needs to be compared with the much higher worldwide frequencies and lethality of pneumonia and myocarditis associated with clozapine. Worldwide, pneumonia is particularly frequent and lethal in patients exposed to clozapine (appendix), although there is no certainty that these deaths can be explained by clozapine. According to an analysis of Danish registry data,[4] once clozapine is started, the annual incidence rate of pneumonia is 1·4%. Some countries consider a 3% average rate of myocarditis in patients exposed to clozapine to be normal.[5] According to the WHO pharmacovigilance database, more patients exposed to clozapine have died from myocarditis than from agranulocytosis since 2000. We think, in the discussion of risk–benefit analyses for clozapine prescription in Finland, the risk and lethality of hematological malignancy should be compared with the risk and lethality of pneumonia and myocarditis. Finnish clozapine prescribers appear to be severely under-reporting pneumonia and myocarditis to their drug agency, although these data should be available in the Finnish registry. In the interest of increasing clozapine safety worldwide, we think that prescribers and drug agencies should not only focus on hematological malignancies, but also on preventing, identifying, and treating myocarditis and pneumonia.[5]

For the **DCCG** see https://www.clozapinepluswerkgroep.nl

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The nationwide 12-year follow-up case-control study of patients with schizophrenia in Finland by Tiihonen and colleagues found increased odds of haematological malignancies in clozapine-users compared with users of other antipsychotic drugs.[1] The authors acknowledge that the absolute risk difference (0·2%) is small compared with the previously observed absolute risk reduction in all-cause mortality (10·0%). Nevertheless, the authors recommend that patients and their caregivers should be informed about warning signs of haematological malignancies. In addition to advising mental health clinicians to be vigilant for early signs and symptoms of haematological malignancies, the authors also recommend monitoring complete blood count instead of just neutrophil count to detect haematological malignancies early.

The Dutch Clozapine Collaboration Group (DCCG) is concerned that this advice will increase so-called clozapine phobia in patients, caregivers, and mental health clinicians,[2] thereby increasing the under-prescription of clozapine in patients, and unintentionally increasing mortality in patients for whom clozapine is indicated.[3] In our opinion, patients and caregivers do not need to be actively informed about the small increase in the risk of haematological malignancies associated with clozapine use. Information on risks in the first months (eg, agranulocytosis and myocarditis) and during long-term treatment (diabetes, dyslipidaemia, hypertension, and paralytic ileus) is sufficient. The lower all-cause mortality in clozapine users should be stressed. If the topic of the small increase in the risk of haematological malignancies in clozapine users is raised, patients and their caregivers should also be informed about the improved prognosis in clozapine users (32·9% mortality in patients with ongoing clozapine use *vs*

50·7% in non-clozapine users in the investigated cohorts).

To prevent clozapine discontinuation due to the burden of monthly white blood cell (WBC) monitoring, the DCCG's clozapine guideline, unlike guidelines in other countries, states that after an initial 6 months of regular monitoring, off-label WBC monitoring at a lower frequency (none or preferably four times a year) is permissible when explicitly requested by patients who have the capacity to provide informed consent.

On the basis of the DCCG's frequently used online facility for professionals seeking advice we estimate that the majority of ambulatory long-term clozapine users in the Netherlands receive WBC monitoring four times a year. The rationale is that after the first 6 months of treatment, the mortality caused by clozapine-induced agranulocytosis is about the same as the mortality associated with other medications (eg, mianserin or phenylbutazone) and with life in general (eg, traffic or occupational accidents).[4] In accordance with the 2015 US Food and Drug Administration regulations, our guideline also replaces the WBC plus granulocyte count with an absolute neutrophil count. Although doing a complete blood count, as suggested by Tiihonen and colleagues, could detect some cases of haematological malignancy earlier than doing only a granulocyte count, it remains to be shown that this gain is not outweighed by the downside of false positive tests followed by invasive procedures such as a bone marrow biopsy.[5]

In accordance with psychosis guidelines in other countries, we endorse annual physical and laboratory examination in all patients with schizophrenia spectrum disorders, whose somatic conditions, including cancer, often remain both undetected and undertreated.

We declare no competing interests.

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Authors' reply

We thank Peter FJ Schulte and colleagues for their interest in our article. We believe that decisions about the treatment of schizophrenia should be made on the basis of clinicians and patients having access to comprehensive information about the benefits and risks of clozapine. We do not believe information about serious—albeit rare—adverse events should be withheld from patients or caregivers for fear of contributing to non-adherence. Instead, an open and comprehensive discussion about the benefits and risks of treatment provides an opportunity for clinicians to address patient concerns about potential adverse events. This approach includes helping patients to interpret and contextualise information about adverse events obtained from other sources. When providing balanced information about possible adverse events is done well, we do not believe that it leads to clozapine phobia. Providing oral and written information about medications could improve adherence.[1] Clozapine was withdrawn worldwide after nine deaths were reported in Finland in July, 1975, due to agranulocytosis and leukaemia.[2] Finnish clinicians appear to have succeeded in communicating the benefits and risks of treatment with clozapine because the rate of clozapine use is substantially higher in Finland than in any other country in a study that included 17 countries,[3] despite mandatory monthly complete blood count. Our results[4] and a meta-analysis from 2019[5] suggest that clozapine is the safest antipsychotic drug in terms of mortality. Informing clinicians and patients about the overall benefits and risks of treatment, including the mortality benefits, should facilitate even wider use of clozapine. In terms of complete blood count, we did not suggest any procedures deviating from the usual standard practice (ie, the standard risk–benefit assessment) used in other patient populations after the detection of abnormal complete blood count.

We thank Jose de Leon and colleagues for their interest in our article. We fully agree that pneumonia, myocarditis, diabetes, and cardiovascular diseases are important safety issues related to clozapine treatment. However, we would like to emphasise that the aim of our study was to investigate the existence of previously unknown adverse haematological events, and not to compare the relative importance of clozapine-related specific causes of death. Agranulocytosis was described as another adverse haematological event in the context of the need of blood monitoring. Concerning the discussion on risk–benefit analyses for clozapine prescription, we compared the absolute risk of haematological cancer with the absolute risk reduction in mortality due to any cause among patients using clozapine.

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