Commentary

The Nature and Evolution of Therapies in Schizophrenia: From Classical Time to Clinical Trials

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Introduction

Schizophrenia is one of the top ten illnesses contributing to the global burden of disease, affects around 24 million people with the prevalence rate of 1% worldwide [1-3]. It largely emerges in late adolescence and early adulthood, mainly characterized by hallucinations, delusions, (psychosis and positive symptoms), apathy, social withdrawal, flat emotions (negative symptoms) and, cognitive impairment [4]. Delineating the intricate roleplay of varied symptoms with developmental alterations marks schizophrenia as a heterogeneous neuropsychiatric mental disorder. Predisposition of genetic factors and their numerous interactions with the environment and biological cues are known to be major contributing risk factors for the disease [5]. To the best of present knowledge, lack of clear demarcation of disease boundaries with substantive overlaps with other psychiatric disorders, are fundamental barriers to progress. Understanding the etiopathology behind these disease characteristics would emphasize a renewed search for novel pharmacological or other psychotherapeutic targets. Addressing the unattended features of the illness, such as negative and cognitive symptoms, and developing hypothesis-driven early interventions and preventive strategies are high-priority goals for the field. Other treatment gaps are variation in response pattern as only half of the patients respond to first line of pharmacotherapies [6]. In addition, around 10% to 30% patients even fail to respond to two (or more) trials of pharmacotherapies thus fall into the category of treatment resistant schizophrenia (TRS) [7]. This variation in response pattern necessitates the discovery of new pharmacotherapy that would be effective against wide spectrum of symptoms and could also targets novel molecular mechanism which is at the juncture of the positive, negative and, cognitive symptoms of the disease. At present, the existing treatment is symptomatic and exhibits positive effect to only certain symptoms primarily psychosis. The efficacy of currently available therapy is limited, prompting redirection of drug development towards translational research and molecular medicine to augment the effects of treatment and better disease remission.

Therefore, in this commentary we are summarizing the gradual evolution of treatment in schizophrenia, primarily emphasizing on the varied therapies that were in use in the classical time, followed by the currently available therapies (both pharmacotherapy and non-pharmacotherapy like surgical or cognitive therapies). Also giving an account on the potential drugs and other therapies that are in different phases of clinical trials with a focus on their mode of action with their targeted therapeutic response. In the concluding remarks, we gave an account on how drug discovery and development can be re-directed with identifying the genetic mechanisms that underlie symptoms of mental illness. This study will reveal new targets for drug development with the scope of genetic advancements like personalized therapies with a hope of development of better anti-psychotic therapy with faster action, higher efficacy for negative or cognitive symptoms, better adherence against positive symptoms, and improved relapse rates [8].

Evolution of Pharmacotherapy in Schizophrenia Treatment

Around 3000 years ago, several techniques were in practice for the treatment of psychosis like symptoms. People then, believed mental illness was caused as a result of supernatural phenomena in which evil spirit inhabiting one's head causes psychopathology, thus making a hole in the skull would help in releasing the evil spirit. This belief system brought popularity to techniques like trepanation and blood-letting, which lasted for several decades [9]. However, the mechanism behind these therapies remained unknown. Later in 18th century many other techniques were developed to treat patients with psychotic symptoms. Initially chloral hydrate was used for reducing the anxiety in the patients [10]. In order to provide additional care (other than family and hospital) patients were send to private mad houses run by members of clergy and also in monasteries until mid-18th century, when asylums were constructed for the patients with severe psychotic symptoms, where several experiments were applied on the patients to reduce the symptoms [11]. Fever therapy was introduced in early

19th century, in which psychiatrist intentionally induced fever for therapeutic purpose[8].Other popular treatments include lobotomy, hydrotherapy, deep sleep therapy, metrazol and cardiazol convulsive therapies and many more were administered but with undefined mechanism of action [12,13]. Later the advent of insulin shock treatment was found to be effective [14,15]. This was replaced by electroconvulsive therapy (ECT) (1938), in which the psychotic symptoms of patients were treated by simulating electric currents in the brain using electrodes. The use of ECT was reduced by mid-19th century with the discovery of first pharmacotherapy [16].

Introduction of pharmacotherapy for the treatment of schizophrenia had provided a vital and advanced insights of pathophysiology. The first antipsychotic drug i.e. chlopromazine was discovered in 1952, by serendipity, provides symptomatic relief by mainly ameliorating the psychotic symptoms [17]. Since the discovery of first antipsychotic drug many other drugs (such as haloperidol, thiothixene, fluphenazine, thioridazine etc.) have been developed, collectively categorized as first generation or typical antipsychotics, that particularly targets psychotic symptoms. Later, mechanism based studies and advancement in tools made it possible to examine in vitro pharmacology and thus aided to find out the binding affinity of antipsychotic drugs with dopamine D2 receptors as antagonist [18]. This finding established the widely accepted dopamine hypothesis i.e. dysregulation of dopaminergic circuits causes hyperactivity of dopamine transmission in the brain of patients with schizophrenia [19]. Over the years, it was observed that D2 antagonists failed to reduce the negative and cognitive impairment symptoms. However several evidences succumbed to establish the relation between these symptoms with altered dopamine transmission [19]. Consequently, the classical hypothesis was re-conceptualized based on the new findings, suggesting the excess dopaminergic activity particularly in the mesolimbic pathway leads to positive symptoms whereas reduced dopaminergic signaling in the mesocortical pathway leads to negative and cognitive impairment symptoms [17,20]. All the atypical antipsychotics primarily exert

therapeutic action on dopaminergic pathways of brain mainly at D2 receptors as antagonist, also causes extrapyramidal symptoms (EPS), tardive dyskinesia and other adverse side effects [21].

Discovery of clozapine was the breakthrough in the history of schizophrenia treatment as it is the only drug which can be used to treat the refractory patients. It has superior clinical efficacy compared to other antipsychotics and also has the affinity for multiple receptor targets (such as Dopamine receptor (D1), serotonin receptor (5HT1, 2A, 2C), Histamine receptor (H1), and adrenergic receptor (α1, α2)). This directed the synthesis of similar drugs but with higher efficacy and lower adverse side effects compared to first generation antipsychotics. As a result many of them were discontinued with time and so replaced by the newer drugs categorized as second generation (atypical) antipsychotics [22]. Meanwhile, substantial evidences suggested that dysfunctioning of neurotransmitter signaling other than dopamine (such as serotoninergic, glutamatergic, GABAergic (gamma-aminobutyric acid), acetylcholine etc.) lead to the abnormal functioning of interneurons consequently found to be implicated in the pathophysiology of disease [23]. Introduction of second generation antipsychotics followed this hypothesis, as they targeted the serotonergic signaling in combination with dopaminergic.

By 1990s, the Food and Drug Administration (FDA) had approved the second generation (atypical) antipsychotics also known as serotonin-dopamine antagonist for the treatment of schizophrenia. This class of antipsychotic were considered to have similar therapeutic efficacy as the first generation antipsychotics though advantage of lower risk of extrapyramidal symptoms favors the use of atypical antipsychotics [24]. They are predominantly involved in reducing the psychotic symptoms, targets serotonin (5HT2A) receptors in combination with dopamine D2 receptor, all of them are dopamine D2 antagonist except Aripiprazole, a partial agonist [25]. Currently available atypical antipsychotic drugs for clinical use include: clozapine, olanzapine, aripiprazole, paliperidone, quetiapine, ziprasidone, risperidone [26]. The existing atypical antipsychotic drugs except clo-

zapine are first line of medications. Clozapine was observed to cause agranulocytosis and could be fatal thus because of high risk, it is not recommended as first line treatment nonetheless can be used if patients can tolerate this drug with continued hematological monitoring [27]. Moreover in 2015, FDA approved two new atypical antipsychotic drugs i.e. brexpiprazole & cariprazine, both function as partial agonist of dopamine D2 receptor and displays insignificant effect on negative and cognitive impairment symptoms [28]. Albeit there are non-pharmacotherapies available that are majorly in practice for the treatment of schizophrenic patients in combination with antipsychotic drugs (with the intent of controlling symptoms) psychotherapy (includes personal psychotherapy, cognitive behavioral therapy (CBT), cognitive enhancement therapy (CET)), psychosocial therapy and electro convulsive therapy (ECT) [29]. At present, the existing antipsychotic treatment is involved in producing the adverse metabolic effects which increases long term health risks. Besides this, unavailability of pharmacotherapy for the treatment of negative and cognitive impairment symptoms is also a major gap in existing treatment facility. Development of new drugs does not involves the novel molecular target rather classical drugs in combination with other therapies are widely prescribed and found to be effective for treating the patients.

Currently researchers are doing plethora of experiments to develop drug/ therapy that would be effective against wide spectrum of symptoms (including negative and cognitive impairment) with superior efficacy and less adverse reactions. Accordingly, over a hundred of drugs or compounds, comprehending wide range of targets are under various stages of ongoing drug development clinical trials. Drugs such as memantine, galantamine, BI 425809, HP-3070, PF-03463275, N-acetylcysteine are under different stages of clinical trials. They target novel receptors and transporters other than conventional dopamine and serotonin receptors thus addressing the prominent unmet needs that are currently existing in schizophrenia [30-32]. A shift in the paradigm was observed with the advent of drugs as well as other non-pharmacotherapies for the treatment of cognitive impairment symptoms (AVN-211) and are also trying to develop some drugs

that targets negative symptoms (ITI-007, MIN-101 and NaBen) [33]. Those patient who show non response to clozapine treatment, both augmentation (include electroconvulsive therapy or mood stabilizers) and combination therapies (with antipsychotics) are considered. A drug in phase 3 trial, LuAF3570, also addresses patient with treatment resistant schizophrenia [34]. Finally, RBP-7000, risperidone ISM, lurasidone-HCl, and pimavanserin from phase 3 trials are expected to offer improved safety profiles [35-39].

Furthermore, studies of genes related to pharmacokinetics and pharmacodynamics of antipsychotics helped to discover the relationship between drugs and their targeted genes. Further advancement in genetic technologies identified the associated genetic variations (single nucleotide polymorphisms) that plays an important role in determining the efficacy and side effect profiles of various pharmacotherapies [40,41] This knowledge provides vital support to produce better drug design and also individualized pharmacotherapy. An interventional clinical project, titled "*5-HTR2A*, *DRD2*,and *COMT* Genes Polymorphisms and Olanzapine Plasma Concentration in Treatment of Early-onset Schizophrenia" involves the administration of olanzapine based on the presence of polymorphism in desired genes such as *5-HTR2A*, *DRD2* and *COMT* [42]. The evolution of therapies (pharmacotherapy and non-pharmacotherapy) and their mechanism of action has been pictorially represented as in Figure 1 and the related detailed information has been provided in the Table 1.Therefore, ongoing clinical trials are moving towards advanced knowledge of evidence-based psychotherapy development in combination with non-pharmacological approaches. This motivated vigorous prevention approaches in early phases of the illness and early interventions with novel pharmacological targets and plasticity-based treatments such as cognitive remediation and genome-based therapeutics.

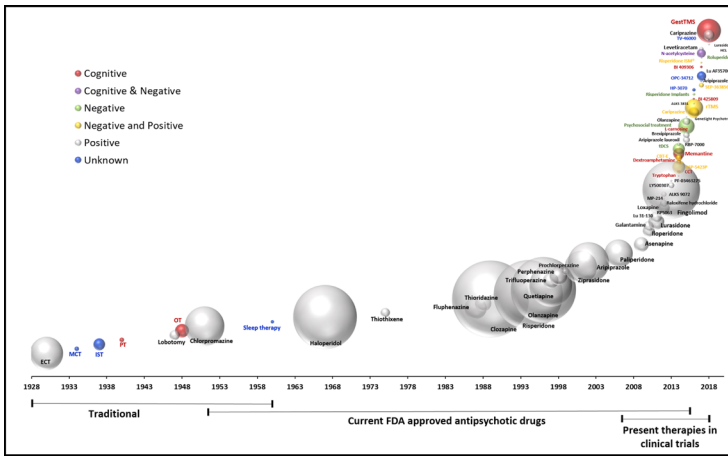

Figure 1: Chronological advancement of antipsychotics and non-pharmacotherapies. The chronological progression of treatment for schizophrenia disease in addition with the advancement in antipsychotic drugs and their targeted symptoms is depicted as a bubble plot and their respective year of development on X axis. Each bubble on the plot represents a therapy or a drug and the color of the bubble is indicating the targeted symptoms of the particular drug/therapy. The size of the bubble representing the number of evidences published till date (September 30, 2018). These treatment are further subdivided into three broad categories: 1. Traditional therapies 2. Currently available antipsychotic drugs (FDA approved) 3. The drugs and other therapies under different stages of clinical trials.

Table 1: A detailed information of chronological advancements in treatments of schizophrenia with their targeted symptoms and mechanism of action.

S.No.	Year	Treatment	Type of therapy	Mode of Action	Targeted symptoms
Traditional mode of therapy					
1	10,000 BC	Trepanation	Non-Pharmacotherapy	Unknown mode of action	Psychotic
2	2nd century AD	Blood Letting	Non-Pharmacotherapy		Unknown
3	1869	Chloral hydrate	Pharmacotherapy		Psychotic
4	1900	Asylums	Non-Pharmacotherapy		Unknown
5	1900	Fever therapy	Non-Pharmacotherapy		Unknown
6	1910	Hydrotherapy	Non-Pharmacotherapy		Psychotic
7	1930	ECT (Electroconvulsive therapy)	Non-Pharmacotherapy		Psychotic
8	1934	MCT (Metrazol/cardiazol therapy)	Non-Pharmacotherapy		Unknown
9	1937	IST (Insulin shock treatment)	Non-Pharmacotherapy		Unknown
10	1940	PT (Psychoanalytic treatment)	Non-Pharmacotherapy		Cognitive
11	1947	Lobotomy	Non-Pharmacotherapy (Surgical)		Psychotic
12	1948	OT (occupational therapy)	Non-Pharmacotherapy		Cognitive
13	1960	Sleep therapy	Non-Pharmacotherapy		Unknown
First Generation Antipsychotic Drugs					
14	1951	Chlorpromazine	Pharmacotherapy	DRD1, DRD2, HTR1A HTR2A, ADRA1A, ADRA1B, HRH1 antagonist	Positive
15	1967	Haloperidol	Pharmacotherapy	DRD2 antagonist	Positive
16	1975	Thiothixene	Pharmacotherapy	DRD2, DRD1A, HTR2A antagonist	Positive
17	1987	Fluphenazine	Pharmacotherapy	DRD2, DRD1A antagonist	Positive
18	1988	Thioridazine	Pharmacotherapy	DRD2, DRD1A antagonist	Positive
19	1997	Trifluoperazine	Pharmacotherapy	DRD1, DRD2 antagonist	Positive
20	1998	Perphenazine	Pharmacotherapy	DRD1, DRD2 antagonist	Positive

21	1999	Prochlorperazine	Pharmacotherapy	DRD2 antagonist	Positive
22	2012	Loxapine	Pharmacotherapy	DRD2, HTR2A antagonist	Positive
Second Generation Antipsychotic Drugs					
23	1989	Clozapine	Pharmacotherapy	DRD2, HTR2A antagonist	Positive
24	1994	Risperidone	Pharmacotherapy	DRD2, HTR2A, HR antagonist	Positive
25	1996	Olanzapine	Pharmacotherapy	DRD2, HTR2A antagonist	Positive
26	1997	Quetiapine	Pharmacotherapy	DRD1, DRD2, HTR1A, HTR2A antagonist	Positive
27	2001	Ziprasidone	Pharmacotherapy	DRD2, HTR2A antagonist	Positive
28	2002	Aripiprazole	Pharmacotherapy	HTR2A antagonist; DRD2, HTR1A partial agonist	Positive
29	2006	Paliperidone	Pharmacotherapy	DRD2, HTR2A antagonist	Positive
30	2009	Asenapine	Pharmacotherapy	DRD2, HTR2A antagonist	Positive
31	2009	Paliperidone palmitate	Pharmacotherapy	DRD2, HTR2A antagonist	Positive
32	2011	Lurasidone	Pharmacotherapy	DRD2, HTR2A antagonist	Positive
33	2010	Iloperidone	Pharmacotherapy	DRD2, HTR2A antagonist	Positive
34	2015	Aripiprazole lauroxil	Pharmacotherapy	HTR2A antagonist; DRD2 HTR1A partial agonist	Positive
35	2015	Brexipiprazole	Pharmacotherapy	HTR1A, DRD2 partial agonist; HTR2A antagonist	Positive
36	2015	Cariprazine	Pharmacotherapy	DRD2 DRD3 partial agonist, high selectivity for DRD3	Positive
Therapies/Drugs On Clinical Trials					
37	2007	Paliperidone ER	Pharmacotherapy	DRD2, HTR2A antagonist	Positive
38	2009	Citalopram	Pharmacotherapy	Sodium-dependent 5-HTT inhibitor	Positive
39	2010	Galantamine	Pharmacotherapy	ACHE Inhibitor	Positive
40	2011	Lu 31-130	Pharmacotherapy	Neurotransmitter receptor modulators	Positive

41	2011	RP5063	Pharmacotherapy	DRD2, DRD3 and DRD4 partial agonists; HTR1A , HTR2A partial agonists; HTR2B, HTR6, HTR7 receptor antagonists	Positive
42	2012	Memantine	Pharmacotherapy	NMDA receptor antagonist	Positive
43	2012	MP-214	Pharmacotherapy	DRD2 and DRD3 partial agonist	Positive
44	2012	ALKS 9072	Pharmacotherapy	DRD2, HTR1A, HTR2A Partial agonist	Positive
45	2013	Fingolimod	Pharmacotherapy	S1PR1, S1PR3, S1PR4, S1PR5 modulator	Positive
46	2013	LY500307	Pharmacotherapy	Selective ESRB agonist	Positive
47	2013	PF-03463275	Pharmacotherapy	Glycine transporter 1 inhibitor; SLC6A9 inhibitor	Positive
48	2014	Tryptophan	Pharmacotherapy	Unknown	Cognitive
49	2014	CCT (Behavioral: Computerized cognitive training)	Psychotherapy	Unknown	Cognitive
50	2014	DSP-5423P	Pharmacotherapy	DRD2, HTR2A antagonist	Positive & Negative
51	2014	Dextroamphetamine	Pharmacotherapy	HTR agonist	Cognitive
52	2014	CBT-E (Emotion-focused Cognitive behavior therapy)	Psychotherapy	Unknown	Positive & Cognitive
53	2014	Memantine	Pharmacotherapy	GRIN3A, GRIN2A, GRIN2B antagonist	Cognitive
54	2014	tDCS (transcranial direct current stimulation)	Non-Pharmacotherapy	Unknown	Negative
55	2014	RBP-7000	Pharmacotherapy	DRD2, HTR2A antagonist	Positive
56	2015	L-carnosine	Pharmacotherapy	Unknown	Cognitive
57	2015	Psychosocial treatment	Psychotherapy	Unknown	Negative
58	2015	Olanzapine	Pharmacotherapy	DRD2, HTR2A antagonist	Positive
59	2015	GeneSight Psychotropic	Pharmacotherapy	DRD2 and HTR1A antagonist	Positive
60	2016	Cariprazine	Pharmacotherapy	DRD2 DRD3 Partial agonist, high selectivity for DRD3	Positive & Negative

61	2016	rTMS (Repeated transcranial magnetic stimulation)	Non-Pharmacotherapy	DRD agonist	Positive & Negative
62	2016	ALKS 3831	Pharmacotherapy	DRD1, DRD2 antagonist; OPRM1 antagonists; HTR2 antagonists	Positive
63	2016	BI 425809	Pharmacotherapy	GlyT1 inhibitors	Cognitive
64	2016	Risperidone Implants	Pharmacotherapy	DRD2, HTR2A antagonist	Negative
65	2016	HP-3070	Pharmacotherapy	ADRA1,DRD , HRH1 , HTR antagonists	Unknown
66	2017	SEP-363856	Pharmacotherapy	HTR1A, TAAR1 agonists	Positive & Negative
67	2017	Aripiprazole IM	Pharmacotherapy	DRD2, HTR2A antagonist	Positive
68	2017	OPC-34712	Pharmacotherapy	HTR1A, DRD2 Partial agonist; HTR2A Antagonist, NARA1B, NARA2C	Unknown
69	2017	Lu AF35700	Pharmacotherapy	DRD1, 5-HT2A HTR6 antagonist	Positive
70	2017	BI 409306	Pharmacotherapy	PBE 9A inhibitors	Cognitive
71	2017	Risperidone ISM®	Pharmacotherapy	DRD2, HTR2A antagonist	Positive & Negative
72	2017	Roluperidone	Pharmacotherapy	HTR2A and σ2 receptor antagonist	Negative
73	2017	N-acetylcysteine	Pharmacotherapy	GST stimulator and CT/GLT activator	Cognitive & Negative
74	2017	Levetiracetam	Pharmacotherapy	SV2A agonist	Positive
75	2018	Lurasidone HCL	Pharmacotherapy	DRD2, HTR2, HTR7, ADRA2A, ADRA2C antagonist; partial HTR1A agonist	Positive
76	2018	TV-46000	Pharmacotherapy	DRD2, HTR2A antagonist	Unknown
77	2018	GestTMS	Non-Pharmacotherapy	Unknown	Cognitive

DRD1: Dopamine D1 receptor; DRD2: Dopamine D2 receptor; DRD3: Dopamine D3 receptor; DRD4: Dopamine D4 receptor HTR1A:5-hydroxytrptamine receptor 1 A; HTR2A: 5-hydroxytrptamine receptor 2A; HTR2B: 5-hydroxytrptamine receptor 2B; HTR6: 5-hydroxytrptamine receptor 6 ; HTR7: 5-hydroxytrptamine receptor 7; ADRA1A: Alpha-1A adrenergic receptor; ADRA1B: Alpha-1B adrenergic receptor; ADRA2A: Alpha-2A adrenergic receptor; ADRA2C: Alpha-2C adrenergic receptor; HRH1: Histamine H1 receptor; ACHE: Acetylcholinesterase ; S1PR1: sphingosine 1-phosphate receptors; S1PR3: sphingosine 3-phosphate receptors; S1PR4: sphingosine 1-phosphate receptors; S1PR5: sphingosine 1-phosphate receptors; NMDA: N-methyl –D- aspartate; GAT1: Sodium and chloride-dependent GABA transporter 1; 5-HTT: Sodium-dependent serotonin transporter; SLC6A9: ; ESRB: Selective Estrogen Receptor beta; GRIN3A: Glutamate receptor ionotropic NMDA 3A; GRIN2A: Glutamate receptor ionotropic NMDA 2A , GRIN2B: Glutamate receptor ionotropic NMDA 2B; GlyT1: Glycine transporter 1; OPRM1: Opioid mu receptor;TAAR1: Trace amine-associated receptor 1; NARA1B noradrenaline alpha1B; NARA2C: noradrenaline alpha1B; PBE 9A:Phosphodiesterase 9A; GST: Glutathione synthetase; Synaptic vesicle glycoprotein 2 A; GLT: glutamate transporter; CT: cysteine transporter; SV2A: Synaptic vesicle glycoprotein 2 A.

Future Directions

Over a past decade, a tremendous advancement in treatment of schizophrenia has been observed yet essentially requires a modification in current paradigm of treatment approach. Most of the neuropsychiatric disorders are characterized by overlapping symptoms however due to limited knowledge of etiopathogenesis we are unable to demarcate the boundaries of disease. Consequently the current diagnostic criteria is still symptomatic, currently available tools (Diagnostic and Statistical Manual for Mental Disorders, Fifth edition: DSM-5 and International Classification of Disorders: ICD-11) classifies the disease solely based on the symptoms [43]. Therefore, necessitates modification in current diagnostic criteria that employs genetic biomarkers and advance neuroimaging techniques. Also, increased evidences of genetic overlapping with the disease, suggested us to direct the future diagnostic criteria towards more genetic evidence-based classification system [44]. Besides the modification in diagnostic criteria it is suggested that genetic advancement not only aided as diagnostic tool but also provided the novel target for drug development. Future effort in identifying the variation in genes will provide support to develop predictive, diagnostic, symptomatic biomarkers which could potentially be applied for clinical perspective. Similarly, several studies reported the genes *neuregulin* (*NRG1*), *COMT*, *dysbindin*, *GRM3*, *RGS4*, *calcineurin*, *BDNF*, *PRODH* etc and its variation are implicated to involved in the etiology of disease as well as in determining the efficacy of drug response [45]. Thus, knowledge of genetic variation with clinical response data offers a bright future for individualized medicine.

There are several possible ways that could enhance the treatment efficacy and will also provide deeper insights of biological mechanisms. We know that, currently the researchers are exploring better drug designs and novel targets for better and effective treatment and pharmaceutical companies are facing a major challenge of developing a multi-targeted monotherapy but a significant increase in devel-

opment of adjunctive therapies has turned the interest of researchers towards this upcoming treatment strategy. This approach found to produce better safety profiles and increased patient compliance to therapy. Upcoming adjunctive therapies which are under clinical trials involves NaBen®, EVP-6124, pimavanserin, prednisolone, exenatide, etc. [46-49]

In conclusion, we think to create a reliable scientific basis for improved and effective treatment, a collaborative consortium is needed that involves preclinical researchers, geneticists, neuroimaging experts, drug developers (various pharmaceutical companies) and clinicians. Their collective work and effort will definitely help to shift the current paradigm of drug development from symptomatic treatment approach to genetic variation based personalized treatment [18].

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