

# Music medicine to improve the tolerability of onabotulinumtoxinA injections for chronic migraine: an open-label prospective cohort study

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## ABSTRACT

**Introduction** OnabotulinumtoxinA for migraine involves 31 injected repeated every 12 weeks. Tolerability is a significant factor impacting discontinuation. Music medicine has not been studied previously as an intervention to improve the tolerability of injections.

**Methodology** A single-centre prospective cohort study was undertaken. Following baseline, patients had music played during the procedure. Change in Visual Analogue Score (VAS) was assessed as the primary outcome.

**Results** Over 6 months, 50 patients were recruited with a median age of 42, and median duration of therapy of 13.5 months. ‘Quiet calm classical music’ was associated with a significant reduction in VAS ( $z=-4.7$ ,  $p<0.001$ ). Duration of therapy, disease state or headache frequency had no correlation with change in VAS.

**Conclusion** Music medicine is associated with a significant reduction in the procedural pain of onabotulinumtoxinA injections in prospective study. Further study is required to explore other modifiable factors to improve patient experience.

## INTRODUCTION

OnabotulinumtoxinA (BoT-A) is an effective preventative treatment for chronic migraine that involves 31 local injections administered at 12-weekly intervals following the PREEMPT protocol.<sup>1</sup> Despite the efficacy of BoT-A, the discomfort of the injections is a significant factor in the tolerability of treatment, and is the primary reason for discontinuation in 1.3% of patients.<sup>2</sup> Currently, there is limited data addressing the tolerability of BoT-A in treatment of chronic migraine.

Music medicine is the provision of pre-recorded music by a healthcare professional, and has been studied as an adjunct in pain management in multiple other settings.<sup>3</sup> It is distinct from music therapy, which is the clinical utilisation of music in a therapeutic encounter by an appropriately trained professional. The use of music medicine on the experience of pain during BoT-A injections

for chronic migraine has not been previously investigated.

## METHODOLOGY

A single-centre prospective cohort study was performed in the tertiary headache clinic of Alfred Health, Melbourne, Australia. Patients with chronic migraine per International Classification of Headache Disorders 3rd edition criteria<sup>4</sup> that were receiving BoT-A injections by the PREEMPT protocol following local regulatory guidelines were enrolled in the study. Patients were excluded from the study if they had not received BoT-A injections prior to the first visit.

Patients were recruited from September 2022 to February 2023. Following a baseline visit and injection, a ‘quiet calm classical’ playlist (online supplemental appendix 1) was played on a portable speaker in the corner of the room during the next clinical visit. Two injectors participated in the study, and there was no variability with injector at each appointment. There was no variability with injector at each appointment. Change in 11-point Visual Analogue Scale (VAS) of injection was chosen as the primary endpoint. Patients were asked ‘on a scale of 1–10, how painful was the injection?’. Monthly headache days (MHD) were measured by patient report from headache diary in the month prior to each appointment (ie, week 9–12 after previous BoT-A administration). Disease state on the day of the injection was recorded as either ictal or interictal.

Statistical analysis was performed using SPSS V.28.0. Population characteristics were summarised with descriptive statistics. Longitudinal change was assessed with Wilcoxon signed rank test for non-normally distributed data. Spearman’s rank-order correlation was

**Table 1** Population demographics at baseline and follow-up

	Baseline, n=50	Follow-up, n=50
Age, Median (IQR)	42 (20)	
Female, n (%)	42 (84.0)	
Duration of BoT-A, Median (IQR)	13.5 (27)	
VAS, Median (IQR)	6 (3)	4 (2.9)
MHD, Median (IQR)	8 (12)	8 (13)

BoT-A, onabotulinumtoxinA; MHD, monthly headache days; VAS, Visual Analogue Score.

used to assess correlation. Tests results were considered significant when  $p < 0.05$ .

## RESULTS

A total of 50 patients were enrolled in the study over a 6-month period. Population characteristics are summarised in table 1. The population had a median age of 42 (SD 15.1), had been on treatment for a median of 13.5 months (IQR 20), and had a baseline MHD frequency of 8 days (IQR 12).

Playing 'quiet calm classical music' during the injection was associated with a significant reduction in VAS ( $z = -4.7$ ,  $p < 0.001$ ), with a median reduction by 1 (IQR 2.0). Over the 3-month follow-up period, there was also a significant reduction in MHD ( $z = -2.9$ ,  $p = 0.004$ ). A Spearman's rank-order correlation found no correlation between change in VAS and MHD ( $r = -0.09$ ,  $p = 0.535$ ), or with change in VAS and duration of therapy with BoT-A ( $r = -0.270$ ,  $p = 0.058$ ). The individual percentage change in VAS is represented in figure 1.

The impact of disease state on the day of injection on VAS was also investigated as a possible confounder. A Kruskal-Wallis H test showed there was no significant difference in pain score between patients who had both

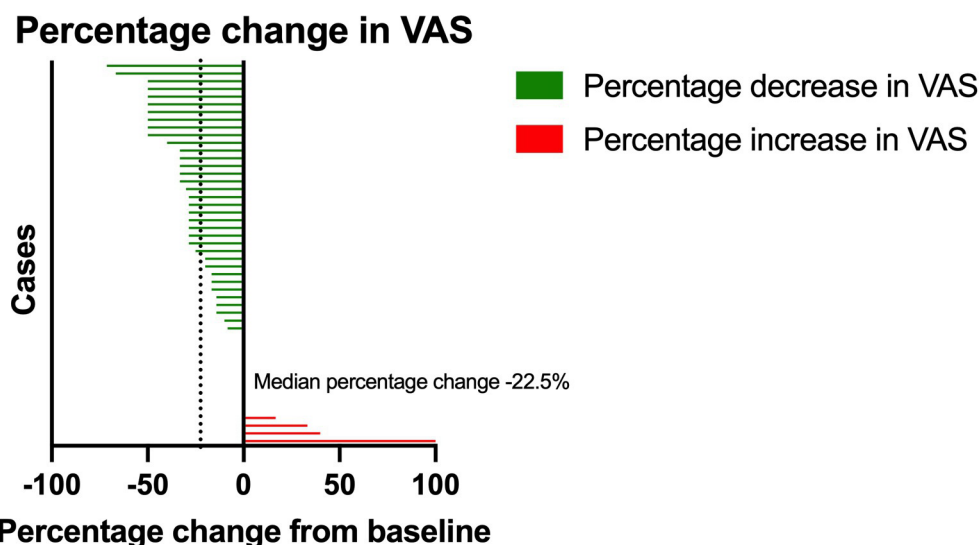
injections in an interictal state, and those who had either injection while experiencing a headache ( $p = 0.322$ ).

## DISCUSSION

This is the first prospective study to evaluate the use of music as a therapeutic technique to lessen the discomfort of BoT-A in chronic migraine, and has shown that playing 'quiet calm classical music' significantly reduces the pain of injections following the PREEMPT protocol, improving the tolerability of the procedure. This relationship appears independent of duration of therapy, ictal/interictal disease state or change in headache frequency.

Music medicine is effective at modulating pain in experimental conditions, however, the underlying mechanism remains uncertain, with hypotheses including cognitive and emotional modulation.<sup>3</sup> Listening to 'relaxing' music has been shown to modulate the hypothalamic-pituitary-adrenal axis and modulate stress in several studies.<sup>5,6</sup> Physiological effects of music have also been noted, with an improvement in blood pressure, respiration rate, heart rate and cortisol levels.<sup>7,8</sup> In a 2016 meta-analysis of the effects of music on pain, Lee reported a reduction of VAS with a similar magnitude of effect of 1.13 (95% CI  $-1.44$  to  $-0.82$ ,  $p < 0.00001$ ) on a 0–10 VAS.<sup>7</sup> There remains significant variability in the literature on the reporting of the impact of different music genre, with limited head-to-head comparisons.<sup>7</sup> Overall, studies show stronger benefit in classical music, however, Trappe reported that particular songs appeared more beneficial in different clinical settings.<sup>7,8</sup>

Ayinde and colleagues have previously studied other methods to reduce the discomfort of intramuscular injections, that have not previously been investigated in migraine.<sup>9</sup> In a 2021 systematic review and meta-analysis, they reported improvement in pain post intramuscular injection with applying manual pressure or skin tapping, but variable evidence regarding the speed of injection.



**Figure 1** Percentage reduction in VAS over study period with classical music. VAS, Visual Analogue Score.

These techniques were explored in the setting of higher volume injections in the gluteal or deltoid region and typically did not involve multiple injections in the same session, so the applicability in PREEMPT BoT-A requires further evaluation. Evaluation of low-risk techniques such as music medicine and manual pressure is valuable given the ease of implementation and beneficial impact on patient experience.

There are some limitations to this study. First, as a non-blinded study, an assessment of causation is limited. The study was designed as a prospective, single group cohort with paired-sample analysis. The fact that the study occurred at a single centre, and with a relatively small cohort, also represents a further limitation which limits generalisability. While this design is methodologically sound and controls for co-confounders such as differential experience and report of pain, it is possible that successive exposure to BoT-A reduces peripheral sensitisation and thus the perception of pain irrespective of other factors.<sup>1</sup> No association between duration of BoT-A therapy and change in VAS was observed, which suggests that this was not a significant factor. The genre of music was the same for all patients enrolled, however, potentially other genres of music, or allowing the patient to choose their genre or the individual songs played may yield different results and could be an area for further study.

## CONCLUSION

Music medicine with ‘quiet calm classical music’ is associated with a significant reduction in discomfort during BoT-A injections for chronic migraine. Further study is now required to determine if reduction in VAS is associated with improved tolerability and reduced discontinuation of the procedure.

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**Competing interests** JR has received funding for educational presentations Allergan, Novartis and has served on medical advisory boards for Pfizer, Viartis and Lilly. SR has no conflict of interest to declare.

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