THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

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

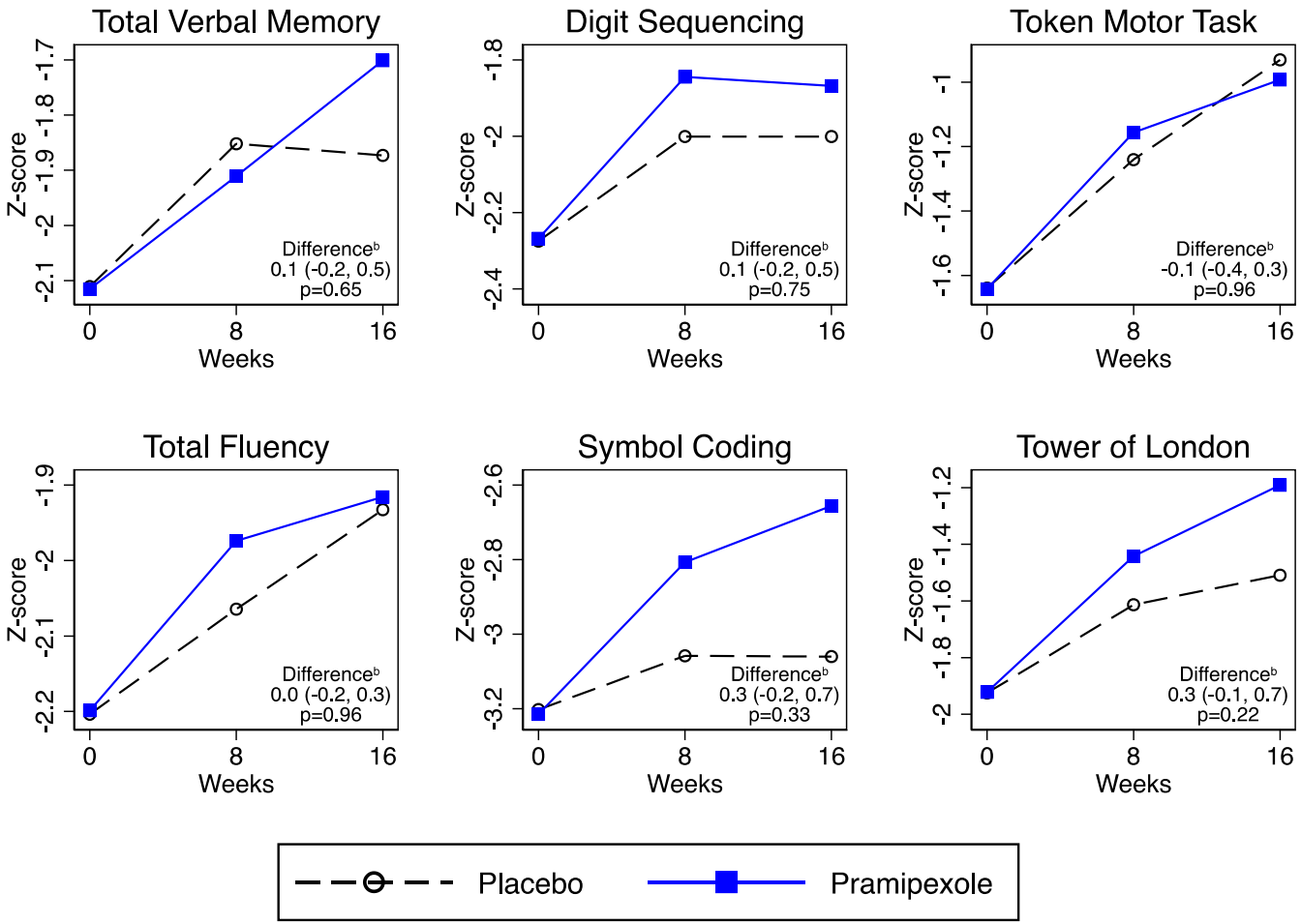
List of Supplementary Material for the article

1. Figure 1 — BACS Subsets Over Time According to Randomization Group (n=200)
2. Table 1 — Primary and Secondary Endpoints at Weeks 8 and 16 - Per Protocol Sample
3. Table 2 — Adverse Events Experienced at Least Once During the Study
4. Table 3 — Concomitant Psychiatric Medications Reported at Least Once During the Study
5. Figure 2 — Between-Group Differences in Total PANSS at Week 16 According to Baseline Characteristics
6. Figure 3 — Effect of Group Assignment on Negative and Total PANSS According to Baseline Poor Attention & Impulse Control
7. Table 4 — Total Simpson-Angus Scale at Each Visit

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

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

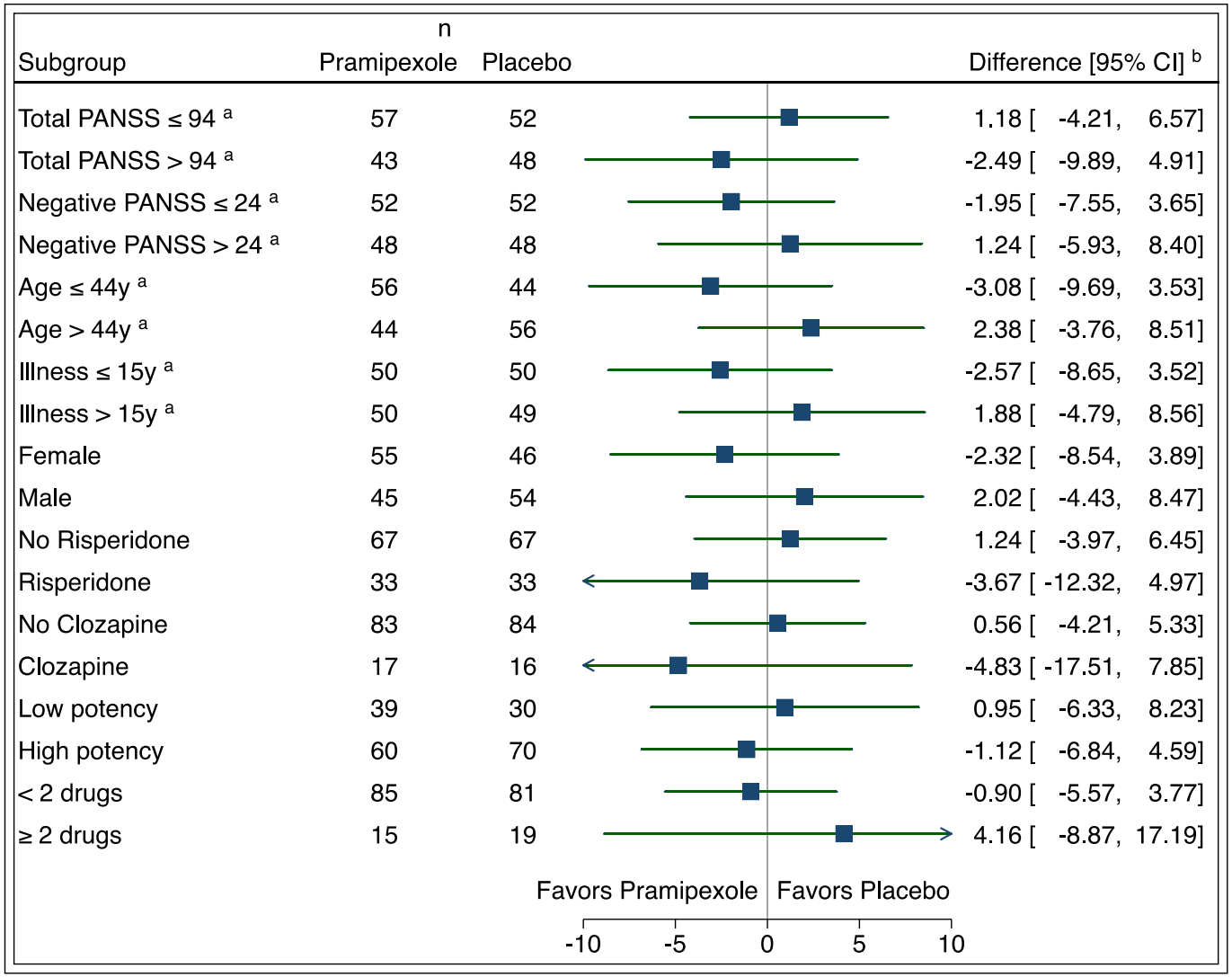
[a] Fisher's exact test (two-tailed). P-values are Sidak-adjusted to account for the three between-group comparisons.

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

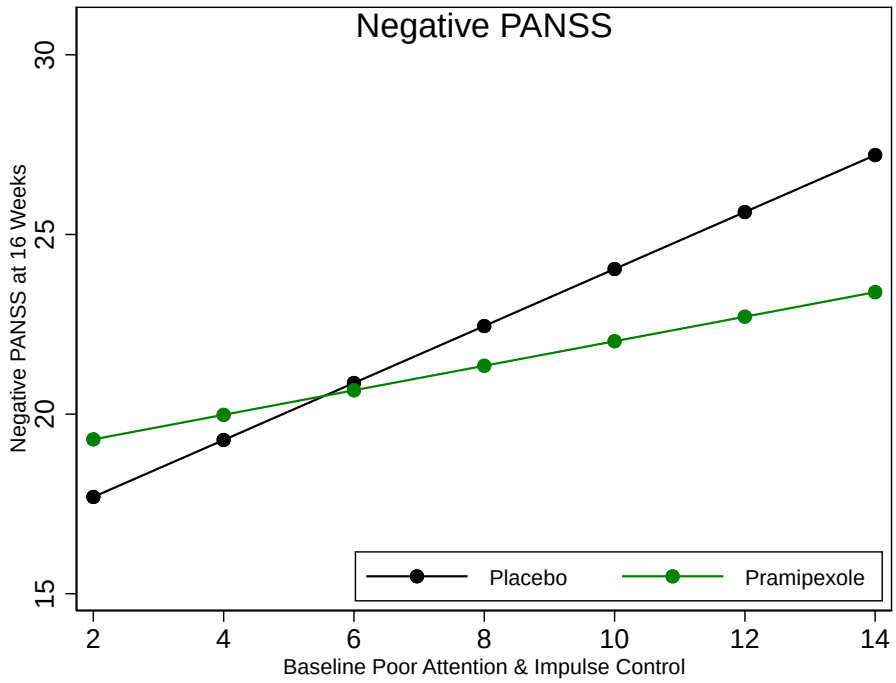
[a] Fisher's exact test (two-tailed). P-values are Sidak-adjusted to account for the three between-group comparisons.

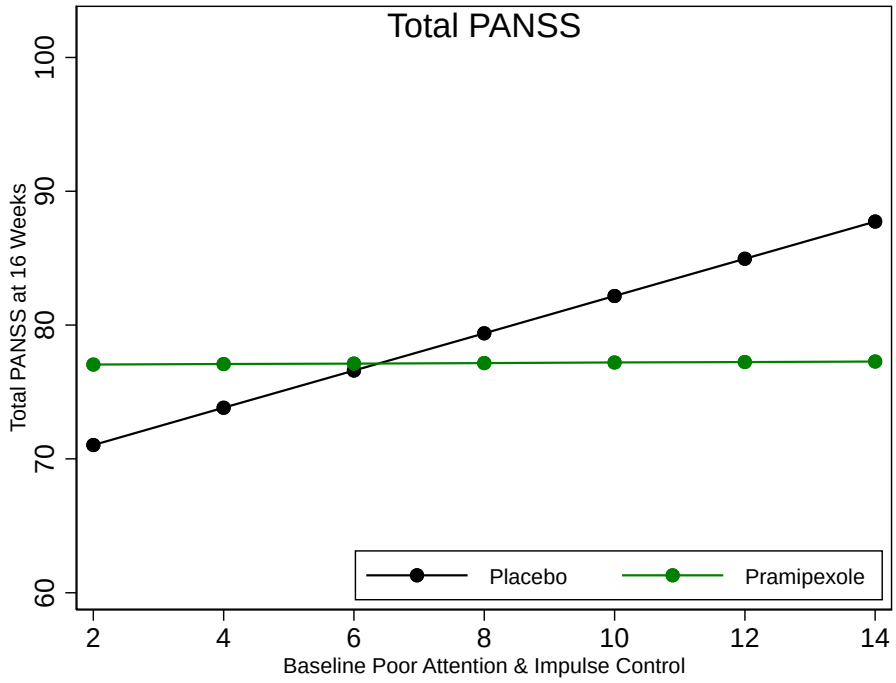
Supplementary Figure 2. Between-Group Differences in Total PANSS at Week 16 According to Baseline Characteristics



[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.