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EDITORIAL

Data From the World Health Organization's Pharmacovigilance Database Supports the Prominent Role of Pneumonia in Mortality Associated With Clozapine Adverse Drug Reactions

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Although clozapine is underprescribed in many countries, it may be the most efficacious antipsychotic and the best for treatment-refractory schizophrenia. Moreover, a meta-analysis[1] reported significantly lower deaths in patients continuously treated with clozapine compared to other antipsychotics.

This editorial proposes that clozapine mortality may be further decreased by paying more attention to pneumonia. The prominent role of pneumonia in clozapine mortality is supported by an update of a review article[2] and by the new data from a global database of adverse drug reactions (ADRs) for comparing the mortality associated with pneumonia and other clozapine ADRs.

Update of a Review Article

The experience with his state's mortality reviews led the first author to complete a comprehensive review[2] of the literature on the swallowing disturbances associated with antipsychotics, including complications such as pneumonia. In 2005, using postmarketing surveillance, the Food and Drug Administration reported the association between antipsychotics and deaths in dementia patients was partly linked with pneumonia and began requiring a warning about "esophageal dysmotility and aspiration." Clozapine is rarely used in dementia patients, but the warning was included in its package insert.[2]

An updated review describing 10 prior relevant studies (supplementary references) supports 3 findings[2]: compared with other antipsychotics, clozapine may be associated with a greater number of pneumonia cases (finding 1) and greater mortality (finding 2) (supplementary table S1). Pneumonia may be among the greatest causes of mortality in clozapine patients (finding 3) (supplementary table S2).

The association between clozapine and increased risk of pneumonia is partly explained because all antipsychotics can interfere with swallowing, increasing the potential for aspiration.[2] The potential for aspiration and aspiration pneumonia during antipsychotic treatment may be further increased by sedation and hypersalivation.[2] As clozapine is more prone to cause sedation and hypersalivation than other antipsychotics,[2] it is not surprising that it may be more strongly associated with pneumonia. Once pneumonia develops, clozapine co-prescription may be particularly lethal and worse than other antipsychotics. Severe inflammation during pneumonia releases cytokines that inhibit clozapine metabolism[3] and increase serum clozapine concentrations, further increasing risk of hypersalivation, sedation, aspiration or even arrhythmia, creating very dangerous positive feedback.[2]

New Data

VigiBase, the World Health Organization's global database, is located at the Uppsala Monitoring Centre, Uppsala, Sweden. It currently has >20 million reports of spontaneously reported ADRs from the drug agencies of 134 countries. New reports arrive daily. On July 15, we searched reports of clozapine ADRs from database inception in 1968 to that date. The clozapine ADRs are classified by the reporting clinician using the categories provided by the database. Each patient can be classified in 1 or several clozapine ADR categories. Currently there are >140 000 clozapine reports classified in over 5000 ADR categories. The

upper panel of supplementary table S3 lists the clozapine ADRs that are likely to be associated with clozapine and have fatal outcomes >100 times. The lower panel lists other ADRs which may overlap with the fatal outcomes listed in the upper panel but may provide additional fatal outcomes from the same type of ADR. The relative lethality percentage was calculated by dividing fatal outcomes by reports. Supplementary table S1 footnote C provides details on the statistical analyses used by VigiBase.

Table 1 summarizes the top 8 fatal outcomes after grouping ADR categories which are likely to have overlapping reports from the same case. The category with the highest number of fatal outcomes was "broad pneumonia" (defined by adding pneumonia, lower respiratory infection, and aspiration),[2] associated with 2077 fatal outcomes from 6983 reports and relatively high lethality of 30%.

The category second in number with 1449 reported fatal outcomes was "sudden death and cardiac arrests," defined by adding these 2 categories. This is probably the least specific of the 8 ADR categories, and it is very likely that a substantial number of deaths were explained by causes other than clozapine. In many cases, it would be difficult to establish the probability that the fatal outcome was explained by a clozapine ADR by using an ADR scale because in this type of death it is not easy to rule out other causes.

The third, fourth, fifth, sixth, seventh, and eighth categories were, respectively, broad agranulocytosis with 550 fatal outcomes, broad myocarditis with 539 fatal outcomes, broad constipation with 326 fatal outcomes, broad arrhythmia with 319 fatal outcomes, broad seizures with 308 fatal outcomes, and broad syncope with 299 fatal outcomes.

Comparing the associations between pneumonia and other antipsychotics may help to better understand these results. An April 9, 2019, search focused on the significance of association of the narrow definition of pneumonia; it compared found vs expected ADRs.[4] At that time, 4865 pneumonia cases were found vs 1195 expected for clozapine, 393 vs 845 for risperidone, 622 vs 650 for quetiapine, and 493 vs 529 for olanzapine (supplementary table S1). On July 15, we calculated cases and fatal outcomes using the more relevant definition for clinicians, "broad pneumonia": 508 with 181 fatal outcomes for risperidone, 848 with 189 fatal outcomes for quetiapine, and 685 with 221 fatal outcomes for olanzapine (supplementary table S4). These are much lower than clozapine's numbers: 6926 broad pneumonia cases and 2175 fatal outcomes.

The database's strength is its access to a large number of ADRs from multiple countries including >140 000 for clozapine and 60 000–100 000 for risperidone, quetiapine, and olanzapine (supplementary table S5). The major limitations of the database are: (1) inclusion of mainly spontaneous reports (eg, the reporting clinician decides whether to report the ADR including pneumonia in the patient taking clozapine, another antipsychotic, or another drug), (2) lack of certainty that clozapine caused the ADR or its fatal outcomes; other coincidental causes, or co-medications, may explain them, and (3) lack of control for presumably greater severity of illness in clozapine patients compared to those taking other antipsychotics.

To conclude, despite the limitations, first, the Vigibase data points out that reorienting psychiatrists' education regarding clozapine ADRs may be necessary. The large number of pneumonia deaths in VigiBase related to clozapine is extremely concerning and suggests that prior published literature (supplementary tables S1 and S2) may be only the "tip of the iceberg." To decrease deaths associated with pneumonia, we

Table 1. Eight Major Causes of Fatal Outcomes After Grouping Clozapine ADRs Reported to VigiBase

ADRs	Fatal Outcomes	Relative Lethality[a] (%)	Cases
Broad pneumonia[b]	2077	30	6983
Sudden deaths and cardiac arrests[c]	1449	90	1614
Broad agranulocytosis[d]	550	2	34 931
Broad myocarditis[e]	539	12	4586
Broad constipation[f]	326	12	2814
Broad arrhythmia[g]	319	5	6927
Broad seizure[h]	308	5	6231
Broad syncope[i]	299	7	4058

Note: ADRs, adverse drug reactions.
[a]Relative lethality = fatal outcomes/cases.
[b]By adding pneumonia, lower respiratory infection, and aspiration. From 7181 reports we obtained 6983 cases.
[c]By adding cardiac arrest and sudden death. From 1633 reports we obtained 1614 cases.
[e]By adding agranulocytosis, WBC decrease, neutropenia, leukopenia, neutrophil count decrease, and granulocytopenia. From 47 879 reports we obtained 34 931 cases.
[e]By adding cardiac failure, myocarditis, and cardiomyopathy. From 4839 reports we obtained 4586 cases.
[f]By adding constipation, toxic megacolon, and paralytic ileus. From 2971 reports we obtained 2814 cases.
[g]By adding tachycardia and arrhythmia. From 6987 reports we obtained 6927 cases.
[h]By adding seizures and generalized tonic-clonic seizures. From 6327 reports we obtained 6231 cases.
[i]By adding hypotension, syncope, and orthostatic hypotension. From 4343 reports we obtained 4058 cases.

recommend: (1) using lower efficacious clozapine doses in each patient to decrease risk for hypersalivation, sedation and swallowing disturbances; (2) educating patients and families about the risk of pneumonia (or other severe infections), so that clinicians are contacted when infection occurs; and (3) decreasing the clozapine dosage as long as the infection is present. In the absence of better empirical evidence for reduced dosing of clozapine during an episode of pneumonia, it may be wise to reduce the dose to half to avoid high clozapine blood levels..[2,3] The high number of pneumonia fatal outcomes (N = 2077) and high lethality (30%) in VigiBase appear to reinforce the view that a clozapine package insert warning should be considered.[2] Finally, important educative tools such as the clozapine guidelines for clinicians and the programs for educating residents in clozapine clinics may need to be updated to include pneumonia risk. Greater awareness of clozapine ADRs associated with fatal outcomes, particularly pneumonia, may further decrease mortality in clozapine patients, which appears to be lower than in other patients taking other antipsychotics.[1]

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin* online.

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