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Serum brain-derived neurotrophic factor and clozapine daily dose in patients with schizophrenia: A positive correlation

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) plays a critical role in neurodevelopment and neuroplasticity. Altered BDNF signaling is thought to contribute to the pathogenesis of schizophrenia (SZ) especially in relation to cognitive deficits. Clozapine (CLZ) has been shown a beneficial effect on cognition in SZ in some studies and a detrimental effect in others. To examine serum BDNF, two groups of chronically medicated DSM-IV SZ patients ($n = 44$), on treatment with clozapine ($n = 31$) and typical antipsychotics ($n = 13$) had 5 ml blood samples collected by venipuncture. Serum BDNF levels were significantly correlated with CLZ daily dose ($r = 0.394$, $p = 0.028$), but not with typical antipsychotic daily dose ($r = 0.208$, $p = 0.496$). This study suggests that serum BDNF levels are correlated with CLZ daily dose, and this may lead to the cognitive enhancement as seen in patients with SZ under CLZ. Despite the strong evidence that chronic administration of CLZ is effective for patients with SZ, it is still unknown whether atypical antipsychotic drugs regulate BDNF expression. Serum BDNF levels concentration in SZ merits further investigations with regard to the role of neurotrophins in the cognitive response to treatment with CLZ and other atypical antipsychotics.

Schizophrenia (SZ) is a complex and severe brain disorder with poorly defined etiology and pathophysiology [27]. Cognitive function may be markedly impaired in patients with SZ [20]. Several neuroimaging and postmortem findings, along with the behavioral and cognitive deterioration observed in schizophrenic patients, could reflect a significant neurodegenerative process [19]. General cognitive ability assessed either by formal cognitive tests or by using educational achievement as a proxy measure, is lower in children at risk to develop SZ compared to their healthy counterparts [27].

Brain-derived neurotrophic factor (BDNF) is the most widely distributed neurotrophin in the central nervous system, important for neurogenesis, neuronal survival, and normal maturation of neural developmental pathways [25]. Eventually in the adult, it is not only important for synaptic plasticity and dendritic growth, but also essential to long-term memory [3,25]. Altered BDNF-signaling is thought to contribute to the pathogenesis of SZ, especially in relation to cognitive deficits [5,9] and it is suggested that genetic variation in the BDNF gene modulates prefrontral and limbic functioning [2]. Nevertheless, analysis of serum BDNF as a potential biomarker in this disease has provided controversial data [5].

Serum BDNF levels in patients with SZ have been widely reported in literature, some findings of decreased [16,24,33] and others of increased BDNF serum levels [10] compared to controls. A recent meta-analysis with SZ patients reported an association between reduced BDNF and age, but not between BDNF and medication dosage [15]. Studies with drug naïve patients identified decreased BDNF at the onset of psychosis [18,23] and indicated that low serum BDNF levels at the onset of SZ is associated with a long duration of untreated psychosis [28]. It was also reported that BDNF levels at the onset of SZ may be associated with the pathophysio-

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Table 1
Characteristics of patients with schizophrenia (SZ) under clozapine or typical antipsychotic.

	SZ clozapine ($n = 31$)	SZ typical ($n = 13$)	p-Value
Gender (male/female)	24/7	11/2	0.703*
Age (years)[a]	42.7 (10.0)	39.5 (8.3)	0.283**
IMC (kg/m^2)[a]	27.3 (4.6)	29.4 (5.2)	0.268**
Years of illness[b]	20.0(17.0)	12.0(17.5)	0.268***
BDNF (pg/μg)[a]	0.14 (0.08)	0.14 (0.08)	0.957**
BPRS score[b]	10.5 (13.0)	16.0 (13.5)	0.791***
Antipsychotic daily dose, in mg of chlorpromazine equivalents[a]	553.2 (192.8)	472.8 (268.8)	0.269**

BPRS, Brief Psychiatry Rating Scale.
[a] Shown as mean (standard deviation).
[b] Shown as median (interquartile range).
* Chi-square.
** *T*-Test.
*** Mann–Whitney.

logical processes as well as the severity of positive and negative psychotic symptoms [29].

The introduction of clozapine (CLZ), an atypical antipsychotic, for the treatment of poorly responsive patients with SZ has fostered widespread hope among patients, their families, and caregivers [14]. Importantly, CLZ has been shown a beneficial effect on cognition in SZ in some studies and a detrimental effect in others [26].

Given the evidence of the pharmacological role of antipsychotics on BDNF levels, and its correlation to cognition, we assessed serum BDNF levels in chronically stable schizophrenic patients in order to establish a relationship with CLZ daily doses.

This study protocol was approved by the Ethical Committee of the Hospital de Clínicas de Porto Alegre, RS, Brazil (HCPA). In accordance with the Declaration of Helsinki, all subjects were advised about the procedure and signed the informed consent form prior to participation in the study. Forty-four outpatients from the HCPA Schizophrenia Program were enrolled to this study protocol. They all were on chronic medication, thirty-one subjects taking CLZ, and thirteen, typical antipsychotics. Patients receiving typical antipsychotics were all treated with haloperidol and some with adjunctive chlorpromazine to it. Medications doses are presented in mg of chlorpromazine equivalents to facilitate comparisons between them.

None of them had any neurological disease, brain tumor, thyroid disease, severe hepatic disease, severe cardiac disease or any other psychiatric diagnosis. This group of patients had to fulfill Diagnostic and Statistical Manual of Mental Disorders; fourth Edition (DSM-IV) [6] criteria for SZ and their psychopathological state was measured with 18-item Brief Psychiatry Rating Scale (BPRS) [30]. Each subject had 5 ml blood samples collected by venipuncture without anticoagulants, and serum was obtained by centrifugation at $300 \times g$ for 5 min and kept frozen at $-70\,^{\circ}$C for up to 6 months, until the assay.

BDNF levels were measured with ELISA, using a commercial kit according to the manufacturer's instructions (Chemicon, USA) as described elsewhere [10].

Analysis was performed using Statistical Product and Service Solutions 16.0 Version (SPSS). Demographic and clinical characteristics were analyzed using Chi-Square, Mann–Whitney or *T*-test. Descriptive analyses are presented as mean (standard deviation) or median (interquartile range) and p-values < 0.05 were considered significant. Relationships between variables were assessed with Pearson rank correlation coefficient.

The subjects' characteristics are summarized in Table 1. Serum BDNF levels were significantly correlated with CLZ daily dose ($r = 0.394$, $p = 0.028$; Fig. 1), but not with typical antipsychotic daily dose ($r = 0.208$, $p = 0.496$), both in mg of chlorpromazine equivalents.

Our study showed that serum BDNF levels are directly associated with CLZ daily dose in schizophrenic patients. Higher BDNF levels were found in patients with higher antipsychotic daily doses, which are in line with both the property of atypical antipsychotics to increase BDNF, and the literature demonstrating higher BDNF levels in chronically medicated SZ patients [10].

In line with our findings, previous studies have reported that serum BDNF levels were positively correlated with CLZ dose [16,32]. It was also found that chronic treatment with the atypical antipsychotics CLZ and olanzapine increase BDNF expression in the rat hippocampus while haloperidol decreases BDNF expression [1]. Xiu et al. [36] reported a significant difference in BDNF levels between antipsychotic types: risperidone was found to produce a more robust effect on BDNF compared to CLZ and typical antipsychotic. However, some studies could not conclude that treatment with antipsychotics alters serum BDNF levels in patients with SZ [15,24,33]. Such differences between typical and some atypical drugs regarding neurotrophic and neuroprotective mechanisms could have implications on the clinical course of the disorder and on brain loss associated with SZ [11–13,15,16].

Despite some inconsistency, these findings seem to corroborate the hypothesis of a positive relationship between the dose of the antipsychotic medication CLZ and serum BDNF level. Furthermore, it has already been reported that different effects of typical and atypical antipsychotics may differently affect blood and brain BDNF levels in SZ and that atypical antipsychotics may favorably modulate BDNF expression [15,16].

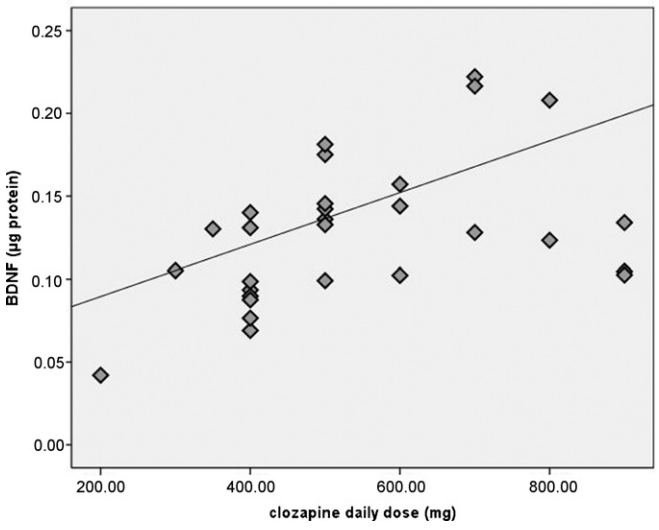

Fig. 1. Positive correlation between serum brain-derived neurotrophic factor (BDNF) and antipsychotic daily dose in mg of chlorpromazine equivalents in 31 patients with schizophrenia under clozapine ($r = 0.394$, $p = 0.028$, Pearson rank correlation coefficient).

Cognitive deficits are increasingly seen as part of the core pathology of SZ and two areas with well-documented roles in multiple domains of cognition, hippocampus and the prefrontal cortex, are noted to have reductions in BDNF mRNA expression and BDNF protein post-mortem [18,21]. A post-mortem study reported a reduction in BDNF production and availability in the dorsolateral prefrontal cortex of patients with SZ and suggested that intrinsic cortical neurons, afferent neurons, and target neurons may receive less trophic support in this disorder [35].

In animal experiments, the acquisition and maintenance of spatial memory are impaired when BDNF signaling is decreased. However, brain BDNF is increased when rodents perform a spatial learning task or are housed in cognitively stimulating environments [34]. A recent study suggested that serum BDNF levels might serve as a peripheral biomarker for the effects of intensive cognitive training [34]. Concerning behavioral intervention, it has been found that BDNF levels were significantly higher in patients on a hypocaloric diet [17]. Nevertheless, there are no empirical methods to identify any specific features in patients with SZ, in particular, to determine their cognitive status [4]. These findings seem to corroborate that BDNF is related to cognition, and since CLZ increases serum BDNF levels, as found by us and others [16,32], we could hypothesize that schizophrenic patients treated with CLZ may have a cognitive enhancement.

These data also support the growing body of evidence regarding the modulating effect of CLZ on cognition. There are some reports that CLZ may produced symptomatic and cognitive improvements (psychomotor speed, verbal fluency, verbal learning and memory), positive changes that appeared to occur independently of one another and may reflect an impact on remediable brain functioning and may offer an advantage to patients with schizophrenia by enhancing the possibility of better vocational functioning and quality of life [20,21,31]. Zhao et al. [37] reported that CLZ might improve negative symptoms and improve cognitive dysfunction, although it could not improve hypofrontality – reduced cerebral blood flow in the prefrontal lobe. Molina et al. [22] found that CLZ may normalize the pattern of brain activation during an attention test (Stroop) to a higher degree than risperidone in patients resistant to the latter. A recent trial indicated that memantine adjunctive to CLZ, but not any other antipsychotic, significantly improved positive, negative and cognitive symptoms in treatment refractory patients with SZ [7]. However, the symptomatological improvement is not related to BNDF serum levels [8] driving to other pathways of cognitive improvement than neurotrophins.

Our report must be interpreted in light of its limitations. Firstly, a control group was not included. Secondly, this study failed to include clinical parameters of cognition. Nevertheless, this is the first report detailing the relationship between BDNF level and CLZ daily dose. For cognitive improvement approaching by CLZ administration, a cross-sectional design is limited. However, the present results gave us the compelling evidence for a follow-up study of clozapine use, serum BDNF levels and cognitive improvements that has been planned by our group. Finally, despite the fact that we found a statistically significant correlation ($p = 0.028$) between the BDNF and CLZ daily dose, the value of such correlation is quite small ($r = 0.394$) and explains only around 16% of the variance accounted for by such association.

This study suggests that serum BDNF levels are correlated with CLZ daily dose, and this may lead to the cognitive enhancement as seen in patients with SZ under CLZ. Despite the strong evidence that chronic administration of CLZ is effective for patients with SZ, it is still unknown whether atypical antipsychotic drugs regulate BDNF expression. Serum BDNF levels concentration in SZ merits further investigations with regard to the role of neurotrophins in the cognitive response to treatment with CLZ and other atypical antipsychotics.

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