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Review Article

Revisiting Clozapine in a Setting of COVID-19

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Abstract: Clozapine is a highly potent atypical antipsychotic popularly used for treating refractory schizophrenia. Clozapine displays a complex mechanism of action. There are emerging views that its mode of action is immunomodulation rather than neuromodulation. It must be the immunomodulatory properties of clozapine that contributes to its superior efficacy and such a view help to validate the autoimmune ethology of a subset of schizophrenia. Agranulocytosis, one of the major side effects of clozapine is thought to be an autoimmune reaction. Because higher incidence of Flu related complications has been reported among clozapine users, there has been concern about the impact of COVID-19 among the patients on clozapine. As in the case of general population, infections with SARS-CoV-2 have been reported among clozapine users, but these are early days to make any firm conclusions about the higher risks of COVID-19 posing to clozapine treated patients. It is possible that clozapine may have therapeutic effects other than its antipsychotic effect and that needs further exploration.

Keywords: Clozapine, Neuromodulation, Immunomodulation, Agranulocytosis, COVID-19, Autoimmune Reaction

1. Introduction

Clozapine (CLZ) is a dibenzazepine that is structurally related to loxapine. When orally administered the absorption of CLZ is almost complete, but its oral bioavailability is only 60% to 70% because of first-pass metabolism. The time to peak concentration after oral dosing is about 2.5 hours, and the elimination half-life of CLZ is about 14 hours at steady-state conditions depending on the dose. CLZ is extensively metabolised in the liver via the cytochrome P450 system to polar metabolites suitable for elimination in the urine and faeces. The major metabolite, norclozapine (desmethyl-clozapine), is pharmacologically active. Agents which induce (e.g. cigarette smoke) or inhibit (e.g. theophylline, ciprofloxacin, and fluvoxamine) CYP1A2 may increase or decrease the metabolism of CLZ. The induction of metabolism caused by smoking means that compared with non-smokers, smokers require up to double the dose of CLZ to achieve an equivalent plasma concentration [1]. CLZ and norclozapine plasma levels may also be monitored, although they show a significant degree of variation, are higher in women and increase with age [2].

CLZ is primarily used in patients with treatment-resistant schizophrenia or schizoaffective disorder, defined as persistent moderate to severe delusions or hallucinations despite two or more clinical trials with other antipsychotic drugs. It is also recommended for patients with schizophrenia or schizoaffective disorder who are at a high risk for suicide, and patients with tardive schizophrenia. CLZ has been established as a superior drug to ameliorate positive symptoms in refractory patients [3]. CLZ has favorable effects on negative symptoms like cognitive deficits, improve social functions and, on the whole, higher quality of life and longer periods of compliance with decreased relapse. Intramuscular clozapine is now available in the Netherlands and produced by Brocacef and imported to the UK via Durbin PLC. It is classed as an unlicensed product in U.K.

2. Side Effects

Agranulocytosis, metabolic side effects, myocarditis, hypersalivation and convulsive disorders are well established side effects of CLZ. Rapid titration of CLZ and particularly in combination with sodium valproate can cause autoimmune myocarditis. The peak risk period for neutropenia and agranulocytosis is between weeks 6-18 and the risk declines

after the first year of treatment. Approximately 70% of agranulocytosis cases happen within the first 18 weeks of treatment. Both neutropenia and agranulocytosis are not dose related [4, 5]. Myocarditis is also not dose related and is an idiosyncratic reaction. Seizure is dose related. The mechanism of clozapine-induced agranulocytosis and the risk factors for its development are not well defined. It is not clear whether combinations of other medications could be a risk factor and patients receiving carbamazepine and clozapine concurrently are considered to be at a higher risk of developing agranulocytosis [6]. The metabolic side effects lead to development of type-2 Diabetes Mellitus among CLZ users which carries an additional vulnerability to get infected with COVID-19.

The uncommon adverse effects include ischemic colitis, paralytic ileus, hematemesis, gastroesophageal reflux disease, priapism, urinary incontinence, pityriasis rosea, intertriginous erythema, pulmonary thromboembolism, pseudo-pheochromocytoma, periorbital edema and parotitis [7]. These rare side effects are influenced by other variables, including age, early diagnosis, and previous/current pharmacological therapies [7]. Some of these adverse effects, although unpredictable, are often manageable if quickly identified and handled. However, sound knowledge of the drug, clinical alertness and a speedy intervention can significantly lessen the morbidity and mortality related to CLZ treatment. There is an overlap of symptoms of COVID-19 and CLZ side effects and such a situation can be confusing. During hematological investigations of COVID-19 patients using CLZ, lymphocytopenia (33%-83%) have been recorded [8, 9], but not neutropenia [10]. Clozapine induced transient and reversible eosinophilia predictive of the development of pneumonia has been suggested [11].

3. Dose Regime

Subramanian et al. (2017) analysed different CLZ studies on the varying doses of CLZ prescription, such as a very low dose (up to 150 mg/day), a low dose (150 mg/day to 300 mg/day) and a standard dose -300 mg/day to 600 mg/day [12]. (Table-1) Beyond these doses are high and remarkably high doses. Oliver Freudenreich (2009) compared 3 non-overlapping ranges of CLZ and found that 200 to 300 mg is a good initial target (medium range) and 50 to 150 mg (low range) is not as effective as medium or high levels. [Table 1] He suggests that 350-450mg (high range) could be tried if clinical response is poor, but not more effective than the medium range and above 1000mg (very high range) brings about serious side effects [13].

Unfortunately, there are no clear studies on the efficacy of CLZ, particularly those comparing the effects of CLZ at high versus standard doses. Weight gain is greater in those receiving the standard dose than in those receiving a low dose. The incidence of unpleasant side effects (e.g. lethargy, hypersalivation, and dizziness) is lesser at a low dose compared with the standard dose. Most of the side effects become evident at a high dose. In India, the drug is given in lower l doses, such as less than 200 mg/day, with favorable effects.

Table 1. *Varying doses of Clozapine.*

A. Subramanian et al's criterion:
1. Very low dose-up to 150mg/day
2. Low dose-150mg to 300mg/day
3. Standard dose-300mg to600mg/day
4. High doses-above 600mg/day
B. Freudenreich's criterion:
1. Medium" range-200 to 300 mg/mL, initial target
2. Low range-50 to 150 mg/m is not as effective as medium or high levels
3. High range-350 to 450 mg/mL not more effective than the medium range
4. Very high levels-ie > 1,000 mg/mL levels have no proven benefit, increase seizure risk.

Clinicians who are mindful of dose related side effects tend to limit the dose of CLZ and combine with other antipsychotics. Combining CLZ with amisulpiride or aripiprazole has yielded positive results without adding to the serious side effect profile of the drug. There are no clear guidelines regarding the use of combination therapy [14]. Psychotropic medications likely to increase clozapine levels included fluvoxamine, lamotrigine, carbamazepine, and aripiprazole. Non-psychotropic medications associated with clozapine level changes included erythromycin, ciprofloxacin, omeprazole, cimetidine, oral contraceptive pills containing ethinylestradiol, and amiodarone. Smoking cessation also increased clozapine levels. Alcohol can increase the CNS side effects of CLZ such as dizziness, drowsiness, and impairment of concentration and judgement.

A possible multiple drug interaction between clozapine, antifungals, and oral contraceptive, which resulted in an elevated clozapine blood level, eosinophilia and pericarditis with pericardial effusion has been reported [15]. Such cases prompt clinicians involved in CLZ therapy to acquire sound knowledge of drugs that act as substrates, inhibitors, or inducers of P450 so as to take appropriate cautions.

4. Neuromodulation

There have been many theoretical speculations about the mechanism of action of CLZ, particularly its superior effect over other antipsychotics, but there are no conclusive verdicts. CLZ is classified as an atypical antipsychotic drug because of its profile of binding to serotonergic and dopamine receptors. Its effects on various dopamine-mediated behaviors also differ from those exhibited by more traditional antipsychotics. In particular, CLZ interferes to a lower extent with the binding of dopamine at the D_1, D_2, D_3 and D_5 receptors, and it has a high affinity for the D_4 receptor, but it does not induce catalepsy nor inhibit apomorphine-induced stereotypy in animal models as seen with typical antipsychotics. This evidence suggests that CLZ is preferentially more active at limbic than at striatal dopamine receptors. Drugs that are more active at limbic dopamine receptors have cleaner EPSE profile and strong anticholinergic activity. It is a partial agonist at the 5-HT1A receptor, apparently improving depression, anxiety, and negative/cognitive symptoms. It is also a strong antagonist at

different subtypes of adrenergic, cholinergic, and histaminergic receptors. Cholinergic and histaminergic antagonism determine the side effect profile of CLZ. Glutamate enhancing effect of CLZ lacks in depth studies. Many theories of CLZ's superior effect have been made redundant and the mystery of CLZ's mechanism of action remains [16].

5. Immunomodulation

A subset of schizophrenia is hypothesized to be an autoimmune disorder, and the symptoms are thought to be the outcome of autoantibody production against the brain. This hypothesis is founded on several observations. The co-existence of other autoimmune disorders amongst patients and immediate relatives and a series of immunological abnormalities attributed to schizophrenia are the supporting evidence for such a conjecture [17-20]. Having a first-degree relative with schizophrenia has been found to increase the risk of autoimmune disorders by 6% [21], and a family history of autoimmunity has been found to increase the risk of both schizophrenia and non-affective psychoses by 10% [22].

There are many immunological abnormalities associated with CLZ. (Table 2) They include the following: elevated serum immunoglobulin levels [23], decreased mitogenic response of peripheral blood lymphocytes to phytohaemagglutinin and pokeweed mitogen [24, 25], the presence of morphologically abnormal large lymphocytes in the blood and bone marrow [26], increased serum IL-2 receptor levels [27], decreased IL-2 levels [28], IFN-g production [26], and a high serum level of IL-6 [29]. An increase in T suppressor lymphocytes in drug-naive schizophrenic patients and an increase in T helper lymphocytes in drug-treated patients have been noted by Masserini et al. [30].

Table 2. *Immunological abnormalities associated with CLZ.*

Elevated serum immunoglobulin levels
Decreased mitogenic response of peripheral blood lymphocytes to phytohaemagglutinin and pokeweed mitogen
Presence of morphologically abnormal large lymphocytes in the blood and bone marrow Increased serum IL-2 receptor levels
Decreased IL-2 levels
IFN-g production
High serum level of IL-6
Increase in T helper lymphocytes

Coffey et al. (1983) reported a decrease in the percentage of T cells in schizophrenic patients during acute relapse and an increase in the helper suppressor T cell ratio, which is correlated with clinical improvement [31]. CLZ's superior efficacy in controlling schizophrenia symptoms may be attributed to its immune modulation in addition to neuromodulation. Leykina et al. (1997) observed that immune suppression by neuroleptics presumably builds up slowly and reaches a steady state after a period of weeks [26]. They hypothesized that at this inhibited state of immunity, the inherent cellular and humoral autoimmune responses against neurotransmitters may recede, which could act synergistically with the direct effect induced by the binding of the drug to brain receptors; a part of the clinical superiority claimed for CLZ might be attributed to its rather unanticipated action as an immunosuppressant.

Agranulocytosis, one of the rare and serious side effects of CLZ, may be caused by the immune effect of this drug. Capannoloa et al. (2015) proposed that CLZ inhibits polymorphonuclear leukocyte chemotaxis [32]. They found that within the therapeutic concentration range, CLZ potentially and selectively inhibits polymorhponuclear chemotaxis induced by interleukin 8 (IL-8). They added that this effect is not due to its action at dopamine, serotonin, and muscarinic receptors or to a direct antagonism to IL-8 receptors. Furthermore, CLZ did not inhibit polymorhponuclear chemotaxis by its presumed toxic mechanism. Capannoloa et al. (2015) hypothesised that an interference of CLZ with the autocrine release of leukotriene B4 (LTB4), a secondary chemoattractant secreted by neutrophils in response to the primary chemoattractant IL-8, weakens the IL-8-induced release of LTB4 in polymorhponuclears [32]. They claimed that a series of experiments with an antagonist of the LTB4 receptor, U75302, and an inhibitor of LTB4 synthesis, zileuton, confirmed this conjecture, which supports the immune effects of CLZ.

Roge et al (2012) argue that immunological mechanisms may be involved in the development of agranulocytosis and myocarditis or in the unique antipsychotic efficacy in subgroups of schizophrenia patients [33]. They have presented the immunomodulatory effects of CLZ from human in vitro and in vivo studies. The immunomodulatory actions of CLZ have been more or less confirmed, but there are only few studies investigating the relationship to the unique adverse and therapeutic effects of CLZ. Fever and flue like symptoms in the first few months of the commencement of CLZ therapy are attributable to increased cytokines when the immunological mechanism summits and will be discussed later. Roge et al (2012) state [33], "Research relating the immunomodulatory actions of clozapine and its early markers to clinically relevant adverse and therapeutic outcomes is hoped to provide new leads for the understanding of the pathophysiology of schizophrenia and aid the development of novel treatment targets."

6. Clinical Implications

It is a well-understood observation that patients treated with CLZ are highly vulnerable to influenza or its complications if they are infected, although the mechanism of such a higher risk of infection is unclear. This opinion is very well reflected in the fact that patients on CLZ are strongly advised to have flu vaccination before the flu season. COVID-19 is much more infectious and has a higher mortality rate compared with influenza. A spike of cases of COVID-19 coexisting with influenza is anticipated in the coming winter season, and the

added risks of pneumonia should be taken seriously. Hospital admissions because of pneumonia are higher amongst CLZ-treated patients [34, 35]. Ponsford et al. (2018) argued that CLZ use is associated with significantly reduced immunoglobulin levels; consequently, an increased proportion of patients end up using up to five or more antibiotic courses in a year [36]. Apart from the immunodeficiency, the mechanisms proposed for such a high incidence of pneumonia are sialorrhea and aspiration, sedation, agranulocytosis, and smoking [37].

The adherents of the autoimmune aetiology of schizophrenia propose that the very superiority of CLZ over other antipsychotics could be due to its probable partial immunomodulatory/ suppressant effects in addition to its inhibition of dopaminergic transmission. There are also suggestions that CLZ may be working more on immunomodulation rather than neuromodulation [26]. Unfortunately, this situation renders CLZ-treated patients more vulnerable to infections. Including antibody testing in the monitoring programmes of these patients to reduce the risk of pneumonia has also been proposed [36].

The vulnerability to infections may also be linked to the dose of CLZ and the duration of treatment. Whether a reduced dose of CLZ should be encouraged in this critical period of COVID-19 infection is worth discussing. In countries such as India, CLZ is given at a much smaller dose, and it seems to work. It is also to be noted that CLZ does better as time goes by, and at least some patients could be spared from the higher doses if clinicians refrain from rapid titration. The agranulocytosis linked to CLZ is much less serious compared to the mortality caused by respiratory conditions. By causing immunosuppression at higher doses, CLZ invites infection which may lead to inflammatory conditions. These conditions may lead to increase in CLZ levels that lead to CLZ intoxication.

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first identified in December 2019 in Wuhan, Hubei, China, and has resulted in an ongoing pandemic. Common symptoms include fever, cough, fatigue, shortness of breath, and loss olfactory and gustatory faculties. While the majority of cases result in mild symptoms, some progress to acute respiratory distress syndrome possibly precipitated by cytokine storm, multi-organ failure, septic shock, and blood clots. The time from exposure to onset of symptoms is typically around five days, but may range from two to fourteen days.

Even if CLZ does not add to the vulnerability, once patients on CLZ are infected with COVID-19, it may be speculated from our experiences with other pathogens that they might carry a higher risk of pneumonia and its complications. Only time will tell us whether such a conjecture has any validity. There is a high theoretical risk for CLZ-treated patients to be infected with COVID-19, and patients and carers should be on high alert during this critical period. However, so far, any higher incidence of COVID-19 amongst CLZ users has not been reported although a few cases of COVID-19 have been reported among CLZ users. This is indicative that SARS-CoV-2 may be following a totally different trajectory than that of Influenza virus. Initially there was an enthusiasm to compare it to the Flu virus because of its outbreak in the winter season in the west. These are early days to evaluate the risks of COVID-19 amongst CLZ users if additional risks are posed at all. There have been studies on the additional vulnerability of CLZ users when they catch infections and CLZ levels are found to be spiking in severe infections leading to CLZ intoxication [37-43].

It would be prudent to use low dose CLZ in these pandemic days and may take advantage of the immunotherapeutic property of CLZ. Clear evidence should be gathered to prove that CLZ at a low dose can be effective, as most clinicians aim at the standard dose whilst initiating and titrating CLZ. CLZ can be effective at lower doses and becomes more effective as time goes by, but many clinicians do not give the drug a trial at lower doses for sufficient period of time because of various clinical pressures. Proving that a low dose of CLZ can be effective has great bearing in permitting its use in the first episode psychosis as opposed to the current practice of using it as a third antipsychotic, which delays its use and leads to chronicity.

Consideration should be given to dose reduction during COVID infection. Acknowledging the fact that there are no data on COVID-19 in CLZ patients, De Leon et al. (2020) stated that based on what is known about CLZ pharmacology, it may be hypothesized that CLZ, possibly by impairing immunological mechanisms, may increase the risk of pneumonia in infected patients [44]. They cautioned that once fever and/or pneumonia develops, the CLZ dose should be cut in half to decrease the risk of CLZ intoxication. If the signs of CLZ intoxication persist despite the reduction in CLZ, completely stopping drug use is recommended by De Leon et al. CLZ may be recommenced once the signs of inflammation and fever have disappeared [44]. Seizure, myocarditis, and neutropenia have been reported, but as a rule, severe adverse effects are found to be infrequent. The relationship between infection, clozapine levels and adverse events involve complex and multi-factorial components. Cytokine mediated inhibition of CYP1A2 partly accounts for the increase of CLZ levels in systemic inflammation [45].

The risks posed by CLZ treatment during the COVID-19 pandemic must, however, be balanced against the substantial benefit many patients receive from this medication and clinicians should also be mindful of the likelihood of mental health deterioration with unplanned treatment cessation [44]. According to RCPsych policy on CLZ and blood dyscrasias in patients with COVID-19, CLZ levels are to be taken in all patients with suspected symptoms of COVID-19. For those who already suffer with psychotic disorders the pandemic may present new and difficult challenges and there is an amplification of psychotic symptoms. Increased social isolation, loneliness, health anxiety, stress and an economic downturn are a lethal combination that will adversely affect the existing mental health problems and any dose adjustment of CLZ should be done with extreme caution.

7. Rebound Psychosis, Neurotoxicity

Rebound psychosis or super-sensitivity psychosis has been well documented following sudden withdrawal of CLZ [47]. So, it is not advisable to stop the CLZ abruptly if patients develop COVID-19 symptoms. Moreover, complications of COVID-19 have been suggested to involve neurotoxic effects and both together can result in a confusing clinical situation. Two-thirds of patients infected with COVID-19 were observed to initially suffer from olfactory and gustatory symptoms, and the fatigue experienced by most patients is suggestive of neurotoxicity [48].

Early evidence from the COVID-19 pandemic suggests that delirium could be a common problem. The impact of COVID-19 on the brain, and the effect of the potentially altered brain function on mental health issues, are both unclear. COVID-19 has also been linked with encephalitis and Guillain–Barré syndrome where the immune system attacking the nerves akin to cytokine storm which is an overreaction of the immune cells to thwart the viral pathogen. COVID-19 needs to be further explored because of its possibility of having immune-mediated neurotoxic effects on the brain just like SARS. It can be argued that the immunomodulatory effects of CLZ may have some therapeutic effects to negate the autoimmune reactions that occur in COVID-19 conditions. The suggestion of Leon et al to reduce the dose of CLZ appears a prudent action [44] rather than panic withdrawal of the drug.

8. Immune Dysregulation, Cytokine Storm

The immune dysregulation observed in life-threatening infections and hyperinflammatory states, such as pneumonia, is called a cytokine storm. Direct toxic effects and indirect immunomodulatory mechanisms have been described during cytokine release syndrome. The neurotoxic effects of COVID-19 resulting due to the cytokine storm appear to have parallels with the autoimmune reaction causing Schizophrenia symptoms. If that is the case, the immunotherapeutic effect of CLZ might be useful to block cytokine storm. It is worth considering that patients already on CLZ if they develop COVID-19, to reduce the dose to a minimum level; hypothetically that might even block the cytokine storm and protect the patients from complications of COVID-19. These are only theoretical speculations that warrant confirmation, falsification, or modifications.

Plaze et al (2020) hypothesize that chlorpromazine could reduce the adverse course of COVID-19 infection among patients requiring respiratory support without the need for ICU care, and that it could also reduce the contagiousness of SARS-CoV-2 [49]. They observed a lower incidence of symptomatic forms of COVID-19 among patients than among clinical staff. This reflexion led them to assume that psychotropic drugs could have a prophylactic action against the morbidities of SARS-CoV-2.

Cytokine storm puts the clinician in an ambivalent state in the sense that immunosuppressants would make the patient more vulnerable to continued infection, but they are used anyway because of a shortage of choices. What is required is an efficient immunoregulator and immunotherapeutic drug to block the cytokine storm, which is responsible for the associated complications and mortality. As it is increasingly clear that CLZ has an immunoregulatory function, it would be significant to study its usefulness in immune-deregulatory states. There has not been any study regarding the beneficial effect of low dose CLZ in deescalating the cytokine storm. Its potential alternate efficacy to curb the cytokine storm, if at all present, deserve further attention.

A simple variant of cytokine storm has been already recognized during the initiation of CLZ and it is very transient. Patients who were treated with clozapine for the first time have an increased rate of developing a fever. There are several explanations presented for this occurrence of temperature alteration. Fever is always body's defense mechanism to enhance the immune system. This thermal variation is interpreted as a mild variant of malignant neuroleptic syndrome or a sign of infection related to neutropenia. It may also be considered as an allergic reaction and a manifestation of the immune-modulating effects of clozapine [48]. The interpretation of an allergic reaction is unsubstantiated because of the fact that the fever does not recur in cases where CLZ has been stopped and reintroduced. Among these hypotheses, recent evidence has suggested that fever may develop secondarily to a generalized inflammatory response as a manifestation of the immune-modulating effects of CLZ [50]. IL -6 has been postulated to have a specific role in the interaction effect between treatment duration and fever development and the initial fever could be considered as a variant of cytokine storm [51].

Several cytokines, including tumor necrosis factor-α (TNF-α), interferon-γ (INF-γ), interleukin-2 (IL-2), and interleukin-6 (IL-6), are pleiotropic cytokines that mediate the acute response during inflammation or infection.[52] The mix of these cytokines causes an increase in body temperature, and these cytokines are referred to as "endogenous pyrogens"[53]. An endogenous chemical response to an exogenous chemical cannot be equated with an immune response to an exogenous pathogen. The early cytokine release syndrome is self-limiting, although its mechanism is unclear. The initial fever is benign and may be occurring due to immune-dysregulation and later corrected by the build-up of immunotherapeutic effects of CLZ. In the initial phase of CLZ therapy, the immune system is disturbed by the drug and then CLZ seems to aid the autocorrection of the immune system. This short-lived subtle cytokine storm appears like the manifestation of immune stimulant and suppressant effects of CLZ-It functions like "accelerator and break."

Patients suffering from autoimmune disorders are more vulnerable to the complications of COVID-19. Cytokine storm itself is an autoimmune reaction and patients with existing autoimmune conditions automatically spawn violent cytokine storm. There are case reports validating such an assumption. If schizophrenia is an autoimmune disorder,

theoretically the sufferers are also more vulnerable to the complications of any viral infection including COVID-19 that could set off cytokine storm. The complications of COVID-19 are related to the intensity of cytokine storm. It is still unclear whether schizophrenia sufferers are more vulnerable to the complications of cytokine storm and low dose CLZ has any prophylactic effect or it would aggravate the cytokine release syndrome.

9. Multiple Actions

Psychiatric drugs sometimes have multiple actions and idiosyncratic effects as is the case of drugs used in general medical practice. Amitriptyline was a popular traditional antidepressant and is now used as an analgesic. Mirtazapine has a hypnotic effect at lower doses but becomes an alerting agent at higher doses. At a lower dose, it causes weight gain, but at a higher dose, it does not have the same effect. Chlorpromazine had a humble beginning as a sedative antihistamine and later turned out to be "Largactil" meaning large actions. The suggestion that redeployment and adaptation of chlorpromazine for its anti-SARS-CoV-2 activity could offer an alternative strategy to lessen the severity of the circulating infection and the immunomodulatory effects of chlorpromazine could also open new perspectives for the treatment of not only early but also late and severe forms of COVID-19 [49]. This may be comparable to the evolutionary phenomenon where birds developed wings for warmth and later began to use them for flying.

The supposed antiviral effects of psychotropic drugs could be explained in terms of their destressing effects which in turn enhance immunity system. Immunity and stress have direct relation and when patients are cushioned with psychotropics, they are able to unwind themselves and their immunity get a boost. The hypnotic property of the antipsychotic drugs has a direct effect on immunity: sleep is the bedrock of immunity. This is not to devalue the claimed effects of psychotropic medications in warding off infections, but CLZ cannot be recommended for that purpose.

There are several examples of double-action drugs that are prevalent in clinical practice. Glucocorticoids are both anti-inflammatory and pro-inflammatory. Since their discovery in the 1940s, glucocorticoids have been considered anti-inflammatory molecules. However, there are emerging views proposing that glucocorticoid actions may also involve proinflammatory regulations. The anti-inflammatory activity of glucocorticoids is attributed to the repression of pro-inflammatory genes through signal transduction by their steroid receptors, the glucocorticoid receptor [54]. The mechanisms modulating the pro-inflammatory effects of glucocorticoids are not well understood. Corticosteroids have now been well established as causing dose-related immunosuppression and are also immunotherapeutic.

CLZ could be considered a dual-action drug if its effectiveness in controlling the symptoms of tardive dyskinesia which is a neurological disorder is taken into consideration. CLZ is now being used to treat borderline personality disorder and rapid cycling bipolar disorder. Apart from the antipsychotic effect, CLZ may also have other actions that need further exploration. The usefulness of lower doses of this generic drug in other autoimmune reactions need further investigations. In India where CLZ is less feared and not stigmatized, there are unpublished case trials of low dose CLZ with some success in the treatment of rheumatoid arthritis- the apparent beneficial effect could be explained in terms of the hypnotic and anxiolytic properties of CLZ. Extreme caution is warranted in such co-prescribing of CLZ.

Dopamine receptors exist outside of the brain as well. Dopamine receptors arise on the surface of immune cells and synovial cells. These two cells have a significant role in the development and progression of the symptoms of rheumatoid arthritis. Immune T-cells, B-cells, monocytes, and N. K. cells have a part in the degenerative changes that go with rheumatoid arthritis. Animal studies indicate that antipsychotic drugs used to treat schizophrenia might have a positive effect to relieve symptoms of rheumatoid arthritis because of their action at dopamine receptors [55-59]. The negative link between schizophrenia and rheumatoid arthritis is well established. A few initial unfortunate occurrences following introduction of CLZ led to the emergence of *clozophobia* amongst clinicians [60].

10. Discussion

At a higher dose, CLZ has immunosuppressant and pro-inflammatory effects, but at a lower dose, it may be only immunomodulatory—a drug with a double-edged sword. The superior effect of CLZ is supposed to be attributed to its immunity effects. It is an indirect immunosuppressant drug at a higher dose if used for a long duration and may be only a gentle immunoregulator at a smaller dose. It is a drug with serious side effects at a higher dose, but at a smaller dose, it is side effect friendly, except for the rare incidence of agranulocytosis. It is not at all a dangerous drug if given with caution and the side effects can be monitored and corrected. The recommended higher BNF limit is 900 mg/day.

The immunosuppressant effect is related to the duration of drug use and may not come into play if it is used only for a short period. It is well established that CLZ treated patients are prone to respiratory complications if they get infected with Flu virus. This is supposed to be due to the immunosuppressant effects of CLZ. It is feared that such complications can occur in the case of CLZ users in the event of getting infected with SARS-CoV-2. There are no data currently validating this assumption. Future studies should focus on the dosage regime of patients who get infected with SARS-CoV-2. More research is warranted to make any conclusions about the observation that low dose CLZ users are even less vulnerable to COVID-19 or its complications.

The observed reduced incidence of COVID-19 among young users of CLZ needs further evaluation along with its clinical and therapeutic significance. It is to be studied whether young patients receiving CLZ treatment are less

likely to develop complications of CLZ and the rate of mortality among them. Monitoring the intensity of the cytokine storm among the patients receiving CLZ treatment using clinical judgements and biochemical tests can be quite revealing with this effect. It has to be ascertained whether CLZ has any antiviral effect at a lower dose. Case studies focused on COVID-19 among CLZ users are not many and that is also the case in China which utilizes this drug maximum. CLZ has been used with tight restrictions, and it has become the *tomato* of psychopharmacology (tomatoes were considered poisonous fruits a few centuries ago).

Cytokine storm presents with overwhelming clinical syndromes. There is no clear risk benefit ratio for any treatment approaches and clinicians use any available treatment methods out of despair. In schizophrenia sufferers with COVID-19 infections, there is currently no high-grade evidence for any approach to thwart cytokine storm due to lack of sufficient data. Owing to the unclear risk benefit ratio, no strong recommendation can be given. Only a few decades ago, cytokine storm was recognized, and its patho-mechanisms warrants more clarifications.

The mechanism of action of CLZ remains unclear. Clinicians are less cognizant of the immunological effects of CLZ, as its superior effects are attributed to neuromodulation from the beginning of its formulation in 1958. The usefulness of CLZ in other clinical conditions has yet to be explored. COVID-19 patients who are already being treated with CLZ for schizophrenia and related conditions may take advantage of CLZ to calm down the cytokine storm if at all it has the potential to do so. At the moment, this is only a hypothetical possibility. The immunomodulatory effect of CLZ in other autoimmune disorders is worth considering, as current medications have failed in many cases, although the immunity effects of CLZ may not come into play spontaneously. The fact is that the immunoregulatory functions of this powerful drug have been overlooked, and investigators appear to have been barking at the wrong trees.

To date, our knowledge of the immune functions of CLZ has been limited, but such studies can lead to newer forms of therapeutic intervention. CLZ is a highly potent multifaceted drug whose potentialities have not been fully explored because of the fear of its rare fatal side effect. Clinicians all over the world are trying to make a “truce with the viral conqueror” by using any available therapeutic strategies, but it is prudent to repurpose the already familiar drugs with known side effects. It would be incredibly useful to investigate whether CLZ users infected with SARS-CoV-2 develop only less intense cytokine storm and therefore fewer serious complications. So far, there has not been any studies with this effect. CLZ had a slippery historical course because of the erratic side effect profile. There is always the future prospect of identifying derivatives of CLZ free of the serious side effects. If clinicians can demonstrate its effectiveness in other medical conditions, that would give a boost to CLZ research.

Conflicts of Interests

No Funding and No Conflicts of Interests.

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