

# Partial Dopamine Agonists and the Treatment of Psychosis

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**Abstract:** Pharmacologic approaches that diminish dopamine-mediated neural transmission in brain have antipsychotic actions in humans. Blockade of D2 family dopamine receptors is the most common strategy. A paradoxical strategy of using dopamine agonists in particular circumstances to similarly diminish dopaminergic transmission is based on the known function of dopamine autoreceptors and on consideration of the intrinsic activity of dopamine agonists. It was apomorphine that first suggested the effectiveness of dopamine agonist treatment for schizophrenia. Now a partial dopamine agonist aripiprazole has come to market for psychosis and others are in development. This chapter reviews the clinical pharmacology of partial dopamine agonists and their development for the treatment of schizophrenia.

**Key Words:** Affinity, intrinsic activity, apomorphine, N-Propyl-noraporphine, (-)-3PPP Aripiprazole.

## INTRODUCTION

For centuries, there were no effective treatments for persons with schizophrenia or any other psychotic illness. At best, 'compassionate care' was available [33]. When the antipsychotic action of chlorpromazine was discovered [14], the overwhelming clinical need quickly jettisoned chlorpromazine and its congeners into use around the world. Based on this early clinical observation and subsequent laboratory experiments, Carlsson proposed that dopamine receptor blockade by chlorpromazine was the mechanism of this antipsychotic action [9], a hypothesis that has directed antipsychotic development ever since. The effectiveness of these treatments emptied out government hospitals and reduced psychotic symptoms in persons with schizophrenia around the world [12]. Now, even though we know that these drugs do not, by themselves, afford cures and that additional treatments are needed for psychosocial recovery [20], the medicines have become an integral part of the treatment for any person with psychosis and for the long term management of schizophrenia.

This remarkable antipsychotic treatment with its profound clinical effect was compelling enough to stimulate considerable basic research into the role of dopamine in schizophrenia pathophysiology and therapeutics [8]. The hypothesis that an abnormality in

dopaminergic transmission is the molecular basis for schizophrenia has never found uncomplicated support [13]. Nonetheless, the proposition that a diminution in dopamine-mediated transmission provides antipsychotic actions has been repeatedly confirmed [34]. Based on this, the Carlsson laboratory and others went on to demonstrate additional molecular targets within the dopamine system that would diminish dopaminergic neurotransmission: e.g. the inhibition of dopamine synthesis with tetrabenzazine [40] and the modulation of dopamine release with a dopamine autoreceptor agonist [10,11].

This latter antidopaminergic strategy, namely, agonist stimulation of the dopamine autoreceptor, was based on multiple observations supporting a negative feedback role for dopamine itself on dopamine neuronal function [16,23,41]. Considerable data supported an action of dopamine at a receptor on the dopamine neuron (an autoreceptor) to diminish dopamine synthesis and release [6,7]. Distinct types of dopamine autoreceptors, presumably for various kinds of negative feedback, have been described [1,4]. Meanwhile, other laboratories were discovering autoreceptor regulation of the synthesis and release of other monoamine neurotransmission, further supporting this concept [16,28]. Identification of a negative feedback role for dopamine and other monoamines at autoreceptors suggested that they could be rational targets for antipsychotic drug discovery.

Additional distinguishing characteristics of these autoreceptors became apparent, including a higher

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affinity of agonists for the autoreceptor than for the postsynaptic receptor [6]. This characteristic is consistent with the idea of a natural role for the autoreceptor to decrease dopamine synthesis and release when release is sufficient, in response to relatively low ambient dopamine levels. Succinctly, the idea of this action was that a dopamine agonist (at levels insufficient for stimulation of the postsynaptic receptor) could stimulate an autoreceptor and thereby reduce dopamine-mediated neural transmission through a reduction of dopamine synthesis and/or release. The later realization that full dopamine agonists were too potent for a differential autoreceptor action drew attention to the partial dopamine agonists. These full affinity but low intrinsic activity compounds have pharmacologic characteristics consistent with the idea of selective activity at dopamine autoreceptors.

In addition to the idea that dopamine autoreceptors might be optimally stimulated with partial agonists, an added explanation for the antipsychotic actions of these drugs became apparent, somewhat parallel to the action of a false transmitter. Dopamine has a full agonist action at its postsynaptic receptors, transmitting a high intrinsic activity, dopamine-mediated signal to postsynaptic cells; full agonists (with an intrinsic activity similar to dopamine) mimic this agonist effect. However, if an agonist has full affinity but a low intrinsic activity, it will occupy the receptor but deliver a lesser effect, having only partial intrinsic activity. Hence, a partial dopamine agonist can also act as a functional antagonist at synapses where dopamine is present in high concentrations. Whereas, in regions where the natural neurotransmitter is present in low concentrations, the intrinsic activity of the partial agonist is greater than the full activity of low concentrations of dopamine, hence would act as an agonist.

#### MECHANISMS OF PARTIAL AGONIST ACTION

Understanding drug action at a receptor requires knowledge of two aspects of drug-receptor interactions: *affinity* and *intrinsic activity*. Drugs have both “the capacity to bind and the capacity to excite” [24]. Ariens [2] described it classically: “The affinity is the probability of a drug molecule binding to a free drug receptor at any given instant. The intrinsic efficacy of a drug is that inherent property that imparts the biological signal to the drug receptor (and this to the cell) to result in a biological response”. *Affinity* is a measure of the strength with which a drug binds to the

receptor. The reciprocal of the equilibrium dissociation constant of the agonist-receptor complex is its numerical representation. The association of a drug with a receptor is a dynamic one, with molecules associating and dissociating constantly. The quantity of drug attached to the receptor at any one point in time is dependent on the rate the drug binds to the receptor (onset) and its rate of dissociation (offset). Two steps are necessary for drug action, one being diffusion of the drug to the receptor and the next being the specific chemical coupling of the drug to the receptor. Mathematical models describe these processes and govern the estimation of agonist affinity (for details, see [24]).

What the drug does when it is bound to the receptor is described by its *intrinsic activity*. A drug can merely sit on the receptor and prevent the natural neurotransmitter from interacting with the receptor without exerting any activity at that protein (antagonist) or the drug can stimulate the receptor, similar to the natural neurotransmitter (full agonist). But the agonist action can also show differential levels of stimulation, either equal to the natural neurotransmitter (100% intrinsic activity) or of a lesser amount (i.e., a partial agonist, down to <10% intrinsic activity). The estimation of intrinsic activity is characteristically quantified relative to dopamine using a physiological action of the drug. Because the mechanism of agonist action depends on the particular tissue, cerebral process and receptor type, measures of intrinsic activity of a drug are specific to the conditions used in the experiment and will differ in distinct tissues and even behavioral states. While the calculation of relative intrinsic activity is often a handy characteristic, an exact measure of a drug’s intrinsic activity is relative and dependent on the efficiency of the stimulus-response system. It is more often the relative ranking of an agonist with other like agonists that is most useful in predicting an expected magnitude of clinical response with a particular partial agonist.

Distinguishing these concepts is necessary to understand the actions of partial dopamine agonists. In CNS areas where synaptic dopamine concentrations are high (e.g., in striatum), a partial dopamine agonist will act much like a functional antagonist, by blocking the action of dopamine (the full agonist) while providing only minimal agonist action to a receptor system with high tonic activity. In other circumstances, where the receptors for dopamine are in excess and characteristically open (e.g., the D1 receptor in prefrontal cortex) a partial dopamine agonist with its high affinity and low intrinsic activity, will have an overall

functional agonist action. In this fashion, a partial dopamine agonist can have both an overall antagonist effect (e.g., in outcomes related to striatum) and an agonist effect (e.g. in outcomes related to the prefrontal cortex). Thus, for symptoms of psychosis, a partial agonist of rather low intrinsic activity would be therapeutic because of its relative dopamine receptor blockade. At the same time, in cortex where unoccupied D1 dopamine receptors may be available, a partial agonist, even if of low intrinsic activity, would have enough agonist activity to stimulate postsynaptic dopamine systems.

### EARLY TREATMENTS-CONCEPT TESTING OF DOPAMINE AGONISTS IN SCHIZOPHRENIA

Based on the above experimental pharmacology and the evidence of dopamine autoreceptors as negative synaptic regulators for dopamine neurons, the observation that low levels of a dopamine agonist had an antipsychotic action in a person with schizophrenia was interpretable [32]. This hypothesis was first rigorously addressed with apomorphine [39]. Because of the antiemetic action of apomorphine, the drug was tested in schizophrenic persons on low (but suboptimal) levels of antipsychotic medication to block peripheral dopamine agonist actions. In this experiment, each patient volunteer received a single dose of agonist or of placebo, in random order, on each of two days, one week apart. Psychotic symptoms were rated before and after drug [3] and a significant reduction in psychosis found with apomorphine ( $p < .02$ ). The efficacy of the apomorphine (a high intrinsic activity dopamine agonist) was likely dependent on the partial agonist action of the apomorphine/ antipsychotic drug combination. The high intrinsic activity of apomorphine was practically reduced by its combination with the dopamine antagonist, as had already been shown for agonists and antagonists of the other drugs [25]. This study specifically noted that the volunteers became more social and interactive, in addition to less psychotic, as one might expect with a dopamine agonist. It is interesting to see that, long before this study, apomorphine was used empirically in the earliest days of psychopharmacology to treat 'trench' psychosis in WWI [17], and help with patient management in hospitals well before chlorpromazine was discovered [15].

When bromocriptine and CF 25-397 (both, full dopamine agonists) were each evaluated in schizophrenia for their antipsychotic actions in otherwise

drug-free volunteers, neither drug showed a therapeutic action [38]. Bromocriptine was tested at doses from 5-35 mg/day and CF 25-397 at 60 mg/day. This was also true in other laboratories and with other agonists [18,29]. These are full dopamine agonists, so they might have lacked a therapeutic window for differential action at the dopamine autoreceptor. This interpretation is supported by the lack of efficacy of either of these drugs on tardive dyskinesia, also a putatively hyperdopaminergic condition [36].

The availability of a new series of aporphine compounds, including N-propyl-norapomorphine (NPA), enabled another dopamine agonist to be tested in schizophrenia volunteers [37]. This aporphine has pharmacologic characteristics similar to apomorphine and was developed as an antiparkinsonian medication. The drug had a positive antipsychotic action in single dose studies, across a dose range of 10-40 mg/dose, especially in the neuroleptic-responsive (but drug-free) volunteers. However, after repeated administration (over a course of less than 7 days), the antipsychotic effect of NPA attenuated and could no longer be demonstrated. This action is consistent with the idea that agonists gradually desensitize a receptor after repeated stimulation, producing tachyphylaxis. It is a feature characteristically associated with agonist administration, reflecting normal neuroplasticity. However, it creates a treatment-limiting clinical problem when the drug action of interest alters the tissue substrate to neutralize the target drug action. The idea developed that an agonist with reduced intrinsic activity, a partial dopamine agonist, would also have a reduced tendency to produce tachyphylaxis.

### LATER TESTING: CONCEPT TESTING WITH PARTIAL DOPAMINE AGONISTS

3-(3-hydroxyphenyl)-N-n-propylpiperidine [(-)-3PPP] is a partial dopamine agonist, the prototypical one, developed in the laboratory of Carlsson, *et al.* [7]. It is partially limbic-selective; low doses in animals show behavioral actions consistent with D-2 dopamine autoreceptor agonism and higher doses show antagonist effects at the normosensitive postsynaptic D-2 dopamine receptor [10,11]. An estimate of agonist intrinsic activity in nigrostriatal preparations was 35%- 40% [27]. Early Phase 1 studies with (-)-3PPP in schizophrenia demonstrated a plasma level range where antipsychotic activity could be detected without significant side effects [35]. The action of (-)-3PPP to increase plasma growth hormone levels, suggested its

agonist properties. A positive antipsychotic response in two of the four volunteers after single dose administration was consistent with its antipsychotic potential. Curiously, the antipsychotic action, when it occurred after a single dose, out-last ed measurable drug plasma levels by many hours.

Subsequent oral administration was evaluated in a rising dose placebo-controlled design, followed by a 3 week repeated dose design in otherwise drug free schizophrenia volunteers [26]. After one week of treatment, (-)-3PPP showed a clear antipsychotic action, both in comparison to baseline and in comparison to placebo ( $p < .05$ ). But at later rating times (two or three weeks) in the same patient group, no antipsychotic action was evident. The parsimonious interpretation of these results is that the initial antipsychotic action induced by the partial agonist desensitized its target receptor with time, sacrificing therapeutic action.

One solution to this problem was to find an even lower intrinsic activity agonist for this receptor, of sufficiently low intrinsic activity to impart the clinical action without treatment-emergent desensitization. At least two ways exist to reduce partial agonist activity: one technique is to diminish agonist activity by mixing the partial agonist with an antagonist to reduce effective activity [13,25]; the other approach would be to develop a new molecule with lower intrinsic activity.

## ARIPIPRAZOLE

It was Otsuka Pharmaceuticals who developed a new partial dopamine agonist with low intrinsic activity [19,21]. Testing confirmed that this compound had low enough partial agonist activity to avoid tachyphylaxis, having an intrinsic activity estimated to be in the range of 15% [5,22]. In preclinical studies, the drug blocks apomorphine-induced behavior but also caused prolactin reduction in rats. At the same time, the drug is an antagonist at the 5HT<sub>2A</sub> receptor and a partial agonist at the 5HT<sub>1A</sub> receptor and demonstrates pharmacologic actions consistent with these affinities. Aripiprazole has a high affinity for the D<sub>2</sub> dopamine receptor showing >90% occupancy in humans, thus being a high affinity, low intrinsic activity agonist.

The clinical actions of aripiprazole were identified within its highest occupancy dose range (15-30 mg/day). Occupancy is linear over 1-15 mg with a high final plateau of occupancy (>90%) after 15 mg. No increased

antipsychotic benefit is apparent clinically across 10-30 mg/day in the group mean data registration studies, consistent with predictions from the occupancy data. Studies of aripiprazole compared with a traditional antipsychotic, like haloperidol, and with a new antipsychotics, like risperidone and olanzapine, all show aripiprazole to have equivalent antipsychotic action in the acutely psychotic patient [30,31]. The effects of aripiprazole to decrease prolactin suggest that a core part of its action *in vivo* is an agonist action.

Given the partial agonist profile of aripiprazole and its equivalent antipsychotic action, it would be reasonable to expect that this drug ought to have a better action than a full antagonist in treating cognitive dysfunction in schizophrenia. Moreover, if any dopaminergic compound would improve mood and reverse negative symptoms, it would be the prediction that this compound should. Hypothetically, treatment with a partial dopamine agonist over the long term could help reduce psychosocial dysfunction, by improving cognition and affect in the illness. But all of these actions remain theoretical and still need to be evaluated properly in the clinic with aripiprazole or any other partial dopamine agonist.

## NEW PARTIAL DOPAMINE AGONISTS

The partial agonist target is continuing to stimulate new drug development. Several partial agonist compounds are in development. Each of these new compounds could possess considerably different pharmacologic activity, based on their different intrinsic activity and target receptor profile. The higher the intrinsic activity, the greater the propensity the drug will have to produce tachyphylaxis. The lower the intrinsic activity, the greater its propensity to behave like a conventional dopamine receptor antagonist, including motor side effects. It is intriguing that this class of drugs can have such disparate actions, based not only on their receptor profile (as for an antagonist), but also on their intrinsic activities at each relevant receptor.

Although we cannot specify the mechanism whereby reducing dopamine-mediated neuro-transmission improves psychosis, its repeated demonstration adds confidence to the prediction. The addition of partial dopamine agonists to our antipsychotic drug armamentarium provides drugs lacking important side effects (especially motor and possibly affective) and agents which may provide additional benefits based on their

intrinsic activities. However, caution is always appropriate since clinical experience with these new compounds is still modest.

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