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Effect of lurasidone vs olanzapine on neurotrophic biomarkers in unmedicated schizophrenia: A randomized controlled trial

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ABSTRACT

Neurotrophic factors like Brain-Derived Neurotrophic Factor (BDNF), Neurotrophin 3 (NT3) and Nerve Growth Factor (NGF), play a role in neuroplasticity and neurogenesis contributing to the pathogenesis of schizophrenia. The objective of the present study was to investigate and compare the effect of olanzapine and lurasidone on the change in serum neurotrophins in patients with schizophrenia. The present study was a randomized, open-label, active-controlled, parallel design clinical trial. After randomization baseline evaluations of serum BDNF, NGF, NT3, Positive and Negative Syndrome Scale (PANSS) scoring, Social and Occupational Functioning Assessment Scale (SOFAS) scoring of 101 unmedicated schizophrenia patients were done. Patients were reassessed after 6 weeks of monotherapy with olanzapine or lurasidone. Serum BDNF increased after treatment with both the drug groups but rise with olanzapine was found to be significantly higher (916.22; 95 %CI: 866.07 to 966.37; $p < 0.001$) in comparison to lurasidone. Increase in levels NGF and NT3 was also observed but there was no significant difference between the groups (NGF: 2.32; CI: 3.54 to −3.53; $p = 0.57$ and NT3: 0.99; CI: 2.11 to 0.14; $p = 0.086$). The difference in improvement in PANSS and SOFASS with both the drugs was not statistically significant. Both the drugs alleviate the symptoms of schizophrenia but olanzapine was better tolerated. Our findings suggest that increase in serum BDNF with olanzapine monotherapy is significantly higher than that with lurasidone but there is no significant difference in change in serum NGF and NT3.
Trial registration: ClinicalTrials.gov identifier: (NCT03304457).

1. Introduction

Schizophrenia (SCZ) is a chronic, severe disabling mental disorder with unclear etiopathogenesis correlated to neuro-developmental and neurodegenerative abnormalities affecting 1% of the general population worldwide (Ashe et al., 2001; Matza et al., 2006; Perez-Neri et al., 2006; van Os et al., 2008; Archer, 2010; Gejman et al., 2011; Owen et al., 2011; Yamamori et al., 2013; Mauri et al., 2014). Adequate neurotrophic support is essential for normal brain development which suggests that a deficit in neurotrophins in cortical neurons is an important factor in the pathophysiology of SCZ (Ghosh et al., 1994; Gorski et al., 2003). Brain-derived neurotrophic factor (BDNF) regulates neuronal survival, differentiation, and growth during brain development with important effects on neurogenesis and neuronal plasticity. According to the neurotrophic hypothesis, the changes in the brain development result due to the inappropriate modulation of neurotrophic factors, especially the decreased serum brain-derived neurotrophic factor (BDNF) (Koeva et al., 2014; Simsek et al., 2015; Zhao et al., 2015). Reduced level of BDNF is also thought to contribute to age-related memory loss and cognitive impairment (Peng et al., 2005). Several studies report altered BDNF mRNA protein in prefrontal cortical regions and hippocampus of post-mortem brain tissues of SCZ (Weickert et al., 2003; Wong et al., 2010; Rao et al., 2015). Reis et al. observed an increase in serum BDNF levels in chronic schizophrenia patients when

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compared with healthy controls (Reis et al., 2008). Whereas in other studies while measuring serum BDNF concentrations in unmedicated or relapsed schizophrenic patients observed a decrease in the concentration(Rizos et al., 2010). Other two important members of neurotrophin family are nerve growth factor (NGF) and neurotrophin 3 (NT3) which are essential mediators of synaptic and morphological plasticity, neuronal growth, survival, and differentiation (McAllister et al., 1999; Vega et al., 2003). It was observed that there is a decrease in serum NGF amongst first episode SCZ and this could become a potential biomarker for SCZ and useful in conjunction with clinical assessment(Xiong et al., 2011; Qin et al., 2017). NT3, responsible for promoting neuronal survival, differentiation, and plasticity, was found to be lowered significantly in SCZ patients by Vargas et al. (2008) However, the regulation of NGF and NT3 in SCZ still remains unclear due to the dissonant evidence from the previous clinical studies (Nanko et al., 1994; Qin et al., 2017).

Antipsychotics are the mainstay of the treatment of SCZ and most of the antipsychotic therapeutics revolve around dopamine hypothesis. However, the neurotrophic hypothesis has gained momentum in the pathophysiology of SCZ and modulation in neurotrophins like BDNF, NGF and NT-3 have been evidenced to be an important therapeutic strategy in SCZ. Olanzapine is an atypical antipsychotic drug which along with clinical improvement in SCZ showed significant improvement in plasma BDNF level (Gonzalez-Pinto et al., 2010; Lee et al., 2011; Nowakowska et al., 2014; Zhang et al., 2018). Hori et al. observed that olanzapine therapy had no effect on plasma BDNF levels in patients of schizophrenia(Hori et al., 2007). Lurasidone, a second-generation antipsychotic having once-daily dosing regimen, highly favourable metabolic profile and minimal alterations in body weight has obvious advantages over some other second-generation antipsychotics (Citrome, 2012; Mauri et al., 2014). Fumagalli et al. (2003) studied the effect of antipsychotics on rat psychosis models by calculating the BDNF mRNA levels in hippocampus and concluded that olanzapine normalized the BDNF expression in MK-801 induced hypoglutamatergic hippocampus while haloperidol decreased the BDNF expression further (Fumagalli et al., 2003). Calabrese et al. (2013) compared the effect of combination therapy of lurasidone and valproate with either drug alone on BDNF protein in rat hippocampus and showed a significant upregulation of mBDNF protein levels with concomitant therapy which was not seen either with lurasidone or valproate whereas proBDNF was increased by valproate but not by lurasidone (Calabrese et al., 2013).

Our literature review revealed that there was no study on the effect of lurasidone on neurotrophins in SCZ and lurasidone had not been directly compared with olanzapine. So, the present study was conducted with an objective to evaluate the effect of lurasidone on neurotrophins in comparison to olanzapine in patients with SCZ. The outcome of this study may enable the clinicians to choose a better alternative among olanzapine and lurasidone which can encompass both dopaminergic and neurotrophic aspects of SCZ.

2. Materials and methods

The present study was conducted after getting approval from the Institutional Ethics Committee, AIIMS, Bhubaneswar, following ICMR's National ethical guidelines for biomedical and health research involving human participants (2017). The study was registered with ClinicalTrials.gov (Identifier: NCT03304457).

2.1. Study population and eligibility

Patients aged 18–45 years, of either sex attending Psychiatry outpatient department of AIIMS, Bhubaneswar with unmedicated SCZ (ICD10) were screened and 101 patients were enrolled following inclusion and exclusion criteria. The recruited patients were treatment naïve or had not taken any treatment for at least 4 weeks before inclusion. Patients with other psychotic spectrum disorders (F21- F29); highly agitated or suicidal patients who need immediate treatment; patients with known history of hypertension, diabetes mellitus or any long-standing significant medical or surgical illness; patients with substance abuse or history of organicity or clinically observable mental retardation were excluded from the study. Patients who were already under treatment for the presenting conditions, with a history of allergy to the study drugs or with a medication history of psychoactive or central nervous system depressant drugs were not included for the study. Pregnant and lactating mothers were also excluded from the study.

2.2. Study design

The present study is a parallel design, open-label, active-controlled randomized clinical trial and was conducted in a single tertiary care centre with an allocation ratio of 1:1. A written informed consent was taken from all patients after explaining the diagnosis, the nature, purpose, risk, and benefits of the proposed treatment. After recruitment, 3 ml blood samples were taken in morning hours after overnight fasting for estimation of serum BDNF, NGF, and neurotrophin 3 estimations at baseline. A detailed history and clinical evaluations were also done including PANSS (Positive and Negative Syndrome Scale) scoring and SOFAS (Social and Occupational Functioning Assessment Scale) scoring at the baseline. The recruited patients were randomized by simple randomization into two treatment groups using computer-generated random codes. The random allocation code of the participants was generated by an investigator who was not involved in patient recruitment. The codes were assigned to a sequence of numbers which was given to another investigator who was responsible for patient recruitment. This process ensured allocation concealment. One group received monotherapy with tablet olanzapine 10 mg daily and another group received tablet lurasidone 80 mg daily. All patients were followed up at the end of 6 weeks of therapy with clinical and biochemical parameters. The patients presenting with worsening of symptoms during unscheduled visits were treated with suitable rescue medication and excluded from the study.

2.3. Outcome measures

2.3.1. Biochemical

Change in the serum BDNF, NGF, and NT3. Serum levels of above biomarkers were estimated by ELISA using Human BDNF, Human NGF, and Human NT3 ELISA kits from Boster Biological Technology Co. Ltd.

2.3.2. Clinical

- Change in the positive and negative syndrome scale (PANSS) scoring (Kay et al., 1987) to assess the change in the symptom severity of SCZ
- Change in the SOFAS scoring to assess the level of functioning in patients with SCZ (Samara et al., 2014).
- Response rate (Percentage of patients achieving < 50% of the reduction in PANSS)

2.4. Safety measures

The occurrence of adverse effects was sought by the nondirective questioning of the patient at the follow-up visit. Patients had free access to the investigators for reporting any adverse effects experienced by them.

2.5. Statistical analysis

Continuous variables have been represented as mean ± standard deviation (SD)/standard error of the mean (SEM) and categorical variables as percentages. Comparison of means of continuous variables

within the groups was done using two-sided paired *t*-test and between groups were done by unpaired *t*-test. Fisher's exact test was used for categorical variables. Pearson product-moment correlation coefficient was calculated for measuring the correlation between PANSS and serum BDNF. Intention to treat (ITT) analysis was performed for all the end-points. Per-protocol analysis was also done to detect a significant difference in the change in BDNF values between the groups. ITT was facilitated by handling the missing values using multiple imputations. Statistical analyses were performed using statistical software SPSS 23.0 (IBM, NY USA) and R 3.5. $P < 0.05$ is considered significant. Receiver operator characteristic (ROC) analysis was performed to detect the cut-off value for the change in BDNF and NT3 levels to differentiate the responders and non-responders. The package pROC was used for ROC analysis (Robin et al., 2011). The sample size of 50 in each group was calculated to detect a difference of 1.5 ng/ml in the change in serum BDNF levels with a standard deviation of 2.5. The study was powered at 80% to detect the significant difference in the change in BDNF levels and the alpha error allowed was 0.05.

3. Results

3.1. Patient demographics and baseline characteristics

Patient enrolment process was started in September 2017 and the study was completed in April 2018. A total of 142 diagnosed unmedicated SCZ patients were screened, out of which 29 did not meet the selection criteria and 12 patients declined to participate. Four patients in the lurasidone group and five patients in the olanzapine group were lost to follow-up at 6 weeks. (Fig. 1). Out of these, one patient in the lurasidone group developed akathisia and two developed extrapyramidal symptoms. For rest of the patients, the reason for the loss to follow-up was unknown. At baseline, there was no significant difference in demographic and clinical parameters between the two treatment groups (Table 1). The overall mean age of the participant's recruitment was 32.7 years and 42.6% amongst them were female.

3.2. Change in serum BDNF

Mean serum BDNF levels (pg/ml) at baseline in the olanzapine and lurasidone groups were 763.96 ± 154.16 and 730.29 ± 150.72 respectively and the difference between the groups was not significant ($p = 0.314$) (Table 1). There was a significant increase in serum BDNF levels in both the treatment groups but the increase was greater with olanzapine than lurasidone and difference in increase between the drug groups was also found to be significant (889.93 pg/ml; 95% CI: 844.12 to 935.74; $p < 0.001$). (Table 2). The cut-off value for the change in BDNF level with ROC analysis (AUC = 0.73) to differentiate responders

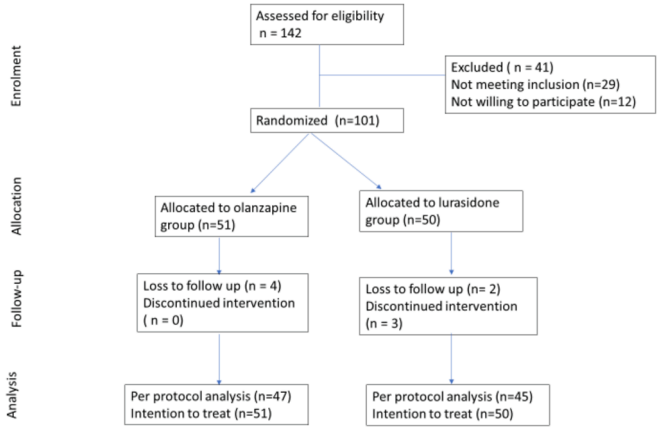

Fig. 1. CONSORT diagram showing the flow of participants through each stage of the randomized trial.

Table 1
Baseline demographic data & clinical characteristics

Characteristics	Olanzapine Group	Lurasidone Group	P Value
Number of patients recruited	51	50	
Number of patients who completed the study	47	45	
Male: Female Ratio	33:18	25:25	0.13
Mean age in Years	31.59 ± 10.30	33.88 ± 9.25	0.24
SOFAS score	50.14 ± 16.28	50.00 ± 14.95	0.96
Positive PANSS score	22.47 ± 8.10	21.18 ± 7.13	0.40
Negative PANSS score	26.08 ± 7.65	26.78 ± 7.82	0.65
General PANSS score	45.08 ± 14.30	45.44 ± 12.20	0.89
Total PANSS score	93.63 ± 27.16	93.40 ± 22.79	0.96
Serum BDNF (pg/ml)	763.96 ± 154.16	730.29 ± 150.72	0.31
Serum NT3 (pg/ml)	6.42 ± 2.24	5.99 ± 1.97	0.61
Serum NGF (pg/ml)	44.97 ± 26.02	38.34 ± 22.52	0.76

All Data in Mean ± SD.
Unpaired *t*-test/Fisher's exact test.

from non-responders based on PANSS percent change was 1353 pg/ml. This value is 84.6% sensitive and 68.1%. (Fig. 2). Similarly, the cut-off value was 886 pg/ml (AUC = 0.57) to differentiate responders from non-responders based on SOFAS percent change (sensitivity – 71.4% and specificity – 47.5%).

3.3. Change in serum NT3

Mean serum NT 3 levels (pg/ml) at baseline were 6.42 ± 2.24 in olanzapine and 5.99 ± 1.97 in lurasidone group and there was no significant difference ($p = 0.61$) between the groups (Table 1). There was a significant increase in the serum levels of NT 3 in both treatment groups but patients in olanzapine group had a significant advantage over lurasidone (3.39; 95% CI:2.09 to 4.68, $p < 0.001$) (Table 2). The cut-off value for the change in NT3 level with ROC analysis (AUC = 0.632) to differentiate responders from non-responders based on PANSS percent change was 20.94 pg/ml. This value is 37.5% sensitive and 92.3%. (Fig. 3). Similarly, the cut-off value was 886 pg/ml (AUC = 0.53) to differentiate responders from non-responders based on SOFAS percent change (sensitivity – 23.8% and specificity – 93.7%).

3.4. Change in serum NGF

Mean serum NGF (pg/ml) were 44.97 ± 26.02 and 38.34 ± 22.52 at baseline in olanzapine and lurasidone group respectively and there was no significant difference ($p = 0.76$) between the groups (Table 1). Increase in the serum NGF levels were significant in both the treatment arms but there was no statistical significance when the mean change of the individual groups was compared (−0.601; 95% CI: 1.79 to 0.591; $p = 0.323$). (Table 2).

3.5. Change in SOFAS score

There was no significant difference in SOFAS score between the groups at baseline (p value = 0.96). There was a significant increase in the score in patients receiving either olanzapine or lurasidone but the difference between the groups was not found to be significant (0.42; 95% CI: 2.78 to 1.93; $p = 0.725$). (Table 2).

3.6. Change in PANSS score

All the domains of PANSS score were assessed separately to assess global symptom severity. There was no significant difference of PANSS score between the groups at baseline in all domain. The positive, negative and general symptom domain, as well as global score, showed improvement over time in both the treatment groups. The olanzapine group had better overall improvement than the lurasidone group (8.06;

Table 2
Change in efficacy parameters in study groups over a period of 6 weeks (Intention to treat analysis).

Variables	Olanzapine group (n = 51)				Lurasidone group (n = 50)				Difference between groups Δ olanzapine vs Δ lurasidone		
	Baseline	Follow up	Mean diff Δ (95%CI)	P Value[$]	Baseline	Follow up	Mean diff Δ (95%CI)	P Value[$]	Mean diff Δ (95%CI)	P Value[€]
SOFAS score	50.14 ± 2.28	61.85 ± 4.61	11.71 (1.85 to 21.58)	0.027	50.00 ± 2.11	62.2 ± 3.6	12.197 (4.746 to 19.647)	0.004	0.423 (−2.78 to 1.93)	0.72
Positive PANSS score	22.47 ± 1.13	10.65 ± 2.93	−11.825 (−18.028 to −5.633)	< 0.001	21.18 ± 1.00	16.2 ± 1.71	−4.978 (−8.624 to −1.332)	0.008	−6.58 (- 8.58 to – 4.58)	< 0.001
Negative PANSS score	26.08 ± 1.07	19.35 ± 0.66	- 6.724 (−9.09 to −4.335)	< 0.001	26.78 ± 1.10	20.03 ± 0.72	−6.748 (−8.98 to −4.51)	< 0.001	−0.028 (−1.01 t0 0.95)	0.95
General PANSS score	45.08 ± 2.00	35.63 ± 1.06	- 9.45 (−13.26 to −5.63)	< 0.001	45.44 ± 1.72	37.17 ± 1.28	- 8.27 (−12.06 to – 4.47)	< 0.001	−1.143 (−2.76 to 0.47)	0.166
Total PANSS score	93.63 ± 3.80	65.63 ± 3.48	−27.99 (−37.35 to −18.64)	< 0.001	93.40 ± 3.22	73.4 ± 2.79	−19.99 (−27.61 to −12.38)	< 0.001	−8.06 (−11.64 to –4.48)	< 0.001
Serum BDNF (pg/ml)	764.65 ± 28.29	2351.13 ± 70.90	1586.47 (1452.19 to 1720.76)	< 0.001	730.29 ± 21.31	1428.7 ± 57.87	698.41 (583.67 to 813.15)	< 0.001	889.93 (844.12 to 935.74)	< 0.001
Serum NT3 (pg/ml)	5.97 ± 1.12	25.46 ± 1.7	19.48 (15.5 to 23.45)	< 0.001	5.82 ± 1.05	22.04 ± 1.33	16.21 (12.65 to 19.78)	< 0.001	3.39 (2.09 to 4.68)	< 0.001
Serum NGF (pg/ml)	41.11 ± 0.92	69.14 ± 1.36	28.03 (25.37 to 30.69)	< 0.001	40.33 ± 1.23	68.86 ± 1.42	28.53 (24.83 to 32.22)	< 0.001	−0.601 (−1.79 to 0.59)	0.32

All data in Mean ± SEM, CI: Confidence interval, [$]Paired *t*-test, [€]Unpaired *t*-test.

Fig. 2. ROC curve for change in BDNF to differentiate responders from non-responders based on PANSS percent change.

Fig:3. ROC curve for change in NT3 to differentiate responders from non-responders based on PANSS percent change.

95% CI: 4.48 to 11.64, $p < 0.001$). Similarly, the decrease in scores of positive symptoms domain was significant (6.58; 95% CI: 4.58 to 8.58; $p < 0.001$ (Fumagalli et al., 2012)) in the olanzapine group over lurasidone. Whereas, when the negative and general symptom group were considered, there was no significant difference between the two drugs (Table 2).

3.7. Correlation between PANSS score and serum concentrations of BDNF, NT3 & NGF

The study result found no significant correlation between PANSS score and serum BDNF at baseline (Pearson correlation coefficient: 0.105; $p = 0.337$). But there was a negative correlation between the change in PANSS score and change in serum BDNF level over 6 weeks (Pearson correlation coefficient: 0.276; $p = 0.001$). No significant correlation was found between total PANSS and NT3 or NGF either at baseline or with change in serum concentrations with therapy. The correlation between individual scores of the positive or negative domain of PANSS and BDNF, NT3 or NGF were not statistically significant, neither at baseline nor with change in serum concentrations with therapy. The results of correlation analysis have been depicted in Table 3.

3.8. Safety evaluation

There was no complaint of any adverse events from patients who were on olanzapine. However, two patients developed weight gain, one developed somnolence and three developed nausea and vomiting in the lurasidone group. One patient in the lurasidone group developed akathisia and two developed extrapyramidal symptoms for which the drug was discontinued in these three patients. Other adverse drug reactions such as constipation, dizziness, headache, abdominal pain, dry mouth,

Table 3
Correlation between PANSS and BDNF, NT3 or NGF.

Baseline Values						
	BDNF		NT3		NGF	
	r	p	r	p	r	p
Total PANSS	−0.105	0.337	0.128	0.516	0.468	0.349
Positive PANSS	−0.093	0.393	0.227	0.246	0.285	0.584
Negative PANSS	−0.054	0.620	−0.139	0.481	0.421	0.406
Change in variables from baseline						
Total PANSS	−0.276	0.001	−0.007	0.942	−0.099	0.323
Positive PANSS	−0.060	0.551	−0.107	0.287	−0.144	0.151
Negative PANSS	−0.172	0.086	−0.046	0.648	−0.084	0.406

r = pearson's correlation co-efficient; p = significance level.

somnolence, nausea were mild in severity and the drug was continued. This indicated that the drug olanzapine was better tolerated than lurasidone ($p < 0.001$ for adverse events comparison between the groups).

4. Discussion

The study results show a decrease in global PANSS scores with olanzapine as well as lurasidone suggesting that both the drugs are efficacious in improving the symptoms of SCZ. The olanzapine group had better overall improvement than the lurasidone group. Similarly, the decrease in scores of positive symptoms domain was significant with olanzapine over lurasidone. Social functioning comprises self-care and activities of daily living, communication and interpersonal relations, instrumental living, and work skills. Social and Occupational Functioning Assessment Scale (SOFAS) was used to assess impairment as a direct consequence of mental and physical health problem associated with the disease. Considering social and occupational functioning on a continuum from excellent functioning to grossly impaired functioning, both the study drugs significantly improved function based on social scoring but there was no significant difference between the groups. Thus, the improvement in PANSS and SOFAS in both the treatment groups suggest a decrease in disease severity by both the drugs which is an important treatment goal in SCZ. However, the overall results were in favor of olanzapine which was similar to the studies by Zhang et al. which showed that olanzapine improves psychiatric symptoms and cognitive dysfunction, particularly attention and immediate memory, in patients with acute schizophrenia, in parallel with increased plasma BDNF levels and Harvey et al. established that olanzapine yielded statistically significant results vs placebo for both total and positive PANSS scores(Harvey et al., 2016; Zhang et al., 2018).

Comparing the serum BDNF level of both the study group at baseline showed no significant difference. Rizos et al. suggested that the baseline level of BDNF in patients with SCZ was significantly less in comparison to a healthy individual (Rizos et al., 2010). However, in another study by Martinez-Cengotitabengoa et al. showed no difference in plasma levels of BDNF and NGF between patients of SCZ and control groups(Martinez-Cengotitabengoa et al., 2016). The reduction in serum BDNF indicates a potential deficit in neurotrophic factor release in patients with SCZ and support the concept that alterations in BDNF levels might be associated with SCZ(Koeva et al., 2014). In the present study, we evaluated the change in serum BDNF over 6 weeks of treatment with either olanzapine or lurasidone. After the follow-up period of 6 weeks, serum BDNF level increased significantly in both the groups but the increase is in level with olanzapine was significantly higher. At baseline, there was no significant correlation between PANSS score and serum BDNF but the change in serum BDNF and the change in total PANSS over 6 weeks showed a significant inverse correlation. However, a positive correlation between serum BDNF and negative domain scoring of PANSS has been observed in the previous study (Reis et al., 2008). As suggested by two studies on olanzapine, response to monotherapy in SCZ patients might be influenced by BDNF(Gonzalez-Pinto et al., 2010; Nikolac Perkovic et al., 2014). Fumagalli F et al. found that BDNF transcripts in prefrontal cortex and hippocampus are modulated by chronic lurasidone treatment and thus affects BDNF regulation which in turn is associated with neuronal plasticity and cognition impairments in SCZ (Fumagalli et al., 2012).

Evaluation of other two neurotrophic factors like serum NGF and NT3 as potential biomarkers were also done in this study. Serum NT3 levels were lower in SCZ patients suggests that the NT3 signaling system may play a role in the pathophysiology of SCZ Vargas HE et al. also showed decreased NT3 levels in SCZ male patients(Vargas et al., 2008). Nanko S et al. and Jonsson E et al. also suggested an association between Neurotrophin-3 gene polymorphism and schizophrenia which supports the current hypothesis that neurotrophins are involved in the pathophysiology of SCZ(Nanko et al., 1994; Jonsson et al., 1997; Vargas et al., 2008). There was a significant increase in the serum NT3 in both treatment groups after 6 weeks of treatment but the difference between the groups was statistically non-significant. Similarly, there was a significant increase in serum NGF in both the therapy groups over 6 weeks of treatment but the difference between the groups was not significant. Recent preclinical and clinical data show that dysfunction of central neurotrophins such as NT3, NGF, and BDNF might contribute to impaired brain development and neuroplasticity leading to SCZ(Durany et al., 2001). Kessler RM et al. demonstrated olanzapine sparing of D2/D3 receptor in substantia nigra/ventral tegmental area which may contribute to the low incidence of extrapyramidal side effects in olanzapine-treated patients(Kessler et al., 2005). In common marmosets Compared to olanzapine, lurasidone has the ability to preferentially bind to D2/D3 receptors rather than 5-HT_{2A} receptors. These findings might be conclusive of the contribution of in vivo 5-HT_{2A} receptor blocking activity to the difference in the pharmacological profile of lurasidone and olanzapine in terms of the efficacy against negative symptoms and low risk of the extrapyramidal syndrome(Nakazawa et al., 2013).

Limitations: An open-label design and short follow-up period were the major limitations of this study. A longer follow-up is required to see whether there is any further difference between the groups as 6-week duration may not be enough to evaluate the long-term effect of the antipsychotics on biomarkers.

5. Conclusions

Serum BDNF, NGF, NT3 in patients with unmedicated SCZ were increased significantly with treatment with both olanzapine and lurasidone. Considering the improvement in PANSS and SOFAS scores, the efficacy of olanzapine in reducing the severity of diseases and increasing social functioning were proved to be better than lurasidone and olanzapine was better tolerated than lurasidone. Serum BDNF is an already established biomarker but serum NT3 and NGF could also be used as potential prognostic biomarkers for SCZ patients. Keeping the limitations of the present study in mind, a randomized, double-blind, multicentric clinical trial is warranted to further evaluate and confirm the findings of this study.

Conflicts of interest

Nil.

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References

Archer, T., 2010. Neurodegeneration in schizophrenia. Expert Rev. Neurother. 10, 1131–1141.

Ashe, P.C., Berry, M.D., Boulton, A.A., 2001. Schizophrenia, a neurodegenerative disorder with neurodevelopmental antecedents. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 25, 691–707.

Calabrese, F., Luoni, A., Guidotti, G., Racagni, G., Fumagalli, F., Riva, M.A., 2013. Modulation of neuronal plasticity following chronic concomitant administration of the novel antipsychotic lurasidone with the mood stabilizer valproic acid. Psychopharmacology (Berlin) 226, 101–112.

Citrome, L., 2012. Lurasidone in schizophrenia: new information about dosage and place in therapy. Adv. Ther. 29, 815–825.

Durany, N., Michel, T., Zochling, R., Boissl, K.W., Cruz-Sanchez, F.F., Riederer, P., Thome, J., 2001. Brain-derived neurotrophic factor and neurotrophin 3 in schizophrenic psychoses. Schizophr. Res. 52, 79–86.

Fumagalli, F., Calabrese, F., Luoni, A., Bolis, F., Racagni, G., Riva, M.A., 2012. Modulation of BDNF expression by repeated treatment with the novel antipsychotic lurasidone under basal condition and in response to acute stress. Int. J. Neuropsychopharmacol. 15, 235–246.

Fumagalli, F., Molteni, R., Roceri, M., Bedogni, F., Santero, R., Fossati, C., Gennarelli, M., Racagni, G., Riva, M.A., 2003. Effect of antipsychotic drugs on brain-derived neurotrophic factor expression under reduced N-methyl-D-aspartate receptor activity. J. Neurosci. Res. 72, 622–628.

Gejman, P.V., Sanders, A.R., Kendler, K.S., 2011. Genetics of schizophrenia: new findings and challenges. Annu. Rev. Genom. Hum. Genet. 12, 121–144.

Ghosh, A., Carnahan, J., Greenberg, M.E., 1994. Requirement for BDNF in activity-dependent survival of cortical neurons. Science 263, 1618–1623.

Gonzalez-Pinto, A., Mosquera, F., Palomino, A., Alberich, S., Gutierrez, A., Haidar, K., Vega, P., Barbeito, S., Ortiz, A., Matute, C., 2010. Increase in brain-derived neurotrophic factor in first episode psychotic patients after treatment with atypical antipsychotics. Int. Clin. Psychopharmacol. 25, 241–245.

Gorski, J.A., Zeiler, S.R., Tamowski, S., Jones, K.R., 2003. Brain-derived neurotrophic factor is required for the maintenance of cortical dendrites. J. Neurosci. 23, 6856–6865.

Harvey, R.C., James, A.C., Shields, G.E., 2016. A systematic review and network meta-analysis to assess the relative efficacy of antipsychotics for the treatment of positive and negative symptoms in early-onset schizophrenia. CNS Drugs 30, 27–39.

Hori, H., Yoshimura, R., Yamada, Y., Ikenouchi, A., Mitoma, M., Ida, Y., Nakamura, J., 2007. Effects of olanzapine on plasma levels of catecholamine metabolites, cytokines, and brain-derived neurotrophic factor in schizophrenic patients. Int. Clin. Psychopharmacol. 22, 21–27.

Jonsson, E., Brene, S., Zhang, X.R., Nimgaonkar, V.L., Tylec, A., Schalling, M., Sedvall, G., 1997. Schizophrenia and neurotrophin-3 alleles. Acta Psychiatr. Scand. 95, 414–419.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Kessler, R.M., Ansari, M.S., Riccardi, P., Li, R., Jayathilake, K., Dawant, B., Meltzer, H.Y., 2005. Occupancy of striatal and extrastriatal dopamine D2/D3 receptors by olanzapine and haloperidol. Neuropsychopharmacology 30, 2283–2289.

Koeva, Y.A., Sivkov, S.T., Akabaliev, V.H., Ivanova, R.Y., Deneva, T.I., Grozlekova, L.S., Georgieva, V., 2014. Brain-derived neurotrophic factor and its serum levels in schizophrenic patients. Folia Med. (Plovdiv) 56, 20–23.

Lee, A.H., Lange, C., Ricken, R., Hellweg, R., Lang, U.E., 2011. Reduced brain-derived neurotrophic factor serum concentrations in acute schizophrenic patients increase during antipsychotic treatment. J. Clin. Psychopharmacol. 31, 334–336.

Martinez-Cengotitabengoa, M., MacDowell, K.S., Alberich, S., Diaz, F.J., Garcia-Bueno, B., Rodriguez-Jimenez, R., Bioque, M., Berrocoso, E., Parellada, M., Lobo, A., Saiz, P.A., Matute, C., Bernardo, M., Gonzalez-Pinto, A., Leza, J.C., PEPs, F., 2016. BDNF and NGF signalling in early phases of psychosis: relationship with inflammation and response to antipsychotics after 1 year. Schizophr. Bull. 42, 142–151.

Matza, L.S., Buchanan, R., Purdon, S., Brewster-Jordan, J., Zhao, Y., Revicki, D.A., 2006. Measuring changes in functional status among patients with schizophrenia: the link with cognitive impairment. Schizophr. Bull. 32, 666–678.

Mauri, M.C., Paletta, S., Maffini, M., Colasanti, A., Dragogna, F., Di Pace, C., Altamura, A.C., 2014. Clinical pharmacology of atypical antipsychotics: an update. EXCLI J 13, 1163–1191.

McAllister, A.K., Katz, L.C., Lo, D.C., 1999. Neurotrophins and synaptic plasticity. Annu. Rev. Neurosci. 22, 295–318.

Nakazawa, S., Yokoyama, C., Nishimura, N., Horisawa, T., Kawasaki, A., Mizuma, H., Doi, H., Onoe, H., 2013. Evaluation of dopamine D(2)/D(3) and serotonin 5-HT(2)A receptor occupancy for a novel antipsychotic, lurasidone, in conscious common marmosets using small-animal positron emission tomography. Psychopharmacology (Berlin) 225, 329–339.

Nanko, S., Hattori, M., Kuwata, S., Sasaki, T., Fukuda, R., Dai, X.Y., Yamaguchi, K., Shibata, Y., Kazamatsuri, H., 1994. Neurotrophin-3 gene polymorphism associated with schizophrenia. Acta Psychiatr. Scand. 89, 390–392.

Nikolac Perkovic, M., Nedic Erjavec, G., Zivkovic, M., Sagud, M., Uzun, S., Mihaljevic-Peles, A., Kozumplik, O., Muck-Seler, D., Pivac, N., 2014. Association between the brain-derived neurotrophic factor Val66Met polymorphism and therapeutic response to olanzapine in schizophrenia patients. Psychopharmacology (Berlin) 231, 3757–3764.

Nowakowska, E., Kus, K., Ratajczak, P., Cichocki, M., Wozniak, A., 2014. The influence of aripiprazole, olanzapine and enriched environment on depressant-like behavior, spatial memory dysfunction and hippocampal level of BDNF in prenatally stressed rats. Pharmacol. Rep. 66, 404–411.

Owen, M.J., O'Donovan, M.C., Thapar, A., Craddock, N., 2011. Neurodevelopmental hypothesis of schizophrenia. Br. J. Psychiatry 198, 173–175.

Peng, S., Wuu, J., Mufson, E.J., Fahnestock, M., 2005. Precursor form of brain-derived neurotrophic factor and mature brain-derived neurotrophic factor are decreased in the pre-clinical stages of Alzheimer's disease. J. Neurochem. 93, 1412–1421.

Perez-Neri, I., Ramirez-Bermudez, J., Montes, S., Rios, C., 2006. Possible mechanisms of neurodegeneration in schizophrenia. Neurochem. Res. 31, 1279–1294.

Qin, X.Y., Wu, H.T., Cao, C., Loh, Y.P., Cheng, Y., 2017. A meta-analysis of peripheral blood nerve growth factor levels in patients with schizophrenia. Mol. Psychiatr. 22, 1306–1312.

Rao, J., Chiappelli, J., Kochunov, P., Regenold, W.T., Rapoport, S.I., Hong, L.E., 2015. Is schizophrenia a neurodegenerative disease? Evidence from age-related decline of brain-derived neurotrophic factor in the brains of schizophrenia patients and matched nonpsychiatric controls. Neurodegener. Dis. 15, 38–44.

Reis, H.J., Nicolato, R., Barbosa, I.G., Teixeira do Prado, P.H., Romano-Silva, M.A., Teixeira, A.L., 2008. Increased serum levels of brain-derived neurotrophic factor in chronic institutionalized patients with schizophrenia. Neurosci. Lett. 439, 157–159.

Rizos, E.N., Papadopoulou, A., Laskos, E., Michalopoulou, P.G., Kastania, A., Vasilopoulos, D., Katsafouros, K., Lykouras, L., 2010. Reduced serum BDNF levels in patients with chronic schizophrenic disorder in relapse, who were treated with typical or atypical antipsychotics. World J. Biol. Psychiatr. 11, 251–255.

Robin, X., Turck, N., Hainard, A., Tiberti, N., Lisacek, F., Sanchez, J.-C., Müller, M., 2011. pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinf. 12, 77.

Samara, M.T., Engel, R.R., Millier, A., Kandenwein, J., Toumi, M., Leucht, S., 2014. Equipercentile linking of scales measuring functioning and symptoms: examining the GAF, SOFAS, CGI-S, and PANSS. Eur. Neuropsychopharmacol. 24, 1767–1772.

Simsek, S., Gencoglan, S., Yuksel, T., Kaplan, I., Aktas, H., 2015. Lower brain-derived neurotropic factor levels in untreated adolescents with first-episode psychosis. J. Clin. Psychopharmacol. 35, 596–599.

van Os, J., Rutten, B.P., Poulton, R., 2008. Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. Schizophr. Bull. 34, 1066–1082.

Vargas, H.E., Gama, C.S., Andreazza, A.C., Medeiros, D., Stertz, L., Fries, G., Palha, J., Cereser, K.M., Berk, M., Kapczinski, F., Belmonte-de-Abreu, P.S., 2008. Decreased serum neurotrophin 3 in chronically medicated schizophrenic males. Neurosci. Lett. 440, 197–201.

Vega, J.A., Garcia-Suarez, O., Hannestad, J., Perez-Perez, M., Germana, A., 2003. Neurotrophins and the immune system. J. Anat. 203, 1–19.

Weickert, C.S., Hyde, T.M., Lipska, B.K., Herman, M.M., Weinberger, D.R., Kleinman, J.E., 2003. Reduced brain-derived neurotrophic factor in prefrontal cortex of patients with schizophrenia. Mol. Psychiatr. 8, 592–610.

Wong, J., Hyde, T.M., Cassano, H.L., Deep-Soboslay, A., Kleinman, J.E., Weickert, C.S., 2010. Promoter specific alterations of brain-derived neurotrophic factor mRNA in schizophrenia. Neuroscience 169, 1071–1084.

Xiong, P., Zeng, Y., Wan, J., Xiaohan, D.H., Tan, D., Lu, J., Xu, F., Li, H.Y., Zhu, Z., Ma, M., 2011. The role of NGF and IL-2 serum level in assisting the diagnosis in first episode schizophrenia. Psychiatr. Res. 189, 72–76.

Yamamori, H., Hashimoto, R., Ishima, T., Kishi, F., Yasuda, Y., Ohi, K., Fujimoto, M., Umeda-Yano, S., Ito, A., Hashimoto, K., Takeda, M., 2013. Plasma levels of mature brain-derived neurotrophic factor (BDNF) and matrix metalloproteinase-9 (MMP-9) in treatment-resistant schizophrenia treated with clozapine. Neurosci. Lett. 556, 37–41.

Zhang, Y., Fang, X., Fan, W., Tang, W., Cai, J., Song, L., Zhang, C., 2018. Brain-derived neurotrophic factor as a biomarker for cognitive recovery in acute schizophrenia: 12-week results from a prospective longitudinal study. Psychopharmacology (Berlin) 235, 1191–1198.

Zhao, X., Huang, Y., Chen, K., Li, D., Han, C., Kan, Q., 2015. The brain-derived neurotrophic factor Val66Met polymorphism is not associated with schizophrenia: an updated meta-analysis of 11,480 schizophrenia cases and 13,490 controls. Psychiatr. Res. 225, 217–220.