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Improvement of Schizophrenia Social Amotivation and Expressive Deficits Over Time After Cariprazine and Risperidone Treatment: Post Hoc Analysis of a Phase-3 Trial

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INTRODUCTION

- Schizophrenia is a complex disorder comprising positive, negative, and mood symptoms, as well as cognitive impairment. Negative symptoms of schizophrenia affect 15-60% of patients.
- The most prominent concepts in the negative symptom subdomain are blunted affect, alogia, anhedonia, asociality, and avolition. [1]
- Factor analysis yielded a two-factor structure of negative symptoms. The first factor consisted of PANSS items flat affect, poor rapport, lack of spontaneity, mannerisms and posturing, motor retardation, and avolition. The second factor consisted of emotional withdrawal, passive/apathetic social withdrawal, and active social avoidance. The first factor could be related to expressive deficits, reflecting a loss of initiative, and the second factor to social amotivation, related to community interaction. [2]
- Cariprazine is an orally active and potent dopamine D3/D2 receptor partial agonist with preferential binding to D3 receptors, which has demonstrated efficacy in treating various symptoms of schizophrenia in short and long term treatment trials. Cariprazine is approved by EMA in 2017 for the treatment of schizophrenia and by FDA in 2015 for the treatment of schizophrenia and bipolar mania in adult patients.
- In a Phase III trial cariprazine was significantly more effective than risperidone in treating negative symptoms of schizophrenia and improving patients' functionality. [3]

STUDY OBJECTIVE

To utilize Liemburg factors to conduct post-hoc analysis of expressive deficits and social amotivation over time in patients with predominant negative symptoms of schizophrenia.

METHODS

Study Design

- The study (EudraCT 2012-005485-36) was a 26-week, randomized, fixed-dose, double-blind, active-controlled study in adults with predominantly negative symptoms of schizophrenia.
- Patients had to have a schizophrenia diagnosis for at least 2 years with predominant negative symptoms for at least 6 months prior inclusion; PANSS-FSNS ≥ 24 and at least moderate severity (score ≥4) on ≥ 2 of the following PANSS negative items: blunted affect, passive/apathic social withdrawal, lack of spontaneity and flow of conversation; no predominance of positive symptoms (PANSS-FSPS ≤ 19), depression (Calgary Depression Scale Score CDSS ≤ 6) or clinically relevant parkinsonian symptoms (Simpson Angus Scale (first 8 items) ≤ 3).
- Patients received either cariprazine 4.5 mg/d (dose range: 3-6 mg/d) or risperidone 4.0 mg/d (dose range: 3-6 mg/d).

Study Treatments

- The 26-week double-blind study treatment period comprised of 2 phases: a 14-day cross-titration phase (Part-1), followed by a 24-week study treatment phase (Part-2).
- Part-1: Patients were up-titrated in 2 weeks to the target dose of cariprazine 4.5 mg/day, or risperidone 4.0 mg/day. Antipsychotic medication was down-titrated as in a mirror to the up-titration of the former study medication.
- Part-2: Continuation of the study treatment. At the end of Week 3 and at every subsequent visit, the dose of the double-blind study medication could be decreased to 3.0 mg/day in case of poor tolerability. In case of impending psychotic deterioration, the dose could be increased to 6.0 mg/day.

Statistics

- Post hoc analyses evaluated the individual PANSS items and the change from baseline of PANSS derived Liemburg factors.
- Modelling approach: Mixed effects model for repeated measures (MMRM) with treatment group, visit, study center, the treatment group-by-visit interaction as fixed effects and the baseline value and baseline value-by-visit interaction as the covariates.

RESULTS

Figure 1 Change of PANSS Single Items of Liemburg Factor – Expressive Deficits

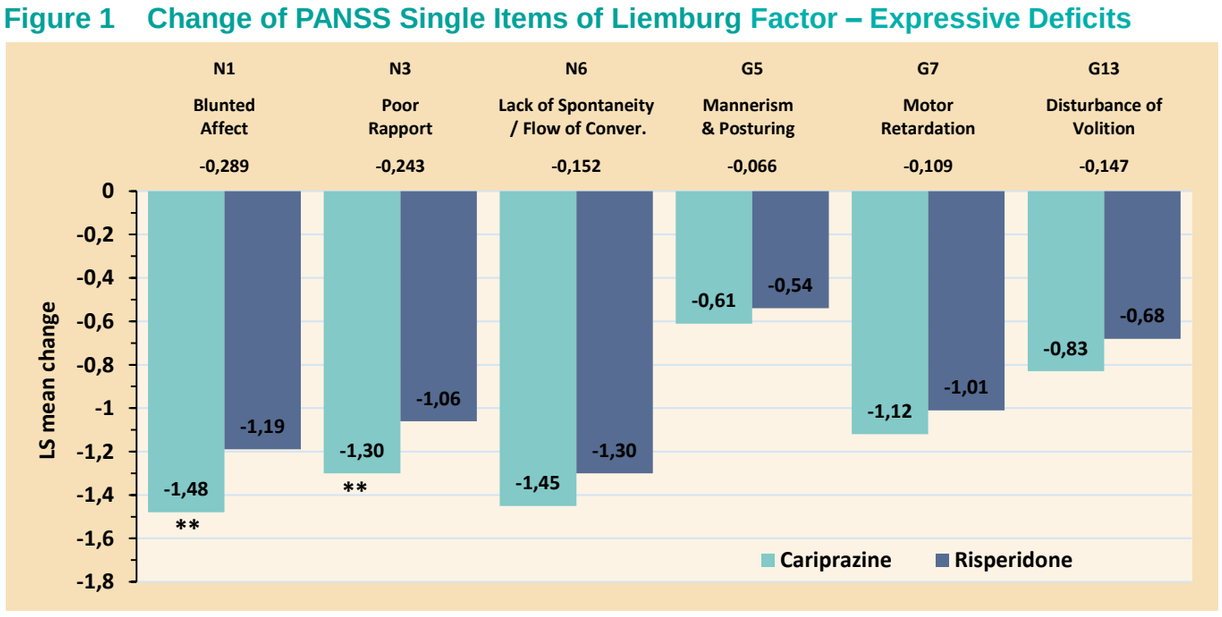
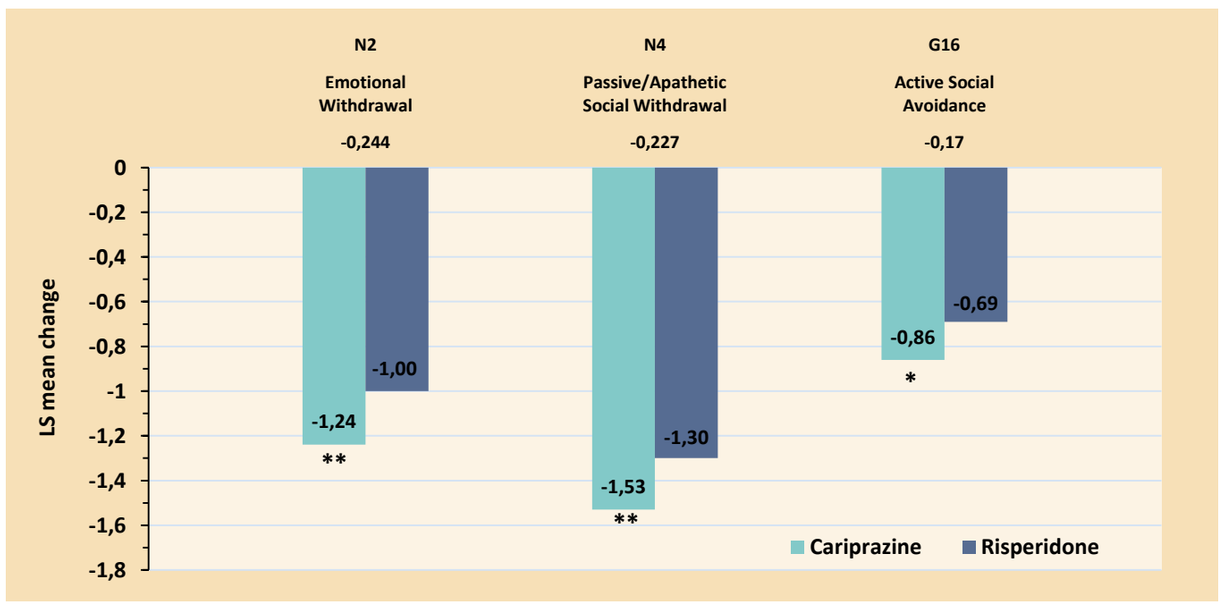


Figure 2 Change of PANSS Single Items of Liemburg Factor – Social Amotivation



CONCLUSIONS

- **By targeting the two major negative symptom domains of schizophrenia significant improvement on expressive deficits and social amotivation factors as well as on several PANSS single items was seen in favor of cariprazine over risperidone.**
- **Cariprazine can be a possible solution for patients who are attempting to gain back their lost initiative and their ability to interact with the community.**

Changes of PANSS Single Items of Liemburg Factors *(Figure 1 & 2)*

- Significantly greater improvement at Week 26 in favor of cariprazine was seen on the following PANSS items belonging to the two Liemburg factors:
  - Expressive deficits
    - N1 (p= 0.002)
    - N3 (p= 0.007)
  - Social amotivation
    - N2 (p= 0.004)
    - N4 (p= 0.016)
    - G16 (p= 0.042)

Changes of Liemburg Factors over Time *(Figure 3 & 4)*

- Statistically significant greater improvement in favor of cariprazine versus risperidone was seen on the Liemburg "core negative symptoms" (expressive deficits LSMD -1.092; p=0.004; effect size 0.30) and "social emotive withdrawal" (social amotivation LSMD -0.628; p=0.004; effect size 0.29) at Week 26.
- The mean change from baseline always favored cariprazine at each visit with statistically significant differences from Week 18 onward for expressive deficits and from Week 14 onward for social amotivation.

Figure 3 Expressive Deficits Change Over Time

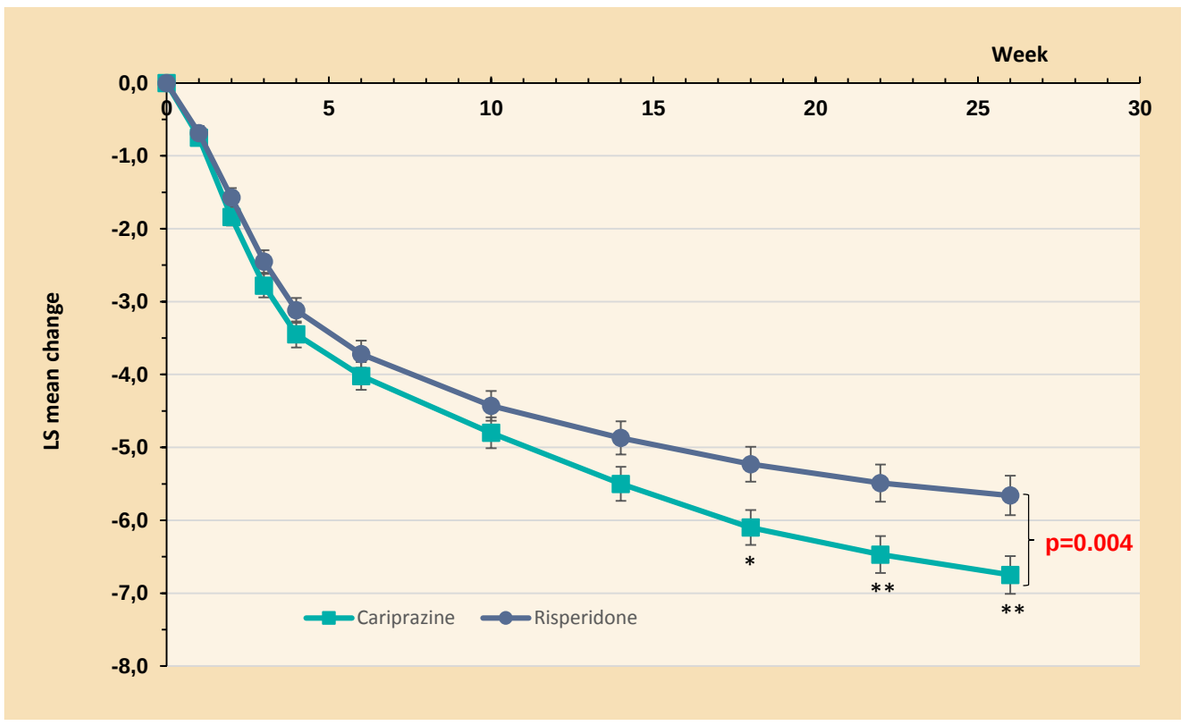
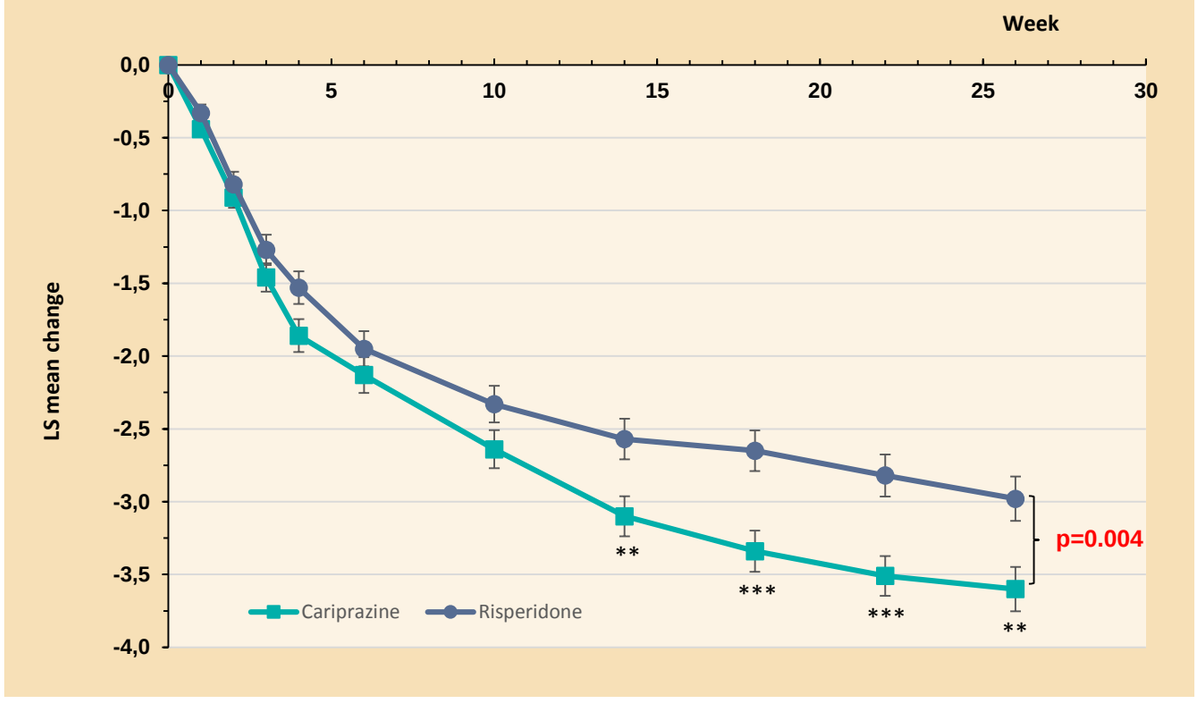


Figure 4 Social Amotivation Change Over Time



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[2] Liemburg E, Castelein S, Stewart R et al., 2013. Two subdomains of negative symptoms in psychiatric disorders: Established and confirmed in two large cohorts. *J Psych Res* **47**, 718-725.

[3] Németh G, Laszlovszky I, Czobor P et al., 2017. Cariprazine as monotherapy for the treatment of predominant negative symptoms in patients with schizophrenia: A randomized, double-blind, active-comparator controlled trial. *The Lancet* **389**, 1103-1113.

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