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Effects of Asenapine, Olanzapine, and Risperidone on Psychotomimetic-Induced Reversal-Learning Deficits in the Rat

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Abstract

Background: Asenapine is a new pharmacological agent for the acute treatment of schizophrenia and bipolar disorder. It has relatively higher affinity for serotonergic and α_2 -adrenergic than dopaminergic D₂ receptors. We evaluated the effects of asenapine, risperidone, and olanzapine on acute and subchronic psychotomimetic-induced disruption of cued reversal learning in rats.

Methods: After operant training, rats were treated acutely with D-amphetamine (0.75 mg/kg intraperitoneally [i.p.]) or phencyclidine (PCP; 1.5 mg/kg i.p.) or sub-chronically with PCP (2 mg/kg i.p. for 7 days). We assessed the effects of acute coadministration of asenapine, risperidone, or olanzapine on acute D-amphetamine– and PCP-induced deficits and the effects of long-term coadministration of these agents (for 28 additional days) on the deficits induced by subchronic PCP.

Results: Deficits in reversal learning induced by acute D-amphetamine were attenuated by risperidone (0.2 mg/kg i.p.). Acute PCP-induced impairment of reversal learning was attenuated by acute asenapine (0.025 mg/kg subcutaneously [s.c.]), risperidone (0.2 mg/kg i.p.), and olanzapine (1.0 mg/kg i.p.). Subchronic PCP administration induced an enduring deficit that was attenuated by acute asenapine (0.075 mg/kg s.c.) and by olanzapine (1.5 mg/kg i.p.). Asenapine (0.075 mg/kg s.c.), risperidone (0.2 mg/kg i.p.), and olanzapine (1.0 mg/kg i.p.) all showed sustained efficacy with chronic (29 d) treatment to improve subchronic PCP-induced impairments.

Conclusion: These data suggest that asenapine may have beneficial effects in the treatment of cognitive symptoms in schizophrenia. However, this remains to be validated by further clinical evaluation.

Keywords: asenapine, D-amphetamine, PCP, reversal learning, schizophrenia, risperidone, olanzapine

INTRODUCTION

Cognitive dysfunction is a core component of schizophrenia [19]. Deficits affecting attention, perception, executive function, and memory may even be present in schizophrenics experiencing their first psychotic episode [34]. These cognitive deficits have significant bearing on patient recovery, functional capacity, and societal reintegration [4,8,9].

Given the negative impact of cognitive dysfunction on long-term patient function and quality of life, the lack of reliably effective treatment is considered to be a key unmet clinical need [16]. However, the clinical literature has generally reported no consistent, substantial improvement in cognition with the current pharmacotherapies for schizophrenia [20,42]. In one long-term naturalistic study, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, some antipsychotics produced small but statistically significant improvements in cognition [32]. In further recognition of the need to address cognitive dysfunction in patients with schizophrenia and to encourage the development of cognition-enhancing drugs for schizophrenia, the National Institute of Mental Health, in collaboration with the University of California at Los Angeles and the US Food and Drug Administration, initiated the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) and Treatment Units for Research on Neurocognition and Schizophrenia (TURN) programs.

Preclinical studies have routinely demonstrated that second-generation antipsychotics (SGAs) enhance cognitive function in animal models that assess reversal learning, working and nonspatial memory, and selective attention [1-3,11,18,24,25,35,39,55,56]. In a rodent operant reversal-learning paradigm based on tasks developed by Smith et al [48] and Jones et al [30], deficits in reversal learning produced

by phencyclidine (PCP) were attenuated by the SGAs clozapine, ziprasidone, and olanzapine, but not by the first-generation antipsychotics haloperidol or chlorpromazine [2,3,25]. Similarly, deficits in novel object recognition and attentional set shifting induced by 7 days of treatment with PCP are reversed by clozapine and risperidone but not by haloperidol [18,39]. Importantly, doses of SGAs that attenuate the effects of PCP do not generally have an effect on reversal learning in nonimpaired rats, and we have recently demonstrated lack of impairment in control rats treated with clozapine and risperidone at doses that improve PCP-induced deficits, including the doses of risperidone shown to be effective in the present study [40].

Cognitive deficits induced by drugs affecting glutamatergic function—in particular, N-methyl-D-aspartate (NMDA) receptor antagonists such as PCP and ketamine—mimic cognitive dysfunction in schizophrenia [7,27,33]. These findings support the NMDA hypothesis of schizophrenia, which proposes that cognitive deficits in schizophrenics may be partially attributed to NMDA receptor hypofunction [43]. Therefore, inducing cognitive deficits with subchronic PCP treatment may be useful for assessing the treatment of cognitive dysfunction in schizophrenia [26,29].

Asenapine is a novel psychopharmacologic agent recently approved for the treatment of schizophrenia and bipolar disorder. It has been shown to be effective and well tolerated in the treatment of schizophrenia [44] and mania in bipolar disorder patients [38]. It shows nanomolar level binding and antagonist activity at cloned human serotonin (5-HT; 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT₅, 5-HT₆, 5-HT₇), dopamine (D₁, D₂, D₃, D₄), α -adrenergic (α_{1A} , α_{2A} , α_{2B} , α_{2C}), and histamine (H₁, H₂) receptors but minimal affinity for muscarinic receptors [46,47]. In particular, asenapine

has higher affinity for some serotonergic (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT₆, 5-HT₇), adrenergic (α_{2B}), and dopamine receptors (D₃) when compared with dopamine D₂ receptors [47].

In this report, we assess the effects of asenapine on reversal-learning deficits induced by acute PCP or D-amphetamine, or subchronic PCP. Because modulation of dopaminergic and glutamatergic activity may be mediated through antagonism of 5-HT receptors, it was hypothesized that asenapine would exhibit beneficial effects in these models of psychomimetic-induced cognitive deficits. The effects of olanzapine and risperidone monotherapy were independently examined to provide comparators for asenapine. Both have shown efficacy to reverse PCP-induced impairments in this and other models [1,18,39,41]; however, neither has previously been tested against D-amphetamine-induced cognitive deficits.

MATERIALS AND METHODS

Animals

Adult female Lister hooded rats (n=100 in all 3 studies combined) obtained from Harlan, UK, were used in these studies. Female rats were used because they show robust cognitive deficits induced by PCP in several other paradigms and perform better in certain cognitive tasks compared with male rats [50,51]. Stage of the estrous cycle does not affect the ability of rats to perform in novel object recognition or reversal-learning tasks [40,50].

Rats were housed in groups (4–5 per cage) and maintained under standard laboratory conditions (temperature, 21°±2° C; humidity, 40%–50%). A 12-hour

light/dark cycle (lights on at 7:00 AM) was maintained. All procedures were performed during the light phase. All rats were reduced to approximately 85% of their free-feeding body weight (225–250 g) before each study and maintained at this weight by restricting food access to 12 g/d of standard laboratory chow (Special Diet Services, Essex, UK). Free access to water was provided. All experiments were conducted in accordance with the Animals (Scientific Procedures) Act, UK, of 1986 and approved by the University of Bradford ethical review process.

Drugs

Asenapine, olanzapine, and risperidone were supplied by Schering-Plough Corporation (Newhouse, Lanarkshire, UK). Asenapine was dissolved in 0.9% saline and administered subcutaneously (s.c.). Asenapine was given s.c. in an attempt to provide a surrogate for the sublingual route used in clinical studies [44], as well as for consistency with other preclinical studies that have assessed the effects of asenapine [15,23,53,54]. Olanzapine and risperidone were dissolved in a small volume of acetic acid, adjusted to their final concentration with 0.9% saline, pH-adjusted to 5.5 to 6.0 with 0.1 M NaOH, and administered intraperitoneally (i.p.). PCP hydrochloride and D-amphetamine sulfate (Sigma-Aldrich, Irvine, Scotland, UK) were dissolved in 0.9% saline and administered as an i.p. injection. All doses are base equivalent weight and were administered in a volume of 1 mL/kg.

Protocols

Operant Training

Following habituation to the operant chambers, rats were trained to respond for food on a fixed ratio 1 (FR1) schedule of reinforcement with both levers active, as described in detail previously [2]. Rats were trained to press either the left or right lever for food delivery according to a visual cue (LED on or off). The experimental session was terminated following a total of 128 lever presses, which took approximately 30 minutes. Rats were trained once daily for 5 days, and this was repeated until rats had reached criterion (ie, 90% correct responding for 3 consecutive days).

The day before each reversal-learning session, a full 30-minute operant training session (as described above) was conducted to ensure stable responding (ie, 90% correct responding). The reversal-learning session involved animals being first exposed to a 5-minute period during which the active lever was the same as on the previous training day. During this period, responses on both correct and incorrect levers were recorded. This part of the session was the initial phase. This was followed by a 2-minute time-out period, which was signalled by the house light being turned off. The 2-minute time-out period acts as a cue that the rule is about to change. In the subsequent 5-minute period, the active lever was reversed. Responses made on the correct and incorrect levers were again recorded. This second period was the reversal phase. Animals undertook several of these reversal-learning sessions before beginning the drug studies to ensure that they attained a stable level of performance (ie, 90% correct responding and at least 25 lever presses in total, in both the initial and reversal phases of the task).

Studies 1a and 1b: Effects of Acute Intervention on Deficits Induced by Acute D-Amphetamine or PCP

Rats were tested on a cycle of 4 days. On day 1, each animal had a 30-minute operant training session. The following day, animals received the appropriate drug(s) and undertook a reversal-learning session. On day 3 and day 4, each animal underwent a further operant training session and reversal-learning session, respectively, to ensure that normal responding was regained following drug treatment. If responding was not normalized, the 4-day cycle was repeated. The order of treatment exposure was determined randomly for each rat. This cycle of testing has previously been described in detail [25]. For drug treatments we used 9 to 10 rats per treatment. The PCP (1.5 mg/kg) and D-amphetamine (0.75 mg/kg) doses used were chosen based on previous studies [2,25]. Both were administered 30 minutes before testing. Based on preliminary tests with asenapine (0.003–0.1 mg/kg s.c.) that assessed effects on spontaneous locomotor activity, doses of asenapine (0.025, 0.05, and 0.075 mg/kg s.c.) were chosen that were expected to have minimal effects on motor function. The asenapine doses and s.c. route used in these studies were also based on studies demonstrating D₂ receptor occupancy in rat brain [46] and demonstrating antipsychotic-like activity in established neurochemical and behavioral paradigms [15,23,54]. Asenapine was administered 40 minutes before testing and 10 minutes before PCP or D-amphetamine. The risperidone (0.05, 0.1, and 0.2 mg/kg i.p.) and olanzapine (0.5, 1.0, and 1.5 mg/kg i.p.) doses were also based on previous studies from this laboratory [3,18,39] and do not exceed the range that is suggested to be clinically relevant, based on dopamine D₂ receptor occupancy in rat brain [31]. Olanzapine and risperidone were given 45 minutes before testing and 15 minutes before PCP or D-amphetamine.

Study 2: Effects of Acute Intervention on Deficits Induced by Subchronic PCP

After completion of reversal-learning training as described above, another group of rats was treated twice daily for 7 days with PCP 2 mg/kg (n=40) or 0.9% saline at 1 mL/kg (n=10). The PCP dose was chosen based on previous work in our laboratory demonstrating robust and enduring cognitive and social behavior deficits [1,3,18,39,49]. During PCP treatment and the subsequent 7-day drug-free period, reversal-learning sessions were discontinued to prevent the development of an association between PCP treatment and the reinforcement contingencies of the reversal-learning task and to ensure that PCP-induced deficits were enduring and not related to acute PCP withdrawal. Treatment with asenapine, risperidone, olanzapine, and respective vehicles was performed according to the same 5-day cycle and procedures described for study 1. Overall, it took 3 to 4 weeks complete this study.

Study 3: Effects of Chronic Intervention on Deficits Induced by Subchronic PCP

After completing study 2, the same rats then continued to be treated for 28 days with twice-daily asenapine 0.075 mg/kg, once-daily risperidone 0.2 mg/kg, once-daily olanzapine 1.5 mg/kg, or vehicle. Because it took 3 to 4 weeks to complete study 2, chronic treatment during study 3 was initiated approximately 4 to 5 weeks after subchronic PCP treatment had ended.

In vehicle- and asenapine-treated rats, injections were administered at 8:00 AM and 4:00 PM. In risperidone- and olanzapine-treated rats, drug injections were administered at 8:00 AM, and an additional vehicle injection was administered at 4:00 PM. Performance was assessed on treatment days 3, 7, 14, 17, 21, and 28, as well as 1 day

after chronic treatment ceased. Testing followed the 8:00 AM treatment on all test days, except for day 17, when testing preceded treatment to ensure that any improvements in performance were the result of chronic treatment and not acute treatment effects.

Statistical Analysis

Accuracy (indexed by the percentage of correct responses) and total session responses were recorded during each phase of the task. All data are reported as the mean $\pm$ standard error. Accuracy data were arcsin-transformed [arcsin (square root percentage correct responses)] before statistical analysis. Total responding (ie, lever presses) was used to assess the potential nonspecific motor, arousal, or motivational effects of treatment (data not shown). Overall, the effects of treatment on total session responding were small (generally <10%) and unlikely to contribute to changes in the main endpoint (ie, accuracy).

In studies 1 and 2, initial- and reversal-phase performance data were assessed using 1-way analysis of variance (ANOVA). In study 3, performance during the initial and reversal phases was assessed independently based on the results of studies 1 and 2 and previously published reports [1,3] indicating that subchronic PCP does not alter performance during the initial phase of this task. Data were analyzed by 2-way ANOVA with day of treatment as the within-subject factor and drug treatment as the between-subjects factor. When appropriate, all pairwise post hoc comparisons were conducted using Dunnett *t* test, and statistical significance was defined as $P < 0.05$.

RESULTS

Study 1a: Acute Intervention Effects on Acute D-Amphetamine–Induced Deficit

Effects of Asenapine

Statistical analysis of accuracy revealed that there was no interaction in the initial phase [$F(4,48)=0.08$, $P=0.99$]. A 1-way ANOVA in the reversal phase showed a significant interaction [$F(4,48)=4.29$, $P<0.01$]. Post hoc analysis revealed that accuracy was significantly reduced by D-amphetamine compared to the vehicle-treated group ($P<0.01$, **Figure 1A**). Asenapine did not significantly reverse the deficit in accuracy induced by D-amphetamine (**Figure 1A**). Asenapine at 0.075 mg/kg decreased total responding compared with the vehicle group from approximately 26 lever presses to 23 (data not shown).

Effects of Risperidone

Statistical analysis of accuracy revealed that there was no interaction in the initial phase [$F(4,48)=0.09$, $P=0.98$]. A 1-way ANOVA in the reversal phase showed a significant interaction [$F(4,48)=4.28$, $P<0.01$]. Post hoc analysis revealed that accuracy was significantly reduced by D-amphetamine compared with the vehicle-treated group ($P<0.01$, **Figure 1B**). Risperidone at 0.2 mg/kg significantly reversed the deficit in accuracy induced by D-amphetamine ($P<0.05$, **Figure 1B**). Risperidone did not affect total session responding during either phase (data not shown).

Effects of Olanzapine

Statistical analysis of accuracy revealed that there was no interaction in the initial phase [$F(4,48)=0.09$, $P=0.98$]. A 1-way ANOVA in the reversal phase showed a significant interaction [$F(4,48)=5.59$, $P<0.001$]. Post hoc analysis revealed that accuracy was significantly reduced by D-amphetamine compared with the vehicle-treated group ($P<0.001$, **Figure 1C**). Deficits induced by D-amphetamine were not reversed by olanzapine (**Figure 1C**), and total responding was unaffected in either phase (data not shown).

Study 1b: Acute Intervention Effects on Acute PCP-Induced Deficit

Effects of Asenapine

Statistical analysis of accuracy revealed that there was no interaction in the initial phase [$F(4,49)=1.16$, $P=0.34$]. A 1-way ANOVA in the reversal phase showed a significant interaction [$F(4,49)=7.38$, $P<0.001$]. Post hoc analysis revealed that accuracy was significantly reduced by PCP compared with the vehicle-treated group in the reversal phase ($P<0.001$, **Figure 2A**). All asenapine doses significantly attenuated PCP-induced deficits in reversal performance ($P<0.05$ – 0.01 , **Figure 2A**). Asenapine at 0.075 mg/kg decreased total responding compared with the vehicle group from approximately 26 lever presses to 19 (data not shown).

Effects of Risperidone

Statistical analysis of accuracy revealed that there was no interaction in the initial phase [$F(4,49)=0.34$, $P=0.85$]. A 1-way ANOVA in the reversal phase showed a significant interaction [$F(4,49)=7.73$, $P<0.001$]. Post hoc analysis revealed that accuracy

was significantly reduced by PCP compared with the vehicle-treated group in the reversal phase ($P<0.001$, **Figure 2B**). Risperidone at 0.2 mg/kg significantly reversed the PCP-induced accuracy deficit ($P<0.01$) and restored accuracy to levels observed following vehicle (**Figure 2B**). Risperidone at 0.1 mg/kg and 0.2 mg/kg decreased total responding in both phases compared with all other treatments (data not shown).

Effects of Olanzapine

Statistical analysis of accuracy revealed that there was no interaction in the initial phase [$F(4,49)=0.38$, $P=0.82$]. A 1-way ANOVA in the reversal phase showed a significant interaction [$F(4,49)=4.51$, $P<0.01$]. Post hoc analysis revealed that accuracy was significantly reduced by PCP compared with the vehicle-treated group in the reversal phase ($P<0.01$, **Figure 2C**). Olanzapine at 1.0 mg/kg significantly reversed the PCP-induced accuracy deficit ($P<0.05$). Olanzapine at 1.5 mg/kg did not significantly improve performance compared with PCP treatment ($P=0.078$), but this trend suggested that there was some partial reversal of the effects of PCP. Olanzapine at the dose range tested did not alter total responding during either phase (data not shown).

Study 2: Acute Intervention Effects on Subchronic PCP-Induced Deficit

Effects of Asenapine

Statistical analysis of accuracy revealed a significant interaction in the initial phase [$F(4,44)=3.53$, $P<0.05$]; however, post hoc comparisons did not reveal any significant difference from the vehicle-treated group. A 1-way ANOVA in the reversal phase showed a significant interaction [$F(4,44)=5.17$, $P<0.01$]. Post hoc analysis revealed

that accuracy was significantly reduced by subchronic PCP compared with the vehicle-treated group in the reversal phase ($P<0.001$, **Figure 3A**). Asenapine at 0.075 mg/kg significantly attenuated this PCP-induced deficit ($P<0.05$, **Figure 3A**) and restored accuracy to a level observed with vehicle. After asenapine at 0.05 mg/kg, a trend toward a reversal of PCP-induced deficits was also observed ($P=0.083$). Asenapine at 0.075 mg/kg decreased total responding compared with the vehicle group from approximately 26 lever presses to 23 (data not shown).

Effects of Risperidone

Statistical analysis of accuracy revealed that there was no interaction in the initial phase [$F(4,44)=2.18$, $P=0.09$]. A 1-way ANOVA in the reversal phase showed a significant interaction [$F(4,44)=5.97$, $P<0.01$]. Post hoc analysis revealed that accuracy was significantly reduced by subchronic PCP compared with the vehicle-treated group in the reversal phase ($P<0.001$, **Figure 3B**). Risperidone at 0.2 mg/kg significantly attenuated this PCP-induced deficit ($P<0.05$, **Figure 3B**). At the dose range tested risperidone did not affect total session responding during either phase (data not shown).

Effects of Olanzapine

Statistical analysis of accuracy revealed that there was no interaction in the initial phase [$F(4,44)=0.25$, $P=0.91$]. A 1-way ANOVA in the reversal phase showed a significant interaction [$F(4,44)=13.16$, $P<0.001$]. Post hoc analysis revealed that accuracy was significantly reduced by subchronic PCP compared with the vehicle-treated group in the reversal phase ($P<0.001$, **Figure 3C**). Olanzapine at 0.5 mg/kg and 1.5 mg/kg

significantly attenuated the subchronic PCP-induced deficit ($P<0.05$ and $P<0.001$, respectively), with olanzapine at 1.5 mg/kg fully reversing the effects of subchronic PCP (**Figure 3C**). At the dose range tested olanzapine did not affect total session responding during either phase (data not shown).

Study 3: Chronic Intervention Effects on Subchronic PCP-Induced Deficit

Effects of Asenapine

A 2-way ANOVA in the reversal phase with day of treatment as the within-subject factor and drug treatment as the between-subjects factor showed a significant interaction [$F(2,25)=13.46$, $P<0.001$]. Accuracy was significantly reduced by subchronic PCP treatment compared with the vehicle-treated group on days 3 ($P<0.001$), 7 ($P<0.01$), 17 ($P<0.01$), and 21 ($P<0.05$), and reduced to a level closely approaching significance on day 28 ($P=0.063$). Accuracy of PCP-treated rats was significantly improved by asenapine (0.075 mg/kg) on days 3 ($P<0.01$), 7 ($P<0.05$), and day 17 ($P<0.05$) when testing occurred 16 hours after the last asenapine treatment and to a level approaching significance on day 28 ($P=0.078$). Asenapine did not affect total session responding during either phase of the test (data not shown).

Effects of Risperidone

A 2-way ANOVA in the reversal phase with day of treatment as the within-subject factor and drug treatment as the between-subjects factor showed a significant interaction [$F(2,25)=9.90$, $P<0.01$]. Accuracy was significantly reduced by subchronic PCP treatment compared with the vehicle-treated group on days 3 ($P<0.001$), 7 ($P<0.01$), 17

($P<0.05$), 21 ($P<0.05$), and 28 ($P<0.05$). Accuracy of PCP-treated rats was significantly improved by risperidone (0.2 mg/kg) on days 3 ($P<0.01$), 7 ($P<0.05$), and 28 ($P<0.05$) and to a level approaching significance on day 17 ($P=0.083$) when testing occurred 24 hours after the last risperidone treatment. Risperidone did not affect total session responding during either phase of the test (data not shown).

Effects of Olanzapine

A 2-way ANOVA in the reversal phase with day of treatment as the within-subject factor and drug treatment as the between-subjects factor showed a significant interaction [$F(2,25)=11.69$, $P<0.001$]. Accuracy was significantly reduced by subchronic PCP treatment compared with the vehicle-treated group on days 3 ($P<0.001$), 7 ($P<0.01$), 17 ($P<0.01$), 21 ($P<0.05$), and 28 ($P<0.05$). Accuracy of PCP-treated rats was significantly improved by olanzapine (1.5 mg/kg) on days 3 ($P<0.01$) and 17 ($P<0.05$) when testing occurred 24 hours after the last olanzapine treatment; accuracy was improved to a level closely approaching significance on day 7 ($P=0.058$). Olanzapine did not affect total session responding during either phase of the test (data not shown).

DISCUSSION

The main findings of these studies demonstrate that acute administration of either D-amphetamine or PCP produces a reproducible and selective deficit in cued reversal learning that is attenuated by risperidone, whereas asenapine and olanzapine were effective against the deficit produced by PCP but not against the deficit produced by D-amphetamine. Subchronic PCP administration across independent experiments produced

a reproducible and selective deficit in cued reversal learning, which endured for up to 4 weeks after the cessation of PCP treatment. This effect of PCP was most prominent in the first week of testing, and was maintained as a partial impairment over the next 3 weeks of testing. The impairment was abolished following acute administration of asenapine and olanzapine, and after chronic administration of asenapine, risperidone, and olanzapine. This improvement in performance was maintained when animals were tested on day 17, a minimum of 16 hours after antipsychotic treatment which may have important implications for therapy. Recent studies from this laboratory have demonstrated that SGAs do not generally have any effect on reversal learning in non-impaired rats [2,3,25]. Therefore, it is hypothesized that the effects of asenapine, risperidone, and olanzapine observed in these studies represent an “attenuation” or “reversal” of the impairment produced by PCP or D-amphetamine.

The subchronic PCP studies add to the existing literature on this model by providing insight on the persistent nature of PCP-induced cognitive dysfunction, as well as its reversibility by chronic drug treatment. Furthermore, the acute-treatment studies provide detailed dose-effect analyses for the drugs used in 2 mechanistically distinct models of cognitive dysfunction.

The assessment of within-session cued reversal learning in these studies is relatively novel when compared with other models that employ between-session assessments and within-session reversal learning [10,13,30]. The main advantage of this within-session cued reversal-learning model is that it allows for the rapid assessment of reversal-learning performance, with the appropriate reversal of behavior being observed over the course of a small number of trials. Despite this procedural difference, the ability

of the tested agents to reverse PCP-induced deficits was consistent with previous reports of the cognitive-enhancing effects of SGAs in animal models in general [11,13,18,28,29,39] and in different types of reversal-learning tasks [10,28]. Furthermore, these data are fully consistent with the effects of other SGAs and novel antipsychotics that have been observed in this reversal-learning task [1-3,25].

In these studies, the effects of drug treatment were selective for the reversal phase. Psychotomimetics, asenapine, risperidone, and olanzapine had no impact on accuracy during the initial phase of the task. The effects of D-amphetamine and PCP were robust and reproducible, supporting previous studies on reversal learning [1-3,25]. Although all treatments had some impact on total session responding, the magnitude of the treatment effects was generally small, suggesting that nonspecific treatment effects are unlikely to influence overall performance of the task. The inconsistent pattern of reductions across studies also supports this interpretation.

Asenapine did not significantly attenuate D-amphetamine-induced deficit at 0.075 mg/kg, suggesting modest antidopaminergic activity at the dose range tested. A similar profile was observed with olanzapine; however, a more robust effect was observed with risperidone, indicating strong dopaminergic blockade with this agent at the dose range tested. This is consistent with the higher D₂ receptor affinity of risperidone compared with that of olanzapine [47]. However, asenapine and risperidone have similar D₂ receptor affinities [46], suggesting that some other aspect of the receptor pharmacology of asenapine may moderate its in vivo antidopaminergic action. In agreement with this, asenapine has recently been shown to have antidopaminergic activity in other models,

such as amphetamine-induced hyperactivity [36]. Our apparent lack of such an effect may be due to the nature of the test procedure and the mechanism of action of asenapine.

PCP, given as a single injection, produced a robust and reproducible deficit in reversal learning in a manner consistent with previous reports from this laboratory [2,25]. Asenapine attenuated the effects of PCP at all doses tested, whereas the effects of olanzapine and risperidone were not observed at the lower doses tested. However, direct comparisons of the potency of asenapine versus olanzapine and risperidone should be made cautiously because their routes of administration differed in these studies.

Results from the subchronic PCP study are also consistent with previous reports of atypical antipsychotics [1,3]. Both acute and chronic asenapine treatment attenuated the reversal-learning deficit produced by subchronic PCP treatment. Olanzapine and risperidone showed a similar profile of effect. The attenuation of reversal-learning deficits by these agents does not seem to be solely attributed to their ability to attenuate deficits after acute exposure. On day 17, when testing was done 16 to 24 hours after the last drug treatment, performance was still enhanced in PCP-exposed rats treated with asenapine, olanzapine, or risperidone compared with PCP-exposed rats treated with vehicle. The implication is that chronic treatment with these agents may produce enduring changes that mitigate the effects of subchronic PCP treatment. Taken together, these data demonstrate that asenapine, like risperidone and olanzapine, is capable of attenuating cognitive dysfunction caused by repeated exposure to PCP.

In reversal-learning tests, animals are required to acquire a new strategy and in doing so demonstrate the ability to maintain attention and motivation, suppress a previously learned response, and implement a new response. Jentsch et al [28]

demonstrated that PCP selectively impairs the ability of rats to reverse an already-learned stimulus-reward association. The disruption induced by PCP in the study by Jentsch et al [28] was characterized by perseveration on the previously acquired stimulus-reward association, a profile that echoes the perseveration seen in patients with schizophrenia performing the Wisconsin card-sorting test [12]. Thus, psychotomimetic-induced deficits in reversal learning or switching tasks in animals may be useful for modeling cognitive deficits that reflect prefrontal cortical dysfunction in patients with schizophrenia. In this regard, the operant reversal-learning paradigm used in the present studies demonstrates good predictive validity. PCP-induced reversal-learning impairments in rats are attenuated by asenapine (as shown in the present study), risperidone, olanzapine (as shown in the present study and previously [3]), and ziprasidone [2,3]. These same agents demonstrate some efficacy in improving neurocognition in patients with schizophrenia [14,32]. It is of interest to note that although antipsychotics have demonstrated cognitive-enhancing effects in patients with schizophrenia, the effects have generally been found to be small and inadequate [17,32,42], whereas effects in animal models have been more consistent and more pronounced. The reasons for discrepancies between cognitive efficacy in patients with schizophrenia and animal models are not fully understood. Potential contributing factors may include the heterogeneous populations assessed in clinical trials versus the homogenous populations used in rodent studies; previous drug therapy in patients and not in rodents (in rodents, studies are typically performed in antipsychotic naive subjects); the assessment tools used in clinical versus preclinical studies; differences between treating a chronic disorder versus a drug-induced deficit,

albeit a robust and long-lasting deficit; and species differences in the effects of these agents.

The ability of asenapine, olanzapine, and risperidone to attenuate PCP-induced cognitive deficits may be a function of their modulation of dopaminergic and glutamatergic activity through antagonism of 5-HT receptor subtypes. In rat and monkey models, acute treatment with PCP produces dopaminergic hyperactivity in frontal cortical regions, whereas repeated PCP treatment decreases cortical dopaminergic activity [26,29]. Antagonism of the 5-HT_{2A} receptor selectively regulates mesocortical dopamine projections, with both asenapine and the selective 5-HT_{2A} antagonist M100907 increasing prefrontal cortical dopamine release [15,45]. Thus, drugs that block 5-HT_{2A} receptors within the prefrontal cortex may increase dopamine transmission and consequently alleviate subchronic PCP-induced cognitive dysfunction. Alternatively, the ability of asenapine and the other drugs to attenuate PCP-induced deficits in reversal learning could be related to influences on glutamatergic activity. PCP and other NMDA antagonists increase 5-HT release in the prefrontal cortex [37], which may lead to excessive glutamatergic activity [5]. Excessive prefrontal cortical glutamatergic activity associated with enhanced 5-HT efflux is also reversed by antagonism at the 5-HT_{2A} receptor [6]. In regard to 5-HT receptor antagonism, asenapine also displays high affinity for the 5-HT_{2C}, 5-HT₆, 5-HT₇ receptors [47], which may be of relevance to its ability to attenuate PCP-induced cognitive dysfunction. This is based on demonstration that selective 5-HT_{2C}, 5-HT₇ [40], and 5-HT₆ [21,22] receptor antagonists have cognition-enhancing effects in animal models. Indeed, it could be speculated that the combined potent and broad serotonergic antagonism by asenapine may be the important feature with regard to its

mechanism underlying the efficacy in models of cognitive dysfunction. A recent study supports our findings and demonstrates a pro-cognitive effect of asenapine in animals with prefrontal cortical lesions, which has particular relevance for schizophrenia [52].

In summary, the current studies further demonstrate that psychotomimetic-induced impairment in reversal learning in the rat serve as models for mimicking certain aspects of cognitive deficits in schizophrenia. Asenapine potently and robustly attenuated reversal-learning deficits induced by acute PCP but not D-amphetamine. It also offset the enduring reversal-learning deficit induced by subchronic PCP treatment, with no evidence of decreased effectiveness over time. Similar profiles were seen with chronic administration of risperidone and olanzapine. Uniquely strong antiserotonergic properties (eg, high affinity for 5-HT_{2A}, 5-HT_{2c}, 5-HT₆, and 5-HT₇ receptors) may be a key driver in the mode of action of asenapine. It is concluded that the improvement seen with asenapine in the rat PCP-induced reversal-learning deficit model is comparable to that of risperidone and olanzapine. The clinical relevance of the current findings for asenapine in the treatment of cognitive deficits associated with schizophrenia remain to be established.

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Contributors: JCN and NFI designed and conducted the studies with guidance from HMM, MS, and EHFW. SLM prepared the figures, carried out all statistical analyses, and made a major contribution to preparing the manuscript. All authors assisted in drafting the manuscript and have approved the final manuscript.

Conflicts of Interest: HMM and MS are employees of MSD. EHFW was employed at Pfizer Global R&D at the time these studies were conducted. JCN, NFI and SLM have no conflicts of interest.

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Figure Legends

Figure 1. Acute effects of (A) asenapine, (B) risperidone, and (C) olanzapine on response accuracy after acute D-amphetamine (d-amph) treatment (0.75 mg/kg). Data represent the mean $\pm$ SE of the mean (n=9–10 per group). Significant difference from vehicle (veh) + veh in the same phase (Dunnett *t* test: ** $P \leq 0.01$, *** $P \leq 0.001$). Significant difference from veh + d-amph in the same phase (Dunnett *t* test: # $P \leq 0.05$).

Figure 2. Acute effects of (A) asenapine, (B) risperidone, and (C) olanzapine on response accuracy after acute phencyclidine (PCP) treatment (1.5 mg/kg). Data represent the mean $\pm$ SE of the mean (n=10 per group). Significant difference from vehicle (veh) + veh in the same phase (Dunnett *t* test: ** $P \leq 0.01$, *** $P \leq 0.001$). Significant difference from veh + PCP in the same phase (Dunnett *t* test: # $P \leq 0.05$, ### $P \leq 0.01$).

Figure 3. Acute effects of (A) asenapine, (B) risperidone, and (C) olanzapine on response accuracy after 7 days of phencyclidine (PCP; 2 mg/kg twice daily) treatment followed by 7 days of washout. Data represent the mean $\pm$ SE of the mean (n=8–10 per group). Significant difference from vehicle (veh) + veh in the same phase (Dunnett *t* test: *** $P \leq 0.001$). Significant difference from veh + PCP in the same phase (Dunnett *t* test: # $P \leq 0.05$, ### $P \leq 0.001$).

Figure 4. Chronic effects of (A) asenapine (0.075 mg/kg), (B) risperidone (0.2 mg/kg), and (C) olanzapine (1.5 mg/kg) on response accuracy after 7 days of phencyclidine (PCP) treatment. Data represent the mean $\pm$ SE of the mean (n=8–10 per group). Significant difference from vehicle (veh) + veh in the same phase (Dunnett *t* test: * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$). Significant difference from PCP + antipsychotic in the same phase (Dunnett *t* test: # $P \leq 0.05$, ## $P \leq 0.01$).

Figure 1.

A

B

C

Figure 2.

A

B

C

Figure 3.

A

B

C

Figure 4.

A

B

C