Application for inclusion of antipsychotic and antidepressant drugs – comments with reference to clozapine.

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Introductory comments
Clozapine is one of six antipsychotic drugs proposed for addition to the Essential Drugs List by Dr Dale L. Johnson, President, World Fellowship for Schizophrenia and Allied Disorders. The application cites only limited results of clinical studies to support the efficacy of clozapine, but notes that “Clozapine is especially important because it is effective with about one-third of cases who are not helped with other antipsychotic medications.” This commentator agrees that clozapine has this reputation in developed countries and has no reason to doubt its usefulness. Clozapine does, however, have a number of safety issues unique to it amongst the currently available antipsychotic drugs.

Safety issues.
1. Agranulocytosis  The application states that “A major side effect for clozapine is agranulocytosis. This blood condition occurs in about 1 patient per 1000, and is therefore, quite rare, but because it may result in death patients who take clozapine must have their white blood cell counts checked at regular intervals, typically weekly in the early stages of treatment. Most health authorities change the blood tests to every two weeks or once a month after several months of early treatment.”

The incidence of severe agranulocytosis is higher than stated in the application. An estimate of severe agranulocytosis developing in about 0.8% of patients treated with clozapine in widely quoted. A similar incidence has been reported recently from a company-sponsored monitoring programme in Mexico. The following Table reproduces the incidence (per thousand patient years) of agranulocytosis in the USA, UK and Australia, reported by Novartis to a US Food and Drug Administration Advisory Committee in June 2003.

<table>
<thead>
<tr>
<th>Duration of clozapine treatment</th>
<th>Incidence of clozapine-induced agranulocytosis (per 1000 patient years)</th>
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<tbody>
<tr>
<td>0 – 18 weeks</td>
<td>United States 7.77, United Kingdom 21.37, Australia 8.27</td>
</tr>
<tr>
<td>18 – 52 weeks</td>
<td>United States 0.83, United Kingdom 1.44, Australia 2.17</td>
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<tr>
<td>&gt; 52 weeks</td>
<td>United States 0.37, United Kingdom 0.7, Australia 0.52</td>
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A mortality rate from agranulocytosis of 3% to 4% (11 of 310 affected patients) is also quoted widely, but it should be noted that the source of this figure was an oral communication from a doctor at the innovator pharmaceutical company in February.
1994. Details of the basis for this estimate were not published, but it is almost certainly derived from a cohort of clozapine users who were participating in a monitoring programme. When used initially in the early 1960’s without regular white cell monitoring, the mortality from agranulocytosis was much higher – a figure of 50% mortality in 16 cases in Finland has been reported. 

The haematological monitoring protocol used in the State of Victoria, Australia has been published:

“The current haematological monitoring protocol stipulates that a blood sample be collected within 10 days prior to initiating clozapine and WBCs and neutrophils counted. Results are categorised as being in the ‘green range’ when the WBC count is >3.5 \( \cdot \) 10^9/L and the neutrophil count is >2.0 \( \cdot \) 10^9/L; in the ‘amber range’ when the WBC count is between 3.0 and 3.5 \( \cdot \) 10^9/L and/or neutrophil count is between 1.5 and 2.0 \( \cdot \) 10^9/L; in the ‘red range’ when the WBC count is <3.0 \( \cdot \) 10^9/L and the neutrophil count is <1.5 \( \cdot \) 10^9/L. Patients whose results are within the green range may apply to register and clozapine may be initiated at this point. Patients whose results are within the amber range must have a repeat blood test after 1 week. If the results of the second blood test are within the green or amber range the patient may first apply to register. Patients are not eligible for treatment with clozapine if the results of their blood tests are within the red range, or if they are identified during the registration process, by checking on a government maintained database, as having previously had a result in the red range. According to the current haematological monitoring protocol, patients are informed about the warning signs of neutropenia and impending agranulocytosis, including flu-like symptoms, mouth ulcers, sore throat or fever. WBC and neutrophil counts should be conducted 7 days after initiating clozapine treatment, then weekly for the first 18 weeks and every 28 days after the first 18 weeks of treatment. A result in the amber range requires initiation of twice-weekly blood testing until results return to the green range. A result in the red range requires immediate discontinuation of clozapine treatment.”

2. Myocarditis and cardiomyopathy

Myocarditis and cardiomyopathy associated with clozapine were described in Australia in 1999. A review of 116 cases of suspected myocarditis associated with clozapine reported spontaneously to the national pharmacovigilance centre in Australia from 1993 to 2003 found a median age of 30 years (SD 11.1 years) compared with a median age of 37 years of clozapine users in a registry of patients maintained by one of the companies supplying clozapine in Australia. Myocarditis developed within a median 16 days of commencing clozapine with 80.2% developing myocarditis within 6 months. More than 90% of the cases were prescribed clozapine within the dose range 100mg/day to 450 mg/day. 51.8% of the 116 patients recovered and 10.3% were known to have died. The outcomes of the remaining 38% were either unknown or described as “not yet recovered”.

The incidence of myocarditis was estimated in the Australian review as being between 0.7% and 1.2% of treated patients. This is considerably higher than that reported following a review of reporting to the US Food and Drug Administration. The FDA estimate was conservative, assuming that all patients had taken clozapine for at least one month and including only 5 cases with autopsy-confirmed myocarditis during the first month of therapy. The incidence of fatal myocarditis in the first month of therapy was estimated as 321 per million person-years of observation, which still greatly exceeds the background rate of 4 per million per year. The authors commented that although the risk of fatal myocarditis is greatest in the first month of treatment with clozapine, it is not limited to this period, and patients may be at increased risk as long as they are taking the drug.
“The initial symptoms may be non-specific, such as tachycardia, fever, and flu-like symptoms. These initial symptoms can overlap considerably with those of other cardiac and non-cardiac conditions, including neuroleptic malignant syndrome (NMS), which may itself be caused by antipsychotics. Prescribers should be aware that potentially fatal myocarditis may develop early after the commencement of clozapine. Patients who develop persistent tachycardia, arrhythmias, shortness of breath or other signs of heart failure, or unexplained fatigue, chest pain or fever, should be evaluated urgently for the presence of myocarditis. Strong consideration should be given to ceasing clozapine while suspicious symptoms and signs are evaluated. If myocarditis is confirmed, clozapine should be discontinued.”

Cardiomyopathy, which is typically a chronic disorder and clinically distinct from myocarditis, has also been associated with use of clozapine.

3. Clozapine gastrointestinal obstruction
The United Kingdom regulatory authority warned in 1999 about the potential consequences of constipation caused by clozapine, following the receipt of twenty reports of gastrointestinal obstruction. Three of the affected patients had died. The authority recommended that patients should be encouraged to adopt measures which may prevent constipation, such as high fibre diet and physical exercise. A similar warning was published in the same year by the Australian Adverse Drug Reactions Advisory Committee. There had been nine reports of severe constipation due to clozapine, including four with faecal impaction. One Australian patient had died, probably as a result of inhalation of faeculent vomitus secondary to faecal impaction. The New Zealand regulatory authority issued a warning in 2007, after four reports of death from complications of severe constipation, such as bowel perforation and toxic megacolon. The problem was also highlighted more recently by the Singapore Health Sciences Authority.

Conclusion
Clozapine is a very useful drug for the treatment of psychotic illnesses not responding to other therapies. Even when taking relatively effective medications such as clozapine, however, patients with psychotic illnesses may have less than optimal ability to care for themselves. Because of the drug’s association with agranulocytosis, safe use can only be achieved when patients have regular white cell counts, initially each week. The associations with myocarditis and bowel obstruction secondary to severe constipation require regular interaction of patients with doctors, nurses or other healthcare providers trained to have a high index of suspicion for these problems. Use of clozapine in the absence of robust haematological monitoring and patient supervision will be accompanied by unacceptable mortality.

References


