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Research Article

0.075% Capsaicin cream and wind-up in chronic lumbar radicular neuropathic pain - a phenotype-stratified, case series

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Abstract. Personalized treatment for low back pain disorders is a high research priority and stratified medicine using sensory profiling can potentially improve the outcomes. Wind-up, or temporal summation, is the progressive increase in action potential firing rate of spinal cord neurons to repetitive stimulation of C-fibre afferents at a constant intensity. Wind-up can occur in neuropathic pain, and it is augmented by the presence of central sensitization, which can lead to Aδ-fiber-induced wind-up rather than solely being activated by C-fibre stimuli. Topical capsaicin activates the transient receptor vanilloid-1, which is expressed in C-fibres and some Aδ-fibers of the peripheral nervous system, leading to a reduction in skin evoked pain. Despite the supporting evidence for the 8% capsaicin patch, there is evidence that specific patient subgroups treated with 0.04% capsaicin formulation obtained better analgesia compared to the higher dose. However, that research did not evaluate sensory profiles nor predictive biomarkers.
Due to the common neurophysiological pathways implicated in wind-up and capsaicin, our study posited that the adjunctive use of low-dose capsaicin cream (0.075%), coupled with physiotherapy, may offer analgesia in a subset of patients with chronic lumbar radicular neuropathic pain ($n = 9$, median pain duration of 5 years) who exhibit wind-up phenomena. The combination of topical capsaicin and physiotherapy yielded clinically significant analgesia (Hedges' $g = 2.96$). Therefore, we propose investigating through a randomised controlled trials the utility of a simple bedside test as a predictive marker for a favourable response to 0.075% capsaicin cream in individuals with chronic lumbar radiculopathies who exhibit wind-up.

Keywords: Radiculopathy; Sciatica; Neuralgia; Capsaicin; Phenotype; Precision Medicine; Low Back Pain; Chronic Pain; Case Reports.

1 Introduction

First-line oral pharmacological treatment for neuropathic pain (NP) is hindered by the relatively poor number needed to treat (NNT) (Finnerup et al., 2015), an adverse effect profile coupled with a failure rate of ≥70% (Moore et al., 2013). Therefore, evidence-based oral pharmacological management of NP is probably not very effective (NICE, 2020). Besides, individualizing treatment for low back pain disorders has been identified as a high research priority by international expert panels (Vollert et al., 2017). The current treatment of NP, including radicular NP, is usually empirical, it is not guided by foreseen efficacy, but instead, it is based on tolerability and personal preference of the prescriber. Persons with NP exhibit different profiles in respect to their comorbidities, pain intensity, dysesthesias, and neurological changes. The sensory profile is the cluster of signs that a particular individual exhibits when undergoing sensory testing. In turn, this profile can be predictive of the outcome of certain treatments and hence can be exploited in stratified medicine by matching treatments to persons who have a higher likelihood of a

NP — neuropathic pain
NNT — number needed to treat
TRPV-1 — transient receptor potential vallinoid-1
TS — temporal summation
IASP — International Association for the Study of Pain
NRS — numerical pain rating scale
PGIC — patient global impression of change scale
PHN — postherpetic neuralgia
PDN — painful diabetic neuropathy

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better outcome (Themistocleous et al., 2018). Such examples include the efficacy of oxycodone being predicted by the magnitude of heat pain threshold (Eisenberg et al., 2010), and high temporal summation (TS), especially in a pain-free control site, which predicted the immediate analgesic response to acupuncture in chronic pain patients (Baeumler et al., 2019). Due to the shared neurobiology underlying wind-up/TS (Woolf, 2011) and capsaicin (Basith et al., 2016), mediated by transient vanilloid receptor-1 (TRPV-1) within the peripheral nervous system (Kupers et al., 2011), we hypothesized that the application of a low dose capsaicin cream (0.075%), would provide analgesia in a phenotype-stratified cohort of patients, specifically exhibiting skin-evoked wind-up/TS and having a definite NP grade (Finnerup et al., 2016) due to chronic lumbar radicular pain. The null hypothesis was that the capsaicin would not provide an analgesic effect. To the authors' best knowledge, there are yet no reports evaluating the effect of 0.075% capsaicin cream in a phenotype-stratified cohort of patients, specifically exhibiting wind-up.

2 Material and Methods

The participants were recruited from a larger study (Schembri et al., 2020) and were identified during their initial physiotherapy examination for chronic low back pain and lumbar-related leg pain within the Musculoskeletal Physiotherapy Outpatients Department (secondary level of care) at a local rehabilitation hospital in Malta, Europe, between March and November 2019. These patients were approached by an intermediary (doctor at the pain clinic), and written informed consent was obtained from all of them. A convenience sampling strategy was adopted. The sample size of the case series ($n = 9$) was determined by the number of patients with radicular pain and simultaneously exhibiting wind-up who attended the clinic during the eight-month data collection period, which culminated in the onset of the COVID-19 pandemic. Ethical approval for the study was obtained from the research committee at a local rehabilitation hospital in Malta, Europe (04/03/2019). Figure 1 provides a flow diagram of the participants in this study.

Participants from both sexes were included in this case series if they fulfilled all the following criteria: 1) over 18 years of age; 2) referred to the Musculoskeletal Physiotherapy Outpatient's facilities for chronic low back and/or lumbar-related leg pain; 3) with pain duration of $\geq$ three months; 4) had a definite NP grade according to the International Association for the Study of Pain (IASP) grading system (Finnerup et al., 2016); 5) exhibited wind-up on bedside sensory examination, based on the protocol by Kupers, Lonsdalel, Aasvangl & Kehletl, (2011) and Scholz et al. (2009). The exclusion criteria were the presence of any implanted medical device specifically to treat NP, fibromyalgia, complex regional pain syndrome, severe musculoskeletal pain other than chronic low back pain and/or lumbar-related leg pain, significant medical and/or psychiatric comorbidity, cognitive impairment, or intellectual disability, ex-smokers, pregnant, known diabetic/metabolic/drug-induced neuropathy and known hypersensitivity to capsaicin.

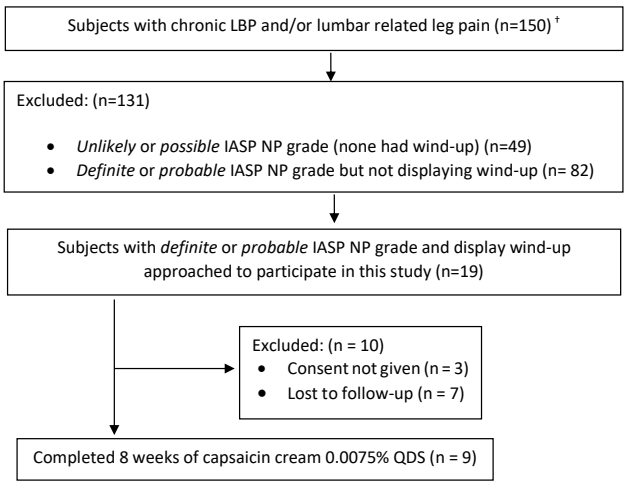

Figure 1: Flow diagram of the participants in the study. †Participants were identified from Schembri, Massalha, Spiteri, Camilleri & Lungaro-Mifsud, (2020).

2.1 Pain assessment

Demographic data on sex, age, and pain chronicity (years) were recorded. The primary outcome measure was pain intensity, which was assessed using three separate Numeric pain Rating Scales (NRS) for lowest, mean, and highest pain intensity. Each of the three individual NRS had the anchors "no pain" and "pain as bad as you can imagine (0-10)." The worst pain location was classified as either in the lower limb or in the low back. The most distal pain radiation was categorized into five sections: the low back, knee level, upper calf, lower calf and/or ankle and in the foot (Hasvik et al., 2018). The STarT Back (Hill et al., 2008) and the DN4 questionnaires (Bouhassira et al., 2005; Schembri et al., 2019) were also scored.

The procedure to grade the certainty of NP in the participants was adopted from Schembri, Massalha, Spiteri, Camilleri & Lungaro-Mifsud, (2020) and it is briefly reported hereunder. The bedside sensory examination was conducted by the primary author (ES) and it included the response to static pressure, dynamic light tactile touch (SENSELab™ Brush-05, Somedic SenseLab AB, Sösdala, Sweden), pinprick (5.1g Semmes-Weinstein type monofilament, Baseline® Tactile Monofilaments™, Fabrica-

tion Enterprises Inc, White Plains, NY, USA), vibration (Rydel-Syffer 128 Hz graduated [8/8 scale] tuning fork, Baseline® Rydel-Syffer, Fabrication Enterprises, White Plains, NY, USA), warm and cold (using two test tubes each one filled with water at 25°C or 40°C), and sensory threshold to punctate tactile stimulation (Semmes-Weinstein type monofilaments, 0.07g - 300.0g, Baseline® Tactile Monofilaments™, Fabrication Enterprises, White Plains, NY, USA). Initially, a demonstration was performed on the patients' arm, followed by testing in the most painful lower quadrant area. The latter was compared to a homologous contralateral reference site. Two repetitions of each test procedure were done.

2.2 Testing for wind-up

The terms wind up or TS will be used interchangeably throughout this report. They refer to a neurophysiological process coined by Mendell and Wall (1965) describing the progressive increase in action potential firing rate of spinal cord neurons to repetitive stimulation (minimum stimulation of 0.3Hz; though more substantial effects occur at 1-2Hz) of C-fibre afferents at a constant intensity (Woolf, 2011).

Wind-up was assessed using a 5.1g Semmes-Weinstein type monofilament (Baseline® Tactile Monofilaments™, Fabrication Enterprises, White Plains, NY, USA), and applied at 2Hz for 30 seconds (Kupers et al., 2011; Scholz et al., 2009). The stimuli were delivered by hand but taking great care to standardize the stimulus delivery mode aided with an Android mobile metronome (Pro Metronome, Soundcorset) to cue the frequency of the stimulation. Windup was tested via an Aδ-fibre stimulating modality (using Monofilaments) rather than a C- fibre modality (via heat) for ease at bedside examination (Papagianni et al., 2018; Suzan et al., 2015) and since Aδ- neurons exhibit wind-up specifically after peripheral nerve injury (Kupers et al., 2011) such in the case of lumbar radiculopathies. Two possibilities occurred in the presence of wind-up, depending on the severity of the pain elicited during the procedure. If the participant experienced intolerable pain during wind-up testing and asked to stop the test, the intensity and the time ($\leq$30 seconds) for the onset of such pain intensity was recorded. In the case of tolerable pain, the NRS score (0-10) was recorded at the end of the 30 seconds.

2.3 Therapeutic intervention

The pain consultant at a local hospital prescribed the 0.075% capsaicin cream, which was bought and self-applied by the patients four times daily for eight weeks, spread evenly over the painful area that exhibited windup. During this treatment period, the patients were advised not to change their chronic pain medications or use any other topical pain medication on the affected area, including different capsaicin formulations. However, in case of an initial burning sensation, the patients were instructed to pre-emptively use a topical local anaesthetic cream 10 minutes before applying the capsaicin cream until the patient got used to the initial burning sensation.

Apart from 0.075% capsaicin cream, all the patients underwent individualized physiotherapy as usually provided by the department, including pain neuroscience education, sleep hygiene, cognitive restructuring of counter-productive beliefs, pacing, lifestyle modifications, dealing with flare-ups, and an individualised graded exercise program, comprising stretching and strengthening exercises. Previously, most of the participants had received multiple treatments for their pain, including medications, spinal infiltrations and surgery. These treatments were provided at least four months before the participants' acceptance to engage with the current therapeutic regimen. Hence it did not affect the outcome of the current intervention. Due to the large recall bias from the patients, these treatments were not recorded.

2.4 Clinical outcome

Follow-up assessments were conducted at one month, two months, and six months post-treatment. Pain intensity was measured using the 0-10 NRS at each time point. Additionally, global improvement with treatment compared to baseline was assessed using the 7-point scale Patient Global Impression of Change (PGIC) scale. This scale ranges from 'very much improved' to 'very much worse', with 'no change' positioned at the midpoint (Perrot & Lantéri-Minet, 2019).

2.5 Statistical analysis

Two statistical tests were used to make inferences about the patient population using the data set drawn from this population. The Wilcoxon rank test compared the median scores between the median baseline NRS and the median NRS scores at one month, two months, and six months. The estimate of effect using Hedges' *g* statistic was calculated using the same time points. The same test was used to compare the PGIC score at one month and two months and then from 1 month to 6 months. A 0.05 level of significance was used for both tests, where P values less than this 0.05 criterion indicate a significant difference between the two median scores. Statistical analysis was done using Jamovi version 1.6.23.

3 Results

Table 1 demonstrates the baseline characteristics of the nine participants recruited for this phenotype-stratified case series. Of note there was a high percentage of current smokers (77.8%) and who previously underwent

Age (years)†	63 (50 to 68)
Gender (% female)	44.4%
Chronicity (years)†	5 (3 to 5)
Current smoker (% yes)	77.8%
Past lumbar surgery (% yes)	44.4%
Least NRS (0-10)†	5 (0 to 5)
Median NRS (0-10)†	8 (7 to 10)
Highest NRS (0-10)†	10 (9 to 10)
Analgesic drug classes consumed†	2 (0 to 2)
Worst pain location (% lower limb)	100%
Most distal radiation (% into the foot)	55.6%
STarT Back score (0-9)†	7 (5 to 8)
DN4 score (0-10)†	4 (3 to 5)
Hypoesthesia within a neuroanatomically plausible distribution	100%
Myotomal weakness*	66.7%
Tendon reflex reduction or loss*	66.7%

Table 1: Baseline characteristics ($n = 9$).*At least having a deficit in one modality. †Median (interquartile range).

lumbar surgery (44.4%).

Compared to the baseline NRS, the intervention led to a statistically significant reduction in the median NRS already from the first month ($P = 0.048$, Hedges' $g = 0.2533$), however this became larger by the second month ($P = 0.009$, Hedges' $g = 2.0186$) and at the sixth month ($P = 0.009$, Hedges' $g = 2.96$) (Table 2). The patients started to show improvement in the PGIC values from the first month of follow-up. Yet, a significant change in the PGIC was experienced at the second month of follow-up ($P = 0.01$) compared to 1-month follow-up, which further improved at six months follow-up ($P = 0.008$), indicating that the intervention continues to exert its effect on the PGIC until at least six months in our cohort (Table 2).

At 2 months follow-up, 5 participants continued to experience wind-up in the previously tested skin area, but at 6 months follow-up only 2 participants continued to experience wind-up. However, the latter two participants reported at six months follow-up an improvement in the NRS. Four patients reported very mild, transient (maximum 1 hour) burning, itching sensation after applying the capsaicin cream, which either reduced or they got accustomed to it after the initial applications, and none of the participants required the pre-emptive use of a topical local anaesthetic cream. The other five patients did not report any adverse effects. None of the participants self-reported difficulties with adhering to the treatment regime, and none required the use of rescue medications to manage any adverse effects. Furthermore, all patients reported positively on the intervention, despite the commitment to the frequent application of the cream and the need to actively engage with the physiotherapy regimen.

4 Discussion

This phenotype-stratified case series provides seminal evidence for the predictive effect of wind-up in mediating the analgesic effect of 0.075% capsaicin cream applied four times daily for eight weeks, in combination with physiotherapy, to treat skin-evoked wind-up pain in subjects diagnosed with definite NP due to chronic lumbar radicular pain. The type, intensity and frequency of physiotherapy interventions were not controlled within this study to reflect real-life clinical practice. Already in the initial one-month follow-up, the reduction in NRS reached statistical significance ($P = 0.048$). However, at the second and sixth month follow-up, there was a more significant change in median NRS ($g = 2.96$, $P = 0.009$). Such results were mirrored in the PGIC scores too.

4.1 Temporal summation and capsaicin

Initially, TS was thought to reflect an alteration in neuronal excitation of the dorsal horn. However, this is also regulated by supraspinal mechanisms (Cheng et al., 2015) and it frequently occurs in healthy individuals (Wong et al., 2023), but the presence of central sensitization enhances this process, and it can predict pain outcomes (Arendt-Nielsen et al., 2010). TS is thought to arise mainly due to increased C-fiber induced second pain, which under normal conditions, can only be elicited by stimulation at C-fibre strength (Woolf, 2011). Yet, a peripheral nerve injury can lead to an Aδ-fiber induced wind-up (Kupers et al., 2011).

The primary target of capsaicin is the TRPV-1 receptor, which is predominantly expressed in C-fibres and some Aδ-fibers of the peripheral nervous system. Capsaicin application leads to an overstimulation of the cutaneous nociceptors and TRPV-1 channels, causing the defunctionalization of the terminal nociceptive nerve fibres, ultimately reducing spontaneous nerve activity, reducing skin-evoked nociception, in turn, leading to a reduction in peripheral NP since the area becomes "desensitized" (Baeumler et al., 2019). However, usually, the epidermis becomes re-innervated within six weeks after discontinuation of the 0.075% capsaicin cream (Nolano et al., 1999). Considering that both wind-up and capsaicin share underlying neurophysiological processes, primarily through activation of C-fibres and Aδ-fibres, it was theoretically, expected to obtain positive results in a phenotype-stratified group. The identification of the presence of wind-up as a possible biomarker facilitates the identifica-

Outcome measure	Baseline	1 month	2 months	6 months	P-value*	P-value‡
NRS Scale† (0 to 10)	8 (7 to 10)	8 (6 to 9)	3 (2 to 4)	2 (1 to 7)	0.008	0.008
PGIC Scale† (-3 to +3)	/	1 (0 to 1)	2 (1 to 2)	3 (2 to 3)	0.010	0.008

Table 2: Numeric pain Rating Scale (NRS) and the Patient Global Impression of Change (PGIC) scale at the follow-up points ($n = 9$). *Wilcoxon rank test, change from one month to two month follow-up. ‡Wilcoxon rank test, change from one month to six month follow-up. / means that it could not be measured at baseline. †Median (interquartile range).

tion of responder subgroups.

4.2 Current indications for the low-dose capsaicin cream

In the UK, the 0.075% capsaicin cream is indicated for the treatment of postherpetic neuralgia (PHN) and painful diabetic neuropathy (PDN) in adults and the elderly, with a recommended daily application of 3-4 times for eight weeks (Teva UK Ltd., 2024). Furthermore, NICE, (2020) considers using the 0.075% capsaicin cream in non-specialist settings for patients with localized NP who cannot tolerate or wish to avoid oral pharmacological treatments.

4.3 Responder subgroups for the low dose capsaicin cream

Despite studies (Derry et al., 2017) showing the inferiority of the lower dose capsaicin formulation compared to the higher dose patch for peripheral NP, a previous Cochrane review (Derry et al., 2012) and a subsequent study (Martini et al., 2013), both concluded that the lower dose capsaicin formulations [0.075% (Derry et al., 2012), 0.04% (Martini et al., 2013)], may still provide some analgesia. The Cochrane review (Derry et al., 2012) included six double-blind RCTs comparing topical capsaicin cream (0.075%) ($n = 198$) to placebo ($n = 191$) for NP, with the cream being applied four times daily for 6, 8 or 12 weeks, depending on the individual study design, and it found that 41% of the subjects treated with the 0.075% capsaicin cream had a positive outcome compared to 26% who received a placebo. This review concluded that the 0.075% topical capsaicin cream had an NNT of 6.6 (4.1 to 17) over 6 to 8 weeks, which is comparable to the NNT of oral pregabalin ($NNT = 7.7$) (Finnerup et al., 2015), which is considered as first line of treatment for NP. However, an update of this Cochrane review (Derry et al., 2017) revealed that there was insufficient data to draw any conclusions about the efficacy of low-concentration capsaicin cream (< 1%) in the treatment of NP. Hence it concluded that its effect is comparable to placebo and that it is unlikely that low-concentration topical capsaicin has any meaningful use in clinical practice. However, both Cochrane reviews (Derry et al., 2012, 2017) did not evaluate specific responder subgroups. Furthermore, both reviews evaluated the effect of the low dose capsaicin in patients based on the aetiology of their NP condition rather than on particular patient characteristics and sensory profiles at baseline, which can provide a higher chance of identifying responder subgroups (Themistocleous et al., 2018).

Martini et al. (2013) pooled data from four double-blind, randomized controlled trials (RCTs) comparing the efficacy of capsaicin 8% patch ($n = 722$) to an active control (0.04% capsaicin cream) ($n = 526$) in patients with PHN and highlights the importance of identifying patient responder subgroups. This study found that both formulations had similar response profiles, yet the proportional distribution of patients favoured the high-dose preparation. Nonetheless, the group randomized to 0.04% capsaicin patch obtained an overall 23.9% reduction in the NRS score. Martini et al. (2013) found that out of the available five patient subgroups, one of these subgroups (subgroup 5) experienced a 69.6% reduction in pain intensity score at 12 weeks with the low dose capsaicin, while an analogous subgroup using the high dose capsaicin experienced a decrease in pain scores by 67.4% at 12 weeks. The current case series results are reminiscent of subgroup five by Martini et al. (2013) since our phenotype-stratified group continued to experience a decline in mean NRS values with an increase in the follow-up period. However, our participants did not obtain the same level of analgesia (57% reduction in NRS).

However, there are considerable methodological differences between Martini et al. (2013) and the current report. First, the aetiology of the NP is different since Martini et al. (2013) evaluated subjects with PHN while the present study looked at NP originating from chronic lumbar radicular pain. Secondly, the studies evaluated by Martini et al. (2013) used a 0.04% capsaicin patch applied as a single dose for either 30 or 60 or 90 minutes by a clinician. In the current study, a 0.075% cream was used to deliver capsaicin, and it was applied four times daily for eight weeks by the patient him/herself. Thirdly, Martini et al. (2013) did not provide any information on the sensory profiles of the patients, not even at the level of responder subgroups. Most importantly, Martini et al.

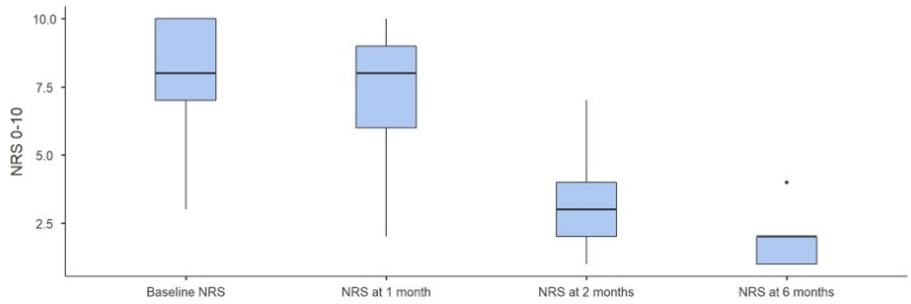

Figure 2: The change in numeric pain rating scale (NRS) values (0-10) over the six months follow-up period.

(2013) obtained data from large RCTs, while we adopted an observational approach.

4.4 Strengths and limitations

In this case series, the application of capsaicin was through a self-applied cream, which avoided the need for further hospital visits, being highly practical since it was applied by the patients themselves in the comfort of their own homes. However, such a length of treatment (8 weeks) necessitated a substantial level of compliance and adherence from the patients, which cannot be ascertained. The fact that the patients within this report were compliant and motivated enough to comply/adhere to the whole length of the treatment could potentially be a source of bias.

Previous studies looked at the prognostic potential of quantitative sensory testing (QST) (Georgopoulos et al., 2019), but this is an expensive piece of equipment, the procedure is time-consuming and necessitates specific clinician training. However, the simple procedure adopted for testing for TS in this report could be completed in the clinic in less than 30 seconds, necessitating only everyday clinical equipment, which is relatively cheap, and no lengthy training is necessary for the clinician doing this testing procedure.

The methodology adopted, i.e., case series, poses severe limitations on the strength of the evidence of the current study. Furthermore, having a single clinician performing the assessment and treatment improves the standardization of the testing procedures but greatly increases the chance of introducing bias. Besides, the combination of capsaicin cream and physiotherapy precludes any conclusion on the isolated positive effect of either intervention in this population of chronic low back pain sufferers. Still, it can portray a synergistic effect targeting various modifiable aspects within the biopsychosocial model of pain.

5 Conclusions

Given the study participants, despite previous treatments, had pain chronicity of approximately five years, where spontaneous recovery (da C Menezes Costa et al., 2012) and regression to the mean are limited, the combination of physiotherapy and the 0.075% capsaicin cream provided analgesia in persons with previously refractory chronic lumbar radicular NP. Given such treatment effect (Hedges' $g = 2.96$ at six months follow-up), it is unlikely that this outcome is attributed solely to the placebo effect despite the biases imposed by the methodology of this case series. Hence, this treatment approach warrants further evaluation in a phenotype-stratified, placebo-controlled RCT.

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Conflict of Interest None declared.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from all individual participants prior to enrolment in the study.

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