

Careful use of clonazepam and alpha lipoid acid in burning mouth syndrome treatment

Dear Editor,

We read the article regarding burning mouth syndrome (BMS) and clonazepam titled "Treatment outcomes and related clinical characteristics in patients with burning mouth syndrome" from Dr. Kim of Seoul National University, South Korea, with maximum interest (Kim et al., 2020). They evaluated the treatment outcomes of BMS treatment. The authors prescribed clonazepam for long term, and they offered combination therapy of clonazepam and alpha lipoid acid (ALA) for BMS patients, which brought favorable results. However, the article would need more attention to the risk of side effects of clonazepam and ALA.

Review articles provided many treatment options for BMS, including clonazepam, ALA, and some antidepressants (Jaaskelainen & Woda, 2017). Among rare randomized controlled studies conducted regarding BMS treatment, clonazepam and ALA showed effectiveness but the problem is the short-period follow-up. In terms of the first-line medication for BMS, it may vary from country to country. In particular, Japanese doctors have prescribed tricyclic antidepressants since half century ago (Tu et al., 2019). In France, the prescription of clonazepam is limited to only neurologists and pediatricians due to some concerns about its side effects and antidepressants are commonly used (Fenelon et al., 2017). Instead, in Brazil, benzodiazepines could be used in common prescription. In Iran, antidepressants, anticonvulsant, and topical clonazepam are used (Derafshi et al., 2019).

Even though benzodiazepines have advantages in reduction in stress and improvements in sleep for short term (4–12 weeks), they would produce risks and harms in long-term prescription (DeKosky & Williamson, 2020). In fact, clonazepam would induce many side effects such as drowsiness, cognitive impairment, and intestinal motor disturbances (Jaaskelainen & Woda, 2017), or in a worst scenario might lead to dependence. The National Institute of Health and Care Excellence (NICE) recommended that benzodiazepines should be prescribed at lowest dose for minimum period. However, in a 1-year follow-up BMS study, ethyl loflazepate, a long-acting benzodiazepine, is promising and better choice since no incidence of dependence was reported (Paudel et al., 2020).

In terms of ALA, it was used originally for diabetes. It has been used for dieting, diabetic neuropathy, or antioxidant supplement in many countries. However, ALA possesses risk of hypoglycemia (Golbidi et al., 2011). Further, ALA can induce autoimmune syndrome in patients with some types of HLA (DRB1*0406, high prevalence in East Asian populations) (Uchigata, 2007). Altogether, the Ministry of Health, Labor, and Welfare in Japan has remarks of hypoglycemia induced by ALA on its website.

There is undeniable that every medication has its unwanted side effects besides the desired effectiveness. In some cases, the adverse effects could lead to serious outcomes. Considering there will be more elderly patients with BMS in near future (Suga et al., 2018), and this population, who are often prescribed polypharmacy, will be most vulnerable by side effects. Careful selection, monitoring, and dose titration therefore would lead to successful prescription. In pursuit of treatment efficacy, we should pay attention to a "not-so-little" side effect of medications used in BMS treatment. Otherwise, safe and efficient new treatment option or refined treatment regimen needs to be sought.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Takayuki Suga: Writing-original draft. **T.H Trang Tu :** Writing-review & editing. **Akira Toyofuku:** Supervision; Writing-review & editing. **Takahiko Nagamine:** Supervision; Writing-review & editing.

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