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Rational antipsychotic polypharmacy in psychotic and bipolar disorders: A focus on D2 receptor partial agonists

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Abstract

Aripiprazole, brexpiprazole, and cariprazine have a unique pharmacology as demonstrated by their high affinity to the dopamine type-2 receptor (ie, D2 receptor). These agents may be preferred over others for the treatment of psychotic and bipolar disorders due to their lower incidence of movement disorders and sedation. When prescribed adjunctively to full antagonist agents, partial agonist antipsychotics can mitigate adverse effects such as hyperprolactinemia. However, their high affinity for the D2 receptor may interfere with the efficacy of full antagonist antipsychotics when used in combination. Some partial agonists may be less preferred in particular patient scenarios based on their demonstrated clinical efficacy. Three illustrative patient cases highlight clinical pearls related to the safe and effective use of antipsychotic polypharmacy involving partial agonist antipsychotics.

Keywords: partial agonists, adjunctive, psychosis, adverse effects, polypharmacy

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Introduction

Serious mental illnesses, including bipolar disorder, schizophrenia, and schizoaffective disorder, can significantly affect quality of life and reduce life expectancy for those affected.[1] Antipsychotics, which primarily act through dopamine and serotonin antagonism, are a key component of treatment for these disorders.[2] Despite available treatments, up to a third of patients with schizophrenia and bipolar disorder may have treatment refractory symptoms,[3-5] and up to 60% of patients with schizophrenia may not respond adequately to clozapine treatment.[6] In the setting of inadequate response to antipsychotic treatment in schizophrenia, up to 30% of clinicians use antipsychotic polypharmacy.[7] Additionally, up to 40% of patients with bipolar disorder are prescribed 3 or more medications[8] though antipsychotic polypharmacy is less common than in patients with schizophrenia.[9] The prevalence of antipsychotic polypharmacy, reported to have increased steadily from 1970 to 2023, varies by geographic region and treatment setting but, worldwide, appears to be approximately 20% with first and second generation antipsychotics most commonly combined.[10,11] When using multiple antipsychotics, cost and regulatory concerns, patient-specific factors, and individual agents' pharmacologic target profiles should be considered as part of the risk–benefit assessment.[12] Combination therapy using multiple antipsychotics with high affinities at the same receptors may provide little benefit and increase the risk of adverse effects. However, when a desired clinical response is not achieved with a single antipsychotic agent, combination therapy using antipsychotics

Take Home Points:

1. The high affinity and occupancy of partial agonist antipsychotics at the D2 receptor may reduce the ability of full D2 antagonists to bind to the D2 receptor, which can limit efficacy when prescribed concurrently. If antipsychotic polypharmacy is used, clinicians should be mindful of the agents pharmacologic binding affinities.
2. Partial agonist antipsychotics can reverse signs and symptoms of hyperprolactinemia caused by full D2 antagonists.
3. Cariprazine is the only partial agonist antipsychotic that has demonstrated efficacy in patients with bipolar depression.

with complementary mechanisms may be both rational and effective.

The traditional dopamine hypothesis of schizophrenia and bipolar disorder suggests that the resolution of psychotic and manic symptoms are linked to antipsychotics' ability to bind to and antagonize the dopamine type-2 receptors (ie, D2 receptor).[13,14] The introduction of muscarinic agonists, however, modifies the treatment approach, allowing for upstream dopamine modulation without direct D2 receptor antagonism.[15] First and second generation antipsychotics that fully antagonize the D2 receptor demonstrate efficacy at 60% to 80% receptor occupancy with occupancy beyond this often associated with movement-related adverse effects.[16] Partial agonist antipsychotics (PAAs; aripiprazole, brexpiprazole, cariprazine) allow for dopamine agonist activity, known as intrinsic activity, and, thus, require a higher degree of receptor occupancy (80% to 100%) to produce the same therapeutic effect.[17] Intrinsic activity is the degree to which PAAs activate the receptor when binding, relative to the natural ligand (ie, dopamine at the D2 receptor).[18,19] PAAs are often prescribed earlier in the course of illness due to their favorable adverse effect profile.[20] In contrast to PAAs' high affinity to the serotonin type-2A (5-HT_{2A}) receptor and partial agonism at the D2, serotonin type-1A (5-HT_{1A}), and dopamine type-3 (D3) receptors, their low affinity for muscarinic, histaminic, and serotonin type-2C (5-HT_{2C}) receptors results in a theoretical lower risk for sedation and metabolic dysfunction compared with other second generation agents.[21,22] However, despite their tolerability, combining them with full dopamine antagonists, other than clozapine, has limited evidence of additional benefit in managing psychiatric symptoms.[23,24] Adjunctive use of PAAs with full antagonist agents can reduce dopamine blockade–related adverse effects, such as elevations in prolactin; however, PAAs may also displace agents with a lower binding affinity at the D2 receptor, potentially exacerbating psychotic symptoms.[23] In this article, 3 cases explore the use of PAAs with other antipsychotics in commonly encountered clinical scenarios. All patient cases in this article represent scenarios that may be encountered in practice but are illustrative or educational in nature.

Case 1: Transitioning from a Partial Agonist Antipsychotic in the Setting of Poor Response

A 35-year-old patient was brought into the emergency room by the mental health response team after the patient's family notified their physician of an increase in disorganized behavior and aggression. The patient has a past psychiatric history of schizoaffective disorder, bipolar type diagnosed at age 20 with at least 4 known inpatient hospitalizations, most recently 4 months ago related to treatment nonadherence. At discharge, the patient was started on aripiprazole monohydrate 400 mg intramuscularly every 4 weeks, following titration to an oral aripiprazole dose of 15 mg daily. They received their most recent monthly injection 7 days prior to presenting to the emergency department and had received their injections consistently prior to presentation. The patient has no other documented medical conditions or medications, and a urine drug screen in the emergency department was negative for all substances. A mental status examination found the patient to be guarded with an illogical thought process and pressured speech and oddly related during the interview. The patient was admitted to the hospital for further treatment, and due to partial response of the long-acting injectable (LAI) aripiprazole, the treatment team decided to switch to haloperidol. Haloperidol 10 mg orally was initiated nightly. The patient continued haloperidol, which was titrated to 10 mg orally twice daily over 7 days, and demonstrated little improvement. The treatment team elected to discontinue haloperidol and initiated treatment with olanzapine 10 mg orally at bedtime.

Incomplete symptom resolution following treatment with an LAI PAA leaves clinicians in a challenging clinical scenario due to the medication's unique binding profile and extended half-life. Tables 1 and 2 describe antipsychotic binding affinities and receptor occupancies. Despite high-potency first generation antipsychotics' (ie, haloperidol) potent D2 receptor antagonism and binding affinity (haloperidol Ki 1.2), PAAs' higher binding affinity (aripiprazole Ki 0.34) and extensive occupancy of the D2 receptor may limit the ability of full D2 antagonists to bind and exert their antipsychotic effect.[17,25,26] Further, the half-life of the aripiprazole LAI ranges from 30 to 46 days, prolonging exposure and potentially extending the time until the D2 antagonist can work. Although it may be impossible to tell whether haloperidol or aripiprazole is occupying the D2

TABLE 1: Antipsychotic receptor affinity[16,73,84,88-91]

Antipsychotic	D2	D3	5-HT_{2A}	5-HT_{2C}	5-HT_{1A}	Alpha-1A	H1	M1
Full Antagonist Antipsychotic Receptor Affinity (Ki, nM) In Vitro								
Fluphenazine	0.8	1.75	3.2	418	145	6.5	14	1100
Haloperidol	1.2	8.5	3.2	4700	>1000	12	1700	>10 000
Chlorpromazine	3.6	4.65	3.6	30	>3000	0.3	3.1	32
Risperidone	3.2	7.3	0.2	32	427	5	20	>10 000
Olanzapine	31	38.1	3.7	4.1	>2000	110	2.2	2.5
Lumateperone	32	NA	0.54	173	NA	73	>1000	>100
Clozapine	160	310	5.4	4.8	105	1.6	1.1	6.2
Quetiapine	380	394	640	3500	431	22	6.9	37
Endogenous dopamine	540	60	—	—	—	—	—	—
Partial Agonists Receptor Affinity (Ki, nM) In Vitro								
Brexpiprazole	0.30[a]	1.1[a]	0.47	34	0.12[a]	3.8	19	>1000
	Intrinsic activity 45%				Intrinsic activity 60%			
Aripiprazole	0.34[a]	0.8[a]	3.4	15	1.7[a]	26	28	>1000
	Intrinsic activity 60%				Intrinsic activity 73%			
Cariprazine	0.59[a]	0.08[a]	19	134	2.6[a]	155	23	>1000
	Intrinsic activity 30%				Intrinsic activity 73%			

[a]Indicates partial agonist activity.

receptor when the 2 molecules are prescribed together, as positron emission tomography (PET) studies investigating the interaction do not exist, both agents are competing for D2 receptor occupancy. It can be hypothesized that the agent with the higher binding affinity is more likely to occupy the majority of D2 receptors. Even if PAAs occupy 100% of the D2 receptors, intrinsic agonist activity prevents PAAs from achieving the same amount of D2 antagonism as a full antagonist occupying 100% of receptors. Despite the lack of objective evidence in controlled settings, case reports describe patients maintained on full antagonist antipsychotics decompensating when aripiprazole is added to their treatment regimen.[25] Inversely, similar to the current case, 1 report describes a woman with schizophrenia, who historically responded positively to paliperidone, fail to respond to paliperidone 1 month after receiving 1064 mg of long-acting aripiprazole lauroxil.[27] The authors hypothesize that aripiprazole's high binding affinity impeded paliperidone from antagonizing the D2 receptor, limiting the clinical benefit.

As demonstrated in the patient case, symptoms of psychosis and mania may fail to respond to the strong D2 blocking agent during transition periods, requiring a switch to an agent that exerts activity at other relevant receptors. A medication such as olanzapine offers benefit in managing symptoms of mania due to an increased sedative effect, which may be related to H1 antagonism.[28] High potency serotonin 2A (5-HT_{2A}) receptor antagonism by olanzapine may additionally target symptoms of mania and psychosis, bypassing the need to antagonize D2 receptors for clinical benefit.[29,30] Careful consideration of antipsychotic receptor profiles can allow clinicians to acutely target symptoms while waiting for the long-acting PAA to wash out and decrease its occupancy of the D2 receptor.

TABLE 2: Partial agonist antipsychotics D2 receptor occupancy by dose, an estimate[92,93]

Medication	Dose, mg	D2 Receptor Occupancy, %	Plasma Concentration, ng/mL	Therapeutic Reference Range, ng/mL
Aripiprazole	0.5	33.7	~5	100 to 350
	1	57.2	~10	
	2	71.6	~20	
	5	85.3	~60	
	10	91.1	~100	
	30	98.1	~300	
Brexpiprazole	0.5	38.4	~10	40 to 140
	1	48	~20	
	2	71.4	~40	
	4	90	~80	
	6	93.6	~120	
Cariprazine	1	45	~5	10 to 20
	3	92	~15	
	6	91.2	~30	

Trying to bypass the PAA affinity at the D2 receptor with large doses of D2 antagonists may not be beneficial and could cause harm. This approach leaves the patient vulnerable to developing movement-related adverse effects without any additional antipsychotic benefit. If D2 antagonism is needed, the best approach is to wait until the D2 receptor occupancy of the partial agonist antipsychotic has dropped enough to allow the full D2 antagonist to access the D2 receptor.[18,31] Further, if the patient has had prior exposure to a D2 receptor antagonist, the previous effective and tolerated dose can be resumed while waiting for PAA concentrations to become undetectable. As the plasma concentration of the PAA drops, the full antagonist will theoretically have more available receptor binding sites to exert antipsychotic effect. This situation can also be applied in the setting of treating an episode of acute agitation in a patient maintained on aripiprazole.[32] If the goal is to transition the patient to a full antagonist LAI antipsychotic, a reasonable approach is to administer the LAI on schedule and, as the LAI PAA washes out over time, adjust the dose of the full antagonist LAI based on response and tolerability. However, response and tolerability to the full antagonist LAI may not be fully appreciated until the PAA LAI has tapered sufficiently. Without studies on specific switching methods, clinicians must develop plans using pharmacokinetic and pharmacodynamic data combined with careful assessment of clinical response.[33]

In situations in which patients who have previously not responded to multiple monotherapies end up having a partial response to a PAA, long-term dual antipsychotic therapy may be an option rather than cross-titrating to an alternative. When polypharmacy with PAAs appears to show the most benefit is adjunctive to clozapine. Clozapine and PAAs have complementary pharmacodynamic profiles as clozapine appears to exert its antipsychotic effect with little D2 receptor antagonism. A large Finnish cohort study found that patients receiving aripiprazole and clozapine were least likely to be rehospitalized (hazard ratio = 0.42).[34] Although not well researched, the comparative pharmacology of cariprazine and brexpiprazole suggests that these agents would also be complementary when added to clozapine due to a lack of interaction between the pharmacologic targets of clozapine and the addition of D3 agonism from cariprazine. Only one small prospective study (n = 10) assessed the effect of adjunct cariprazine to patients receiving clozapine treatment who had demonstrated an inadequate response and long-term negative symptoms and found a considerable improvement in positive and negative symptoms over a 3-month period.[35] With the emergence of novel antipsychotics, such as lumateperone and xanomeline/trospium, which achieve their antipsychotic effects without primarily antagonizing D2 receptors,[15,36] applying the same idea of complementary polypharmacy may serve useful in patients who have not fully responded to monotherapy. Future studies are warranted to support this theory.

Returning to our patient, after 7 days on olanzapine titrated to 15 mg orally at bedtime, the patient's thought process improved and aggression had diminished. Clinicians observed an improvement in the patient's sleep patterns and attention to personal hygiene, and the patient was engaging appropriately with peers in their age cohort. Olanzapine was well tolerated, and the patient requested to no longer receive aripiprazole monohydrate but instead transition to olanzapine pamoate.

Case 2: Using Partial Agonist Antipsychotics to Manage Adverse Effects

A 22-year-old male patient with 1 previous psychiatric hospitalization for an episode of psychosis who has been maintained on risperidone 5 mg orally at bedtime presented to the outpatient psychiatric clinic for medication management accompanied by his mother. The patient reports last experiencing auditory hallucinations 12 months ago and has been working in an auto repair shop 5 days per week for the past 4 months. On exam, he is well groomed and appropriately dressed, his thought process is coherent and logical without evidence of delusions, and he denies symptoms of paranoia. He reports adherence to risperidone since hospital discharge but does admit to missing a few doses here and there. He reports satisfaction with the medication, but is concerned about how his shirts fit and that he is embarrassed to take off his shirt due to enlarged breast tissue. The patient and his mother are worried about changing his medications as he is scheduled to begin school next fall and has been doing well psychiatrically.

Antipsychotic-induced hyperprolactinemia occurs via dopamine antagonism, preventing endogenous dopamine from inhibiting prolactin release from pituitary lactotrophs.[37] Risperidone and the active metabolite 9-hydroxyrisperidone (ie, paliperidone) are more likely to cause prolactin elevations than other antipsychotics even compared with first generation agents.[38,39] This may be due to risperidone's incomplete penetration of the blood-brain barrier, leading to increased D2 receptor binding at the pituitary level.[40] Hyperprolactinemia can result in myriad symptoms related to sexual dysfunction, including impairment of libido, arousal, and anorgasmia.[41,42] Along with impairing sexual function, hyperprolactinemia is associated with amenorrhea, gynecomastia, and galactorrhea, which significantly affect satisfaction with and overall adherence to treatment.[43,44] There are several proposed strategies in managing antipsychotic-induced hyperprolactinemia leading to sexual dysfunction, including reducing the dose of the dopamine antagonist, switching agents, adding a dopamine agonist, or augmenting the dopamine antagonist with a PAA.[45] Clinicians should exercise caution when considering reducing the dose of the current antipsychotic or prescribing dopamine agonists to patients with a history of psychosis. These approaches may increase the risk of exacerbating psychotic symptoms,

making augmentation with a PAA the most attractive option in many cases. PAAs have a reduced incidence of sexual dysfunction compared with full antagonists[46] and lower prolactin when combined with full antagonist agents.[24,47]

PAAs appear to lower prolactin by agonizing the D2 receptors on lactotrophs, increasing the dopaminergic tone, and shutting down prolactin secretion.[41,48] When used adjunctively with a full D2 receptor antagonist, PAA can displace the full antagonist at the lactotroph D2 receptor, allowing endogenous dopamine to inhibit prolactin secretion.[49] The use of adjunctive PAAs to manage hyperprolactinemia has been most extensively studied with aripiprazole although the mechanism of action suggests that all PAAs could be effective.[50,51] Studies indicate that low-dose aripiprazole ($\leq$5 mg/day) is not significantly less effective than higher doses (>5 mg/day) in achieving a therapeutic response. However, if a patient fails to respond to 5 mg/day, it is appropriate to increase the dose in 5-mg increments until the lowest effective dose is reached.[52] Based on a meta-analysis of randomized controlled trials, adjunctive aripiprazole appears to reduce elevated prolactin levels within 4 to 8 weeks with clinical normalization often occurring by 12 weeks.[51] As described in Table 2, as the dose of the PAAs increases, so does D2 receptor occupancy, which theoretically may displace a full antagonist agent, risking loss of efficacy from the D2 full antagonist. Using the minimally effective dose of the PAA and routinely monitoring for a reduction in adverse effect is recommended when using this approach. Brexpiprazole, although having less intrinsic activity at D2 receptors than aripiprazole,[19,53] has been shown to decrease prolactin levels over time.[54] In a post hoc analysis of a 52-week, open-label study that examined the long-term safety and efficacy of brexpiprazole in patients with schizophrenia, patients who were transitioned from a full antagonist antipsychotic to brexpiprazole, who at the time of the switch had abnormally elevated prolactin, observed their prolactin level drop into the normal range. Interestingly, 28/34 patients who were transitioned from aripiprazole to brexpiprazole in this study had a low baseline prolactin level, and the transition to brexpiprazole shifted prolactin values to within the normal range.[55] Cariprazine has also demonstrated a low likelihood of increasing prolactin in clinical studies;[56] however, prolactin elevation with PAAs remains unexpected though not exclusionary.[57] Although neither brexpiprazole nor cariprazine has been studied as an adjunct therapy in antipsychotic-induced hyperprolactinemia, their mechanism and these results make it a reasonable option to consider in such a scenario.

Hyperprolactinemia is not the only adverse effect that can be managed by taking advantage of PAA receptor binding profiles. PAAs have demonstrated value in mitigating weight gain and metabolic dysfunction when used adjunctively with high-risk agents, such as clozapine, olanzapine, and quetiapine, in both human and animal studies.[58,59] Partial agonism at the 5-HT_{2C} receptor by PAAs may explain the reversal of clozapine-/olanzapine-induced metabolic dysfunction. Additionally, combining PAAs with antipsychotics that have a high affinity for the H1 receptor may help to reduce overall sedation though the overall clinical benefit is unclear.[60,61]

Returning to our patient, the clinician proposed adding a PAA, brexpiprazole 1 mg orally at bedtime, to the patient's nightly risperidone. The clinician also requested that the patient visit the laboratory after the appointment to assess serum prolactin levels and return to the clinic in 4 weeks for reassessment. The prolactin level resulted at 55 ng/mL prior to initiation of brexpiprazole (typical range in men 2-19 ng/mL). A month later, the patient continued to report doing well without a reemergence of psychotic symptoms. He reported adherence with both brexpiprazole and risperidone and was pleased to observe a normalization of his breast tissue. Following the appointment, his prolactin level was collected and resulted at 15 ng/mL—within the normal range. The patient was advised to report any emergent adverse effects, including involuntary movements, and to maintain routine metabolic monitoring in accordance with clinical guidelines.

Augmentation with brexpiprazole in this clinical scenario is appropriate due to the patient's positive response to risperidone. Alternatively, transitioning to brexpiprazole as the sole antipsychotic replacing risperidone is not unreasonable. As brexpiprazole is introduced, however, monitoring for a reemergence of psychotic symptoms is important as brexpiprazole could displace the full antagonist risperidone at the D2 receptor.[25,31,62] Compared with aripiprazole, switching to brexpiprazole or cariprazine may pose a lower risk of psychotic symptom reemergence as these agents have lower intrinsic activity relative to aripiprazole, suggesting that brexpiprazole and cariprazine behave more as dopamine antagonists at the D2 receptor than aripiprazole (see Table 1).[63] As intrinsic activity increases at the D2 receptor, PAA receptor activity approximates that of a full D2 receptor agonist.[19]

Case 3: Choosing a Partial Agonist Antipsychotic

A 29-year-old patient was admitted to the hospital following a suicide attempt. The past medical history was significant for bipolar I disorder, cannabis use disorder, and prediabetes. Current medications included olanzapine 15 mg orally at bedtime, sertraline 200 mg orally daily, and metformin 500 mg orally twice daily with meals. The patient reports adherence to prescribed medications but describes worsening feelings of depression over the past 6 weeks, including loss of interest in previously enjoyed activities, excessive guilt, feelings of worthlessness, and hypersomnia. The Montgomery-Asberg Depression Rating

Scale (MADRS) was conducted and resulted in a score of 30, indicating moderate depression. The patient first reported experiencing mania and hallucinations at the age of 21, but symptoms have resolved with antipsychotic medications. Prior to treatment with olanzapine, the patient had received medication trials of paliperidone, ziprasidone, haloperidol, and divalproex but experienced intolerable adverse effects, including sexual dysfunction and tremor. Cannabis has reportedly provided temporary improvements in mood, and thus, the patient has been smoking cannabis 3 to 4 times per day (half of a cannabis cigarette per patient). The patient is open to trying a new medication if there is potential for it to work differently than previous medication trials. When treating bipolar depression, the use of standard antidepressant medications may not effectively alleviate depressive symptoms and could cause mood fluctuations or mania, especially in the absence of an antimanic agent.[64] One approach in improving depressive symptoms could be augmentation or monotherapy with lithium or lamotrigine.[65] In patients expressing suicidal ideation or those who present with self-harming behaviors, lithium may be exceptionally beneficial due to its antisuicide properties.[66] Another strategy could be to recommend initiating an antipsychotic with evidence for improving bipolar depression. Although most antipsychotics have FDA approval in treating mania, only 5 antipsychotic medications have approval for acute bipolar depression: olanzapine/fluoxetine combination, quetiapine, lurasidone, cariprazine, and lumateperone.[65] Cariprazine is the only PAA that has demonstrated a positive effect in bipolar depression in large clinical trials.[67] In contrast, aripiprazole monotherapy has shown negative results,[68] and brexpiprazole has low-level evidence of benefit based on a small open-label study of 21 patients.[69] Clinicians should be mindful that, although PAAs share many properties, they can have distinct differences; therefore, available pharmacodynamic and clinical evidence should be carefully examined when initiating or adjusting therapy.

Compared with the other available antipsychotics, cariprazine has the highest binding affinity to the D3 receptor (ki = 0.08 nM).[70,71] The clinical significance of this is not fully understood; however, it is hypothesized to improve cognitive function and negative symptoms in schizophrenia.[72] The D3 receptor may play a role in reward processing and mood via disinhibiting dopamine release in the prefrontal cortex, thus resulting in a positive dopamine tone.[73] Cariprazine also has a high binding affinity and is a partial agonist at the 5-HT_{1A} receptor, which may contribute to the overall antidepressant effects.[41,71] However, patients experiencing a bipolar depressive episode often fail to respond to treatments that rely solely on increasing serotonin availability, suggesting that cariprazine's efficacy in bipolar depression could come via a different mechanism, possibly a norepinephrine or glutamatergic signal.[74]

When used for the treatment of bipolar depression, cariprazine has been studied as a monotherapy. To date, there is no evidence that antipsychotic polypharmacy with cariprazine has additional benefit in treating bipolar depression. However, if cariprazine's high affinity to the D3 receptor is found to be responsible for improving depressive symptoms, use with an agent with low D2 receptor affinity and evidence in bipolar depression (ie, lumateperone, quetiapine) could potentially be useful. Currently, a more evidence-based approach would be to transition patients prescribed D2 antagonists to cariprazine monotherapy. As cariprazine is introduced, the full antagonist will, theoretically, be displaced from the D2 receptor. This could be problematic if the patient is prone to developing psychotic symptoms that only improve with >80% D2 receptor occupancy as cariprazine may be unable to provide enough D2 antagonism to quell psychotic symptoms in certain patients. If no psychotic exacerbation occurs by the time cariprazine reaches steady state (approximately 7 to 21 days),[75,76] then the full antagonist can be tapered and discontinued. Gradually lowering the dose of the full antagonist by 25% to 50% for 4 to 5 half-lives is a reasonable approach. During this transition, clinicians should be mindful of the potential loss of antihistaminic and sedative effects to prevent cholinergic rebound or insomnia. When switching from a more antihistaminic agent (ie, olanzapine, quetiapine) to an agent with less histamine blockade (ie, PAAs), a cross-titration can help to reduce uncomfortable withdrawal phenomena.[77] If the clinician feels that discontinuing the full antagonist agent requires more urgency, temporarily providing as-needed agents with an anxiolytic/antihistaminic effect (ie, hydroxyzine, mirtazapine, benzodiazepines) could be considered as a preemptive measure.[78] If transitioning from an agent with minimal sedating effects (ie, lurasidone), the agent may be discontinued more rapidly.

In addition to considering the efficacy of a new treatment option, it is important to be mindful of the adverse effect profile that would be introduced. Compared with other second generation antipsychotics, PAAs have a favorable metabolic profile with a lower incidence of weight gain and glucose abnormalities.[79] Furthermore, although PAAs exhibit high D2 receptor occupancy, their intrinsic activity at D2 receptors is higher than that of full antagonists, which reduces the risk of extrapyramidal symptoms.[80-82] If patients are to experience an extrapyramidal symptom associated with PAAs, akathisia appears most likely. Akathisia usually occurs within the first few weeks of treatment and at higher doses, particularly with cariprazine.[75] In a 2019 meta-analysis that assessed the efficacy and tolerability of 32 oral antipsychotics in the treatment of schizophrenia, the authors concluded that aripiprazole and cariprazine were associated with a significantly increased risk of akathisia (relative risk [RR] 1.95, 95% confidence interval [CI] 1.30, 2.74

and 3.16, 95% CI 2.02, 4.56), respectively.[83] However, the risk for brexpiprazole was lower and not significant (RR 1.35, 95% CI 0.80, 2.08).[83] High affinity and full antagonism at the 5-HT_{2A} receptor is also thought to contribute to the low risk of movement-related adverse effects with PAA agents. Sedation, although unlikely with PAA due to lower affinity for the H1 receptor, may be more likely with brexpiprazole compared with aripiprazole and cariprazine.[49,84] Additionally, differences in intrinsic activity at the D2 receptor could explain the variable incidence of nausea among the PAAs as nausea may stem from dopamine agonism with aripiprazole having the highest rates of nausea.[80,85] Intrinsic activity at the D2, D3, and possibly the 5-HT_{1A} receptors may also account for the higher incidence of impulse control problems (ie, pathological gambling, excessive shopping) associated with PAAs compared with full antagonist agents.[86,87]

Returning to our patient, olanzapine was reduced to 10 mg for 4 days while treatment with cariprazine 1.5 mg was initiated; both medications were administered at bedtime. Olanzapine was reduced in 5 mg increments every 4 days and then discontinued. Hydroxyzine 50 mg was available as needed every 6 hours to assist with any anxiety, agitation, or insomnia. As the patient had not experienced an episode of mania on 15 mg of oral olanzapine, the clinician chose to increase cariprazine to 3 mg orally at bedtime prior to discharge to achieve a comparable occupancy of the D2 receptor with instructions to follow up with their outpatient provider. After 21 days, the patient no longer expressed suicidality, had a brighter affect, was motivated to continue outpatient treatment, and reported no adverse effects from the medication adjustment. At the time of discharge, the MADRS was 12, demonstrating a response to cariprazine. The patient was educated on the potential for adverse effects to occur over the next few weeks associated with the long half-life of cariprazine and, thus, prolonged time to reach steady state. Whereas polypharmacy was not used in the traditional sense, similar considerations and pharmacodynamic principles should be applied during cross-titration or transition periods.

Conclusion

Overall, when using antipsychotic polypharmacy, it is imperative that clinicians employ agents with complementary pharmacologic profiles, avoiding combinations that are unlikely to add any additional clinical benefit but may contribute to the overall adverse effect burden. Additionally, when transitioning from one agent to another, being mindful of the off-target receptor affinities can reduce patient discomfort and reduce the likelihood of symptom relapse. If transitioning from a full antagonist to a PAA, monitoring for clinical worsening and reduced effectiveness is suggested. PAAs have shown benefit in reducing metabolic and dopamine antagonism–related adverse effects associated with full antagonist antipsychotics, potentially serving as an augmentation strategy without requiring discontinuation of a previously effective agent. Whereas PAAs share many features, nuanced differences make some stand out as more or less preferred in particular clinical scenarios. Thoughtful selection of a PAA is warranted to increase the likelihood of positive patient outcomes.

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