

## A REVIEW ON PHARMACOLOGICAL AND ADJUVANT THERAPIES FOR SCHIZOPHRENIA

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### SUMMARY

Schizophrenia is a psychological disorder, diagnosed by observed behavior and patient reported experiences. Antipsychotic medication mainly works by suppressing dopamine activity. Neuroleptics are also called as antipsychotic drugs. There is a increased risk of extrapyramidal side effects with typical antipsychotics. Atypical antipsychotics refers to newer antipsychotics that confer to less risk of extrapyramidal side effects.

Along with these Neuroleptic treatment other adjuvant treatments like Insulin shock, Electroconvulsive, Oestrogen, Glycine, Cox 2 and Antioxidant therapies are also used for Schizophrenia. Insulin is a hormone that maintain blood sugar level. Repeated injections with large doses of insulin causes daily comas over several weeks during which the patient lost psychotic thoughts. In electroconvulsive therapy controlled electric currents pass through the brain, altering brain chemistry and reducing depression and schizophrenic symptoms. Repeated applications of electric current alter the neurotransmitter level in central nervous system. In oestrogen therapy epidemiological, clinical and animal studies exploring the protective effect of oestrogen against schizophrenic symptoms. Psychoprotective action of oestrogen appears to be mediated by central dopaminergic and serotonergic mechanisms. Glycine(amino acid) , antioxidants and vitamins are potential treatments for the negative symptoms of Schizophrenia. There is an imbalance between the type 1 and type 2 immune systems in patients with psychosis, this imbalance can be restored by Cox 2 inhibitors.

**KEY WORDS:** Schizophrenia, Neuroleptics, Insulin, Electric current, Oestrogen Glycine.

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### INTRODUCTION

Schizophrenia is a psychological disorder characterized by disintegration of thought processes and of emotional responsiveness.<sup>1</sup> It most commonly manifests as auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking, and it is accompanied by significant social or occupational dysfunction. The onset of

symptoms typically occurs in young adulthood, with a global lifetime prevalence of about 0.3–0.7%.<sup>2</sup> Diagnosis is based on observed behavior and the patient's reported experiences. Genetics, early environment, neurobiology, and psychological and social processes appear to be important contributory factors; some recreational and prescription drugs appear to cause or worsen symptoms. Current research is focused on the role of

neurobiology, but this inquiry has not isolated a single organic cause. The many possible combinations of symptoms have triggered debate about whether the diagnosis represents a single disorder or a number of discrete syndromes.<sup>3</sup>

The mainstay of treatment is antipsychotic medication, which primarily works by suppressing dopamine activity. Psychotherapy and vocational and social rehabilitation are also important. In more serious cases—where there is risk to self and others—involuntary hospitalization may be necessary, although hospital stays are now shorter and less frequent than they were.<sup>4</sup> The disorder is thought mainly to affect cognition, but it also usually contributes to chronic problems with behavior and emotion. People with schizophrenia are likely to have additional (comorbid) conditions, including major depression and anxiety disorders; the lifetime occurrence of substance abuse is almost 50%.<sup>5</sup> Social problems, such as long-term unemployment, poverty and homelessness, are common. The average life expectancy of people with the disorder is 12 to 15 years less than those without, the result of increased physical health problems and a higher suicide rate (about 5%).<sup>2</sup>

## DRUG TREATMENT

Effective pharmacologic treatment of schizophrenia has been available since the 1950s. In the early 1950s, the term “neuroleptic” was introduced to denote the effects of chlorpromazine (Thorazine; brand no longer available in the United States) and reserpine on laboratory animals. It was intended to distinguish their effects from those of sedatives and other central nervous system depressants.<sup>6</sup> Although “neuroleptic” is still used synonymously with “antipsychotic,” the

term now usually refers to first-generation antipsychotics that confer an increased risk of extrapyramidal side effects, such as dystonic reactions (e.g., fixed upper gaze, neck twisting, facial muscle spasms), parkinsonian symptoms (e.g., rigidity, bradykinesia, shuffling gait, tremor), and akathisia (e.g., inability to sit still, restlessness, tapping of feet). Tardive dyskinesia, which is a chronic disorder of the nervous system characterized by involuntary jerking movements (primarily of the face, tongue, and jaw), often is considered an extrapyramidal side effect. However, it is actually a separate and mechanistically different phenomenon. The term “atypical antipsychotic” refers to newer antipsychotics that confer less risk of extrapyramidal side effects than traditional antipsychotics. *Table 1* lists antipsychotic agents currently available in the United States. Nonadherence to medications is a significant problem; in a recent study, 74 percent of patients discontinued their medication within 18 months.<sup>7</sup> Nonadherence often leads to relapse of symptoms. Atypical antipsychotics were initially thought to help with adherence because of their lower rate of neurologic side effects. However, meta-analyses have found that drop-out rates and relapse prevention are no better with atypical antipsychotics than with neuroleptics.<sup>8,9</sup> Meta-analyses also have found that in terms of symptom scores and drop-out rates, atypical antipsychotics are better than high dosages (i.e., more than 12 mg per day) of haloperidol (Haldol); there was no advantage when the dosage of haloperidol was less than 12 mg per day.<sup>8</sup> In other words, many of the perceived benefits of atypical antipsychotics actually were a result of the excessive doses of first-generation antipsychotics that were used for comparison in randomized trials.<sup>8</sup> Evidence suggests that delays in initiating

therapy with antipsychotics may result in a lifetime deleterious effect on psychotic episodes and social adjustment.<sup>10,11</sup>

### **Mechanism of action**

There are different types of DA-receptors<sup>12</sup> and it appears that antipsychotic drugs probably owe their therapeutic effects mainly by blocking the D2 receptors. The main groups, phenothiazines, thioxanthenes and butyrophenones, show preference for D2 over D1 receptors. Some newer agents (e.g. remoxipride) are highly selective for D2 receptors, whereas clozapine is relatively non-selective between D1 and D2, but has high affinity for D4 dopamine receptor. The naturally occurring agonist interacts with D1 and D2 receptors, and both receptors are found in high density in the corpus striatum and nucleus accumbens. It has been observed that mostly striated neurons exhibit D1 responses whereas accumbens neurons exhibit D2 responses.<sup>13</sup>

### **ADJUVANT THERAPIES**

#### **Insulin shock therapy**

Insulin shock therapy or insulin coma therapy was a form of psychiatric treatment in which patients were repeatedly injected with large doses of insulin in order to produce daily comas over several weeks.<sup>14</sup>

A standardized treatment protocol was developed. Insulin injections led to two to three hours of low blood sugar levels. (Insulin is a hormone that drives sugars from the blood to storage in the liver.) When blood sugar levels fall precipitously, the brain cannot sustain consciousness and the patients become stuporous. When the patients developed

stupor or coma, they lost their psychotic thoughts.

Insulin coma therapy was a labour-intensive treatment that required trained staff and a special unit.<sup>15</sup> Patients, who were almost invariably diagnosed with schizophrenia, were selected on the basis of having a good prognosis and the physical strength to withstand an arduous treatment.<sup>16</sup> There were no standard guidelines for treatment; different hospitals and psychiatrists developed their own protocols.<sup>16</sup> Typically, injections were administered six days a week for about two months.<sup>14</sup> The daily insulin dose was gradually increased to 100–150 units until comas were produced, at which point the dose would be levelled out.<sup>14</sup> Occasionally doses of up to 450 units were used.<sup>17</sup> After about 50 or 60 comas, or earlier if the psychiatrist thought that maximum benefit had been achieved, the dose of insulin was rapidly reduced before treatment was stopped.<sup>16,18</sup> Courses of up to 2 years have been documented.<sup>18</sup> After the insulin injection patients would experience various symptoms of decreased blood glucose: flushing, pallor, perspiration, salivation, drowsiness or restlessness.<sup>18</sup> Sopor and coma—if the dose was high enough—would follow. Insulin shock therapy would follow.<sup>18</sup> Each coma would last for up to an hour and be terminated by intravenous glucose.<sup>14</sup> Seizures sometimes occurred before or during the coma.<sup>19</sup> Many would be tossing, rolling, moaning, twitching, spasming or thrashing around.<sup>16</sup> Some psychiatrists regarded seizures as therapeutic and patients were sometimes also given electroconvulsive therapy or cardiazol/metrazol convulsive therapy during the coma, or on the day of the week when they didn't have insulin treatment.<sup>18,19</sup> When they were not in a coma, insulin coma patients were kept together in a group and given special

treatment and attention; one handbook for psychiatric nurses, written by British psychiatrist Eric Cunningham Dax, instructs nurses to take their insulin patients out walking and occupy them with games and competitions, flower-picking and map-reading, etc.<sup>20</sup> Patients required continuous supervision as there was a danger of hypoglycaemic aftershocks after the coma.<sup>15</sup> In "modified insulin therapy", used in the treatment of neurosis, patients were given lower (sub-coma) doses of insulin.

### **Electroconvulsive therapy**

During electroshock therapy, controlled electric currents pass through the brain, altering brain chemistry and reducing depression and schizophrenia symptoms. When schizophrenia patients don't respond to antipsychotic medication, doctors may recommend electroshock therapy.<sup>21</sup>

Early electroshock therapy methods exposed fully conscious patients to dangerously high levels of electricity, sometimes resulting in death. Although electroshock therapy has become significantly safer over the years, public opinion continues to view it as cruel and dangerous.

Electroshock therapy is rarely the first choice for schizophrenia treatment. Schizophrenia symptoms are generally treated with antipsychotic medication first. If this method fails, doctors may then consider electroshock therapy.

Electroshock therapy works faster than antipsychotic medication, which can take several weeks to alleviate schizophrenia symptoms. In certain circumstances, the fast-acting nature of electroshock therapy may make it a preferable first line of schizophrenia treatment. People suffering from exceptionally severe schizophrenia

symptoms may experience relief after two or three sessions of electroshock therapy. Schizophrenia patients who are a threat to themselves or others may also benefit from electroshock therapy before taking antipsychotic medication. An electroshock therapy session lasts approximately fifteen minutes, plus preparation and recovery time. During the procedure, the patient is under general anesthetic, so she feels nothing. As the electric current stimulates a seizure, a muscle relaxant prevents convulsions.

Electrodes are positioned on the head and a controlled electric current is sent through the electrodes and into the brain.<sup>22</sup> The patient's heart rate, blood pressure and breathing are carefully monitored during an electroshock therapy session. The patient may also wear a protective mouth guard during the induced seizure. Electroshock therapy usually lasts two to four weeks, with two to three treatments a week. Since schizophrenia symptoms often return after electroshock therapy, patients may require "maintenance" sessions to prevent relapse. The exact mechanisms by which ECT exerts its therapeutic effect are not known, but studies show that repeated applications have effects on several kinds of neurotransmitters in the central nervous system. ECT seems to sensitize two subtypes of serotonin (5-HT) receptor, thereby strengthening signaling. ECT also decreases the functioning of norepinephrine and dopamine inhibiting auto-receptors in the locus ceruleus and substantia nigra, respectively, causing more of each to be released<sup>23</sup>.

### **Complications**

Electroshock therapy requires general anesthetic, which can cause an increase in blood pressure and heart rate. Death due

to general anesthesia is rare in healthy individuals, but can occur.

Memory loss is a common complication of electroshock therapy. Patients often have difficulty remembering events in the weeks prior to or during treatment. These issues may continue after electroshock therapy ends, but generally improve in the months after treatment. Permanent memory loss due to electroshock therapy is rare.

Electroshock therapy patients commonly report side effects after treatment, including:

- Headaches
- Jaw pain
- Muscle aches
- Nausea
- Vomiting.

### Oestrogen therapy

The oestrogen protection hypothesis proposes that oestrogen has a protective effect against onset of schizophrenia. In support of this:

- Epidemiological studies have shown that young women are less likely to develop schizophrenia than men of the same age, and women are more likely to develop late-onset schizophrenia after menopause.
- Clinical studies have shown higher psychotic symptoms in perimenopausal women, and women at the low oestrogen phase of the menstrual cycle.

Animal studies provide further evidence in support of the oestrogen protection hypothesis.

One of the most compelling hypotheses to emerge in the understanding of the possible causes and potential new treatments for schizophrenia is the oestrogen protection hypothesis.<sup>24,25</sup> The hypothesis is described in two parts:

- In women, oestrogen “protects” women from developing severe schizophrenia at an early age.
- Fading oestrogen secretion at menopause in vulnerable women leads to relapse of schizophrenia symptoms or new, late-onset schizophrenia.

There are three main areas of support for the oestrogen protection hypothesis — epidemiological findings, clinical evidence and animal studies exploring the effects of oestrogens on key neurotransmitters that are implicated in producing psychotic symptoms. Randomised controlled trials are providing evidence for the use of oestradiol to ameliorate the symptoms of schizophrenia.

### Epidemiological evidence

Epidemiological sex differences in schizophrenia have been reported for over a century. In 1910, Kraepelin described a later age of first admission for women with schizophrenia compared with men<sup>26</sup>. A review of over 50 studies showed the same sex difference in the age of admission and onset of the first episode of schizophrenia<sup>27</sup>. In a population-based sample of 232 first-episode schizophrenia presentations, there was a steep early increase in the age of schizophrenia onset in men between the ages of 15 and 25 years.<sup>28</sup> In women, the rates of onset were less steep and had a broader age of onset between the ages of 15 and 30 years plus a smaller, second peak between the ages of 45 to 50 years.<sup>27</sup> This pattern of sex differences has been replicated worldwide in population studies, such as the Danish Case Register.<sup>29</sup>

### **Clinical support**

A clinical study has shown that perimenopausal women with schizophrenia required increased antipsychotic drug doses to maintain remission.<sup>25</sup> This study strongly suggested that due to the declining oestrogen levels during menopause and beyond, the “protective” or “antipsychotic” effect of oestrogen is diminished, leading to the patient requiring a greater dose of antipsychotic medication to treat symptoms of schizophrenia. A small study of 32 women found that psychotic symptoms were worse during the low-oestrogen phase of their menstrual cycles.<sup>30</sup> This suggests that higher circulating oestradiol levels provide an antipsychotic effect for women with schizophrenia.<sup>31</sup>

### **Animal studies**

Many animal studies have demonstrated several neuroprotective effects of oestrogens. Dopamine and serotonin are key neurotransmitter systems involved in the formation of the main symptoms of schizophrenia, and oestrogen has a psychoprotective action that appears to be mediated by central dopaminergic and serotonergic mechanisms.<sup>32</sup> The effects of oestrogen are broadly classified into the slower, classical, intracellular “genomic” and the more rapid, direct, non-genomic actions.<sup>33</sup> Both the genomic and direct effects of oestrogen on the central nervous system are thought to contribute to oestrogen’s antipsychotic properties.

### **Glycine therapy**

Glycine (an amino acid ) has been a subject of research for over 15 years as a potential treatment for the negative

symptoms of schizophrenia. One hypothesis of schizophrenia pathology suggests that NMDA-receptor dysfunction (a special kind of glutamate receptor in the brain) may contribute to disordered synapses and brain atrophy, which ultimately result in the visible symptoms. Glycine may turn out to be a very beneficial supplemental treatment (when added to standard antipsychotic medications) for some people with schizophrenia. We hope to see longer and larger trials for glycine supplemental treatments.

The clinical trials have shown that Glycine did not help people who are taking Clozapine, but it did help (in reducing negative symptoms) in people who were taking risperidone (Risperdal), and olanzapine (Zyprexa). The clinical trials suggest that the optimal dosage may be in the range of 30 grams to 60 grams a day. The biggest downside to taking glycine seems to be upset stomach and nausea which, researchers tell us, is quite common in people who take 60 grams of glycine a day for a month or two. Approaches used by the researchers to minimize this problem have been to start at lower doses (e.g. 5 to 10 grams split into two doses per day) and then to slowly phase up to higher doses over a period of weeks.<sup>34</sup> Also - taking it after meals may assist in reducing side effects.

### **Cox-2 Inhibitors as an Adjunctive Treatment for Schizophrenia**

Recently, increased attention has been paid to the interface between the immune system and the treatment of schizophrenia. Historically, it has been noted that in patients with typhus, there appears to be decreased rate of infection in those afflicted with mental illness when

compared with a control group. It was also noted that when the mentally ill group was afflicted with an infection, half showed improvements in their psychotic symptoms. Today, it is believed that there may be an imbalance between the type 1 and type 2 immune systems in patients with psychosis. Schizophrenic patients who are treatment-resistant appear to have an increase in interleukin-6 levels, which is part of the type 2 system. It is felt that in schizophrenic patients, there is relative decrease in activity in the type 1 immune system. Cox 2 inhibitors inhibit the synthesis of IL-6 and also inhibit prostaglandin E2 synthesis, which ordinarily increases IL-6 levels. Celecoxib, as an inhibitor of prostaglandin E2, is felt to restore the balance between the type 1 and 2 systems. In a double-blind, prospective, placebo-controlled, randomized study,<sup>35</sup> 50 schizophrenic patients were evaluated, with half of them receiving risperidone 6 mg/day plus celecoxib 400 mg/day while the other half received placebo instead of celecoxib for a 5-week trial. During weeks 2-4, the PANSS (Positive and Negative Schizophrenia Symptoms) total score was reduced in the risperidone plus celecoxib group. In addition, benzodiazepine usage was decreased for this group. Drug interactions between the risperidone and celecoxib did not appear to explain this finding. It will be interesting to note whether the above study will be replicated, showing celecoxib to be a useful adjunct in the acute treatment the schizophrenia.

### **Antioxidant & Vitamin therapy**

Researchers have found a positive correlation between superoxide generation and the negative symptoms of schizophrenia, indicating a possible role

for oxidative stress in the development of the disease (and the potential for antioxidants to help in decreasing the risk or severity of the disease). "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."<sup>36</sup>

Higher than normal intake of foods known to have a high content of antioxidants, as well as supplements of high antioxidant vitamins (Alpha Lipoic Acid, Vitamin E, Vitamin C) may have some beneficial impact on the incidence and progression of the disease.

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**Table 1: Currently available Antipsychotic Drugs**

<i>Medication class</i>	<i>Medication</i>	<i>Year approved by the FDA*</i>	<i>Usual effective dosage</i>
Dopamine D2 antagonists (high-potency)	Perphenazine (Trilafon‡)	1957	16 mg twice daily
	Trifluoperazine (Stelazine‡)	1959	6 mg twice daily
	Fluphenazine (Prolixin‡)	1960	2.5 mg twice daily
	Haloperidol (Haldol)	1967	5 mg three times daily
	Thiothixene (Navane)	1967	10 mg three times daily
	Fluphenazine decanoate (Prolixin Decanoate‡)	1972	25 mg IM every three weeks
	Haloperidol decanoate (Haldol Decanoate)	1986	100 mg IM every four weeks
Dopamine D2 antagonists (mid-potency)	Molindone (Moban)	1974	25 mg three times daily
	Loxapine (Loxitane)	1975	50 mg twice daily
Dopamine D2 antagonists (low-potency)	Chlorpromazine (Thorazine‡)	1957	100 mg three times daily
	Thioridazine (Mellaril‡)	1962	100 mg three times daily
Atypical (mixed neuroreceptor antagonists [low-affinity D2 antagonists, high-affinity 5HT <sub>2A</sub> antagonists])	Clozapine (Clozaril)	1989	125 mg twice daily
	Risperidone (Risperdal)	1993	4 mg once daily
	Olanzapine (Zyprexa) Quetiapine (Seroquel)	1996 1997	10 mg once daily 200 mg twice daily
	Ziprasidone (Geodon) Aripiprazole (Abilify)	2001 2002	40 mg twice daily 20 mg once daily

*FDA = U.S. Food and Drug Administration;*

*IM = intramuscular.*

\*—Information from

<http://www.accessdata.fda.gov>.

‡—Brand no longer available in the United States

**Table 2. Neurologic Side Effects of Antipsychotics**

<i>Side effect</i>	<i>Features</i>	<i>Time of maximal risk</i>	<i>Proposed mechanism</i>	<i>Treatment</i>
Acute dystonia	Muscle spasms of the tongue, face, neck, and back; may mimic seizures; not hysteria	One to five days	Unknown	Antiparkinsonian agents are diagnostic and curative*
Akathisia	Motor restlessness; not anxiety or agitation	Five to 60 days	Unknown	Reduce dose or change drug; antiparkinsonian agents (benzodiazepines or propranolol [Inderal]) <sup>†</sup> may help
Parkinsonism	Bradykinesia, rigidity, variable tremor, mask facies, shuffling gait	Five to 30 days (can recur even after a single dose)	Antagonism of dopamine	Antiparkinsonian agents helpful
Neuroleptic malignant syndrome	Catatonia, stupor, fever, unstable blood pressure, myoglobinemia; can be fatal	One or more weeks (can persist for days after stopping medication)	Antagonism of dopamine may contribute	Stop medication immediately; dantrolene (Dantrium) or bromocriptine (Parlodel) <sup>‡</sup> may be helpful; antiparkinsonian agents not effective
Perioral tremor (i.e., rabbit syndrome)	Perioral tremor (may be a late variant of parkinsonism)	After months or years	Unknown	Antiparkinsonian agents often helpful
Tardive dyskinesia	Oral facial dyskinesia; widespread choreoathetosis or dystonia	After months or years (worse on withdrawal)	Excess function of dopamine hypothesized	Prevention crucial; treatment unsatisfactory

\*—Many drugs have claimed to be helpful for acute dystonia. The most commonly employed treatments are diphenhydramine (Benadryl) 25 or 50 mg intramuscularly; or benztropine (Cogentin) 1 or 2 mg intramuscularly or slowly intravenously, followed by oral medication with the same agent

*for a period of days to perhaps several weeks.*

†—Propranolol often is effective in relatively low dosages (20 to 80 mg per day). Selective beta1-adrenergic receptor antagonists are less effective.

‡—Despite the response to dantrolene, there is no evidence of an abnormality of Ca<sup>2+</sup> transport in skeletal muscle; with lingering neuroleptic effects,

*bromocriptine may be tolerated in large dosages (10 to 40 mg per day).*

*Adapted with permission from Goodman LS, Gilman A, Hardman JG, Limbird LE. Goodman and Gilman's The Pharmacological Basis of Therapeutics.*