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Asian Journal of Psychiatry 60 (2021) 102658

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

Letter to the Editor

Clozapine prescribing and safety during COVID-19

Schizophrenia is a chronic mental disorder affecting 20 million people worldwide (James et al., 2018). Clozapine remains the most effective pharmacological treatment for schizophrenia but requires regular blood monitoring due to its propensity to cause agranulocytosis. The Coronavirus disease 2019 (COVID-19) begot unprecedented restrictions on provision of psychiatric services and precautionary measures stood as major obstacles to healthcare access (Grover et al., 2020). An expert subgroup of the *Treatment Response and Resistance in Psychosis Working Group (TRRPG)* developed recommendations to face COVID-related challenges, including the dispensation of medication for up to 90 days and reducing the frequency of *Absolute Neutrophil Count* (ANC) testing to once every 3 months for patients who had been on clozapine for more than one year with no previous record of neutropenia (Siskind et al., 2020). We aimed to evaluate the trend of clozapine prescriptions during the COVID-19 pandemic in Qatar. Our secondary objectives were to evaluate the rate of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection among patients on clozapine; rates of neutropenia and related medical complications; clozapine toxicity; psychiatric and medical admissions during this period and whether these variables were associated with revised clozapine dispensation and blood monitoring.

The study design was a retrospective case-note review. The study received approval from the HMC Institutional Review Board (MRC-01-20-931). All patients maintained on clozapine were included in the study. During the study period (March 2020 – September 2020), 95 patients were registered out of which 25 were being managed in the inpatient settings and 70 in the community setting.

Published studies and commentators have drawn attention to the concern that the pandemic may have a disproportionate impact on patients maintained on clozapine. Table 1 shows the sociodemographic and clinical characteristics and pattern of clozapine dispensation and monitoring details of our sample. Patients were mainly Qatari nationals followed by non-Qatari Arabs. The mean age was 36 years and the majority were males. Most patients were diagnosed with schizophrenia and under the care of outpatient mental health services. The COVID-19 pandemic brought unique challenges to management of patients maintained on clozapine. Clozapine was initiated only for one new patient during the study period. New clozapine initiations during COVID-19 pandemic had the potential to lead to diagnostic confusion due to overlap of COVID-19 symptoms and clozapine side-effects. It appears that the potential risk of initiating clozapine was deemed more than the benefits during the pandemic. Based on clozapine initiation date and blood results, 79 patients met the criteria for revised frequency of ANC testing as per TRRPG monitoring guidelines. Only 28 patients were put on revised monitoring schedule Patients on revised monitoring had no incidence of neutropenia and fewer admissions to psychiatric (1 (1.1 %) vs 3 (3.2 %)) and medical (1(1.1 %) vs 3(3.2 %)) facilities. It is not surprising that patients on revised monitoring had no incidence of neutropenia and fewer incidences of medical complications as they were a select group of stable patients maintained on clozapine for more than one year with no previous record of neutropenia. Two patients (2.1 %) tested positive for SARS-Cov-2 PCR test in our study, lower than the 5 % infection rate among the general population in Qatar at the time ("COVID19 Home, " n.d.). Both patients were in the revised guidelines group as they were stable patients maintained on clozapine for many years. Reduction in immunoglobulin levels in patients taking long term clozapine has been reported as a possible causal factor for increased risk of infection (Cranshaw and Harikumar, 2020). Leon et al. have suggested that clozapine may increase the risk of infection and pneumonia (De Leon et al., 2020). Govind et al. investigated the association between clozapine treatment and the risk of COVID-19 infection in patients with schizophrenia and other psychoses. After adjusting for potential confounders, the risk of infection was found to be higher compared to individuals on other antipsychotic regimens (Govind et al., 2020). Neutropenia was reported in ten patients (10.5 %) under routine monitoring. None of the patients in this group tested positive for SARS-CoV-2 or developed neutropenia-related medical complications such as neutropenic fever or recurrent sinusitis. These patients were within the first year of their clozapine treatment, when the risk of agranulocytosis is highest. It is important to note that over 80 % of cases of agranulocytosis occur in the first 18 weeks of treatment. By the end of the first year of treatment, the risk of agranulocytosis is comparable to that of other antipsychotics (Cranshaw and Harikumar, 2020). The proportion of neutropenia in our cohort was relatively high compared to other regions (Li et al., 2019). This suggests that people of Middle Eastern descent might have a higher tendency to develop neutropenia with clozapine treatment.

Clozapine toxicity was suspected for one patient in the revised monitoring group. This was based solely on clinical suspicion as plasma level monitoring of clozapine is not available in our center. In addition, psychiatric and medical admissions were not linked to clozapine-related complications or monitoring. Admissions to inpatient mental health services were largely due to relapse in the context of partial or poor compliance. The main reason for nonadherence was adverse effect intolerability.

In conclusion, patients maintained on clozapine were safely managed without any major medical complications. Revised monitoring did not adversely impact patients maintained on clozapine. Despite its clinical superiority, clozapine continues to be underutilized. Prescriber, patient and health system-related factors have been identified as possible barriers to clozapine utilization in the Arabian Gulf countries (Ismail et al., 2019). The need for indefinite monthly monitoring is one of the important barriers and research must emerge assessing the necessity of such monitoring (Leung et al., 2020).

https://doi.org/10.1016/j.ajp.2021.102658
Received 15 March 2021
Available online 10 April 2021
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Table 1
Patient demographic, clinical characteristics and pattern of clozapine dispensation and monitoring (n = 95).

Variable	n(%)
Age, Years	
0–20	3(3.2)
21–30	27(28.4)
31–40	36(37.9)
41–50	22(33.2)
51–64	4(4.2)
≥65	3(3.2)
Sex	
Male	63(66.3)
Female	32(33.7)
Nationality	
Qatari	49(51.6)
Non-Qatari Arab	26(27.4)
Indian	7(7.4)
Pakistan	4(4.2)
North American	3(3.2)
Other	6(6.3)
Diagnosis	
Schizophrenia	83(87.4)
Schizoaffective	3(3.2)
Unspecified Psychosis	3(3.2)
Mood Disorder	4(4.2)
Patient Category	
Outpatient	84(88.4)
Long-Term Inpatient	10(10.5)
New Clozapine Initiation	1(1.1)
Revised (TRRPG) Guidelines	
Met criteria	79(83.2)
Did not meet criteria	16(16.8)
Dispensation/Monitoring	
Monitoring as per revised guidelines	28(29.5)
Routine monitoring	67(70.5)

Author contributions

All authors made substantial contributions to the conception and design of the study, data collection and analysis, drafting and revising the article, and approval of the final version for submission.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors report no declarations of interest.

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