Clinical Trials in Psychiatry: Focusing on Antipsychotic Development

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Clinical trial is referred to an experiment to investigate novel therapies including drug, vaccines, dietary choices, dietary supplements, and medical devices or other intervention to a certain disease or illness, and to assess the contingent side effects. This overview is to focus on the clinical trial in the development of antipsychotic drugs. Pharmacotherapy is the mainstay of treatment for mental disorders in modern medicine, while there were many interesting and strange therapies implemented in the early days. These therapies include malaria-induced fever to treat neurosyphilitic paresis, insulin-induced coma and convulsions to treat schizophrenia, pentyleneetetrazole-induced convulsions and electroconvulsive shock therapy to treat schizophrenia and affective psychoses, and prefrontal lobotomy to treat psychosis and personality disorder. Lithium, chlorpromazine, imipramine, chlordiazepoxide, and iproniazid (MAOI) were developed serendipitously by careful clinical researchers and became the founders of modern psychopharmacology. Currently there are strict regulations and paradigms for clinical trial after decades of evolution. Recently approved antipsychotic drugs such as lurasidone, brexpiprazole, cariprazine and blonanserin are introduced. They have different receptor affinity and carry different side effect profiles. Cognition enhancers are developing using the mechanism of glutamate system modulation, phosphodiesterase inhibition and nicotinic receptor agonism. Inverse agonist in an old concept and a new antipsychotic has been developed using this concept. Also the clinical trials and clinical pharmacological studies in psychiatric field done in Taiwan are reviewed. In the future, precise medicine as getting the right treatment at the right time to the right person is also important for mental disorders. More precise diagnostic categories based on biological, psychological, and socio-cultural variables, which need many kinds of data to reach precision of a clinical trial.

Key words: lurasidone, brexpiprazole, cariprazine, cognitive impairment associated with schizophrenia


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Antipsychotic Drug Development

Introduction

Clinical trial is referred to an experiment to investigate novel therapies including drug, vaccines, dietary choices, dietary supplements, and medical devices, or other intervention to treat a certain disease or illness, as well as to assess the contingent side effects. Currently any new compound needs many clinical trials to be approved as a prescribed medicine. There are strict regulations such as following the good clinical practice (GCP) and ethical considerations such as approved by the institutional review board (IRB) to run a clinical trial. GCP is an international quality standard that is provided by the International Council for Harmonization (ICH), an international body that defines standards, which governments can transpose into regulations for clinical trials involving human subjects. The IRB is to protect human subjects from physical, psychological and social harms when involved in a clinical trial in the ethical and scientific points of view.

Pharmacotherapy is the mainstay of treatment for mental disorders in modern medicine, while many interesting and strange therapies existed in the early days. The psychotropic drugs have helped stabilize and maintain the patients, as well as recover to a certain degree. But some unmet needs of the therapy still exist for the patients not to have full remission, and to return to their normal lives. In this overview, I am reviewing psychiatric clinical trials for modern psychotropic drugs, covering the past, at present, and the future.

History of Clinical Trials in Psychiatry

Before modern pharmacotherapy for psychosis, many interesting therapies had ever tried to treat patients with schizophrenia. Between 1917 and 1935, four methods for producing physiological shock were discovered, tested, and used in the psychiatric practice in Europe [1]. They included malaria-induced fever to treat neurosyphilitic paraparesis, discovered in Vienna by Wagner-Jauregg in 1917; insulin-induced coma and convulsions to treat schizophrenia, discovered in Berlin by Sakel in 1927; pentylenetetrazole-induced convulsions to treat schizophrenia and affective psychoses, discovered in Budapest by von Meduna in 1934; and electroconvulsive shock therapy to treat schizophrenia and affective psychoses, discovered in Rome by Cerletti and Bini in 1937 [1]. Prefrontal lobotomy or leucotomy was a widely accepted procedure to treat many mental disorders from 1940 to 1950 [2], but it was completely abandoned following the introduction of antipsychotic medications. Of four methods to cause seizures, only electroconvulsive shock therapy is still used as a treatment modality at present.

The first controlled clinical trial in psychiatry was to compare the surgical procedure of removing infected teeth and tonsils to non-operation group, with the results showing no more mental benefit [3, 4]. In 1935, the first single blind (to patient), crossover randomized controlled trial (RCT) was done by Prinzmetal and Bloomberg [3, 5] to compare benzedrine with ephedrine and sodium chloride (placebo) in treating narcolepsy.

Modern Clinical Trials in Psychiatry

The modern psychopharmacology was inaugurated from the accidental finding of chlorpromazine [6, 7], as well as the serendipitous discovery of the first two antidepressants [8] in early 1950s. Between 1954 and 1975, about 15 antipsychotic
drugs had been introduced in the United States and about 40 throughout the world [9]. Most of these antipsychotic drugs carry a strong affinity to block D2 receptor and have many side effects such as tremor, restlessness, dyskinesia, dry mouth, and sedation. Neuroleptic malignant syndrome and tardive dyskinesia are rare but serious side effects. Those compounds developed during this period are called first-generation antipsychotic (FGA). Most of them did not have placebo-controlled trials, rather a head-to-head comparison of efficacy design.

In the 1980s, the concept of serotonin-dopamine antagonist antipsychotic emerged from clozapine, which is a potent serotonin 5-HT2A antagonist [10]. They generally have lower risk of motor side effects, but are associated with high frequencies of weight gain, serum lipid elevation, and the development of metabolic syndrome or type 2 diabetes. Contrary to FGAs, those new compounds are second-generation antipsychotic drugs (SGAs), and most of them have been run by a placebo-controlled design [11] to be approved before being on the market. Lurasidone was approved in 2010 in the USA, and in 2015 in Taiwan. In 2015, the FDA also approved two antipsychotic drugs—brexpiprazole and cariprazine. Blonanserin is approved for treatment of schizophrenia in Japan and South Korea [12].

**Lurasidone**

Lurasidone has a potent dopamine D2 and serotonin 5HT2A antagonist and serotonin 5HT1A partial agonist properties, with additional potent 5HT7 and alpha2c noradrenergic antagonism [13]. It is less likely to cause metabolic syndrome and/or weight gain than most other SGAs [14]. Lurasidone is approved by FDA to treat schizophrenia, bipolar depression as monotherapy or add-on regimen. In a cost-utility analysis of lurasidone versus aripiprazole in the treatment of patients with schizophrenia [15], the results showed that lurasidone is likely to provide overall savings due to lower relapse rates and greater improvements in quality of life when compared with aripiprazole.

**Brexpiprazole**

Brexpiprazole works through a combination of partial agonist activity at serotonin 5-HT1A and dopamine D2 receptors, and antagonist activity at serotonin 5-HT2A receptors [16]. The term “serotonin-dopamine activity modulator” is used to describe the pharmacological characteristics of brexpiprazole. It is considered a second-generation version of aripiprazole, and with slightly different activity at the serotonin and dopamine receptors, could mean an improved clinical profile with fewer side effects such as restlessness or akathisia [17]. The indications approved by FDA in 2015 are schizophrenia and as an add-on treatment to an antidepressant medication to treat major depressive disorder [18].

**Cariprazine**

Unlike many antipsychotic drug that are D2 and 5-HT2A receptor antagonists, cariprazine is a D2 and D3 partial agonist, with preferential binding to D3 receptors, and partial agonism at serotonin 5-HT1A receptors [17, 19]. A multinational, randomized, double-blind, placebo- and active-controlled study revealed that cariprazine 3 and 6 mg/day is efficacious in treating patients with acute exacerbation of schizophrenia [20]. Cariprazine has also shown to have efficacy on bipolar mania [21] and bipolar depression [22]. Cariprazine was approved by the FDA to treat schizophrenia and bipolar disorder in adults.
Blonanserin

Blonanserin is an atypical antipsychotic agent indicated for use in patients with schizophrenia in Japan and Korea [12]. In vitro, blonanserin acts as an antagonist at dopamine D₂, D₃, and serotonin 5-HT₂A receptors. Blonanserin has low affinity for 5-HT₃, adrenergic α₁, histamine H₁, and muscarinic M₁ receptors, but displays relatively high affinity for 5-HT₆ receptors [23]. Blonanserin is generally well-tolerated and appears to have an acceptable profile in terms of bodyweight gain [24]. Currently, the world’s first transdermal patch formulation is under phase 2 clinical trial in Asian countries including Taiwan [www.ds-pharma.com/news/pdf/ene20120727_2.pdf].

Unsuccessful trials

After the promising trial results from glutamate modulators such as sarcosine and D-serine, two potential compounds related to this mechanism – bitopertin and pomaglumetad methionil were undergone trial in either as monotherapy or add-on regimen. Bitopertin is a potent and non-competitive GlyT₁ inhibitor [25], and pomaglumetad methionil is a potent and highly selective agonist for the metabotropic glutamate receptors 2 and 3 [26]. Unfortunately, both compounds did not separate from placebo in the phase III large-scale randomized placebo controlled trial [27, 28]. In the exploratory analysis for a targeted patient population responsive to pomaglumetad methionil in schizophrenia [29], it revealed that only patients early-in-disease or previously treated with D₂ drugs have exhibited greater improvement relative to those receiving placebo in the dosage of 40 mg twice a day.

Psychiatric Clinical Trials in Taiwan

The first psychiatric clinical trial ever published (text in Chinese language) in Taiwan was done by Hwu [29] in this journal in 1995, while Hong et al. in 1997 [30] and Lin et al. in 1997 [31] have published double-blind randomized controlled trial in two separate international journals.

In 1993, the administrative authority of Department of Health announced a new strategy for new compound approval in Taiwan. It is required to have domestic clinical data for at least 40 cases. Under this new regulation, numbers of clinical trials have increased remarkably including psychotropic drugs. Most of these trials belong to bridging study, namely, an additional study executed in the new region to “build a bridge” with the foreign clinical data on efficacy, safety, dosage and dose regimen according to the International Council for Harmonization (ICH) guideline E5. Such studies could include additional pharmacokinetic information. The representative compounds include buspirone [29], lofexidine [31], zotepine [32], amisulpride [33], aripiprazole [34], atomoxetine [35], and milnacipran [36].

Besides these trials, Bai in 2012 has reviewed pharmacological studies on patients with schizophrenia published by Taiwanese researchers [37]. These studies covered from efficacy trials to pharmaeco-economics and pharmaco-genetics, and have offered empirical results of pharmacotherapy for schizophrenia in Taiwan, and will be the basis for the development of the Taiwan consensus of pharmacological treatment for schizophrenia. López-Muñoz et al. in 2012 did a bibliometric study on research for SGA drugs in Taiwan [38]. They identified 359 original Taiwanese papers (original articles, reviews, editorials, case reports,
letters to the editor, etc.) dealing with different aspects related to SGAs including clozapine, risperidone, aripiprazole, olanzapine, quetiapine, and others. The investigators concluded that there had been a markedly increased number of SGA papers generated from Taiwan over the previous 20 years, and predicted that research in this field will possibly continue to grow in the coming years.

Along with those flourishing activities in clinical trials in multiple disciplines, the infrastructure and study team are getting mature and sophisticated, more and more international, multiple center registration trials for US Food and Drug Administration (FDA) (www.clinicaltrials.gov) or Japan Pharmaceuticals and Medical Devices Agency (PMDA) (www.pmda.go.jp) have been implemented. Most of these trials have been published without the authorship from Taiwan. On the other hand, lots of investigator-initiated trials of existing compounds have been published in Taiwan. Those drugs include sarcosine and D-serine [39, 40], venlafaxine [41], metformin [42], dextromethorphan [43, 44], memantine [45, 46], etc.

**Psychiatric Clinical Trials in the Future**

Cognitive impairment associated with schizophrenia (CIAS) is a common consequence of this disorder, causing a huge humanistic burden [47]. It is an important therapeutic target for many pharmaceutical companies to develop, while no compounds have been approved by the authorities yet. Garay et al. have published an article to review potential compounds currently under clinical trials [48]. Many cognition enhancers to treat CIAS are under development through the mechanism of glutamate system, phosphodiesterase inhibitors and many others. Followings are some potential compounds under development as an antipsychotic drug with cognitive enhancing effects and less side effects.

**ITI-007**

ITI-007 has a unique and novel mechanism of action. It is regarded as a modulator of serotonin, dopamine and glutamate transmission. It acts as a 5-HT$_{2A}$ receptor antagonist, a partial agonist of presynaptic D$_2$ receptors and an antagonist of postsynaptic D$_2$ receptors, and a serotonin transporter blocker [49]. ITI-007 also possesses affinity for the D$_1$ receptor and weak affinity for the α1A- and α1B-adrenergic receptors and D$_4$ receptor, and has no affinity to the 5-HT$_{2B}$, 5-HT$_{2C}$, H$_1$, or mACH receptors. It is regarded as a multi-acting receptor targeted antipsychotics (MARTA), yet the side effect profiles are much better than the “pine”-category antipsychotics such as quetiapine or olanzapine. In a phase II RCT for 4 weeks, ITI-007, 60 mg/day but not 120 mg/day, has demonstrated to have antipsychotic efficacy superiority over placebo on the change of Positive and Negative Syndrome Scale total score [50]. ITI-007 was well-tolerated in this patient population, as evidenced by low discontinuation and adverse event rates, and are associated with a benign metabolic profile as evidenced by significantly lower levels of prolactin, fasting glucose, total cholesterol, and triglycerides than risperidone. ITI-007 has also been tried on bipolar depression as a monotherapy (NCT02600494).

**Pimavanserin**

Pimavanserin is a selective serotonin inverse agonist (SSIA) on the serotonin receptor subtype 5-HT$_{2A}$, with 40 folds selectivity over 5-HT$_{2C}$, and no significant affinity or activity at 5-HT$_{2B}$ or dopamine receptors [51]. Inverse agonist is an agent that binds to the same receptor as an agonist but
induces a pharmacological response opposite to that agonist [52]. Pimavanserin has been tried for patients with Parkinson’s disease psychosis [53] and had shown efficacy without prominent side effects. Pimavanserin was recently approved by FDA for this indication in 2016. For the treatment of schizophrenia, adjunctive pimavanserin can reduce the antipsychotic dose (such as risperidone 2 mg/day) and side-effects [54].

**Phosphodiesterase inhibitors**

A phosphodiesterase (PDE) is any enzyme that breaks or degrades the phosphodiester bond in the second messenger molecules cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). PDE inhibitor, on the other way, prevents the inactivation of the intracellular second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). Several PDE types have been identified as therapeutic targets for immune/inflammatory diseases [55], and erectile dysfunction [56], cardiovascular disease and hypertension [57]. The PDE 5 inhibitor sildenafil has been trialed to improve the CIAS in a single dose design but did not show any benefit [58]. Other PDE subtype inhibitors are studied on the way such as PDE 1 inhibitor [59], PDE 9 inhibitor BI 409306 (NCT02281773) and PDE 10 inhibitor OMS-824 (NCT01952132) and TAK-063 (NCT02477020).

**α7 ACh nicotinic receptor agonist**

Nicotinic receptor has been associated with sensory gating deficit characterized in patients with schizophrenia [60]. Activation of the α7 nicotinic ACh receptor (nACh receptor) is considered a potential target for the treatment of CIAS. To date, many compounds of this mechanism were trialed as cognition enhancers such as ence-
Table 1. Characteristics of mode of action and clinical indication of approved and potential compounds

<table>
<thead>
<tr>
<th>Compounds</th>
<th>References</th>
<th>Modes of receptor action</th>
<th>FDA indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lurasidone</td>
<td>Bruijne et al. 2015 [13] Citrome 2011 [14] Rajagopalan et al. in press [15]</td>
<td>(D_2) and (5HT_{2A}) antagonist, (5HT_{1A}) partial agonist, (5HT_7) and alpha (_\alpha_2C) antagonism</td>
<td>Schizophrenia, bipolar depression (monotherapy or add-on)</td>
</tr>
<tr>
<td>ITI-007</td>
<td>Synder et al. 2015 [49] Lieberman et al. 2015 [50]</td>
<td>(5-HT_{2A}) antagonist, presynaptic (D_2) partial agonist and postsynaptic, (D_2) antagonist, serotonin transporter blocker</td>
<td>Targeted indication: schizophrenia, bipolar depression</td>
</tr>
<tr>
<td>BI 409306</td>
<td>NCT02281773</td>
<td>PDE9 inhibitor</td>
<td>Targeted indication: CIAS</td>
</tr>
<tr>
<td>OMS-824</td>
<td>NCT01952132</td>
<td>PDE10 inhibitor</td>
<td>Targeted indication: CIAS</td>
</tr>
<tr>
<td>TAK-063</td>
<td>NCT02477020</td>
<td>PDE10 inhibitor</td>
<td>Targeted indication: CIAS</td>
</tr>
<tr>
<td>Enceneline</td>
<td>Alder et al. 1998 [60]</td>
<td>(\alpha_7) ACh nicotinic receptor agonist</td>
<td>Targeted indication: CIAS</td>
</tr>
<tr>
<td>AQW051</td>
<td>Feuerbach et al. 2015 [62]</td>
<td>(\alpha_7) ACh nicotinic receptor agonist</td>
<td>Targeted indication: CIAS</td>
</tr>
<tr>
<td>RG3487</td>
<td>Umbricht et al. 2014 [63]</td>
<td>(\alpha_7) ACh nicotinic receptor agonist</td>
<td>Targeted indication: CIAS</td>
</tr>
</tbody>
</table>

D, dopamine; 5-HT, serotonin; PDE, phosphodiesterase; NCT, ClinicalTrials.gov Identifier; CIAS, cognitive impairment associated with schizophrenia

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