Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Starting clozapine in patients with schizophrenia during the ongoing pandemic

1. Introduction

Clozapine is one of the most effective antipsychotics in patients with treatment resistant schizophrenia. However, during the ongoing pandemic some of the reports suggest that patients on clozapine have higher risk of COVID-19 infection (Govind et al., 2020), have drop in the neutrophil count with COVID-19 infection, which recovers to near normal with subsidence of infection (Bonaccorso et al., 2021). Some of the data also suggest that COVID-19 infection and associated pneumonia can lead to clozapine toxicity (Cranshaw and Harikumar, 2020).

On the other hand some of the consensus statements have emerged which suggest that for patients on clozapine for more than 1 year, the frequency of monitoring of absolute neutrophil count (ANC) can be reduced to every 3 months, if the patients does not have a history of ANC count going below 2000/μL (or <1500/μL if history of benign ethnic neutropenia) (Siskind et al., 2020). However, it is further recommended if the patients who are on clozapine experience symptoms of infection, urgent consultation with the physician and evaluation for ANC need to be considered. It is suggest that this assessment could be either done in person or by tele-health based on local protocols. The third recommendation suggest that if a person on clozapine develops COVID-19 infection or signs and symptoms of infection, dose of clozapine can be reduced to half to avoid clozapine toxicity (Siskind et al., 2020). Other authors have suggested that if a patient on clozapine presents with respiratory symptoms, it is better to get an urgent antigen test along with a full blood count, to distinguish between the side effects of clozapine and COVID-19 infection (Gee et al., 2020). With regard to continuation of clozapine in persons who develop COVID-19 infection, it is suggested that clozapine should be continued, wherever possible, and if required the dose should be reduced with monitoring of clozapine levels. Another suggestion which has been made includes use of vitamin-D in all patients on clozapine to protect them against the likelihood and severity of COVID-19 infection (Gee et al., 2020). Some of the studies have also shown safety of the extended haematological monitoring (Hata et al., 2021).

Although, lot has been discussed about, what is to be done for patients receiving clozapine, little information is available for starting of clozapine during the ongoing pandemic in patients requiring the same. Further, the recommendations suggest that the monitoring of patients who have been recently started on clozapine must be monitored as per the earlier recommended protocol (Siskind et al., 2020). One of the case series reported starting of clozapine in an elderly person, who had a exposure to a person with COVID-19 infection, and responded well to clozapine (Boland and Dratcu, 2020).

COVID-19 pandemic has led to reduction in physical contact with the patient and emergence of Telepsychiatry services across the globe. In India too, Government of India, notified the telemedicine practice guidelines (Telemedicine Practice Guidelines, India, 2020), at the beginning of the pandemic and this has helped the needy patients in a big way. However, there are issues with regard to the prescription of certain medications which can be issued through tele-consultations. The medications which can be prescribed have been categorized into 4 categories: Category O, Category A, Category B, and prohibited list (Category C). Category O includes the over the counter medications, which can be prescribed during the first teleconsultation. The Category A includes medications which are relatively safe and have low potential for abuse and the oral antipsychotics which are categorized in this list includes olanzapine, risperidone, and haloperidol, etc. These can also be prescribed during the first/new consultation. The Category B drugs include 'add on drugs', which can be prescribed during the tele-follow up consultations. Category C includes the prohibited drugs which cannot be prescribed by the teleconsultations. Clozapine accordingly does not fall in the category O, A and B drugs and necessarily requires prescription only by physical consultation.

As is evident from the literature, efforts must be made to minimize the exposure of the patients on clozapine to reduce their chances of infection and appropriate monitoring must be done to detect neutropenia at the earliest. Hence, prescribing clozapine to patients in need has become difficult. In this series, we present the report of 17 patients who were started on clozapine, during the ongoing pandemic (from mid Jan 2020 onwards), and were monitored by a combination of lower number of inperson visits and intervening period of monitoring by telepsychiatry.

2. Case descriptions

Retrospective analysis of this data was approved by the Ethics Committee of the Institute. As is evident from the Table 1, all the patients were diagnosed with psychotic illnesses and were on treatment for long, and fulfilled the criteria for treatment resistant schizophrenia as given by Kane et al. (1988). During the ongoing pandemic, families were finding it difficult to manage them. These patients contacted the psychiatry telepsychiatry services or emergency services with acute symptoms. As it was not possible to start clozapine by teleconsultations, these patients were either admitted to the psychiatry inpatient setting or were called for physical consultation (in the emergency setting or the physical outpatient setting). The patients and the family members were explained about the need for treatment, treatment options including clozapine, need for haematological monitoring during the use of clozapine and need for regular follow-up with the services physically, and increased risk of COVID-19 infection while on clozapine. After obtaining informed consent, these patients were started on clozapine after the physical consultation. They were given clozapine prescription for 2–4 weeks, depending on the distance, and were asked to send the haemogram

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Table 1
Profile of patients started on Clozapine.

Sl no	Age in years	Gender	Place of starting clozapine (inpatient/ outpatient/ emergency)	Date of starting clozapine	CGI-severity score at the time of starting clozapine	Clozapine dose achieved (in mg/day)	Concomitant medications	CGI-severity score at the time of last follow-up while on clozapine	CGI-improvement score at the time of last follow-up while on clozapine	Side effects encountered
1	30	M	Outpatient	18.1.2020	7	287.5	None	3	2	H
2	41	M	Outpatient	10.2.2020	6	125	None	3	2	C, H
3	33	M	Inpatient	10.2.2020	7	225	None	3	2	C, S, H,
4	28	M	Inpatient	11.2.2020	7	100	Valproate 750 mg Lorazepam 2 mg	3	2	C, S, H, T
5	37	M	Inpatient	11.2.2020	7	175	None	3	2	S, H
6	31	M	Inpatient	10.03.2020	6	200	Sertraline 100 mg	3	2	C, S, H, W
7	28	M	Inpatient	4.4.2020	7	200	Fluoxetine	3	2	S, H, W
8	22	F	Inpatient	8.4.2020	7	150	Escitalopram 20 mg Metoprolol 12.5 mg ECT	4	2	C, S, H, W,T
9	40	M	Inpatient	4.5.2020	7	250	ECT Olanzapine LAI	4	2	S, T
10	20	F	Emergency	12.6.2020	7	150	None	4	2	H
11	29	F	Outpatient	20.8.2020	6	200	None	3	2	S, W
12	29	M	Outpatient	8.9.2020	6	150	None	3	2	C, H
13	29	M	Inpatient	10.9.2020	7	337.5	Amitriptyline 25 mg Metoprolol 12.5 mg ECT Olanzapine LAI	4	3	S, C, T
14	19	M	Outpatient	26.9.2020	6	100	Fluoxetine 20 mg	4	2	S
15	23	M	Outpatient	16.11.2020	7	125	None	3	2	S,H
16	36	F	Outpatient	3.12.2020	6	175	None	3	2	S, H
17	22	F	Outpatient	27.1.21	6	100	None	3	2	S, H

C-Constipation; S-Sedation; H-Hypersalivation; T-Tachycardia; W-Weight gain; ECT-Electroconvulsive therapy; LAI: Long acting injectable; M- Male; F- Female.

reports on weekly basis by using the Whatsapp. The prescription for 2–4 weeks included charting of the clozapine doses for next 2–4 weeks in escalating doses, with a rider that the medicines could be increased only when the clinician approves the haemogram reports. Further, they were allowed to contact the clinicians telephonically at any time in case of the emergency. Patients started on clozapine as inpatients were initially monitored in the inpatient setting for 6 to 12 weeks and then the monitoring was continued at the outpatient basis, with a combination of in-person visits and Telepsychiatry consultations. This model led to successful use of clozapine in all these patients, with all experiencing significant improvement in their psychopathology (Table-1). None of our patient started on clozapine, did not develop COVID-19 infection, and all of them showed significant clinical improvement.

However, during the ongoing pandemic we could not start clozapine in few of the patients, who were not able to visit us at least once due to various reasons. Additionally, some of the patients/caregivers were judged by the clinicians that they would not be able to understand the prescription with respect to when and how to increase the dose of clozapine. Hence, clozapine was not started for such patients.

3. Discussion

The ongoing pandemic has led to difficulties in starting clozapine due to the absence of regular outpatient services and most of the consultations shifted to telepsychiatry or emergency setting. However, the telepsychiatry guideline does not allow starting of clozapine for the new tele-consultations (Telemedicine Practice Guidelines, India, 2020). Due to this many patients requiring clozapine could not be started on the same. This has been further complicated by the emerging reports of higher risk of COVID-19 infection in patients on clozapine (Govind et al., 2020). The emerging recommendations have suggested no change in the haematological monitoring during the initial 6 months, with some disagreement between monitoring between 6 months to 1 year, and decrease in the frequency of monitoring of haemogram after 1 year (Siskind et al., 2020; Remington and Powell, 2020). This left the patients in lurch, who were started on clozapine, but with the emergence of pandemic, could not follow-up with the outpatient services like before.

In the past, traditionally clozapine, if started on outpatient basis required weekly visits of the patients to the outpatient services for haemogram monitoring. This could be a costly affair, as this involves traveling of the patient and the caregivers (Verma et al., 2021). Prior to pandemic, telepsychiatry monitoring had no legal mandate and any adverse outcome could lead to a legal consequence for the prescriber. However, with the emergences of telepsychiatry services, from our case series, it can be said that, now a combination of in-person and telepsychiatry consultation can help in reduction in number of visits to the hospital, without interfering with the monitoring of the haemogram. Possibly this can also improve the adherence to the haematological monitoring and possibly medication adherence too.

Further, our case series suggests that clozapine can be safely started in patients requiring the same, with close monitoring during the ongoing pandemic. Hence, the clinicians should not refrain from starting of clozapine in patients who require the same. However, while recommending clozapine, clinicians should psychoeducate the patients and caregivers about the haematological monitoring, the precautions to be taken to avoid COVID-19 infection and report to the clinicians at the earliest in case patient manifests any signs of respiratory infection or any other kind of infection. Based on our experience of safe use of clozapine during the ongoing pandemic and incorporation of telepsychiatry consultation in the monitoring of patients on clozapine, certain recommendations can be made for the clinical practice (Table 2). Following these recommendations even after the pandemic is over can help in

Table 2
Recommendations for starting clozapine and monitoring by telepsychiatry consultations.

1. Evaluate the patient for possible treatment resistant schizophrenia
2. Seek consent of the patient/caregiver for starting of clozapine
3. Inform the patient and the caregiver about the side effects of clozapine, including neutropenia/agranulocytopenia and need for haematological monitoring, possible increased risk of COVID-19 infection in patient on clozapine
4. Inform the patient and the caregiver about the need to visit the hospital at the time of starting clozapine and for few times during the initial few months of clozapine
5. Check the availability of smart phone or any other devise, that can be used by the patient and family to send the haemogram reports to the clinician
6. Patient has access to a local laboratory to get the haemogram done
7. While prescribing clozapine and recommending the escalating doses for period of 2–4 weeks, the instructions should be clearly mentioned as to when to go the next level of clozapine dose (i.e., after the haemogram report has been approved by the clinician) and when to stop clozapine (as per the recommendation by the clinician)
8. Ensure that patient and family are able to understand how to taper off the ongoing medications
9. Patient and family be prepared to report to the hospital, if the clinicians desired them to come, in the emergence of any side effect requiring immediate clinical attention or patient has features of infection (including COVID-19 infection)
10. Patient and family are prepared to contact the clinician at the time of emergency

monitoring patients on clozapine with lower cost of treatment in developing countries and resource poor setting.

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Declaration of competing interest

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