# **Review Article**



# A Review on Schizophrenia: Outline and Treatment

Sarika Chaudhary\*, Stepi Chaudhary<sup>1</sup>, Vishal Tyagi<sup>2</sup>

\*Department of pharmacology, D.J. College of Pharmacy, AKTU, India.

Department of Pharmaceutics, HIMT College of Pharmacy, AKTU, India.
 Department of Pharmacy, ITS College of Pharmacy, AKTU, India.

\*Corresponding author's E-mail: saruchaudhary37@gmail.com

#### Received: 09-01-2022; Revised: 23-03-2022; Accepted: 30-03-2022; Published on: 15-04-2022.

#### ABSTRACT

Schizophrenia is a debilitating, genetic brain condition caused by anomalies that appear early in infancy and interrupt normal brain development. It has a lifetime risk of 1% and affects people of all ages, with around 10% dying by suicide. COVID-19 may raise the risk of mortality and morbidity in people with schizophrenia. Although antipsychotic medications of the first, second, and third generations are the most commonly prescribed treatments for schizophrenia, they are linked to major side effects such as tardive dyskinesia, oxidative stress, and EPS. Ayurvedic herbal medications and some dietary supplements score well in this category since they can be taken for a long time without causing major adverse effects and have antioxidant properties. Low potency first generation antipsychotics, sedating antihistamines, and benzodiazepines, as well as inhalable antipsychotics, oral and short acting injectable olanzapine, and ziprasidone, as well as low potency first generation antipsychotics, sedating antihistamines, and benzodiazepines, should be avoided or closely monitored for patients with COVID-19. Mentally ill patients with COVID -19 should be segregated if at all possible, and employees should be adequately protected.

Keywords: Schizophrenia, covid-19, antipsychotic, herbal treatment.

QUICK RESPONSE CODE  $\rightarrow$ 



DOI: 10.47583/ijpsrr.2022.v73i02.010

DOI link: http://dx.doi.org/10.47583/ijpsrr.2022.v73i02.010

## INTRODUCTION

ental contamination is any disorder or situation affecting the mind that impacts the manner someone thinks, feels, behaves and/or pertains to others and to his or her surroundings. Although the signs of intellectual contamination can variety from slight to excessive and are one-of-a-kind relying at the form of intellectual contamination, someone with an untreated intellectual contamination regularly is not able to address life's day by day exercises and demands.

Schizophrenia is a devastating infection with an early maturity onset and chronic course. The infection influences all elements of cognition, emotion, perception, and conduct in methods that effect the man or woman with the infection, his or her family, and society. Schizophrenia is a worldwide disorder, affecting 1 percentage of the populace worldwide.<sup>1</sup> In the United States, an anticipated three million guys and women (in same numbers) have schizophrenia <sup>2</sup>, and unfortunately, best 1/2 of acquire treatment <sup>3</sup>. Despite its particularly small numbers, the financial effect is significant <sup>1</sup>. History has supplied many reasons for the genesis of

schizophrenia; contemporary studies indicates that it's miles a multifactorial disorder primarily based totally in genetics, susceptibilities, and environment. Sometimes humans with schizophrenia appear flawlessly best till they communicate approximately what they're actually thinking.

In addition, relapse may also arise due to tremendous signs, which include suspiciousness, delusions, and hallucinations. The inherent heterogeneity of schizophrenia has ended in a loss of consensus concerning the disorder's diagnostic criteria, etiology, and pathophysiology.<sup>4-6</sup> The modern antipsychotic regiment is powerful in treating tremendous signs of the disease, however remedies to mitigate bad signs and cognitive regions are nonetheless limited.<sup>7-8</sup>

Abnormalities in neurotransmission have furnished the idea for theories at the pathophysiology of schizophrenia. Most of those theories middle on both an extra or a deficiency of neurotransmitters, together with dopamine, serotonin, and glutamate. Other theories implicate aspartate, glycine, and gamma-aminobutyric acid (GABA) as a part of the neurochemical imbalance of schizophrenia.<sup>4</sup> Four dopaminergic pathways have been implicated as figure-1.<sup>9-10</sup>



International Journal of Pharmaceutical Sciences Review and Research



### Figure 1: Dopaminergic pathway

The serotonin speculation for the improvement of schizophrenia emerged due to the invention that lysergic acid diethylamide (LSD) more suitable the consequences of serotonin withinside the brain.<sup>1</sup> Subsequent studies brought about the improvement of drug compounds that blocked each dopamine and serotonin receptors, in evaluation to older medications, which affected most effective dopamine receptors. The more recent compounds have been observed to be powerful in assuaging each the fantastic and bad signs of schizophrenia.

Another concept for the signs of schizophrenia entails the pastime of glutamate, the essential excitatory neurotransmitter withinside the brain. This concept arose in reaction to the locating that phenylciclidine and ketamine, non-aggressive NMDA/ glutamate antagonists, result in schizophrenia-like signs. <sup>11</sup>

Many human beings tormented by schizophrenia smoke. This may be attributed to the ailment itself or its remedy.<sup>12</sup> There are severa reviews approximately disturbed mind cholinergic transmission in sufferers with schizophrenia.<sup>13</sup> Patients speak that smoking enables them to alleviate bad signs and symptoms<sup>14,15</sup> which may be connected to their deficiencies concerning nicotinic receptors. The excessive fee of people who smoke amongst sufferers with schizophrenia inspired the studies at the position of nicotinic receptors on this disorder. Studying of  $\alpha$ 7 receptors with precise venomous pollution confirmed that  $\alpha$ 7 receptors are placed in mind areas worried in cognition (e.g., the cortex and hippocampus). Deterioration of cognitive capabilities along with running reminiscence and cognitive flexibility, in addition to attention, assume psychotic signs and symptoms and are a prognosticator of purposeful outcome.<sup>16</sup> The position of irritation and oxidative strain in schizophrenia is a focal point of many studies.<sup>17</sup> It became suggested that extreme infections and immune problems at some point of the life-time are a further danger component for the improvement of schizophrenia.<sup>18,19</sup> As a result of irritation position in schizophrenia, antibiotics and anti-inflammatory retailers were examined to deal with this ailment however with a instead restricted success.<sup>20</sup> However, a tribulation of one thousand mg in line with day of aspirin as upload on remedy confirmed enhancements with inside the Positive and Negative Syndrome Scale (PANSS) general and fantastic signs and symptoms.<sup>21</sup>

The specific reason of schizophrenia maintains to elude investigators. It is extensively accepted, however, that the numerous phenotypes of the infection get up from more than one elements, such as genetic susceptibility and environmental influences.<sup>5,22</sup> One cause of the improvement of schizophrenia is that the disease starts off evolved in utero. Obstetric complications, such as bleeding at some point of pregnancy, gestational diabetes, emergency cesarean section, asphyxia, and occasional beginning weight, had been related to schizophrenia later in life. Fetal disturbances at some point of the second one trimester—a key degree in fetal neurodevelopment—had been of specific hobby to researchers. Infections and extra strain stages at some point of this era had been connected to a doubling of the threat of offspring growing



schizophrenia. Scientific proof helps the concept that genetic elements play a vital function withinside the causation of schizophrenia; research have proven that the threat of infection is about 10% for a first-diploma relative and 3% for a second-diploma relative.<sup>23</sup> Environmental and social elements may additionally play a function with inside the improvement of schizophrenia, specifically in people who are at risk of the disease. Environmental stressors connected to schizophrenia consist of early life trauma, minority ethnicity, house in an city area, and social isolation. In addition, social stressors, which includes discrimination or monetary adversity, can also additionally predispose people towards delusional or paranoid thinking.<sup>4</sup>

The Diagnostic and Statistical Manual IV-TR establishes the scientific standards for schizophrenia, with the most records regarding Criterion A.<sup>24</sup> Two or greater symptoms and symptoms and signs from Criterion A ought to be gift for a widespread part of time in the course of a 1-month period (or much less if correctly treated): delusions, hallucinations, disorganized speech, e.g., common derailment or incoherence, grossly disorganized or catatonic conduct, or poor signs, i.e., affective flattening, alogia, or avolition. Only one Criterion A symptom is needed if delusions are weird or hallucinations encompass a singlevoice jogging statement at the person's conduct or thought, or greater voices speaking with every other. Though now no longer always for diagnostic purposes, hallucinations and delusions are maximum related to schizophrenia. Hallucinations are disturbances in sensory perceptions now no longer primarily based totally in reality. They arise in any sensory modality, however maximum are auditory. Visual hallucinations also can be common. When tactile, gustatory, or olfactory hallucinations are observed, clinicians must recollect investigating a natural etiology. Delusions are fixed, fake beliefs.

The poor symptoms and symptoms or disorganized speech and conduct are obvious to the analyzing clinician, while delusions and hallucinations are inner phenomena that may be determined most effective through asking. Occasionally, sufferers reply to inner stimuli through searching across the room while nobody is present, sporting on a communique alone, or behaving or interacting as though a person or some thing else is present. Clinicians who look at those behaviors verify their scientific suspicion through follow-up inquiry. Medical college students and citizens are taught that the important thing to organising rapport is empathizing with sufferers. But how does someone construct rapport with a person whose speech is incomprehensible, who avoids eye contact, and who will now no longer or can't move? It's smooth to peer how those sufferers are quick categorised as "difficult" or "crazy," euphemisms for unimportant. Yet they're a number of our maximum ill sufferers.

Historical and collateral facts are crucial to the diagnosis. It is vital to affirm that the signs and symptoms constitute schizophrenia, given that all psychosis isn't schizophrenia. People with numerous different main intellectual illnesses, such as main melancholy and bipolar disorder, can show off signs and symptoms much like the ones of schizophrenia. In those individuals, however, the temper signs and symptoms of melancholy or mania are extra prominent. Several training of materials such as hallucinogens, amphetamines, and stimulants can purpose intoxication syndromes that mimic schizophrenia, however the length of signs and symptoms need to be restricted through the pharmacology of the drug.

From the early ranges of the COVID-19 pandemic, worries were raised approximately its impact on intellectual fitness and on sufferers with intellectual contamination. Yet numerous months later, we nonetheless realize little approximately the intellectual fitness outcomes of COVID-19 (its psychiatric sequelae) and the susceptibility of sufferers with intellectual contamination to COVID-19 (its psychiatric antecedents).<sup>25-28</sup>

Several surveys have advised that sufferers with COVID-19 have signs of anxiety (consisting of posttraumatic strain disorder, depression, and insomnia. Cross-sectionally, 22•5% of sufferers with COVID-19 had a concurrent neuropsychiatric analysis.<sup>29-34</sup> the scientific effect of COVID-19 on humans with intense intellectual problems (SMD) including schizophrenia has been quite overlooked. Predictors of disorder severity in COVID-19 including CVD, DM, continual obstructive pulmonary disorder (COPD) and continual immune dysregulation are greater usual in humans with schizophrenia, than the overall population. CORONERVE, a UK-huge surveillance programme, recognized 23 sufferers with a psychiatric analysis following contamination with intense acute breathing syndrome coronavirus 2 (SARS-CoV-2).<sup>35</sup> A meta-evaluation of pooled facts from research that predicted the occurrence of psychiatric problems after the intense acute breathing syndrome (SARS) and Middle East breathing syndrome outbreaks advised that coronavirus infections can result in delirium, anxiety, depression, manic signs, terrible memory, and insomnia.

More than 70% of all schizophrenia sufferers additionally have one or greater scientific conditions, consisting of diabetes type II, pulmonary persistent sickness, and hypertension/coronary coronary heart sickness. Smoking estimates amongst schizophrenia sufferers range from 50 to 90%, in comparison to 20-30% withinside the fashionable populace, and contain better smoking intensity, some other capacity chance element for respiration complications, even though it isn't always but clean whether or not COVID-19 consequences are worse amongst smokers. Spirometric evaluation shows that schizophrenia sufferers have impaired lung function, and they may be greater frequently recognized with restrictive and obstructive pulmonary diseases. In addition, whilst hospitalized for pulmonary conditions, schizophrenia sufferers have better quotes of in depth care unit admissions, acute respiration failure, mechanical ventilation, and in-health facility dying than different sufferers. They even have a better chance of acute



International Journal of Pharmaceutical Sciences Review and Research

organ disorder than the overall populace whilst admitted to the in depth care unit, irrespective of cause. Overall, maximum schizophrenia sufferers might healthy at the least one recognised chance institution for COVID-19 and, if admitted to a health facility, need to be taken into consideration at expanded chance of worse scientific consequences [figure2]. Nonetheless, we trust that publicity to the sort of annoying existence event, modifications of routine, and interpersonal tension because of extended quarantine or maybe the worry of contracting the sickness may also act as essential triggers.<sup>36</sup>

#### **Management for Schizophrenia**

The desire in the treatment of schizophrenia involves focusing on the signs, stopping recurrence, and improving adaptive function so that affected individuals can return to their communities. Drugs should be used to optimize longterm results. — Also known as a nerve relaxant, major sedative, or antipsychotic — a drug commonly used to treat schizophrenia. Pharmacotherapy is the mainstay of schizophrenia management, but the remaining symptoms may persist. For this reason, non-pharmacological treatments such as psychotherapy are also important.<sup>37</sup>

Patients with schizophrenia who forestall taking their remedy are at multiplied threat of relapse, that may result in hospitalization. Therefore, it's far essential to preserve sufferers knowledgeable approximately their infection and approximately the dangers and effectiveness of treatment. Some psychotherapies can assist train sufferers approximately the significance of taking their medications. These projects encompass cognitive behavioral therapy (CBT), non-public therapy, and compliance therapy. [Figure 3]



Figure 3: Non-Pharmacological treatment



Antipsychotic medicines of the first generation primarily work by inhibiting dopamine D2 receptors in the brain. They have no selectivity for any of the dopamine pathways in the central nervous system, therefore they can cause a variety of adverse effects, including extrapyramidal symptoms and increased prolactin. Because the risk of developing TD is about 3 to 5% per year of FGA exposure<sup>38</sup> and treatment is difficult once it has begun, it must be factored into the riskbenefit analysis at the outset of treatment.

After nearly forty years since the introduction of chlorpromazine, the first antipsychotic, the FDA approved the clinical use of clozapine in cases of treatment-resistant schizophrenia, ushering in a new era in schizophrenia treatment. Clozapine was the first antipsychotic medicine

to have a stronger ability to diminish negative symptoms while causing fewer extrapyramidal effects than previous antipsychotics.<sup>39,40</sup> In terms of treating treatment-resistant schizophrenia, clozapine is the most effective antipsychotic. In treatment-resistant patients, this medication is about 30% successful in managing schizophrenia episodes, compared to 4% efficacy with the combination of chlorpromazine and benztropine.<sup>41</sup> Clozapine has also been shown to raise sodium levels in the blood in patients suffering from polydipsia and hyponatremia.<sup>42</sup>

The newest group of antipsychotic drugs, described as the third generation, consists of aripiprazole, brexpiprazole and cariprazine.

The antipsychotic drugs treatment describes as: Table 1

| S.NO | Treatment   | Description  | Therapeutic Uses  | Adverse effect/ Side<br>effects  | Ref |
|------|---|--|---|--|-----|
| 1.   | First Generation<br>Anti-pyschotic  | MOA- Block dopamine<br>receptor  | <ul> <li>schizophrenia</li> <li>bipolar disorder</li> <li>anxiety</li> <li>obssesive<br/>compulsive<br/>disorder</li> <li>dementia</li> <li>autism spectrum<br/>disorder</li> </ul> | <ul> <li>o high risk of<br/>extrapyramidal<br/>syndrome like<br/>akathesia, dyskinesia,<br/>parkinson like<br/>movement</li> <li>o tardive dyskinesia</li> <li>✓ resolved by ↓ dose or<br/>change in<br/>antipyschotic or<br/>anticholinergic drugs</li> </ul> | 38  |
| 2.   | Second Generation<br>Anti-pyschotic<br>Drugs(Atypical)<br>Clozapine<br>Risperidone<br>Olanzapine<br>Quentapine<br>ziprasidone | <b>MOA</b> - Exhibit higher ability<br>to block 5HT <sub>2</sub> A receptor<br>than D <sub>2</sub> receptor  | <ul> <li>schizophrenia</li> <li>bipolar disorder</li> <li>anxiety</li> <li>obssesive<br/>compulsive<br/>disorder</li> <li>dementia</li> <li>autism spectrum<br/>disorder</li> </ul> | <ul> <li>Lower risk of EPS &amp; TD<br/>but metabolic<br/>syndrome like<br/>hypertension,<br/>dyslipidemia</li> <li>✓ Require supportive<br/>care, discontinuation<br/>of drugs</li> </ul>   | 40  |
| 3.   | Third Generation<br>Antipyschotic Drugs   | <ul> <li>Aripiprazole-</li> <li>Inhibition of cAMP accumulation through D₂ receptor (Gα-signaling) →in the presence of high extracellular dopamine conc. It compete with dopamine →result in partial antagonism (clinical benefits)</li> </ul> | <ul> <li>Aripiprazole-</li> <li>Schizophrenia</li> <li>Bipolar disorder</li> <li>Depression</li> <li>OCD</li> <li>Autism</li> </ul>   | Aripiprazole-<br>Akathisia, Weight gain,<br>Agitation, Insomnia,<br>Anxiety, Headache,<br>Constipation, Nausea<br>Brexpiprazole- akathisia,<br>weight gain, infections of<br>upper respiratory tract,<br>somnolence, headache<br>and nasopharyngitis           | 43  |

### **Table 1:** Pharmacological treatment for Schizophrenia



Available online at www.globalresearchonline.net

©Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

|    |        | <ul> <li>When extracellular dopamine conc. is on low level it bind to additional receptor(serotonin 5HT<sub>1</sub>A &amp; 5HT<sub>2</sub>A) → activate them partially → "dopamine stabilizer"</li> <li>Brexpiprazole-</li> <li>partial agonist to dopamine D<sub>2</sub>, D<sub>3</sub> and serotonin 5-HT<sub>1</sub>A receptors, and exhibits also antagonist properties to 5-HT<sub>2</sub>A, 5-HT<sub>2</sub>B and 5-HT<sub>7</sub> receptors</li> <li>Cariprazine-</li> <li>dopamine D<sub>2</sub>, D<sub>3</sub> and serotonin 5HT<sub>1</sub>A and serotonin 5HT<sub>1</sub>A</li> </ul> | Effectiveness is higher<br>than chlorpromazine<br>or ziprasidone<br>Brexpiprazole-<br>• Similar to<br>aripiprazole<br>antipsychotic efficacy<br>is comparable but<br>brexpiprazole causes<br>less akathisia, EPS<br>and activation<br>Cariprazine-<br>• Similar to<br>aripiprazole but<br>can be used for<br>the treatment of<br>schizophrenia<br>patients with<br>dominant<br>negative<br>symptoms | <b>Cariprazine</b> -sedation,<br>akathisia, weight gain,<br>nausea, constipation,<br>anxiety, and dizziness |       |
|----|--------|--|---|---|-------|
| 4. | Others | <ul> <li>GABA agonist attenuates schizophrenia symptoms</li> <li>α 7 Nicotinic receptors agonists can be an attractive drug target but require further investigation</li> <li>certain genetic changes of the CNR1 gene may be effective</li> </ul>   | • Schizophrenia   | o akathisia   | 43,44 |

Because of the unpleasant or severe side effects of modern drugs, many patients stop taking them. This is an area where Ayurvedic herbal medications and some nutritional supplements score well, as they can be used for a long time without causing major negative effects. Ayurvedic medicines and dietary supplements can be used as adjuvant therapy with modern medicines to improve the therapeutic effect while reducing side effects.<sup>45</sup> Antipsychotic medicines are the mainstay of schizophrenia treatment, yet

they are linked to significant side effects include tardive dyskinesia and tremor. Furthermore, approximately 20% of persons do not react to treatment satisfactorily.<sup>46</sup> Some previous studies have demonstrated that Chinese herbal therapy is effective for psychosis, and that combining treatments (drugs and herbs) can improve antipsychotic efficacy or shorten the recovery period while reducing side effects. Table : 1a<sup>47,48</sup>



International Journal of Pharmaceutical Sciences Review and Research

Available online at www.globalresearchonline.net

©Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

| S.NO. | Herbal treatment            | Description   | Application  | Adverse effect   | Ref   |
|-------|-----------------------------|---|--|--|-------|
| 1     | Piper methysticum<br>(Kava) | <ul> <li>Kava is an extract.</li> <li>Contain kavapyrones act as muscle relaxants and anticonvulsants, reduce limbic system excitability</li> <li>Kava act by increasing GABAA receptor densities and suppressing the release of glutamate, this mechanism might explain its usefulness in schizophrenia</li> </ul>                         | <ul> <li>✓ schizophrenia</li> <li>✓ muscle relaxants</li> <li>✓ anticonvulsants</li> </ul>   | <ul> <li>slight morning tiredness</li> <li>allergic reactions</li> <li>yellowing or scaling of the skin</li> <li>gastrointestinal complaint</li> <li>pupil dilation</li> <li>blurred vision</li> </ul> | 45    |
| 2     | Ginkgo biloba               | <ul> <li>Ginkgo extracts contain a large<br/>number of substances ginkgo<br/>flavonoids, ginkgolides that<br/>have been found to have a<br/>variety of pharmacological<br/>effects due to antioxidant<br/>nature</li> </ul>   | <ul> <li>✓ improve vascular<br/>perfusion</li> <li>✓ inhibit<br/>plateletactivating<br/>factor</li> </ul>  | <ul> <li>treat memory problems</li> <li>headache</li> <li>gastrointestinal upset</li> <li>allergic skin reactions</li> </ul>   | 49,50 |
| 3     | Valeriana<br>officinalis    | <ul> <li>In laboratory animals,<br/>valerenic acids have sedative<br/>and anticonvulsant effects,<br/>and valerian extracts have<br/>been demonstrated to have a<br/>variety of effects on GABA-<br/>ergic neurons, including<br/>increased release of GABA,<br/>decreased GABA reuptake,<br/>and decreased GABA<br/>degradation</li> </ul> | ✓ Sedative<br>✓ Anti-convulsant  | <ul> <li>gastrointestinal<br/>upset</li> <li>contact allergies</li> <li>headache</li> <li>restle</li> <li>sleep</li> <li>mydriasis</li> </ul>  | 51-53 |
| 4.    | Rhodiola Rosea              | <ul> <li>contains a variety of compounds that may contribute to its effects32 including the class of rosavins which include rosavin, rosarin, and rosin.</li> <li>Having antioxidant properties</li> </ul>  | <ul> <li>✓ Depression</li> <li>✓ Anxiety</li> <li>✓ Dementia</li> <li>✓ this herbal<br/>supplements along<br/>with antipsychotics<br/>medication can<br/>reduces the risk of<br/>side effects and<br/>improve therapeutic<br/>value of drug</li> </ul> | <ul> <li>headache</li> <li>stomach upset</li> <li>drowsiness</li> </ul>  | 54    |
| 5.    | Zizyphus jujuba             | <ul> <li>Contain jujubosides</li> <li>have inhibitory effects on glutamate-mediated excitatory signal pathway in the hippocampus and probably act through their anticalmodulin action.</li> </ul>   | <ul> <li>✓ used to reduce<br/>glutamate mediated<br/>excitotoxicity in<br/>schizophrenia</li> <li>✓ sedative</li> <li>✓ immunostimulant</li> <li>✓ Wound healing<br/>properties</li> <li>✓ anxiety and insomnia</li> </ul>                             | ○ well tolerated   | 55-57 |



|    |  |   |  |   | -     |
|----|--|---|--|---|-------|
| 6. | Crocus sativus L   | <ul> <li>Contain carotenoids including zeaxanthin, lycopene, and various α- and βcarotenes</li> <li>Antioxidant property</li> </ul>   | <ul> <li>✓ antidepressant,45</li> <li>✓ anti-inflammatory</li> <li>✓ anti-tumor effects</li> <li>✓ radical-scavenging</li> <li>✓ learning and memory improving properties</li> </ul>   | <ul> <li>drowsiness</li> <li>stomach upset</li> <li>nausea</li> </ul> | 58-60 |
| 7. | Panax ginseng,<br>P.japonica, P.<br>notoginseng, and<br>P. quinquefolium | <ul> <li>They are grouped as Ginsenosides, panaxosides, chikusetsusaponin.</li> <li>Ginsenosides prevented scopolamine-induced memory deficits in laboratory animals by increasing central cholinergic activity.</li> <li>They may also protect neurons from ischemic damage and facilitate learning and memory by enhancing nerve growth</li> <li>Ginsenosides appear to modulate neurotransmission through - aminobutyric acid (GABA), and by inhibiting neurotransmitter reuptake</li> </ul> | <ul> <li>✓ Schizophrenia</li> <li>✓ immunomodulatery<br/>drug</li> </ul>   | ○ sleep disturbed   | 45    |
| 8. | Withania<br>somnifera  | <ul> <li>Withianine is main constituents</li> <li>ashwagandha led to more acetylcholine receptor activity</li> <li>similar to GABA</li> </ul>   | <ul> <li>✓ anti-stress</li> <li>✓ cognition facilitating</li> <li>✓ anti-inflammatory<br/>and</li> <li>✓ anti-aging effect</li> </ul>  | <ul> <li>stomach upset</li> <li>nausea</li> </ul>                     | 45    |
|    |  | DIETARY SUPPLE  | MENTS  |   |       |
| 1. | Glycine  | <ul> <li>act as an agonist for NMDA</li> <li>The clinical trials have shown<br/>that Glycine did not help<br/>people who are taking<br/>Clozapine, but it did help (in<br/>reducing negative symptoms)<br/>in people who were taking<br/>risperidone, and olanzapine</li> </ul>   | <ul> <li>✓ treatment for the<br/>negative symptoms of<br/>schizophrenia</li> <li>✓ anti-inflammatory</li> </ul>  | <ul> <li>upset stomach and<br/>nausea</li> </ul>                      | 45,61 |
| 2. | Antioxidant<br>vitamins  | <ul> <li>There are several lines of evidence to support the contribution of oxygen free radicals in schizophrenia, including increased lipid peroxidation, fatty acids, and alterations in blood levels of antioxidant enzymes</li> <li>A fall of the activities of the secondary antioxidant enzymes (glutathione-Stransferase, glucose-6-phosphate dehydrogenase, caeruloplasmin, Ferroxidase) and as well as an in increase in the peroxidation of the lipid</li> </ul>                      | <ul> <li>✓ Oral supplementation<br/>of vitamin C with<br/>atypical antipsychotic<br/>reverses ascorbic acid<br/>levels, reduces<br/>oxidative stress, and<br/>improves BPRS (brief<br/>psychiatric rating<br/>scale score), hence<br/>both the drugs in<br/>combination can be<br/>used in the treatment<br/>of schizophrenia</li> <li>✓ vitamin E (mixed-<br/>tocopherols), in the<br/>treatment and</li> </ul> | <ul> <li>constipation</li> <li>upset stomach</li> </ul>               | 45,62 |

International Journal of Pharmaceutical Sciences Review and Research

|    |   | <ul> <li>was noted among schizophrenic patients</li> <li>Alpha Lipoic Acid, Vitamin E, Vitamin C may have some beneficial impact</li> </ul>   | prevention of tardive<br>dyskinesia   |  |       |
|----|---|---|---|--|-------|
| 3. | EPA omega-3 fish<br>oils                      | • people that have<br>schizophrenia may benefit by a<br>reduction in symptoms when<br>they take fish oil capsules that<br>are high in the EPA   | ✓ schizophrenia   | <ul> <li>fishy breath</li> <li>stomach upset</li> </ul>  | 45    |
| 4. | N-methylglycine<br>(also called<br>sarcosine) | <ul> <li>schizophrenia pathology<br/>suggests that NMDA-receptor<br/>dysfunction (a special kind of<br/>glutamate receptor in the<br/>brain) may contribute to<br/>disordered synapses and brain<br/>atrophy, which ultimately<br/>result in the visible symptoms</li> <li>Sarcosine) may turn out to be<br/>a very beneficial supplemental<br/>treatment (when added to<br/>standard antipsychotic<br/>medications) for some people<br/>with schizophrenia</li> <li>acts by increasing the synaptic<br/>availability of glycine by<br/>inhibiting its reuptake through<br/>a compound called the glycine<br/>transporter – 1 or GlyT-1.</li> </ul> | ✓ N-methylglycine<br>(sarcosine) treatment<br>had significant (on the<br>order of 10 to 15%)<br>improvements in<br>their positive,<br>negative, cognitive,<br>and general<br>psychiatric symptoms | <ul> <li>Irritability</li> <li>Well tolerated</li> </ul> | 45,64 |

People with schizophrenia are a particularly vulnerable group, with a lower immunological response than the overall population. SARS-CoV-2 infection is said to be moderate when it first appears.<sup>65</sup> Dexamethasone has not vet been tried in early covid-19, and its immunesuppressive properties demand caution when recommended to persons with schizophrenia, as it may result in poor treatment outcomes accidentally.<sup>66,67</sup> In a heterogeneous population with COVID-19, data from pilot RCTs and observational studies has revealed mortality advantages for antiplatelet and anticoagulant medications like aspirin and heparin, non-steroidal anti-mitotic drugs like colchicine, and oral hypoglycemic agents like metformin.<sup>68-70</sup> All of these drugs have been clinically shown to be safe and are now being used to treat various diseases. To determine the success of such treatments for patients with schizophrenia, however, robust, well-powered clinical trials would be required. Finally, potential drug-drug interactions (DDI) with COVID-19 medicines and antipsychotics must be considered. Such DDIs can lead to decreased medication tolerance, decreased efficacy, or decreased safety. Risk of QT-prolongation and Torsade de Pointes, as well as cytochromes P450, were identified as important interactions between COVID-19 medicines and antipsychotics in a recent comprehensive study involving three drug interaction databases. This comprehensive review found a high risk of DDI with lopinavir/ritonavir plus quetiapine and ritonavir/indinavir plus risperidone, a haematological risk with clozapine and baricinitib, caution with favipiravir plus chlorpromazine and quetiapine, and no risk of DDI with remdesivir, baricinitib.<sup>71</sup> Self-isolation has been found in studies to cause significant psychological distress in patients with schizophrenia.<sup>72,73</sup> Furthermore, such self-isolation may prevent the patient from receiving their usual antipsychotic treatment, particularly when treatment is administered by a healthcare provider, as is the case with long-acting injectable antipsychotics, or when relatively intensive monitoring is required, as is the case with clozapine. Antipsychotic drug delays or interruptions may raise the chance of psychosis relapse.<sup>74</sup>

# CONCLUSION

Schizophrenia is a complicated multi-factor condition, and it does not appear likely that all symptoms of the disease can be treated with a single-target therapy, based on current knowledge. Treatment for schizophrenia, like many other chronic illnesses, necessitates a collaborative effort between doctors, family, and the community. We can assist these people cope with their condition and reach their full potential by providing vigorous and progressive treatment and compassion. As a result, more research in the field of herbal medicine is needed to improve schizophrenia



treatments. So that patients can receive health-promoting treatment options that include herbs, conventional drugs, and lifestyle adjustments. To ensure the safety of both people with schizophrenia and the general public, recommendations stress quick implementation of steps to reduce the risk of COVID-19 transmission while also maintaining continuity of clinical care and research.

#### REFERENCES

- 1. World health report—mental health: New understanding, new hope. 2001. World Health Organization; 2008 November 16.
- Regier DA, Narrow WE, Rae DS, Manderscheid RW, Locke BZ, Goodwin FK. The de facto US mental and addictive disorders service system. Epidemiologic catchment area prospective 1-year prevalence rates of disorders and services. Arch Gen Psychiatry. 1993;50(2):85-94. Doi: <u>10.1001/archpsyc.1993.01820140007001</u>; PMID: 8427558
- Sadock BJ, Sadock VA. Kaplan and Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007.
- Lavretsky H. History of Schizophrenia as a Psychiatric Disorder. In: Mueser KT, Jeste DV. Clinical Handbook of Schizophrenia. New York, New York: Guilford Press; 2008:3–12.
- Crismon L, Argo TR, Buckley PF. Schizophrenia. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach. 9th ed. New York, New York: McGraw-Hill; 2014:1019– 1046.
- Beck AT, Rector NA, Stolar N, Grant P. Biological Contributions. In: Schizophrenia: Cognitive Theory, Research, and Therapy. New York, New York: Guilford Press; 2009:30–61
- Mailman RB and Murthy V. Third generation antipsychotic drugs: partial Agonism or receptor functional selectivity? Curr Pharmaceut Des. 2010;16(5):488–501. Doi: 10.2174/138161210790361461; PMID: 19909227.
- MaricNP, Jovicic MJ, Mihaljevic M, and Miljevic C. Improving current treatments for schizophrenia. Drug Dev Res. 2016;77(7):357–367. Doi:10.1002/ddr.21337; PMID: 27633376
- Schwartz JH, Javitch JA. Neurotransmitters. In: Kandel ER, Schwartz JH, Jessell TM, et al, eds. Principles of Neural Science. 5th ed. New York, New York: McGraw-Hill; 2013:289–305.
- Stahl SM. Psychosis and Schizophrenia. In: Stahl SM, ed. Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 2nd ed. Cambridge, United Kingdom: Cambridge University Press; 2000:365–399
- Jentsch JD, Roth RH. The neuropsychopharmacology of phencyclidine dopamine hypothesis of schizophrenia. Neuropsychopharmacology. 1999;20(3):201–225. DOI: <u>10.1016/S0893-133X(98)00060-8</u>; PMID: 10063482.
- Manzella F, <u>Malonev</u> SE, <u>Taylor</u> GT. Smoking in schizophrenic patients: A critique of the self-medication hypothesis. World J Psychiatry.2015;5(1):35-46. doi: 10.5498/wjp.v5.i1.35; PMID: 25815253.
- Raedler TJ, Bymaster FP, Tandon R, Copolov D, Dean B. Towards a muscarinic hypothesis of schizophrenia. Mol Psychiatry. 2007;12(3):232-46. doi: 10.1038/sj.mp.4001924; PMID: 17146471.
- Brunzell DH, McIntosh JM. Alpha7 Nicotinic Acetylcholine Receptors Modulate Motivation to Self-Administer Nicotine: Implications for Smoking and Schizophrenia. Neuropsychopharmacology. 2012; 37(5):1134-43. doi: 10.1038/npp.2011.299; PMID: 22169946.
- Forchuk C, Norman R, Malla A, Martin ML, McLean T, Cheng S, Diaz K, McIntosh E, Rickwood A, Vos S, <u>Gibney</u> C. Schizophrenia and the motivation for smoking. Perspect Psychiatr Care. 2002; 38(2):41-9. doi: 10.1111/j.1744-6163.2002.tb00656.x; PMID: 12132630.

- Wallace TL, Bertrand D. Neuronal α7 Nicotinic Receptors as a Target for the Treatment of Schizophrenia. Int Rev Neurobiol. 2015;124:79-111. doi: 10.1016/bs.irn.2015.08.003; PMID: 26472526.
- 17. Yang AC, Tsai SJ. New Targets for Schizophrenia Treatment beyond the Dopamine Hypothesis. Int J Mol Sci. 2017; 18(8):1689. doi: 10.3390/ijms18081689; PMID: 28771182.
- Watkins CC, Andrews SR. Clinical studies of neuroinflammatory mechanisms in schizophrenia. Schizophr Res. 2016; 176(1):14-22. doi: 10.1016/j.schres.2015.07.018; PMID: 26235751.
- Benros ME, Pedersen MG, Rasmussen H, Eaton WW, Nordentoft M, Mortensen PB. A nationwide study on the risk of autoimmune diseases in individuals with a personal or a family history of schizophrenia and related psychosis. Am J Psychiatry. 2014; 171(2):218-26. doi: 10.1176/appi.ajp.2013.13010086; PMID: 24129899.
- Girgis RR, Zoghbi AW, Javitt DC, Lieberman JA. The past and future of novel, non-dopamine-2 receptor therapeutics for schizophrenia: A critical and comprehensive review J Psychiatr Res. 2018; 108:57-83. doi: 10.1016/j.jpsychires.2018.07.006; PMID: 30055853
- Laan W, Grobbee DE, Selten JP, Heijnen CJ, Kahn RS, Burger H. Adjuvant aspirin therapy reduces symptoms of schizophrenia spectrum disorders: Results from a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2010; 71(5):520-7. doi: 10.4088/JCP.09m05117yel; PMID: 20492850.
- Siever LJ, Davis KL. The pathophysiology of schizophrenia disorders: perspectives from the spectrum. Am J Psychiatry 2004;161(3):398– 413. doi: 10.1176/appi.ajp.161.3.398; PMID: 14992962
- 23. McDonald C, Murphy KC. The new genetics of schizophrenia. Psychiatr Clin North Am 2003;26(1):41–63. doi: 10.1016/s0193-953x(02)00030-8; PMID: 12683259
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders DSM-IV TR. 4th ed. Text Revision. Washington, DC: American Psychiatric Publishing; 1994.
- Xiang YT, Yang Y, Li W, Zhang L, Zhang Q, Cheung T, Ng CH. Timely mental health care for the 2019 novel coronavirus outbreak is urgently needed. Lancet Psychiatry. 2020; 7(3):228-229. doi: 10.1016/S2215-0366(20)30046-8; PMID: 32032543.
- 26. Mental health and psychosocial considerations during the COVID-19 outbreak. WHO. March 18, 2020
- Holmes EA, O'Connor RC, Perry VH, Tracey I, Wessely S, Arseneault L, Ballard C, Christensen H, Silver RC, Everall I, Ford T, JOohn A, Kabir T, King K, Madan I, Michie S, Przybylski AK, Shafran R, Sweeney A, Worthman CM, Yardley L, Cowan K, Cope C, Hotopf M, Bullmore E. Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. Lancet Psychiatry. 2020; 7(6):547-560. doi: 10.1016/S2215-0366(20)30168-1; PMID: 32304649
- Yao H, Chen JH, Xu YF. Patients with mental health disorders in the COVID-19 epidemic. Lancet Psychiatry 2020; 7: e21. doi: 10.1016/S2215-0366(20)30090-0; PMID: 32199510
- Paz C, Mascialino G, Adana-Díaz L, Rodríguez-Lorenzana A, Simbaña-Rivera K, Gómez-Barreno L, Troya M, Páez MI, Cárdenas J, Gerstner RM, Ortiz-Prado E. Anxiety and depression in patients with confirmed and suspected COVID-19 in Ecuador. Psychiatry Clin Neurosci 2020; 74(10):554-555. doi: 10.1111/pcn.13106; PMID: 32609409.
- Gennaro Mazza M, De Lorenzo R, Conte C, Poletti S, Vai B, Bollettini I, Melloni EMT, Furlan R, Ciceri F, Rovere-Querini P. COVID-19 BioB Outpatient Clinic Study group; Francesco Benedettiet al. Anxiety and depression in COVID-19 survivors: role of inflammatory and clinical predictors. Brain Behav Immun 2020; 89: 594–600. doi: 10.1016/j.bbi.2020.07.037; PMID: 32738287
- Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L, Walshaw C, Kemp S, Corrado J, Singh R, Collins T, O'Connor RJ, Sivan M. Postdischarge symptoms and rehabilitation needs in survivors of

Available online at www.globalresearchonline.net ©Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited. COVID-19 infection: a cross-sectional evaluation. J Med Virol 2020; 93(2):1013-1022. doi: 10.1002/jmv.26368; PMID: 32729939.

- Bo HX, Li W, Yang Y, Wang Y, Zhang Q, Cheung T, Wu X, Xiang YT. Posttraumatic stress symptoms and attitude toward crisis mental health services among clinically stable patients with COVID-19 in China. Psychol Med 2021; 51(6):1052-1053. doi: 10.1017/S0033291720000999; PMID: 32216863.
- Zhang J, Lu H, Zeng H, Zhang S, Du Q, Jiang T, Du B. The differential psychological distress of populations affected by the COVID-19 pandemic. Brain Behav Immun 2020; 87: 49–50. doi: 10.1016/j.bbi.2020.04.031; PMID: 32304883.
- Nalleballe K, Reddy Onteddu S, Sharma R, Dandu V, Brown A, Jasti M, Yadala S, Veerapaneni K, Siddamreddy S, Avula A, Kapoor N, Mudassar K, Kovvuruet S. Spectrum of neuropsychiatric manifestations in COVID-19. Brain Behav Immun 2020; 88: 71–74. doi: 10.1016/j.bbi.2020.06.020; PMID: 32561222
- Varatharaj A, Thomas N, Ellul MA, Davies NWS, Pollak TA, Tenorio EL, Sultan M, Easton A, Breen G, Zandi M, Coles JP, Manji H, Salman RA, Menon DK, Nicholson TR, Benjamin LA, Carson A, Smith C, Turner MR, Solomon T, Kneen R, Pett SL, Galea I, Thomas RH, Michael BD. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. Lancet Psychiatry 2020; 7: 875–82. doi: 10.1016/S2215-0366(20)30287-X; PMID: 32593341.
- Fonseca L, Diniz E, Mendonc G, Malinowski F, Mari J, Gadelha A. Schizophrenia and COVID-19: risks and recommendations. Braz J Psychiatry. 2020; 42(3):236-238. doi: 10.1590/1516-4446-2020-0010; PMID: 32294689.
- Dickerson FB, Lehman AF. Evidence-based psychotherapy for schizophrenia: 2011 update. J Nerv Ment Dis 2011;199(8):520–526. doi: 10.1097/NMD.0b013e318225ee78; PMID: 21814072
- Correll CU, Schenk EM. Tardive dyskinesia and new antipsychotics. Curr Opin Psychiatry. 2008;21(2):151-156. doi: 10.1097/YCO.0b013e3282f53132; PMID: 18332662.
- Crilly, J. The history of clozapine and its emergence in the US market: A review and analysis. Hist. Psychiatry 2007, 18, 39–60. doi: 10.1177/0957154X07070335; PMID: 17580753.
- Strange, P.G. Antipsychotic drugs: Importance of dopamine receptors for mechanisms of therapeutic actions and side effects. Pharmacol. Rev. 2001, 53, 119–133. PMID: 11171942
- Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatmentresistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988;45(9):789–796. doi: 10.1001/archpsyc.1988.01800330013001; PMID: 3046553.
- Spears NM, Leadbetter RA, Shutty MS. Clozapine treatment in polydipsia and intermittent hyponatremia. J Clin Psychiatry 1996;57(3):12. PMID: 8617697.
- Stepnicki P, Kondej M, Kaczor AA. Current Concepts and Treatments of Schizophrenia. Molecules 2018, 23(8):2087. doi: 10.3390/molecules23082087; PMID: 30127324.
- Wallace TL, Bertrand D. Neuronal α7 Nicotinic Receptors as a Target for the Treatment of Schizophrenia. Int Rev Neurobiol. 2015; 124:79-111. doi: 10.1016/bs.irn.2015.08.003; PMID: 26472526.
- 45. Kumari R, Kaundal M, Ahmad Z, Ashwalayan VD. Herbal and dietary supplements in treatment of Schizophrenia: An approach to improve therapeutics. Int J Pharm Sci Rev Res. 2011; 10(1): 217-24.
- Brenner HD, Dencker SJ, Goldstein MJ, Hubbard JW, Keegan DL, Kruger G, Kulhanek F, Liberman RP, Malm U, Midha KK. Defining treatment refractoriness in schizophrenia. Schizophr Bull. 1990;16(4):551-61. doi: 10.1093/schbul/16.4.55116; PMID: 1981813.
- Saku M. The current clinical practice of herbal medicine in psychiatry in mainland China: a review of literature. Jpn J Psychiatry Neurol. 1991;45(4):825-32. doi: 10.1111/j.1440-1819.1991.tb00521.x; PMID: 1813678.

- Wang B. Traditional Chinese medical treatment to invigorate blood and relieve stasis treatment of schizophrenia: comparison with antipsychotic treatment. Psychiatry Clin Neurosci. 1998;52 Suppl:S329-30. doi: 10.1111/j.1440-1819.1998.tb03259.x; PMID: 9895184
- Kleijnen J, Knipschild P. Ginkgo bilob. Lancet. 1992;340(8828):1136-9. doi: 10.1016/0140-6736(92)93158-j; PMID: 1359218.
- Vale S. Subarachnoid haemorrhage associated with Ginkgo biloba. Lancet. 1998;352(9121):36. doi: 10.1016/S0140-6736(05)79516-7; PMID: 9800751.
- Kaplan HI, Sadock BJ. Comprehensive Textbook of Psychiatry. In: Williams & Wilkins, Baltimore MD, editor; 1995.
- 52. Willey LB, Mady SP, Cobaugh DJ, Wax PM. Valerian overdose: a case report. Vet Hum Toxicol. 1995;37(4):364-5. PMID: 8540231.
- Chan TY, Tang CH, Critchley JA. Poisoning due to an overthe-counter hypnotic, Sleep-Qik (hyoscine, cyproheptadine, valerian). Postgrad Med J. 1995;71(834):227-8. doi: 10.1136/pgmj.71.834.227; PMID: 7784284.
- Panossian A, Nikoyan N, Ohanyan N, Hovhannisyan A, Abrahamyan H, Gabrielyan E, Wikman G. Comparative study of Rhodiola preparations on behavioral despair of rats. Phytomedicine. 2008;15(1-2):84–91. doi: 10.1016/j.phymed.2007.10.003; PMID: 18054474.
- Goetz P. Demonstration of the psychotropic effect of mother tincture of Zizyphus jujube. Phytotherapie. 2009; 7(1):31-36. Doi: 10.1007/s10298-008-0362-7.
- Jiang JG, Huang XJ, Chen J, Lin QS. Comparison of the sedative and hypnotic effects of flavonoids, saponins, and polysaccharides extracted from Semen Ziziphus jujube. Nat Prod Res. 2007;21(4):310-20. doi: 10.1080/14786410701192827; PMID: 17479419
- 57. Mahajan RT, Chopda MZ. Phyto-pharmacology of Ziziphus jujuba mill - A plant review. Pharmacog Rev. 2000;3(6):320-329.
- Abdullaev FJ. Biological effects of saffron, Biofactors. 1993;4(2):83-86. PMID: 8347278.
- Zhang Y, Sugiura M, Saito H, Shoyama Y. Acute effects of Crocus sativus L. on passive avoidance performance in mice. Biol Pharmacol Bull. 1994;17(2):217-221. doi: 10.1248/bpb.17.21717,1994, 217-21. PMID: 8205119.
- Abe K, Sugiura M. Ymaguchi S, Shoyama Y, Saito H. Saffron extract prevents acetaldehyde-induced inhibition of long-term potentiation in the rat dentate gyrus in vivo. Brain Res. 1999;851(1-2):287-9. doi: 10.1016/s0006-8993(99)02174-5; PMID: 10642859.
- Chatterjee M, Ganguly S, Srivastava M, Palit G. Effect of 'chronic' versus 'acute' ketamine administration and its 'withdrawal' effect on behavioural alterations in mice: implications for experimental psychosis. Behav Brain Res. 2011;216(1):247-254. doi: 10.1016/j.bbr.2010.08.001; PMID: 20699106.
- Grima G, Benz B, Parpura V, Cuénod M, Do KQ. Dopamine-induced oxidative stress in neurons with glutathione deficit: implication for schizophrenia. Schizophr Res. 2003; 62(3):213-24. doi: 10.1016/s0920-9964(02)00405-x; PMID: 12837517.
- Devi U, Chinnaswamy P. Oxidative injury and enzymic antioxidant misbalancein schizophrenics with positive, negative and cognitive symptoms. Afr J Biochem Res. 2008;2(4):92-97.
- Guochuan T, Lane HY, Yang P, Chong MY, Lange N. Glycine Trnasporter 1 Inhibitor, NMethylglycine [sarcosine], Added to Antipsychotics for the Treatment of Schizophrenia. Biol Psychiatry. 2004;55(5):452-6. doi: 10.1016/j.biopsych.2003.09.012; PMID: 15023571.
- 65. Grant MC, Geoghegan L, Arbyn M, Mohammed Z, McGuinness L, Clarke EL, Wade RG. The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): a systematic review and meta-analysis of 148 studies from 9



countries. PLoS ONE. 2020;15(6):e0234765. doi: 10.1371/journal.pone.023476; PMID: 32574165.

- Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, de Castilla DL, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh MD, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC, ACTT-1 Study Group Members. Remdesivir for the treatment of Covid-19 - final report. N Engl J Med. 2020; 383(19):1813–1826. doi: 10.1056/NEJM0a2007764; PMID: 32445440.
- Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384(8):693–704. doi: 10.1056/NEJMoa2021436; PMID: 32678530.
- National Institute for Health and Care Excellence. COVID-19 Rapid Evidence Summary: Remdesivir for Treating Hospitalised Patients With Suspected or Confirmed COVID-19. National Institute for Health and Care Excellence ;2020. Available online at: <u>https://www.nice.org.uk/advice/es27</u> (accessed March 11, 2021).
- Perantie DC, Brown ES. Corticosteroids, immune suppression, and psychosis. Curr Psychiatry Rep. 2002;4(3):171–176. doi: 10.1007/s11920-002-0023-8; PMID: 12003678.
- Nelson JC, Davis JM. DST studies in psychotic depression: a metaanalysis. Am J Psychiatry. 1997;154 (11):1497–1503. doi: 10.1176/ajp.154.11.1497; PMID: 9356556.

- 71. McCullough PA, Alexander PE, Armstrong R, Arvinte C, Bain AF, Bartlett RP, Berkowitz RL, Berry AC, Borody TJ, Brewer JH, Brufsky AM, Clarke T, Derwand R, Eck A, Eck J, Eisner RA, Fareed GC, Farella A, Fonseca SNS, Geyer Jr CE, Gonnering RS, Graves KE, Gross KBV, Hazan S, Held KS, Hight HT, Immanuel S, Jacobs MM, Ladapo JA, Lee LH, Littell J, Lozano I, Mangat HS, Marble B, McKinnon JE, Merritt LD, Orient JM, Oskoui R, Pompan DC, Procter BC, Prodromos C, Rajter JC, Rajter JJ, Ram CVS, Rios SS, Risch HA, Robb MJA, Rutherford M, Scholz M, Singleton MM, Tumlin JA, Tyson BM, Urso RG, Victory K, Vliet EL, Wax CM, Wolkoff AG, Wooll V, Zelenko V. Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19). Rev Cardiovasc Med. 2020;21(4):517–530. doi: 10.31083/j.rcm.2020.04.264; PMID: 33387997.
- Bramante CT, Ingraham NE, Murray TA, Marmor S, Hovertsen S, Gronski J, , McNeil C, Feng R, Guzman G, Abdelwahab N, King S, Tamariz L, Meehan T, Pendleton KM, Benson B, Vojta D, Tignanelliet CJ. Metformin and risk of mortality in patients hospitalised with COVID-19: a retrospective cohort analysis. Lancet Healthy Longev. 2021;2(1):e34–41. doi: 10.1016/S2666-7568(20)30033-7; PMID: 33521772.
- Cameron AR, Morrison VL, Levin D, Mohan M, Forteath C, Beall C McNeilly AD, Balfour DJK, Savinko T, Wong AKF, Viollet B, Sakamoto K, Fagerholm SC, Foretz M, Lang CC, Rena G. Anti-Inflammatory effects of metformin irrespective of diabetes status. Circ Res. 2016;119(5):652–665. doi: 10.1161/CIRCRESAHA.116.308445; PMID: 27418629.
- Plasencia-García BO, Rodríguez-Menéndez G, Rico-Rangel MI, Rubio-García A, Torelló-Iserte J, Crespo-Facorro B. Drug-drug interactions between COVID-19 treatments and antipsychotics drugs: integrated evidence from 4 databases and a systematic review. Psychopharmacology (Berl). 2021;238(2):329–340. doi: 10.1007/s00213-020-05716-4; PMID: 33410987.

**Source of Support:** The author(s) received no financial support for the research, authorship, and/or publication of this article.

**Conflict of Interest:** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

For any question relates to this article, please reach us at: globalresearchonline@rediffmail.com

New manuscripts for publication can be submitted at: submit@globalresearchonline.net and submit\_ijpsrr@rediffmail.com

