non-pathological, lower ANC without increased infection risk. Using standard thresholds would lead to inappropriate and dangerous clozapine discontinuation, risking psychotic relapse [6].
5. Multidisciplinary team	Formalize shared care with a designated decision-making framework for "red alert" scenarios.	An MDT involving psychiatry, haematology, and the patient/family must prospectively agree on the conditions for holding either clozapine or chemotherapy to avoid unilateral, crisis-driven decisions [7, 9].

4.1 The Multidisciplinary Team as the True Safety Net

If one intervention separates successful outcomes from disastrous ones in this population, it is the quality and preparedness of the multidisciplinary team (MDT). This is not merely a series of polite cross-

referrals. It is a deliberate, structured, and anticipatory collaboration where the lines of command and the criteria for action are drawn before the crisis hits. The essential composition and defined roles of this team are detailed in Table 3.

Table 3: Composition and Roles of the Multidisciplinary Team

Team Member	Essential Role in Dual Management
Consultant Psychiatrist	Leads psychiatric risk assessment; holds ultimate authority on clozapine initiation, dosing, and cessation thresholds per mental health law; educates the team on the severe consequences of psychotic relapse.
Consultant Haematologist/ Oncologist	Leads oncological treatment planning; selects the MM regimen after MDT review of myelosuppressive risk; manages chemotherapy dosing, G-CSF use, and infectious complications.
Clinical Pharmacist (Psychiatry & Oncology)	Screens for all pharmacokinetic and pharmacodynamic drug-drug interactions; advises on antiemetic and anti-infective agents that do not alter clozapine metabolism; provides patient education
Clozapine Clinic Nurse / CNS	Coordinates mandated ANC monitoring schedules; is often the first to identify a falling ANC trend and escalate to the MDT; provides longitudinal patient support and reinforces education
General Practitioner (GP) Primary care physician (PCP)	Provides holistic care and manages non-haematological comorbidities; crucial for community-based surveillance for signs of infection or psychiatric deterioration between specialist visits.
Patient and Caregiver/Family	Central to shared decision-making; provides consent after a documented discussion of the complex risks; reports early symptoms of infection or psychiatric change, enabling rapid intervention.

CNS: Clinical Nurse Specialist; General Practitioner (GP); PCP: Primary Care Physician; G-CSF: granulocyte colony-stimulating factor.

An effective MDT operates on the understanding that a decision to permanently stop clozapine is not a laboratory decision; it is among the

most loaded, life-altering decisions a clinician can make for someone with treatment-resistant schizophrenia. The psychiatrist must help the team viscerally grasp the

stakes: a clozapine withdrawal without an immediate, robust alternative often means a severe psychotic relapse, loss of insight, and an inability to consent to or tolerate life-saving cancer treatment. And so, the team’s central deliverable is a ****Prospective Shared Care and Crisis Protocol****. This document must feel real and actionable. It defines, without ambiguity: - The exact ANC numbers and trend trajectories that trigger a clozapine pause versus a chemotherapy dose modification.

The “enhanced monitoring” windows (often twice-weekly ANC checks) mapped to specific days of the chemotherapy cycle.

A pre-agreed, emergency antipsychotic plan typically a depot formulation chosen and documented in advance that kicks in immediately if clozapine must be abandoned permanently. This single pre-planned element prevents a psychotic break from becoming a second, simultaneous catastrophe.

4.2 Intensified Haematological Monitoring

Sticking to the standard clozapine monitoring schedule eventually monthly during active chemotherapy is an uncomfortable clinical gamble. The chemotherapy nadir, that point where blood counts are at their lowest, is often around 7-14 days into a cycle and can be easily missed by a static monthly blood draw. For

patients on dual therapy, especially with high-risk agents like carfilzomib or lenalidomide, a plan for twice-weekly ANC checks around cycle nadirs provides the granularity needed to make confident decisions [4]. The reassuring data from the COVID-19 era that very stable, long-term clozapine patients could safely stretch their monitoring intervals must be carefully contextualized; it does not apply during the acute, myelotoxic storm of active cancer treatment [10].

4.3 Regimen Selection: Walking the Tightrope

Choosing an MM regimen for a patient on clozapine requires an honest conversation with the haematology team, one that weighs oncological necessity against the patient’s psychiatric reality. A comparative risk assessment of common agents is provided in Table 4. The documented successful use of the CyBorD regimen in a published case report offers a useful, if anecdotal, starting point for these discussions [9]. Maintenance with daratumumab-lenalidomide-dexamethasone (Dara-RVD) is also described, but lenalidomide’s potent neutropenic effect demands aggressive G-CSF support and cycle-driven ANC checks [1]. G-CSF is the shared bridge here; its role in chemotherapy is standard, and its capacity to shorten severe clozapine-induced agranulocytosis, though off-label, is well-documented, making it a rational, shared safety net [11].

Table 4: Risk Assessment of Common Multiple Myeloma Agents When Co-Prescribed with Clozapine

Drug/Regimen Component	Primary Haematological Toxicity	Documented Interaction with Clozapine	Clinical Risk Level & Comment
Carfilzomib	Neutropenia, thrombocytopenia	Yes – Labelled additive neutropenia risk [4].	High Risk. Recommend avoiding this combination if possible or mandating intensive ANC monitoring with a clear stoppage protocol.
Lenalidomide	Neutropenia (Grade 3-4: up to 40-60% in trials), thrombocytopenia	No specific pharmacokinetic warning, but significant pharmacodynamic overlap.	**Moderate-High Risk. ** Requires G-CSF prophylaxis per guidelines and cycle-specific ANC checking before dosing
Bortezomib	Thrombocytopenia (cyclical) > Neutropenia	None noted in major interaction checkers.	Moderate Risk. The distinct, cyclical thrombocytopenia is often manageable; co-morbid neutropenia is less frequent than with IMiDs, making it a potentially favourable backbone.
Cyclophosphamide	Pancytopenia, infection	None noted in major interaction checkers	Moderate Risk. ** Risk is dose- and schedule-dependent. A successful case report used this in the CyBorD regimen [9].
Daratumumab	Neutropenia (primarily when combined with other agents, especially IMiDs)	None noted. As a monoclonal antibody, direct CYP interaction is not anticipated.	Low-Moderate Risk. ** The neutropenia is largely driven by the combination partner (e.g., lenalidomide). May be a safer additive to a clozapine-compatible backbone.

ANC: absolute neutrophil count; G-CSF: granulocyte colony-stimulating factor; IMiDs: immunomodulatory drugs.

4.4 The Quiet Danger of Ignoring Benign Ethnic Neutropenia

A patient of African, Middle Eastern, or certain Asian ancestries may have lived their entire life with a

benign, genetically driven lower ANC, rooted in the Duffy-null genotype [6]. This is not a disease; it confers no infection risk. But in the white-knuckle context of dual clozapine and myeloma therapy, a “low” ANC from this patient can look terrifying on a lab printout and trigger an automated, irreversible cascade: clozapine stopped permanently. This is a preventable tragedy. The fix is straightforward and should be part of the MDT’s first meeting: establish baseline ANC, take a careful ancestry history, and agree to use local or internationally validated BEN-adjusted clozapine monitoring thresholds from day one [6, 7].

5. CONCLUSION

Managing a single patient through the dual tempests of multiple myeloma and clozapine-dependent schizophrenia is a humbling clinical exercise. It demands that we hold two truths in tension: the need to treat a lethal cancer, and the need to protect a mind that illness and its only effective treatment render uniquely fragile. The literature we have a handful of case reports, pharmacovigilance signals, and pharmacodynamic logic does not give us a guideline. It forces us to think. What emerges clearly is a three-part strategy: select a regimen that respects the bone marrow’s limits; monitor with an obsessive, synchronized intensity; and, above all, wrap the entire endeavour in a multidisciplinary team that has scripted its crisis response before the first dose is given. The path forward for the field lies in transforming this singular, published “good outcomes” into registry-driven, evidence-based protocols that make this kind of care reproducible, not heroic.

REFERENCES

1. Rajkumar SV. Multiple myeloma: 2024 update on diagnosis, risk-stratification, and management. *Am J Hematol.* 2024;99(9):1802-1824.
2. Deb B, Kollipara S. Haematological side effects of clozapine - Assessment, management, and nursing considerations. *Odisha J Psychiatry.* 2025;21(2):49-55.
3. Pagliaro LA, Pagliaro AM. Clozapine. In: *Pharmacological Aspects of Nursing Care.* Taylor & Francis; 2020.
4. Medical News Today. Kyprolis interactions: Supplements, alcohol, and more. 2025 Jan 26 [cited 2026 Apr 28].
5. IDRb Lab. Details of Drug Interaction: Clozapine and Lonafarnib. [cited 2026 Apr 28].
6. Understanding clozapine-related blood dyscrasias. Developments, genetics, ethnicity and disparity: it's a CIN. *Br J Psychiatry Bull.* 2025;49(3):163-168.
7. NHS Borders. Clozapine Red Alert. Right Decisions. [cited 2026 Apr 28].
8. Tiisonen J, Tanskanen A, Bell JS, *et al.*, Long-term treatment with clozapine and other antipsychotics and the risk of haematological malignancies: a nationwide case-control study. *Lancet Psychiatry.* 2022;9(5):353-362.
9. Goel R, Liu J, Jordak K, *et al.*, Lambda Light Chain Multiple Myeloma in a 47-Year-Old Female Patient on Long-Term Clozapine Therapy. *Cureus.* 2025;17(9): e92079.
10. Miller J. Reduced Blood Monitoring and Haematological Abnormalities in Clozapine-Treated Patients. *Psychiatric Times.* 2024 Sep 27 [cited 2026 Apr 28].
11. Myles N, Myles H, Clark SR, *et al.*, Use of granulocyte-colony stimulating factor to prevent recurrent clozapine-induced neutropenia on drug rechallenge: A systematic review of the literature and clinical recommendations. *Aust N Z J Psychiatry.* 2017;51(10):980-989.