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DRUG EVALUATION

Evaluating pimavanserin as a treatment for psychiatric disorders: A pharmacological property in search of an indication

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ABSTRACT

Introduction: Pimavanserin is FDA-approved to treat hallucinations and delusions associated with Parkinson's disease psychosis. As a potent 5-HT_{2A} inverse agonist/antagonist, it could be efficacious in other psychiatric disorders. Recently, several studies have investigated this potential.

Areas covered: The authors review the efficacy and adverse effects of pimavanserin for hallucinations in dementia, major depression, and schizophrenia.

Expert opinion: Two controlled studies suggest pimavanserin has potential as a treatment for hallucinations in dementia. In patients with depression who did not respond to antidepressant treatment, pimavanserin augmentation was efficacious in a phase 2 study. Pimavanserin augmentation also alleviated sexual side effects of SSRI and SSNI. However, Acadia Pharmaceuticals stated in a press release that it does not plan further antidepressant trials based on its phase 3 trial, which showed a nonsignificant trend toward an antidepressant effect. Since almost all existing antipsychotics fail to substantially benefit negative symptoms, better treatments are needed. Pimavanserin augmentation of antipsychotics did benefit negative symptoms (effect size≈0.2) but failed to reduce the total PANSS score significantly in two large, well-controlled double-blind studies. Pimavanserin has a good safety profile.

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KEYWORDS
Pimavanserin; alzheimer's disease; hallucinations; dementia; depression; schizophrenia

1. Introduction

Pimavanserin is a 5-HT_{2A} receptor antagonist/inverse agonist [1]. Inverse agonists have the opposite effect of agonists on intrinsic activity in contrast to blockers or antagonists which block the effect of agonists but have no intrinsic effect of their own [2,3]. Pimavanserin is slightly less potent on the 5-HT_{2C} receptor, and this property may also be important. Pimavanserin was developed by screening a wide variety of compounds to develop a drug with a specific pharmacological property, a 5-HT_{2A} inverse agonist, using a mutant human receptor that exhibits constitutive activity [4]. This is supported by in vitro evidence in the human brain [5]. In vivo evidence of inverse agonism properties of pimavanserin is absent [2]. Similar pharmacological profile is claimed for clozapine and, in this case, less evidence of inverse agonism properties on 5-HT_{2A} receptors is available in native tissue. The rationale is that clozapine is a potent 5-HT_{2A} antagonist, and it is effective in treating hallucinations induced by DOPA and other dopaminergic drugs used to treat Parkinson's disease [6]. Clozapine is also the most effective antipsychotic treatment in schizophrenia [7], based on the assumption that being a 5-HT_{2A} antagonist was responsible for the mechanism of action. Similar pharmacological inverse agonist profile is claimed for clozapine and, in this case, less evidence of inverse agonism properties on 5-HT_{2A} receptors is available in native tissue. Pimavanserin has no effect at all on blocking dopamine receptors nor does it block adrenergic histaminergic or muscarinic receptors [1]. Pimavanserin was first developed to treat hallucinations caused by DOPA and other dopaminergic drugs used to treat Parkinson's disease and has been approved by the FDA for this purpose (see Box 1) [4,8–10]. Hallucinations secondary to dopaminergic treatment of Parkinson's disease occur in about half of the patients. Positron emission tomography (PET) studies show that Parkinson's disease patients with dopaminergic-drug-induced hallucination have upregulated 5-HT_{2A} receptors [11,12]. This is supported by autoradiographic postmortem studies [13]. According to pharmacological principles, an inverse agonist should reduce basal constitutive activity of the respective receptor. Therefore, a basal condition characterized by enhanced 5-HT_{2A} receptor activity would be the ideal condition to show the efficacy of a selective inverse agonist as pimavanserin. Thus, studies that focus on Parkinson's disease hallucinations and hallucinations in dementia represent the best candidate conditions to obtain positive results. Both conditions may be benefited by drugs with antagonist properties on 5-HT_{2A} receptors.

Most conventional first-generation antipsychotics make the Parkinson's disease symptoms worse. Low dose clozapine is effective, and quetiapine may be somewhat effective in treating DOPA hallucinations [4,14]. In a phase 3 double-blind randomized controlled trial (RCT), pimavanserin substantially

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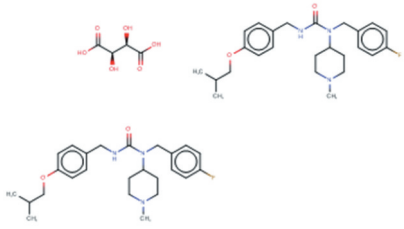
Article highlights

- Pimavanserin is a potent 5-HT2A inverse agonist/antagonist, a property hypothesized to be efficacious in several psychiatric disorders because clozapine has this property and is effective in treating DOPA-induced hallucinations and is the most effective drug for schizophrenia.
- Pimavanserin is only FDA-approved for the treatment of hallucinations and delusions in Parkinson's disease psychosis.
- Two controlled trials found pimavanserin to be efficacious in treating hallucinations in dementia in select groups.
- Existing SSRI and SSNI antidepressants fail to substantially reduce depression in a minority of patients with depression but do produce sexual side effects such as decreased desire. Augmentation with pimavanserin reduced depression in a phase 2 RCT and also alleviated the sexual side effects of baseline antidepressant treatment. But a phase 3 trial, found only a non-significant trend toward improvement. Its sponsor has decided not to pursue its development for depression.
- Since almost all existing antipsychotics fail to substantially benefit negative symptoms, better treatments are needed. Augmentation of antipsychotic medications with a 5-HT_{2A} inverse agonist/antagonist was hypothesized to be more effective for negative symptoms. Pimavanserin augmentation of antipsychotics did benefit negative symptoms with an effect size of about 0.2 but failed to reduce the total PANSS score significantly in two large well controlled double blind studies.
- Pimavanserin had a good safety profile based on the combined data from the studies for these three indications.

Box 1. Drug Summary Box

Drug name	Pimavanserin
Phase	Launched
Indication	Parkinson's Disease Psychosis
Pharmacology description	5 Hydroxytryptamine 2A receptor antagonist
Route of administration	Oral
Chemical structure	
Pivotal trial(s)	[10,19,30]

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reduced hallucinations without impairing Parkinson's disease or impairing cognition [10]. The degeneration of dopaminergic neurons is responsible for Parkinson's disease but also there is a loss of serotonergic neurons accompanied by an upregulation of postsynaptic 5-HT_{2A} receptors, creating an imbalance between dopaminergic and serotonergic function. This upregulation of the 5-HT_{2A} receptor may be responsible for the hallucinations. The exact mechanism by which pimavanserin reduced DOPA hallucinations by its 5-HT_{2A} inverse agonist/antagonist properties is not fully known, but psychedelic drugs such as LSD or psilocybin stimulate the 5-HT_{2A} receptor.

The purpose of this paper is to review and contextualize the existing clinical data on pimavanserin in psychiatric disorders. Below, we summarize the main efficacy findings from RCTs among patients with hallucinations secondary to dementia, major depression, and schizophrenia. We also summarize common side effects reported in the depression and schizophrenia trials as well as serious adverse events reported in all completed pimavanserin RCTs for any indication.

2. Agitation and aggression in Alzheimer's disease

The trial targeting agitation and aggression in Alzheimer's disease (the SERENE trial) has results posted on ClinicalTrials.gov in which 83 patients completing 12 weeks of treatment 34 mg/day or 20 mg/day showed no hint of benefit in agitation over placebo [15]. This trial was terminated early when only a quarter of the planned participants had been enrolled and was thus not adequately powered to detect a treatment difference. The primary outcome was the Cohen–Mansfield Agitation Inventory (CMAI), a 29-item scale to assess agitation with a range of 29–203 points (higher scores indicate more severe agitation). The difference in CMAI scores at the end of the study relative to placebo (n = 37) was 5.1 (95% CI −4.8 to 15.0) for the pimavanserin 20 mg group (n = 34) and 1.0 (−8.5 to 10.5) for the pimavanserin 34 mg group (n = 35).

3. Hallucinations in dementia

Pimavanserin may be a treatment for hallucination in dementia because various dementias, especially with Lewy bodies, upregulate the 5-HT_{2A} receptor [16,17]. In a study of 181 nursing home residents with Alzheimer's disease with associated psychotic symptoms, 90 patients were assigned to pimavanserin and 91 patients to placebo [18]. The best results were seen at 6 weeks, with a statistically significant decrease in 1.84 points on the Neuropsychiatric Inventory-Nursing Home (NPI-NH) psychosis score from baseline (p = 0.045, effect size = 0.32). At 9 and 12 weeks, pimavanserin trended toward improvement but was not statistically significant. The group with a baseline NPI-NH psychosis score ≥12 achieved a clearly significant improvement.

A phase 3 study – HARMONY [19] – enrolled patients with hallucinations, delusions, and/or dementia related to Alzheimer's disease, Parkinson's disease, Lewy bodies, frontotemporal dementia, or vascular dementia. Subjects (n = 392) underwent a 12-week open phase of pimavanserin 34 mg/day. Those who improved were randomized 1:1 to pimavanserin or placebo for 26 weeks. Improvement was defined as a 30% reduction in the Scale for the Assessment of Positive Symptoms – Hallucinations + Delusions (SAPS-H + D) and a Clinical Global Impressions-Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved). There was a clear reduction of hallucination and delusions in all types of dementia in the open phase, with 253 patients meeting improvement criteria at 8 weeks of open-label use. In the double-blind phase, pimavanserin had a statistically significant reduction

Table 1. **CLARITY study endpoints**. Reproduced from [21,22] with permission.

		Stage 1		Stage 2		
		Pimavanserin (n = 51)	Placebo (n = 152)	Pimavanserin (n = 29)	Placebo (n = 29)	Overall
HAMD-17 total	LS mean (SE)	−11.5 (0.94)	−7.5 (0.55)	−2.8 (0.89)	−3.3 (0.94)	−1.7 (0.85)
	p-value	0.003		0.694		0.04
	Effect size	0.626		−0.107		
Sheehan Disability Scale	LS mean (SE)	−3.3 (0.35)	−2.1 (0.20)	−0.9 (0.29)	−0.4 (0.30)	−0.84 (0.29)
	p-value	0.004		0.256		0.004
	Effect size	0.498		0.311		
CGI-S	LS mean (SE)	−1.9 (0.17)	−1.2 (0.10)	−0.5 (0.12)	−0.5 (0.16)	−0.4 (0.15)
	p-value	<0.001		0.94		0.008
	Effect size	0.667		0.021		
CGI-I	LS mean (SE)	2.2 (0.17)	2.8 (0.10)	3.0 (0.18)	3.1 (0.19)	−0.4 (0.16)
	p-value	0.001		0.817		0.03
	Effect size	0.574		0.063		
Karolinska Sleepiness Scale	LS mean (SE)	−1.7 (0.26)	−0.6 (0.15)	−0.4 (0.28)	−0.3 (0.30)	−0.6 (0.26)
	p-value	<0.001		0.842		0.02
	Effect size	0.627		0.056		
MGH-SFI	LS mean (SE)	−0.8 (0.15)	−0.2 (0.08)	−0.5 (0.14)	−0.2 (0.14)	−0.47 (0.13)
	p-value	<0.001		0.127		<0.001
	Effect size	0.614		0.412		
Sheehan Irritability Scale	LS mean (SE)	−19.5 (2.17)	−11.2 (1.28)	−5.7 (2.34)	−6.2 (2.47)	−3.9 (2.12)
	p-value	0.001		0.889		0.07
	Effect size	0.561		−0.039		
HAMD-17 anxiety/ somatization factor at baseline	LS mean (SE)	−3.7 (0.36)	−2.1 (0.21)	−0.6 (0.33)	−0.6 (0.35)	−0.8 (0.32)
	p-value	<0.001		0.98		0.02
	Effect size	0.634		−0.007		
Subgroup:	n	29	76	19	18	
HAMD-17 anxiety/ somatization factor ≥7 at baseline	LS mean (SE)	−5.0 (0.56)	−2.8 (0.35)	−1.3 (0.44)	−1.5 (0.49)	−1.0 (0.47)
	p-value	0.001		0.847		0.03
	Effect size	0.781		−0.067		
Subgroup:	n	17	36	10	8	
HAMD-17 total score ≥24 and HAMD-17 anxiety/ somatization factor ≥7 at baseline	LS mean (SE)	−17.4 (1.97)	−9.3 (1.40)	−3.7 (1.43)	−1.3 (1.68)	−5.2 (1.64)
	p-value	0.002		0.295		0.001
	Effect size	1.037		0.536		
	n	44	118	25	22	
	LS mean (SE)	−2.3 (0.30)	−1.7 (0.18)	−1.0 (0.35)	−0.4 (0.39)	−0.5 (0.32)
	p-value	0.13		0.301		0.09
	Effect size	0.284		0.319		

in the risk of psychotic exacerbation by >2.8-fold over placebo, with a hazard ratio of 0.35 (0.17 to 0.73, p = 0.002). There was also a clear reduction in time to all-cause discontinuation, with a hazard ratio of 0.45 (0.26 to 0.79, p = 0.002).

In both studies, there was no change in cognition associated with drug treatment. HARMONY was designed for patients who improved at hallucinations and delusions with pimavanserin in the open phase and thus represent a selected subgroup (only 217 were randomized of the original 392 enrolled in the open phase). It strongly suggests that there is a subgroup who are benefited by pimavanserin. It remains to be determined whether this subgroup could be identified other than by a therapeutic trial. In April 2021, Acadia Pharmaceuticals announced a Complete Response Letter from the FDA for pimavanserin for the treatment of dementia-related hallucinations indicating that the application cannot be approved in its present form [20].

4. Major depression

5-HT_{2A} antagonism has been thought to contribute to the properties of some antidepressants. In the phase 2 CLARITY study [21], treatment-resistant, primary, major depressive patients in a current episode who were unresponsive to two antidepressants were randomized in a double-blind trial with sequential parallel comparison design. In stage 1, 207 patients were randomized to either 34 mg/day of pimavanserin (n = 52) or placebo (n = 155) for 5 weeks of treatment augmenting their antidepressants. In stage 2, non-responders to the placebo in stage 1 were re-randomized to pimavanserin or placebo, with 29 patients in each group for an additional five-week augmentation. Nonresponse was defined as a score of greater than 14 on the total score of the 17-item Hamilton Depression Rating Scale (HAMD-17) and less than 50% reduction from baseline. In stage 1, there was a substantial reduction in the HAMD-17 by four points (effect size = 0.63) with similar improvements in both the Clinical Global Impressions-Severity (CGI-S) and CGI-I scales (Table 1). A similar reduction was seen in the Sheehan Disability Scale with an effect size of 0.5. This is a scale reflecting improvement in workplace function and a decrease in functional disability due to depression. There were also improvements in the Karolinska Sleepiness Scale, Massachusetts General Hospital Sexual Functioning Inventory (MGH-SFI), and Sheehan Irritability Scale with effect sizes similar to HAMD-17. The results in stage 2, however, are relatively disappointing. Placebo did slightly better than pimavanserin on the HAMD-17 and the Sheehan Irritability Scale. While pimavanserin was directionally better than placebo on most of the other scales, the results were not statistically significant. The purpose of sequential parallel comparison

design is to cope with the high placebo response rate in the treatment of depressive disorders. However, pimavanserin augmentation seems to help the population with an expected high placebo response rate, but it does not help the population which eliminates placebo responders.

In a post-hoc analysis, there was a large improvement (effect size = 0.63) of pimavanserin over placebo in the HAMD-17 anxiety/somatization factor in stage 1 (Table 1) [22]. In a subgroup with baseline scores ≥7 on this factor, pimavanserin improved with an effect size of 0.78 in stage 1 (n = 105). When this subgroup was further reduced to patients with baseline HAMD-17 total scores ≥24 (indicating severe depression), the effect size became 1.04 in stage 1 (n = 53). It appears that this subgroup was particularly helped by pimavanserin, as it is a highly selective inverse agonist of 5-HT_{2A}, with consequent implications toward the biology of antidepressants. However, this subgroup represents only a quarter of the patients randomized to stage 1 and results were not presented for the remainder. There is little to say about stage 2 other than the results show little benefit. When both stages are combined, there is statistically significant evidence of efficacy. We speculate that there is at least one subtype for whom pimavanserin is helpful, which by chance is a larger share of the sample in stage 1 but smaller in stage 2.

4.1. Adverse events

Pimavanserin had a benign side effect profile in the CLARITY study, where adverse events leading to discontinuation were one out of 52 (1.9%) in the pimavanserin arm and 3 out of 155 (1.9%) in the placebo arm in stage 1, and only one out of 29 (3.4%) in the placebo arm in stage 2. [21] Moreover, pimavanserin augmentation was not associated with an increase in suicidal ideation (suicide item on the HAMD-17) compared with placebo and no suicidal behaviors were observed in either group during the study. [23].

4.2. Sexual dysfunction as a side effect of SSRIs

Sexual dysfunction is a common side effect of MAO inhibitors and selective serotonin uptake inhibitors (SSRI), and particularly problematic for women is the inability to have an orgasm. Pimavanserin augmentation of SSRI or serotonin and norepinephrine reuptake inhibitors (SNRI) in the CLARITY study had a substantial effect in improving sexual function in stage 1 among women [24]. As measured by the MGH-SFI, interest in sex, sexual arousal, ability to have an orgasm, and overall sexual satisfaction improved ($p < 0.01$, effect sizes of 0.56–0.75). Men of all ages, which comprised 25% of the sample, did not have a statistically significant improvement, but men >50 years of age improved on all factors ($p < 0.01$, effect sizes of 0.65–0.87) except the ability to maintain an erection. There was greater improvement in sexual functions in remitters than in nonremitters and in responders than in nonresponders. The MGH-SFI mean score in the whole sample improved in stage 1 (Table 1). However, in stage 2, although the results were not significant, there was a trend toward improved sexual function ($p = 0.13$, effect size = 0.41).

The phase 3 investigations evaluating pimavanserin as adjunctive treatment of major depressive disorder have not been published, but data in a press release reported results in 298 treatment-resistant patients with depression [25]. In the 6-week parallel-group, randomized, double-blind, placebo-controlled trial, pimavanserin augmentation of SSRI or SNRI showed reductions on the HAMD-17 ($p = 0.30$), CGI-S ($p = 0.04$), and Karolinska Sleepiness Scale ($p = 0.005$), and no meaningful differences on other outcomes compared to placebo. It would seem the favorable finding in stage 1 of the CLARITY study did not hold up, but it may help identify a subgroup of treatment-resistant patients with depression that could benefit from pimavanserin or explore its use in monotherapy.

5. Schizophrenia

Since pimavanserin was developed because clozapine is the most effective antipsychotic [7] and is a very potent 5-HT_{2A} antagonist, its efficacy in schizophrenia has been studied so far in four studies: one published RCT, one published open case series, and two RCTs available as poster presentations. Drugs which antagonize 5-HT_{2A} receptors reduce extrapyramidal side effects. 5-HT_{2A} blockage is not well correlated with differential efficacy in the various antipsychotics in meta-analysis [7], but this does not rule out the potential benefit of particularly potent drugs with this property. The premise is that augmenting 5-HT_{2A} inverse agonists/antagonists to an antipsychotic might convert it to a clozapine-like drug by adding a critical mechanism.

5.1. Meltzer et al. 2012

The first double-blind random assignment study compared suboptimal doses of risperidone and haloperidol, each augmented with pimavanserin or placebo, as well as a group treated with an adequate dose of risperidone and placebo [26]. Patients had multi-episode schizophrenia with a recent exacerbation of their illness. Each group consisted of about 75 patients and was treated for 43 days. There is good evidence that 2 mg/day of risperidone achieves approximately half of

Table 2. **Mean Change in PANSS from Baseline to Endpoint. Reproduced from [29] with permission.**

	Risperidone 2 mg + Placebo (n = 77)		Risperidone 2 mg + Pim. 20 mg (n = 69)		Risperidone 6 mg + Placebo (n = 76)		Haloperidol 2 mg + Placebo (n = 77)		Haloperidol 2 mg + Pim. 20 mg (n = 77)	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Total	−16.3	(1.9)	−23.0	(1.8)	−23.2	(2.2)	−25.1	(1.9)	−21.8	(1.6)
Positive	−5.9	(0.6)	−7.4	(0.6)	−8.1	(0.7)	−8.1	(0.6)	−6.9	(0.6)
Negative	−3.7	(0.6)	−5.1	(0.6)	−4.9	(0.6)	−5.9	(0.6)	−5.1	(0.5)
Cognition	−2.7	(0.5)	−3.4	(0.4)	−4.1	(0.5)	−4.1	(0.5)	−3.6	(0.4)
General	−6.7	(1.0)	−10.5	(1.0)	−10.2	(1.1)	−11.1	(1.0)	−9.8	(0.8)

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the expected efficacy. Less is known of the dose–response characteristics of haloperidol, but 2 mg/day is consistent with the half efficacious dose. The results are shown in Table 2.

The low-dose risperidone-pimavanserin group compared to the low-dose risperidone-placebo group had a significant improvement in the PANSS total score, the primary outcome variable, as well as negative and general symptoms, and near significant improvement on positive symptoms. Interestingly, the greatest absolute improvement was in the low-dose haloperidol-placebo group. Compared to the haloperidol-pimavanserin group, the haloperidol-placebo group had a nonsignificant improvement in the PANSS total score. Since 5-HT_{2A} antagonism reduces extrapyramidal side effects, it should also reduce their corresponding secondary negative symptoms. This was not clearly observed in the risperidone arms of this study, but there was a trend in the haloperidol-pimavanserin group compared to the haloperidol-placebo group where the Simpson Angus Scale score was reduced ($p = 0.07$). Since clozapine is a less potent dopamine D2 blocker than the other antipsychotics, and if 5-HT_{2A} antagonism was the relevant property, pimavanserin could potentially be another clozapine; but this was not observed. Pimavanserin did improve the efficacy of low-dose risperidone, but it worsened the efficacy of low-dose haloperidol, so it is difficult to draw a sweeping conclusion.

5.2. Nasrallah et al. 2019

This was an open case series of 10 severely ill patients who had chronic schizophrenia with persistent hallucinations, were resistant to clozapine (n = 6) or multiple antipsychotics (n = 4), and were treated with 34 mg/day of pimavanserin [27]. While several of the patients were elderly, some were middle aged, and one was 21. The researchers determined that all subjects had reduced hallucinations and delusions within 4–8 weeks, based on clinical observation.

5.3. ADVANCE trial

This study was a 26-week, randomized, double-blind, placebo-controlled trial of adjunctive pimavanserin in stable outpatients with schizophrenia from Europe and North America who had predominant negative symptoms [28,29]. Patients were stable on antipsychotics for at least 8 weeks and remained on antipsychotics for the duration of the trial. The most common antipsychotics were aripiprazole, olanzapine, and risperidone. Patients were selected for the presence of high Marder negative symptoms factor scores, low Marder positive symptoms factor scores, and a Clinical Global Impression of Schizophrenia-Severity (CGI-SCH-S) negative symptoms score ≥4. Pimavanserin or placebo was used as augmentation first with a two-week fixed dose of 20 mg/day followed by a six-week flexible dose of either 10, 20, or 34 mg/day, and then a fixed dose for weeks 8–26. The change from baseline in Negative Symptom Assessment-16 (NSA-16) was the primary outcome. The intent-to-treat analysis for NSA-16 and Personal and Social Performance Scale (PSP) were reported in a poster [28]. At week 26, the patients receiving pimavanserin versus placebo had a mean NSA-16 reduction of −10.4 vs −8.5, respectively ($p = 0.043$, effect size = 0.21). The improvement was very gradual, only being significant by about 20 weeks. There was no change in the PSP score from baseline to week 26. About half of the patients were administered the maximum dose of 34 mg/day and the improvement of negative symptoms were slightly (1.2 points) better in this group. Results for other outcomes (among completers only) were available on ClinicalTrials.gov (Table 3, part A) [29]. There was no improvement over placebo on the PANSS positive

Table 3. Mean Change in Outcomes from Baseline to Endpoint in the ENHANCE and ADVANCE studies.

A. ADVANCE[28,29]

	Pimavanserin (n = 174) Mean (SE)	Placebo (n = 173) Mean (SE)	Difference (95% CI)	p-value	Cohen's d Effect Size
NSA-16 Total[a]	−10.4	−8.5	−1.9	0.043	0.21
PANSS Total	−8.7 (0.75)	−8.6 (0.76)	−0.1 (−2.2, 2.0)	0.93	−0.01
Positive	−0.6 (0.19)	−0.8 (0.21)	0.2 (−0.4, 0.8)	0.48	0.08
Negative	−4.0 (0.29)	−3.8 (0.31)	−0.2 (−1.0, 0.6)	0.64	−0.05
General	−4.1 (0.43)	4.0 (0.43)	−0.1 (−1.3, 1.1)	0.87	−0.02
CGI-SCH-S	−0.6 (0.06)	−0.6 (0.06)	0 (−0.2, 0.2)	1	0
NSA-16 Negative Symptoms	−0.7 (0.06)	−0.7 (0.06)	0 (−0.2, 0.2)	1	0

B. ENHANCE[30,31]

	Pimavanserin (n = 173) Mean (SE)	Placebo (n = 189) Mean (SE)	Difference (95% CI)	p-value	Cohen's d Effect Size
PANSS Total	−15.4 (0.89)	−13.3 (0.86)	−2.1 (−4.5, 0.4)	0.09	−0.17
Positive[b]	−5.4 (0.34)	−4.9 (0.30)	0.5 (−1.4, 0.4)	0.27	−0.12
Negative	−2.8 (0.27)	−2.0 (0.26)	−0.7 (−1.5, 0)	0.05	−0.21
General[b]	−7.2 (0.47)	−6.4 (0.47)	−0.8 (−2.1, 0.5)	0.23	−0.13
CGI-S	−0.8 (0.06)	−0.7 (0.05)	−0.1 (−0.3, 0)	0.05	−0.2
Marder Factor Score – Negative Symptoms	−3.4 (0.30)	−2.5 (0.29)	−0.9 (−1.7, −0.1)	0.04	−0.22

[a]Intent-to-treat analysis from poster presentation (pimavanserin, n = 199; placebo, n = 201). SEs for the means and 95% CI for the difference were not available[28].
[b]Results from completer analysis as reported on ClinicalTrials.gov[31].
Parts of this table courtesy of Acadia Pharmaceuticals.

subscale, and the PANSS total as well as negative and general symptom subscales were not significantly better than placebo.

5.4. ENHANCE trial

This study was a six-week, randomized, double-blind, placebo-controlled trial of adjunctive pimavanserin in stable outpatients with schizophrenia from Europe and North America who had an inadequate response to antipsychotics [30,31]. Subjects had a PANSS total score between 65 and 110, a CGI-S score ≥4, and a PANSS item score ≥4 on at least two items (delusions, hallucinations, or suspiciousness/persecution). This is a different population than that of the ADVANCE trial which selected for negative symptoms and excluded patients with marked hallucination or delusions. The primary outcome measure was PANSS total.

The preliminary results are presented in Table 3, part B. There was a nonsignificant trend for pimavanserin to produce more improvement than placebo in the PANSS total and general symptom scores. For the PANSS positive symptom score, there was a nonsignificant trend for placebo to produce more improvement than pimavanserin. The results were significant in the PANSS negative subscale as well as the Marder factor score reflecting negative symptoms, particularly withdrawal symptoms. There is a large overlap of items between these two subscores. At the completion of the study, 56.5% of pimavanserin and 50.5% of placebo subjects had a 20% reduction in the PANSS total score [31]. Also, of the observed cases 39.3% of pimavanserin and 34.4% of placebo subjects were considered responders according to the CGI-I scale. Pimavanserin did produce an almost significant effect on the CGI-S scale ($p = 0.054$). This is important because a new drug might produce an improvement in a few items, but at the cost of a worsening in other items. There is no evidence from the three RCTs that adding pimavanserin converse an existing antipsychotic to clozapine, suggesting that this property by itself is not what makes clozapine uniquely effective in schizophrenia.

As far as side effects, there was little change at end point in the Simpson Angus Scale total score [32]. No analysis was reported on whether changes in extrapyramidal symptoms might explain changes on secondary negative symptoms, and no attempt to separate primary from secondary negative symptoms was made. It is important when thinking about negative symptoms to consider what is happening to extrapyramidal symptoms. The occurrence of side effects was similar in the pimavanserin augmentation group to the placebo augmentation group. The changes from baseline to week 6 for glucose, prolactin, blood lipids, and weight were similar between pimavanserin and placebo. There was no clinically significant effect on blood pressure. No patient in either arm had QTcF (QT interval corrected using Fridericia's formula) prolongation >500 msec or torsades de pointes during the study period; but two patients (1.1%) in the pimavanserin arm and none in the placebo arm had post-baseline QTcF prolongation >60 msec. Mean (SE) change from baseline in QTcF interval was −0.6 (1.07) msec in the placebo arm and 1.3 (1.23) msec in the pimavanserin arm.

We present the side effects common in the ADVANCE and ENHANCE trials in Table 4, part B. In both trials, the occurrence of side effects was similar in the pimavanserin and placebo groups.

6. Administration

Pimavanserin is orally administered without needing titration, with or without food, is 95% protein bound, and has linear dose proportional pharmacokinetics with an apparent plasma elimination half-life (t½) of about 57 hours and steady state is achieved in 12 days [8]. Its major active metabolite is N-desmethyl-pimavanserin), which has similar receptor activity to pimavanserin with a half-life of 65 hours. Pimavanserin undergoes hepatic metabolism by CYP450 3A4 and 3A5, so that CYP3A4 inhibitors such as ketoconazole, substantially reduce plasmas level, and CYP450 3A4 and 3A5 such as carbamazepine, phenytoin, rifampin, and St John's wart increase plasma levels.

7. Serious adverse events

The information on side effects for pimavanserin augmentation of antidepressants or augmentation of antipsychotics, is that side effects of pimavanserin would have to surface above the noise of the antidepressants or antipsychotics themselves. In order to provide a wider context, we summarize the incidence of serious adverse effects across studies pimavanserin use without other psychotropic drugs in Parkinson's disease, mixed dementias, as well as augmentation in depression and

Table 4. Adverse events during the, ADVANCE and ENHANCE studies [28,30].

	ADVANCE		ENHANCE	
	Pimavanserin (n = 201) n (%)	Placebo (n = 202) n (%)	Pimavanserin (n = 198) n (%)	Placebo (n = 198) n (%)
AE leading to discontinuation	10 (5.0%)	6 (3%)	5 (2.5%)	0
Common adverse events				
Headache	13 (6.5%)	10 (5%)	13 (6.6%)	18 (9.1%)
Somnolence	11 (5.5%)	10 (5%)	13 (6.6%)	7 (3.5%)
Insomnia	6 (3%)	6 (3%)	10 (5.1%)	7 (3.5%)
Nasopharyngitis	4 (2%)	9 (4.5%)	5 (2.5%)	4 (2%)
Dizziness	4 (2%)	5 (2.5%)	5 (2.5%)	3 (1.5%)
Anxiety	6 (3%)	6 (3%)	2 (1%)	5 (2.5%)

Courtesy of Dr. Dragana Bugarski-Kirola at Acadia Pharmaceuticals.

Table 5. Serious adverse effects reported in randomized controlled trials of oral pimavanserin.

				Pimavanserin			Placebo		
NCT number	Condition	Phase	Completion	n	Serious Adverse Events		n	Serious Adverse Events	
NCT02035553[18]	Alzheimer's Disease Psychosis	Phase 2	2016	90	15	(16.7%)	91	10	(11%)
NCT03325556[19]	Dementia-Related Psychosis	Phase 3	2019	105	5	(4.8%)	112	4	(3.6%)
NCT03018340[21]	Major Depressive Disorder	Phase 2	2018	52*	0	(0%)	155*	1	(0.6%)
NCT00087542[6]	Parkinson's Disease Psychosis	Phase 2	2005	29	2	(6.9%)	31	2	(6.5%)
NCT00477672[34]	Parkinson's Disease Psychosis	Phase 3	2009	197	10	(5.1%)	98	2	(2%)
NCT00658567[35]	Parkinson's Disease Psychosis	Phase 3	2009	82	4	(4.9%)	39	2	(5.1%)
NCT01174004[10,36]	Parkinson's Disease Psychosis	Phase 3	2012	104	11	(10.6%)	94	4	(4.3%)
NCT00361166[26]	Schizophrenia	Phase 2	2007	146	8	(5.5%)	230	15	(6.5%)
NCT02970292[32]	Schizophrenia	Phase 3	2019	198	2	(1%)	198	2	(1%)
NCT02970305[28]	Schizophrenia	Phase 2	2019	201	4	(2%)	202	1	(0.5%)
Total				1204	61	(5.1%)	1250	43	(3.4%)

*Stage 1

schizophrenia. We compiled the number of serious adverse events reported in the 10 published RCTs of pimavanserin Table 5. They represent a total of 2454 participants and 104 serious adverse events; 61 occurred in the pimavanserin groups and 43 occurred in the placebo groups. Using a random effects meta-analysis of these data, we calculated an overall risk ratio of 1.40 (95% CI 0.94 to 2.08; p = 0.10). Thus, the higher risk of serious adverse events for pimavanserin is not statistically significant. While the follow-up time in these trials may not be long enough to approximate normal use in a free-living population, in 2018 the U.S. Food and Drug Administration (FDA) conducted a comprehensive review of all post-marketing reports of deaths and serious adverse events reported with the use of Nuplazid (pimavanserin) and found no new or unexpected safety concerns [33]. That analysis included information submitted to the FDA Adverse Event Reporting System, drug utilization data, safety data from the Nuplazid new drug application, the sponsor's Periodic Adverse Drug Experience Reports, the sponsor's analysis of fatal adverse event reports with Nuplazid and published medical literature. Their conclusion was that the benefits from pimavanserin outweigh its risks for patients with hallucinations and delusions of Parkinson's disease psychosis.

8. Conclusion

Pimavanserin has been shown to be effective in the treatment of Parkinson's disease psychosis and has FDA approval for that use. It is not currently FDA-approved for hallucinations/psychosis in dementia, major depression or schizophrenia. Based on two controlled studies, pimavanserin clearly has potential for reducing hallucinations in mixed dementia. Acadia Pharmaceuticals has stated in a press release that it does not plan further antidepressant studies based on its phase 3 trial. As far as schizophrenia, since many patients have an incomplete response to antipsychotics on negative symptoms, effective augmentation agents are needed. Pimavanserin has not been reported to reduce total PANSS score significantly. We had hoped for clozapine's efficacy, but what was achieved was the effect size was about 0.2 on negative symptoms.

9. Expert opinion

Antipsychotics, mood stabilizers, and antidepressants were all discovered by clinical serendipitous observations. Subsequent drugs were developed initially from structurally similar compounds in animal models. Later, much more sophisticated molecular techniques were used so that advantageous properties could be built into the molecule and unwanted properties could be eliminated. Pimavanserin is proposed as a drug to target states of 5-HT_{2A} upregulations. In other words, this drug is a single property in search of an indication. Therefore, in searching for the indication, it is important to determine not only what the drug does, but also what it does not do. Pimavanserin is clearly beneficial in dopaminergic agonists produced hallucination in the elderly and in hallucination in the elderly per se [37]. Its actions should be considered in the context of the disease state more generally than just 5-HT_{2A}. Changes downstream of the 5-HT_{2A} receptor specific to a disease may be important [38]. Abnormal redox homeostasis and oxidative stress may play a role in the etiology of Parkinson's disease, dementia, schizophrenia, depression, and several neuropsychiatric spectrum disorders [39–41]. Based on preclinical models, six atypical antipsychotic drugs were studied with six different stressor/toxic agents (i.e. rotenone, hydrogen peroxide, MPP+, serum withdrawal, beta-amyloid, and corticosterone) and were reported to induce neuroprotective effects with consistently hormetic dose response patterns [42]. Thus, there may be another receptor involved, such as glutamate [43]. In phase 1 of the CLARITY study pimavanserin produced a considerable antidepressant effect and the direction of chance in the phase 3 study was toward benefit, but paradoxically Psilocybin which is a 5-HT_{2a} agonist has been found to have an antidepressant effect [41,44,45]. Many diseases are complex, and as more is understood, pimavanserin might be a harbinger of drugs with one specific property to be used based on biological tests to target a specific aspect of the disease.

Geriatric psychiatry has assumed that geriatric patients have the same disorders as adults. The finding that 5-HT_{2A} upregulation occurs in some elderly patients with dementia or Parkinson's disease and can be successfully treated by a specific 5-HT_{2A} antagonist/partial agonist suggests there is potential for unique drugs to treat mental illnesses associated

with advanced age. However, both in vivo and in vitro studies have also reported a reduction of 5-HT_{2A} receptors in some aging populations [46]. It would be helpful to establish which symptoms or characteristics might predict a favorable response to pimavanserin based on the completed clinical trials (e.g. presence of visual hallucinations). Then another RCT can establish, based on this entrance criteria, the efficacy of pimavanserin over placebo.

Although the phase 3 antidepressant program has been discontinued by Acadia Pharmaceuticals, that pimavanserin has some efficacy in depression particularly in patients with high anxiety and somatic symptoms suggests that non-responders to antidepression might respond to drugs with high 5-HT_{2A} antagonism. Pimavanserin alleviation of the sexual side effects of SSRI and SSNI in the phase 2 CLARITY trial is important. The sexual side effects induced by the SSRI and SSNI are important quality-of-life side effects, which suggests a treatment using 5-HT_{2A} antagonists could be useful. This finding offers the hope of further research to verify these findings, to explore new indications for pimavanserin in disorders of sexual function and may help us better understand the biology of sexual function.

There is some agreement that pimavanserin shows some efficacy for negative symptoms with an effect size of 0.2 but does not show clear efficacy for positive symptoms in schizophrenia patients. One psychometric problem is there may be a ceiling effect. The answer might be in the design of these trials: pimavanserin has been tested as an adjunctive drug to antipsychotic treatment. However, atypical antipsychotics are, among other properties, antagonists of 5-HT_{2A} receptors. Therefore, olanzapine, risperidone, and clozapine could contribute to mask the anti-hallucinogenic properties of pimavanserin by a pharmacological antagonism on 5-HT_{2A} receptors. This is why the addition of pimavanserin does not converse an existing antipsychotic to clozapine. In fact, the study of Meltzer et al., (2012) shows better efficacy of pimavanserin plus low-dose of risperidone versus placebo plus low-dose risperidone. Note however the finding with haloperidol with negative results. Therefore, it seems necessary to test pimavanserin as an anti-hallucinogenic drug for schizophrenia in the absence of atypical antipsychotic administration. Furthermore, it has been suggested that there is a subset of schizophrenic patients that might respond to a 5-HT_{2A} receptor antagonist/inverse agonist [47]. Indeed, one day it might be possible to use PET imaging to identify patients with certain patterns of increased 5-HT_{2A} receptor binding that would make them candidates for treatment with pimavanserin. A proof-of-principle study (The Sub-Sero Study [48]) is underway in which patients with schizophrenia (antipsychotic-naïve) will undergo PET imaging of the 5-HT_{2A} receptor-binding potential before starting on 34 mg/day of pimavanserin [49]. The goal is to identify a 5-HT_{2A} receptor subtype of schizophrenia spectrum disorders. There is a case report of ketanserin, a 5-HT_{2A} antagonist, successfully treating intractable visual hallucinations in a 29-year-old woman with chronic schizophrenia since the age of 10 with marked reduction of visual hallucinations but not in auditory hallucinations or delusion [47]. There was some improvement in negative symptoms, but it is not clear whether this was due to primary or secondary negative symptoms. It would be helpful to know if this was a small change in many patients or a marked improvement in a few, and if so, can this subgroup be characterized. The hypothesis was that this 5-HT_{2A} antagonist/inverse antagonist property was the mechanism explaining clozapine superiority in treatment-resistant schizophrenia. Its failure to do so has negative implications for this hypothesis.

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