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## Research Article

# An increase in corrected QT interval may indicate a good clinical response to amitriptyline in female patients with burning mouth syndrome

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## ABSTRACT

Burning mouth syndrome (BMS) is characterized by a burning sensation of the oral mucosa in the absence of underlying causes. BMS patients can pose a therapeutic challenge to clinicians. Amitriptyline has been a first-line treatment for BMS and is known to prolong corrected QT interval (QTc) in a dose dependent manner. However, little is known about the QTc lengthening effect of amitriptyline at analgesic dosages. The objective of this study was to evaluate changes in QTc in female BMS patients treated with amitriptyline. We conducted a single-center retrospective observational study and evaluated 40 female BMS patients. The QTc interval did not show statistically significant increase with amitriptyline ( $p=0.1502$ ). However, the change in QTc of amitriptyline-responders was significantly longer than that of non-responders ( $p=0.0142$ ). The change in QTc may be a non-invasive maker of clinical responses to amitriptyline in female BMS patients.

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## Introduction

Burning mouth syndrome (BMS) is an oral mucosal disorder that is characterized by a chronic and often debilitating intraoral burning sensation for which no localized or systemic cause can be found [1]. BMS patients can also pose a therapeutic challenge to clinicians who are consulted to evaluate these patients [2]. Amitriptyline is widely used as an analgesic in chronic pain as it helps inhibit pain signals by activating descending pain inhibitory pathways [3]. Thus, amitriptyline has been a first-line treatment for BMS. However, amitriptyline is known to

prolong corrected QT interval (QTc) in a dose dependent manner, which may be associated with an increased risk of Torsades de Pointes (TdP) [4]. Moreover, sex differences have been described in QTc. Women are more prone to develop TdP than men during administration of medicines that share the potential to prolong QTc [5]. Little is known about the QTc lengthening effect of amitriptyline for female BMS patients at analgesic dosages (10-30 mg/day). The objective of this study was to evaluate changes in QTc in female BMS patients treated with amitriptyline.

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## Material and Methods

We conducted a single-center retrospective observational study and evaluated 40 female BMS patients who underwent 12-lead electrocardiography (ECG) examinations both before and after receiving amitriptyline from April 2017 to March 2018. We confirmed that participants had neither hypokalemia nor any cardiac diseases. We calculated QTc interval by the Bazett formula [6]. Amitriptyline-responders were defined as a decrease in visual analogue scale (VAS) by more than 20mm [7]. The statistical analysis was performed by Mann-Whitney U test. Values of  $p < 0.05$  (two-tailed test) were considered as statistically significant. The ethics committee of *Sunlight Brain Research Center* approved this study, and informed consent was obtained in the form of opt-out on the in-hospital bulletin board.

**Table 1:** Clinical characteristics of subjects: age, amitriptyline dosage, improvement in VAS, baseline heart rate, baseline QTc, change in heart rate, and change in QTc.

	Responder	Non-responder	p-value
<b>Sample size</b>	10	30	/
<b>Age years, mean <math>\pm</math> SE</b>	66.4 $\pm$ 2.5	61.3 $\pm$ 1.8	0.1374
<b>Amitriptyline dosage, mg/day</b>	18.2 $\pm$ 2.4	20.3 $\pm$ 3.1	0.3812
<b>Improvement in VAS</b>	35.2 $\pm$ 3.5	-2.2 $\pm$ 3.9	0.000*
<b>Baseline heart rate, beats/min</b>	62.7 $\pm$ 2.3	62.3 $\pm$ 1.7	0.7545
<b>Baseline QTc, msec</b>	411.2 $\pm$ 9.1	424.1 $\pm$ 3.9	0.2001
<b>Change in heart rate, beats/min</b>	10.1 $\pm$ 2.1	7.5 $\pm$ 1.4	0.42472
<b>Change in QTc, msec</b>	7.0 $\pm$ 5.6	-8.0 $\pm$ 3.2	0.0142*

Abbreviation: VAS, visual analogue scale.

Mann-Whitney U test \*  $p < 0.05$

## Discussion

The important findings of our study are that low dose of amitriptyline (<30 mg/day) has proved to be safe and a slight increase in QTc with amitriptyline may indicate a good clinical response. The QTc interval is influenced by myocardial damages, the potassium concentration, various drugs that affect the human Ether-a-go-go Related Gene (hERG) channel, and autonomic nervous function [8]. Since it's unlikely that low dose amitriptyline clinically blocks hERG channel and myocardial diseases and hypokalemia were excluded in this study, the change in QTc may depend on the change in autonomic nervous function [9]. Thus, an increase in QTc within an acceptable range in amitriptyline-responders may have suggested improvement of autonomic nervous function. For example, the diabetic patients with severe autonomic dysfunction had significantly shorter QTc compared with those without autonomic neuropathy [10]. The sympathetic nerves shorten QTc, while the parasympathetic nerves prolong it [11]. Recent studies indicated that chronic pain induces brainstem noradrenergic sympathetic activation that enhances descending pain facilitation from the dorsal reticular

## Results

The QTc intervals before and after amitriptyline treatment were 420.9 $\pm$ 3.8 msec (mean $\pm$ SE) and 416.6 $\pm$ 2.6 msec, respectively. The QTc interval did not show statistically significant increase with amitriptyline ( $p=0.1502$ ). Of 40 subjects, 10 (25.0%) were responders and 30 (75.0%) were non-responders. The change in QTc of responders was significantly longer than that of non-responders, whereas there were no differences in age, amitriptyline dosage, baseline heart rate, and baseline QTc. Amitriptyline-responders indicated an increase in QTc (7.0 $\pm$ 5.6 msec), whereas non-responders showed a decrease in QTc (-8.0 $\pm$ 3.2 msec;  $p=0.0142$ ; Table 1).

nucleus [12]. An increase in QTc in amitriptyline-responders showed activation in parasympathetic tone and pain relief, while a decrease in QTc in non-responders indicated an increase in sympathetic tone and pain facilitation from brainstem. The change in QTc may be a non-invasive marker of clinical responses to amitriptyline in female BMS patients.

The limitations of this study include a small sample size and lack of control group. Despite these limitations, an increase in QTc may predict a good clinical response for female patients with BMS. Further studies are needed to elucidate relationship between changes in QTc and autonomic nervous function in BMS patients.

## Disclosure Statement

The authors have no conflicts of interest relevant to the content of the article.

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