the CYP2D6 of all antidepressants (Ki = 0.065-4.65 micromoles) (Nevels et al. 2016). Paroxetine's potent inhibitory effect on CYP2D6 significantly inhibits the metabolism of the CYP2D6 substrates including risperidone and paroxetine, resulting in elevated levels of both risperidone and paroxetine. The addition of risperidone could deprive CYP2D6 and cause a decrease in paroxetine metabolism, resulting in serotonin excess. Recently, it has been reported that concomitant use of antipsychotics and antidepressant agents, which share a common metabolic enzyme, can lead to serotonin excess (Nagamine 2022a). The patient developed SS but was also in a hypodopaminergic state and was at risk for developing NMS, so the risperidone dose was reduced. Not all cases will develop SS or NMS, and the risk is thought to vary according to genetic polymorphisms of serotonin receptors in SS and dopamine receptors in NMS. Genetic polymerphisms in CYP2D6 markedly increase psychotropic drug concentrations under polypharmacy. Although the genetic polymorphism in the present case has not been investigated, it is possible that the patient was a poor metabolizer of CYP2D6. In the future, if personalized medicine is developed, it will be possible to adjust the optimal dosage for each patient, which will lead to the prevention of SS and NMS.

During the COVID-19 pandemic, patients with unknown fever require a careful differential diagnosis, and NMS and SS are differential diseases in febrile patients taking psychotropic drugs (Nagamine 2022b). Psychotropic polypharmacy increases the concentration of each drug because each drug is metabolized by a common metabolic enzyme, making NMS and SS more likely to develop. Increased psychotropic drug concentrations due to drug interactions should be noted, and differences in extrapyramidal symptoms are key to differentiating NMS from SS.

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OPTIMAL DOSAGE OF ANTIDEPRESSANTS IN THE TREATMENT OF BURNING MOUTH SYNDROME

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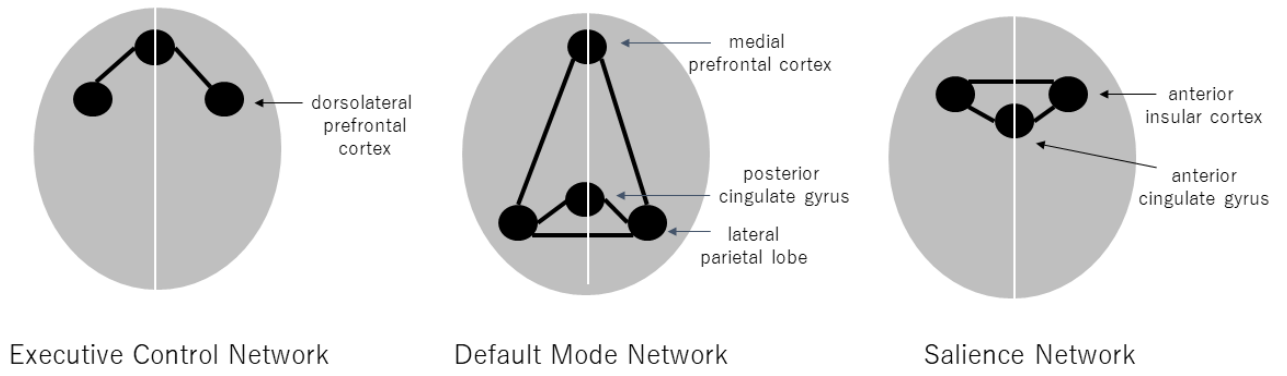
Dear editor,

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. Treatment options include antidepressants, benzodiazepines, antipsychotics, anticonvulsants, analgesics, hormone replacement therapy, and psychotherapy, with antidepressants being the most commonly used and effective. BMS patients have difficulty being understood about their pain by their families and health care providers, and tend to be anxious and depressed after the onset of the disease (Sikora et al. 2018). However, antidepressants are effective for BMS not because they improve depressive symptoms. The doses of antidepressants used in BMS treatment are much lower than the doses that produce antidepressant effects and increase side effects in a dose-dependent manner. The most commonly used and proven effective antidepressants for BMS patients in Japan are amitriptyline and aripiprazole. Amitriptyline and aripiprazole used in BMS averaged 10 mg/day and 1.0 mg/day, respectively, with roughly equivalent efficacy, but these doses are less than one-fifth the dose used as an antidepressant (Watanabe et al. 2022). Amitriptyline is a serotonin stimulator and aripiprazole is a dopamine neuromodulator, which have very different mechanisms of action. Given that small doses of antidepressants are effective and that both serotonin and dopamine regulation are equally effective in neurotransmitters, how should we think about the pathogenesis of BMS?

Antidepressants are generally thought to be effective for pain management because they activate the descending pain inhibitory pathway, but does this also apply to BMS patients? Pain stimuli have an ascending circuit that travels upward to the brain and a descending pathway that travels from the cerebral cortex to the spinal cord. The periaqueductal gray matter (PAG) is an important hub that relays the ascending and descending pathways of pain sensation. The PAG accepts not only ascending sensory input from the spinal cord but also information from the limbic system and transmits it descending to the dorsal horn of the spinal cord, inhibiting pain transmission. This descending pain inhibitory pathway is activated by serotonin, noradrenaline, GABA, and dopamine. Since both amitriptyline and aripiprazole act on the descending pain inhibitory pathway, this conventional mechanism may explain the pain-improving effects of antidepressants in BMS. However, it should be difficult for BMS patients to ameliorate pain by activation of the descending pain inhibitory pathway alone, because pain-inducing nociceptive stimuli are not present in the oral mucosa.



Large-scale brain networks are functional connections of brain cells: the executive control network when the brain is performing a task, the default mode network when the brain is dreaming or meditating without performing a task, and the change-sensitive salience network as a switch between the two

Figure 1. Schematic diagram of large-scale brain networks

Furthermore, the dose at which antidepressants show pain amelioration is only slightly less than the antidepressant effect from studies such as duloxetine (Hirase et al. 2021), so it unlikely that this small amount would adequately activate this pain inhibitory pathway.

Chronic pain patients lack distinct activity in primary and secondary somatosensory cortices activated by nociceptive pain, pointing to alterations in the large-scale brain networks, the functional connectivity of neural networks within the brain (Kim et al. 2019). Brain neurons work by connecting neurons in various different locations. When the brain performs certain tasks while conscious, the dorsolateral prefrontal cortex becomes more active, while the posterior cingulate gyrus and medial frontal lobe, two regions located farther apart, become less active. This is referred to as the executive control network (ECN). Conversely, when the brain is not performing any task, the ECN is less active and the posterior cingulate gyrus and medial frontal lobes are activated, called the default mode network (DMN). The DMN is so named because it is the resting ground state, as it does not involve thought, interest, or concern, but interestingly, it is far above the ECN in terms of brain energy expenditure. Activation of the anterior cingulate gyrus is prominent in chronic pain patients, and the functional linkage between the anterior cingulate gyrus and insular cortex, called the salience network (SN), is known to trigger emotional responses sensitive to changes in surrounding circumstances (Figure 1). A recent study using functional magnetic resonance imaging (fMRI) showed connectivity within the DMN was decreased and connectivity within the SN was increased for chronic pain patients (van Ettinger-Veenstra et al. 2019). Changes in neurotransmitter signaling cause functional reorganization of large-scale brain networks, with serotonin signaling dominating DMN activity and dopamine signaling dominating SN activity (Conio et al. 2020). These latest findings suggest that amitriptyline may be effective in BMS patients by increasing DMN activity as a result of altered serotonin neurotransmission and aripiprazole may be effective by weakening SN activity as a result of altered dopamine neurotransmission.

The effective dose of antidepressants in BMS patients is a modulation of large-scale brain networks, which may be achieved with much lower doses than the antidepressant effect. Dose-response studies on pain improvement in BMS patients are eagerly awaited, with DMN activity measured by fMRI for amitriptyline and SN activity measured by fMRI for aripiprazole.

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