Contrasting Typical and Atypical Antipsychotic Drugs

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The beliefs that antipsychotic drugs (APDs) are 1) effective *only* to treat delusions and hallucinations (positive symptoms), 2) that typical and atypical APDs differ *only* in ability to cause extrapyramidal side effects, and 3) that their efficacy as antipsychotics is due *solely* to their dopamine D_2 receptor blockade are outmoded concepts that prevent clinicians from achieving optimal clinical results when prescribing an APD. Atypical APDs are often more effective than typical APDs in treating negative symptoms, cognitive impairment, and mood symptoms as well as reducing the risk for suicide and decreasing aggression. This applies not only to those diagnosed with schizophrenia or schizoaffective disorder but also to bipolar disorder, major depression, and other psychiatric diagnoses. The greater advantage of an atypical APD is not evident in all patients for every atypical APD due, in part, to individual differences in genetic and epigenetic endowment and differences in the pharmacology of the atypical APDs, their mode of action being far more complex than that of the typical APDs. A common misconception is that among the atypical APDs, only clozapine is effective for reducing psychosis in treatment-resistant schizophrenia. Aripiprazole, lurasidone, olanzapine, and risperidone also can be more effective than typical APDs for treatment-resistant schizophrenia; clozapine is uniquely indicated for reducing the risk for suicide. The ability of the atypical APDs to improve cognition and negative symptoms in some patients together with lower propensity to cause tardive dyskinesia (an underappreciated advantage) leads to better overall outcomes. These advantages of the atypical APDs in efficacy and safety are due, in part, to initiation of synaptic plasticity via direct and indirect effects of the atypical APDs on a variety of proteins, especially G proteins, and release of neurotrophins (e.g., brain-derived neurotrophic factor). The typical APDs beneficial effects on psychosis are mainly the result of D_2 receptor blockade, which can be associated with serious side effects and lack of tolerability.

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The goal of this contribution is to provide a clinically useful guide to antipsychotic drugs (APDs) based on clinical evidence and mechanism of action. It emphasizes the choice of, and optimal use of, an APD based on receptor profiles, preclinical studies, and proven actions. The main focus is on their use in schizophrenia. Much of what has been learned about their efficacy, side effects, and mechanism of action is relevant to their uses in other psychiatric disorders. The results from meta-analyses are not prioritized as they are in other reviews (1–4), as the emphasis here is to alert the reader to clinically relevant information that may be helpful for specific patients, which as meta-analysts note is difficult to discern in meta-analysis (4). The dichotomization of the antipsychotics into atypical versus typical classes is the key organizing principle for this article. It was first proposed in the 1960s based on the minimal motor side effects of clozapine, the prototypical atypical APD, to contrast it with chlorpromazine, the prototypical typical antipsychotic and other APDs with similar functionality. This simple classification had, and still has, merit; however, it is misleading, not only to clinicians but also to basic scientists, who may be unaware of the important differences in efficacy, side effects, and mechanisms of action that differentiate the diverse group of atypical APDs from one another. Powerful voices have minimized the differences between typical and atypical APDs, often referring to them as first- and second-generation APDs (5). The goal here is to highlight important differences that should inform clinical practice. The pharmacologic basis for the differential ability of the atypical APDs to improve psychosis, negative symptoms, and cognitive impairment is discussed throughout, particularly cognition, because it is so critical for achieving good outcomes and because there is so much misinformation about the effect of APDs on cognition. Table 1 highlights the receptor profiles of the typical and atypical APDs.

The relevance of these diverse receptor profiles, with an emphasis on dopamine and serotonin, for the clinical differences between typical and atypical APDs has been discussed in more detail elsewhere (6–9). The main inhibitory neurotransmitters in the brain are GABA, glycine, and serine. It is likely that these three neurotransmitters are highly significant for the pathophysiology of schizophrenia and other neuropsychiatric disorders and greatly influence the actions of APDs. Only brief discussion of the potential to treat schizophrenia with drugs influencing these neurotransmitters could be included here. Drugs targeting these systems will likely come to the fore in the near future. Similarly, relatively little attention is given to pharmacogenomic studies that can inform choice of medications. Such studies, as well as other types of biomarkers, can ultimately

TABLE 1. Receptor Affinity Values (Ki) for Atypical and Typical Antipsychotic Drugs[a]

	Receptor								
Drug Name	D1	D2	D3	5-HT_{1A}	5-HT_{2A}	5-HT_{2C}	α2	H–1	M–1
Amisulpride	>10K	3	2.4	>10K	8,304	>10K	1,114	>10K	>10K
Aripiprazole	387	0.95	5.35	5.6	4.6	181	74	29	>6K
Asenapine	NA	2	NA	15	0.8	0.3	16.1	9.3	24.3
Brexpiprazole	NA	0.3	1.1	0.1	0.5		0.6	19	negligible
Cariprazine	NA	9.2	0.085	8.6	7.7	6.9	<6.0	7.6	negligible
Chlorpromazine	112	2	4.65	>3K	3.2	26	184	0.18	47
Clozapine	189	431	240	105	13	29	142	2	14
Fluphenazine	21	0.54	1.75	145	7.4	418	314	7.3	>1K
Haloperidol	83	2	8.5	>1K	73	>10K	>1K	>3K	>10K
Iloperidone	129	3.3	7.1	33	0.2	14	3	12.3	>1K
Loxapine	54	10	22	>2K	3.9	21	151	2.8	175
Lumateperone	52	32	NA	NA	0.5	173	NA	>1K	NA
Lurasidone	NA	1.7	NA	6.8	2		40.7	>1K	>1K
Olanzapine	58	72	49	>2K	3	24	314	4.9	24
Paliperidone	41	9.4	0.5	637.8	1.9	100.3	4.7	5.6	>10K
Perphenazine	28.2	1.4	2.1	421	5.6	132	810.5	8	NA
Pimavanserin	NA	NA	NA	NA	0.4	16	NA	NA	NA
Pimozide	5,495	0.65	0.25	650	19	>3K	>1K	692	800
Quetiapine	900	567	940	431	366	>1K	>3K	7.5	858
Risperidone	60.6	4.9	9.6	427	0.19	94.9	151	5.2	>10K
Thioridazine	89	10	7.4	108	11	69	134	14	33
Thiothixene	51	1.4	0.4	410	111	>1K	80	12	>10K
Trifluoperazine	NA	1.3	NA	950	13	378	653.7	63	NA
Ziprasidone	30	4	7.2	76	2.8	68	160	130	>10K

[a] NA=not available.

guide clinical decision-making regarding APDs, as they do in many other areas of medicine, but are not yet mature enough to be useful for general clinical practice (10, 11).

While the APDs are the most versatile, and perhaps most powerful, of the pharmacologic armamentarium available to treat behavioral disorders, their misuse can lead to significant harm. Clozapine has been identified as the most unique and powerful of this diverse group of drugs, often referred to as the "gold standard." However, because it has a greater side effect burden than any other APD and requires monitoring for agranulocytosis, it is underused, even for suicide risk reduction, where it is the only APD approved for this life-saving indication (12, 13). Clozapine may also have benefit for this purpose in bipolar disorder (14) and other diagnostic groups (e.g., PTSD). The risk of using clozapine has been exaggerated, just as have been some of its benefits (15). Insufficient use of clozapine is due, in part, to weakly supported challenges to its efficacy for suicide prevention (16) and, in part, because of the side effects of clozapine and weekly monitoring of the white blood cell count (15).

The failure to appreciate the pharmacologic diversity of the atypical APDs has hindered the development of superior APDs that could rely, in part, on some of their differential pharmacology, e.g., 5-HT_7 receptor blockade, release of cortical glutamate, and indirect and direct 5-HT_{1A} partial agonism (7, 17). Many clinicians and basic scientists believe that the atypical APDs are effective only for delusions and hallucinations. However, as adjunctive agents, they are also effective for treating aggression, anxiety, mood symptoms, and obsessive-compulsive symptoms, to name other established common uses (18). Most importantly, their ability to treat cognitive impairment, the most controversial aspect of their utilization, and to this author their most compelling advantage, has been challenged despite much preclinical and clinical evidence that they are effective in this regard in many patients, enabling dramatic restoration of work and social function (9).

Subchronic phencyclidine (PCP) treatment followed by withdrawal in rats has been shown to produce *N*-methyl-D-aspartate receptor (NMDAR) hypofunction in cortical slices. Lurasidone and clozapine have been shown to correct this defect in a 5-HT_7-dependent manner (19). Subchronic PCP treatment has been shown to dysregulate the balance between GABA and glutamate in mouse hippocampus, leading to an increased threshold for inhibition in hippocampal slices (20). Two drugs which enhance $GABA_A$ function in vivo, the neurosteroid pregnenolone, and the $GABA_A$ agonist, TPA-023, have been shown to restore novel object recognition in mice that had received subchronic PCP treatment (21, 22). Pregnenolone has shown some promise in the treatment of cognitive impairment and negative symptoms in schizophrenia (23).

CONTRASTING THE LIMITED VERSUS DIVERSE PHARMACOLOGY OF THE TYPICAL AND ATYPICAL APDS

The efficacy of chlorpromazine, the first APD shown to treat the positive symptoms of schizophrenia, was discovered by

Delay and Deniker in 1952 (24). This discovery transformed the treatment of this previously intractable illness that affects 1%−1.5% of the population worldwide. The subsequent identification of striatal dopamine D_2 receptor blockade as the basis for its antipsychotic action by Arvid Carlsson and others led to the development of many antipsychotic agents—with the same mechanism of action—of diverse chemical classes. Of these, the most widely used have been haloperidol, fluphenazine, trifluperazine, perphenazine, mesoridazine, and thiothixene. Many, especially haloperidol, are still used for maintenance treatment. Although varying slightly in affinities for receptors other than dopamine D_2 receptors, the evidence that these other actions add significantly to their efficacy as antipsychotics is minimal (7). Indeed, until recently it was widely believed that all APDs act only through D_2 receptor blockade (7, 25). It has been suggested that differences in their rate of dissociation from the D_2 receptor was a critical variable in their relative ability to produce motor side effects (26). However, the evidence for this hypothesis has not been confirmed (27). Sertindole, olanzapine, and asenapine are atypical APDs with rates of dissociation from the D_2 receptor that are the same as, or even slower, than that of haloperidol. Efforts by major pharmaceutical companies to develop novel atypical APDs on the basis of fast dissociation from the D_2 receptor have been unsuccessful.

Development and application of a rational psychopharmacology is necessary for optimal choice and use of APDs. This contrasts with the irrational psychopharmacology that is widely practiced that takes many forms. These include trial durations that are too short before switching to another drug, initiating polypharmacy without an adequate trial of monotherapy, nonscience-based choice of adjunctive treatments, dosages that are too low or too high, failure to address nonadherence to oral or long-acting formulations, underutilization of long-acting formulations to improve compliance, and failure to appreciate the differences in mechanism of action among the ever increasing numbers of atypical APDs. A rational psychopharmacology must be based on greater understanding of the domains of psychopathology found in the wide spectrum of clinical diagnoses for which APDs are used, including bipolar disorder, major depression, OCD, and aggression. Appreciation of schizophrenia as a syndrome made up of four types of clinical symptoms—cognitive impairment (which includes disorganized thinking), positive symptoms (delusions and hallucinations), negative symptoms (predominantly deficits in social interaction, experience of reward, and motivation), and mood symptoms—is essential for a rational psychopharmacology and the development of treatments that are superior in efficacy and safety. The importance of a multidimensional perspective became evident to me through my initial clinical experience with using clozapine in treatment-resistant schizophrenia (28). That experience led to a greater understanding that the goal of treating schizophrenia goes far beyond treating positive symptoms, which unfortunately is the clinical standard too often applied (15). The overemphasis on positive symptoms as the goal of drug development for APDs and their clinical applications contributed greatly to the stagnation in the development of superior treatments of schizophrenia.

THE IMPORTANCE OF TARDIVE DYSKINESIA

The persistent widespread use of typical APDs is due, in part, to underappreciation of the importance of tardive dyskinesia (TD) and its importance to the development of cognitive impairment and its amelioration. Emil Kraepelin (29) and others reported dyskinesias in patients prior to the discovery of APDs. My first use of clozapine confirmed its remarkable ability to improve psychosis and TD in treatment-resistant schizophrenia and to improve cognition. All aforementioned domains of psychopathology responded to clozapine in a patient near death due to TD (30). The ability to improve cognition in this patient was confirmed in a larger group of patients with and without TD (31). That report helped to initiate many additional studies with other newly developed atypical APDs, including risperidone, olanzapine, and quetiapine, which were meta-analyzed (32, 33). Preexisting dyskinesia and the emergence of TD during treatment with typical APDs is associated with cognitive impairment (34). As will be discussed, TD can impair the cognitive improvement made possible by treatment with atypical APDs (35).

TD can develop rapidly or slowly, depending on genetic vulnerability, age, sex, and psychiatric diagnosis. In younger patients, the annual rate is between 3% and 5%. It is higher in bipolar disorder than schizophrenia, particularly in patients 60 years old or older. The average maintenance doses of haloperidol (6–12 mg/day or its equivalent) are twice the 3–4 mg/day required for optimal efficacy in most patients (36). Although it may be reversible in some patients, TD can be irreversible, extremely severe, and in rare instances life-threatening (37). Its occurrence can be minimized by using an atypical APD without supplementation by a typical APD, which enhances D_2 receptor blockade.

Recently, inhibitors of the vesicular monoamine transporter VMAT2, valbenazine and deutetrabenazine, have been shown to diminish the motor symptoms of TD and have received FDA approval for this indication (38). VMAT2 is present in the membrane of secretory vesicles and transports dopamine (DA), norepinephrine, serotonin, histamine, glutamate, and GABA into vesicles for presynaptic release (39). An acute dose of NBI-98782, the active metabolite of valbenazine, given to mice attenuated PCP- and amphetamine-induced hyperlocomotion, suggesting possible beneficial antipsychotic effect, as well as effects on cognition and negative symptoms. Acute NBI-98782 also enhanced cortical acetylcholine and GABA efflux and suppressed clozapine-, olanzapine- and risperidone-induced dopamine efflux in both the cortex and striatum and cortical acetylcholine efflux. NBI-98782 also suppressed haloperidol-induced striatal dopamine efflux (39). These effects may account for its beneficial effects on TD. Thus, VMAT2 inhibitors may have clinical utility beyond the control of TD. There is no published evidence of their effect on cognitive impairment in

patients. Despite the iatrogenic nature and potential gravity of TD, lack of information and the low cost of typical relative to that of atypical APDs contributes greatly to the continuing use of typical APDs.

THE NEUROBIOLOGY OF APDS AS A GUIDE TO THEIR OPTIMAL USE

The serendipitous discovery of the antipsychotic properties of chlorpromazine in chronic schizophrenia patients was followed quickly by the demonstration by Arvid Carlsson and others that ability to inhibit the action of dopamine at striatal D_2 dopamine receptors was the main basis for its antipsychotic efficacy. The D_2 receptor is highly expressed in the basal ganglia and the brain stem, less so in the prefrontal cortex and hippocampus, which is enriched in dopamine D_1 receptors (40). These two types of DA receptors oppose each others' cellular effects and must be optimally balanced for normal cognitive function; too little or too much D_1 receptor activity interferes with working memory and other cognitive measures and other behavioral domains (41). A placebo-controlled randomized trial demonstrated that a selective D_1 receptor antagonist increased, not decreased, the severity of psychosis in patients with schizophrenia (42). Atypical APDs, because of their ability to stimulate the release of dopamine in cortex and other brain regions, may be thought of as indirect dopamine D_1 agonists. Clozapine is also a D_1 agonist and produces equal occupancy of D_1 and D_2 receptors in humans, indicating that clozapine may enhance D_1 receptor stimulation, both indirectly and directly (43, 44)

A key advance in our understanding of the role of dopamine in brain function was the identification of the phosphorylation of DARPP-32 (dopamine- and cyclic-AMP-regulated phosphoprotein of molecular weight 32,000) by dopamine and cyclic AMP in intact nerve cells. DARPP-32 impacts the concentration of the second messenger, cyclic AMP, via inhibition of protein phosphatase-1 (PP1) and through that mechanism, neuronal signaling (45). This led to the Nobel Prize for Paul Greengard, which was shared with Carlsson and Eric Kandel, whose research on the cellular basis of memory in invertebrates helped to understand the role of dopamine and other neurotransmitters in the cognitive impairment of schizophrenia (46). The change in PP1 activity following the release of dopamine can, in turn, alter the activity of many downstream proteins critical for brain function. This process is an example of the signaling induced by all neurotransmitters and neuromodulators required for an organism to respond to changes in its environment and to internally generated perturbations that enable harm avoidance, achievement of a desired goal (e.g., reward), experience less stress, avoidance of cell injury, and death. Signaling by dopamine is a critical means of inducing synaptic plasticity, which is the basis for learning and memory (46).

Synaptic plasticity refers to changes in synaptic structure and function that enable learning and memory. This is the process by which synapses strengthen or weaken over time in response to increases or decreases in their activity, leading to learning and memory. Atypical APDs have been shown to have profound effects on synaptic plasticity (47). For example, acute and chronic treatments with the atypical antipsychotic lurasidone, which has been shown to be effective to improve psychosis, depression, and cognitive impairment, was shown to alter the expression of the activity-regulated genes that are related to these actions (48). This multireceptor targeting agent shares with most atypical APDs higher affinity for 5-HT_{2A} than D_2 receptors. However, its efficacy as an antipsychotic is also related to its potent 5-HT_7 receptor antagonism and 5-HT_{1A} partial agonism (49). These two serotonergic effects combined with weak D_2 receptor antagonism are synergistic. There is conflicting clinical data concerning the relevance of 5-HT3 receptors to the efficacy and side effect of APDs (50), so this receptor will not be further discussed.

Recent genetic studies with lurasidone indicate that its effects on synaptic plasticity may be of great importance for its ability to ameliorate positive and negative symptoms as well as cognitive impairment (51, 52). The antidepressant action of amisulpride, a novel atypical antipsychotic that lacks 5-HT_{2A} antagonism and is not approved in the United States (although widely used in many other countries to treat schizophrenia and major depression), was prevented in 5-HT_7 receptor knockout mice (53). 5-HT_7 receptor antagonism is also central to the action of asenapine, clozapine, and risperidone but not olanzapine or ziprasidone. The 5-HT_7 receptor has multiple influences on dopaminergic function, which enable it to fine tune dopamine function in a manner not available to typical APDs (54, 55), even though some typical APDs (pimozide, chlorprothixene, chlorpromazine, clothiapine, and fluphenazine) have high affinities for 5-HT_7 receptors (56). This is because of their high potency to block D_2 receptors. Thus, the diversity in affinities for 5-HT_7 receptors relative to dopamine D_2 and 5-HT_{2A} receptors of the atypical APDs is highly likely to be relevant to intraindividual differences in clinical effects of atypical APDs. As noted by Li et al. (52), the expression of 44.5% of the genes that predicted response to lurasidone were inversely related to the expression of 5-HT_7 receptors in the hippocampus and prefrontal cortex of postmortem brain tissue from schizophrenia patients. These included genes that are significantly decreased in schizophrenia patients (52).

HIGHLIGHTING DIFFERENCES AMONG ATYPICAL APDS

There are now many clinical studies that have compared typical and atypical APDs, providing the basis for many meta-analyses and reviews. These have generally, but not always, shown significant advantages for specific domains of psychopathology, including positive and negative symptoms and cognition, side effects (particularly extrapyramidal side effects), and prolactin elevations (with the exception of risperidone, which has a still unexplained ability to produce prolactin elevations comparable to typical APDs). These

advantages for efficacy and safety, especially avoidance of TD, have been found in first-episode schizophrenia (57) as well as chronic schizophrenia (10) and bipolar disorder (58). They are not disorder specific or age related. Because of the diversity of the atypical antipsychotic drugs, weight gain (clozapine, olanzapine) and prolactin elevations (risperidone) can be avoided by choice of an atypical with little or no problem in these regards (e.g., aripiprazole, cariprazine, lurasidone, and ziprasidone). Nevertheless, because of their low cost, some have argued for continued use of typical APDs as first-line treatments, minimizing the lost opportunities for benefits discussed herein (59, 60). Both typical and atypical APDs are available as long-acting formulations. The atypicals with long-acting formulations include aripiprazole, olanzapine, paliperidone, and risperidone. Long-acting formulations have distinct advantages for compliance in both recent-onset schizophrenia and chronic schizophrenia. They are relatively costly compared with oral atypicals that are now generic but should be used when compliance with oral medication is erratic (61).

The most influential publication that has contributed to the continued use of the typical APDs despite the evidence that the atypical APDs are more effective and safer is the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study (62). The current generation of prescribers may need to be reminded of its history. CATIE was an 18-month randomized controlled trial in nearly 1500 chronic schizophrenia patients with mild-moderate symptoms despite treatment with typical or atypical APDs. The drugs studied included aripiprazole, quetiapine, olanzapine, and risperidone, the first-line atypical APDs available at that time, along with perphenazine, a representative typical APD. Perphenazine was chosen to represent the typical APDs because it was seldom used compared with haloperidol. The CATIE study was funded by NIMH, and its conclusions were trumpeted by the authors and NIMH as the first unbiased comparison of these agents. The results of the study received vast publicity in popular media worldwide. As of September 24, 2020, there were 7000 citations in PubMed. The CATIE study, a noninferiority study, concluded that there was an absence of evidence for the superiority of atypical versus typical APDs for nonacute schizophrenia. Both types of APDs were said to have similar therapeutic potential and to produce nonsignificantly different outcomes. It was also concluded that both types of APDs are similar in mechanism of action, thus explaining their lack of difference for treating positive symptoms, negative symptoms, and cognitive impairment. The CATIE study provided a minimal examination of the efficacy of clozapine in subjects who completed or dropped out of the main study (63). Although intended to include only nonresponders to the drugs in the main study, it allowed patients who did not meet that criteria to be included, minimizing its value (64). According to the CATIE lead authors, the CATIE study had little, and even then short-lived, impact on clinical practice as use of atypical APDs changed little. This led the CATIE leadership to reiterate their perspective that the widespread utilization of atypical APDs was the result of pernicious marketing skills of industry, not valid proof of special benefit, while always being cautious to put clozapine in a favorable light (5). They called for better education of physicians about adhering to the recommendations of the CATIE study to minimize the use of atypical antipsychotics other than clozapine (65). It is beyond the scope of this article to provide a full critique of the CATIE study. The self-corrected error with regard to greater cognitive benefits of the atypical APDs in patients without TD (35) will be discussed subsequently. Leucht et al. (1) compared the efficacy and tolerability of 15 typical and atypical APDs in a meta-analysis involving 212 studies and 47,000 patients. It included a number of findings, including all-cause discontinuation, the chief outcome measure of the CATIE study, that favored the atypical APDs over haloperidol, which clearly had the poorest outcome. The conclusion of the study was, as noted here, that APDs differed substantially in side effects and have small but robust differences in global measures of efficacy. The authors recommended clinicians focus their choice of APDs for individual patients on the specific domains identified herein.

HOW THE COMPLEX PHARMACOLOGY OF ATYPICAL APDS AND THE NEUROBIOLOGY OF SCHIZOPHRENIA INFORMS OPTIMAL UTILIZATION OF APDS

It is no longer tenable to conclude that only dopamine D_2 receptor blockade contributes to the antipsychotic actions of typical and atypical APDs. D_2 receptor blockade is clearly the major basis for initiating the antipsychotic action of typical antipsychotics but downstream effects on other intracellular mechanisms may also contribute. However, D_2 receptor blockade is only partially responsible for initiating the antipsychotic action of the atypical antipsychotics. The atypical APDs have been aptly described as "magic shotguns" (6) because of the large number of different G-protein receptors whose activity is directly or indirectly affected by some, but not all, of the atypical APDs. From a receptor perspective, the antipsychotic effect of the atypical agents is derived from their more potent 5-HT_{2A} relative to weaker D_2 receptor antagonism, with additional contributions from direct actions at 5-$HT_{1A,}$ 5-$HT_{6,}$ 5-HT_7, histaminergic, and $alpha_2$ adrenergic receptors (17). The demonstration of the importance of more potent 5-HT_{2A} than D_2 receptor antagonism for distinguishing atypical from typical antipsychotics facilitated the development of risperidone and olanzapine and most of the other atypical APDs. The combination of these two actions enabled a more rapid onset of antipsychotic action than strong D_2 receptor antagonism with equivalent or weaker 5-HT_{2A} receptor antagonism (8).

These direct effects of the atypical APDs also contribute to some of their indirect actions, especially the release of acetylcholine, glutamate, and dopamine (66, 67), effects which the typical APDs are not only devoid of, but may even block when the two classes of drugs are prescribed simultaneously

(68). This type of polypharmacy is common in the treatment of schizophrenia and bipolar disorder and may lead to lesser efficacy and more side effects (69, 70). The release of acetylcholine by lurasidone, leading to the stimulation of both nicotinic and muscarinic receptors in rat cortex, is an essential component of the ability of lurasidone to restore declarative memory in rats with memory impaired by prior treatment for 7 days with PCP (71), the most widely studied rodent model of cognitive impairment in schizophrenia (72, 73). 5-HT_{2A} receptor blockade, produced by 5-HT_{2A} inverse agonists such as pimavanserin, have been shown to be critical to the antipsychotic action of atypical APDs in the PCP model of schizophrenia (68, 74). Inverse agonists block the constitutive activity of receptors. They may also block the activation of the receptor from endogenous or exogenous neurotransmitters, as is the case with pimavanserin. This is highly relevant to the efficacy of pimavanserin, which has been shown to be effective to treat psychosis in Parkinson's disease (75). The top-line unpublished results of a single phase 3 study of pimavanserin (the ADVANCE trial) reported it to be superior to placebo as augmentation treatment of persistent negative symptoms in chronic schizophrenia (see Clinicaltrials.gov NCT02970305 for design of the trial). These results require confirmation. Pimavanserin has been shown to be useful when combined with low-dose risperidone—but not low-dose haloperidol—in acutely psychotic schizophrenia patients (76) but has not been tested for efficacy as monotherapy. Other selective 5-HT_{2A} inverse agonists (e.g., SR43469B) have been shown to be effective as monotherapy in acute schizophrenia (77).

Lumateperone is a 5-HT_{2A} inverse agonist, D_2 antagonist, and 5-HT transporter inhibitor that has recently been shown to be more effective than placebo in acutely psychotic schizophrenia patients (78). Unlike the other atypical APDs, which are more potent 5-HT_{2A} inverse agonists as previously discussed, it has insignificant binding to other G-protein receptors (e.g., 5-HT_{1A} and 5-HT_7 receptors) that contribute to atypical APDs' clinical advantages over typical APDs. In addition to being a postsynaptic D_2 receptor antagonist, it is also a partial agonist at presynaptic striatal D_2 receptors, as is aripiprazole. This presynaptic effect would be expected to contribute to its ability to increase mesocortical DA release, and most likely, indirect D_1 and D_4 agonism (79). Its occupancy of D_2 receptors in vivo in human volunteers is comparable to that of atypical APDs that lack D_2 partial agonism (80) and is much lower that of aripiprazole. It indirectly modulates glutamatergic neurotransmission in rats by several novel mechanisms (79). There are no reported data as to its ability to affect cognition in rodents or humans or to enhance acetylcholine release in brain.

Aripiprazole has been reported to improve some domains of cognition in schizophrenia (81). Aripiprazole and brexpiprazole are atypical APDs that are dopamine D_2 receptor partial agonists with 5-HT_{1A} receptor partial agonist properties. However, there are significant differences with regard to receptor pharmacology. Aripiprazole has significant 5-HT_{2A} inverse agonism, which brexpiprazole does not. Nevertheless, both are effective in treating acute schizophrenia with minimal motor side effects and weight gain. They produce small increases in cortical DA efflux in rodents without increased cortical acetylcholine efflux; the effect on cortical DA release is related to its 5-HT_{1A} partial agonism as is its efficacy in restoring declarative memory in the PCP test (82). Both may benefit from supplementation with a selective 5-HT_{2A} inverse agonist that has no D_2 receptor-blocking properties of note (e.g., pimavanserin).

Cariprazine, another novel atypical APD, also has potent dopamine D_2 and D_3 receptor antagonism (but lacks both 5-HT_{1A} partial agonism and 5-HT_{2A} receptor blockade) and is effective for treating both schizophrenia and mood disorders (83–85). Cariprazine, aripiprazole, and brexpiprazole may be of particular interest for treating patients who do not respond adequately to one of the canonical 5-HT_{2A}/D_2 antagonists (e.g., risperidone) and prior to a trial of clozapine. Of these three, cariprazine has the most robust ability to enhance acetylcholine (86).

The subchronic PCP-induced deficit in cognition in rodents may result from abnormalities in GABAergic neurotransmission, which in turn, produce abnormalities in glutamatergic function, disrupting the synchrony between GABA and glutamate required for effective oscillations and inhibitory and excitatory balance in the brain (20). Stimulation of the release of acetylcholine by the atypical APDs in cortex, hippocampus, and other brain regions is one of the major reasons for their ability to improve cognitive function. Typical APDs do not increase cortical acetylcholine efflux (66, 67). The loss of cholinergic stimulation in the aging brain and in neurodegenerative diseases such as Alzheimer's disease and Lewy Body Dementia is a major cause of memory impairment in these disorders and can be at least temporarily and partially remedied by pharmacologic means such as cholinesterase inhibition (87, 88). There is clinical evidence that release of acetylcholine and stimulation of muscarinic and nicotinic receptors in cortex and hippocampus by clozapine or the *N*-desmethylmetabolite of clozapine, or both, contributes to the improvement in working memory in both adult and childhood schizophrenia (89, 90). There is also strong preclinical evidence that supports the efficacy of this mechanism to improve cognition with other atypical APDs (91).

The direct and indirect actions of the atypical APDs at G-proteins and chromatin trigger a variety of intracellular signaling events that lead to modifications of multiple second messengers, including cyclic AMP, protein modifications and protein-protein interactions, release of neurotrophins such as neuregulin and brain-derived neurotrophin (BDNF), and short- and long-term changes in gene expression (7). Fumagalli et al (92) demonstrated that the NMDAR uncompetitive PCP-like NMDAR antagonist MK-801 decreased the BDNF expression in the hippocampus; olanzapine, an atypical antipsychotic, restored BDNF levels, while haloperidol exacerbated the decrease. This study is evidence that BDNF biosynthesis is differentially modulated by typical and atypical APDs when NMDA-mediated transmission is reduced, which is believed to be a key reason for cognitive impairment in

schizophrenia (93) and the target for the rescue of cognitive impairment in the subchronic PCP-induced model of cognitive impairment in schizophrenia (72). Further study is indicated to determine which atypical APDs can modulate BDNF expression and, thus, lead to improvement in cognition through enhancing synaptic plasticity.

Thus, differences in the efficacy of atypical APDs are related to the underlying neurobiology of the schizophrenia syndrome and how APDs restore neuronal function. Through knowledge of these differences and pharmacogenetic guidance, clinicians will someday be able to choose the best APD and adjunctive treatments for a patient based on the patient's genetic and epigenetic endowment, so-called personalized medicine. Only some of the knowledge needed for a personalized approach to prescribing APDs is currently available even with whole genome scanning and an epigenetic chip analysis of the epigenome at low cost relative to the cost of the illness. Much additional research is needed to enable this to be an effective means of choosing a specific drug, but partial implementation is possible. An example of this would be measuring the *N*-desmethylclozapine/clozapine ratio in plasma and adding a muscarinic or nicotinic agonist.

Common variants in genes related to synaptic function have been identified as the best predictors of response to lurasidone in acutely psychotic patients with schizophrenia in an association study of GWAS data and changes in total Positive and Negative Syndrome Scale (PANSS) scores (ΔPANSS-T) from the combined data of two 6-week randomized, placebo-controlled trials of lurasidone treatment in Caucasian schizophrenia patients (51, 52). However, none reach genome-wide significance. The genomic loci identified in these hypothesis-free studies include: 1) synaptogenic adhesion genes (*PTPRD, LRRC4C, NRXN1, ILIRAPL1, SLITRK1, NTRK3*); 2) scaffolding proteins (*MAGI1, MAGI2, NBEA*), both essential for synaptic function; and 3) other synapse-associated genes including, NRG1/3, KALRN, and the neuron-specific splicing regulator *RBFOX1*. Although none of these biomarkers reached genome-wide significance, most of the genes and associated pathways have been identified as risk genes for schizophrenia and shown to be under expressed in postmortem dorsolateral prefrontal cortex of schizophrenia patients. Some of these genes have been also shown to predict response to other atypical APDs (52). These findings add to the evidence that synaptic plasticity is related to multiple aspects of APD response, not just cognitive impairment, adding to the rationale for favoring the use of atypical rather than typical APDs.

Awareness of the similarities and differences in pharmacology of the atypical APDs should increase their utilization and lead to better outcomes. Rodents treated with competitive NMDAR antagonists for 3–14 days have demonstrated that diverse atypical improve some types of cognitive impairment and social interaction deficits in rodents and nonhuman primates, while typical APDs do not (72, 73, 94). The pharmacologic mechanisms that enable the atypical APDs to restore cognition and social interaction in rodents are diverse and include dopamine D_1 and D_4 agonism and 5-HT_{1A} partial agonism, as well as restoration of cholinergic function (71, 91, 94). Ziprasidone, which has 5-HT_{1A} partial agonist properties and enhances the release of acetylcholine and dopamine, is among the many atypical APDs with a similar profile that have been shown to improve cognition in schizophrenia (95, 96).The extensive evidence for the role of glutamate, including NMDA receptors in the pathophysiology of schizophrenia, have made this model very attractive for identifying novel treatments for the cognitive impairment associated with schizophrenia (97). More importantly for the purpose of this article, the studies with the subchronic PCP are consistent with the findings of multiple clinical trials (98) that atypical antipsychotics are able to improve cognition in patients with schizophrenia (9, 32, 95, 96, 99), which was rejected by Keefe et al. (100) based on the CATIE study. These authors later revised their conclusions after demonstrating superior efficacy of atypical APDs to improve cognition in CATIE patients who did not have overt TD (35). Unfortunately, Caroff et al. (35) did not call particular attention to this critical issue and it received little attention subsequently based on the failure to note this very important caveat when discussing whether or not the atypical antipsychotics have an advantage over the typical antipsychotic or how effective they are in treating schizophrenia. The possibility that cognitive impairment in patients with masked TD (because of maintenance treatment with antipsychotics) also impairs their ability to respond to atypical APDs has not been investigated.

When considering the choice of an APD, the risk of TD must be given high priority because of its impact on potential improvement in cognition, effect on compliance, and mortality. This is a major reason for utilizing an atypical rather than a typical APD for maintenance treatment and even brief treatment, as TD can sometimes develop during the first months of treatment with typical APDs (37, 101). TD can have a negative impact on quality of life, with particular impact on social interaction in patients with bipolar disorder, major depression, and schizophrenia (102). Other types of extrapyramidal symptoms produced by typical APDs, including increased muscle tone, rigidity, and inaccuracies in fine motor skills can produce negative subjective responses that lead to noncompliance in patients regardless of diagnosis (103). The risk of TD with atypical APDs is variable, with clozapine having the lowest risk and risperidone the highest because of its strong dopamine D_2 receptor blockade (104). Antipsychotic-induced movement disorders should be assessed at each clinical visit and monitored with rating scales as needed to facilitate treatment choices (105).

CLARIFYING THE UNIQUE CLINICAL APPLICATIONS OF CLOZAPINE

As previously noted, clozapine is considered by many to be an atypical APD in a class of its own, the "gold standard" with regard to superior efficacy for patients who do not respond to typical antipsychotics or other first-line atypical

antipsychotics. I have argued here that it is unique for suicide risk but not for improving cognition. Is it unique for improving psychosis and overall function in treatment-resistant schizophrenia? The efficacy of clozapine for treatment-resistant schizophrenia patients was first established in a randomized clinical trial codirected by the author and others (106). The main conclusion of that study, i.e., that clozapine is effective in treating positive and negative symptoms in 30%−40% of patients who meet criteria for treatment-resistant schizophrenia, has been supported by several decades of experience and numerous other trials throughout the world in a variety of clinical settings (107). However, other atypical APDs have also been shown to be effective in subgroups of patients with treatment-resistant schizophrenia. This was first reported in a study of melperone (108). Melperone is a member of the same butyrophenone chemical class as haloperidol. Melperone was never developed as an APD in the United States because of a single paper that claimed that the basis for the efficacy of clozapine in treatment-resistant schizophrenia was dopamine D_4 receptor antagonism (109). The studies supporting this claim were rejected on a number of grounds and are inconsistent with the contrary evidence that D_4 receptor *stimulation* can enhance the ability of clozapine to improve its efficacy in improving memory in rodents treated with PCP for 3–14 days (91). The Van Tol et al. (109) report led to a massive effort by at least four pharmaceutical companies to be the first to develop selective D_4 antagonists, all of which failed! Indeed, in one study, the selective D_4 antagonist worsened psychopathology in acutely psychotic patients (110). This is noteworthy since a similar worsening of schizophrenia occurred in the one clinical trial with a D_1 receptor antagonist (42), an indication of the translational value of rodent studies with regard to schizophrenia. No further effort to develop melperone for schizophrenia, which has been shown to be effective to treat psychosis even in patients with Parkinson's psychosis (111), occurred in the United States, a great loss. Subsequently, in randomized controlled trials, olanzapine (112), long-acting injectable risperidone (113), lurasidone (114), and aripiprazole (115) were also found to be effective in treating positive and negative symptoms in 30%−40% of patients with treatment-resistant schizophrenia. The overall response rates were similar to that of clozapine based on historical controls or in the case of olanzapine, with clozapine as an active comparator. There is also some evidence that treatment-resistant schizophrenia with no response to olanzapine or risperidone will improve by prespecified criteria with aripiprazole (115). Efficacy of various atypical APDs in patients who fail to respond to typical antipsychotics has been widely reported (116).

Based on these studies the argument for early use of clozapine (i.e., after failure to respond to two APDs, regardless of whether neither or both are atypical [117]), needs to be reconsidered. Like the suggestion that trials of clozapine in treatment-resistant schizophrenia should be limited to a few weeks on safety grounds if there is no improvement after 2 weeks (118), this recommendation to start clozapine is not supported by the evidence (119). This is also the case for other atypical APDs. During more prolonged trials, major changes in synaptic structure and function are quite possible. Related to this, clinicians should be cautious about embracing suggestions that clozapine should be initiated very early in the course of the illness without adequate trials of other atypical APDs that have been shown to be effective in treatment-resistant schizophrenia (120).

CONCLUSIONS

Atypical APDs have broader efficacy for treating the major types of psychopathology, including positive, negative, and mood symptoms and suicidality, compared with typical APDs. These benefits are evident in a wide range of psychiatric disorders, not just schizophrenia. There is much greater diversity among the atypical than the typical APDs. Atypical APDs initiate their actions by targeting multiple receptors and neurotrophin, leading to synaptic plasticity, unlike the typical APDs, which selectively act through D_2 receptor blockade to mainly target positive symptoms and produce serious mechanism-based side effects, especially tardive dyskinesia. 5-HT_{2A} receptor blockade and release of neurotrophins, such as BDNF, are the most common mechanisms by which atypical APDs supplement weaker D_2 receptor blockade to achieve their broader action. Direct effects on 5-HT_{1A} and 5-HT_7, and indirect effects on dopamine D_1, D_4, nicotinic, and muscarinic receptors due to the release of cortical and hippocampal dopamine and acetylcholine, are principal contributors to their broader actions. The benefits from atypical APDs are achieved, in part, through synaptic plasticity that may take weeks to months to be achieved. Because of differences among the atypical APDs and genetic and epigenetic differences among patients, multiple trials of atypical agents may be required to find the best drug for a patient until pharmacogenetic and other predictors of differential response are identified. Clozapine, while uniquely effective to reduce the risk of suicide, is not the only atypical APD useful for patients who fail to respond to first-line typical and atypical APDs. Clinicians should be aware of the risk of TD with typical APDs and its potential to reduce the ability of atypical APDs to improve cognition. Atypical agents that target GABA receptors and use of biomarkers, especially pharmacogenomics markers, will likely expand the advantages of atypical APDs in the near future.

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