INTRODUCTION

Buspirone, introduced in 1986, revealed some benefits when used for both primary and adjunctive treatment of depression. In addition, the recent STAR*D study has shown that augmenting buspirone with citalopram produces similar efficacy as combining bupropion with citalopram in patients with major depressive disorder (MDD). Thus, buspirone seems to have the property of boosting antidepressant effects. However, there is no clear evidence of this strategy. Some researchers assume that the antidepressant boosting effect of buspirone is revealed under a poop-out state, which means a phenomenon where some patients having an initial response to an antidepressant may worsen or not improve any more even though they continue treatment because of serotonin depletion. Loudness dependence of auditory evoked potential (LDAEP) is a reliable marker of central serotonergic activity, and is inversely correlated with central serotonergic activity. Thus LDAEP will be a biological marker for prediction of treatment response with buspirone augmentation with SSRI because it can measure central serotonergic activity such as serotonin depletion. Two cases will be introduced and the literature evidence about whether LDAEP can predict the treatment response of buspirone augmentation in patients with MDD will be reviewed.
mentation have been introduced and the literature evidence on whether LDAEP can predict the treatment response to buspi-rone augmentation in patients with MDD has been reviewed.

CASE SERIES

Case 1
A male patient in his 40s visited my outpatient clinic with complaints of stress from work and death of his mother. He was diagnosed with MDD and panic disorder and initiated treatment with alprazolam and escitalopram. His baseline Clinical Global Impression-Severity Scale (CGI-S) score was 5 points. After 2 months of treatment, his symptoms were improved to some extent. However, he still complained of reduced motivation and interest. His CGI-S score was 3 points. Even 5 months after the treatment, he did not reach a remission state. The baseline LDAEP before the escitalopram treatment was 1.99, and this value exceeded the two standard deviations of the mean LDAEP of other male depressed patients attending my clinic. This signified that the central serotonergic activity was relatively weak at baseline. LDAEP also negatively correlates with the amount of serotonin in the synaptic cleft. This was regarded as a poop-out state and buspirone 10 mg was added twice a day (a total of 20 mg). After buspirone augmentation, the patient improved from reduced motivation and energy and reached the remission state. The theoretical background of LDAEP as a feedback system with the auditory cortex. When we hear auditory stimuli of 55, 65, 75, 85, and 95 dB sequentially, our brain tries to stimulate serotonin to secrete GABA in the GABA interneuron, thereby inhibiting the secretion of glutamate by reducing the strength of the response to stimuli to protect the brain. The degree of suppression of auditory stimuli is such that the stronger is the activity of an individual’s serotonin, the weaker is the suppression. Based on these hypotheses, the sum of the amplitude (N100 and P200) at 100 and 200 ms of each of the five auditory stimuli can be plotted on the Y-axis to calculate the slope. LDAEP Thus, a large LDAEP value signifies that as the auditory stimuli increase, the auditory response becomes relatively large as serotonin is less active. On the other hand, a small LDAEP value means better auditory response suppression with an increase in the auditory stimuli, and therefore, the auditory response becomes relatively less active implying that the serotonin activity is high.

Case 2
A female patient in her 30 s was hospitalized due to depression, lethargy, dizziness, and panic symptoms. Her baseline Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HAMA) scores were 34 and 25, respectively. Initial treatment, such as venlafaxine 150 mg, alprazol-am 0.25 mg in the morning, and Ativan 1 mg at bedtime was administered. By two weeks, some symptoms disappeared, but the patient still complained of low energy, lethargy, and lack of motivation and interest. The HAMD and HAMA scores were 11 and 15, respectively. In addition, the baseline LDAEP of the patient before the venlafaxine treatment was 1.64, and this value exceeded the two standard deviations of the mean LDAEP of other female depressed patients attending my clinic. This signified that the central serotonergic activity was relatively weak at baseline. Thus, this was regarded as a poop-out state and buspirone 5 mg was added twice a day (a total of 10 mg). After three weeks of buspirone augmentation, the symptoms of low energy, lethargy, and lack of motivation and interest were improved and the patient reached a remission state.

LDAEP AND ITS CLINICAL APPLICATION WITH BUSPIRONE AUGMENTATION

In these two cases, buspirone most likely exerted an additional antidepressant boosting effect when the serotonin activity was low, i.e. when the synaptic cleft was depleted of serotonin. In particular, some studies have revealed that LDAEP negatively correlates with the amount of serotonin in the synaptic cleft. Therefore, it may be clinically useful to use LDAEP to decide augmenting the effect of buspirone with an antidepressant.

LDAEP was first described by Jukel and Hegerl. It is calculated using the amplitude of event-related potentials, such as N100 and P200 elicited by auditory stimuli, and this has recently been used to evaluate central serotonergic activity. LDAEP is a reliable marker of central serotonergic activity and is inversely correlated with the central serotonergic activity. The theoretical background of LDAEP as a feedback system with the auditory cortex. When we hear auditory stimuli of 55, 65, 75, 85, and 95 dB sequentially, our brain tries to stimulate serotonin to secrete GABA in the GABA interneuron, thereby inhibiting the secretion of glutamate by reducing the strength of the response to stimuli to protect the brain. The degree of suppression of auditory stimuli is such that the stronger is the activity of an individual’s serotonin, the weaker is the suppression. Based on these hypotheses, the sum of the amplitude (N100 and P200) at 100 and 200 ms of each of the five auditory stimuli can be plotted on the Y-axis to calculate the slope. LDAEP Thus, a large LDAEP value signifies that as the auditory stimuli increase, the auditory response becomes relatively large as serotonin is less active. On the other hand, a small LDAEP value means better auditory response suppression with an increase in the auditory stimuli, and therefore, the auditory response becomes relatively less active implying that the serotonin activity is high.

PREDICTION OF TREATMENT RESPONSE USING LDAEP IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

Some studies have evaluated the association between LDAEP and response to antidepressants. While estimating LDAEP at
baseline (pretreatment) in patients with MDD and comparing the low with the high LDAEP group according to the median value, patients with a low serotonin activity at baseline were more responsive to SSRI treatment than those with a high serotonin activity.12-15 Subsequent studies have also shown that both the groups had better treatment responses when the high LDAEP group was treated with SSRI and the low LDAEP group was treated with reboxetine, an NRI without any serotonin-related mechanisms of action.16,17 Another study evaluated the relatively long-term treatment response after 12 weeks of SSRI administration, and patients with a high LDAEP at baseline showed a better response.18 In the high LDAEP group, the post-treatment BDI scores were >30% lower and the number of treatment responders was >30% higher after 12 weeks as compared to those in the low LDAEP group. A study evaluated the treatment response using LDAEP in patients with a generalized anxiety disorder (GAD).19 HAMA, CGI-S, and Beck Anxiety Inventory Beck Anxiety Inventory (BAI) scores were evaluated in 25 GAD patients. The pretreatment LDAEPs of all the patients were positively correlated with the treatment response rates at 4 and 8 weeks using the CGI-S, and with the treatment response rates at 8 weeks using HAMA and BAI. MDD or GAD patients with high LDAEP were more responsive to SSRI treatment than those with a low LDAEP. In other words, MDD patients with a low LDAEP at baseline are less responsive to SSRI treatment, and even a case report suggests that more adverse effects occur with SSRIs.

CONCLUSION AND FUTURE DIRECTIONS

In conclusion, patients with a high LDAEP at pretreatment are expected to have better treatment response following SSRI and buspirone treatment. This is because it is expected that buspirone augmentation would ensure a better treatment response when the central serotonin activity is low, the initial treatment response to serotonin agents like SSRIs is better, and then a poop-out phenomenon occurs later. Further studies in more patients will be needed to prove this hypothesis in the future.

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Conflicts of Interest

The author has no potential conflicts of interest to disclose.

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