1 # The management of patients with predominant

2 # negative symptoms in Slovakia: A 1-year longitudinal,

3 # prospective & multicentric cohort study

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5 ## Short title

6 Predominant negative symptom patients in Slovakia

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8 ## Authors

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Abstract

Background

Predominant negative symptoms (PNS) in schizophrenia can affect the patients' psychosocial functioning immensely and are less responsive to treatment than positive symptoms.

Aims

The aim of the study was to observe negative symptoms and psychosocial functioning in PNS schizophrenia patients and to understand whether PNS can be improved and with what treatment strategies.

Methods

This was a 1-year, prospective, multicentric cohort study conducted in Slovakia. Adult outpatients with diagnosis of schizophrenia according to ICD-10 and PNS evaluated using the criteria by the European Psychiatric Association's guidance were included. Change in negative symptoms, functionality and treatment patterns were observed. Treatment effectiveness was evaluated using the modified Short Assessment of Negative Domain (m-SAND), the Self-evaluation of Negative Symptoms (SNS) scale, the Personal and Social Performance Scale (PSP), and the Clinical Global Impression Severity (CGI-S) and Improvement (CGI-I) scales. Least squares (LS) means were calculated for the change from baseline to final visit for the outcomes.

Results

The study included 188 patients. Functionality improved as by the end of the study, fewer patients were unemployed (53%) and more worked occasionally (21%). PNS improved significantly according to both physicians and patients (LS mean change from baseline in m-SAND total score: -10.0 (p-value <0.0001). Most patients received polytherapy throughout the study. Cariprazine was utilized most

44   (20% monotherapy and 76% polytherapy). Only a few patients discontinued treatment due to adverse

45   drug reactions.

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47   **Conclusions**

48   With the right treatment strategy, it is possible to achieve improvement in PNS and everyday

49   functioning in schizophrenia outpatients.

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54 Introduction

55 Schizophrenia is a chronic psychiatric disorder affecting approximately 1% of the general population

56 [1] and is one of the most disabling health conditions in the world [2]. It is also associated with

57 significant financial and health burdens; patients with schizophrenia have increased risk of non-

58 communicable diseases as well as higher mortality rates [3,4]. In addition, due to functional

59 impairment and the costs of treatment and care, there is a major loss of productivity, affecting not only

60 the patients themselves, but their caregivers too [5]. A recent epidemiological study examining the

61 burden of schizophrenia in Central and Eastern Europe (CEE) found 14% of Slovakian schizophrenia

62 patients to be unemployed and 63% to live on a disability pension [5]. In addition, on average, 4% of

63 caregivers had to stop working to take care of their relatives [5].

64

65 Characterized by a wide range of symptoms, schizophrenia is a multidimensional disorder [6].

66 According to recent conceptualizations, negative symptoms are comprised of five constructs, the so-

67 called "5As": anhedonia, alogia, avolition, asociality and affective flattening [7–9]. If the severity of

68 negative symptoms exceeds that of the positive symptoms, the patient is called a predominant negative

69 symptom (PNS) schizophrenia patient [7]. Negative symptoms can be primary or secondary depending

70 on their root cause: while primary negative symptoms are intrinsic to the disorder, secondary negative

71 symptoms are triggered by other factors such as adverse effects of treatment, or other symptom

72 domains [7].

73

74 Negative symptoms are well-known to affect daily functioning and quality of life (QoL) immensely

75 [7,10–12]. For instance, in a 3-year study with 17,384 outpatients from 37 countries, QoL was found

76 to correlate with negative symptoms more than with positive symptoms [12]. Furthermore, a recent

77 study by D'Anna et al. evaluating the relationship between negative symptoms and daily time use

78 found that patients with more negative symptomatology spent more time with non-productive

79 activities compared to patients with milder symptoms [11].

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81   Schizophrenia is primarily treated with antipsychotic medications [13]. According to a recent study in

82   Slovakia, first-line treatment of schizophrenia based on expert opinion is risperidone (36%),

83   olanzapine (28%), and quetiapine (13%) [13]. Having a more balanced safety profile, second-

84   generation antipsychotics are preferred over first-generation ones (~70% vs 30%) in Slovakia in

85   general [13]. In terms of negative symptoms, a recent proposal by Cerveri et al. recommends

86   cariprazine as a first-line medication due to its partial agonist effect on the dopamine D3-D2 receptors

87   [14,15]. Indeed, according to a review involving 17 experts from the Central and Eastern European

88   region, the Cerveri treatment algorithm, has been adapted in Slovakia as well [16].

89

90   The aim of the present cohort study was twofold. First, to observe the negative symptom domain and

91   its association with psychosocial functioning in patients with PNS and the typical treatment patterns in

92   Slovakia. Second, to observe whether PNS can improve in an outpatient setting throughout a 1-year

93   treatment period and with what pharmacological and non-pharmacological treatment strategies.

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95   ## Methods

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97   ## Study design

98   This was a longitudinal, prospective, multicentric cohort study conducted in 20 sites in Slovakia. The

99   study duration was 1 year, with three visits after baseline at 3, 6, and 12 months.

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101   ## Patient characteristics

102   The inclusion criteria were the following: adult outpatients (between ages 18-65) with a schizophrenia

103   diagnosis according to the International Classification of Diseases 10th edition (ICD-10) who exhibited

104   predominant negative symptoms according to the European Psychiatric Association's (EPA) guidance

105   were included in the study [17]. The EPA guidance suggests the presence of at least moderate severity

106 of at least two symptoms, which was evaluated and decided by the doctors based on the patient's

107 anamnesis [17]. Patients with comorbid neurological disorders were excluded. The cohort study

108 received approval by the Ethics Committee of the Košice Self-Governing Region (3618/2020/ODDZ-

109 07169) and informed written consent was obtained from all participants. The study complies with the

110 Declaration of Helsinki.

111

Measures

113 Epidemiologic measures were general patient characteristics (sex, age, duration of illness,

114 comorbidities), changes in the frequency of functionality outcomes (employment status, disability

115 status, and disorder insight), changes in the frequency of primary and secondary negative symptoms,

116 as well as changes in the frequency of treatment patterns (frequency of monotherapy, polytherapy and

117 non-pharmacotherapy) throughout the 1-year observational period. Primary and secondary negative

118 symptoms were differentiated using a structured interview based on the guidance provided by the EPA

119 [17]. Insight was defined as *"a person's capacity to understand the nature, significance, and severity*

120 *of his or her own illness"* [18] and whether a patient had full, partial or no insight was determined by

121 the physician based on the clinical interview.

122

123 The effectiveness of the different treatment strategies was assessed via the modified Short Assessment

124 of Negative Domain (m-SAND) scale, the Self-evaluation of Negative Symptoms (SNS) scale [19],

125 the Personal and Social Performance Scale (PSP) [20], and the Clinical Global Impression Severity

126 (CGI-S) and Improvement (CGI-I) scales [21]. Given the nature of the study, safety parameters and

127 adverse events were monitored and addressed as in a routine clinical setting.

128

129 **Modified Short Assessment of Negative Domain (m-SAND) scale**

130 The original SAND was utilized in a Latvian observational study evaluating the effectiveness of

131 cariprazine in predominant negative symptom patients [22]. The SAND is an anamnesis-based scale

132 that is composed of 7 items: two positive items (delusions and hallucinations), which make the SAND

6

133   Positive sub-scale (SAND-P) and five negative items (anhedonia, alogia, avolition, asociality and

134   affective flattening), which make the SAND Negative sub-scale (SAND-N) [22]. Each item is rated

135   from 0 to 6 (not observed; minimal; mild; moderate; moderately severe; severe; and extreme). The

136   SAND was chosen due to its simplicity and ability to capture all constructs of the negative symptom

137   domain however, the rating was modified since it is highly difficult to differentiate between 'minimal'

138   and 'mild' severities. Therefore, the m-SAND includes the same items, but it is rated from 0 to 5 (not

139   observed, mild, moderate, moderately severe, severe, and extreme).

140

Self-evaluation of Negative Symptoms (SNS) scale

142   The Self-assessment of Negative Symptoms (SNS) scale is a self-administered questionnaire that

143   measures the five sub-domains of negative symptoms (the 5As) in schizophrenia and schizoaffective

144   disorder [19]. Being a self-administered questionnaire, SNS is an easily understandable instrument for

145   patients with schizophrenia that provides meaningful information for clinicians regarding the patients'

146   own perception of their negative symptoms [19]. Thus, the SNS can complement observer ratings of

147   negative symptoms as well as increase patient engagement.

Personal and Social Performance Scale (PSP)

149   The Personal and Social Performance Scale (PSP) is a clinical tool used to measure the routine social

150   functioning of patients with psychiatric disorders [20]. It measures four areas of social and individual

151   performance independently of symptomatology: socially useful activities, personal and social

152   relationships, self-care, and disturbing and aggressive behaviours [20]. The PSP is a useful tool for

153   providing additional valuable information when evaluating social functioning related to schizophrenia

154   and the effectiveness of the treatment [23].

155

Clinical Global Impression Severity (CGI-S) and Improvement (CGI-I) scales

157   The Clinical Global Impressions (CGI) scale provides an overall clinician-determined summary

158   measure regarding the severity of illness (CGI-S) and improvement (CGI-I) in patients with

7

159 psychiatric disorders [21]. The CGI is rated on a 7-point scale [21]. It is considered to be a widely

160 accepted tool that synthesize the clinician's impression of the global illness state of the patient [21].

161

Statistical analyses

163 Epidemiologic measures were summarised using descriptive statistics in percentages, means and

164 standard deviations. Least squares (LS) means were calculated for the change from baseline to final

165 visit for the effectiveness measures (m-SAND, SNS, PSP and CGI-S) using a mixed model for

166 repeated measures (MMRM). Bland-Altman agreement plots were created to compare how clinicians

167 (m-SAND-N) vs how patients (SNS) rated negative symptoms. All analyses were conducted using

168 Statistical Analysis Software (SAS).

169

Results

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Epidemiologic measures

173

174 **Patient characteristics**

175 Baseline patient characteristics are summarized in Table 1. The mean age of the 188 patients who were

176 included in the cohort study was 39.8 and 64.9% of them was men. The mean duration of illness was

177 12 years, and most of the cohort was diagnosed with paranoid schizophrenia (51.6%). Patients

178 exhibited both psychiatric and somatic comorbidities such as depression (13.3%), substance abuse

179 disorder (11.7%), and personality disorder (8.0%), as well as hypertension (10.6%), obesity (10.1%)

180 and hyperlipidaemia (5.3%). During the 12-month observational period, 148 patients stayed in the

181 cohort study.

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183 **Functionality & insight**

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184   At baseline, most patients were unemployed (63.8%), worked occasionally (10.6%) or part-time

185   (11.2%) as displayed in Table 2. At the end of the 12-month observation, only 53.4% were

186   unemployed and more patients worked occasionally (20.9) or part-time (12.8%). The disability status

187   on the other hand increased from 76.1% to 83.3%. In terms of disorder insight, at baseline, most

188   patients had partial (70.2%) or full (20.2%) insight, while around 10% of patients had no insight at all.

189   By the end of the observational period 53.4% had partial, 44.6% full and 0.2% no insight.

190

191   **Primary and secondary negative symptoms**

192   All patients had primary negative symptoms, both at baseline and at the end of the study Table 3. At

193   baseline, 93% of patients had blunted affect, 87% apathy, 82% anhedonia, 76% asociality and 53%

194   alogia. After one year, most patients still experienced affective blunting (93%); nonetheless, the other

195   aspects of negative symptomatology improved: only 62% of the patients had apathy, 56% anhedonia,

196   50% asociality and 38% alogia. In addition to primary negative symptoms, a significant proportion of

197   patients also had secondary negative symptoms (56%) due to affective symptoms (37%), positive

198   symptoms (26%) and adverse drug reactions (21%) at baseline. Similarly to primary negative

199   symptoms, fewer patients experienced secondary negative symptoms (30%) at the end of the

200   observational period.

201

202   **Treatment patterns**

203   The treatment approaches of PNS changed slightly throughout the 1-year observational period. At

204   baseline, all patients received pharmacotherapy, 18% antipsychotic monotherapy (M) and 82%

205   polytherapy (P) (Table 4). In addition, 86% of patients received non-pharmacological therapy in the

206   form of supportive psychotherapy (47%), social skills training (13%), and occupational therapy (11%).

207   After 12 months, there was a slight decrease in the number of patients receiving polytherapy (78%)

208   and an increase in non-pharmacological therapies (93%).

209   Regarding the specific type of antipsychotics, cariprazine (M: 5%, P: 72%), olanzapine (M: 6%, P:

210   32%), clozapine (M: 3%, P: 18%) and quetiapine (M: 2%, P: 14%) were prescribed most at baseline.

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211   At the final visit, there was an increase in the proportion of patients receiving cariprazine monotherapy

212   (20%) and polytherapy (76%), as well as clozapine polytherapy (21%), while those who received

213   olanzapine (M: 0%, P: 23%) and quetiapine (M: 1%, P: 12%) decreased. All in all, throughout the 1-

214   year period, over 200 patients received cariprazine either as monotherapy or polytherapy, 88 received

215   olanzapine, 46 clozapine, 39 quetiapine, 32 haloperidol, 26 aripiprazole, 20 flupentixol, 16 risperidone

216   and 14 paliperidone (Figure 1). The most common reason for stopping any antipsychotic treatment

217   was akathisia, extra-pyramidal symptoms, and insomnia (1.6%) (Table 4).

218

Effectiveness of treatment

220   The mean m-SAND score at baseline was 23.6 with an average 4.6 score on the Positive sub-scale and

221   19.1 on the Negative sub-scale (Table 5). A statistically significant 10-point LS mean change from

222   baseline was observed at the end of the observational period on the m-SAND total score with an effect

223   size (ES) of -2.5. The change from baseline was statistically significant from the first visit onwards

224   (Figure 2). In terms of the two sub-scales, both m-SAND-P (LS mean change: -1.8, p-value <0.0001,

225   ES: -1.6) and m-SAND-N (LS mean change: -8.3, p-value <0.0001, ES: -2.4) changed significantly

226   over the 12 months. Importantly, patients also reported their negative symptoms to have improved as

227   measured by the SNS (LS mean change -12-point in the SNS total score, p-value <0.0001, ES: -1.7)

228   with significant improvement in all five sub-domains from the first visit onward (Figure 3). When

229   comparing the views of patients vs. doctors at baseline, patients rated alogia and avolition to be the

230   most severe (based on the SNS), while doctors found affective blunting and then avolition to be the

231   most problematic (based on the m-SAND-N). By the end of the observational period patients had the

232   highest self-reported scores in avolition and affective blunting. Similarly, physicians rated blunted

233   affect, avolition and anhedonia to be the most severe. These similarities between the ratings by the

234   patients and doctors are confirmed by a Bland-Altman agreement plot as well, which shows that the

235   difference between the mean changes from baseline to final visit in the SNS and SAND-N lies within

236   the 95% confidence interval around the zero-bias line with doctors reporting a slightly greater

237   improvement compared to patients in negative symptoms (Figure 4). Furthermore, according to the

10

238   CGI-S scale, the participants were moderately ill at baseline (mean score: 4.3) and mildly ill at the end

239   of the observational period (mean score: 3.0). This detected change was also significant (LS mean

240   change: -1.3, p-value <0.0001, ES: -1.5). Indeed, the mean CGI-I score was 2.2 at the end of study,

241   meaning much improvement. Finally, 54.3% of patients manifested disabilities according to the total

242   PSP scores (scores between 31 and 70) and 45.7% poor functioning (scores under 30) at baseline

243   (Table 5). By the end of the observational period this changed to 92.6% 'manifest disabilities' and

244   only 7.4% 'functioning is poor'. This was reflected on the subscales as well where statistically

245   significant change was detected in all categories: socially useful activities (LS mean change: -1.4, p-

246   value <0.0001, ES: -1.5), personal and social relationships (LS mean change: -1.7, p-value <0.0001,

247   ES: -2.0), self-care (LS mean change: -1.5, p-value <0.0001, ES: -1.6), and disturbing and aggressive

248   behaviour (LS mean change: -0.9, p-value <0.0001, ES: -1.9).

249

250 Discussion

251   This was the first outpatient, longitudinal, prospective, multicentric cohort study in Slovakia that

252   focused specifically on patients with schizophrenia and predominant negative symptoms. The aim was

253   to do an epidemiologic assessment of the characteristics of negative symptoms, functionality status,

254   disorder insight and treatment patterns in this patient population throughout a 1-year observational

255   period, along with evaluating the effectiveness of treatment approaches.

256

257   According to the results, throughout the 1-year observational period, there has been a significant

258   improvement in all negative symptom domains. Importantly, this positive change was observed by

259   both physicians and patients. As articulated in the most recent guidance by the European Psychiatric

260   Association (EPA), including self-report measures is encouraged in negative symptom studies as they

261   can further complement the observer-rated scales when assessing negative symptoms of schizophrenia

262   [17]. In the present case, results based on the SNS and the m-SAND-N scales indicated an agreement

263   between patients and doctors regarding the changes in negative symptoms and highlighted some slight

264   differences in terms of what subdomains of the negative construct are most affected. This comparison

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265   was only possible since the SNS and m-SAND-N scales measure the same negative symptom

266   subdomains, the 5As (anhedonia, affective blunting, avolition, alogia, and asociality). It is important to

267   note however that one negative symptom, blunted affect (the decreased expression of emotion),

268   seemed to be the most difficult to treat since both at baseline and final visit 93% of patients were

269   described to exhibit it. Indeed, blunted affect is often unresponsive to treatment and is difficult to

270   measure via rating scales as they are relatively insensitive to change [24]. Nonetheless, according to

271   both the SNS and m-SAND-N scales, the severity of blunted affect decreased significantly, suggesting

272   that some improvement is still possible.

273

274   By the end of the study, patients also improved in their functioning, with fewer patients being

275   unemployed and more working occasionally and significant changes in the PSP scores. This is not

276   surprising given the fact that negative symptoms are known to impact everyday functioning [7] and

277   numerous studies reported a link between greater negative symptoms and reduced work functioning

278   [25,26]. It is important to note however that even though there had been a reduction in the

279   unemployment status, the proportion of patients being unemployed was still higher than what was

280   reported in a study by Szkultecka-Dębek et al. in 2016 (53% vs. 14%) [5]. Additionally, while

281   Szkultecka-Dębek et al. reported 63% of Slovakian patients with schizophrenia to live on disability

282   pension or retirement or employed on sick leave, in the current study 84% had a disability due to

283   psychiatric illness. Both aspects might be explained by the fact that the participants in the former study

284   were not patients with PNS specifically. In terms of disability status, no improvement was found as the

285   frequency of patients being disabled due to psychiatric illness increased. It is important to note

286   however that in most social care systems [27,28], schizophrenia is recognized as a qualified condition

287   for disability benefits. Therefore, improvements in overall functioning due to successful treatment

288   does not necessarily translate into a decline of financial support needed that is associated with

289   disability status.

290

291   Besides employment and disability status, there was a change in the patients' insight as well. Insight is

292   defined as „the patient's capacity to acknowledge some awareness of having an illness" [29] and has

293   also been repeatedly reported to be associated with negative symptoms [30]. For instance, Kemp and

294   Lambert found a correlation between negative symptoms and insight in subjects who improved with

295   treatment [31]. This also seemed to be the case in the present study where alongside the improvement

296   in negative symptoms, the proportion of patients with full insight doubled (from 20% to 45%) and the

297   number of participants with no insight declined.

298

299   In terms of typical treatment approaches in Slovakia, the present study showed that most patients

300   received combination therapy (78% at final visit). Although it is not recommended by guidelines,

301   polytherapy is quite common in everyday clinical practice [32]. Indeed, in a survey conducted in five

302   European countries, polypharmacy rates were reported to increase from 19% to 27% between 2000

303   and 2015 [33]. Interestingly, various studies underline the superiority of polypharmacy compared to

304   monotherapy, especially on parameters such as re-hospitalisation rates [34] or total symptom reduction

305   [35]. In fact, clozapine combined with a D_2 partial agonist antipsychotic medication was associated

306   with the lowest risk of rehospitalization even compared to clozapine monotherapy [34], the gold

307   standard in treatment resistant schizophrenia. Similarly, the most often used augmentation strategy in

308   the present study was an atypical antipsychotic and cariprazine. This might be related to the unique

309   mechanism of action of cariprazine and its efficacy on negative symptoms [15,22,36]. Additionally,

310   recent evidence also endorsed the augmentation strategy of clozapine with cariprazine [37–40] by

311   reporting good tolerability and safety, as well as further reduction in negative symptoms. [14,41]

312

313   Cariprazine was the most popular medication as monotherapy too with 20% of participants being on

314   cariprazine treatment alone at final visit. This is in line with the treatment algorithm by Cerveri et al

315   [42]. The results also provide confirmation to the claim that this algorithm has been adapted in

316   Slovakia [16]. Rancans et al. conducted a 16-week observational study on the effectiveness of

317   cariprazine with PNS patients as well [22]. The results of the observational study are comparable to

318 this cohort study; participants in both studies were patients with PNS with a baseline CGI of moderate

319 severity (present study: 4.3, Rancans et al.: 4.4) and the primary outcome measure was the SAND [22]

320 and the m-SAND. [22]In addition, it also shows that improvement in this symptom domain is slower

321 and continuous with no plateauing of improvement at any point of the 12 months.

322 The present study has multiple limitations. First, due to the nature of the study design, results have

323 limited internal validity due to probable selection and different biases such as observer bias, inter-rater

324 bias, information bias and measurement bias [43,44]. Internal validity plays a crucial role in

325 establishing the effectiveness of a treatment, it ensures that the observed effects are directly

326 attributable to the treatment itself, rather than being influenced by other external factors [44].

327 However, the primary objective of this study was not to establish efficacy, but to understand the

328 typical treatment and symptom patterns of patients with schizophrenia and PNS in Slovakia. The

329 second limitation is that the primary outcome measure of the study was a non-validated scale.

330 Nonetheless, using standardized scales in real-life settings is often not feasible and thus to better

331 mimic real-life settings, the m-SAND was utilized [22]. Although the m-SAND scale is not validated,

332 it is based on the Clinical Global Impression Severity (CGI-S) scale, which is known to have good

333 inter-rater reliability among clinicians [21,22]. Future research should aim to further investigate what

334 combinations are the most effective in improving PNS as we have seen that besides cariprazine, most

335 patients took an additional antipsychotic medication as well.

336

Conclusion

338 In conclusion, with the right treatment strategy, it is possible to improve PNS as well as everyday

339 functioning in outpatients with schizophrenia. One of the most used antipsychotic medications in this

340 patient population was cariprazine, which had been utilized both alone and in combination with other

341 antipsychotics. This strategy is in line with the treatment algorithm for negative symptoms in

342 schizophrenia suggested by Cerveri et al., which recommends cariprazine as a first-line medication for

343 the treatment of negative symptoms [42]. It is also important to note that the improvement in negative

344   symptoms was continuous throughout the one-year observation with no plateauing at any point,   15

345   suggesting that patience is key in negative symptom treatment.

346

347 # Tables & Figures

348 ## Table 1. Patient characteristics

Population	
Safety population, n (%)	188 (100)
Demographics	
Age, mean (SD), y	39.8 (10.8)
Males, n (%)	122 (64.9)
Schizophrenia characteristics	
Duration of illness, mean (SD), y	12.0 (9.0)
Schizophrenia diagnosis, n (%)	
Paranoid schizophrenia	97 (51.6)
Residual schizophrenia	36 (19.1)
Undifferentiated schizophrenia	24 (12.7)
Simple schizophrenia	17 (9.0)
Other type of schizophrenia	14 (7.4)
Comorbidities	
Psychiatric comorbidity, n (%)	
Depression	25 (13.3)
Substance abuse	22 (11.7)
Personality disorder	15 (8.0)
Somatic comorbidity, n (%)	
Hypertension	20 (10.6)
Obesity	19 (10.1)
Hyperlipidaemia	10 (5.3)

349

350 Table 2. Functionality & insight

	BASELINE (n = 188)	FINAL VISIT* (n = 148)
Employment status, n (%)		
Full-time job	17 (9.0)	10 (6.8)
Part-time job	21 (11.2)	19 (12.8)
Occasionally working	20 (10.6)	31 (20.9)
Unemployed	120 (63.8)	79 (53.4)
Student	5 (2.7)	4 (2.7)
Prisoner	5 (2.7)	5 (3.4)
Disability, n (%)		
No disability	44 (23.4)	23 (15.5)
Disability due to psychiatric illness	143 (76.1)	124 (83.8)
Disability due to non-psychiatric illness	1 (0.05)	1 (0.07)
Insight, n (%)		
Full insight	38 (20.2)	66 (44.6)
Partial insight	132 (70.2)	79 (53.4)
No insight	18 (9.6)	3 (0.2)

12 months from baseline

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353   Table 3. Primary & secondary negative symptoms

	BASELINE (n = 188)	FINAL VISIT* (n = 148)
Primary negative symptoms, n (%)		
Total	188 (100.0)	148 (100.0)
Affective blunting	175 (93.1)	137 (92.6)
Alogia	100 (53.2)	56 (37.8)
Avolition, apathy	163 (86.7)	91 (61.5)
Anhedonia	154 (81.9)	83 (56.1)
Asociality	143 (76.1)	74 (50.0)
Secondary negative symptoms, n (%)		
Total	105 (55.9)	44 (29.7)
Due to positive symptoms	48 (25.5)	21 (14.2)
Due to affective symptoms	69 (36.7)	33 (22.3)
Due to adverse drug reactions	38 (21.2)	9 (6.1)

12 months from baseline

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356   Table 4. Treatment approaches

	BASELINE (n = 188)		FINAL VISIT* (n = 148)	
Type of therapy, n (%)				
Pharmacotherapy	188 (100.0)		148 (100.0)	
Antipsychotic monotherapy	34 (18.1)		33 (22.3)	
Antipsychotic polytherapy	154 (81.)		115 (77.7)	
Non-pharmacological therapy	162 (86.2)		138 (93.2)	
Supportive psychotherapy	89 (47.3)		73 (49.3)	
Other types of psychotherapy	10 (5.3)		14 (9.5)	
Social skills training	24 (12.8)		20 (13.5)	
Occupational therapy	21 (11.2)		17 (11.5)	
Electroconvulsive therapy	2 (1.1)		1 (0.7)	
Other	16 (8.5)		13 (8.8)	
Type of antipsychotic, n (%)**	**Mono**	**Poly**	**Mono**	**Poly**
Cariprazine	10 (5.3)	135 (71.8)	29 (19.6)	113 (76.4)
Olanzapine	12 (6.4)	60 (31.9)	-	44 (23.4)
Clozapine	5 (2.7)	34 (18.1)	2 (1.4)	31 (20.9)
Quetiapine	3 (1.6)	27 (14.4)	1 (0.7)	17 (11.5)
Aripiprazole	1 (0.5)	22 (11.7)	-	12 (8.1)
Haloperidol	-	23 (12.2)	-	11 (7.4)
Flupentixol	1 (0.5)	17 (9.0)	-	8 (5.4)
Risperidone	1 (0.5)	13 (6.9)	-	7 (4.7)
Paliperidone	1 (0.5)	10 (5.3)	1 (0.7)	7 (4.7)
Reason for stopping antipsychotic treatment, n (%)				
Attenuation	1 (0.5)			
Anxiety	2 (1.1)			
Akathisia	3 (1.6)			
Extra-pyramidal symptoms	3 (1.6)			

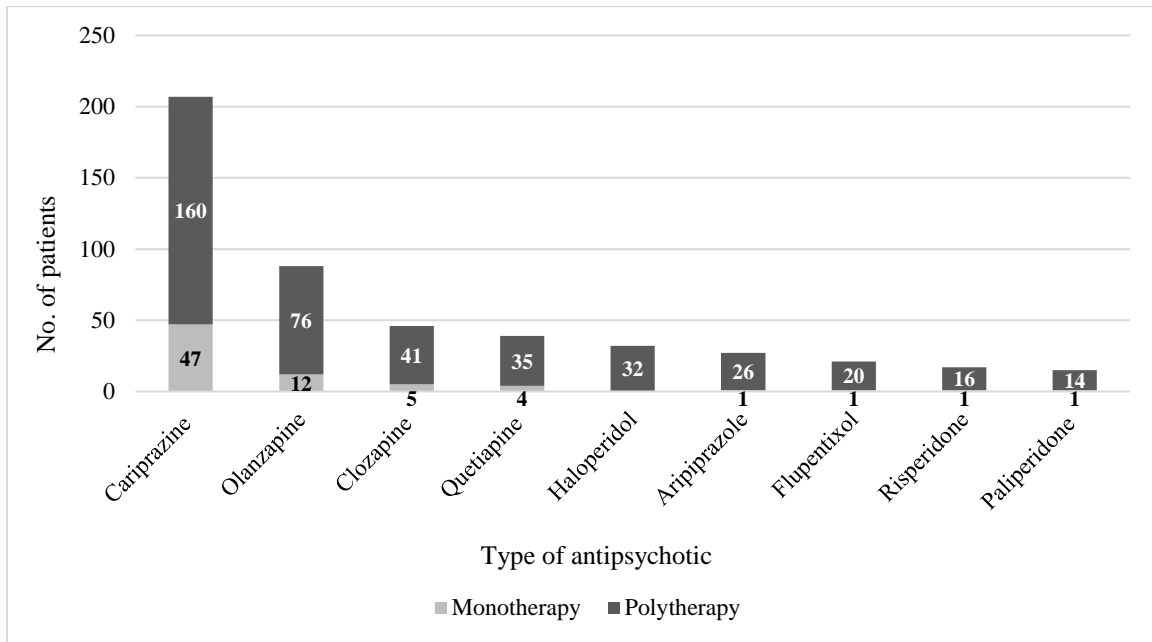|	
Insomnia	3 (1.6)
Other	5 (2.7)

*12 months from baseline

**Taken by more than 5% of patients

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358

359   Figure 1. Number of patients taking different types of antipsychotics throughout

360   the observational period*

361

362   *Patients taking multiple medications are counted at each drug, drugs with multiple occurrences within a

363   patient are counted only once

364

365 Table 5. Effectiveness of treatment

	BASELINE mean (SD)	FINAL VISIT means (SD)	LS mean change (SE)	ES
m-SAND Total	23.6 (5.0)	13.8 (4.4)	-10.0 (0.33)***	-2.5
m-SAND-P	4.6 (2.2)	2.9 (1.3)	-1.8 (0.09)***	-1.6
Hallucinations	2.1 (1.2)	1.4 (0.7)	-0.7 (0.05)***	-1.2
Delusions	2.5 (1.3)	1.5 (0.8)	-1.1 (0.06)***	-1.5
m-SAND-N	19.1 (3.8)	11.0 (3.7)	-8.3 (0.28)***	-2.4
Anhedonia	4.0 (1.0)	2.2 (1.0)	-1.8 (0.08)***	-1.9
Affective blunting	4.3 (0.9)	2.7 (0.9)	-1.6 (0.07)***	-1.9
Avolition, apathy	4.2 (1.0)	2.3 (1.0)	-1.9 (0.07)***	-2.1
Alogia	2.9 (1.4)	1.8 (0.9)	-1.2 (0.06)***	-1.6
Asociality	3.6 (1.3)	1.9 (1.0)	-1.7 (0.07)***	-1.9
SNS Total	27.4 (7.3)	15.4 (7.1)	-12.0 (0.56)***	-1.7
Asociality / items 1-4	5.5 (2.1)	2.9 (1.7)	-2.7 (0.13)***	-1.6
Affective blunting / items 5-8	5.2 (1.7)	3.2 (1.5)	-1.9 (0.11)***	-1.3
Alogia / items 9-12	5.7 (1.9)	3.1 (1.7)	-2.7 (0.13)***	-1.6
Avolition / items 13-16	5.7 (2.0)	3.3 (1.8)	-2.4 (0.14)***	-1.4
Anhedonia / items 17-20	5.3 (1.9)	2.9 (1.6)	-2.4 (0.12)***	-1.6
CGI-I	-	2.2 (0.8)	-	-
CGI-S	4.3 (1.1)	3.0 (1.0)	-1.31 (0.07)***	-1.5
PSP				
Socially useful activities	3.9 (1.1)	2.6 (1.0)	-1.35 (0.07)***	-1.5
Personal and social relationships	4.2 (1.0)	2.5 (0.9)	-1.70 (0.07)***	-2.0
Self-care	3.3 (1.0)	1.9 (1.0)	-1.52 (0.07)***	-1.6
Disturbing and aggressive behaviour	2.0 (1.3)	1.2 (0.5)	-0.90 (0.4)***	-1.9
PSP Total	BASELINE n (%)	FINAL VISIT n (%)		
only mild difficulties (100-70)	0 (0.0)	0 (0.0)		

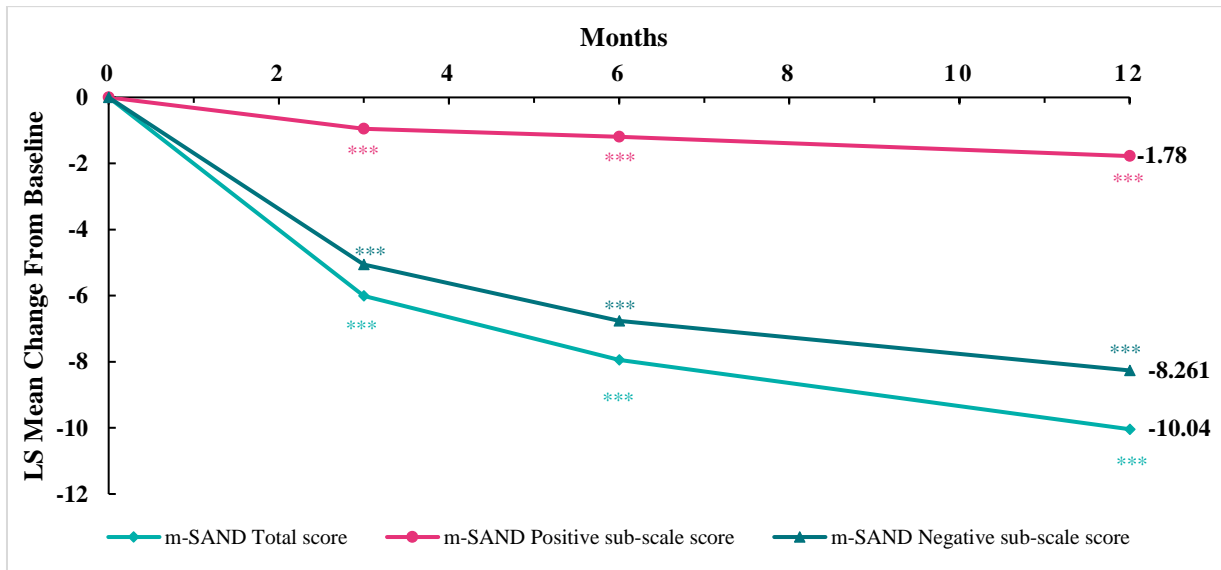|		
manifest disabilities (70-31)	102 (54.3)	137 (92.6)
functioning is poor (30-0)	86 (45.7)	11 (7.4)

*** p-value <0.0001

CGI-I, Clinical Global Impressions-Improvement; CGI-S, Clinical Global Impressions-Severity; ES, effect size; LS, least squares; PSP, the Personal and Social Performance Scale; m-SAND, modified Short Assessment of Negative Domains; m-SAND-N, modified Short Assessment of Negative Domains Negative symptom sub-scale; m-SAND-P, modified Short Assessment of Negative Domains Positive symptom sub-scale; SNS, Self-evaluation of Negative Symptoms; SD, standard deviation; SE, standard error

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367

368   Figure 2. Mean change from baseline in m-SAND Total, Positive sub-scale, and

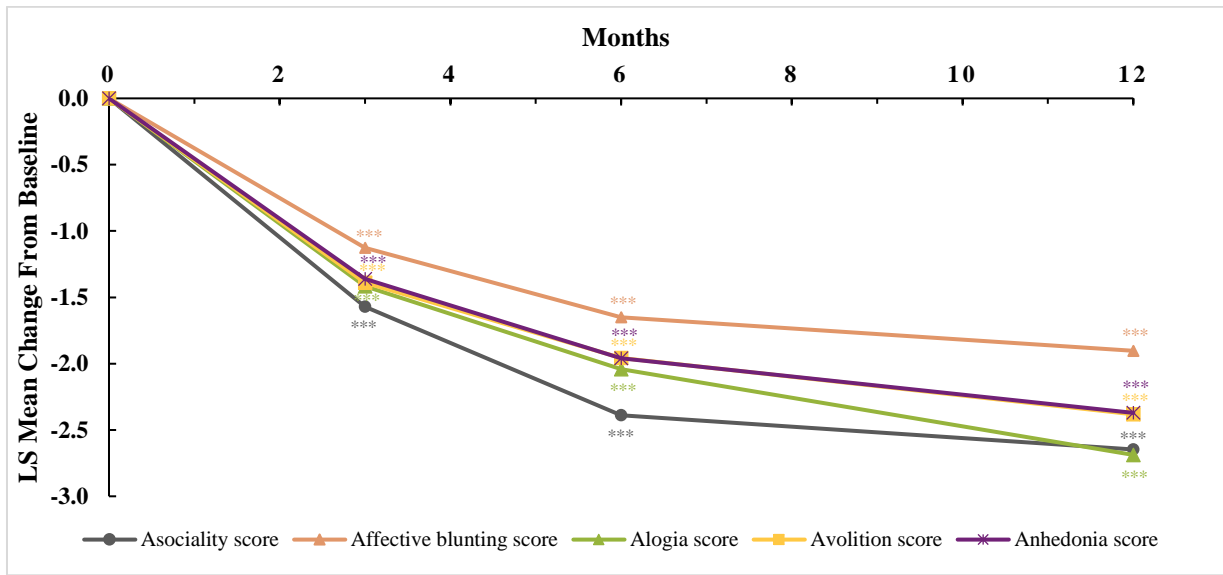369   Negative sub-scale scores by months

370

371   *** p-value <0.0001

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373 Figure 3. Mean change from baseline in SNS sub-scores by months
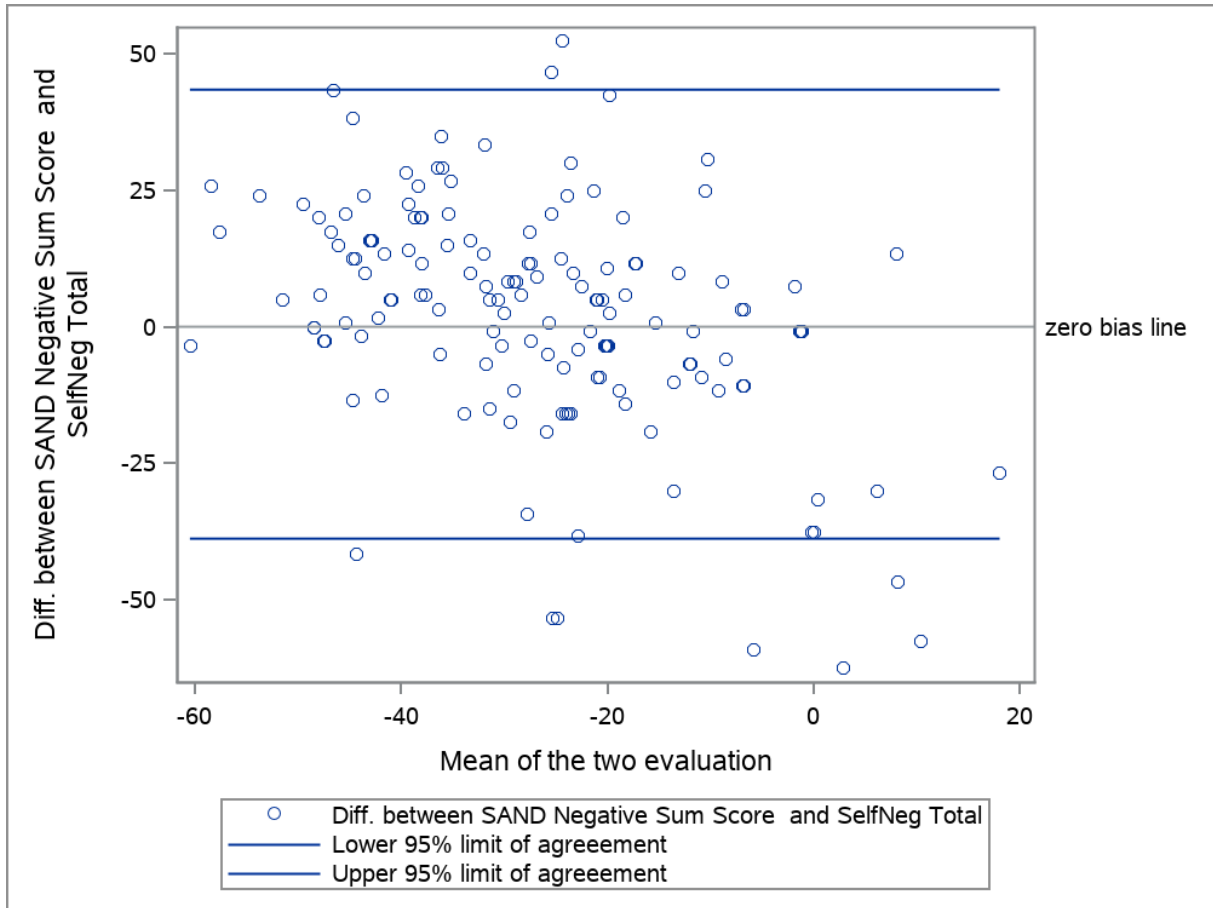

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375 *** p-value <0.0001

376

377   Figure 4. Bland-Altman agreement plot: difference between SAND Negative Sub-

378   Score and SNS Total score (or change) vs. their average scores are expressed as

379   % of the corresponding max value

380

381

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Competing interests

Z. B. Dombi, K. Acsai, V. Dzurilla and Á. Barabássy are employees of Gedeon Richter Plc., the originator company of cariprazine. J. Dragašek received honoraria or consultation fees outside of this work from Gedeon Richter Slovakia.

Ethical standards

The cohort study received approval by the Ethics Committee of the Košice Self-Governing Region (3618/2020/ODDZ-07169) and informed written consent was obtained from all participants.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author, Z. B. Dombi , upon reasonable request.

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