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Antipsychotics and COVID-19: the debate goes on

In a meta-analysis on the association of mental illness, its treatment, and COVID-19 risk, Benedetta Vai and colleagues reported a strong association between exposure to antipsychotics and COVID-19 mortality (odds ratio 3·71 [1·74–7·91]).[1] This has serious implications for the care of patients with severe mental illness receiving or about to receive antipsychotics during the pandemic. It also raises questions as to whether the use of electronic health records might have limited the scope of the analysis.

Firstly, in all three studies reviewed in the analysis in which antipsychotic use was an exposure variable, patients on antipsychotics were included independently of diagnoses. Vai and colleagues acknowledged that unaccounted-for confounding factors might then have affected their analysis, as patient groups with disparate clinical profiles were included in single cohorts. For example, off-label prescription of antipsychotics in older patients with dementia or delirium is commonplace and a marker of frailty, itself a major risk factor for poor outcomes in COVID-19.[2] Yet two of the studies reported a median age of 84·2 years and 82 years, respectively, among patients who died of COVID-19. Although Vai and colleagues did conduct a sensitivity analysis adjusting for minimum age of the recruited cohorts, the outcomes they encountered are unlikely to represent outcomes in most patients with severe mental illness, the majority of whom are of working age and physically able.

Secondly, all three studies considered antipsychotics as a single homogenous pharmacological group. However, individual drugs can differ widely in their pharmacological profile. This is reflected in the differences in all-cause mortality rates in patients receiving different classes of antipsychotics, regardless of COVID-19 status.[3] Moreover, there is emerging evidence that the anti-inflammatory properties of some antipsychotics could in fact protect from severe COVID-19 by hindering the cytokine storms implicated in its pathogenesis.[4]

Lastly, none of the studies tested adherence to treatment. However, non-adherence to antipsychotics is common and a major contributor to treatment failure. The risk of complicated COVID-19 associated with untreated psychosis might far outweigh any risk associated with the proper use of antipsychotics that are recommended for its treatment. There is evidence that, when adherence to antipsychotic treatment is ensured, patients with severe mental illness could actually have better COVID-19 outcomes than the general population.[5]

Vai and colleagues highlight risks associated with the use of antipsychotic drugs in the context of the COVID-19 pandemic. However, unless specific criteria are used, scrutiny of data from electronic health records might not always reflect the complex needs of patients with severe mental illness. Further research is needed to better inform clinicians in adjusting psychotropic drug prescribing during these unprecedented times.

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Authors' reply

We thank Xavier Boland and Luiz Dratcu for their comments on our meta-analysis.[1] They have accurately identified an essential gap in the current understanding of COVID-19 impact on patients with mental disorders. Most of the available evidence in our meta-analysis relied on electronic health records, which indeed did not allow calculation of the risk associated with antipsychotics without confounding by indication. Nevertheless, risk estimates associated with antipsychotics remained significant in pooled odds ratios for adjusted estimates (2·43 [95% CI 1·81–3·25], I^2=61·35%), accounting for age in all three studies and comorbidities in two of the three studies.[1]

To differentiate the risks associated with specific drugs and the condition they are meant to treat, we have previously recommended reporting of medication-stratified risk estimates for each psychopharmacological drug class in patients with mental disorders.[2] We are glad to see emerging evidence answering our plea. In a recently published study by Nemani and colleagues,[3] antipsychotic treatment was not associated with increased mortality among a US cohort of 464 patients with severe mental illness, 196 of whom were treated with antipsychotic medication. However, this does not preclude potential risks associated with specific antipsychotics,[4] nor does it exclude the possibility of unaccounted-for confounding. Considering current treatment guidelines for severe mental illness, in particular among patients with

schizophrenia, an unmedicated status might be an indicator of treatment non-adherence, associated with an increased risk of psychiatric relapse, and a decreased adherence to physical health-care recommendations. In the absence of clear evidence about the detrimental role of antipsychotics, we recommend clinicians to stress the importance and benefit of antipsychotic treatment adherence, while also closely monitoring patients, ensuring timely COVID-19 testing and treatment referral.

This ongoing debate proves that an increased understanding of the role of psychiatric treatment modalities on the COVID-19 outcomes of patients with mental disorders, including not only different psychotropic compounds but also psychiatric treatment settings (eg, inpatient *vs* outpatient care), remains an urgent research priority.

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Psychiatry in Kashmir: a call for action

The mental health burden in Kashmir and the scarce and poor mental health services available need to be addressed in the context of wider social and economic paradigms.[1,2] We believe there is dire need for a collaboration between mental health experts in India and Pakistan for an organised response to the mental health crisis. We plead to the psychiatric community in both countries to set aside their differences and help address the mental health problem in Kashmir. As psychiatrists, we have a variety of tools at our disposal to make a difference, including clinical care, field worker training, and community-level interventions. Psychiatrists can work together to improve Kashmir's mental health services, human resources, educational resources, and infrastructure.

Training of nursing officers, field workers, teachers, and social workers can be extremely beneficial during a psychosocial crisis.[3] Telepsychiatry, electronic referral systems, and the formation of mobile emergency treatment teams to support local practitioners are required.[4] Over the past few decades in Kashmir, the government and WHO have provided, and continue to provide, emergency psychosocial assistance, crises interventions, and long-term treatment.

Owing to the severe volatility in Kashmir, and the absence of culturally adapted psychotherapeutic interventions, only a few epidemiological studies have been done in the region. Designing, adapting, and validating local interventions are required for crisis management. Academic institutions in India and Pakistan could provide expertise to develop cost-effective culturally relevant management strategies for Kashmir. To support this proposal, we urge international organisations

***Panel*: Suggestions to reduce the mental health burden in Kashmir**

- Collaborations between mental health professionals in Kashmir and professional associations in other countries who have faced similar conflicts to conduct online workshops for mental health workers in Kashmir
- National policies to defend human rights, alleviate poverty, build infrastructure, ensure access to education, employment, decent wages, health, and housing
- Creating a referral system from the first contact worker to the specialist, incorporating medical, psychological, and social services in Kashmir
- Establishing community-based information transfer systems, conducting local needs assessments, and engaging local populations
- Expanding emotional resilience through culturally adapted psychological interventions deployed via field workers in the context of loss, bereavement, and displacement
- Improving mental health awareness through affordable psychoeducation material such as online leaflets on social media platforms and radio talk shows
- Mental health services to liaise with other sectors, including education, economic development, cultural affairs, and policy development
- Encouraging communities to help one another through non-specialist mediated interventions, such as peer support groups involving village leaders and teachers; places such as mosques, temples, churches, and schools can be successful in bringing people together for mental health interventions
- Political support should be offered to foster social cohesiveness and sustain national, cultural, and religious identity; overseas and local non-governmental organisations should be allowed to facilitate partnerships between ethnic groups
- Developing and implementing media reporting guidelines for suicide and other mental health-related news; empowering media in conflict areas to educate people and politicians