EDITORIAL

Are the Effects of Amitriptyline and Aripiprazole on Pain Catastrophizing in Patients with Burning Mouth Syndrome Associated with Changes in QTc and Prolactin Levels?

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ABSTRACT

Background: **Burning mouth syndrome (BMS) is an intractable chronic pain disorder of unknown cause characterized by burning sensation without any organic abnormality in the oral mucosa. In a chronic pain disorder such as BMS, the ability to control pain catastrophizing that accompany the pain determines the outcome of treatment. Pain catastrophizing is associated with the dopamine nervous system and can be quantitatively assessed with the Pain Catastrophizing Scale (PCS). Treatment options include antidepressants, benzodiazepines, antipsychotics, anticonvulsants, analgesics, hormone replacement therapy, and psychotherapy, with antidepressants being the most commonly used and effective.**

Methods: **We analyzed whether amitriptyline and aripiprazole, typical drug therapies for BMS patients, improve PCS using a 2-year case series from our department. We also examined whether changes in QTc and serum prolactin levels were associated with improvement in PCS as an indicator of the efficacy of these monoamine modulators.**

Results: **Both amitriptyline and aripiprazole statistically significantly improved PCS. Amitriptyline increased heart rate and mildly shortened QTc, while aripiprazole did not alter heart rate or QTc. Both amitriptyline and aripiprazole caused very mild increases in prolactin levels. Only prolonged QTc in the aripiprazole group correlated with improved PCS.**

Discussion and Conclusions: **Monoamine-targeted pharmacotherapy for BMS is effective against pain catastrophizing in patients with BMS. Since the dopaminergic nervous system is primarily involved in pain catastrophizing, a mild increase in prolactin levels was therefore found to be associated with efficacy. However, changes in prolactin levels were not predictive of individual treatment response. The anticholinergic effects of amitriptyline on QTc and prolactin may have prevented these markers from predicting treatment response at the individual level. Only prolonged QTc in the aripiprazole group was correlated with efficacy. Aripiprazole has no anticholinergic effects and dopamine stability was observed at QTc, but its agonist effect on prolactin on pituitary cells may not have been a marker of its effect on pain catastrophizing.**

KEY WORDS

amitriptyline, aripiprazole, burning mouth syndrome, pain catastrophizing, prolactin, QTc

INTRODUCTION

Burning mouth syndrome (BMS) is a form of chronic oral pain characterized by a burning sensation in the tongue, gums, and entire oral cavity, typically in the absence of a corresponding organic cause. According to the International Classification of Headache Disorders, 3rd edition (ICHD-3), BMS is defined as "An intraoral burning sensation or dysesthesia, recurring daily for more than 2 h/day lasting > 3 months, without clinically evident causative lesions"[1)]. Because of the absence of detectable organic cause or abnormal findings, many BMS patients are regarded as normal by doctors, but the pain persists[2)]. The reported incidence ranges from 0.7%[3)] to 10%[4)]. More than 300 patients visit our department with this complaint per year, and so BMS is common[5)]. Tricyclic antidepressant (TCA) amitriptyline is known to be effective against chronic pain in the oral cavity, including BMS[6)]. However, the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults as published by the American Geriatrics Society recommends refraining from using amitriptyline in the elderly[7)]. Therefore, we use aripiprazole in patients at high risk of side effects, such as the elderly. Aripiprazole is a partial dopamine agonist. Recently, the relationship between the dopamine system and pain control has

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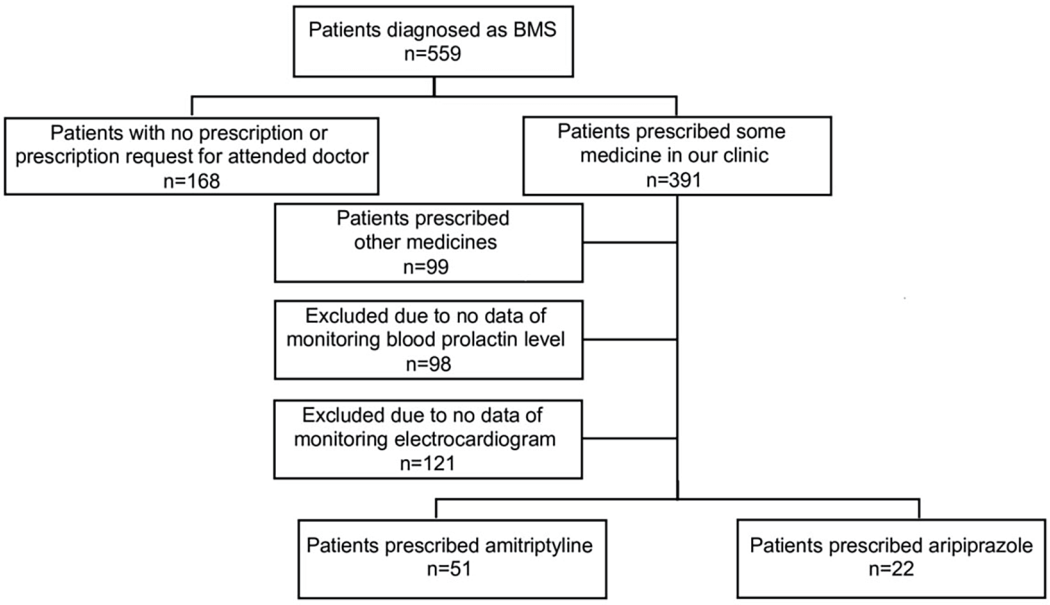

Figure 1: Flowchart diagram of analyzed cases

attracted attention[8] and reports have described cases where aripiprazole was effective for headache and low back pain[9]. Moreover, some neuroimaging studies have suggested that dysfunction of the dopaminergic pathway plays an important role in the pathogenesis of BMS[10,11]. Furthermore, some polymorphisms in genes involved in the dopamine system, such as the dopamine D2 receptor gene, have been suggested as playing important roles in the pathogenesis of BMS[12].

By the way, it is no exaggeration to say that in BMS, a chronic pain disorder, the ability to control catastrophic thoughts of pain determines the outcome of treatment. Pain catastrophizing is characterized by the tendency to magnify the threat value of a pain stimulus and to feel helpless in the presence of pain, as well as by a relative inability to prevent or inhibit pain-related thoughts in anticipation of, during, or following a painful event[13]. Therefore, we decided to retrospectively examine the effectiveness of two typical BMS drugs, amitriptyline and aripiprazole, on pain catastrophizing and whether it is related to changes in biological signals such as electrocardiogram (ECG) and prolactin, which are associated with the autonomic and dopaminergic nervous systems.

SUBJECTS AND METHODS

This single-center cohort study was conducted by analyzing retrospective data from 559 consecutive patients diagnosed as having BMS based on the ICHD-3 criteria who had visited first the Psychosomatic Dentistry Clinic in Tokyo Medical and Dental University Hospital, Tokyo, Japan, between April 2016 and April 2018. We prescribed amitriptyline as the first-line drug treatment for BMS except in patients with the following contraindications: 1) history of other medical conditions that are contraindications to amitriptyline use, such as glaucoma, myocardial infarction, and urinary retention; and 2) use of medications with known interactions with amitriptyline. Patients who could not use amitriptyline were treated with aripiprazole. In addition, selective serotonin reuptake inhibitors are also used for treatment. Patients who consented to the study were then monitored using ECG and blood prolactin levels at the initial visit and at one-month follow-up. Prolactin was measured in the morning blood draw of all patients and was determined by Enzyme-Linked Immuno-Sorbent Assay (ELISA). Pain catastrophizing was assessed using the Pain Catastrophizing Scale (PCS). The PCS contains 13 descriptors as follows: 1) I worry all the time about whether the pain will end; 2) I feel I can't go on; 3) It's terrible and I think it's never going to get any better; 4) It's awful and I feel that it overwhelms me; 5) I feel I can't stand it anymore; 6) I become afraid that the pain will get worse; 7) I keep thinking of other painful events; 8) I anxiously want the pain to go away; 9) I can't seem to keep it out of my mind; 10) I keep thinking about how much it hurts; 11) I keep thinking about how badly I want the pain to stop; 12) There's nothing I can do to reduce the intensity of the pain; and 13) I wonder whether something serious may happen. These descriptors were rated as follows: 0) Not at all, 1) To a slight degree, 2) To a moderate degree, 3) To a great degree, and 4) All the time[14].

Statistical processing was done as follows. Data were analyzed using Wilcoxon signed-rank tests, Student's *t*-test, and Spearman's rank correlation coefficient using EZR statistical software (The R Foundation for Statistical Computing, Vienna, Austria)[15]. Results are expressed as mean (± standard error, SE) or number of patients (%).

Ethical approval was appropriately addressed as follows. All patients gave written informed consent to participate in this study. The study protocol was approved by the Ethical Committee of Faculty of Dentistry Tokyo Medical and Dental University (D2018-085).

RESULTS

Of the 559 patients, the reasons for missing in this study and the numbers are shown in Figure 1. Therefore, in this study, we analyzed the amitriptyline group (n = 51) and the aripiprazole group (n = 22). The age of the amitriptyline group was 61.2 ± 1.6 years, while the aripiprazole group was 73.0 ± 1.9 years. Gender differences were, as is characteristic of BMS, predominantly female, with 78.5% of the amitriptyline and 95.5% of the aripiprazole group being female. The average dose of amitriptyline was 17.6 ± 0.7 mg/day and that of aripiprazole was 06 ± 0.1 mg/day. Comparative analysis of demographic data revealed that patients in the aripiprazole group were significantly older than those in the amitriptyline group. There were no significant differences in gender and prescription duration. Both the amitriptyline and aripiprazole groups showed statistically significant improvement in PCS scores, and both drugs were effective in treating BMS at low doses. (Figure 2).

In BMS patients prescribed amitriptyline, there was a significant increase in heart rate (HR) with a significant shortening of QTc (Figure 3). In contrast, there was no significant increase or decrease in HR or QTc in the aripiprazole group (Figure 4). In the amitriptyline group, improvement in PCS score was not associated with QTc, but in the aripiprazole group, there was a significant correlation between QTc prolongation and improvement in PCS score (Figure 5).

Although prolactin levels did not increase above 30 ng/mL, a slight increase was observed in both the amitriptyline and aripiprazole groups, which was found to be significant (Figure 6). However, there was no significant correlation between the increase in blood prolactin levels and the degree of improvement in PCS scores in both groups (Figure 7).

DISCUSSION

Amitriptyline is effective in the treatment of orofacial pain includ-

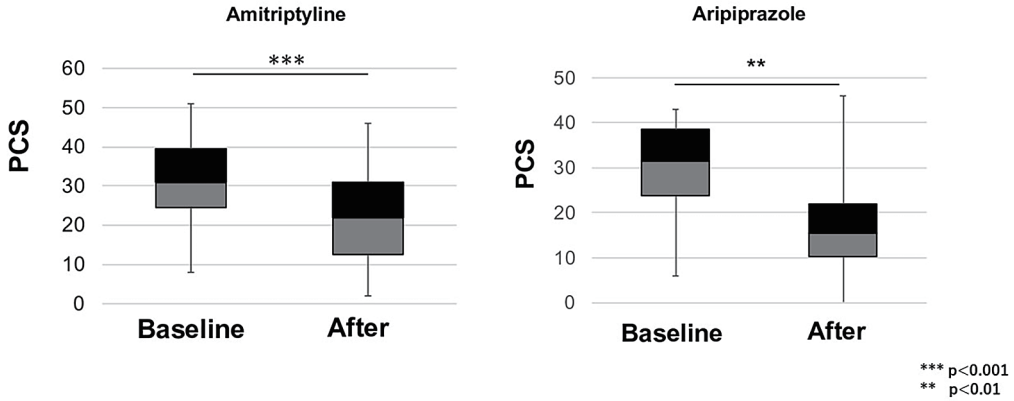

Figure 2: Changes in Pain Catastrophizing Scale with amitriptyline and aripiprazole

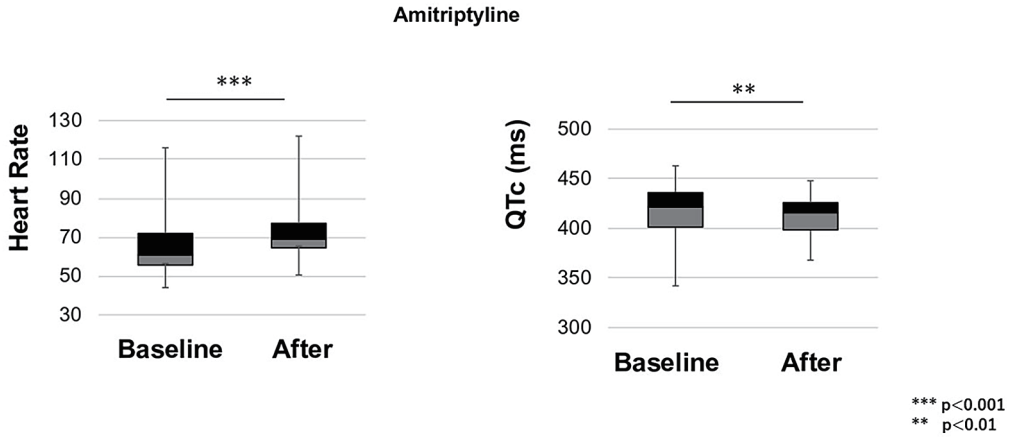

Figure 3: ECG changes with amitriptyline

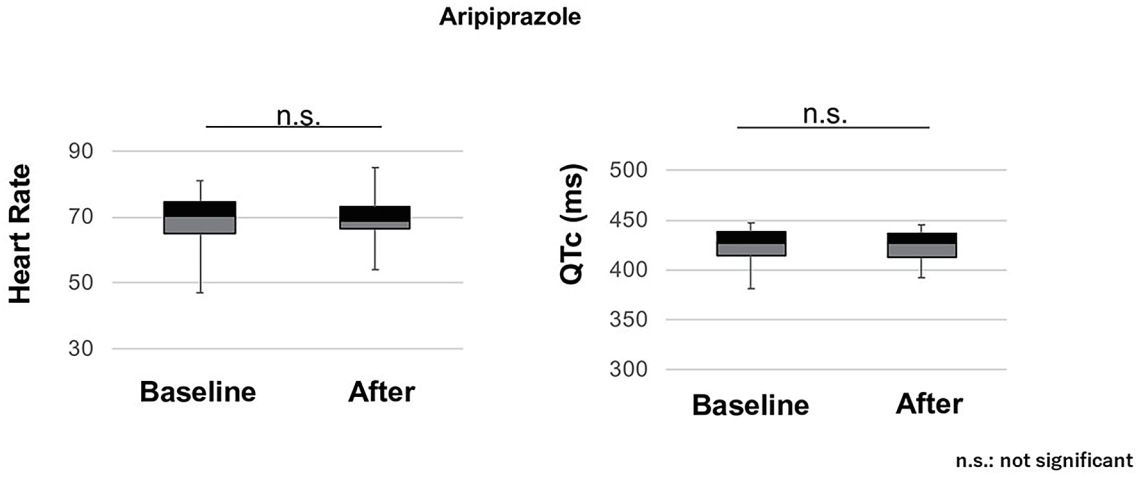

Figure 4: ECG changes with aripiprazole

ing BMS, although the degree of scientific evidence regarding the efficacy of pharmacotherapy for BMS is limited[16]. Amitriptyline is prescribed as a first-line treatment for BMS in our practice, but its effectiveness varies from patient to patient. Recent reports also indicate that low-dose aripiprazole is effective in the treatment of BMS patients for pain catastrophizing[17,18]. According to the present results, both amitriptyline and aripiprazole significantly reduced PCS scores, confirming their therapeutic efficacy. Amitriptyline improves pain by stimulating the descending pain inhibitory system via the serotonergic nervous system. In recent years, a relationship has been proposed between pain catastrophizing and the mesolimbic dopamine system[19]. Production of dopamine in the ventral tegmental area is thought to promote the production of opioids in the nucleus accumbens and ventral pallidus, and thus activates the descending pain inhibitory system[19]. In contrast, in patients with chronic pain, the mesolimbic dopamine system has been reported to be in a hypodopaminergic tone[20,21] Reports have also shown that levodopa and dopamine agonists such as pramipexole are effective for treating BMS[22]. Low-dose aripiprazole has been suggested to inhibit pain via partial agonistic action on D2 receptors and 5-HT1A receptors. However, aripiprazole functions as a partial agonist for dopamine D2 receptors as well as dopamine D3 receptors[23]. Furthermore, dopamine D3 receptor expression and dopamine signaling are reduced under chronic stress[23]. It therefore follows that low-dose aripiprazole functions as a partial D3 receptor agonist and activates dopamine signaling, and thus alleviates chronic pain. Moreover, antinociception induced by aripiprazole is mediated by δ-opioid receptors[24]. Taken together, findings from these previous reports suggest that low-dose aripiprazole activates dopamine signaling and promotes opioid production, thereby alleviating

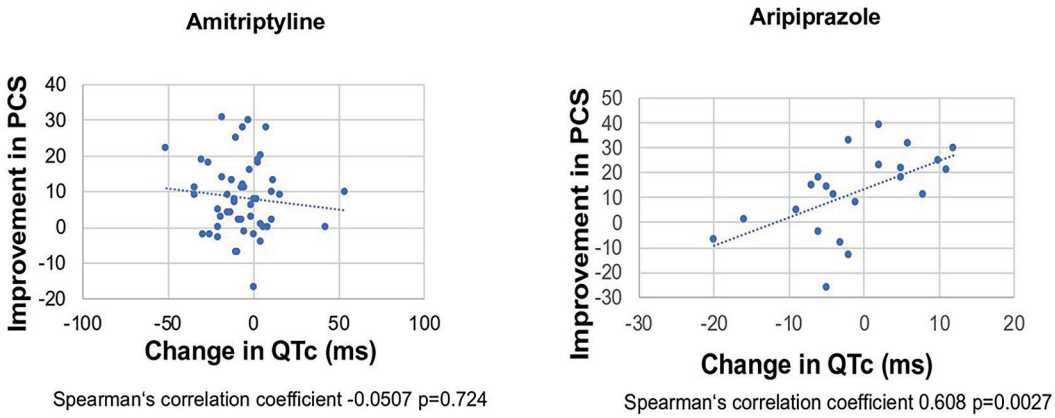

Figure 5: Correlation between changes in QTc and Pain Catastrophizing Scale with amitriptyline and aripiprazole

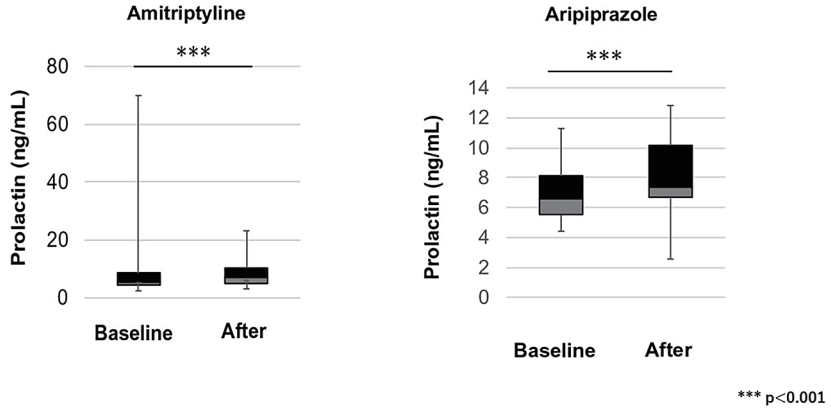

Figure 6: Prolactin changes with amitriptyline and aripiprazole

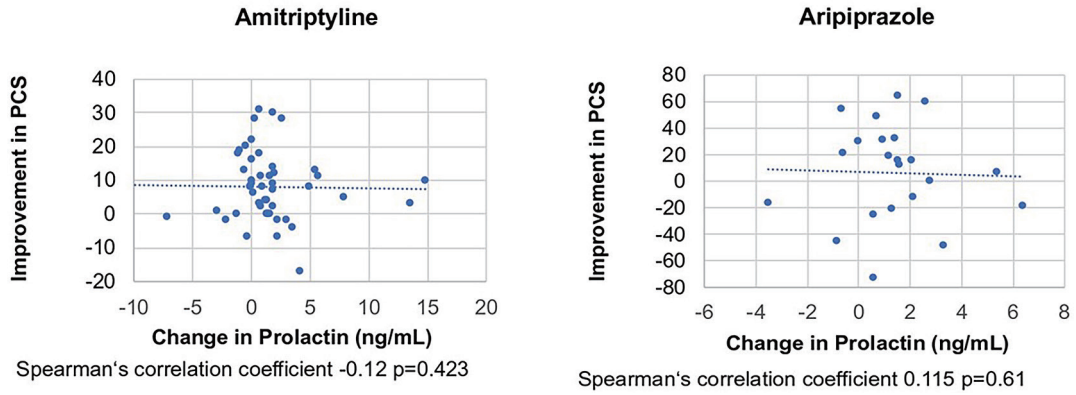

Figure 7: Correlation between changes in prolactin and Pain Catastrophizing Scale with amitriptyline and aripiprazole

pain. Chronic pain patients have not only a dopaminergic system, but also a serotonergic system that is correspondingly impaired. Both amitriptyline and aripiprazole appear to have a therapeutic effect by stimulating the monoaminergic nervous system, which is experiencing a loss of function.

The QTc in the ECG measured in this study is important in two ways: one is to check for side effects of psychotropic drugs, and the other is its potential to act as a biological signal of treatment efficacy. Prolongation of the QT interval is a known side effect of antipsychotics and antidepressants[25]. Because QT prolongation can cause Torsades de Pointes, a lethal arrhythmia, meticulous ECG monitoring is required when using antipsychotics and antidepressants. Tricyclic antidepressants (TCAs) including amitriptyline and antipsychotics have been reported to prolong QT interval by interacting with and inhibiting the hERG channel. However, TCAs have been known to have an anticholinergic effect, which may result in a shortened QT interval. Aripiprazole, on the other hand, is said to have low affinity for hERG channel and has little arrhythmogenic effect. Therefore, in this study, amitriptyline increased heart rate and mildly shortened QTc, while aripiprazole did not alter heart rate or QTc. Recently, we reported that QTc prolongation exceeding 460ms does not occur with use of low-dose amitriptyline in patients with chronic oral pain[26]. Moreover, we also showed that improvement in VAS scores correlates with prolongation of QT interval[27]. However, in the present study, PCS, a catastrophic sensation, did not correlate with QTc. This was thought to be because dopamine is mainly involved in the destructive sensation and amitriptyline acts more on monoamines other than dopamine. In support of this phenomenon, aripiprazole is a primary target of dopamine receptors, and PCS correlated with QTc. Aripiprazole has no anticholinergic effects and dopamine stability was observed with a change in QTc.

Both amitriptyline and aripiprazole increased mild prolactin levels. Hyperprolactinemia is a known side effect of antipsychotic drugs and is caused by dopamine D2 receptor blockade in the anterior pituitary lactotrophs[28]. Aripiprazole is the only antipsychotic that reduces prolactin levels[29]. However, in the present study it showed the same prolactin-raising behavior as amitriptyline. It has been suggested that this may

reflect stabilization of dopamine by reducing disruptive behavior rather than direct pituitary agonist action. However, minor prolactin increases and improved PCS were not associated at the individual level. The agonist effect of aripiprazole on pituitary cells may not have been a marker of its effect on pain catastrophizing. Another reason why prolactin was not a marker of efficacy may be that the hormone fluctuates diurnally, so small changes were drowned out by the diurnal fluctuations. Although destructive ideas include presumed increases in dopamine and catecholamines, it would probably be expected that measuring dopamine and catecholamines would not correlate with PCS. Biological signals such as QTc and blood glucose levels are better predictors of improvement in destructive thinking than catecholamines and hormones[30]. We plan to study whether biological signals can be used as targets for predicting the effects of drug therapy.

There are some limitations of this study. First, there is a possibility of selection bias between the groups because aripiprazole was prescribed to patients for whom amitriptyline was contraindicated. Thus, we could not simply compare the efficacy of amitriptyline and aripiprazole. Second, the treatment duration as assessed in this study was less than 40 days. Third, the study was conducted by analyzing single-center data retrospectively. Further studies are warranted, such as a multicenter cohort study and a randomized controlled trial.

CONCLUSIONS

Monoamine-targeted pharmacotherapy for BMS is effective against pain-induced destructive thoughts in patients with BMS. Because pain catastrophizing is thought to involve primarily the dopaminergic nervous system, mild elevations in prolactin levels were associated with efficacy. However, changes in prolactin levels were not effective in predicting treatment efficacy in individual patients. Only QTc prolongation in the aripiprazole group correlated with treatment response. The anticholinergic effects of amitriptyline on QTc and prolactin may have prevented these markers from predicting treatment response at the individual level.

FUTURE PROSPECTS

Orofacial pain is often caused by dental disease, and its management is considered within the scope of oral procedures. However, an increasing number of patients are complaining of orofacial pain for which no dental cause can be found. BMS is one of the most common medically unexplained orofacial pain. Neural circuit defects are suspected as the mechanism, but psychosomatic aspects are important in its treatment. Most BMS patients are middle-aged women, and many of them suffer from somatization[31]. These patients may have increased pain as a result of some dental treatment for unexplained pain. In order to prevent unnecessary dental treatment, it is necessary to assemble a pharmacotherapy for pain that takes into account the psychosomatic medicine. As Singh points out, psychosomatic research is still in its developmental stage[32]. The present study is a psychosomatic study that utilizes psychopharmacology and biological signals such as electrocardiograms, and the new findings are based on this psychosomatic study.

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