247 - Summary

Summary

Schizophrenia and related psychoses CHAPTER 1 Clozapine: serious haematological adverse effects Agranulocytosis Clozapine is a somewhat toxic drug. Despite this, clozapine reduces overall mortality in schizophrenia,1 in part owing to a reduction in the rate of suicide.2–4 Non-clozapine antipsychotics also reduce natural-cause mortality,5 possibly because of improved adherence to cardiometabolic medication.6 Clozapine is more effective than any other antipsychotic in this regard.6 Clozapine can cause serious, life-threatening adverse effects, of which agranulocytosis is the best known, and which is seen in 0.4% of patients.7 The incidence of death related to agranulocytosis following clozapine prescription is 0.013%, with a case fatality rate for agranulocytosis of 2.1%.8 Risk is clearly well managed by the approved clozapine monitoring systems. The incidence of severe neutropenia declines to negligible levels after the first year of treatment.8 Successful rechallenge after neutropenia occurring during clozapine treatment may be possible,9 but rechallenge should not be attempted after confirmed clozapine-related agranulocytosis.10 Most neutropenia occurring in the context of clozapine treatment is coincidental to the use of clozapine.11 Distinguishing between benign, clinically insignificant neutropenia and clozapine-related life-threatening agranulocytosis (CRLTA) is vital. CRLTA is usually characterised by a continuous and rapid neutrophil count decline to zero, or near zero, mostly within the first 18 weeks of clozapine treatment. A prolonged nadir and delayed recovery (range 4–16 days) follow12 unless GCSF is given. Non-CRLTA episodes are more often brief, show a non-continuous and/or slow decline in neutrophils, or have an obvious cause that is not clozapine.12,13 However, if clozapine is withdrawn very early, the typical catastrophic fall in neutrophil counts may not develop.13 Distinguishing between non-clozapine-related neutropenia and CRLTA is difficult, but cases can usually reliably be classified as non-CRLTA, possible CRLTA and definite CRLTA. The mandatory threshold-based method of detecting agranulocytosis has a very low specificity for CRLTA – the system creates a huge number of false positives. Pattern- based criteria based on the above factors are more specific without loss of sensitivity.14 Misdiagnosing benign neutropenia as CRLTA has resulted in many thousands of patients being denied access to clozapine.11 The most common reason for misdiagnosis is the failure to detect BEN.15 Summary ■ ■Overall mortality is lower for those on clozapine than in schizophrenia as a whole. ■ ■Risk of fatal agranulocytosis is less than 1 in 8,000 during standard monitoring. ■ ■Real clozapine-related agranulocytosis usually follows a distinctive, catastrophic pattern. ■ ■Pattern-based criteria are more specific for clozapine-related agranulocytosis than standard threshold-based monitoring.

Revision #1
Created 2026-01-04 20:13:26 UTC by Omar Ayman
Updated 2026-01-04 20:13:26 UTC by Omar Ayman