REVIEW ARTICLE

A brief history of drug development for patients with schizophrenia: toward improving their potential in rehabilitation

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Abstract

Background: Schizophrenia is one of the most disabling diseases with remarkable functional loss. Drug treatment is still the mainstay in managing patients with schizophrenia. In this article, the author intends to briefly recount a history of the drug development in the treatment for the patients with schizophrenia, and to suggest short list of most suitable drugs for them.

Methods: The author comprehensively reviewed the benefits and side effects of all available drugs for treating patients with schizophrenia. Focuses are on drugs with least potential of producing liability of extra-pyramidal symptoms (EPS), and those with mild side effect of weight gain.

Results: The drugs for treating patients with schizophrenia were originally targeting at improving positive symptoms of schizophrenia. Those dopamine antagonists (such as chlorpromazine, haloperidol, etc.) improve disorganized behaviors, hallucinations, delusion, and looseness of association effectively but produce unbearable EPS. Recent drugs (mixed receptor antagonists, serotonin-dopamine antagonists, patial dopamine and serotonin agonists) can improve positive, negative symptoms with least EPS but produce body weight gain and other metabolic side effects. Some recently introduced new drugs (such as amisulpride, lurasidone, lumateperone, aripriprozole, brexpiprazole and cariprazine) have least liability of causing EPS but with mild side effect on weight gain (less than 1 kg during the treatment course for an episode of acute exacerbation in patients with schizophrenia). But patients' cognitive improvement from drugs for treating patients with schizophrenia and comorbid depressive symptom are still often overlooked.

Conclusion: Clinicians prescribe drugs with minimal EPS and mild weight gain for patients with schizophrenia, and pay attention to minimalize patients' cognitive impairment and to treat comorbid depression. Then, patients with schizophrenia can expand new better potentials and opportunities for occupational rehabilitation.

Key words: *antipsychotic drugs, extrapyramidal symptoms, drug-induced weight gain, cognitive function*

AN ANECDOTAL STORY SUGGESTING THE DOPAMINE HYPOTHESIS OF SCHIZOPHRENIA

According to the description in an article (Prince, 1956), a very important person (VIP) from Nigeria became psychotic with vivid hallucinations and delusion while he was visiting London, the United Kingdom. All doctors consulted in London could not treat his psychotic condition successfully. Finally, a traditional healer was brought in from Nigeria, and he was able to get this VIP treated. Some herbs of *Rauwofia serpina* was found in his room of the living quarter after all Nigerians left London.

The key pharmacologic component of *Rauwofia serpina* is reserpine, which was used to get this VIP patient remitted from psychotic condition. To note, reserpine is an obsolete antihypertensive drug now. In monoaminergic neurons, reserpine has been shown (Giachetti, 1978) to specifically attach to amine carrier sites at the level of the membranes of amine storage granules. Because the attachment to the membramce is irreversible, monoamine (including dopamine, DA) storage granules can leak out from the damaged membrance and is oxidized by monamine oxidase (MAO) through deamination intracellularly, a physiologically meaningful amount of DA granules cannot be pumped from presypnatic neurons into the synpnatic gaps, and a limited amount of DA granules even reach the gaps, but they are easily hydroxylated through enzymatic destruction of catechol-*O*-methyltransferase (COMT) extracelluarly.

In sum, reserpine can eventually deplete DA in the central nervous system, resulting in decresing DA in the DA mesolimbic tract, and improving psychotic symptoms. Reserpine is presented here only as a thought-provoking idea in blocking catecholamine (DA and norepinephrine, NE) transmission for academic interest only, its uses in treating psychotic disorder and hypertension, respectively, are already obsolete.

CLASSIC DRUGS FOR TREATING PATIENTS WITH SCHIZOPHRENIA IN THE PAST

The history of antipsychotic drug development had a long and torturous course (Shen, 1999). The discovery of an antipsychotic drug was often based on serendipity (López-Muñoz, 2020), which has little relationship to the intellectual idea and intended observations.

Methyline blue, a phenothiazine derivative, is an important material in the flourishing dye industry in England during the time of industrial revolution in the 19th century (Shen, 1999). In 1891, Paul Ehrlich observed the antimalarial effects of methylene blue. Later in 1953, the phenothiazines were synthesized by Courvoisier of Specia Laboratories at Rhône-Poulenc, a French pharmaceutical company, and developed for their antihistaminergic uses. In 1951 in Paris, Henri Laborit, an anesthesiologist gave aliphatic phenothiazine, chlorpromazine (CPZ, Figure 1), to patients as a "pre-anesthetic medication" to safely potentiate the depth of anesthesia for patients receiving surgery. Shortly Laborit gave CPZ to (a) Hamon and colleagues at Val de Grâce, a military hospital in Paris (Hamon, 1952; Pichot 1996; Shen, 1998), as well as (b) Jean Delay who worked previously at Clinic of Neurology at la Salpêtrière and studied psychology at the Sorbonne and his co-worker Pierre Deniker at Sainte Anne Hospital in Paris, to treat psychiatric patients and serendipitously discovered its antipsychotic activity (Shen, 1998; Shen, 1999; López-Muñoz, 2005).

Delay and Deniker at Sainte Anne Hospital in Paris had been widely recognized as the first discoverers for the CPZ use on psychiatric patients. But a marble plaque was installed in 1993 at Val de Grâce in Paris with an inscription saying "Hommaage à Laboit, Lasker prize 1957, and to J. Hamon, J. Paraire and J. Velluz for their discovery in 1952, of the therapeutic effects of chlorpromazine in psychiatry" (Pichot, 1996). To note, the investigators at both Sainte Anne Hospital and Val de Grâce have never been awarded for those important discoverers of CPZ for the psychiatric use with Nobel prize probably because Swedish nominating committee members were afraid of being involved in an argument between two teams (Pichot, 1996).

Between 1954 and 1975, about 15 "me too" drugs used for treating patients with schizophrenia were introduced in the United States of America and about 40 drugs totally throughout the world. The common mechanism of those so-called first-generation (typical) antipsychotics (FGAs) is DA antagonistic effect of DA of the brain. The blockage of DA transmission in the central nervous system is effective in treating positive symptoms, such as hallucinations, delusion, disorganized behaviors, and looseness of association of patients with schizophrenia. The efficacies of FGAs for depressive, cognitive, and negative symptoms of schizophrenia are not good. Table 1 is a sample list of FGAs which were or have been commonly heard or seen.

Although effective in treating positive symptoms in patients with schizophrenia, FGAs cause inevitable acute side effects of extra-pyramidal symptoms (in-

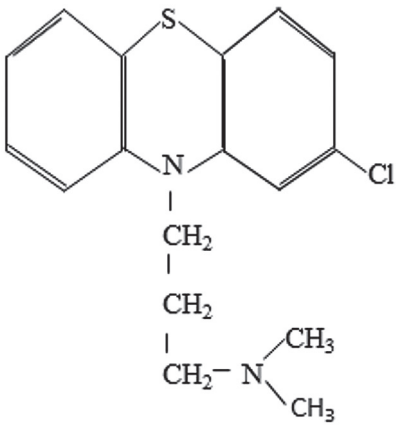


Figure 1. The chemical structure of chlorpromazine

Table 1. A sample list of the first-generation antipsychotic drugs

Antipsychotic drug	Antipsychcotic equivalent dose*
Phenothiazine	
Aliphatic groups	
Chlorpromazine	100
Triflupromazine	25-50
Piperazine groups	
Perpherazine	8
Trifluoperazine	5
Fluphenazine	2
Acetophenazine	25
Piperidine groups	
Thioridazine	100
Mesoridazine	50
Thioxanthenes	
Aliphatic groups	
Chlorprothixene	50
Piperazine groups	
Thiothixene	4
Dibenzoxazepines	
Clothiapine	50
Loxapine	15
Dihydroindole	
Molindone	15
Butyrophenones	
Haloperidol	2
Diphenylbutylpiperidine	
Pimozide	1-2

Source: Shen WW. *Keio Journal of Medicine* (Tokyo) 1994
*Compared with chlorpromazine 100 mg
Modified from original table by removing clozapine and risperidone

cluding shakiness, slowness and stiffness, i.e. three "S") of Parkinsonian disease (Groves, 1975) as well as akathisia, inability to sit or stand quietly (Shen, 1981). For the reason of EPS induced by FGAs, European doctors, such as Jean Delay, tend to call as them as "neuroleptics" (Pichot, 1996). Those EPS symptoms were once described as the second most unbearable and unbearable side effects among all categories of drugs for human, just next to those side effects produced by anticancer drugs. Even worse, some EPS patient victims even developed irreversible tardive dyskinesis, or self-induced water intoxication (Shen and Sata, 1983, 1984).

NEW DRUGS HAVE LESS LIABILITY OF EXTRAPYRAMIDAL SYMPTOMS BUT HAVE METABOLIC SIDE EFFECTS

Since 1975 after the marketing of molindone (Table 1), a hiatus with a period without any new drugs introduced for patients with schizophrenia had lasted in the development of new drugs until the introduction of clozapine treatment in the United States of America in 1990 (Shen, 1999). The introduction of clozapine heralds the opening a new era of the second-generation (atypical) antipsychotic (SGA) drugs, showing a remarkably reduced possibility for EPS. Those SGAs have increased efficacy for the negative symptoms of schizophrenia, no elevation of prolactin after chronic use (except risperidone), and, at least for clozapine, effectiveness in some patients previously regarded as treatment-refractory (Kane, 1988).

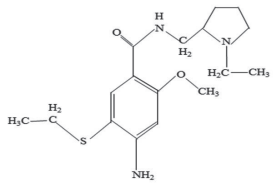
Patients treated with FGAs can be easily recognized on the streets because they still have (a) negative symptoms of schizophrenia showing flattening facial affect, (b) EPS with apathetic facial expression, and (c) depressive mood which not being improved by FGAs. Since 1990, various classes of SGAs had been marketed. By 2011, SGAs occupied about 98% antipsychotic drugs in treating patients with schizophrenia in the USA. When the patients with schizophrenia treated with SGAs are more expressive in facial expression, they cannot be easily identified on the streets.

Compared to those treated FGAs, the patient treated SGAs feel more comfortable because FGAs tightly bind D_2 receptors of the brain whereas most SGAs do not (de Haan, 2000, 2003). SGAs can also bind the D_2 receptors of the brain, but the binding between SGAs and D_2 receptor becomes slowly dissociated, allow-

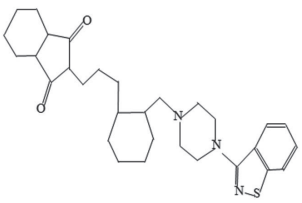
ing some DA surging in the DA neurotransmission. This transient DA transmission in the brain make patients' good in self-feeling (*kimochi*), optimistic, comfortable and less-oppressive. Those patients' good subjective feeling and the proper use of long-acting injectable SGAs (Kishimoto, 2021), improve patients' medication compliance remarkably. In a re-admission study in Taiwan on a cohort of 75,986 patients with schizophrenia who were hospitalized for the first time in their life (Lin, 2022), the investigators found that 62.05% of them have at least one inpatient re-admission within four years. Compared to the period under treatment with oral risperidone, that under monotherapy with long-acting injectable antipsychotics (LAIs) has been found to have the lowest risk for psychotic re-admission, with a risk reduction of 15% - 20% (Lin, 2022). For this clinical benefit, the Taiwanese Society of Psychiatry and Taiwanese government are actively advocating LAIs for all patients with schizophrenia with government's fund to prevent relapse (Tsai, 2022). In Taiwan, psychiatrists often cannot find enough inpatients with schizophrenia in actute exacerbation to fill in inpatient beds on psychiatry service at medical centers.

Although the earlier SGAs such as olanzapine, quetiapine, risperdone, aripiprazole, etc., improve EPS induced by the FGAs, they have brought out the side effects of weight gain and other metabolic side effects (American Diabetes Association, 2004a, 2004b). Body weight gain has become one of the most important side effects of the drugs for patients with schizophrenia. It is also linked to metabolic problems such as increased blood levels of glucose, cholesterol and lipids (Wu, 2022). Those emerging side effects induced by earlier SGAs have impact on health and mortality of patients with schizophrenia tremendously (De Hert, 2009; Heald, 2010).

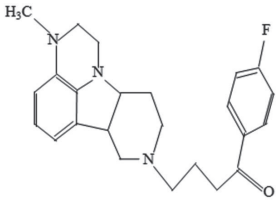
Of the above-listed four drugs, olanzapine had lost market share remarkably as shown in 2006 due to the side effect of weight gain (Allison, 1999; Maloney, 2010). Now available on the market is a combination compound drug, Libalvi (Pokins, 2020), which consists of olanzapine and samidorphan, a weight-control dieting drug, in an attempt to keep the market share of olanzapine.



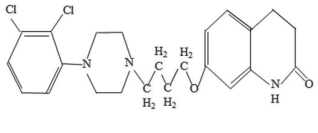
Amisulpride



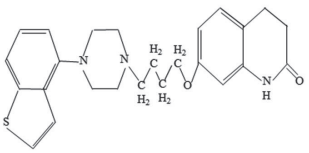
Lurasidone



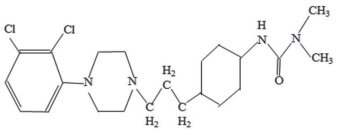
Lumateoperone



Aripiprazole



Brexpiprazole



Cariprazole

Figure 2. Chemical structures of six drugs of choice for patients with schizophrenia.
All those six drugs have minimal side effects for extrapyramidal symptoms, and produce mild weight gain comparing to placebo with a mean difference at any dose ≤ 1 kg (Wu, 2022) during the treatment for patients with schizophrenia in acute exacerbation (Wu, 2022). Amisulpride is dopamine D_2 and D_3 receptor antagonists as defined in neuroscience-based nomenclature system (www.NbN.ECNP.org). Lurasidone is a strong D_2, 5-HT_{2A} and 5-HT_7 antagonist and mild 5-HT_{1A} agonist (Ishibashi, 2010). Lumeteoerone is a potent 5HT_{2A} receptor antagonist, a D_2 receptor presynaptic partial agonist, and D_1-dependent modulator of glutamate as well as a 5-HT reuptake inhibitor (Snyder, 2021). Aripiprazole is dopamine D_2 and 5-HT_{1A} partial agonist as well as dopamine D_4 and 5-HT_{2A} antagonists (Kikuchi, 1995; Stahl, 2016). Brexpiprazole is partial D_2, D_3, 5-HT_{1A} agonist and 5-HT_{2A} antagonist (Maeda, Sugino, 2014; Stahl, 2016). Cariprazine is a partial D_2, D_3, 5-HT_{1A} receptor agonist and 5-HT_{2A} antagonist (Kiss, 2010; Citrome 2015).

SOME RECENT DRUGS IN TREATNG PATIENTS WITH SCHIZOPHRNIA HAVE LEAST CHANCE TO HAVE EXTRAPYRAMAL SYMPTOMS AND MILD WEIGHT GAIN

Using the method of dose response relationship (Crippa, 2016), a dose-response meta-analysis of randomized controlled trials of newer antipsychotic-induced weight gain was conducted (Wu, 2022). The investigators studied 97 studies on patients with acute exacerbation with 333 dose arms and 36, 326 participants. They also studied whether the dose response relationships of the drugs are monotonic, hyperbolic or bell-shaped, and found that only seven drugs (amisulpride, aripiprazole, brexpiprazole, caripizole, haloperidol, lumateperone, and lurasidone) produce mild weight gain comparing to placebo with a mean differences at any dose ≤ 1 kg during the treatment for an acute episode in patients with schizophrenia in acute exacerbation (Wu, 2022).

Figure 2 are chemical structures of six newer drugs with mild weight gain, showing the absence of haloperidol, a CPZ-like drug for patients with schizophrenia. Except amisupride, all other five drugs have been licensed by the Food and Drug Administration (FDA) of the United States of America for the indication in treating patients with schizophrenia. Aripiprazole and brexpiprazole have extra adjuctive treatment FDA indications for treating patients with major depressive disorder, while lurasidone and lumateperone have additional FDA indication for treating patient with depressive episode of bipor disorder (www.fda,org).

FURTHER PRECLINIAL FINDINGS SUGGEST MORE BENEFITS IN USING THOSE SIX DRUGS IN TREATNG PATIENTS WITH SCHIZOPHRENIA

In an animal study (Maeda, 2014a), investigators found that subchronic treatment with phencyclidine (PCP) induces cognitive impairment in both novel object recognition (NOR) and attentional set-shifting (ID-ED) tests in rats. Brexpiprazole can reverse the PCP-induced cognitive impairment in the NOR test at 1.0 and 3.0 mg/kg, and in the ID-ED test at 1.0 mg/kg of brexpiprazole. But aripiprazole (10 mg/kg) is found to be ineffective in both tests, despite achieving relevant D_2 occupancies (Maeda, 2014a). To note, both aripripazole and brexpiprazole belong to the compounds of are partial DA receoptor agonists (Kikuchi, 1995). But the “intrict activity” of brexpiprazole is weaker than that of aripiprazole (Maeda, 2014b), giving less liability of causing akathisia and EPS.

In another animal study (Meltzer, 2013), investigators found that lurasidone which has 5-HT_7 antagonistic property, can restore novel object recognition (NOR), and that enhanced cortical and hippocampal dopamine and acetylcholine efflux, may contribute to the restoration of NOR.

The same investigators (Meltzer, 2013) also suggested that serotonergic mechanisms, including 5-HT_{2A} and 5-HT_7 antagonism, 5-HT_{1A} angonism, and $GABA_A$ agonism, contribute to the efficacy of drugs in treatment for patients with schizophrenia in the subclincally NMDA receptor antagonist rodent models, which are relevant to the loss of GABA interneuron/hyperglutamate hypothesis of the etiology of cognitive impairment of schizophrenia. To note, lumeteoerone is the only drug for patients with schizophrenia and involves in D_1-dependent modulator of glutamate (Snyder, 2021).

CONCLUSION

Cognitive impairment is not included as one of key features of schizophrenia in *the Diagnostic and Statistical Manual of Mental Disorders, the Fifth Edition* (APA, 2013; APA 2022). But cognitive impairment in patients with schizophrenia has long been well-recognized (Kaneda, 2011; Sumiyoshi, 2008). Furthermore, cognitive impairment due to prescribed antipsychotic drugs (Hori, 2006; Joshi, 2021), and reduction of anticholinergic burden (Lupu, 2017) have been well-addressed in the literature. The clinicians are also reminded of treating concurrent depression aggressively to improve patients’ cognitive function and quality of life (Sumiyoshi, 2021).

Shuzo Kure, the father of Japanese psychiatry was unhappy with the treatment opportunity of Japanese patients with schizophrenia at the turn of the century. In 1918, Kure remarked “Mental patients in Japan have double miseries, one is to have a disease and the other is to be born in this country” (Kazamatsuri, 2012; Shinfuku, 2016). Japan has had strong background of pharmaceutic industry including the field of drugs for schizophrenia (López-Muñoz, 2013). Now, Japanese pharmcetical companies have participated in the drug development of 3 of 6 drugs, namely lurasidone, aripiprazole and brexpiprazole.

To put this fact in perspective, Japanese patients with schizophrenia can expand new better potentials and opportunities for occupational rehabilitation. For clinical purpose, this is my intended reason to write this brief version on drugs for treating patients with schizophrenia.

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In this article, the author attempted to use neuroscience-based nomenclature (Uchida, 2017, 2021) to describe the drugs mentioned in this article. The psychiatrists are advised to consult with information in packet inserts of those six drugs carefully first before prescribing them for patients with schizophrenia.

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