Rapid Response:

**Potential Risk of COVID-19 in Clozapine Treated Patients. Re: Covid-19: outbreak could last until spring 2021 and see 7.9 million hospitalised in the UK**

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Dear Editor,

Clozapine is a transformative drug and the most effective drug for refractory schizophrenia. It is a dibenzodiazepine and is a forerunner atypical antipsychotic. Clozapine has recognized side effects. It is a well-understood observation that patients treated with clozapine are highly vulnerable to influenza or its complications if they catch it, although the mechanism of such higher risk of infection is not clear. This opinion is very well reflected in the fact that patients on clozapine are strongly advised to have the flu-vaccination before the flu season. COVID-19 is much more infectious and has a higher mortality rate when compared to the influenza virus.

Hospital admissions due to pneumonia are higher among clozapine treated patients (1,2,3). So, even if clozapine does not add to the vulnerability, once patients on clozapine catch COVID-19, they may carry a higher risk of pneumonia and its complications. Ponsford et al have argued that clozapine use was associated with significantly reduced immunoglobulin levels and, consequently, an increased proportion of patients end up using up to five or more antibiotic courses in a year (4). Apart from the immunodeficiency, the mechanisms proposed for such a high incidence of pneumonia are sialorrhea and aspiration, sedation, agranulocytosis and smoking (5). There are proposals that schizophrenia may be an autoimmune disorder and the very superiority of clozapine over other antipsychotics may be that it has probably a partial immunosuppressant effect in addition to its inhibition of dopaminergic transmission. There are also suggestions that clozapine may be working on immunomodulation rather than neuromodulation (6). Unfortunately, such a situation renders clozapine treated patients more vulnerable to infections. Therefore, clozapine treated patients should be given special attention and education in this uncertain period of COVID-19. Ponsford et al also suggest including antibody testing in the monitoring programmes of these patients to reduce the risk of pneumonia (4).

This vulnerability to infections may also be linked to the dose of clozapine and duration of treatment. It is worth discussing whether a reduced dose of clozapine should be encouraged in this critical period of Coronavirus infection. In countries like India clozapine is given at a much smaller dose and it seems to work. It is also to be remembered that clozapine does better as time goes by and at least some patients could be spared the higher doses administered in the initial phase. The agranulocytosis linked to clozapine is much less serious when compared to the mortality due to respiratory conditions. There is a high theoretical risk for Clozapine treated patients to catch COVID-19 and patients and carers should be on high alert in these critical periods; they should adhere to the preventive measures.

COVID-19 does not seem to follow the trajectory of seasonal flu and the morbidity factors are variable. It can present with full blown pneumonia. Statistical studies indicate the severity of coronavirus rises with age. The Italian experience suggest that the average age of those dying is 80, and this has been confirmed by the Italian national institute of health. According to the Chinese Centre for Disease Control and Prevention, people 70 and older accounted for just 12 percent of all infections but more than half of all deaths. According to the US government data, people 65 and older have thus far accounted for 31 percent of cases, 53 percent of intensive care hospitalizations and 80 percent of deaths. These are early days to evaluate the risks of COVID-19 among clozapine users if at all they pose additional risks.

Acknowledging the fact that there is no data on COVID-19 in clozapine patients, De Leon et al comment (7), “based on what we know about clozapine pharmacology, we can hypothesize that clozapine, possibly by impairing immunological mechanisms, may increase the risk of pneumonia in infected patients. More importantly, once fever and/or pneumonia develops, the clozapine dose should be cut in half to decrease the risk of clozapine intoxication.” They also suggests that if the signs of clozapine intoxication still persist in spite of the reduction of clozapine, complete stopping of the drug is recommended and it may be recommenced once the signs of inflammation and fever have disappeared.

It is informative to note that the antimalarial agent, Chloroquine is claimed to have some prophylactic benefits against the coronavirus. Neither the World Health Organization (WHO) or the Centres for Disease Control & Prevention (CDC) have confirmed the guaranteed efficacy of chloroquine. Its efficacy is so far anecdotal. Chloroquine modifies the immune response and this property is taken advantage in treating rheumatoid arthritis. COVID-19 is going to contribute new insights into virology. There is a diversity of genetically linked immune responses in a given population and the spread, survival and development of complications in an epidemic like this are not well defined. People who are already living with mental health problems will find great difficulty in adjusting to the changed situation and are bound to have anxieties in accessing their prescribed medications. In general, patients receiving clozapine are well monitored and these risks could be contained.

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