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## **Burst Transspinal Magnetic Stimulation Alleviates Nociceptive Pain in Parkinson Disease-A Pilot Phase II Double-Blind, Randomized Study**

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# Neuromodulation: Technology at the Neural Interface

## BURST TRANS-SPINAL MAGNETIC STIMULATION ALLEVIATES NOCICEPTIVE PAIN IN PARKINSON'S DISEASE - A PILOT PHASE II DOUBLE-BLIND, RANDOMIZED STUDY

--Manuscript Draft--

<b>Manuscript Number:</b>	NEUROM-D-22-00240
<b>Full Title:</b>	BURST TRANS-SPINAL MAGNETIC STIMULATION ALLEVIATES NOCICEPTIVE PAIN IN PARKINSON'S DISEASE - A PILOT PHASE II DOUBLE-BLIND, RANDOMIZED STUDY
<b>Article Type:</b>	Clinical Research
<b>Keywords:</b>	Parkinson disease, chronic pain, spinal cord, neuromodulation, trans-spinal magnetic stimulation, burst, nociceptive pain, musculoskeletal pain, spinal cord stimulation
<b>Abstract:</b>	<p>Background and aims: Nociceptive is the most prevalent pain mechanism in Parkinson disease (PD). It negatively affects quality of life and there is currently no evidence-based treatment for its control. Burst spinal cord stimulation has been used to control neuropathic pain, and recently shown to relieve pain of nociceptive origin. Here, we hypothesize that burst trans-spinal magnetic stimulation (bTsMS) reduce nociceptive pain in PD.</p> <p>Materials and Methods: Twenty-six patients were included in a double-blind, sham-controlled, randomized parallel trial design, and the analgesic effect of lower-cervical bTsMS was assessed in patients with nociceptive pain in PD (NCT04546529). Five-daily induction sessions were followed by maintenance sessions delivered twice a week for seven weeks. The primary outcome was the number of responders (<math>\geq 50\%</math> reduction of average pain intensity assessed on a numerical rating scale ranging from 0-10) during the 8 weeks of treatment. Mood, quality of life, global impression of change, and adverse events were assessed throughout the study.</p> <p>Results: Twenty-six patients (46.2% women) were included in the study. The number of responders during treatment was significantly higher after active compared to sham bTsMS (<math>p = 0.044</math>), mainly due to the effect of the first week of treatment, when eight (61.5%) patients responded to active and two (15.4%) responded to sham bTsMS (<math>p=0.006</math>); number needed to treat=2.2 at week 1. Depression symptom scores were lower after active (<math>4.0\pm 3.1</math>) compared to sham bTsMS (<math>8.7\pm 5.3</math>; <math>p=0.011</math>). Patient's global impressions of change were improved after active bTsMS (70.0%) compared to sham bTsMS (18.2%; <math>p=0.030</math>). Minor adverse events were reported in both arms throughout treatment sessions. One major side effect unrelated to treatment occurred in the active arm (death due to pulmonary embolism). Blinding was effective.</p> <p>Conclusion: bTsMS provided significant pain relief and improved the global impression of change in PD in this phase-II trial.</p>

1 **BURST TRANS-SPINAL MAGNETIC STIMULATION ALLEVIATES**  
2 **NOCICEPTIVE PAIN IN PARKINSON'S DISEASE - A PILOT PHASE II**  
3 **DOUBLE-BLIND, RANDOMIZED STUDY**

4 RUNNING HEAD: Burst-TsMS for Parkinson Pain

5  
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7 Jacobsen Teixeira, MD, PhD<sup>a</sup>, Vitor Macedo Brito Medeiros<sup>a</sup>; Ana Mércia Fernandes,  
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9 Gisbert Cury, MD, PhD<sup>a,b</sup>; Daniel Ciampi de Andrade, MD, PhD<sup>a,c</sup>.

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16 *Technology, Faculty of Medicine, Aalborg University, Aalborg, Denmark*

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26 **Authorship Statement:**

1  
2 27 Daniel Ciampi de Andrade and Jorge Dornellys da Silva Lapa conceived and designed  
3  
4 28 the study. Jorge Dornellys da Silva Lapa, Pedro Henrique Martins da Cunha, Vitor  
5  
6  
7 29 Macedo Brito Medeiros, and Adriano Donizeth Silva de Moraes conducted patient  
8  
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10 30 examinations and collected clinical data. Jorge Dornellys da Silva Lapa, Daniel Ciampi  
11  
12 31 de Andrade, Pedro Henrique Martins da Cunha, Vitor Macedo Brito Medeiros, and Ana  
13  
14 32 Mércia Fernandes provided intellectual input in analyzing the data and performed  
15  
16 33 statistical analyses. Jorge Dornellys da Silva Lapa and Daniel Ciampi de Andrade drafted  
17  
18 34 the manuscript. Thomas Graven-Nielsen, Manoel Jacobsen Teixeira, and Rubens Gisbert  
19  
20 35 Cury revised the manuscript for critically important intellectual content.  
21  
22  
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24 36

26 37 **Conflicts of interest**

27  
28  
29 38 No conflict of interest to be reported.  
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48 **ABSTRACT**

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2 49 **Background and aims:** Nociceptive is the most prevalent pain mechanism in Parkinson  
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5 50 disease (PD). It negatively affects quality of life and there is currently no evidence-based  
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7 51 treatment for its control. Burst spinal cord stimulation has been used to control  
8  
9 52 neuropathic pain, and recently shown to relieve pain of nociceptive origin. Here, we  
10  
11 53 hypothesize that burst trans-spinal magnetic stimulation (bTsMS) reduce nociceptive pain  
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13 54 in PD.

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15  
16 55 **Materials and Methods:** Twenty-six patients were included in a double-blind, sham-  
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18  
19 56 controlled, randomized parallel trial design, and the analgesic effect of lower-cervical  
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21 57 bTsMS was assessed in patients with nociceptive pain in PD (NCT04546529). Five-daily  
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23 58 induction sessions were followed by maintenance sessions delivered twice a week for  
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25 59 seven weeks. The primary outcome was the number of responders ( $\geq 50\%$  reduction of  
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27 60 average pain intensity assessed on a numerical rating scale ranging from 0-10) during the  
28  
29 61 8 weeks of treatment. Mood, quality of life, global impression of change, and adverse  
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31 62 events were assessed throughout the study.

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34 63 **Results:** Twenty-six patients (46.2% women) were included in the study. The number of  
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39 65 bTsMS ( $p = 0.044$ ), mainly due to the effect of the first week of treatment, when eight  
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47 69 impressions of change were improved after active bTsMS (70.0%) compared to sham  
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49 70 bTsMS (18.2%;  $p=0.030$ ). Minor adverse events were reported in both arms throughout  
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51 71 treatment sessions. One major side effect unrelated to treatment occurred in the active  
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53 72 arm (death due to pulmonary embolism). Blinding was effective.

73 **Conclusion:** bTsMS provided significant pain relief and improved the global impression  
1 of change in PD in this phase-II trial.  
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7 76 **Keywords:** Parkinson disease, chronic pain, spinal cord, neuromodulation, trans-spinal  
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9 77 magnetic stimulation, burst, nociceptive pain, musculoskeletal pain, spinal cord  
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## 98 1. INTRODUCTION

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2 99 Despite having been reported since the original description of Parkinson disease (PD),  
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4 100 non-motor symptoms (NMS) remained underexplored for a long period(1). Recently,  
5  
6 101 there has been a steady increase in the interest on NMS since they are currently known to  
7  
8 102 substantially impact functioning and quality of life in PD(2). Of the several NMS, pain is  
9  
10 103 often reported by PD patients at all stages of disease. Pain has a large and important  
11  
12 104 negative impact on quality of life even in early-stage disease(3)(4)(5)(6).

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15 105 PD is a multisystemic disease and its associated pathological findings can be  
16  
17 106 identified in extranigral regions including non-dopaminergic systems(7)(8)(9). Indeed,  
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19 107 some NMS are dopamine-responsive, while others are not. Dopamine-replacement  
20  
21 108 therapy may not alleviate all NMS and specific treatments may be necessary to improve  
22  
23 109 quality of life of patients experiencing NMS(10)(11). Dopaminergic treatment improves  
24  
25 110 pain in only some PD patients, and there is no correlation between motor improvement  
26  
27 111 and pain relief after dopaminergic or neuromodulatory treatments(11)(12). Pain in PD is  
28  
29 112 often underassessed, and nearly half of patients do not receive medications or physical  
30  
31 113 therapy. This is partially due to the lack of assessment tools validated to classify pain in  
32  
33 114 PD as well as due to limited evidence-based treatment options. Current recommendations  
34  
35 115 do not distinguish among different pain types in PD and they acknowledge the paucity of  
36  
37 116 treatment options supported by evidence(10).

38  
39 117 Chronic pain (pain lasting for more than three months and present most of the days)  
40  
41 118 affects 18% of the general population(13)(14). Chronic pain is present in 20% of PD  
42  
43 119 patients in the early stages of the disease but up to 80% of patients in later  
44  
45 120 stages(3)(15)(16). PD pain is divided into pain unrelated to PD and pain related to PD.  
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47 121 The later refers to chronic pain aggravated by PD or de novo pain appearing during  
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49 122 disease installation, while PD-unrelated pain refers to previous chronic pain that is not  
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123 influenced by PD(17). PD-related pain is further classified according to the International  
124 Association for the Study of Pain mechanistic classification and subsequent validation  
125 studies into nociceptive, neuropathic, and nociplastic pains syndromes(18). PD-  
126 nociceptive pain is the most frequent pain type and is present in 55% of the patients. It is  
127 more commonly located in the trunk and the lower back regions and is often localized or  
128 regional(17). It is associated with levodopa-induced dyskinesia, thus clustering away  
129 from neuropathic and nociplastic pain types in PD(17).

130 Spinal cord stimulation is a long-known treatment option for neuropathic pain. It  
131 was initially believed its effects stemmed from dorsal column-mediated effects and pain  
132 gate-control mechanisms(19), while it was later shown to have a much wider effect in  
133 spinal cord information processing, affecting extra-lemniscal tracts, including structures  
134 located in the anterior portions of the spinal cord(20). Lately, new evidence has shown  
135 that burst spinal cord stimulation can lead to lower back and axially located pain relief  
136 possibly due to its enhanced effects on wide dynamic range (WDR) cells. A preferential  
137 influence on medial nociceptive pathways leading to modulation of the affective  
138 dimension of pain has also been put forward(21)(22). Indeed, pain relief was shown to be  
139 higher in surgically-implanted burst stimulation compared to conventional continuous  
140 unpatterned stimulation in well-designed studies(23). This led us to conduct a pilot  
141 double-blind parallel trial to test the safety and potential analgesic effects of burst trans-  
142 spinal magnetic stimulation (bTsMS) in PD-related nociceptive pain. We hypothesized  
143 that the benefits of spinal cord stimulation obtained in non-neuropathic or mixed pain  
144 syndromes could be reproduced by non-invasive stimulation to the same spinal segments  
145 by an induced electric current delivered by TsMS.



## 149 2. METHODS

### 150 2.1 Patients

151 Our Institution's Ethics Review Board approved this study (#36024620.8.0000.0068),  
152 which was registered on clinicaltrials.gov (NCT04546529). PD patients with chronic  
153 nociceptive pain related to the disease were recruited from outpatient movement disorders  
154 clinics geographically near the outpatient pain clinics of the Hospital das Clínicas,  
155 University of São Paulo, between July 2020 and May 2021(13). Idiopathic PD was  
156 diagnosed based on the 2015 Movement Disorder Society (MDS) clinical diagnostic  
157 criteria(24). Nociceptive pain was diagnosed according to the Parkinson disease pain  
158 classification system (PD-PCS) by two independent researchers and reviewed by an  
159 expert(17). All patients provided informed consent to participate in the study.

160 The inclusion criteria were adults (18-85 years) with PD-related nociceptive pain  
161 persisting for more than 3 months and present most of the days. The average pain intensity  
162 (24h) score had to be  $\geq 4/10$  on a numerical rating scale (NRS). Exclusion criteria were  
163 pregnancy, breast feeding women, presence of defined chronic neuropathic pain  
164 according to the IASP grading system for neuropathic pain and a positive DN-4 (Douleur  
165 Neuropathique-4 questionnaire), previous diagnosis of dementia, known major  
166 psychiatric disorders (as assessed by the DSM-V), history of substance abuse, or work  
167 litigation issues(17)(25)(26). Demographic and clinical information about the patient was  
168 collected at the inclusion visit including physical examination to confirm PD and the  
169 presence of nociceptive pain.

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## 174 **2.2 Experimental design**

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2 175 This was an exploratory randomized, double-blind, sham-controlled, and pilot  
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4 176 parallel trial to investigate the analgesic effects of active versus sham bTsMS in  
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7 177 nociceptive PD-related chronic pain.

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9 178 Participants were allocated into groups that either received burst trans-spinal  
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11 179 magnetic stimulation (bTsMS) in a prolonged continuous theta burst stimulation or sham  
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13 180 stimulation over the seventh cervical vertebra (C7) in the midline. They were randomly  
14  
15 181 assigned to groups in a 1:1 ratio (using <https://www.random.org/sequences>), and the  
16  
17 182 randomization sequence was stored in a sealed opaque envelope and was only revealed  
18  
19 183 to the researchers responsible for the administration of bTsMS, and who had no other role  
20  
21 184 in the study and were not allowed to interact with patients except for strictly stimulation-  
22  
23 185 related communications.

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28 186 Patients underwent active or sham bTsMS sessions for eight weeks. In the first  
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30 187 week, stimulation sessions were performed daily for five consecutive days (induction  
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32 188 series) followed by two sessions weekly (maintenance series) for seven more weeks.  
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34 189 Patients were followed for four additional weeks after the last treatment session for safety  
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36 190 and assessed on until the 12<sup>th</sup> week from study initiation by a phone call. 

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## 42 **2.3 Burst trans-spinal magnetic stimulation**

43  
44 192 The trans-spinal resting motor threshold (tsRMT) was determined before the first session  
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46 193 with patients positioned in an armchair, relaxed, in a sound-attenuated room using a single  
47  
48 194 pulse TMS pulse (ie, edge of the circular coil) over the C7 vertebral segment with a  
49  
50 195 circular-shaped coil (MCF-125 coil with static cooling, MagVenture, Farum, Denmark)  
51  
52 196 connected to a MagProX100 machine (MagVenture, Farum, Denmark). Trans-spinal  
53  
54 197 motor-evoked potentials (MEP) were recorded using surface electrodes (Natus,  
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199 Middleton, WI, USA) located on the lower abdominal muscle (3<sup>rd</sup> lower bellies of rectus  
200 abdominalis muscles). The trans-spinal rest motor threshold (ts-RMT was defined as the  
201 lowest intensity eliciting a detectable motor-evoked potential in 5 out 10 trials. The  
202 stimulation intensity for the bTsMS was set at the detection threshold of tsRMT.

203 Two different coils were used for the treatment sessions. In all instances, a circular-  
204 shaped coil was positioned over the spinous process of the 7<sup>th</sup> cervical vertebra with the  
205 cable pointing to the side, with the induced electric current flowing lateral from medial  
206 in the spinal cord. A figure-of-eight (B-65) coil with active cooling (Magventure, Farum,  
207 Denmark) was placed orthogonally to circular-shaped coil. For real stimulations, the  
208 circular coil in contact with the skin was turned on, and the figure of eight coil was left  
209 off. Stimulation was delivered by three pulses at 50 Hz and repeated 400 times with an  
210 inter-stimulus interval of 200 milliseconds; 1,200 pulses were delivered per session over  
211 1 minute and 20 seconds(27). For sham sessions, the same set up was used except that the  
212 circular coil was turned off while the figure-of-eight coil was turned on and delivered  
213 stimulation at 100% of maximal stimulator output. The figure-eight coil was placed on  
214 the circular-shaped coil to ensure proper double-blinded conditions. The figure-of-eight  
215 coil is supposed to provide the noise and vibration related to the stimulation, but would  
216 have no specific biological effect on the spinal cord since its several centimeters away  
217 from the skin. The coils were fixed by a mechanical arm, and the position was  
218 systematically controlled during the session. Additionally, in all sessions, a  
219 transcutaneous electric stimulation system was mounted over both sides of the circular  
220 coil touching the skin at the C7 level before the start of stimulation. The two carbon rubber  
221 surface electrodes were placed 5 cm from the coil edges on each side in a longitudinal  
222 orientation (Figure 1). Biphasic square wave impulses at a frequency of 100 Hz and pulse  
223 duration of 50  $\mu$ s were used during both active and sham bTsMS session (Neurodyn

224 Portable TENS, Ibramed). The stimulation intensity was increased until there was local  
225 paresthesia without discomfort. Stimulation was started and stopped time-locked to  
226 bTMS.

227

## 228 **2.4 Pain and related assessments**

229 A full clinical and pain assessments were performed at baseline and after and eight (last)  
230 weeks. Pain intensity and adverse events were also assessed at the first, second and fourth  
231 weeks, and one month after the last stimulation session, this time by a structured phone  
232 interview. The primary outcome of the study was the number of patients reaching  
233 significant average pain relief ( $\geq 50\%$  pain intensity reduction) during the eight weeks of  
234 stimulation sessions versus baseline assessment. The average pain intensity over the past  
235 24h was assessed by a numerical rating scale (NRS) (28) ranging from 0 (no pain) to 10  
236 (maximal pain imaginable).

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## 240 **2.5 Secondary outcomes**

241 Pain intensity and its frequency and severity were assessed by the composite score from  
242 PD-PCS(17). This score ranges from 0 (no pain) to 90 (maximal pain intensity, impact in  
243 activities and high frequency). Mood was assessed by the hospital anxiety and depression  
244 scale(29). Quality of life was assessed by EuroQol-5(30). Parkinson's disease motor  
245 symptoms were assessed by UPDRS part III(31). Pain interference in daily living was  
246 measured by the seven items from the short form of the brief pain inventory ranging from  
247 0 (does not interfere) to 10 (maximal interference)(32). The global impression of change  
248 is a seven-point Likert scale that ranges the amount of improvement or aggravation after

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249 a treatment. We compared percentage of subjects who reported much, and very much  
250 improvement after treatment against all the other options(33).

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## 252 **2.6 Adverse events report**

253 The incidence of treatment-emergent adverse events and the safety of bTsMS were  
254 assessed by measuring the number of participants who experienced serious events.

255 Adverse events assessment was performed after each treatment session by using a  
256 dedicated questionnaire(34). Patients were asked to report any potential side-effects  
257 related to the treatment such as headaches, dizziness, nausea, blurred vision, sleepiness,  
258 paresthesia, and local pain.

259

## 260 **2.7 Blinding assessment**

261 Care was taken not to set patients' appointments simultaneously so that waiting-room  
262 conversations were avoided and ensuring the integrity of blinding. The blinding  
263 assessment was performed at the end of the study (i.e., after eight weeks of treatment) as  
264 previously reported(34)(35), and included the following questions: i. could you tell which  
265 treatment you received?"; ii. "If so, which was it?", iii. "If you were given the option to do  
266 so, would you choose to maintain the treatment for a longer period of time?".

267

## 268 **2.8 Statistical analyses**

269 The normality was verified by asymmetry and kurtosis values in addition to graphical  
270 methods(36). Categorical data were described using absolute and relative frequencies and  
271 compared through Fisher's exact test, and numerical data were described through median  
272 and quartiles and compared through Mann-Whitney's U test.

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273 Longitudinal continuous data were analyzed through two-way repeated measures analysis  
274 of variance (ANOVA). For binary endpoints, generalized estimating equations were  
275 employed, as this approach allows considering participants with missing data on specific  
276 time points and therefore uses all available data without biasing the results under random  
277 dropouts(37)(38), so that data imputation strategies were not required. Treatment effects  
278 were estimated through group versus time interactions. All tests were two-tailed, and final  
279 p-values less than 0.05 were considered significant. All analyses were conducted using  
280 the Statistical Package for Social Sciences software (IBM SPSS Statistics for Windows,  
281 version 24.0. Armonk, NY: IBM Corp.). Since there are no other studies in the literature  
282 reporting non-invasive spinal cord stimulation for pain in PD, we included a convenience  
283 sample of PD based on previous studies using TsMS for other etiologies. Based on our  
284 findings we calculated the number necessary to treat, which will help future studies to  
285 properly estimate sample size.



### 286 3. Results

#### 287 3.1 Sample description

288 Thirty patients were screened for participation, and twenty-six were randomized (Figure  
289 2). Thirteen patients received active and 13 with sham bTsMS. Table 1 shows baseline  
290 demographic and clinical characteristics of the 26 patients that received the allocated  
291 interventions. The active bTsMS and sham bTsMS groups were similar in terms of  
292 baseline characteristics.

#### 293 3.2 Pain assessment

294 Data from twenty-six PD patients were analyzed in an intention-to-treat approach. Pain  
295 intensity reduction  $\geq 50\%$  was higher after active bTsMS compared to sham bTsMS over  
296 the eight weeks of treatment ( $p=0.044$ ) (Table 2). Pain intensity went from  $6.2\pm 1.7$  and  
297  $7.0\pm 1.3$  at baseline to  $2.4\pm 2.2$  and  $3.9\pm 2.6$  on the eighth week of stimulation after the  
298 active and sham bTsMS series, respectively. At the end of the first week (the induction  
299 phase), eight (61.5%) responders to active bTsMS and two (15.4%) responders to sham  
300 bTsMS ( $p=0.006$ ). The number needed to treat was 2.2 after the first week of treatment.  
301 Number of responders were no longer different between groups at 8 weeks and one month  
302 after the last stimulation day ( $P=0.120$ ) (Table S1). We ran supplementary analyses to  
303 investigate differences in response to bTsMS being related to the location of the main  
304 pain syndrome. We divided patients according to the location of the main pain syndrome  
305 as being located above or below the spinal C7. There were no differences between  
306 predominant neck-shoulder-upper limb pain regions (i.e., above C7 spinal cord level)  
307 and thoraco-lumbar-lower limb (below C7 spinal cord segment) pain regions with number  
308 of responders after first week ( $p=0.710$ ) and the last week ( $p=0.218$ ) of treatment.

#### 310 3.3 Secondary outcomes

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311 Depression scores were lower after active bTsMS ( $4.0\pm 3.1$ ) compared to sham bTsMS  
312 ( $8.7\pm 5.3$ ) ( $p = 0.011$ ). Patient's clinical global impressions of change were more  
313 frequently much/moderately improved after active bTsMS (70.0%) compared to sham  
314 bTsMS (18.2%) ( $p=0.030$ ) (Table S2). Other secondary outcomes are shown in Table 3.

315 There were no differences between groups concerning Parkinson motor symptoms  
316 severity (UPDRS part III), anxiety symptoms (HADS-A), pain interference in daily  
317 activities (BPI pain Interference on daily activities), quality of life (EQ-5D-3L total, and  
318 health score), BPI pain intensity index, and PD-PCS score (Table S3).

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### 320 **3.4. Dropouts and adverse events report**

321 Four patients dropped out during the study. One left due to a lack of analgesic effects  
322 (after the 7<sup>th</sup> sham daily session) from the placebo group. In the active group, 3 patients  
323 dropped out of the study. One patient had dizziness that was aggravated after active  
324 stimulation that led to treatment interruption. One dropped out due to SARS-CoV 2  
325 infection, and one had pulmonary embolism leading to death. Concerning adverse events  
326 that did not lead patients to drop out of study, two patients reported headache (one after  
327 1 active stimulation session and one after 1 sham stimulation session) that did not persist  
328 until the next stimulation session, none of them needed analgesics. One had transient  
329 paresthesia after a one active stimulation session, one had dizziness after three sham  
330 stimulation sessions that did not need treatment, and one had transient blurred vision after  
331 two sham stimulation sessions. There were no other side effects such as seizures, nausea,  
332 and drowsiness.

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### 334 **3.5 Blinding assessment**



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335 After the end of the study, 21 patients (95.5%) said they could tell which protocol of  
336 treatment they received, 13 patients (62.0%) guessed it correct. Of these patients, eight  
337 (72.7%) were in sham group, and five (50.0%) were in active group ( $p = 0.36$ ). Twenty  
338 patients (95.2%) said they would like to maintain the sessions of bTsMS for a more  
339 extended period if this option were offered to them.

#### 340 **4. DISCUSSION**

341 The present results show that bTsMS had a significant analgesic effect in PD patients  
342 with nociceptive pain within the first week. An overall effect was found during the 8  
343 weeks of treatment, the most significant pain relief occurring after the first week of daily  
344 stimulation, with 61.5% responders in active bTsMS and 15.4% responders in the sham  
345 bTsMS group. As secondary outcome bTsMS also showed a reduction in depressive  
346 symptoms, and there was an improvement in the patient's clinical global impressions of  
347 change after treatment.

348 Even though we were able to detect an analgesic effect of non-invasive spinal cord  
349 stimulation in PD for the first time, one needs to acknowledge that dopaminergic  
350 medication and treatment states can influence pain perception and impact in PD patients  
351 in very dynamic manner. For example, PD patients in the off medication state have shown  
352 reduced non-painful mechanical and thermal and mechanical pain thresholds compared  
353 to healthy volunteers (3)(12)(39). Dopaminergic replacement and turning on deep brain  
354 stimulation systems can restore pain thresholds towards normal values, mainly due to  
355 modulation of small fiber-mediated sensory inputs(39)(40). These data suggest that PD  
356 patients have an inherent pro-nociceptive state that can be modulated by medication or  
357 neuromodulatory interventions primarily prescribed to treat motor symptoms. However,  
358 one recurrent finding in the PD literature is the lack of correlation between pain  
359 improvement with treatment prescribed for motor symptom control, suggesting that

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360 dopamine replacement therapy and deep brain stimulation may act on motor and NMS by  
361 different mechanism, or on a group level, responders do not have the same degree of  
362 improvement in these two types of symptoms (41). In fact, for deep brain stimulation, it  
363 has been recently shown that slight differences in the volume of activated tissue within  
364 the subthalamic nucleus can influence different cortical networks and potentially explain  
365 different clinical motor and NMS effects after deep brain stimulation (39)(42)(43).

366 The control of PD-related pain is so far limited. In a study using high-frequency  
367 transcranial magnetic stimulation, modulation of the primary motor cortex was attempted  
368 to relieve musculoskeletal pain in PD, there were significant analgesic effects with active  
369 versus sham stimulation as well as impacts on motor symptom, mood symptoms, and  
370 overall disease severity(44). One open label study showed that duloxetine may be  
371 effective at treating pain in PD, but this result was not confirmed in a later double-blind,  
372 randomized, placebo-controlled trial(45)(46). Indeed, the phase II double-blind,  
373 randomized, placebo-controlled study did not show significant improvement of severe  
374 pain in PD with prolonged-release oxycodone–naloxone, while treatment-related nausea  
375 and constipation was more common in the active group than the placebo group(28).  
376 Epidural SCS was tested in a single arm, prospective, non-randomized case series to treat  
377 predominant neuropathic pain in PD patients. The electrodes were implanted in the  
378 cervical or thoracic spine level, and pain average scores decreased 59% in the burst  
379 stimulation group with better results. Basic gait analysis revealed mild improvement in  
380 motor symptoms(47).

381 In the present study we chose to focus on pain of nociceptive mechanisms, mainly due to  
382 PD-related chronic musculoskeletal pain, because it is the most frequent subtype in PD  
383 patients. Treatment options for nociceptive PD pain are rare(3)(17)(42)(48), and it causes  
384 significant negative impact in quality of life(17). Spinal neuromodulation is thought to

1 385 control pain through potential segmental and supraspinal mechanisms. In the early days  
2 386 of spinal cord stimulation, analgesic effects were believed to be caused by stimulation of  
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4 387 large myelinated fibers on the dorsal columns, which would lead to pain reduction  
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7 388 according to the pain gate control theory(19). It was latter shown that spinal cord  
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9 389 stimulation influences the processing of several neurophysiological responses in the  
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11 390 spinal cord, including autonomic and motor processing(20). This argued for a broader  
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13 391 spread of the effects of the spinal electric field, which would be likely related to its  
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16 392 analgesic mechanisms. Additionally, spinal cord stimulation has significant effects in  
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18 393 vasomotor control, being used to treat peripheral chronic artery disease(51) and as a  
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20 394 potential adjunct treatment of orthostatic hypotension in atypical parkinsonism  
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22 395 syndromes(52). More recently, spinal stimulation with burst waves was shown not to  
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24 396 influence the dorsal column activity directly, but lead to a major effect on wide-dynamic  
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26 397 range neurons in the dorsal horn besides and distinct influence in medial spinothalamo-  
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28 398 cortical pathways; suggesting that burst spinal stimulation can engage widespread  
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30 399 suprasegmental structures, including the emotional pathways of pain processing(21)(53).  
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34 400 In experimental studies, the spinal stimulation-mediated analgesia was related to  
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36 401 increased release of inhibitory neurotransmitters, decreased wide-dynamic cells activity,  
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38 402 and activation of rostroventral medulla with descending modulation of  
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40 403 nociception(54)(55)(56). In human studies, it has been reported that SCS inhibits the  
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42 404 nociceptive flexor reflex (RIII), which related to treatment efficacy. Additionally,  
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44 405 decrease in cortical excitability (somatosensory evoked potential-SEP) and a reduction in  
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46 406 thalamic-to-cingulate connectivity were also reported(20)(57).  
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51 407 There is still little knowledge regarding the mechanisms behind TsMS effects. Studies  
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53 408 showed a reduction in corticospinal excitability (e.g., trans-spinal MEP) in healthy  
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55 409 subjects(58)(59). Experimental studies showed that rats under a spinal cord injury model  
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410 undergoing TsMS had higher growth-associated protein-43, 5-hydroxytryptamine  
411 expression than sham rats receiving TsMS with potential benefits in motor function  
412 recovery(60). MEPs reduction was also described in TsDCS studies associated with  
413 reductions in SEPs(49)(61). Others have reported TsDCS led to increased intracortical  
414 facilitation(61)(62)(63). A TsDCS study with chronic pain patients showed anodal  
415 stimulation compared to sham decreases nociceptive flexor reflex (RIII) linearly with a  
416 reduction of pain scores(50). These data suggest that both invasive (SCS) and non-  
417 invasive trans spinal stimulation strategies engage segmental, supra segmental, and  
418 neuro-humoral responses, which may be related to its potential analgesic effects.  
419 However, more studies in chronic pain patients need to be conducted to ascertain if both  
420 approaches are similarly effective. Our results speak for a more widespread analgesic  
421 effect of bTsMS delivered to C7, since pain located below and above the stimulated spinal  
422 cord segment were similarly positively affected by treatment.

423  
424 Minor adverse events were reported in active and sham groups. One directly led one  
425 patient to drop out of study in the active group. The single major side effect (death due to  
426 pulmonary embolism) was not considered to be specifically associated with active  
427 treatment. Spinal cord stimulation is used in patients with chronic arterial insufficiency  
428 and atherosclerosis as a mean to improve blood flow secondary to sympathetic-mediated  
429 arterial vasodilation of arterioles and is considered to be safe in vasculopathy and in  
430 patients at risk for atherothrombosis or arterial occlusion(64). However, venous vascular  
431 side effects need to be taken with caution and actively monitored in future studies.

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433 Blinding is a major challenge in spinal cord stimulation studies, in particular non-invasive  
434 ones. We created an original strategy as an attempt to mitigate this potential source of

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435 bias. Two coils were used during the stimulation setup. Both coils were present during all  
436 sessions. Similar strategies were employed in studies on transcranial magnetic  
437 stimulation(27)(65). Furthermore, active cutaneous electrical stimulation was used to  
438 mitigate unblinding. The efficacy of the blinding strategy suggests participants in the  
439 active group had a similar percentage of correct guessing in which group they were  
440 allocated to as patients from the sham arm.

441 There are several limitations in this study that should be noted. First, due to it is  
442 exploratory nature, it was primarily designed to explore the feasibility, and temporal  
443 profile of the technique in PD patients with pain. The effects found here will be valuable  
444 in the design of future studies, but smaller studies usually tend to overestimate treatment  
445 effects, and this needs to be taken into account when interpreting the results(66). Also,  
446 while we found an overall effect of active stimulation over the first eight weeks, this effect  
447 was only significant, and was mainly driven, by the period when stimulation was  
448 delivered daily, during induction sessions (i.e., after 1 week of treatment). That means  
449 that dosing remains to be determined for bTsMS, and one cannot currently know whether  
450 our maintenance sessions were adapted to maintain the effects seen after induction, or if  
451 these effects will only exist during daily stimulations, not being amenable to be sustained  
452 for longer periods of time by sessions spaced for more than one day. This distinction is  
453 central for a potential future use of the technique in clinical practice. Another point is  
454 that patients included in the study could have pain in body segments above the stimulation  
455 level (ie, C7). We decided to proceed with such a strategy based on several facts. One is  
456 that while the pain location can be located above C7, MSK pain commonly leads to  
457 referred pain, so that pain location and lesion site quite often do not coincide spatially.  
458 Additionally, pain of nociceptive nature in PD is mainly located axially, and in more than  
459 one site (17). Based on data suggesting the rather diffuse analgesic effects of burst spinal

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460 cord stimulation, we hypothesized that the effects would not be segmentary restricted.  
461 However, while it is generally acknowledged that spinal cord stimulation may have  
462 suprasegmental neurophysiological effects, it is not known whether analgesic effects  
463 extend above the stimulation level in non-invasive trans-spinal  
464 approaches(67)(68)(69)(70). Our analyses comparing patients with predominant pain  
465 located above C7 and those with main pain located at body parts innervated by spinal  
466 cord segments below C7 were not different. Still, due to the exploratory nature of this  
467 study and its subsequent small sample, claims that bTsMS had diffuse analgesic effects  
468 need to be tuned down before larger samples are studied. Finally, this study had no  
469 mechanistic exploration of the effects of bTsMS. Neurophysiological, neuroimaging and  
470 psychophysical changes caused by bTsMS may provide valuable insights in following  
471 studies. In conclusion, this pilot trial suggests bTsMS provided analgesia predominately  
472 within the first week of daily sessions and was safe in nociceptive pain in PD. More  
473 studies are needed to deepen knowledge about this technique as an adjunct therapy to  
474 nociceptive pain.

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700 **FIGURE LEGENDS**

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702 Figure 1. Stimulation montage.

703 Figure 2. CONSORT study diagram.

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706 **TABLES**

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2 707 Table 1. Demographic profile and baseline characteristics of subjects included in the  
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4 708 study.

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7 709 Table 2. Influence of bTsMS on pain response within the first eight weeks.  
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Table 1. Demographical profile and baseline assessment characteristics of subjects included in the study.

		Sham bTsMS (n= 13)	Active bTsMS (n= 13)
Age (years) <sup>A</sup>		61.4±9.2(42-79)	61.9±10.3(36-73)
Sex, n (%)	<i>Male</i>	9(69.2)	5(38,5)
Schooling, n (%)	<i>&lt; 12 years</i>	7(53.8)	5(38.5)
	<i>&gt; 12 years</i>	6(46.2)	8(61.5)
Etiology of musculoskeletal pain, n (%)	<i>Myofascial pain syndrome</i>	12(92.3)	12(92.3)
	<i>Coat hanger headache</i>	2(15.4)	2(15.4)
	<i>Localized pain</i>	4(30.8)	3(23.1)
Handedness, n (%)	<i>Right-handed</i>	12(92.3)	13(100.0)
Time since Parkinson disease 's diagnosis (years) <sup>A</sup>		9.3± 7.5(0-26)	10.9± 5.2(1-20)
Levodopa equivalent <sup>A</sup>		936.4±468.7(300-1905)	847.8±425.7(150-1564)

Table 1(continued). Demographical profile and baseline assessment characteristics of subjects included in the study.

Side of initial motor symptom, n (%)	<i>Left</i>	7(50.0)	7(50.0)
	<i>Right</i>	6(50.0)	6(50.0)
	<i>Bilateral</i>	7(53.8)	11(84.6)
Predominant pain side, n (%)	<i>Left</i>	3(23.1)	2(15.4)
	<i>Right</i>	3(23.1)	0(0.0)
Pain location, n (%)	<i>Neck</i>	5(38.5)	4(30.8)
	<i>Shoulder</i>	5(38.5)	6(46.1)
	<i>Upper limb</i>	2(15.4)	3(23.1)
	<i>Upper back</i>	1(7.7)	2(15.4)
	<i>Low back</i>	9(69.2)	10(76.9)
	<i>Lower Limb</i>	9(69.2)	9(69.2)

Table 1(continued). Demographical profile and baseline assessment characteristics of subjects included in the study.

Duration of pain (years) <sup>B</sup>		4.5±3.9(0.5-5)	5.6±5.4(1-8)
Average pain (BPI) <sup>A</sup>		7.0±1.3(5-10)	6.1±1.7(4-10)
New pain in the last evaluation, n (%)		1(7.7)	3(23.1)
Rehabilitation, n (%)		6(46.2)	8(61.5)
Pain catastrophizing scale <sup>A</sup>		26.4±14.5	27.0±9.0
HADS	<i>Depression subscale</i>	7.6±5.6	7.1±3.2
	<i>Anxiety subscale</i>	9.5±5.2	7.7±3.2
Motor complications in Parkinson disease, n (%)	<i>Motor fluctuations</i>	6(46.2)	6(46.2)
	<i>Dyskinesia</i>	5(38.5)	7(53.8)
	<i>Gait problems</i>	9(69.2)	10(61.5)
UPDRS part III		33.2±16.3(10-67)	43.0±16.1(14-66)

Table 1(continued). Demographical profile and baseline assessment characteristics of subjects included in the study.

Hoehn and Yahr scale, n (%)	<i>Unilateral</i>	2(15.4)	2(15.4)
	<i>Bilateral</i>	8(61.5)	11(84.6)
	<i>Bilateral with balance and postural impairment</i>	3(23.1)	0(0.0)
DBS, n (%)		3(23.1)	2(15.4)

<sup>A</sup> Values are presented in: mean  $\pm$  SD (minimum and maximum); <sup>B</sup> Values are present in: medium (quartiles);

bTsMS: burst trans-spinal magnetic stimulation BPI: brief pain inventory; HADS: Hospital anxiety and depression scale;

UPDRS: total unified Parkinson disease rating scale; DBS: Deep brain stimulation.



Table 3. Secondary outcomes.

		(N=26)	(N=22)
	Group	Baseline	Eighth Week
<b>PD-PCS score</b>	Active bTsMS	43.4±20.0(12-90)	10.0±13.8(0-42)
	Sham bTsMS	43.2±22.1(12-72)	26.2±23.1(0-63)
<b>HADS-D*</b>	Active bTsMS	7.1±3.2(2-12)	4.0±3.1(0-9)
	Sham bTsMS	7.6±5.6(1-21)	8.7±5.3(2-18)
<b>HADS-A</b>	Active bTsMS	7.7±3.2(2-12)	4.1±2.3(1-8)
	Sham bTsMS	9.5±5.2(2-20)	6.6±5.1(1-16)
<b>EQ-5D-3L total</b>	Active bTsMS	0.44±0.13(0.30-0.74)	0.67±0.15(0.49-0.85)
	Sham bTsMS	0.49±0.14(0.17-0.69)	0.53±0.19(0.35-0.85)
<b>EQ-5D-3L Health Score</b>	Active bTsMS	56.4±5.23.8(0-95)	71.9±14.5(50-99)
	Sham bTsMS	55.8±29.5(1-85)	62.9±22.7(10-95)
<b>UPDRS part III</b>	Active bTsMS	43.0±16.1(14-66)	36.0±8.6(22-48)
	Sham bTsMS	33.2±16.3(10-67)	38.0±17.0(10-78)
<b>BPI Pain Intensity Index</b>	Active bTsMS	54.8±18.3.8(27.5-90.0)	19.8±19.8(0.0-55.0)
	Sham bTsMS	57.1±12.6(35.0-77.5)	35.6±21.6(0.0-75.0)
<b>BPI Pain Interference on daily activities</b>	Active bTsMS	65.4±17.8(31.9-90.0)	21.3±30.0(0.0-74.3)
	Sham bTsMS	68.2±18.3(42.9-97.1)	45.3±34.3(0.0-94.3)

Values are presented in: mean ± SD (minimum and maximum); bTsMS: burst trans-spinal magnetic stimulation; PD-PCS score: Parkinson Disease Pain Classification system score; HADS-D: depression subscale of the hospital

anxiety and depression scale; HADS-A: anxiety subscale of the hospital anxiety and depression scale; EQ-5D-3L: the three-level EuroQol five-dimensional questionnaire; UPDRS part III: unified Parkinson's disease rating scale part III; BPI: Brief pain inventory; \*  $P < 0.05$  (results obtained by two-way repeated measures ANOVA analysis between baseline and eighth week based on group-by-time interaction effect).



Table 2. Influence of bTsMS on pain response within the first eight weeks.

	$\beta$	Standard Error	(N=26) OR	95% CI	p
<b>Intercept</b>	-1.338	0.5924	0.261	0.082-0.834	0.023*
<b>Week</b>	0.111	0.0784	1.138	0.977-1.327	0.099
<b>Active treatment group</b>	1.347	0.6689	3.844	1.036-14.262	0.044*

Results obtained by Generalized Estimating Equations (GEE) analysis, weeks 1-8 included as a covariate;

Pain intensity [Average NRS (numerical rating scale; 0-10)]; bTsMS: burst trans-spinal magnetic stimulation.

\* P<0.05. Pain response defined as pain intensity reduction of at least 50% compared to baseline.

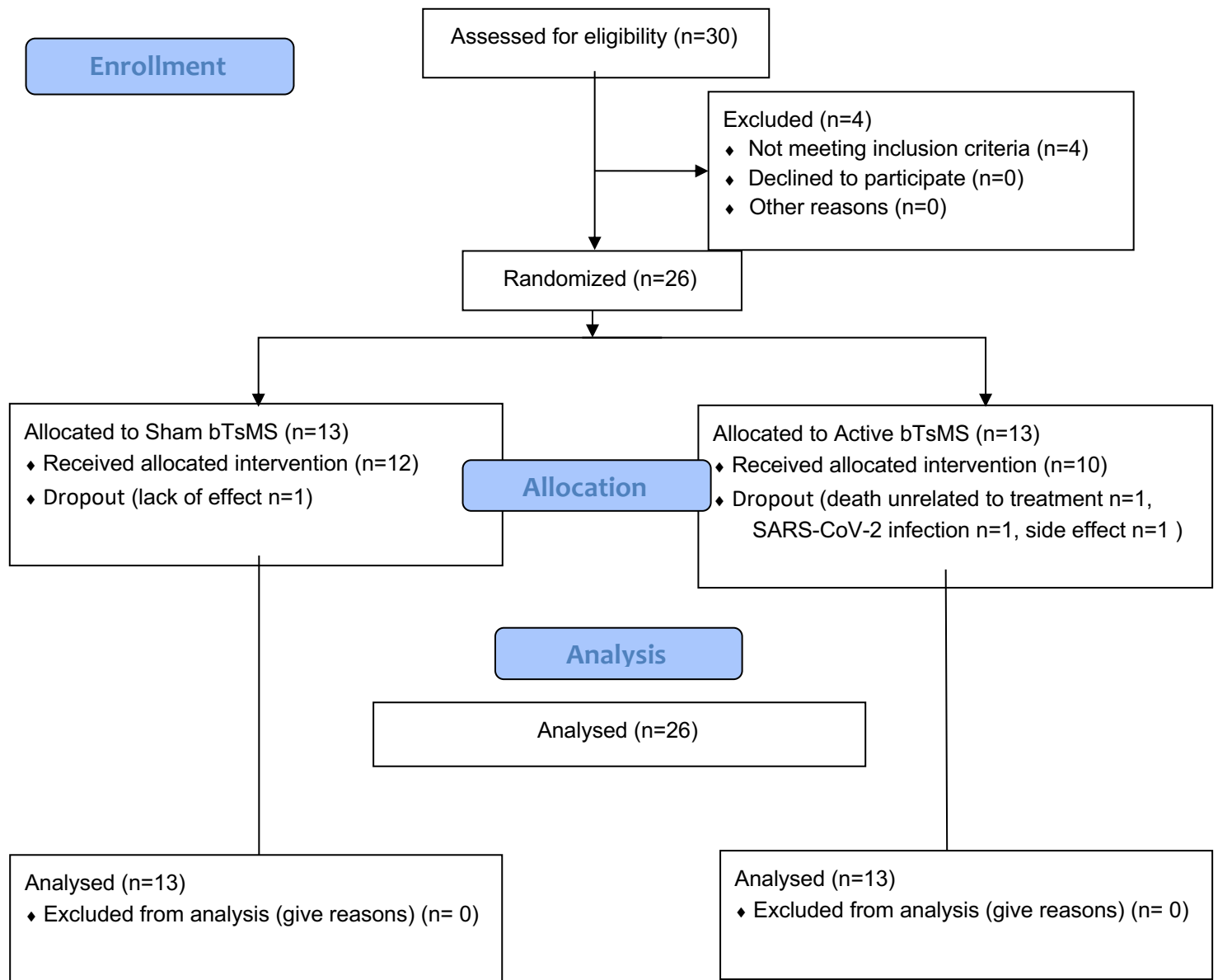
Figure 1. Stimulation montage.



A) Surface electrodes of TENS secured to the skin with adhesive tape at level of C7 in the paraspinal area. B) The circular-shaped coil placed perpendicular to spinal in midline over C7. C) The figure-eight coil was placed orthogonally to circular-shaped coil. This last image shows complete montage during all bTsMS sessions regardless of group.

TENS: Transcutaneous electrical nerve stimulation; C7: Seventh cervical vertebrae; bTsMS: Burst trans-spinal magnetic stimulation

Figure 2. CONSORT study diagram.



bTsMS: burst trans-spinal magnetic stimulation



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