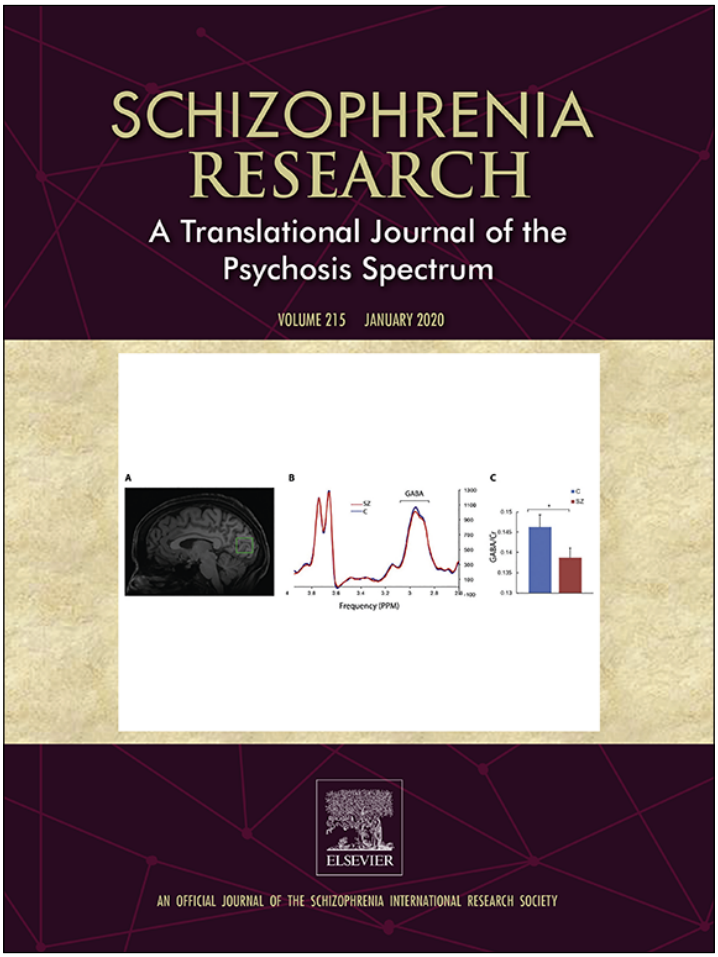

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Effects of Roluperidone (MIN-101) on two dimensions of the negative symptoms factor score: Reduced emotional experience and reduced emotional expression☆,☆☆

Philip D. Harvey [a,*], Jay B. Saoud [b], Remy Luthringer [b], Svetlana Moroz [c], Yuliya Blazhevych [d], Cristinel Stefanescu [e], Michael Davidson [b]

[a] University of Miami Miller School of Medicine, Miami, FL, USA
[b] Minerva Neurosciences, Inc., Waltham, MA, USA
[c] Dnipropetrovsk Regional Clinical hospital, Dnipro 49005, Ukraine
[d] Kyiv Regional Medical Incorporation "Psychiatria", Center, Ukraine
[e] Socola Psychiatric Hospital, Lasi, Romania

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ABSTRACT

Background: Recent research has suggested that negative symptoms (NS) can be considered in terms of two different dimensions: reduced expression (expressive deficit) and reduced experience (experiential deficit). Roluperidone, a compound with high affinities for 5 HT2A and sigma2 receptors, has previously shown superiority over placebo on improving NS in a prospective study in patients with schizophrenia. The objective here is to explore the effect of roluperidone compared to placebo, on the 2 domains of the Negative Symptoms.
Methods: This was a multi-national Phase 2b trial that enrolled 244 symptomatically stable patients with schizophrenia who had baseline scores ≥20 on the NS subscale of the PANSS. Patients were randomized to daily monotherapy with roluperidone 32 mg, roluperidone 64 mg, or placebo in a 1:1:1 ratio. All enrolled patients were Caucasian, and 137 (56%) were male. The 3 treatment groups were balanced on all demographic and illness-related baseline characteristics.
Results: Both doses of roluperidone were superior to placebo on both domains: Reduced Experience ($p \le .006$ for the 32 mg; $p \le .001$ for the 64 mg) with persistent superiority from Week 2 for the 64 mg dose and Week 8 for the 32 mg dose; Reduced Expression ($p \le .003$ for 32 mg; $p \le .001$ for 64 mg) with similar persistence.
Implications: Both doses of roluperidone previously improved PANSS negative symptoms in general and demonstrated tolerability in stable schizophrenia patients. The post hoc analysis reported here found the drug to work on both the reduced emotional experience and reduced emotional expression sub-scales empirically derived from the PANSS.

1. Introduction

The phenomena referred to as negative symptoms reflect several deficient aspects of normative human emotions and behaviors. Although negative symptoms are mostly associated with schizophrenia different aspects of negative symptoms manifest in many DSM/ICD diagnostic categories (Strauss et al., 2013). The overwhelming majority of patients who meet diagnostic criteria for schizophrenia suffer to some extent from negative symptoms (Bobes et al., 2010; Rabinowitz et al., 2013;), which for many, persist on a life-long basis (Millan et al., 2014). The presence and severity of negative symptoms determine to a large extent the degree of social and vocational dysfunction in these patients (Kirkpatrick et al., 2006). Behaviors and emotions grouped under the umbrella of negative symptoms has already been described by Hippocrates and elaborated by Kraepelin and Bleuler (for a history review of negative symptoms see Malaspina et al., 2014). Yet, researchers still debate how to dissect and subdivide these behaviors and emotional experiences in a way that is useful to understand the impact of negative symptoms on patient's everyday life its biological underpinning and hopefully, to devise effective and specific remedies.

Toward this end researchers have factor analyzed large data bases of assessment of patients with schizophrenia mostly, but not exclusively, collected in the course of drug trials. Since the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) has been the most commonly

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* Corresponding author at: University of Miami Miller School of Medicine, 1120 NW 14th Street, Suite 1450, Miami, FL 33136, USA.
E-mail address: philipdharvey1@cs.com (P.D. Harvey).

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used in trials, the majority of analysis was conducted on the PANSS items and scores. The original conceptualization of the PANSS subgrouped the symptoms (items) into positive, negative and general subtypes but several follow-up analysis appear to fit the manifestation of the illness better than the original subgrouping and the negative symptoms factor scale (NSFS) has been most often employed in treatment trials (e.g., Marder and Meibach, 1994; White et al., 1997).

A large-scale factor analysis performed on the NSFS from the PANSS found that best fitting solution in a sample of 7271 subjects with schizophrenia was a two-factor model reflected as reduced emotional experience and reduced expression (Khan et al., 2017). Reduced emotional experience includes emotional withdrawal (N2), passive apathetic social withdrawal (N4), and active social avoidance (G 16) and is also commonly referred to as avolition-anhedonia. Reduced emotional expression includes blunted affect (N1), poor rapport (N3), lack of spontaneity (N6), and motor retardation (G7), often referred to as affective blunting and alogia. A follow up analysis in a sample of 821 patients with schizophrenia reported that reduced emotional experience, but not reduced expression, accounted for 21% of the variance in everyday social functioning and the total PANSS negative symptom factor accounted for 19% of the variance in social outcomes (Harvey et al., 2017). The PANSS expression factor accounted for at most 1% of the variance in any of the functional outcomes, with or without the addition of other predictors.

Most recently, Strassnig et al. (2018) reported that everyday social functioning deficits were predicted by the severity of symptoms of reduced emotional expression, but not reduced emotional expression, in patients with moderate or more severe symptoms as well as in patients with lower levels of severity. This finding was replicated in a completely separate sample of 212 people with schizophrenia (Harvey et al., 2019). This suggests that even low levels of negative symptoms, commonly seen in other schizophrenia spectrum cases such as schizotypal personality disorder (SPD) or attenuated psychosis syndrome (APS), can also have relevance for impairments in social functioning.

This report is a reanalysis of data derived from a phase 2b clinical trial that was previously published (Davidson et al., 2017) with a different conception of negative symptoms as the outcome measure. We now examine whether the reduced emotional experience and reduced emotion expression factors derived with factor analysis using the Khan et al. method are also beneficially impacted by a novel compound targeting negative symptoms in patients with schizophrenia The compound tested in the trial is roluperidone, a $5HT_{2A}$, $Sigma_2$ receptor antagonist without affinities for Dopamine (DA) receptors. Roluperidone (also known as MIN-101) is a novel cyclic amide derivative that has high equipotent affinities for sigma-2 and 5-hydroxytryptamine$_{2A}$ (Serotonin 2A) receptors (inhibitory constants [Ki] of 7.53 nmol/L and 8.19 nmol/L for 5-HT2A and sigma-2, respectively). Roluperidone also shows binding affinity for alpha1-adrenergic receptors but low or no affinity for dopaminergic, muscarinic, cholinergic, and histaminergic receptors (data on file). Although roluperione has no affinities for pre- or postsynaptic dopaminergic receptors, it is probable that sigma-2 receptors are implicated in the modulation of dopamine (Katz et al., 2011; Lever et al., 2014) and glutamatergic pathways (Skuza, 2012), as well as in calcium neuronal modulation (Vilner and Bowen, 2000).

2. Methods

This trial enrolled 244 patients 18–60 years of age, in 36 sites and 6 European countries between May 2015 and December 2015. Patients were symptomatically stable at baseline, patients had to have at least moderately severe negative symptoms expressed as score ≥ 20 on the "classic" 7 item negative symptoms scale of the PANSS (N1-N7) and scores <4 on the following PANSS items: excitement, hyperactivity, hostility, suspiciousness, uncooperativeness, and poor impulse control in order to reduce potential drop-out. Eligible patients were withdrawn from oral antipsychotic medication 2 days and 4 weeks from depot medication prior to randomization. Patients were randomized to roluperidone 32 mg/day, 64 mg/day or, placebo for 12 weeks. No psychotropic medications were allowed during the 12-week trial duration except for rescue medications given for insomnia or agitation in doses allowed by the local regulations (oral lorazepam, zolpidem, or injectable sodium amytal). Assessments for efficacy using the PANSS scale were conducted at baseline before the first dose of medication and at weeks 2, 4, 8 and 12 or upon premature termination (for a detailed description of methods see Davidson et al., 2017). The patient population in these analyses overlaps completely with the previous publication, so demographic information can be found in the previous paper.

2.1. Negative symptoms assessment

Severity of negative symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), which was administered in its entirety by trained raters. These ratings were performed for the entire PANSS and the subsequent subdivisions of the data occurred after the ratings were collected.

2.1.1. Negative symptom models

Based on the previous report of Khan et al. (2017) a 2-factor model of expression and experience was developed and replicated in multiple samples, as well as being tested for relationships to functional outcomes (Harvey et al., 2017; Strassnig et al., 2018). The items in each of the factors were:

2.1.2. PANSS reduced emotional expression

PANSS Blunted Affect (N1), Poor Rapport (N3), Lack of Spontaneity (N6), and Motor Retardation (G7),

2.1.3. PANSS reduced emotional experience

Emotional Withdrawal (N2), Passive Social Withdrawal (N4) and active social avoidance (G16).

We also present results for the negative symptoms factor from the PANSS Pentagonal model (White et al., 1997), which was the previous outcome variable.

2.2. Sample size and statistical analysis

The study was powered at 90% with a 2-sided significance level of 0.05. Based on the results of the previous study a robust treatment effect was assumed of an effect size of 0.60 (3 points with standard deviation of 5) in the mean change from baseline to week 12 in PANSS five factors (pentagonal structure model) negative factor score between either dose of MIN-101 and placebo. Intent-to-treat (ITT) and per-protocol (PP) analyses were performed.

The endpoint analyses, change from baseline to week 12 in PANSS the two negative symptoms factor subscales, reduced emotional experience and reduced emotional expression, was performed using MMRM with treatment arm, pooled study center visit (by country), and treatment arm by visit interaction as fixed effects, patient nested in treatment as random effect, and baseline value as covariate. An unstructured covariance matrix was used to model the covariance of within-patient scores. The Kenward-Roger approximation (Kenward et al., 2003) was used to estimate denominator degrees of freedom. This analysis was performed based on all post-baseline scores using all observed data without imputation of missing values.

Pairwise comparison between high and low doses of roluperidone, versus placebo was performed. In order to maintain the Type 1 error rate due to multiple comparisons for the primary endpoint at or below 0.05%, the Hochberg procedure was used. This procedure allows testing the null hypothesis of no treatment difference for both the 64 and 32 mg doses versus placebo to be rejected if largest p-value comparing either of these 2 doses versus placebo is at or below 0.05. Otherwise, the

lower of these 2 *p*-values must be at or below 0.025 to allow for rejecting the null hypothesis for the representative dose.

3. Results

All enrolled patients ($N = 244$) were Caucasian, and 137 (56%) were male. Median age was 41 years and range from 18 to 60. The 3 treatment groups were balanced on all demographic and illness-related baseline characteristics. Completion rates for randomized patients in this 12-week study were as follows: roluperidone 62 mg = 69%, roluperidone 32 mg = 69% and placebo = 65%.

3.1. Efficacy

As the analyses of the overall PANSS negative symptom factor score were previously published, we present those results in Supplemental Fig. 1. The effect size for the total score for MIN-101 32 mg and 64 mg compared to placebo was (ES = 0.45, $p \leq .024$, and ES = 0.57, ≤ 0.004, respectively) The results for the two negative symptoms subscales scores examined in this study are presented in Fig. 1.

There was a statistically significant reduction in both of the negative symptoms domains scores: Reduced emotional experience and reduced emotional expression. For reduced emotional experience, there was a statistically significant overall effect of time, from baseline to week 12, $F(3,181) = 11.48$, $p < .001$, and treatment, $F(2,206) = 8.81$, $p < .001$. Placebo treated patients improved from baseline to endpoint, $t = 3.90$, $p < .001$, as did patients treated with both doses of active treatment. Changes from baseline to end point compared to placebo were significant for both doses of active treatment, 64 mg.: $t = 3.56$, $p = .0005$, and 32 mg. t:2.84, $p = .005$. (Fig. 1). Changes from baseline compared to placebo for 64 mg were also significant at weeks 2, $t = 2.56$, $p < .001$, 4, $t = 3.71$, $p < .0001$, and 8, $t = 3.07$, $p = .002$ as well. Changes from baseline compared to placebo at week 8 were also significant for 32 mg., $t = 2.25$, $p < .03$, but not for the two earlier assessments, $t < 1.74$, $p > .08$. Effects of country were not significant, $F(7,221) = 0.32$, $p = .95$.

For reduced emotional expression, there was a statistically significant overall effect of time, from baseline to week 12, $F(3,181) = 25.63$, $p < .001$, and treatment, $F(2,206) = 2.18$, $p < .05$. Placebo treated patients improved from baseline, $t = 3.89$, $p < .001$, as did patients

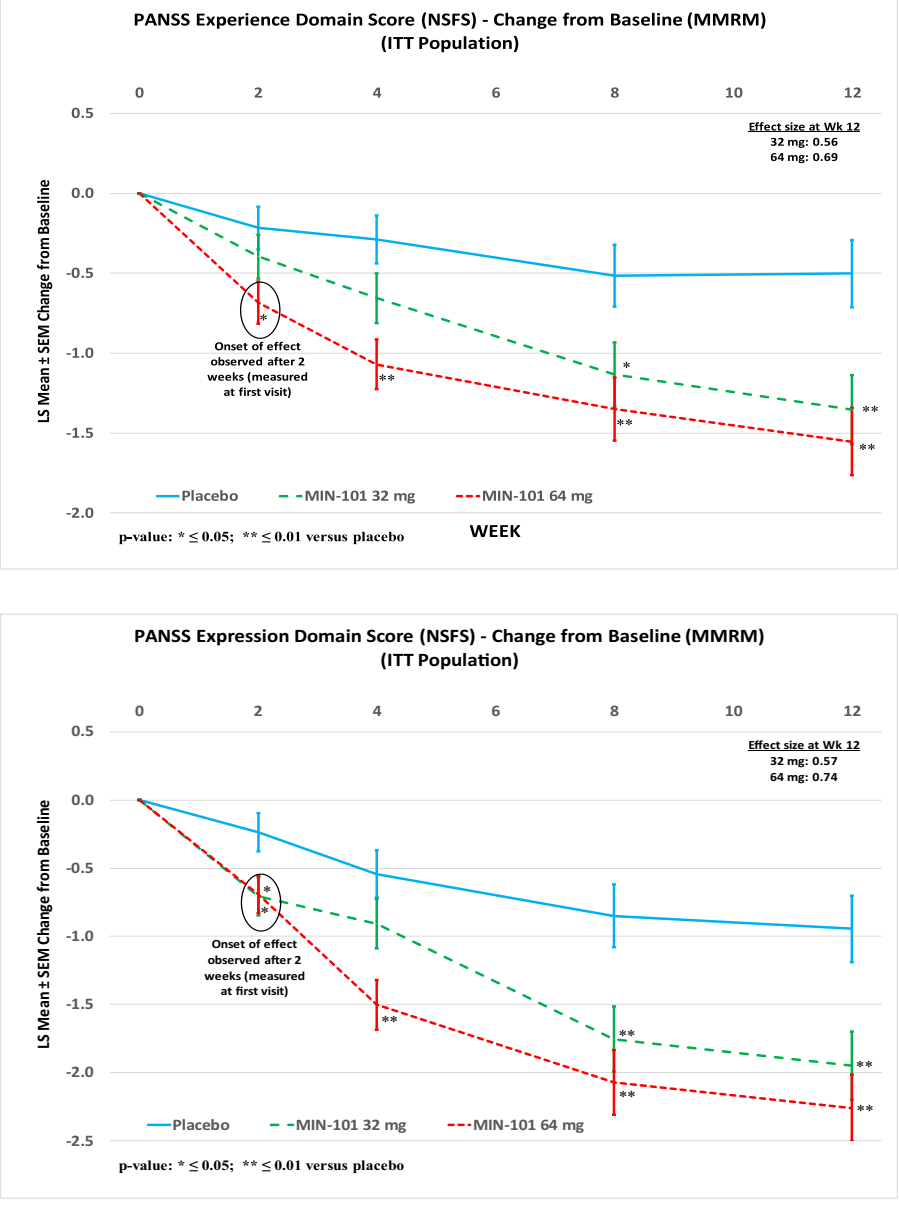

Fig. 1. Treatment response of the PANSS Reduced Emotional Experience and Reduced Emotional Expression Factors.

treated with both doses of the active treatment. Changes from baseline to end point compared to placebo were significant for both doses of active treatment, 64 mg.: $t = 3.85$, $p = .0005$, and 32 mg. t:2.91, $p = .005$. (Fig. 1). Changes from baseline compared to placebo for 64 mg were significant at weeks 2, $t = 2.40$, $p < .02$, 4, $t = 3.87$, $p < .0001$, and 8, $t = 3.75$, $p < .001$ as well. Change from baseline to compared to placebo at week 8, $t = 2.76$, $p = .006$, and at week 2; $t = 2.44$, $p < .01$ was also significant for 32 mg, but not for the week 4 assessment $t < 1.47$, $p = .11$. Effects of country were not significant, $F(7,221) = 0.32$, $p = .95$.

3.2. Covariance of outcomes

In order to examine the extent to which treatment changes on the two domains manifested covariance, we repeated the MMRM analyses for reduced expression and reduced experience, using the other variable as a dynamic co-variate. For both analyses, the results were similar, in that both variables were found to have significant covariate effects. For reduced emotional experience, the time effect was still significant, $F(1,227) = 44.82$, $p < .001$, and the effect of reduced emotional expression as a covariate was also significant, $F(1,702) = 143.79$, $p < .001$. For reduced emotional experience, the time effect was still significant, $F(1,221) = 23.49$, $p < .001$, and the effect of reduced emotional expression as a covariate was also significant $F(1,724) = 143.35$, $p < .001$.

4. Discussion

Two previously identified domains of negative symptoms in schizophrenia, reduced emotional experience and reduced emotional expression, both improved significantly with treatment with roluperidone, compared to placebo treatment. These improvements were similar for the two domains and the changes manifested significant covariance. The higher dose was associated with improvements in these domains by the first assessment and the lower dose separated from placebo later in the treatment period.

If replicated in an ongoing phase 3 trial, these findings could have considerable potential for functional impact in schizophrenia. Avolition-anhedonia has long been known to be a predictor of impaired social outcomes (Strauss et al., 2013) and the current conception, based on items from the PANSS, has been shown to specifically predict social outcomes in people with schizophrenia (Harvey et al., 2017, 2019; Strassnig et al., 2018). Other results from the current trial are consistent with these findings as well. Kirkpatrick et al. (2018) reported that total scores as well as both reduced emotional experience and reduced expression scales on the Brief Negative Symptom Scale (BNSS) were reduced by treatment with roluperidone (Reduced experience ES = 0.48, Reduced expression ES = 0.46). Thus, findings of a two-factor as well as global improvement are replicated across different rating methods.

Importantly, negative symptoms early in the course of schizophrenia tend to be broadly predictive of later outcomes (Ventura et al., 2015), with negative symptom severity at the time of a first psychotic episode predicting multiple domains of everyday functioning 8 years later. Thus, early treatment of negative symptoms may have the potential to lead to wide ranging benefits, much like cognitive training and rehabilitation efforts early in the course of psychosis have greater impacts than later on.

Research on sigma receptors proposed potential new binding sites, such as the progesterone receptor membrane component 1 (PGRMC1), but these data are still under debate (Hayashi and Su, 2005). Additional papers have proposed the transmembrane protein 97 (TMEM97) to be the binding site of sigma-2 (Alon et al., 2017). TMEM97 is an endoplasmic reticulum-resident transmembrane protein. Recent data show that roluperidone is able to increase the release of brain-derived neurotrophic factor (BDNF) and its transcription in cultured brain hippocampal neurons and astrocytes which might indicate that the drug is able to act on neuroplasticity or neuroprotection. Taken together, the data suggest that it could be hypothesized that roluperidone is involved in counteracting dysregulations in key dopamine and glutamate neurotransmitter pathways and neuroplasticity.

There are some limitations in this study. As with all phase 2 clinical trials, the population is not representative of schizophrenia in general and all patients were Caucasian. There are other strategies to assess negative symptoms other than the PANSS and the number of items in each of the two scales are limited. This concerns is slightly obviated by the fact that this model was developed independently from this study, in a very large sample, and has been replicated for its association with social outcomes in two separate large ($N > 200$) and nonoverlapping samples.

Roluperidone appears to impact both reduced emotional experience and reduced emotional expression in people with schizophrenia. Any effective treatment for negative symptoms could be beneficial for people with schizophrenia across the lifespan, as negative symptoms are present at the time of the first episode and into very late life. Further, negative symptoms and associated social functioning deficits are clearly present in individuals who are in the schizophrenia spectrum without psychotic symptoms, including people with schizotypal personality disorder and attenuated psychosis syndrome.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.08.029.

Contributions of the authors

Drs. Davidson, Luthinger and Saoud designed the study and supervised its conduct.

Dr. Harvey designed and supervised the analyses for this paper and wrote the first draft of the paper. All authors reviewed several drafts of the paper and have approved the final version.

Role of funding source

The data in this study were funded by Minerva Pharmaceuticals. As noted in the Acknowledgements, three of the authors are full time employees of Minerva Pharma.

Declaration of competing interest

Dr. Harvey has received consulting fees or travel reimbursements from Alkermes, Boehringer Ingelheim, Intra-Cellular Therapies, Jazz Pharma, Minerva Pharma, Otsuka America, Roche Pharma, Sanofi Pharma, Sunovion Pharma, Takeda Pharma, and Teva during the past year. He receives royalties from the Brief Assessment of Cognition in Schizophrenia. He is chief scientific officer of i-Function, Inc. He has a research grant from Takeda and from the Stanley Medical Research Foundation.

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All authors who contributed to this paper are listed as authors. No professional medical writer was involved in any portion of the preparation of the manuscript.

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