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*BJPsych* Editorial

# Mortality associated with clozapine: what is the evidence?

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**Summary**

While clozapine has risks, relative risk of fatality is overestimated. The UK pharmacovigilance programme is efficient, but comparisons with other drugs can mislead because of reporting variations. Clozapine actually lowers mortality, partly by reducing schizophrenia-related suicides, but preventable deaths still occur. Clozapine should be used earlier and more widely, but there should be better monitoring and better management of toxicity.

**Keywords**

Clozapine; mortality; adverse drug reactions; safety; education and training.



It is undeniable that clozapine can lead to fatal outcomes if its toxic effects are not promptly identified and managed. While acknowledging the risks associated with clozapine, media reports can overestimate the number of fatal outcomes due to the drug. Such reports can alarm patients and their relatives and may prompt patients prescribed clozapine to discontinue their treatment and thus prevent them from using the best medication for the most difficult-to-treat psychosis, thereby increasing their risk of relapse.

This editorial aims to give a balanced summary of the evidence on the effect of clozapine on mortality, to inform evidence-based discussions about the risks and benefits of this medication.

We advocate for enhancing the skills and competencies of professionals managing clozapine and its side-effects. Practitioners should recognise clozapine toxicity and act quickly and effectively. This editorial does not have the scope to detail the management of each adverse effect. However, it strongly advocates for increased training in relation to the use of clozapine. We provide information on resources for professionals to increase their competencies in using clozapine safely.

## Clozapine in the UK – a brief history

Clozapine was first synthesised in 1958 and saw little clinical use until it was marketed in the early 1970s. In 1975, a few months after its launch in Finland, clozapine was observed to be associated with an increased risk of agranulocytosis. Nevertheless, it remained available off-licence in the USA, where it quickly gained a reputation for better treatment outcomes, culminating in the landmark trial by Kane and colleagues,[1] demonstrating its superior efficacy in treatment-resistant schizophrenia (TRS). This led to its reintroduction in the UK in 1990, with mandatory registration of all patients with a monitoring service that ensures that medication supply is contingent on continuing monitoring protocols and satisfactory white blood cell counts.

In the UK, clozapine is the only treatment licensed for TRS and is recommended by the National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN) and all major prescribing guidelines. Clozapine is also licensed, but much less commonly used, for psychosis in Parkinson's disease. Approximately 37 000 individuals are prescribed clozapine in the UK. Prescribers must register with a clozapine supplier and continued treatment is restricted to those shown to have undertaken preliminary and ongoing safety checks.

## Potentially fatal adverse effects of clozapine

Clozapine is associated with an increased risk of agranulocytosis, requiring regular mandatory haematological monitoring in the UK and most other high-income countries. This system has been remarkably successful in reducing deaths associated with agranulocytosis, with the risk of dying from the complications of this in clozapine-exposed patients estimated at 0.013% (just over 1 in 10 000).[2]

Other potentially fatal adverse drug reactions (ADRs) associated with clozapine and potentially conferring increased risks of mortality include myocarditis, seizures, paralytic ileus/constipation, pneumonia and pulmonary embolism. Chronic effects predominantly involve metabolic complications such as weight gain, type 2 diabetes mellitus, hyperlipidaemia and hypertension, among others. There is also emerging evidence linking clozapine to an increased risk of haematological malignancies. Practitioners should be familiar with the recognition and management of all these ADRs.

## Pharmacovigilance in the UK

The Medicine and Healthcare products Regulatory Agency (MHRA) oversees pharmacovigilance in the UK. It ensures product safety partly through 'yellow card' reports about potential medication–ADR links, which anyone can submit, including clinicians, patients, relatives, friends, coroners and the clozapine monitoring services. These reports do not imply causality but instead note observed medication–ADR associations, including fatalities.

Clozapine is treated differently from other drugs licensed in the UK. Because of the strict blood monitoring, each discontinuation is notified to the clozapine supplier, which reports to the MHRA. Hence, all fatalities on clozapine are reported to the MHRA, irrespective of the cause. No other widely used medication in the UK has all deaths reported to the MHRA in this way. This practice has resulted in an average of 410 reported clozapine-related deaths annually over the past 5 years (range: 293–473) (see https://info.mhra.gov.uk/drug-analysis-profiles).

This UK pharmacovigilance approach to clozapine is comprehensive, but can give the erroneous impression that clozapine-related adverse incidents are greater than expected if these figures are compared with either other medications in the UK or data from countries relying solely on clinician reports. A recent analysis of clozapine-related mortality between the UK and 11 Western European countries, using the World Health Organization's



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Adverse Drug Reaction database (VigiBase), illustrates this.[3] Mortality rates for clozapine in non-UK countries ranged between 1 and 10% of the rate reported for the UK. Indeed, the UK alone accounted for 29% of global clozapine mortality reports in the WHO VigiBase, whereas Germany, with a larger population and higher clozapine prescription rate, accounted for only 2%. An analysis of WHO clozapine pharmacovigilance data showed that between 2010 and 2019, the UK reported 968 fatalities (8 due to agranulocytosis), more than the total of 892 reported in the rest of the world combined.[4] These disparities illustrate how different reporting methods can grossly bias mortality data reported via pharmacovigilance.

## Schizophrenia and mortality

Despite efforts to reduce premature mortality in people diagnosed with schizophrenia, life expectancy remains significantly shorter than in the general population, typically by 15–20 years. A comprehensive meta-analysis[5] of 136 studies conducted between 1957 and 2021 showed that the all-cause mortality risk for people with schizophrenia is nearly three times higher (risk ratio = 2.94) than that for the general population. This increased risk is most pronounced among those in the early stages of a psychotic illness. This excess of deaths is greatest for suicide (risk ratio = 9.76), followed by natural causes (risk ratio = 2.16), with pneumonia presenting the highest risk among these (risk ratio = 7.00), alongside a general increased risk ratio for most organs and systems.

This large meta-analysis also indicated that antipsychotic treatment is associated with lower all-cause mortality risk in people with schizophrenia (risk ratio = 0.71) as compared with no antipsychotic treatment.[5] The greatest reduction in mortality from natural causes was seen in people treated with clozapine (risk ratio = 0.50). Nevertheless, several drug and non-drug factors contribute to the heightened mortality rates in this population.

## All-cause mortality in clozapine-treated patients

Given that clozapine is the most effective treatment for TRS and is thus likely to reduce deaths due to schizophrenia itself, how can we assess the balance between these mortality risks and benefits? To obtain an unbiased assessment, mortality of all causes must be measured in people with TRS in a defined population.

Perhaps the best study designs use whole-population databases, such as those completed in Sweden, Finland, Denmark and Taiwan (referenced studies can be found in the abovementioned 2022 meta-analyis[5]). The results of such studies are remarkably consistent: lower mortality in clozapine users compared with patients taking other antipsychotics. These studies also consistently report a reduction in schizophrenia-related suicides among clozapine users, which partly explains the paradoxical finding that medication with known risks of causing fatal adverse effects is associated with reduced mortality overall (notably, clozapine is approved by the US Food and Drug Administration for suicide prevention in schizophrenia, although this is not the case in the UK).

## UK studies of mortality in clozapine-treated patients

In the UK, whole-country studies are more difficult due to the lack of centralised health records. Still, large catchment area studies in South London have shown a lower mortality rate associated with initial clozapine treatment relative to other antipsychotic medications, similar to that seen in other studies, with a hazard ratio of 0.61.[6] An audit in Cambridgeshire[7] that analysed the causes of death using coroners' reports, post-mortem examinations and electronic health records showed that half of the clozapine deaths were deemed 'unexpected', mostly in relatively young individuals experiencing cardiovascular events, with a much smaller fraction attributed to other ADRs. Consistent with this, a study using coronial data for England and Wales[8] revealed 107 unintentional deaths attributed to clozapine toxicity (without other drugs present) between 1993 and 2019 (compared with 5375 fatalities among clozapine patients recorded in the MHRA system in the same period in the UK).

Nevertheless, despite the overall reduction in mortality, some individuals still face the risk of premature death on clozapine due to the drug itself, which might be prevented or delayed. It is outside the scope of this editorial to discuss the management of clozapine ADRs, but UK professionals can access the Royal College of Psychiatrists' continuing professional development online course dedicated to clozapine ADR (now open access on its CPD eLearning hub), the recommendations on clozapine from the Prescribing Observatory for Mental Health (POMH) programme as well as either through the sessions on treatment-resistant psychosis at the RCPsych International Congress, widely available treatment guidelines or open-access comprehensive reviews.[9]

## Conclusion

The UK pharmacovigilance system for clozapine is exceptionally rigorous. The clozapine blood monitoring system has been remarkably successful at preventing deaths associated with agranulocytosis, but the presence of the monitoring system means that all deaths on clozapine in the UK are automatically reported to the MHRA. Comparisons of the deaths reported to the MHRA with those of other medications can be misleading. Indeed, the evidence from many well-conducted studies firmly indicates that clozapine is associated with lower all-cause mortality compared with other antipsychotics. Nevertheless, some deaths on clozapine (as any other medication) are potentially preventable, and addressing this must be a priority.

Overall, the best way to reduce the excess mortality associated with schizophrenia is to ensure that clozapine is prescribed promptly where indicated. All such prescriptions must be monitored appropriately. This includes active discussion and screening for ADRs, physical health assessments, regular plasma clozapine measurements and improved training for psychiatrists, mental health workers, patients and carers, but also those in primary and tertiary care who contribute to patient care. We expect that better monitoring will reduce clozapine-related ADRs. This could lead to an increase in the prescription of clozapine, the only drug offering significant hope for those suffering from TRS.

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## Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.


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