



Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Letter to the Editor

Personal and social adjustment effects of roluperidone in patients with schizophrenia and negative symptoms: Results from an exploratory outcome of a randomized placebo-controlled trial

Negative symptoms in schizophrenia are challenging to treat. While non-pharmacological interventions have shown limited benefits in some (Kane et al., 2016) but not in other studies (Polese et al., 2019) no pharmacological intervention has yet been proven efficacious in this regard. A prominent feature of negative symptoms is poor personal and social adjustment. We examined the effects of roluperidone on personal and social adjustment in patients with negative symptoms.

The trial enrolled 244 patients who had been symptomatically stable for at least 3 months and had scores of at least 20 on negative subscale of the Positive and Negative Syndrome Scale (PANSS). Patients were randomized to receive placebo or roluperidone 32 mg/day or 64 mg/day for 12 weeks. Study methods and primary (PANNS pentagonal negative factor) and secondary outcomes (PANSS total score, Clinical Global Impressions Scale, Brief Negative Symptom Scale, Brief Assessment of Cognition in Schizophrenia, and Calgary Depression Scale for Schizophrenia) have been previously reported (Davidson et al., 2017; Keefe et al., 2018). Here we present results of a protocol specified exploratory outcome, the effects versus placebo of roluperidone on social functioning measured using the PSP (Personal and Social Performance scale) (Morosini et al., 2000) assessed at baseline, and at weeks 4 and 12.

The PSP is rated on a 10-point Likert-type scale on four domains: (1) socially useful activities (e.g., work or study), (2) personal and social relationships, (3) self-care and (4) disturbing and aggressive behaviors during the last month. A final decile score is derived by differentially weighing domain scores (Morosini et al., 2000). A change of at least 10 points on the final score is considered clinically meaningful improvement (Lee et al., 2016; Patrick et al., 2009).

As per study protocol, change from baseline to week 12 was analyzed using a mixed model repeated measures with treatment arm, pooled study center (by country) visit, and treatment arm-by-visit interaction as fixed effects, patient nested in treatment as a random effect, and baseline value as a covariate using an unstructured covariance matrix. Kenward-Roger approximation (Kenward and Roger, 1997) was used to estimate denominator degrees of freedom. Analysis was performed based on all post baseline scores using all observed data without imputation of missing values.

A statistically significant difference on the PSP Final score was observed, with greater improvement for roluperidone 64 mg/day group as compared to placebo group ($p = .003$, effect size, $d = 0.59$) (Fig. 1). On the four domain scores, differences were found on Personal and Social Relationships ($p = .013$, $d = 0.48$), Self-Care ($p = .021$, $d = 0.46$), Socially Useful Activities ($p = .061$, $d = 0.35$) and on Disturbing and Aggressive Behaviors ($p = .006$, $d = 0.46$), a near statistically significant difference was also found on Disturbing and Aggressive

Behaviors when comparing 32 mg and placebo groups ($p = .054$, $d = 0.39$) (Supplementary Fig. 2). At week 4, some improvement from baseline was reported for 20% of the placebo group, 33.8% of the 32 mg group and 30.8% of the 64 mg group. At week 12, improvement was experienced by 29.3% of the placebo group, 34% of the 32 mg and 47.4% of 64 mg (Supplementary Table 1).

Because there was a significant treatment effect on both negative symptoms (as presented elsewhere (Davidson et al., 2017)) and PSP, we examined, in a post-hoc analysis, the extent to which change in PSP was independent of change in negative symptoms. First, we examined the Pearson correlation between change from baseline to endpoint on PSP and negative symptoms pentagonal structure factor model which yielded $r = -0.29$. The low correlation supports that improvements on the PSP were not synonymous with improvements in negative symptoms.

Second, we performed an ANCOVA to examine treatment effects (change from baseline to endpoint) before and after controlling for changes from baseline to endpoint on the PANSS negative pentagonal factor. We found that the superiority of 64 mg of active treatment versus placebo for the PSP Final Score was maintained. After controlling for change in PANNS negative pentagonal factor the effect size on the PSP final score declined by $d = 0.11$ and remained statistically significant ($p = .039$; $d = 0.32$). Given the partial overlap between areas of the two measures, which both cover aspects of social functioning (PANSS, Passive/apathetic social withdrawal, PSP Personal and social relationships) it is noteworthy that both measures show a significant treatment effect.

Our results suggest a possible benefit of roluperidone on personal and social adjustment in individuals with schizophrenia with stable positive symptoms and concurrent clinically significant negative symptoms. A limitation of this study was that the within range scoring adjustment of final score (e.g., for a rating 51–60, adjusting to 54) performed by rater was not captured. The literature suggests that within decile scoring adjustment contributes little additional granularity (Patrick et al., 2009). Future studies of roluperidone should further test its effects on personal and social adjustment.

Contributors

Author Rabinowitz drafted the paper and analyzed data. Authors Davidson, Saoud and Luthringer designed the study. Authors Badescu, Palamarchuk, Filyk, Voloshchuk, Rud, Skrypnikov and Melnyk made substantial contributions to the acquisition of data as site investigators. All authors offered critical comments that helped in meaningful and substantial ways to drafting and revising this work and approved of the final manuscript.

Role of the funding source

The study phase 2b clinical trial was funded by Minerva Neurosciences.

Declaration of Competing Interest

Authors Davidson, Luthringer and Saoud are employees and own stock options in Minerva Neurosciences. Dr. Rabinowitz is a consultant to Minerva Neurosciences. Authors Badescu, Palamarchuk, Filyk, Voloshchuk, Skrypnikov, Rud and Melnyk have no potential conflicts of interest to report.

Acknowledgment

This phase 2b clinical trial was funded by Minerva Neurosciences.

PSP: Final Decile Score (0-100)
Mean Improvement from baseline & 95% confidence interval

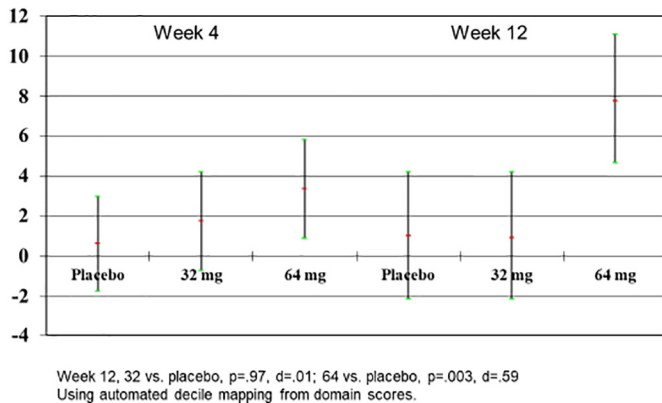


Fig. 1. Change on PSP final decile score.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2019.07.029>.

References

- Davidson, M., Saoud, J., Staner, C., Noel, N., Luthringer, E., Werner, S., Reilly, J., Schaffhauser, J.Y., Rabinowitz, J., Weiser, M., Luthringer, R., 2017. Efficacy and safety of MIN-101: a 12-week randomized, double-blind, placebo-controlled trial of a new drug in development for the treatment of negative symptoms in schizophrenia. *Am. J. Psychiatry* 174 (12), 1195–1202 ([appiajp201717010122](https://doi.org/10.1093/ajp/kax112)).
- Kane, J.M., Robinson, D.G., Schooler, N.R., Mueser, K.T., Penn, D.L., Rosenheck, R.A., Addington, J., Brunette, M.F., Correll, C.U., Estroff, S.E., Marcy, P., Robinson, J., Meyer-Kalos, P.S., Gottlieb, J.D., Glynn, S.M., Lynde, D.W., Pipes, R., Kurian, B.T., Miller, A.L., Azrin, S.T., Goldstein, A.B., Severe, J.B., Lin, H., Sint, K.J., John, M., Heinssen, R.K., 2016. Comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE early treatment program. *Am. J. Psychiatry* 173 (4), 362–372.
- Keefe, R.S.E., Harvey, P.D., Khan, A., Saoud, J.B., Staner, C., Davidson, M., Luthringer, R., 2018. Cognitive effects of MIN-101 in patients with schizophrenia and negative symptoms: results from a randomized controlled trial. *J Clin Psychiatry* 79 (3).
- Kenward, M.G., Roger, J.H., 1997. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics* 53 (3), 983–997.
- Lee, S.C., Tang, S.F., Lu, W.S., Huang, S.L., Deng, N.Y., Lue, W.C., Hsieh, C.L., 2016. Minimal detectable change of the Personal and Social Performance scale in individuals with schizophrenia. *Psychiatry Res.* 246, 725–729.
- Morosini, P.L., Magliano, L., Brambilla, L., Ugolini, S., Pioli, R., 2000. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr. Scand.* 101 (4), 323–329.
- Patrick, D.L., Burns, T., Morosini, P., Rothman, M., Gagnon, D.D., Wild, D., Adriaenssen, I., 2009. Reliability, validity and ability to detect change of the clinician-rated Personal and Social Performance scale in patients with acute symptoms of schizophrenia. *Curr. Med. Res. Opin.* 25 (2), 325–338.
- Polese, D., Fornaro, M., Palermo, M., De Luca, V., de Bartolomeis, A., 2019. Treatment-resistant to antipsychotics: a resistance to everything? Psychotherapy in treatment-resistant schizophrenia and nonaffective psychosis: a 25-year systematic review and exploratory meta-analysis. *Front Psychiatry* 10, 210.

Jonathan Rabinowitz
Bar Ilan University, Ramat Gan, Israel
Corresponding author.
E-mail address: jr827@columbia.edu.

Stefan Badescu
Neuropsychiatric Hospital Craiova, Romania

Pavel Palamarchuk
Kherson Regional Psychiatric Hospital, Ukraine

Viktor Filyk
Kharkiv Railway Clinical Hospital #1, Ukraine

Anatolii Voloshchuk
Odesa Regional Medical Centre of Mental Health, Ukraine

Vadym Rud
Poltava Regional Clinical Psychiatry Hospital, Ukraine

Ellina Melnyk
Ukrainian Medical Stomatological Academy, Dept. of Psychiatry, Ukraine

Andrii Skrypnykov
Michael Davidson
Jay Saoud
Minerva Neurosciences, 1601 Trapelo Road, Suite 286, Waltham, MA 02451, USA

4 June 2019
Available online xxxx