Beyond White Blood Cell Monitoring: Screening in the Initial Phase of Clozapine Therapy

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ABSTRACT

Objective: Clozapine is the preferred option for treatment-resistant schizophrenia. However, since 1975, clozapine has been known to cause agranulocytosis. In the clozapine screening guidelines, white blood cell count is mandatory. In the past 20 years, after its reintroduction, 3 other serious side effects, namely, diabetic ketoacidosis, gastrointestinal hypomotility, and myocarditis have been documented but have so far failed to be incorporated in the screening guidelines. The objective of this review is to determine whether an update of the screening guidelines for serious side effects with clozapine is evidence based.

Data Sources: The English-language literature, available via MEDLINE or PubMed, on the incidence of 4 clozapine-related side effects, using *clozapine, agranulocytosis, diabetic ketoacidosis,* and *gastrointestinal hypomotility* as keywords, that have been published over the period 1976–2010, was collected.

Study Selection: 16 studies that provided incidence rates or data from which these rates could be calculated were included.

Data Extraction: We compared 1-year incidence rates, mortality rates in the whole study population and in the affected cases. When rates reflected longer periods of observation, the given rate was recalculated to obtain a 1-year incidence rate.

Results: The incidence of clozapine-induced agranulocytosis varies between 3.8‰–8.0‰. The mortality rate is 0.1‰–0.3‰, and the case-fatality rate is 2.2‰–4.2‰. In diabetic ketoacidosis, the incidence was calculated at 1.2‰–3.1‰, and the case-fatality rate was 20%–31%. In gastrointestinal hypomotility, the incidence was 4‰–8‰, and the case-fatality rate was 15%–27.5%. The discrepancy in incidence rates between Australia (7‰–34‰) and the rest of the world (0.07‰–0.6‰) impairs a general approach of this side effect.

Conclusions: In 2 of the 3 studied side effects, diabetic ketoacidosis and gastrointestinal hypomotility, reduction of mortality to the level of agranulocytosis is both necessary and feasible. In order to obtain this outcome, the screening guidelines need to be modified; early detection of treatment-emergent hyperglycemia, that might—via diabetes mellitus—develop into diabetic ketoacidosis, requires *obligatory monthly measurement of fasting plasma glucose*. To prevent gastrohypomotility, and complications therefrom, the clinician should be required to choose between either weekly monitoring or standard coprescription of laxatives for prevention. The reported incidence of myocarditis (high in Australia, low in the rest of the world) is too divergent to allow for an overall recommendation outside Australia.

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See also Commentary on page 1313.

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Following the introduction of clozapine in Finland in 1975, 18 patients treated for schizophrenia developed severe hematologic complications, 8 of whom died of agranulocytosis. This prompted the withdrawal of clozapine from the market, both nationally[1] and internationally. However, a double-blind, randomized comparator study[2] with chlorpromazine showed clozapine to be superior for the treatment of treatment-resistant schizophrenia. This finding resulted in the reintroduction of clozapine, with mandatory weekly monitoring of blood cell counts during the initial phase of treatment—18 weeks in Europe[3] and 26 weeks in the United States[4]—and monthly monitoring thereafter. The superior therapeutic effect of clozapine was confirmed in comparison with second-generation antipsychotics.[5–7] However, despite its efficacy, clozapine is considered a dangerous drug because of the serious side effect agranulocytosis, which, in most cases, develops in the initial phase of treatment.[8] Two epidemiologic studies have reported a lower mortality with clozapine than with first-generation antipsychotics[9,10] and second-generation antipsychotics,[10] but these findings have not been verified.[11] Moreover, the study by Tiihonen et al[10] has been criticized on methodological grounds.[12] Thus, for the moment, it is unclear whether clozapine use is associated with a lower or higher mortality.

After clozapine's reintroduction, however, 3 other new, rare, but potentially fatal side effects of clozapine have been identified, namely, diabetic ketoacidosis, gastrointestinal hypomotility, and myocarditis. Like agranulocytosis, diabetic ketoacidosis and myocarditis mainly develop in the first phase of treatment, whereas only in a minority of cases (36.3%) does gastrointestinal hypomotility develop in the first 4 months of treatment.[13] Current monitoring protocols do not cover these complications,[14,15] and the question is whether screening for these potentially fatal complications should be incorporated into the clozapine treatment protocol. This review discusses the incidence and mortality of agranulocytosis and the need for guidance on monitoring and risk management for other potentially fatal complications.

DATA SOURCES

The English-language literature available via MEDLINE or PubMed was searched over the period 1976–2010 for studies on the incidence of 4 clozapine-related side effects, using *clozapine, agranulocytosis, diabetic ketoacidosis,* and *gastrointestinal hypomotility*.

Clinical Points

- Screening guidelines during the initial phase of treatment with clozapine have been restricted to the obligatory white blood cell monitoring. We propose 2 revisions, both extensions, of the existing screening guidelines.
- First, monthly screening of fasting plasma glucose should be obligatory in the first 3 months of clozapine therapy.
- Second, monitoring of gastrointestinal hypomotility should become an integral part of regular screening, not only in the initial but also during the maintenance phase.
- Screening for myocarditis or cardiomyopathy is, outside Australia and New Zealand, not evidence based.

STUDY SELECTION AND DATA EXTRACTION

Sixteen studies that provided incidence rates or data from which these rates could be calculated were included.

We compared 1-year incidence rates, mortality rates in the whole study population, and mortality rates in the affected cases. When rates reflected longer periods of observation, the given rate was recalculated to obtain a 1-year incidence rate.

RESULTS

Agranulocytosis: Incidence and Mortality

Agranulocytosis is characterized by a total leukocyte count lower than 3.0×10^9/L and a granulocyte count lower than 1.5×10^9/L. Granulocyte counts lower than 0.5×10^9/L result in a severely compromised resistance, such that the risk of fulminant and fatal infections is greatly increased. It is not easy to calculate the annual incidence of agranulocytosis for 2 reasons. First, agranulocytosis does not occur at a constant rate throughout treatment. Of the cases of agranulocytosis reported in 1 study,[16] 95.9% (70 of 73) occurred within the first 26 weeks of treatment and 4.1% (3 of 73) in the second 26 weeks; a second study[17] found that 89.6% (43 of 48) of the cases occurred within the first 18 weeks of treatment and 10.4% (5 of 48) in the remaining 34 weeks. Second, the dropout rate during clozapine treatment is substantial. Of 11,555 patients included in the study, 11,033 were still participating at 1 month, 8,608 at 3 months, and 5,780 at 6 months.[16] For these reasons, it is more appropriate to report cumulative incidence rather than the annual incidence.

The incidence of clozapine-induced agranulocytosis, based on 4 studies involving a total of 130,133 patients, varies between 3.8‰—in by far the biggest study (N = 99,502)[18]—and 8.0‰. However, it should be noted that the mandatory nature of white blood cell monitoring means that, in some cases, clozapine might be withdrawn before agranulocytosis develops, when patients are mildly leukopenic. In other words, the real-life incidence of agranulocytosis is probably higher than that reported in the literature. The mortality rate is 0.1‰–0.3‰ and the case-fatality rate is 2.2%–4.2% (Table 1).

Diabetic Ketoacidosis

Diabetic ketoacidosis is characterized by the triad of hyperglycemia, anion gap metabolic acidosis, and ketonemia. Metabolic acidosis is often the major finding. The serum glucose concentration is usually higher than 500 mg/dL (27.8 mmol/L) but lower than 800 mg/dL (44.4 mmol/L). However, serum glucose concentrations may exceed 900 mg/dL (50 mmol/L) in patients with diabetic ketoacidosis who are comatose.[19]

The incidence and mortality of diabetic ketoacidosis were investigated in 3 studies (Table 2). In a large study,[20] the prevalence of the number of patients hospitalized for diabetic ketoacidosis was investigated in 56,849 nondiabetic patients with schizophrenia who had at least 3 months of stable antipsychotic monotherapy. The authors calculated the annual incidence of diabetic ketoacidosis by multiplying the prevalence of diabetic ketoacidosis by a factor of 0.6. This is the same factor used to calculate the annual incidence of diabetes mellitus (4.4%) on the basis of the prevalence of new-onset diabetes mellitus (7.3%). In this way, the annual incidence of diabetic ketoacidosis was calculated at 1.2‰, based on a diabetic ketoacidosis prevalence of 2‰. In 2007, Henderson et al[21] reviewed the records of all patients admitted to a hospital in Boston, Massachusetts, over a 7-year period for diabetic ketoacidosis, comparing patients with schizophrenia with the general population. The 7-year incidence of diabetic ketoacidosis was 2.2%, giving an annual incidence of 0.31% (3.1‰). Koller et al[22] used data from published articles or case reports on new-onset or exacerbations of existing diabetes mellitus to determine the mortality rate of diabetic ketoacidosis in clozapine-treated patients with or without diabetic ketoacidosis. Because the data came from an era when it was not routine practice to screen fasting glucose levels, the calculated incidence rates are probably not reliable because of potential underreporting. The incidence of diabetic ketoacidosis in clozapine-treated patients with schizophrenia was calculated at 1.2‰–3.1‰, much higher than the general population incidence of 0.4‰ in the United States[23] and 0.1‰ in Denmark.[24] The case-fatality rate of diabetic ketoacidosis in patients with schizophrenia was also much higher (20%–31%) than in the general population (4%).[24] A source for mortality rates of diabetic ketoacidosis in the United States comparable to the one calculated by Henriksen et al[24] for Denmark has not been found and is probably not available. The Centers for Disease Control and Prevention comes nearest to providing that information.[23]

Gastrointestinal Hypomotility

In gastrointestinal hypomotility, diminished propulsive activity in the intestines leads to constipation. Constipation is a common side effect of clozapine. A study[25] involving 479 patients monitored for 104 weeks revealed that 25.1% of the patients taking clozapine reported being constipated. In rare

Table 1. Agranulocytosis: Cumulative Incidence (per 1,000 patients) and Mortality

		Agranulocytosis		Mortality		
Study	Study Population, N	n	Incidence, ‰	n	Study Population, ‰	Cases of Agranulocytosis, %
Alvir et al[16]	11,555	73	8.0	2	0.2	2.7
Atkin et al[17]	6,316	43	8.0	2	0.3	4.2
Munro et al[8]	12,760	93	7.3	2	0.2	2.2
Honigfeld et al[18]	99,502	382	3.8	12	0.1	3.1

Table 2. Diabetic Ketoacidosis: Incidence and Mortality

	Population		Diabetic Ketoacidosis		Mortality		
Study	Study Population, N	Clozapine, n	n	Incidence, ‰	n	Study Population, ‰	Cases of Diabetic Ketoacidosis, %
Leslie and Rosenheck[20]	56,849	NA	88	1.2	NA	NA	NA
Henderson et al[21]	2,123[a]	226	5[b]	3.1	1[c]	4.4	20
Koller et al[22]	NA	678,700	80	0.1	25	0.2	31

[a]Number of study population is the sum of the number of patients taking olanzapine (n = 776), risperidone (n = 585), quetiapine (n = 479), clozapine (n = 226), and ziprasidone (n = 57).
[b]Reference Table 1 in Henderson et al.[21]
[c]Reference Table 3 in Henderson et al.[21] Patient 4, who was treated with clozapine (see Table 1 in Henderson et al[21]), died.
Abbreviation: NA = not applicable.

Table 3. Gastrointestinal Hypomotility: Incidence and Mortality

		Ileus		Mortality		
Study	Clozapine, n	n	Incidence, ‰	n	Study Population, ‰	Cases of Ileus, %
De Hert et al[26]	NA	320	NA	70	NA	21.9
Nielsen and Meyer[27]	2,508	20	8	3	1.19	15.0
Palmer et al[13]	25,383	102	4	25	0.98	20.3–27.5[a]

[a]Fifteen of the 74 reported cases (20.3%) died; 28 of 102 reported plus published cases (27.5%) died.
Abbreviation: NA = not applicable.

instances, constipation can lead to paralytic ileus, megacolon, colon ischemia, colon perforation, acute abdomen, and, ultimately, death. Two population studies have documented the incidence and case-fatality rate of gastrointestinal hypomotility in patients being treated with clozapine (Table 3). In a case-register study of 25,383 patients treated with clozapine in Australia or New Zealand (1988–2007), Palmer et al[13] identified 102 cases of gastrointestinal hypomotility or constipation that resulted in hospital admission (28 cases from studies and 74 from case reports); 28 patients died, giving a case-fatality rate of 27.5%. Because of possible publication bias, the mortality rate was calculated for case reports only, which yielded a case-fatality rate of 20.3% (15 of 74). The case-fatality rate of cases reported to the US Food and Drug Administration was 21.9% (7 of 32),[26] nearly identical to 20.3% reported among Australian patients. Danish registry data for psychiatric and somatic hospitals revealed that ileus was diagnosed in 20 of 2,508 patients (0.8%) treated with clozapine in the period 1996–2007, 3 of whom died, a number corresponding with a case-fatality rate of 15%.[27]

Myocarditis

Clozapine-associated myocarditis is characterized by tachycardia or hypotension accompanied by other recent-onset symptoms (dizziness, palpitations, dyspnea, or chest pain) or symptoms of heart failure (arrhythmia, edema, raised jugular venous pressure).[28] Kilian et al[29] were the first to draw attention to the increased incidence and mortality of myocarditis in Australian patients treated with clozapine, and their findings were subsequently replicated in other studies. However, because most studies do not report the exact number of years of exposure to clozapine, it is not possible to calculate the annual incidence of clozapine-associated myocarditis. The incidence of clozapine-associated myocarditis has been reported to be 0.07‰ (based on worldwide Novartis pharmacovigilance reporting and about 3 million patient-years of data[30]). In contrast, incidence rates from much smaller populations in Australia have been reported to be 13‰–34‰ in Brisbane in 1992–2002[28] and 7‰–12‰ in the entire Australian population over the same time period (Table 4).[31]

In the Australian study, 10 of the 116 patients with myocarditis were also diagnosed with cardiomyopathy. This is somewhat unusual because cardiomyopathy, unlike myocarditis, is not an acute but a chronic disorder. Even more unusual, the cardiomyopathy developed within 3 weeks of the start of clozapine in 4 of the 10 patients.[31] In the same period, cardiomyopathy was diagnosed in 90 clozapine-treated patients. Unfortunately, it is not possible to establish how many patients were incorrectly diagnosed with cardiomyopathy or myocarditis.[31] However, even if the lowest figure (0.7%) is correct, the incidence of myocarditis in Australia is still much higher than the Novartis-reported incidence of 0.07‰.[30]

Better functioning pharmacovigilance[31] and colocation of cardiac and psychiatric wards[28] have been suggested to explain not only the higher Australian incidence rate of 0.7%–1.2% (7‰–12‰)[31] but also the lower case-fatality rate (0%–13.5%). The incidence rates outside Australia—which include 0.07‰ (worldwide),[30] 0.15‰ (United States),[32] 0.29‰ (Germany plus Switzerland),[33] and 0.6‰ (Canada),[34]—are

Table 4. Myocarditis: Incidence and Mortality

			Myocarditis		Mortality		
Study	Country	N	n	Incidence, ‰	n	Study Population, ‰	Cases of Myocarditis, %
Reinders et al[28]	Australia	235	3–8[a]	13–34	0	0	0.0
Haas et al[31]	Australia	10,031–17,075[b]	116	7–12	12	0.7–1.2	13.5
Novartis Canada[30]	Canada	15,600	9	0.6	3	0.2	33.0
La Grenade et al[32]	United States	189,405	28	0.15	18	0.09	68.0
Degner et al[33]	Germany and Switzerland	10,263	3	0.29	0	0	0.0
Novartis worldwide[30]		3,000,000	213	0.07	50	Not applicable	23.5

[a]The authors report that "Consensus panel reevaluation of the 8 cases of clozapine-related myocarditis resulted in their stratification into the following categories of diagnostic likelihood: 3 highly probable cases, 3 probable cases, and 2 possible cases."[28(p919)]
[b]The authors (Haas et al[31]) attribute the divergent size of the study population to the existence of 2 Australian registries that are relevant to this table, one by Novartis (N = 13,553) and a second by Mayne Pharmacy (N = 3,522)—"These numbers represent the estimated incidence in Australia up to 2003 by using the 2 extreme scenarios: (1) duplicate patients in both clozapine registries (13,553 – 3,522 = 10,031) and (2) no duplicated patients in either registry (13,553 + 3,522 = 17,075)."[31(p50)]

Table 5. Comparison of Incidence and Mortality

		Mortality	
Variable	Incidence, Study Population, ‰	Study Population, ‰	Affected Cases, %
Agranulocytosis	3.8–8.0	0.1–0.3	2.2–4.2
Diabetic ketoacidosis	1.2–3.1	0.2–4.4	20.0–31.0
Gastrointestinal hypomotility	4.0–8.0	0.98–1.19	15.0–27.5
Myocarditis			
Australia	7.0–34.0	0–1.2	0–13.0
Other countries	0.07–0.6	0–0.2	0–68.0

systematically 10 times or more lower than the rates found in Australia, thereby precluding not only efforts to establish a definite incidence rate but also a worldwide, evidence-based monitoring protocol.

Comparison of the Incidence and Mortality of Agranulocytosis, Diabetic Ketoacidosis, and Gastrointestinal Hypomotility

The incidence of agranulocytosis is 1.2–6.7 times higher than that of diabetic ketoacidosis and 0.95–2 times higher than that of gastrointestinal hypomotility (Table 5). However, as mentioned above, only the incidence of agranulocytosis can be considered established; the incidences of diabetic ketoacidosis and gastrointestinal hypomotility should be considered provisional at the moment. The mortality rate of these complications associated with clozapine use is low, about 0.1‰–1.19‰, with the exception of diabetic ketoacidosis, which has a mortality rate of 4.4‰. The case-fatality rate of agranulocytosis is also relatively low, 2.2%–4.2%, whereas that of the other complications is 10 times higher, ranging from 15%–27.5% (gastrointestinal hypomotility) to 20%–31% (diabetic ketoacidosis).

DISCUSSION

There have been few studies of gastrointestinal hypomotility and diabetic ketoacidosis, and, with the exception of the hospital registry study,[21] available data come from case reports, where a certain form of bias cannot be ruled out as not all cases are reported, and cases in which the patient dies are more likely to be reported. In addition, differences in the design, duration, and execution of studies make comparison difficult.

The incidence of agranulocytosis, diabetic ketoacidosis, and gastrointestinal hypomotility ranges from 1.2‰ to 8‰, with a median around 3‰–4‰. The case-fatality rate ranges from 2%–3% for agranulocytosis to 15%–68% for diabetic ketoacidosis, gastrointestinal hypomotility, and myocarditis. The most plausible explanation for this substantial difference in mortality is a difference in detection: screening for agranulocytosis is mandatory, and the frequency of screening is adapted to the risk, such that weekly screening is mandated during the "high-risk" first 18–24 weeks of treatment and thereafter monthly for the duration of treatment. Thus, neutropenia or agranulocytosis will be detected in an early stage in virtually all patients. Moreover, because clinicians are aware of this complication of clozapine therapy, they will be more likely to recognize fever or, more rarely, fulminant agranulocytosis as side effects of treatment in patients taking clozapine than in other patients not taking clozapine. The case-fatality rate of agranulocytosis has decreased from 46% in the 1970s[32] to 2%–4% nowadays.

In contrast, screening for diabetic ketoacidosis is carried out much more sporadically in patients treated with clozapine, with glucose levels being measured annually in only about 10%–25% of patients.[33–35] It is probably valid to conclude that the frequency of screening during the first 3 critical months of therapy is inadequate not only for diabetic ketoacidosis but also for gastrointestinal hypomotility.

There is currently no monitoring protocol for the adequate and timely detection of diabetic ketoacidosis and gastrointestinal hypomotility. The most recent protocol (2007)[14] does not mention diabetic ketoacidosis or gastrointestinal hypomotility and neither do other articles[15,36] reporting on the advantages/disadvantages of clozapine therapy. We advocate adopting an approach to diabetic ketoacidosis and gastrointestinal hypomotility similar to that used for agranulocytosis and with the same aim: namely, early detection to ensure adequate treatment in the early, mild stage of disease; fewer cases of full-blown disease, with its higher mortality rate; and, ultimately, lower

incidence of and mortality from diabetic ketoacidosis and gastrointestinal hypomotility.

Myocarditis—A Case Apart

The large difference in the incidence of myocarditis between Australia and New Zealand and the rest of the world can probably be partly ascribed to a more active screening policy in the 2 former countries. Indeed, the incidence data are so discrepant that further investigations are needed before screening recommendations can be formulated. Until then, the Victorian consensus statement regarding monitoring for cardiac adverse events[14] cannot be considered valid for other countries. That said, clinicians should be alert to the possible development of myocarditis or cardiomyopathy during the first 3 months of treatment and should order appropriate tests if these disorders are suspected.

Strength of the Evidence

It can be questioned whether the available evidence—3 studies of diabetic ketoacidosis (2 epidemiologic reports and 1 case report) and 3 of gastrointestinal hypomotility—is strong enough to draw valid conclusions about the necessity of screening. In this regard, it might be useful to look at the early history of clozapine. In 1975, clozapine was used to treat 2,500–3,200 patients in Finland, which resulted in a 2.5% annual incidence of clozapine-associated agranulocytosis,[37] a much higher rate than the incidence of 0.3‰ reported in non-Finnish populations.[38] On these grounds, clozapine was withdrawn, only to be relicensed under strict conditions 15 years later. In contrast, the incidence of diabetic ketoacidosis and gastrointestinal hypomotility has been investigated in much larger patient samples (58,972 patients for diabetic ketoacidosis and 25,383 patients for gastrointestinal hypomotility), suggesting that it is not necessary to wait for the results of further studies and that frequent screening for the early detection and treatment of these disorders can be recommended on the basis of available evidence. The aim of such recommendations is to reduce mortality to a level comparable to that for agranulocytosis.

Extension of routine monitoring of glucose measurements and preventive treatment of gastrointestinal hypomotility might aid to overcome the clinician's hesitancy in prescribing clozapine. Despite its superior effect, clozapine is often prescribed late in the disease course, possibly because clinicians are concerned about the risk of agranulocytosis and the associated testing obligations. In clinical practice, the use of clozapine is delayed, on average, for up to 5 years, and patients receive more than 5 antipsychotics before being prescribed clozapine.[39] Studies have revealed that a mean interval of almost 10 years elapses between the first contact with a health provider and the initiation of clozapine treatment.[40] Thus, a drug of proven superior efficacy is prescribed much too late. Not surprisingly, several authors have advocated the earlier use of clozapine,[15,36,41] as do we. However, we advocate adding 2 conditions to its use. First, all treatment with clozapine should be provided by experienced psychiatrists who are fully aware of the potentially serious complications that can occur in the first few months of treatment. Second, psychiatrists should take steps to ensure that patients are seen every week and asked about or investigated for the development of these serious, potentially lethal, complications of clozapine. Only in this way can a balance be achieved between underutilization and delayed clozapine therapy on the one hand and irresponsible treatment with an increased risk of unrecognized serious complications on the other.

CONCLUSION

Screening guidelines during the initial phase of treatment with clozapine have been restricted to the obligatory white blood cell monitoring. On the basis of recent literature, which has shown that mortality rates of diabetic ketoacidosis and of gastrointestinal hypomotility are 10 times as high as the mortality rate of agranulocytosis, we propose 2 revisions, both extensions, of the existing screening guidelines.

First, monthly screening of fasting plasma glucose should be obligatory in the first 3 months of clozapine therapy. Practically, the routine scheme consists of 5 measurements of fasting plasma glucose: at baseline; after 1, 2, 3, and 6 months of treatment; and thereafter annually. Because of the weekly blood sample taking, we consider the additional burden of 4 times fasting to be both acceptable and practicable. In the rare instances in which fasting blood samples cannot be taken, glucose can be measured in nonfasting samples with an important caveat: while hemoglobin A_{1c} levels, which reflect mean glucose levels in the preceding 8–12 weeks, are a reliable predictor of the long-term (10–20 years) complications of diabetes mellitus, they are not a sensitive marker of rapidly developing hyperglycemia. Fasting plasma glucose is clearly superior and therefore preferable.

Second, monitoring of gastrointestinal hypomotility should become an integral part of regular screening, not only in the initial but also during the maintenance phase. Two options are open to the clinician. First, the clinician could integrate questioning of bowel movements as a routine part of every visit of the patient. Whenever indicated, the questioning can be extended to physical examination of the abdomen and/or prescription of macrogol laxative. A second option is preventive laxative maintenance treatment in all patients. Practically, this option would mean that, in every patient, prescription of clozapine is accompanied by prescription of macrogol.

We expect that the introduction and implementation of these guidelines will bring the mortality rate of diabetic ketoacidosis and gastrointestinal hypomotility down to a level comparable to that of agranulocytosis. We also hope that the guideline will contribute to the timely and responsible prescription of clozapine so that more patients will benefit, in an earlier stage, from this drug.

Screening for myocarditis or cardiomyopathy is, outside Australia and New Zealand, not evidence based.

Drug names: clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), ziprasidone (Geodon and others).

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