


# 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

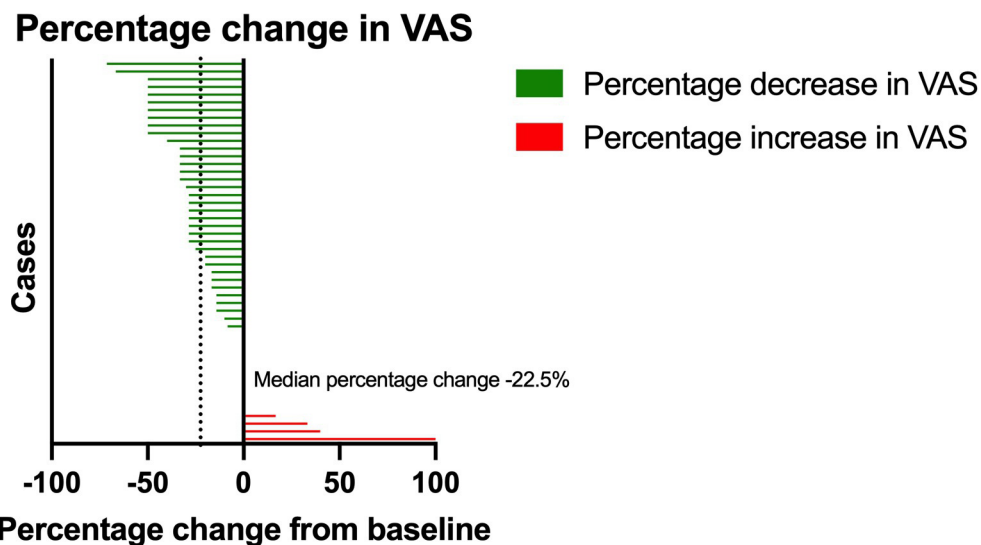
injections in an interictal state, and those who had either injection while experiencing a headache ( $p = 0.322$ ).

## 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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**Ethics approval** This study involves human participants and was approved by Alfred Health Office of Ethics & Research Governance HREC 516/22. Participants gave informed consent to participate in the study before taking part.

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**Appendix 1: Playlist****Calming Classical Mix**

Title	Artist	Album
Clair de Lune, L. 32	Claude Debussy, Martin Jones	Debussy: Clair De Lune and Other Piano Favourites
Hymn	Karl Jenkins	Karl Jenkins: Piano
Bag End	Howard Shore	The lord of the Rings: the fellowship of the ring – the complete recordings
Variations on an original Theme, Op. 36 “Enigma”: 9. Nimrod Adagio	Edward Elgar	Elgar
The Lamb	John Tavener, 12 Ensemble	Tavener: The Lamb
Variations on the Kanon	George Winston	December
Kinderszenen, Op. 15: No. 1, Von fremden Ländern und Menschen	Robert Schumann, Vladimir Horowitz	Schumann: Kinderszenen; Abaresque; Fantasie; Träumerei
Three Romances for violin and piano, Op. 22: I. Andante molto	Clara Schumann, Esther Abrami, Iyad Sughayer	Three romances for Violin and Piano, Op. 22 I. Andante molto
Ave Maria	Johann Sebastian Bach, Charles Gounod, Kian Soltani, Aaron Pilsan	J.S. Bach, Gounod: Ave Maria
Fracture	Stephan Moccio	Tales of Solace
The Lord Bless you and Keep You	John Rutter, The Cambridge Singers	The Ultimate Collection
Lyric Pieces, Book 9, Op. 68: Badnalat (Cradle Song)	Edvard Grieg, Einar Steen-Nøkleberg	Grieg: Lyric Pieces, Books 8-10, Opp. 65, 68 and 71
Still	Ola Gjeilo	Night
Very Old Friends	Howard Shore	The lord of the Rings: the fellowship of the ring – the complete recordings
Dawn – From “Pride & Prejudice” Soundtrack	Jean-Yves Thivaudet	Pride and Prujdice OST
In the Bleak Midwinter (Arr. Gjeilo)	Gustav Holst, Voces8	Winter
Tomorrow’s Song	Oðlafur Arnalds, Lavinia Meijer	The Glass Effect
Thanksgiving	George Winston	December
Lullaby (Guten Abend, gut’ Nacht)	Johannes Brahm, Fabian Müller	Lullaby (Guten Abend, gut’ Nacht)

Concertino bianco: 1. Con intenerimento	Georgs Pelēcis, Johannes Fritzsich, Tamara Anna Cislowska	Into Silence
Carnival of the Animal: Aquarium	Camille Saint Saëns, Isata Kanneh-Mason, Kona Kanneh-Mason	Saint-Saëns: Carnival of the Animals: Aquarium
Ave Maria (Arr. Vikingur Ólafsson) – Upright piano	Sigvaldi Kaldalòns, Vikingur Ólafsson	Kaldalòns: Ave Maria
My Father's Favourite	Patrick Doyle, Tony Hymas, Robert Ziegler	Sense & Sensibility – original motion picture soundtrack
Nuch loved	Rachel portman	Ask the river
The Shire	Howard Shore	The lord of the Rings: the fellowship of the ring – the complete recordings
Robin's Cello	Phoria	Caught a Black Rabbit
Ave Maris Stell	Edvard Grieg, Gabrieli, Paul McCreesh	An evening of classical: grieg
The hours: an unwelcome friend (from "the hours")	Philip Glass, Nicolas Horvath	Philip Glass: Glasssworlds, Vol. 4 – on love
Music for growing flower – Pt. 4	Erland Cooper	Music for growing flowers
Joy	George Winston	December
Elizabethan Masque	Frederico Bayco, Pro arte orchestra, George Weldone	British Composers: Best of british
Anne's Theme	Hagood Hardy	All my best
Kinderszenen, Op. 15: 1. Von fremden Ländern und Menschen	Robert Schumann, Martha Argerich	Schumann: Kinderszenen; Kreisleriana
Days of Beauty	Ola Gjeilo, The choir of royal Holloway, 12 Ensemble	Winter Songs
Frost	Gabriel Ólafsson	Frost
...And at the hour of death	Vikingur Ólafsson	Bach Reworks (Pt. 1)
The passing of the Elves	Howard Shore	The lord of the Rings: the fellowship of the ring – the complete recordings
Carnival of the Animals: the swan	Camille Saint Saëns, Isata Kanneh-Mason, Kona Kanneh-Mason	Saint-Saëns: Carnival of the Animals: The Swan
And so the story began	Jef Martens	Evenings on Instagram, Pt. I
Nimrod from enigma variations	Edward Elgar, Royal Philharmonic Orchestra, Philip Ellis	Last night of the proms
Romantic flight	John Powell	How to train your dragon (Music from the motion picture)

L'Arlésienne Suite No. 2: Menuet	Georges Bizet, Orchestre Symphonique de Montréal, Charles Dutoit	Bizet: Carmen Suits 1 & 2; L'Arlesienne Suites 1 & 2
The arts and the Hours	Jean-Philippe Rameau, Vikingur Ólafsson	Rameau, Ólafsson: The arts and the hours
Merry Christmas Mr. Lawrence	Jess Gillm, Oschar Holch, Rowena Calvert, Sma Becker	Merry Christmas Mr. Lawrence
Pachelbel's Canon in D	Pat Richardson	Pachelbel's Canon in D
Northern Lights	Ola Gjeilo, Voces8	Ola Gjeilo
Ashokan Farewell	Jay Ungar, Nashville Cahamber Orchestra, Paul Gambill	Harvest Home
Rivendell	Howard Shore	The lord of the Rings: the fellowship of the ring – the complete recordings
5 Anniversaries: No. 5 For Susanna Kyle	Leonard Bernstein, Warren Lee	Touches & Traces
Greensleeves	David Nevue	Sweet Dreams & Starlight