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DRUG-DRUG INTERACTIONS

COVID-19 infection and psychotropics

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Between 20% and 70% of patients infected with SARS-CoV-2 (COVID-19) have psychiatric symptoms, such as agitation, anxiety, and delirium, necessitating the need for pharmacological treatment.¹ With antipsychotics commonly used to manage behavioral symptoms, there is a high potential for drug-drug interaction with many medications used to treat COVID-19. Investigators recently conducted a systematic evidence-based review of interactions between these drugs in patients with COVID-19.²

Evidence-based review

The investigators reviewed the quality of information available from three trademarked and commercially available drug interaction databases: Lexicomp, Micromedex Solutions, and Liverpool Drug Interactions Group. The first two databases were ultimately used for retrieving drug interaction information pertaining to antipsychotic drugs and specific COVID-19 therapies, including azithromycin, chloroquine, hydroxychloroquine, lopinavir/ritonavir, remdesivir, and tocilizumab. The evaluated information included interaction type, rating of interaction risk, severity of risk, and patient-management recommendations.

Since use of antipsychotics and some COVID-19 drugs has been associated with prolongation of QT interval and risk of torsades de pointes, a significant and life-threatening ventricular arrhythmia, data were also assessed from the CredibleMeds database for QT-prolonging drugs based on their categorized risk: known risk, possible risk, and conditional risk.

The investigators then reviewed the retrieved data to make consensus recommendations regarding concurrent administration of pairs of drugs from among these four options: not recommended,

recommended with caution and dose adjustment, recommended with caution and monitoring, and recommended. The investigators also conducted a systematic literature review of drug-drug interactions between COVID-19 therapies and antipsychotic drugs, primarily to assess clinical outcomes.

Results of the evidence review indicated that the primary interaction concerns stem from the risk of QT prolongation and torsades de pointes, since several drugs that were used to treat COVID-19 at the time of the investigation (azithromycin, chloroquine, and hydroxychloroquine) have a known risk of inducing torsades de pointes. Concurrent use of asenapine, cariprazine, and brexpiprazole was recommended with all three of these drugs, whereas olanzapine was recommended for concurrent use with azithromycin and hydroxychloroquine, and risperidone was recommended for co-administration with azithromycin. [Editor's note: Controlled studies subsequently showed no benefit of azithromycin, chloroquine, and hydroxychloroquine in the treatment of COVID-19.]

The interaction concern between antipsychotics and lopinavir/ritonavir is related to CYP-mediated metabolism and QT interval prolongation. Lopinavir is metabolized by CYP3A4, whereas ritonavir is a potent inhibitor of the same CYP isoenzyme. In addition, ritonavir has been shown to induce various CYP isoenzymes, including CYP1A2, which mediates the metabolism of olanzapine. Both lopinavir and ritonavir carry the potential risk of inducing torsades de pointes. Indinavir is another highly active antiretroviral drug that has been identified as having drug interaction potential with antipsychotics.

Currently there are no reports of significant interaction between remdesivir

BOTTOM LINE

Several drugs that have been commonly used to treat COVID-19 have been associated with risk of inducing torsades de pointes. Clinicians should be aware of potential cardiovascular effects when antipsychotics and drugs used to treat COVID-19 are used concurrently.

and antipsychotics, but that could be due to the relatively low prevalence of clinical use of remdesivir prior to the COVID-19 pandemic. Similarly, there are no drug interaction reports between tocilizumab and antipsychotics, with the exception of clozapine, in which the additive risk of hematological toxicity should be taken into consideration.

Conclusion

Although the clinical significance of drug-drug interaction is likely dependent on multiple patient-specific factors, clinicians should be aware of the likely additive risk of cardiotoxicity, specifically prolongation of QT interval and risk of torsades de pointes, when certain drugs used to treat COVID-19 are used concurrently with antipsychotics.

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WHAT'S NEW IN RESEARCH

Cognitive effects of cholinesterase inhibitors benefit patients with dementia

précis

- A longitudinal cohort study compared long-term cognitive outcomes for patients with Alzheimer's dementia who received cholinesterase inhibitors and those not using the medications.
- Users of cholinesterase inhibitors showed greater improvement in cognition than nonusers at all time points, with the drugs' effects persisting over the long term.
- Among the three individual drugs studied, only galantamine was associated with reduced risk of developing severe dementia.

Use of cholinesterase inhibitors is associated with cognitive benefits over time and reduced mortality risk in patients with Alzheimer's dementia, a longitudinal cohort study conducted in Sweden has concluded. Among the drugs studied in this category, galantamine was the only medication that showed a significant reduction in risk of developing severe dementia.

Although evidence suggests that cholinesterase inhibitors are effective in improving cognition, few trials have examined their long-term effects in patients with dementia, and whether they have meaningful long-term benefits is controversial. Researchers examined whether the cognitive benefits of the medications persist over the long term and whether their use reduces risk of severe dementia and death.

Study details

The cohort study included patients with incident diagnosed Alzheimer's

dementia or mixed Alzheimer's dementia who were included in the Swedish Dementia Registry. Among those excluded from the analysis were individuals with a baseline score of less than 10 on the Mini-Mental State Examination (MMSE), those with missing demographic data, and those whose first cholinesterase inhibitor prescription date was more than 3 months from the baseline MMSE evaluation.

The researchers stated that the overall effect of cholinesterase inhibitors was modest and of a somewhat smaller magnitude than results from prior studies, attributing that to differences in study design.

Cholinesterase inhibitor treatment was defined as initiation of donepezil, rivastigmine, or galantamine within 3 months of the patient's dementia diagnosis. The researchers examined follow-up MMSE scores and followed patients until onset of severe dementia, death, or end of follow-up, whichever came first. They accounted for potential confounding factors such as age, gender, comorbid illnesses, and concurrent medications.

Results

The final cohort included 11,652 users of cholinesterase inhibitors and 5,826 non-users; mean age of the cohort was 81.2 ± 6.3 years and 62% were women.

Donepezil was the most common cholinesterase inhibitor used, accounting for 62% of cholinesterase inhibitor prescriptions. Hypertension was by far the most common comorbid condition in the cohort.

The researchers found that users of cholinesterase inhibitors had better MMSE scores than nonusers at all visits. The individual cholinesterase inhibitors were associated with higher cognition at follow-up compared with nonusers, with no significant differences between the individual drugs. Cognitive benefits were similar for individuals with lower and higher cognitive scores at the time of the diagnosis of dementia.

The incidence of developing severe dementia was higher among nonusers of cholinesterase inhibitors. An analysis that stratified for individual drugs found that only galantamine users showed a significantly reduced risk of severe dementia. Users of cholinesterase inhibitors also had a lower mortality rate than nonusers (105.78 per 1,000 person-years, compared with 136.93 per 1,000 person-years for nonusers). The association with reduced mortality risk was dose-dependent. Patients taking galantamine at any dose had a lower mortality risk than nonusers of medication, the researchers reported.

Implications

The researchers stated that the overall effect of cholinesterase inhibitors was modest and of a somewhat smaller magnitude than results from prior studies, attributing that to differences in study design.

They pointed out that some studies suggest cholinesterase inhibitors might confer other benefits besides improved cognition, such as reduced risk of myocardial infarction and stroke. They wrote, "Stroke and mortality prevention in mild to moderate dementia stages is desirable,

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