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11-1-2021

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#### Recommended Citation

Gautam M, Kaur M, and Sivananthan M. Parotid Gland Enlargement Associated With Clonazepam: A Case Report. *J Acad Consult Liaison Psychiatry* 2021; 62(6):657-658.

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# Letter to the Editor: Brief Case Report

## ***Parotid Gland Enlargement Associated With Clonazepam: A Case Report***



TO THE EDITOR: Xerostomia is a commonly reported side effect of many psychiatric medications including benzodiazepines. Xerostomia can also be present in the potentially common but less frequently identified condition of burning mouth syndrome. Clonazepam has been associated with exacerbation of xerostomia, but also, paradoxically, with alleviation of burning mouth syndrome.<sup>1</sup> Indeed, the interactions between benzodiazepines and salivary gland dysfunctions are not well understood.

Several investigations have shown that in rodent parotid glands, diazepam and clonazepam reduce salivary secretion.<sup>2,3</sup> Long-term exposure of the rat parotid gland to diazepam has been shown to result in salivary retention and enlarged mass.<sup>4</sup> We searched PubMed and Embase to identify human correlates of parotid gland enlargement in response to either clonazepam or diazepam; however, we were unable to identify definitive cases.

To the best of our knowledge, we present the first reported case of a young man who experienced bilateral parotid gland enlargement associated with clonazepam.

### CASE PRESENTATION

Alex is a 25-year-old South Asian man with autism spectrum disorder,

generalized anxiety disorder, and intermittent explosive disorder. An initial trial of sertraline in March 2020 was followed by extreme disinhibition and psychiatric hospitalization at which time sertraline was discontinued. During his hospitalization, other symptoms indicative of substance-induced or bipolar mania did not emerge; trial of another serotonin modulator, buspirone, produced similar disinhibition without other symptoms of mania.

Later that month, we initiated valproic acid to target intermittent explosive disorder and aggression. Valproic acid was titrated further over several months; however, he was unable to tolerate doses greater than 250 mg b.i.d. owing to lethargy and tremors. As aggression with potential to harm others persisted through August 2020, valproic acid was augmented with risperidone (titrated to 1 mg nightly).

Unfortunately, aggression worsened (most likely due to akathisia). Therefore, risperidone was replaced with olanzapine 5 mg nightly. As he continued to struggle with generalized anxiety disorder, he was also initiated on clonazepam 0.25 mg daily.

In early October 2020, his mother noticed left cheek swelling. His primary care physician suspected parotitis; swelling resolved with clindamycin.

By November 2020, he reported intolerable sialorrhea which was managed well with ipratropium 0.06% spray. Aside from sialorrhea, he demonstrated euthymia without

aggression for the subsequent 2 months, and in January 2021, we discontinued valproic acid.

In late January 2021, his mother noticed bilateral cheek swelling. Concurrently, aggression relapsed but his mother requested to avoid VPA. We suspected the swelling was due to olanzapine and we therefore replaced it with aripiprazole. Unfortunately, aripiprazole caused intolerable nausea and we reinitiated risperidone at a lower dose (0.5 mg daily).

Aggression improved considerably; but, by early March 2021, bilateral face swelling was not improved. We began to suspect an association with clonazepam and tapered it over March 2021. In April 2021, there was greater than 50% improvement. On surgical evaluation, there is concern parotid gland swelling may not fully resolve.

### DISCUSSION

In rats, benzodiazepines decrease salivary secretion from the parotid gland through agonist activity at central-type and peripheral-type benzodiazepine receptors. Diazepam exhibits agonist activity at central-type and peripheral-type benzodiazepine receptors, whereas clonazepam demonstrates activity at only central-type benzodiazepine receptors.<sup>2,3</sup>

Because diazepam is an agonist at multiple benzodiazepine receptors, it may induce greater salivary dysfunction than clonazepam. Indeed, both diazepam and clonazepam demonstrate reduction in pilocarpine

stimulated salivary secretion in the parotid gland of rats,<sup>4</sup> whereas salivary secretion may be more strongly inhibited by diazepam.<sup>5</sup>

The case presented herein suggests that there are potential human correlates of benzodiazepine-associated salivary gland dysfunction. Peripheral-type benzodiazepine receptors are not limited to rodents; more recently, peripheral-type benzodiazepine receptors have also been identified in human salivary glands using photo-labeling with receptor ligands<sup>3</sup> as well as with positron emission tomography.<sup>6</sup> We suggest that specific benzodiazepines may distinctively affect salivary gland dysfunction through disparate mechanisms such as variability in drug-receptor interactions as previously mentioned. These warrant further study and may have significant clinical impact; for example, switching from clonazepam to diazepam may exacerbate parotid gland dysmorphia.

There are several limitations that must be considered. Although we report an association between clonazepam and parotid gland enlargement, we cannot prove causality. There were also several medication trials which could have also influenced salivary dysfunction such

as olanzapine. However, parotid gland enlargement only improved after clonazepam was discontinued.

*Conflicts of Interest: The authors declare that they have no conflict of interest.*

*Informed Consent: Informed consent was obtained from all individual participants included in the study and information has been de-identified to protect anonymity.*

*Disclosure: The authors disclosed no proprietary or commercial interest in any product mentioned or concept discussed in this article.*

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