Add-On Pramipexole for the Treatment of Schizophrenia and Schizoaffective Disorder: A Randomized Controlled Trial

Linda Levi, BSc[a]; Daisy Zamora, PhD[b]; Igor Nastas, MD[c]; Ilan Gonen, MD[d]; Paull Radu, MD[d]; Valentin Matei, MD[e]; Adela M. Ciobanu, MD[e]; Anatol Nacu, MD[c]; Larisa Boronin, MD[c]; Lusian Karakrah, MD[a]; Michael Davidson, MD[f]; John M. Davis, MD[g]; and Mark Weiser, MD[a,h]

ABSTRACT

Objective: Several small clinical trials have reported that the dopamine agonist pramipexole was beneficial in treating patients with schizophrenia. A confirmatory trial was conducted to test this hypothesis.

Methods: This 16-week, multicenter, double-blind, randomized, placebo-controlled study included 200 subjects meeting *DSM-IV-TR* criteria for schizophrenia or schizoaffective disorder. Patients were randomized to receive either pramipexole (0.75 mg twice daily, n = 100) or placebo (n = 100) as an add-on to their regular antipsychotic treatment. The primary outcome measure was the total score on the Positive and Negative Syndrome Scale (PANSS); secondary outcome measures included PANSS subscale and cognitive functioning scores. Recruitment was performed in 30 sites in Romania and 1 site in the Republic of Moldova between January and June 2011.

Results: Analysis of covariance models showed no significant difference between pramipexole and placebo for total PANSS ($P > .99$) and PANSS positive ($P > .99$), negative ($P = .73$), and general psychopathology ($P = .99$) subscale scores. Changes in Clinical Global Impressions–Severity of Illness scale and Brief Assessment of Cognition in Schizophrenia scores showed no significant difference between pramipexole and placebo.

Conclusions: The results of this large randomized controlled trial indicated that pramipexole was not efficacious as an add-on to antipsychotic medications for schizophrenia.

Trial Registration: ClinicalTrials.gov identifier NCT01320982

J Clin Psychiatry 2022;83(5):21m14233

To cite: Levi L, Zamora D, Nastas I, et al. Add-on pramipexole for the treatment of schizophrenia and schizoaffective disorder: a randomized controlled trial. *J Clin Psychiatry.* 2022;83(5):21m14233.

To share: https://doi.org/10.4088/JCP.21m14233

[a]Department of Psychiatry, Sheba Medical Center, Tel Hashomer, Israel
[b]Department of Psychiatry, University of North Carolina, Chapel Hill, North Carolina
[c]Department of Psychiatry, Narcology and Medical Psychology, State University of Medicine and Pharmacy Nicolae Testemitanu, Chișinău, Moldova
[d]Tangent Alzheimer Care, Breaza, Romania
[e]Department of Neuroscience, Discipline of Psychiatry, University of Medicine and Pharmacy "Carol Davila," Bucharest, Romania
[f]Nicosia University School of Medicine, Nicosia, Cyprus
[g]Department of Psychiatry, University of Illinois, Chicago, Illinois
[h]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
**Corresponding author:* Mark Weiser. MD, Department of Psychiatry, Sheba Medical Center, Tel-Hashomer, 52621, Israel (mweiser@netvision.net.il).

The role of dopamine in the symptomatology of schizophrenia has been widely researched. Previous literature has delineated the effect of dopamine in two different ways: Increased dopamine release in the subcortical areas affects positive symptoms.[1] However, decreased dopamine activity in cortical regions has been suggested to affect negative symptoms and cognitive functioning,[1] as has impaired dopamine activity in striatal regions.[2] Research in neuropsychiatric disorders such as Alzheimer's disease has shown that prodopaminergic agents are effective in treatment of apathy.[3]

Pramipexole is a dopamine D_2/D_3 receptor agonist, with selectivity toward D_3 dopaminergic receptors,[4] that is approved for the treatment of Parkinson's disease. Two small clinical trials, one open-label trial by Kasper et al[5] (n = 15) and one randomized trial by Kelleher et al[6] (n = 24), reported improvement in total Positive and Negative Syndrome Scale (PANSS) score, as well as positive and negative subscale scores, when pramipexole was added to antipsychotics in patients with schizophrenia. Kasper et al[5] suggested a presynaptic mechanism limiting synaptic release of dopamine. A meta-analysis by Sabe et al[7] reported that prodopaminergic drugs given as add-on treatment in schizophrenia do not worsen positive symptoms and might have a benefit on negative symptoms with certain dopamine agonists.

Based on these data, the objective of the current study was to perform a larger multicenter, double-blind, parallel-group, placebo-controlled add-on study of pramipexole 0.75 mg twice daily in patients with schizophrenia and schizoaffective disorder.

METHODS

Study Population

Subjects, either inpatients (≥ 3 days after admission) or outpatients, were recruited from 30 sites in Romania and 1 site in the Republic of Moldova between January and June 2011. Participants were eligible if they were aged 18 to 65 years, met *DSM-IV-TR* criteria for schizophrenia or schizoaffective disorder, and had at least 2 prior psychotic episodes and/or had been continually ill for at least 6 months. Other inclusion criteria were the use of an antipsychotic drug for at least 2 weeks prior to the baseline visit; a score of ≥ 4 (moderate or worse) on the PANSS items of delusions, hallucinatory behaviors, conceptual disorganization, and suspiciousness/persecution,

Clinical Points

- Smaller clinical trials and a meta-analysis suggest that prodopaminergic drugs might be efficacious in schizophrenia.
- In this large randomized controlled trial, pramipexole did not improve symptoms of schizophrenia in 200 patients with schizophrenia who were randomized to receive add-on pramipexole or placebo.

and/or a total PANSS negative symptoms score of ≥ 18; and a Clinical Global Impressions–Severity of Illness scale (CGI-S) score of ≥ 4 (moderate or worse).

After giving informed consent, study participants were randomized to receive pramipexole 0.75 mg twice daily or placebo; both of them were taken twice daily. Pramipexole was titrated starting at 0.125 mg twice daily for 1 week, 0.25 mg twice daily for the second week, 0.5 mg twice daily for the third week, and 0.75 mg twice daily for the rest of the study.

This study was part of a larger, 4-arm clinical trial, with patients randomized to aspirin (n = 100), minocycline (n = 100), pramipexole (n = 100), and placebo (n = 100). Each of these compounds has a different mechanism, hence each arm is being published separately, with its own introduction and discussion. The results of the minocycline arm[8] and the aspirin arm[9] have been published.

Study Medication Production, Randomization, and Masking

Medication was purchased from HEXAL and then overencapsulated and packaged by Sharp Clinical Services, formerly Bilcase GCS Ltd, in the United Kingdom. A randomization list was created and provided by data management (Medistat, https://www.medistat.co.il/) to the study drug manufacturer, which assigned the medication; randomization was done in blocks of 4, with 1:1:1:1; pramipexole/minocycline/acetylsalicylic acid/placebo. All study medications and placebo were packaged in identical-appearing capsules.

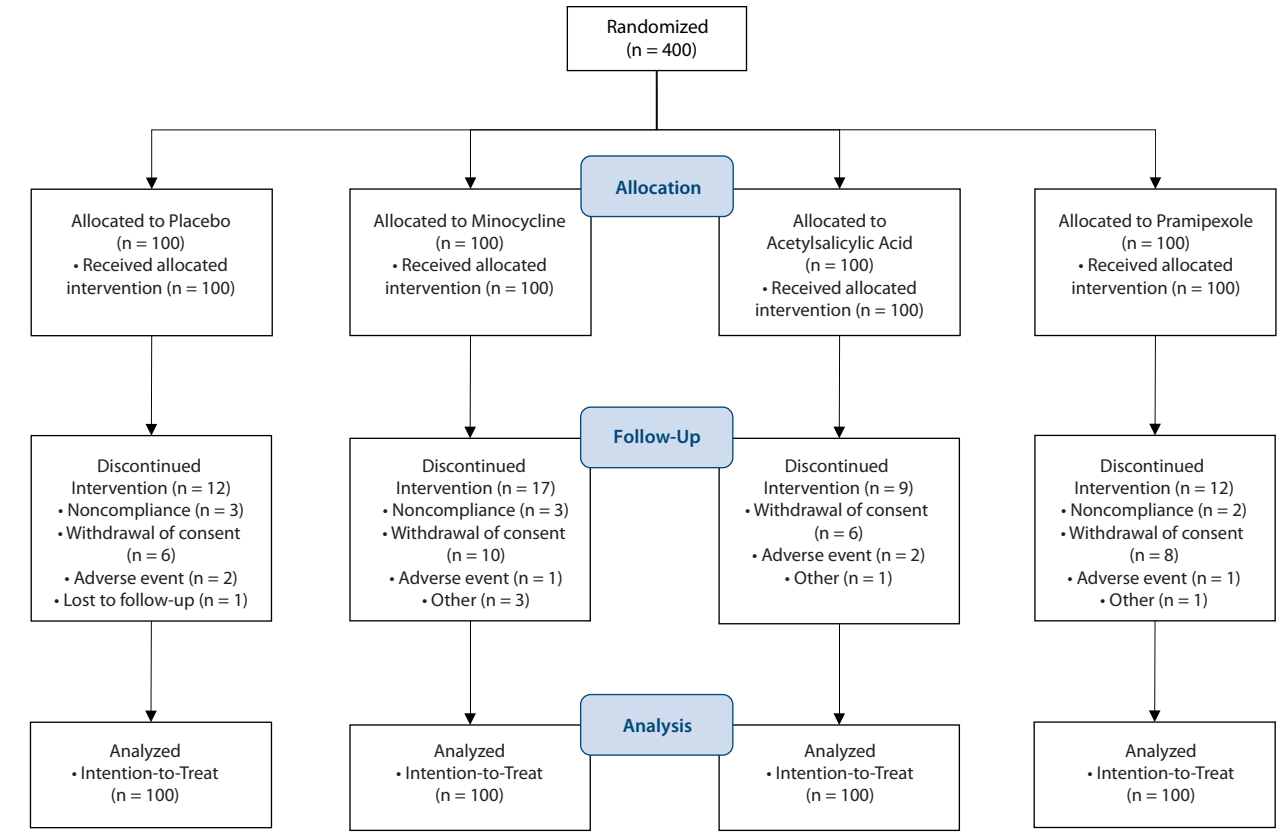
Raters were trained for Good Clinical Practice and board certified. All principal investigators had been involved in a number of previous international clinical trials. All raters who participated in the study had undergone PANSS training before the study. No formal PANSS training was done as part of the study, and interrater reliability was not assessed.

Study Procedures

The study received institutional review board approval from the regulatory authorities according to the local regulations. The study was registered on ClinicalTrials.gov (identifier: NCT01320982).

Psychopathologic symptoms were assessed using the PANSS,[10] the CGI-S,[11] the CGI-Improvement scale (CGI-I),[11] and the Brief Assessment of Cognition in Schizophrenia

Figure 1. CONSORT Diagram



(BACS).[12] Structured assessments of side effects caused by antipsychotics were performed using the Udvalg for Kliniske Undersogelser (UKU) side effect rating scale.[13] The Simpson-Angus Scale (SAS)[14] was used to assess extrapyramidal side effects.

Compliance was monitored through capsule and bottle counts as well through interviews. At each visit, patients returned the bottles and a pill count was performed. Patients were also asked whether they took the pills that they received since the previous visit. During the 16-week study, a minimum of 75% adherence was required for participants to be considered compliant to enter the efficacy analysis. Levels of medication in the blood were not measured. The primary outcome measure of the trial was total PANSS score, while the secondary outcome measures of the study were PANSS positive, negative, and general psychopathology scale scores; CGI-S, CGI-I, and BACS scores; and the rate of dropouts.

Sample Size and Power Calculation

Having 100 subjects in each of the 4 groups permitted power of >85% to detect a medium ($d=0.5$) or larger effect size response, corresponding to a mean 15% improvement from baseline within the active treatment group compared to placebo.

Statistical Analysis

Since this randomized controlled trial was designed as a 4-arm trial with 3 active treatments being compared to a single control group, all P values are adjusted for the 3 pairwise comparisons using the Šidák correction.

We estimated the effect of pramipexole versus placebo on each outcome at 16 weeks post-randomization using analysis of covariance (ANCOVA, with the respective baseline outcome as covariate). This was done in two different ways: using an intention-to-treat approach (last observation carried forward) and a completers-only approach using data from all subjects with observed data at 16 weeks. In addition, as a sensitivity analysis, we used mixed models for repeated measures to determine the effect of pramipexole (vs placebo) on the PANSS, CGI-S, and BACS outcomes. Models included visit-by-group interaction terms, were calculated using restricted maximum likelihood, and included random effects for visit. We also used mixed models to conduct exploratory heterogeneity (subgroup) analyses examining whether baseline PANSS, demographic factors and/or medications used during the study modified the effect of pramipexole versus placebo on PANSS score at week 16. Medications were analyzed according to use of risperidone, use of clozapine, and low versus high potency. When possible, subgroup categories were defined according to the median value. When a baseline variable modifies the effect of treatment relative to placebo, it suggests that this variable may be a moderator. If there were moderation, the confidence interval of the between-group difference in one subgroup would not overlap with the value of the difference in the other subgroup. Data analyses were conducted using Stata version 16. Statistical analysis code is available upon request.

Table 1. Baseline Demographic and Clinical Characteristics[a]

Characteristic	Pramipexole (n = 100)	Placebo (n = 100)
Demographic		
Age, mean (SD), y	43.5 (10.4)	43.5 (9.7)
Male	45 (45.0)	54 (54.0)
Marital status		
Never married	49 (49.0)	50 (50.0)
Presently married	22 (22.0)	18 (18.0)
Divorced/separated	26 (26.0)	26 (26.0)
Widowed	3 (3.0)	6 (6.0)
Formal education		
1–8 y	15 (15.0)	11 (11.0)
9–16 y	83 (83.0)	83 (83.0)
>16 years	2 (2.0)	6 (6.0)
Clinical		
Inpatient	15 (15.0)	14 (14.0)
Schizophrenia	91 (91.0)	90 (90.0)
Schizoaffective disorder	9 (9.0)	11 (11.0)
No. of hospitalizations, mean (SD)	15.6 (18.2)	15.6 (15.3)
Age at onset of psychiatric illness, mean (SD), y	27.6 (7.3)	26.3 (7.7)
PANSS score, mean (SD)		
Total	94.3 (15.1)	96.5 (16.0)
Positive	22.3 (5.0)	23.6 (4.7)
General	46.9 (8.5)	47.1 (9.5)
Negative	25.0 (5.7)	25.8 (6.2)
CGI-S score, mean (SD)	4.8 (0.7)	4.8 (0.8)
BACS composite Z-score, mean (SD)	−3.7 (1.9)	−3.6 (2.1)
Total antipsychotic medication use based on chlorpromazine equivalents		
<100 mg	11 (11.0)	3 (3.0)
100 to 299 mg	20 (20.0)	26 (26.0)
300 to 799 mg	52 (52.0)	56 (56.0)
≥800 mg	17 (17.0)	15 (15.0)

[a]Values are shown as n (%) unless otherwise noted.
Abbreviations: BACS = Brief Assessment of Cognition in Schizophrenia, CGI-S = Clinical Global Impressions–Severity of Illness scale, PANSS = Positive and Negative Syndrome Scale.

RESULTS

A total of 200 patients were randomized to the trial (see CONSORT diagram, Figure 1). The mean age of patients was 43.5 years, 49.5% were male, 15% were inpatients, mean total PANSS score at baseline was 95.4, and mean CGI-S score at baseline was 4.8 (Table 1).

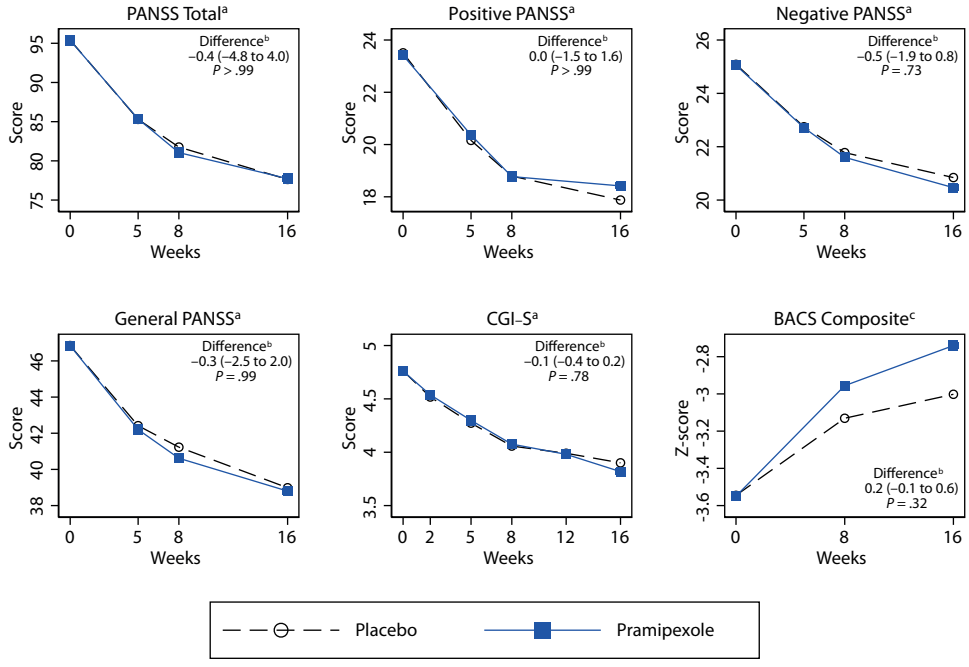
Between-group differences at week 8 and week 16 assessments on psychiatric and cognitive symptoms are shown in Table 2. The improvement with pramipexole was almost identical to that with placebo augmentation, with no consistent trend favoring either group. Adjusting for baseline antipsychotic use did not materially change the estimates for the effect of pramipexole versus placebo. ANCOVA models comparing pramipexole to placebo showed no significance for total PANSS scores ($P>.99$), nor for scores on the positive ($P>.99$), negative ($P=.73$), and general psychopathology ($P=.99$) scales (Figure 2). Comparisons for the CGI-S showed no trend for significance ($P=.78$) (Figure 2). These results were virtually identical to the results of the per-protocol and observed-cases analyses. (Supplementary Table 1). Comparisons of the BACS cognition scale showed no significant difference,

Table 2. Primary and Secondary Endpoints at Weeks 8 and 16

Variable	Week	Mean (SD) Score: Pramipexole (n = 90)	Mean (SD) Score: Placebo (n = 88)	Effect Size, Cohen *d*	Analysis of Covariance[a,b]: Difference (95% CI)	Analysis of Covariance[a,b]: *P* Value[c]	MMRM[b]: Difference (95% CI)	MMRM[b]: *P* Value[c]
PANSS								
Total	8	79.9 (18.7)	82.4 (19.2)	−0.16	−1.0 (−5.0 to 3.1)	.92	−1.1 (−5.1 to 3.0)	.89
Total	16	76.7 (18.1)	77.4 (18.9)	−0.12	−0.4 (−4.8 to 4.0)	> .99	−0.2 (−4.6 to 4.2)	> .99
Positive	8	17.5 (5.0)	18.8 (5.6)	−0.23	−0.4 (−1.8 to 1.0)	.87	−0.5 (−1.8 to 0.9)	.82
Positive	16	17.1 (4.9)	17.6 (5.4)	−0.13	0.0 (−1.5 to 1.6)	> .99	0.1 (−1.5 to 1.6)	> .99
Negative	8	21.6 (5.9)	22.3 (5.8)	−0.16	−0.3 (−1.5 to 0.9)	.88	−0.3 (−1.5 to 0.9)	.88
Negative	16	20.6 (5.5)	21.2 (5.8)	−0.18	−0.5 (−1.9 to 0.8)	.73	−0.5 (−1.8 to 0.9)	.81
General	8	40.8 (10.1)	41.3 (10.3)	−0.08	−0.6 (−2.7 to 1.5)	.86	−0.6 (−2.7 to 1.5)	.86
General	16	39.0 (9.8)	38.6 (10.2)	−0.04	−0.3 (−2.5 to 2.0)	.99	−0.1 (−2.4 to 2.2)	> .99
CGI–Severity of Illness	8	4.1 (0.9)	4.1 (0.9)	−0.08	−0.0 (−0.2 to 0.2)	> .99	0.0 (−0.2 to 0.2)	> .99
CGI–Severity of Illness	16	3.8 (0.9)	3.9 (1.0)	−0.16	−0.1 (−0.4 to 0.2)	.78	−0.1 (−0.4 to 0.2)	.85
CGI-Improvement	8	3.2 (0.8)	3.2 (0.9)	−0.01	−0.0 (−0.3 to 0.3)	> .99	−0.0 (−0.3 to 0.3)	> .99
CGI-Improvement	16	3.0 (0.9)	3.0 (0.8)	−0.10	−0.1 (−0.4 to 0.2)	.84	−0.1 (−0.4 to 0.2)	.85
BACS Composite *Z*-score	8	−3.0 (1.8)	−3.1 (2.0)	0.03	0.1 (−0.1 to 0.4)	.51	0.2 (−0.1 to 0.5)	.50
BACS Composite *Z*-score	16	−2.9 (1.8)	−3.0 (2.1)	0.07	0.2 (−0.1 to 0.6)	.32	0.3 (−0.1 to 0.6)	.31

[a]Based on the last observation carried forward.
[b]Analysis of covariance is the main analysis, and the mixed model for repeated measures (MMRM) is the sensitivity analysis. Differences are adjusted for the respective baseline value of each outcome. For PANSS and CGI, a negative difference indicates the pramipexole group had more improvement than the placebo group. For BACS, a positive difference indicates the pramipexole group had more improvement than the placebo group.
[c]All *P* values are Šidák-corrected to account for the 4-arm design (3 between-group comparisons).
Abbreviations: BACS = Brief Assessment of Cognition in Schizophrenia, CGI = Clinical Global Impressions scale, MMRM = mixed models for repeated measures, PANSS = Positive and Negative Syndrome Scale.

Figure 2. Outcomes Over Time According to Randomization Group (n = 200)



[a]Decreasing score equals increasing improvement.
[b]Estimated effect of pramipexole versus placebo at week 16 derived from ANCOVA models with carried forward observations. *P* values and 95% CIs (in parentheses) are Šidák-corrected.
[c]Increasing score equals increasing improvement.
Abbreviations: ANCOVA = analysis of covariance, BACS = Brief Assessment of Cognition in Schizophrenia, CGI-S = Clinical Global Impressions–Severity of Illness scale, PANSS = Positive and Negative Syndrome Scale.

with *P* = .32 for the BACS composite *Z*-score (Figure 2). The BACS subtests also showed no significant difference (Supplementary Figure 1). No significant difference was found between the two study groups on adverse events (Supplementary Table 2) or on concomitant psychiatric medications (Supplementary Table 3).

Analyses of the difference in PANSS scores between pramipexole and placebo at week 16 by population subgroup revealed no effect differences for males versus females, patients with more rather than fewer hospitalizations, baseline PANSS scores, marital status, low- versus high-potency antipsychotic medications, use of risperidone or

clozapine, and age (Supplementary Figure 2). Moreover, subgroup heterogeneity analyses including a median split for baseline PANSS negative subscale scores found that levels of negative symptoms at baseline had no relevance to the effect of pramipexole on PANSS scores at week 16. Stimulants increase dopaminergic activity, which is hypothesized to be the mechanism of their positive effect on the symptoms of attention-deficit/hyperactivity disorder (ADHD).[15] This hypothesis predicts that pramipexole might improve ADHD-like symptoms in schizophrenia. In a post hoc exploratory analysis, we examined a subgroup of patients who presented with the ADHD-like symptoms of poor impulse control and poor attention at baseline. Patients with these symptoms had a slight, non-significantly better response on negative symptoms and on total PANSS score at week 16 (Supplementary Figure 3).

Side Effects

Since pramipexole is a dopamine agonist, it could potentially reduce the extrapyramidal side effects of antipsychotic treatment. However, the Simpson-Angus scale revealed very few side effects reported in both groups, with no significant between-group differences noted (see Supplementary Table 4).

DISCUSSION

The results of our study contradict those of Kasper et al[5] and Kelleher et al,[6] as they show that pramipexole does not have a significant impact on the symptoms of schizophrenia. Our finding is consistent with an open study[16] in which pramipexole was found to decrease the parkinsonian side effects of antipsychotics, but failed to show benefit based on PANSS total score or subscale scores. Possible reasons for these differences include the larger sample size of our study and the open-label design in Kasper and colleagues' study. Additionally, both Kasper et al[5] and Kelleher et al[6] administered a higher dose, which might be the reason for the different results in comparison with this study. We were unable to identify a subgroup of patients more likely to respond to pramipexole. Our result did not find a significant improvement in cognition, similar to Burdick et al,[17] who administered pramipexole to euthymic patients with bipolar disorder.

Moreover, although the inclusion criteria did not include the classic Kane criteria for treatment resistance (see Howes et al[18]), given that, by definition, the patients in the study were on treatment with antipsychotics and had significant symptomatology, they might be considered treatment resistant. Treatment resistance is hypothesized to be caused by a non-hyperdopaminergic pathology,[19] which may explain why this prodopaminergic drug has little effect.

The use of prodopaminergic drugs in schizophrenia might cause worsening of positive symptoms.[7] Our findings showed no such worsening, suggesting that pramipexole, and possibly other prodopaminergic drugs, can be safely administered to patients with schizophrenia.

These negative results for pramipexole in schizophrenia are dissimilar to the data on pramipexole and depression, in which pramipexole has been found to be effective as an antidepressant in open-label studies,[20] in two randomized controlled trials (RCTs) on the depressed phase of bipolar disorder[21,22] and in two RCTs on major depression.[23,24] A meta-analysis of this literature[25] concludes that it is more effective than placebo. Also, the dose administered in this study, 1.5 mg/d, might not be high enough to improve negative symptoms. Additional studies on pramipexole for schizophrenia could attempt to administer higher doses, but doing so might cause more side effects, as occurred in one of the studies on pramipexole for major depression.[20]

Limitations

No external PANSS rating validation was used to assure that there was no inflation of scores. The use of external blinded PANSS rating validation via video review might have improved the validity of this measure. Moreover, patients recruited in this study were asked about, but not tested for, illicit substance use. As some of these illicit drugs are dopamine agonists,[26] this could have confounded the results. The participants in our studies were chronic patients who had been ill for many years with relatively high levels of symptoms. Therefore, this current study cannot relate to the possibility of administrating pramipexole to patients with less severe symptoms, during earlier stages of the illness, or at a higher dose.

CONCLUSIONS

The results of this randomized controlled trial indicated that pramipexole (0.75 mg twice daily) was not efficacious as an add-on to antipsychotic medications for this group of patients with chronic, treatment-resistant schizophrenia. Further studies could investigate the use of prodopaminergic drugs, such as pramipexole, in a younger, less treatment resistant population.

Submitted: August 31, 2021; accepted February 9, 2022.

Published online: August 1, 2022.

Relevant financial relationships: **Dr Davidson** is an employee and owns stock options of Minerva Neurosciences, a Biotech company developing central nervous system drugs. **Dr Weiser** has received advisory board/speaker's fees/consultant fees from and owns stock in Dexcel, Janssen, Lundbeck, Minerva, Pfizer, Acadia, Roche, MSD and Teva. All other authors have no conflict of interest to disclose.

Funding/support: This trial was funded by the Stanley Medical Research Institute.

Role of the sponsor: The supporters had no role in the design, analysis, interpretation, or publication of this study.

Acknowledgments: Tables and figures were produced by Mr Mark Horowitz, MS, University of Illinois Chicago (UIC), Chicago, Illinois. Mr Horowitz has no potential conflicts of interest relevant to the subject of this article.

Supplementary material: Available at Psychiatrist.com.

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Supplementary Material

Article Title: Add-on Pramipexole for the Treatment of Schizophrenia and Schizoaffective Disorder: A Randomized Controlled Trial

Author(s): Linda Levi, BSc; Daisy Zamora, PhD; Igor Nastas, MD; Ilan Gonen, MD; Paull Radu, MD; Valentin Matei, MD; Adela M. Ciobanu, MD; Anatol Nacu, MD; Larisa Boronin, MD; Lusian Karakrah, MD; Michael Davidson, MD; John M. Davis, MD; and Mark Weiser, MD

DOI Number: https://doi.org/10.4088/JCP.21m14233

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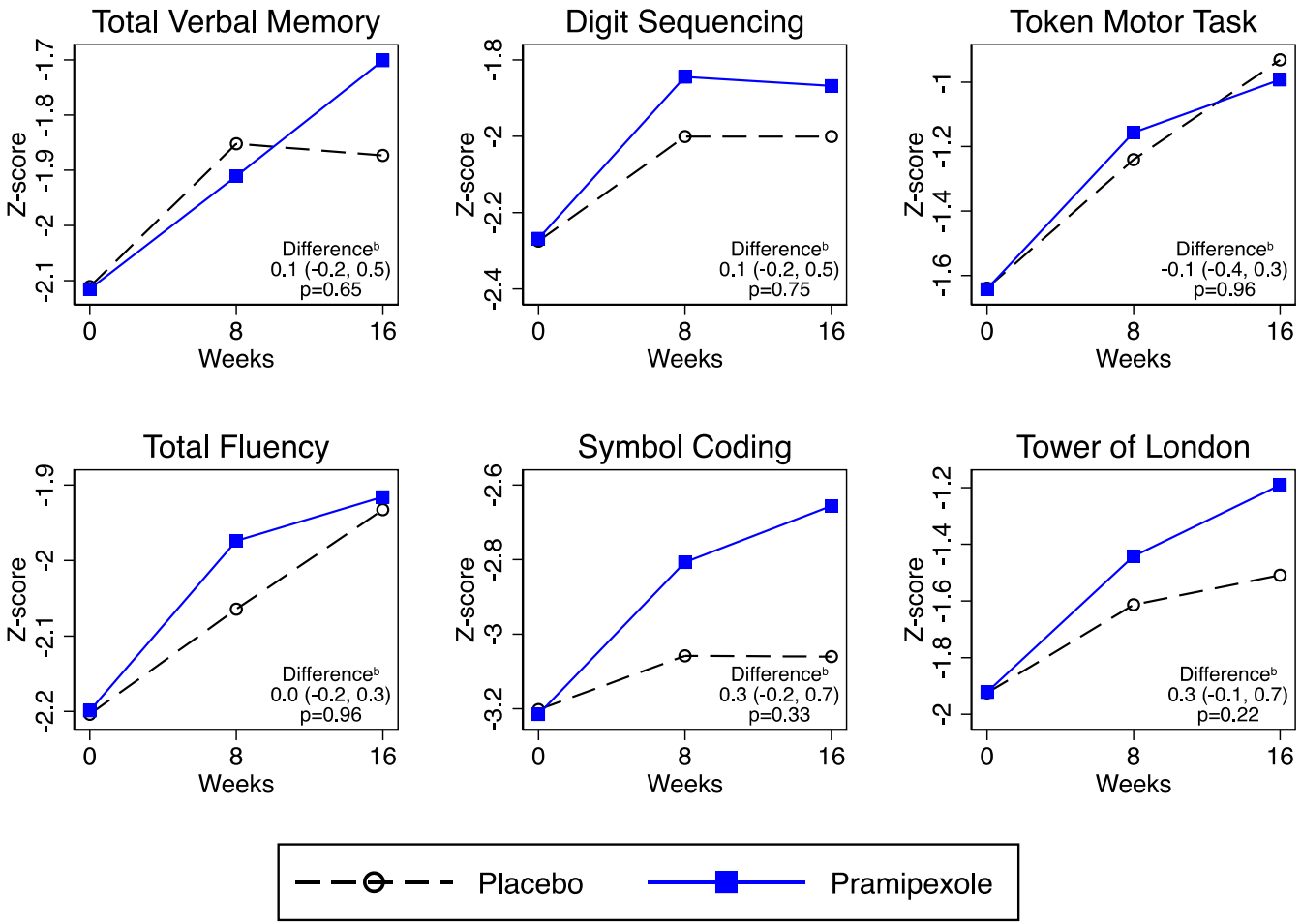
Supplementary Figure 1. BACS Subtests Over Time According to Randomization Group (n=200)[a]



[a] Increasing score equals increasing improvement in well-being.
[b] Estimated effect of pramipexole versus placebo at week 16 derived from ANCOVA models with carried forward observations. P-values and 95% confidence intervals (in parentheses) are Sidak-corrected.

Supplementary Table 1. Primary and Secondary Endpoints at Weeks 8 and 16 - Per Protocol Sample [a]

	Week	Mean (SD)		Effect Size,	Analysis of Covariance [b]		MMRM [b]	
		Pramipexole (n=90)	Placebo (n=87)	Cohen's d	Difference (95% CI)	p-value [c]	Difference (95% CI)	p-value [c]
Total PANSS	8	80.3 (18.7)	81.9 (19.2)	-0.08	-0.5 (-4.7, 3.7)	0.99	-0.5 (-4.7, 3.6)	0.99
Total PANSS	16	76.7 (18.1)	77.3 (18.9)	-0.04	0.3 (-4.2, 4.9)	>.99	0.2 (-4.3, 4.7)	>.99
Positive PANSS	8	17.6 (5.1)	18.6 (5.6)	-0.20	-0.3 (-1.7, 1.1)	0.93	-0.3 (-1.7, 1.1)	0.93
Positive PANSS	16	17.1 (4.9)	17.6 (5.4)	-0.09	0.2 (-1.4, 1.7)	0.99	0.2 (-1.3, 1.7)	>.99
Negative PANSS	8	21.8 (5.9)	22.3 (5.9)	-0.08	-0.1 (-1.4, 1.1)	>.99	-0.1 (-1.4, 1.1)	>.99
Negative PANSS	16	20.6 (5.5)	21.2 (5.9)	-0.11	-0.2 (-1.6, 1.1)	0.96	-0.3 (-1.7, 1.1)	0.93
General PANSS	8	40.9 (10.2)	40.9 (10.3)	-0.00	-0.4 (-2.6, 1.8)	0.97	-0.4 (-2.6, 1.8)	0.97
General PANSS	16	39.0 (9.8)	38.5 (10.2)	0.03	0.1 (-2.3, 2.4)	>.99	0.1 (-2.3, 2.4)	>.99
CGI Severity	8	4.1 (0.9)	4.1 (1.0)	-0.00	0.0 (-0.2, 0.3)	>.99	0.0 (-0.2, 0.3)	>.99
CGI Severity	16	3.8 (0.9)	3.9 (1.0)	-0.09	-0.1 (-0.4, 0.2)	0.89	-0.1 (-0.4, 0.2)	0.93
CGI Improvement	8	3.2 (0.8)	3.2 (0.8)	0.05	0.0 (-0.3, 0.3)	0.98	0.0 (-0.3, 0.3)	0.98
CGI Improvement	16	3.0 (0.9)	3.0 (0.8)	-0.08	-0.1 (-0.4, 0.2)	0.96	-0.1 (-0.4, 0.2)	0.94
BACS Composite Z-score	8	-3.1 (1.8)	-3.1 (2.0)	0.04	0.2 (-0.1, 0.5)	0.44	0.2 (-0.1, 0.5)	0.44
BACS Composite Z-score	16	-2.9 (1.8)	-3.0 (2.1)	0.08	0.3 (-0.1, 0.6)	0.33	0.3 (-0.1, 0.6)	0.30

[a] Analysis excludes subjects who consumed less than 75% of their assigned study medications based on pill counts.

[b] Analysis of covariance is the main analysis, and the mixed model for repeated measures (MMRM) is the sensitivity analysis. Differences are adjusted for the respective baseline value of each outcome. For PANSS and CGI, a negative difference indicates the pramipexole group had more improvement than the placebo group. For BACS, a positive difference indicates the pramipexole group had more improvement than the placebo group.

[c] All p-values are Sidak-corrected to account for the four-arm design (three between-group comparisons).

Abbreviations: CI = confidence interval; MMRM = mixed models for repeated measures; SD = standard deviation

Supplementary Table 2. Adverse Events Experienced at Least Once During the Study

Adverse Event	Pramipexole No. (%)	Placebo No. (%)	p-value [a]
Blood and lymphatic system disorders	2 (2)	0 (0)	.87
Cardiac disorders	3 (3)	1 (1)	.95
Gastrointestinal disorders	15 (15)	15 (15)	>.99
General disorders and administration site conditions	4 (4)	1 (1)	.75
Hepatobiliary disorders	2 (2)	1 (1)	>.99
Infections and infestations	14 (14)	9 (9)	.76
Injury, poisoning and procedural complications	0 (0)	1 (1)	>.99
Investigations	16 (16)	11 (11)	.79
Metabolism and nutrition disorders	0 (0)	1 (1)	>.99
Musculoskeletal and connective tissue disorders	3 (3)	3 (3)	>.99
Nervous system disorders	15 (15)	8 (8)	.45
Psychiatric disorders	8 (8)	3 (3)	.51
Renal and urinary disorders	1 (1)	1 (1)	>.99
Reproductive system and breast disorders	3 (3)	1 (1)	.95
Respiratory, thoracic and mediastinal disorders	6 (6)	5 (5)	>.99
Skin and subcutaneous tissue disorders	3 (3)	2 (2)	>.99
Vascular disorders	1 (1)	3 (3)	.95
Vision disorders	1 (1)	1 (1)	>.99
Any adverse event	53 (53)	44 (44)	.59

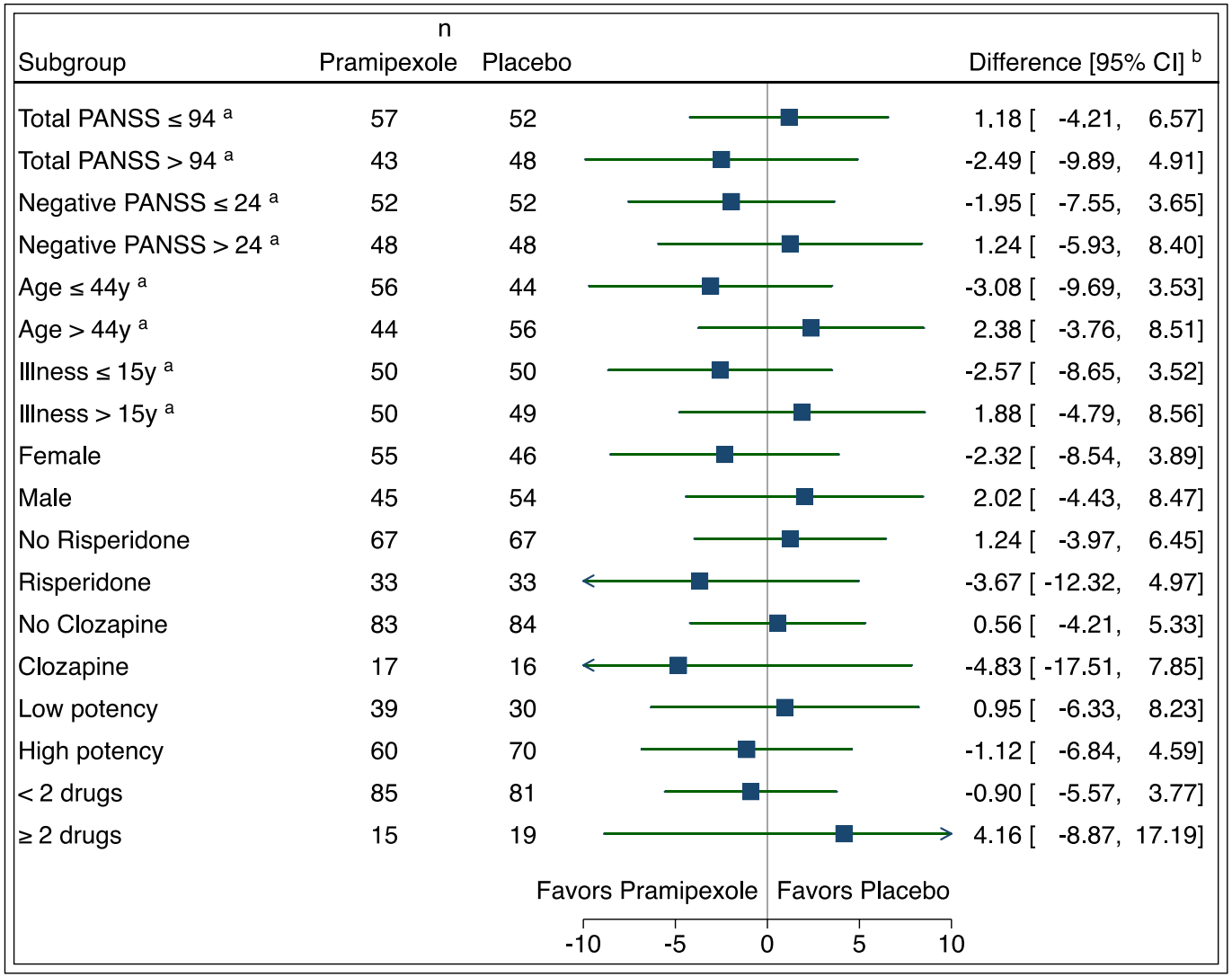
[a] Fisher's exact test (two-tailed). P-values are Sidak-adjusted to account for the three between-group comparisons.

Supplementary Table 3. Concomitant Psychiatric Medications Reported at Least Once During the Study

Drug	Pramipexole No. (%)	Placebo No. (%)	p-value [a]
Olanzapine	15 (15)	15 (15)	>.99
Risperidone (Consta, Risperidole)	33 (33)	33 (33)	>.99
Amisulpride	7 (7)	17 (17)	.14
Aripiprazole (Abilify)	10 (10)	5 (5)	.63
Quetiapine (Seiguexr, Seroquel)	13 (13)	8 (8)	.73
Sertindole	0 (0)	1 (1)	>.99
Flupenthixol	4 (4)	3 (3)	>.99
Ziprasidone	1 (1)	5 (5)	.51
Haloperidol	18 (18)	24 (24)	.77
Chlorpromazine Ceropromazine	15 (15)	16 (16)	>.99
Clopixol	1 (1)	0 (0)	>.99
Clozapine	16 (16)	15 (15)	>.99
Trifluoperazine	19 (19)	15 (15)	.92
Tiapridum	2 (2)	2 (2)	>.99
Thioridazine	1 (1)	0 (0)	>.99
Levomepromazine (use only when sole antipsychotic)	2 (2)	0 (0)	.87
Fluphenazine	4 (4)	4 (4)	>.99
>= 2 drugs	15 (15)	19 (19)	.92
>= 3 drugs	6 (6)	7 (7)	>.99

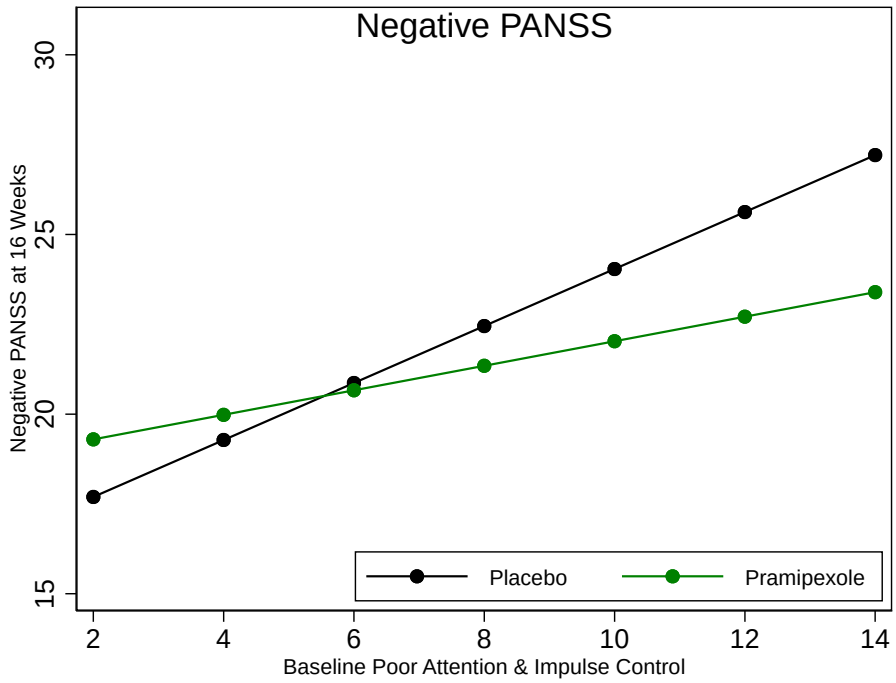
[a] Fisher's exact test (two-tailed). P-values are Sidak-adjusted to account for the three between-group comparisons.

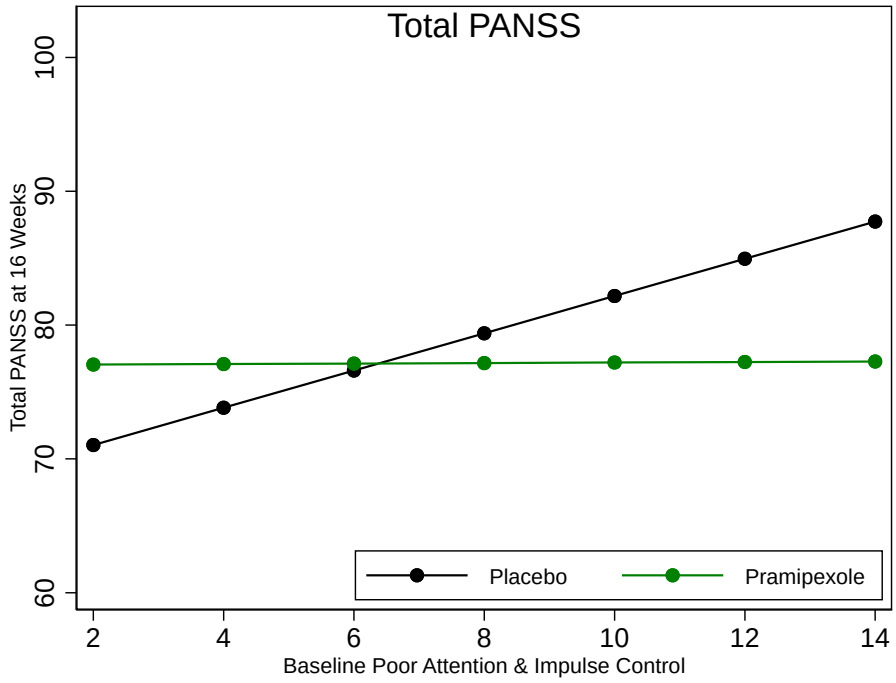
Supplementary Figure 2. Between-Group Differences in Total PANSS at Week 16 According to Baseline Characteristics



[a] Median at baseline.
[b] Differences derived from ANCOVA models using last observation carried forward. Confidence intervals are Sidak-corrected for multiple interventions.

Supplementary Figure 3. Effect of Group Assignment on Negative and Total PANSS According to Baseline Poor Attention & Impulse Control





Heterogeneity analysis exploring the hypothesis that participants with higher baseline scores for PANSS items "poor attention" and "poor impulse control" (G11 and G14, respectively) would experience more benefit from pramipexole at week 16. Predicted curves are based on the linear regression of treatment group on the respective endpoint, with the following covariates: baseline value of the respective endpoint, baseline sum of G11 and G14, and baseline sum of G11 and G14 interacted with treatment group. P-values for the likelihood ratio test for interaction: Negative PANSS, p=0.16; Total PANSS, p=0.21.

Supplementary Table 4. Total Simpson-Angus Scale at Each Visit [a]

	Pramipexole		Placebo		
	n	Median (IQR)	n	Median (IQR)	p-value [b]
Week 0	100	2 (0,6)	100	3 (0,7.5)	0.19
Week 8	91	2 (0,4)	91	2 (0,6)	0.93
Week 16	92	1.5 (0,4)	91	3 (0,5)	0.34

[a] Scale of 0 to 40.

[b] Wilcoxon rank-sum test.