

The Effects of Olanzapine, a Novel Antipsychotic, on Auditory Event-Related Potentials in Schizophrenia¹

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SUMMARY:

THE EFFECTS OF OLANZAPINE, A NOVEL ANTIPSYCHOTIC, ON AUDITORY EVENT-RELATED POTENTIALS IN SCHIZOPHRENIA

Object: A reduced amplitude of N1 and P3 which are recorded from schizophrenic patients, have often been found to be related to this illness psychopathology. There is a controversy on the effects of antipsychotic medication on the event-related potentials. The current study focuses on the effects of olanzapine, atypical antipsychotic medication on clinical status and the event-related potentials in schizophrenia. **Method:** Event-related potentials were recorded in 12 schizophrenic patients when they were free of medication and after 6 weeks of olanzapine (10 mg/day) treatment and 10 control subjects. **Results:** In the schizophrenic patients the N1 and the P3 amplitude was significantly reduced and the P3 latency prolonged when compared with control group. The P3 amplitude increased to values of normal controls after 6 weeks of olanzapine treatment. The N1 amplitude and the P3 latency remained unchanged after treatment in spite of clinical improvement. The amplitude of P3 is correlated with negative symptom scores of Brief Psychiatric Rating Scale (BPRS) before and after the treatment. P3 latency had a positive correlation with total BPRS scores not only before but also after the treatment. **Conclusions:** A prolonged P3 latency and reduced P3 amplitude indicate an impairment of auditory information processing in patients with schizophrenia however, we suggest that these parameters which are dependent on the clinical status of patients are influenced by atypical antipsychotics medication. The finding of a reduced P3 amplitude in schizophrenics before medication that is normalized by olanzapine medication has not been reported previously.

Key Words: schizophrenia, event-related potentials, olanzapine

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ÖZET:

ŞİZOFRENİDE YENİ BİR ANTİPSİKOTİK OLAN OLANZAPİNİN İŞİTSEL OLAYA İLİŞKİN POTANSİYELLER ÜZERİNE OLAN ETKİLERİ

Amaç: Şizofreni hastalarında kaydedilen N1 ve P3 potansiyellerindeki genlik azalmaları genellikle bu hastalığın psikopatoloji ile ilişki bulunmuştur. Bununla beraber antipsikotik ilaçların olaya ilişkin potansiyelleri (OLP) üzerinde olan etkileri hakkında tam bir fikir birliği yoktur. Bu çalışma bir atipik antipsikotik olan olanzapinin şizofrenideki klinik duruma ve olaya ilişkin potansiyeller üzerine olan etkisini araştırmaktadır. **Metod:** Olaya ilişkin potansiyeller şizofrenik hastalardan ilüçsüz dönemde ve 6 haftalık olanzapin (10mg/gün) tedavisi sonrasında ve 10 sağlıklı şahıstan elde edildi. **Sonuçlar:** Kontrol grubu ile karşılaştırıldığında şizofreni hastalarından elde edilen N1 ve P3 genliğinde istatistiki olarak önemli bir azalma ve P3 latansında uzama bulundu. Altı haftalık olanzapin tedavisinden sonra, P3 genliği sağlıklı deneklerin değerlerine yaklaştı. Tedavi ile klinik düzelme izlenmesine rağmen, N1 genliği ve P3 latansı değerlerinde değişiklik gözlenmedi. P3 genlik değerleri, tedavi öncesi ve sonrası Kısa Psikiyatrik Değerlendirme Ölçeği'nin (BPRS) negatif semptom skorları ile korelasyon gösteriyordu. P3 latansı, sadece tedavi öncesi değil, sonrasında da total BPRS skorları ile korelasyon göstermekteydi. **Tartışma:** Uzamış P3 latansı ve azalmış P3 genliği şizofrenik hastalar işitsel bilgi işleme süreçlerindeki bozulmayı göstermekte ise de atipik antipsikotik ilaç tedavisi ile klinik duruma bağımlı bu parametreler değişebileceğini düşünmekteyiz. Şizofrenik hastalarda tedavi öncesi tespit edilebilen ve olanzapin tedavisi ile normalize olan P3 genlik azalması daha önce bildirilmemiştir.

Anahtar sözcükler: şizofreni, olaya ilişkin potansiyeller, olanzapin

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INTRODUCTION

Schizophrenia is a debilitating disorder of the central nervous system whose symptoms have been divided into two classes: positive symptoms, including hallucinations, delusions, and conceptual disorganization; and negative symptoms, including social with-

drawal, blunted affect, and poverty of speech (1). Electrophysiological studies employing a variety of perceptual tasks have reported changes in auditory event-related potentials (ERPs) which distinguish schizophrenic subjects from controls. A consistently reported observation in schizophrenic subjects is a reduction in the amplitude of P3 with auditory (2, 3, 4) and visu-

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al stimuli (5). Although earlier studies have reported no change in P3 latency in schizophrenia, later some researchers (6, 7) have reported prolonged P3 latency in schizophrenia. In addition to midline P3 reductions, chronically ill schizophrenics display asymmetry in P3, with smaller voltage over the left vs the right temporal lobe (1, 8). Although the exact cognitive processes underlying P3 are unknown, P3 latency has been interpreted as metric cognitive processing speed, essentially the time subsumed by stimulus perception and identification/classification (9, 10), while its amplitude has been thought to reflect the amount of information extracted from the stimulus (11).

Changes in the amplitude and latency of the components of auditory ERP have also been reported in schizophrenia. It has been reported that the latency of the N1 component is decreased in schizophrenia (12, 13, 14, 15). This reduction could be related to decreased attention or arousal (1, 16), and perhaps to antipsychotic medication (14). P2 is often reported to be earlier, or larger in schizophrenics (17, 18), and N2 is smaller (12).

One proposal for the etiology of schizophrenia is the dopamine hypothesis. It postulates that hyperactivity of the brain's dopamine system (increased release of dopamine or increased receptor sensitivity of certain brain sites) results in schizophrenic symptoms. If P3 amplitude reduction is related to an excess of dopamine, P3 should increase following antipsychotic medication blocking dopamine system. Some investigators compared a group of medicated schizophrenics to a group of unmedicated schizophrenics. While some of them found larger P3 with medication (19, 20), others found no difference (4, 13, 14, 21, 22). A better design was employed recently, in which the same patients were tested before and after antipsychotic medication. Duncan et al (23) showed an increase in visual (but not auditory) P3 amplitude after medication. Consistent with this study, Blackwood et al (22) studied the same patients before and after medication, and auditory P3 was not increased by clinical improvement. In the study by Ford et al (24), in spite of significant clinical improvement with antipsychotic treatment, amplitudes of auditory P3 were not significantly changed. Although the studies above indicate a typical and unchanged P3 abnormality in schizophrenics, recent studies indicate that antipsychotic medication should affect this abnormality. Coburn et al (25) found that antipsychotic medication normalized P3 latency and increased amplitude, but the latter re-

mained below normal limits overall except for frontal areas. In an experimental animal study (Macaca Fascicularis) (26) sulpiride, a dopamine D2 receptor antagonist increased both the latency and the amplitude of P3.

On the other hand it was demonstrated that P3 amplitude was smaller in unmedicated patients with more negative symptoms which are associated with low dopamine levels in the frontal cortex (26, 13). It is thought that low dopamine levels in the frontal cortex increases dopamine in the dorsal (caudate/putamen) and ventral (nucleus accumbens) striatum which causes positive symptoms.

Recent studies showed that clozapine, an atypical antipsychotic, is effective not only in the treatment of resistant schizophrenia but also of negative symptoms which typical antipsychotics are not very potent to treat (28). It has become apparent that the action mechanism of atypical antipsychotics, such as clozapine and risperidone, can not be explained by dopamine receptor blockage alone (29). It has been proposed that atypical antipsychotics block serotonin receptors, a property not shared by typical antipsychotics. Umbricht et al (30) found that clozapine is associated with a significant increase of P3 amplitude, which was not observed in the haloperidol group.

Olanzapine, a thienobenzodiazepine derivative, has been recently introduced to the treatment of schizophrenic patients. Although its dopamine D2 receptor blockage potential is less than typical antipsychotics, it has a higher serotonin 5HT2 receptor binding capacity which is thought as the explanations for its efficacy for negative symptoms and low extrapyramidal side effects. In clinical trials effectiveness of olanzapine is comparable with typical antipsychotics for the positive symptoms while it is superior in the negative symptoms (31).

In general, the studies examining the effect of medication on abnormal P3 wave of schizophrenics used typical antipsychotic drugs with a high D2 receptor activity and low 5HT2 receptor affinity. While these studies failed to show the normalization of abnormal P3 wave in schizophrenia, only one study (30), a study that was done with atypical antipsychotic clozapine, reported increased P3 wave amplitude. Clozapine has a risk of agranulocytosis. In the present study we report the effects of olanzapine, a new atypical antipsychotic, which has a very similar D2/5HT2 receptor activity to clozapine, and which has no known risk of agranulocytosis.

METHODS

Subjects:

Twelve chronic schizophrenic patients (5 women and 7 men) and 10 healthy control (5 women and 5 men) participated in this study. All patients were recruited from the psychiatry department of Erciyes University. The mean age of the patient group was 29.83 years with a standart deviation (SD) of 9.04 years and that of the control group was 30.5 years (SD 4.93). The mean duration of illness was 6.83 years (SD 4.86). All subjects were right-handed, which was determined by Edinburg Handedness Inventory (32). The inclusion criteria for this study were as follows (for patients): (1) diagnosis of schizophrenia according to DSM IV (Diagnostic Criteria for Mental Disorders) criteria (American Psychiatric Association 1994) was determined by the consensus of two research psychiatrists. One of the patients had paranoid and the others had undifferentiated type of schizophrenia; (2) absence of organic brain disorder, alcohol or drug abuse, cerebral trauma, pregnancy or any other physical illness, as assessed on the basis of personal history, clinical examination and laboratory data including complete blood count, serum electrolyte assay, liver function tests, thyroid function tests, urine analysis, urine drug screen, serological tests for hepatitis and Human Immunodeficiency Virus. No visible morphological abnormality was detected in brain computerized tomography scan. (3) Patients could enter the study with a BPRS score of 24 or higher (4). Informed consent to participate in the study and permission to use information from medical records; (5) adequate motivation during the ERP testing as estimated by the counting performance, the error in counting not exceeding 20%.

ERPs

The recordings were carried out between 1300-1600 while the subjects were comfortably sitting on a chair. In order to minimize the possible effects of "time locked" alpha activity all subjects were tested with their eyes open. The auditory stimuli, presented binaurally through headphones at an intensity level of 70 dB, consisted of a series of 500-Hz nontarget tones and 1000-Hz target tones. The interstimulus interval between tones was constant at 1.5 sec; tone duration was 32 msec and rise/fall time was 2.5 msec. For each subjects there were two trials with 120 tones presen-

ted in each trial. The subjects were asked to count 1000-Hz tones, which occurred randomly with a probability of 0.20. At the end of each trial the subjects were asked how many tones they had counted.

The ERP signals were recorded from four Ag/AgCl scalp electrodes (Fz, Cz, T3, T4), which were placed according to the international 10-20 electrode placement system (33). Right linked ear electrodes was used as reference (34). The signals were filtered with a band-pass filter (0.1 - 100 Hz, Nihon Kohden) and digitized with a sampling rate of 1000 Hz. The ERPs elicited by the target and nontarget tones obtained by on-line computer averaging of the responses elicited by each type of stimulus. Each ERP signal had a duration of 1024 ms, beginning 32 ms before stimulus presentation. Automatic artifact rejection was used, based on signal amplitude ($>50\mu V$ or $<-50\mu V$) in Fz channel.

Data analysis:

Before peak identification EEG epochs were filtered by non-phase shift digital filters (0.3-70 Hz). Then selected fifteen epochs were averaged for non-target and target stimuli, separately. The N1 component was identified as the most negative peak between 70-140 ms, and the P2 was the most positive peak between N1 and 220 ms. N2 was identified as the most negative peak between P2 and P3. The P3 component was identified as the most positive peak between 280-500 ms. The N1 and the P2 components to frequent, non-target stimuli and the N2 and the P3 components to target stimuli are reported below.

Statistical tests:

Three types of comparison were made from the data:

1. To test the hypothesis that ERP components in unmedicated schizophrenics differ from both control and medicated schizophrenics, we used two-way ANOVA with channel and group as factors.
2. To test clinical improvement, clinical rating scores were compared between before and after the treatment in schizophrenics by Wilcoxon signed ranks test.
3. To test the relationship between clinical severity and ERP, correlation test was performed.

All statistical tests were two-tailed, with a 0.05 alpha level.

Medication:

Two of the patients had never been medicated and 6 had been drug-free for over a year. The others had been medicated on admission to the ward and

then the medication was withdrawn, for the study, for 14–19 days (mean 16,5 days) before the first ERP session. None of the patients had a depot injection in the previous 14 months. All the patients were treated with olanzapine in a fixed dose of 10 mg/day. Benzodiazepines (lorazepam or clonazepam) were allowed for akathisia or sedation when needed.

Clinical rating and medical history

Patients were administered the BPRS (Brief

Table 1. The Brief Psychiatric Rating Scale (BPRS), Clinic Global Impression (CGI), Extrapyramidal Side Effects Rating Scale (ESRS) for 12 schizophrenic patients at the baseline and study end point.

	Baseline Mean±SD	End point Mean±SD	Z	P
BPRS total	44,5±12	25,2±13,9	3,0	0,02*
BPRS positive	14,1±5,0	7,8±4,6	2,93	0,03*
BPRS negative	10,7±5,3	6,8±2,8	2,94	0,03*
CGI	4,5±0,5	3,6±0,6	2,6	0,08
ESRS	12,6±1,5	12,3±0,8	0,7	0,46

*Significant (Wilcoxon signed ranks test)

Psychiatric Rating Scale) weekly during the research. It is based semistructured interview and yields measures of symptomatology on 18 items that have been the subject of extensive factor-analytic study (35). Items related to suspiciousness, unusual thought content, grandiosity and hallucinatory behavior are taken as reflection of positive symptoms while items associated with motor retardation, blunted affect, mannerism and posturing and emotional withdrawal for negative symptoms. The clinical Global Impression (CGI) scale with Extrapyramidal Side Effects Rating Scale (ESRS) for measuring side effects were also applied to the patients. ESRS has 12 item related to extrapyramidal side effects of drugs and scored between 1–4. All patients were evaluated at the end of the wash-out period and again 6 weeks after olanzapine treatment. Ratings were done by two trained psychiatrists and the average of the ratings used. A 30% of reduction of total pathology score in BPRS was the criterion for clinical improvement (36).

RESULTS

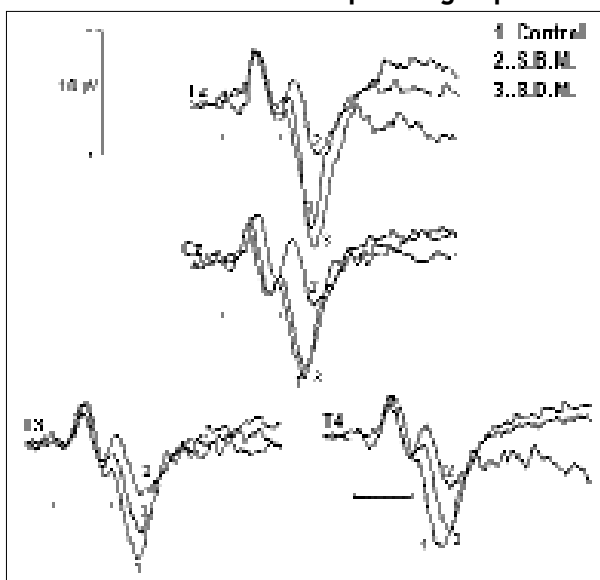
The total, positive and negative BPRS and CGI

scores are shown in Table 1. There was a significant decrease in BPRS parameters while no change was detected in ESRS scores. Global Clinical Scale also indicated improvement with the treatment, changing from 4.5 before the treatment to 3.6 after the treatment, however this change was not significant. Nine of the 12 (75%) patients responded to the olanzapine treatment (>30% reduction in total BPRS scores) The effects of atypical antipsychotic medication on ERP data:

Figures 1 and 2 show the grand averages of the target and non-target ERPs at Fz, Cz, T3 and T4 in con-

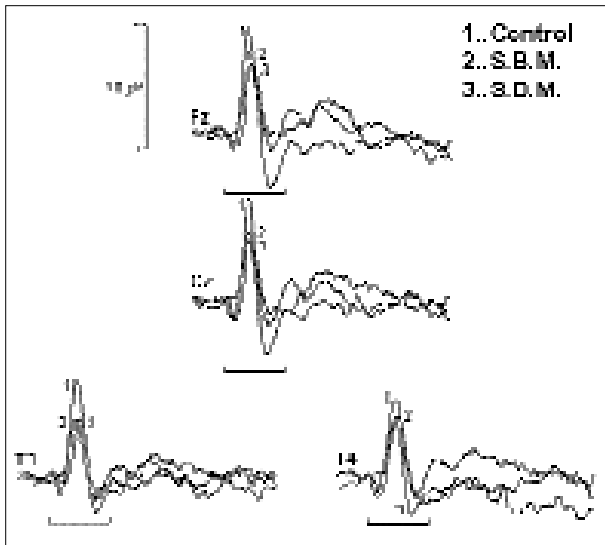
rols and schizophrenic patients at the baseline (medication-free) and study end point (medicated with olanzapine), respectively. As it can be seen in these grand averages, in patients, the baseline P3 were smaller than both the P3 at the study end po-

Figure 1. The grand averages of ERPs in response to target stimuli at the Fz, Cz, T3 and T4 electrodes for the control and the schizophrenic groups.



S.B.M.: schizophrenics before medication. S.D.M.: schizophrenics during medication. Line parts represent a period lasting 250 ms starting with stimulus onset.

Figure 2. The grand averages of ERPs in response to non-target stimuli at the Fz, Cz, T3 and T4 electrodes for the control and the schizophrenic groups. S.B.M.: schizophrenics before medication.



S.D.M.: schizophrenics during medication. Line parts represent a period lasting 250 ms starting with stimulus onset.

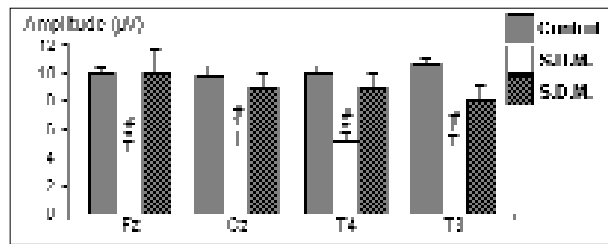
int and the P3 in controls. It can also be seen that schizophrenics had smaller N1 components than control subjects.

The latencies and amplitudes of the components of ERPs were statistically analyzed by two-way ANOVA (group x site). There was neither a side effect nor an interaction ($p > 0.05$). The significant main effects were found for group when N1 and P3 component were analyzed ($F[135,2] = 12.07, 33.89, \text{ and } 17.15$ for N1 amplitude, P3 amplitude, and P3 latency, respectively. All $p < 0.001$). Scheffe test indicated that the baseline P3 were smaller than both the P3 at the study end point and the P3 in controls ($p < 0.05$, Figure 3). The latencies of baseline P3 (mean \pm SEM: 361 ± 10.9 for Cz) were longer than P3 in controls (318.9 ± 7.0) but not different from the P3 at the study end point (333 ± 10.6) in schizophrenia. N1 amplitude in the patients was smaller before the treatment than controls, and remained unchanged after the medication, but a significant difference was revealed only at Cz and T4 (Figure 4).

Relationship between clinical severity and ERP:

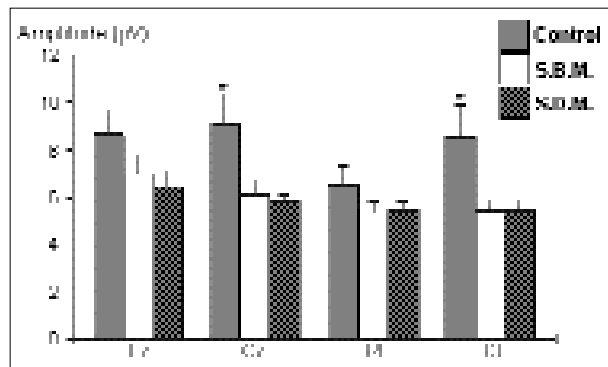
P3 amplitude had a relationship with negative symptoms of BPRS not only before the treatment but also 6 weeks after the treatment was initiated ($r = -0.48$,

Figure 3. The P3 amplitude. S.B.M.: schizophrenics before medication.



S.D.M.: schizophrenics during medication. *: differs from control; #: differs from S.D.M. ($p < 0.05$).

Figure 4. The N1 amplitude. S.B.M.: schizophrenics before medication.



S.D.M.: schizophrenics during medication. *: differs from control; #: differs from S.D.M. ($p < 0.05$).

$p < 0.01$ and $r = -0.50$, $p < 0.01$ respectively). It is seen that P3 amplitude and total score of BPRS had a relationship in medicated patients after 6 weeks of atypical antipsychotic treatment ($r = -0.36$ $p < 0.05$). P3 latency had a positive correlation with total BPRS scores in either measurement ($r = 0.47$, $P < 0.01$ and $r = 0.64$, $p < 0.01$ respectively). There was no correlation between ERP and the duration of illness.

DISCUSSION

The present literature supports an abnormality in cerebral processing of auditory stimulus in schizophrenic patients. The evidence of this abnormality came from both the present and previous works. The most robust change was observed in the N1 and P3 amplitude and P3 latency components of ERP. Findings of decreased N1 and P3 and prolonged P3 components are confirmed from the findings of a large literature on ERPs and schizophrenia: auditory N1 amplitude is reduced in schizophrenia patients compared to controls (12, 13, 14, 23). Auditory P3 is also reduced (2, 3, 4, 23, 38) and prolonged compared to controls (7,17). Reduction of N1

amplitude in schizophrenia may reflect an early stage disturbance in auditory information processing. N1 reduction could be related to decrement to the attention or arousal and at least in our study, not to antipsychotic medication as this finding was seen in drug-free patients. A prolonged P3 latency in ERPs to target stimuli of schizophrenia patients before medication suggests a slowed target classification in these patients.

Although in previous studies it was failed to show normalization of P3 amplitude in schizophrenia patients despite significant clinical improvement with typical antipsychotics (15, 38, 22), the present work suggests that an atypical antipsychotic, olanzapine would affect P3 decrement together with clinical improvement. In our knowledge this is the first study examining P3 in schizophrenia with olanzapine treatment. However, Umbricht et al (30) reported similar results to those in our study for clozapine which has a very similar receptor affinity pattern. The difference in receptor affinity pattern between atypical and typical antipsychotics may explain the contrast described above. In contrast with the typical antipsychotics, olanzapine and clozapine have high a 5HT₂ receptor affinity.

One may assume that if P3 amplitude reduction is related to an excess dopamine in schizophrenia, P3 should increase following administration of the drugs with high dopamine receptor blockage activity. But most of the studies carried out on schizophrenic patients do not support this idea, so that decreased P3 wave in schizophrenia was thought to be a trait marker (15). Recently Coburn et al (25) published a report which shows an increase in P3 amplitudes with antipsychotic treatment but they emphasized that this increase did not reach those of controls. In our study after 6 weeks of olanzapine treatment the P3 wave in the patients with schizophrenia was not different from control. Our study suggests that decreased P3 amplitude of schizophrenic patients might be a state marker as it is normalized with atypical antipsychotic treatment.

What was the reason for P3 normalization with olanzapine (if antidopaminergic effects are not responsible from this)? Although antipsychotic effects of 5HT₂ blockers (like ritanserin) is still controversial (21), their addition to a antipsychotic with high dopamine blockage activity decreases not only the extrapyramidal side effects of antipsychotics but also the negative symptoms (41). It is suggested that 5HT₂ blockage acts as a buffer system to regulate dopamine activity (This subject has been extensively reviewed by Abi-Dargham et al. 1997, see reference 29). The functional brain imaging studies (42, 43) done in schizophrenic patients showed cortical pathologies in prefrontal regions which may induce hypoactivity of corticostri-

atal and cortic limbic glutamatergic projections, leading to a decrease in release of dopamine, which may be associated with negative symptoms. The decreased dopamine activity induces a state of hypersensitivity to dopamine which may explain the positive symptoms. In our study, together with the normalization of P3 and clinical improvement in negative symptoms, the finding that P3 amplitude is negatively correlated with negative symptoms both before and after the administration of olanzapine suggests that olanzapine may play a role in the balance between serotonin and dopamine. Thus balanced 5HT₂/D₂ antagonism is necessary for the treatment of both positive and negative symptoms and we suggest that the balanced 5HT₂/D₂ receptor activity may be responsible from the P3 normalization with atypical antipsychotic treatment.

Olanzapine has also high affinity to muscarinic receptors. In the healthy individuals anticholinergic drugs may reduce the amplitude and increase the latency of P3 (44). Therefore the effects of olanzapine on ERP can not be explained by its anticholinergic effects. We may speculate that high anticholinergic activity of olanzapine might prevent the prolongation of P3 latency to reach significant level. However total BPRS scores are correlated with P3 latencies of schizophrenic patients before and after medication. Consistent with our findings Blackwood et al (22) also reported that P3 latencies of unmedicated schizophrenic patients were correlated with total BPRS scores although some researchers did not find any correlation between symptoms and P3 latencies (25, 45).

As a result, our study suggests that P3 amplitude in schizophrenic patients might not be a trait marker because of being normalized after treatment with atypical antipsychotic. Furthermore, our results support Coburn et al's (25) findings which state that normalized P3 latency is also a state marker for schizophrenia. Although a lot more studies in this field are needed, we speculate that serotonin-dopamine imbalance might be responsible for cognitive dysfunction in schizophrenia.

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