Clinical Pain Research

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Effects of deep brain stimulation and verbal suggestions on pain in Parkinson's disease

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Abstract

Background and objectives – In Parkinson's disease (PD) patients, verbal suggestions have been shown to modulate motor and clinical outcomes in treatment with subthalamic deep brain stimulation (DBS). Furthermore, DBS may alleviate pain in PD. However, it is unknown if verbal suggestions influence DBS' effects on pain.

Methods – Twenty-four people with PD and DBS had stimulation downregulated (80–60 to 20%) and upregulated (from 20–60 to 80%) in a blinded manner on randomized test days: (1) with negative and positive suggestions of pain for down- and upregulation, respectively, and (2) with no suggestions to effect (control). Effects of DBS and verbal suggestions were assessed on ongoing and evoked pain (hypertonic saline injections) via 0–10 numerical rating scales along with motor symptoms, expectations, and blinding.

Results – Stimulation did not influence ongoing and evoked pain but influenced motor symptoms in the expected direction. Baseline and experimental pain measures showed no patterns in degree of pain. There was a trend toward negative suggestions increasing pain and positive suggestions decreasing pain. Results show significant differences in identical stimulation with negative vs positive suggestions (60% conditions AUC 38.75 vs 23.32, $t(13) = 3.10$, $p < 0.001$). Expectations to pain had small to moderate effects on evoked pain. Patients estimated stimulation level correctly within 10 points

Conclusion – Stimulation does not seem to influence ongoing and evoked pain, but verbal suggestions may influence pain levels. Patients appear to be unblinded to stimulation level which is an important consideration for future studies testing DBS in an attempted blind fashion.

Keywords: Parkinson disease, pain, deep brain stimulation, placebo effect, suggestion

1 Introduction

Parkinson's disease (PD) is characterized by its defining motor symptoms of bradykinesia in combination with resting tremor and/or rigidity [1]. Deep brain stimulation (DBS) to the subthalamic nucleus (STN) is used in treatment of these motor symptoms and involves electrical stimulation through bilaterally implanted electrodes [2,3]. Beside motor impairments, pain is a prevalent non-motor symptom [4] including nociceptive, neuropathic, and nociplastic components [5] with musculoskeletal pain [4,6] being the most predominant subtype. DBS has shown pain alleviating effects in PD [7,8], however with new pain arising longitudinally [9], and with some pain worsening while other pain improves [10]. Therefore, effects of DBS on pain relief in PD remain inconclusive.

In PD patients with DBS, motor symptoms are susceptible to verbal suggestions about the effect [11], raising the question if this is also the case for pain. Modulatory effects have been found in bradykinesia [12–14]. Other studies, however, have only detected effects of suggestion for proximal movements, but not in distal movements [15] or in a subgroup of patients on resting tremor [16]. Thus, the extent to which verbal suggestions modulate treatment effects may be symptom-specific. The extent to which suggestions

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modulate effects on pain has, to our knowledge, not yet been investigated.

Previous studies of verbal suggestions in DBS have aimed for blinded designs. However, none have verified if patients were, in fact, blinded to study conditions. It has been emphasized that patients with DBS cannot be fully blinded to their treatment, as active stimulation is registered through sensory input or through changes in motor symptoms [17]. As such unblinding could potentially be an influence on study results. Consequently, this study applied a down- and upregulating design wherein patients at all times received some level of stimulation, similar to a previous study design [12]. There is no current definition of successful blinding with DBS and therefore this study assessed the accuracy of patients' own estimations to evaluate blinding.

To our knowledge, this is the first study aiming to investigate interrelated effects of DBS and suggestions on pain in PD. We hypothesized an effect of suggestion on evoked pain compared to no suggestion. We further hypothesized this effect would be greatest at therapeutic stimulation. Patients with and without pain were included and primary study outcomes were patients' ongoing pain and experimentally evoked muscle pain [18]. As a secondary outcome, the study examined individual pain profiles, comprising pain diaries, baseline ongoing pain, and evoked pain trajectories.

2 Methods and materials

Twenty-four patients diagnosed with PD and implanted with STN DBS were recruited from the Department of Neurology, Aarhus University Hospital, Denmark, from December 2019 to June 2022. The study conforms with the World Medical Association Declaration of Helsinki [19] and all subjects gave written consent to participate in the study. The study was approved by The Central Denmark Region Committees on Health Research Ethics (1-10-72-12-19) and registered at ClinicalTrials.gov (ID: NCT04151043).

Patients were eligible for participation if they fulfilled the following inclusion criteria:

- Diagnosis of PD, confirmed by a neurologist
- Bilaterally implanted STN DBS for a minimum of 6 months

Exclusion criteria were

- Other neurological or medical disorders (e.g., stroke, diabetes)
- Other disorders (e.g., musculoskeletal diseases) with expected influence on pain
- Dementia (a score <24 on the Montreal Cognitive Assessment (MoCA) [20])
- Untreated depression (a score ≥15 on the Major Depression Inventory (MDI) [21])
- Patients unable to pause Parkinsonian medication
- Patients unable to cooperate
- Patients treated with painkillers except paracetamol and NSAID.

Patients participated on two test days, with an interval of minimum 1 week, before which they paused their usual Parkinsonian medication (last dose on the evening before the test day) and paused any pain medication on the test days. Test days were scheduled outside of regular clinical visits and treatment regulation. Each test day consisted of a sequence of five study conditions; the study design is illustrated in Figure 1. The sequence of study conditions entailed down- and upregulation of DBS intensity, i.e., the amplitude of stimulation (or voltage in older systems). Stimulation intensities for each condition were calculated based on individually clinically predefined DBS amplitudes, for the purposes of this study defined as 100% stimulation [12]. The experimental sequence was downregulating from baseline 100% stimulation in decrements of 20–80 to 60–20%. Hereafter an upregulating sequence, also in increments of 20% of the baseline amplitude, from 20% stimulation and up to 60% and to 80% of usual stimulation. This sequence was not randomized to keep contextual factors equal across test days (e.g., hours since medication, food intake, and fatigue). Prior to and following the experimental conditions, the DBS system of each patient was assessed for irregularities in stimulation of system impedance. As patients were not regulated above normal stimulation intensities, none experienced additional stimulation-related side-effects. Regulation of DBS was done by a physician and study outcomes were assessed after 30 min of stabilization. During all sequences, regulation was performed out of view of the patient, but with the regulating physician in the room. Therefore, patients were aware when regulation was taking place, but were blinded to the specific stimulation intensities. Study conditions were either accompanied by (1) suggestions to the effect (negative and positive according to regulation) or (2) neutral suggestions to the effect (no suggestion), in a randomized manner.

Using random draw, patients were randomized in blocks of eight randomization combinations in a balanced manner. The order of conditions with suggestions/no suggestions was randomized in blocks of down- and upward regulation, meaning that patients either received verbal suggestions or no suggestions in all downregulating conditions (before 80, 60, and 20% downregulating) of a test day, and vice versa for upregulating conditions (before 60 and 80% upregulating) of a test day.

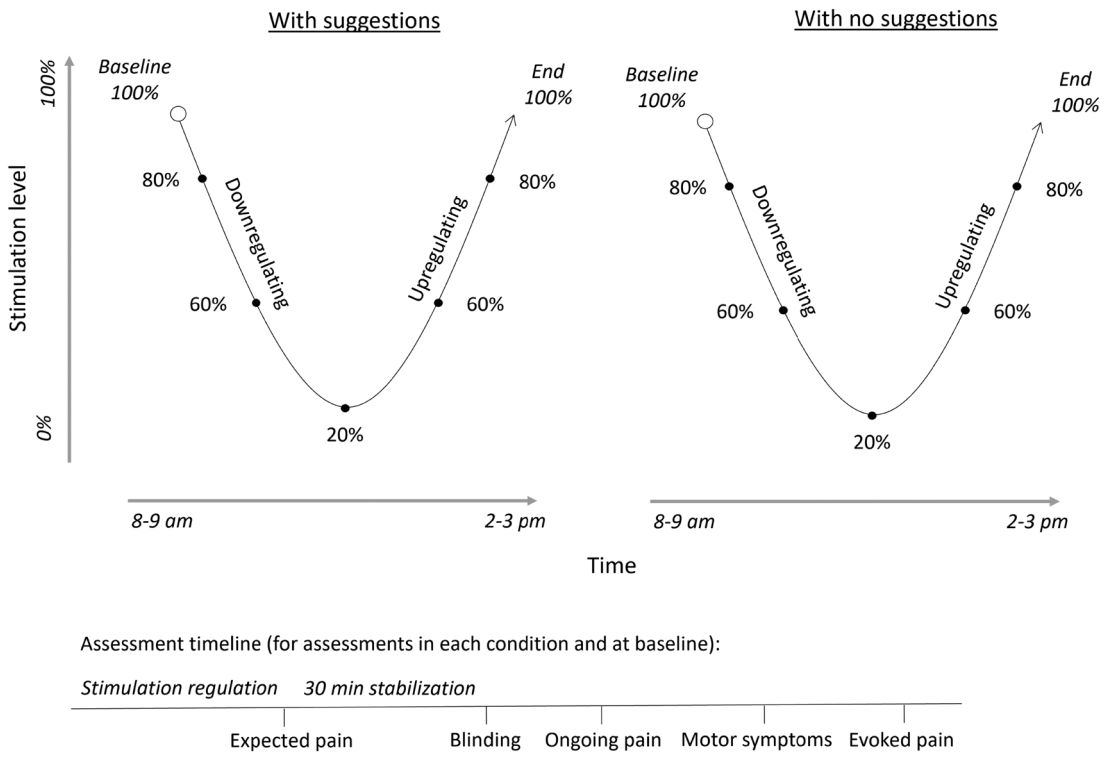

Figure 1: Stimulation level refers to the percentage of stimulation amplitude, relative to the patients' usual stimulation. In addition to the assessments presented in the figure, assessments at baseline included: MoCa, MDI, KPPS, DN4, and pain diary. Conditions were completed either with suggestions or with no suggestions to treatment effect in a randomized manner. With no suggestions (control): "We have now regulated your stimulation." With suggestions downregulating: "We have now regulated your stimulation. Many people experience a significant worsening in pain at this regulation." With suggestions upregulating: "We have now regulated your stimulation. Many people experience a significant improvement in pain at this regulation."

2.1 Suggestions and pain stimuli

In conditions with suggestions, these were given in accordance with the expected effect. Suggestions for downregulating conditions were "We have now regulated your stimulation. Many patients experience a significant worsening in pain at this regulation" (negative suggestion). Suggestions for upregulating conditions were "We have now regulated your stimulation. Many patients experience a significant improvement in pain at this regulation" (positive suggestion). In conditions with no suggestions to the effect, patients were told: "We have now regulated your stimulation" (no suggestion).

Pain was induced by injection of 1 mL of hypertonic saline (5, 8%) administered over 1 min into the medial gluteal muscle using a 10 mL syringe with a disposable 23G stainless needle [22,23]. Hypertonic saline was injected at baseline and in every study condition by a trained doctor. The exact injection site was marked at baseline for consistent injections. For a response of "no pain elicited" to be recorded, patients had to report no pain on two consecutive administrations of hypertonic saline.

2.2 Measures

This study assessed subcategories of pain by King's PD Pain Scale (KPPS) [24] and assessed neuropathic pain by the Douleur Neuropathique-4 (DN4) [25]. Upon inclusion the following measures were obtained once at baseline on the first test day: cognition (MoCA: 0–30 points, 0 = no points) [20], depression (MDI: 10 items, scores from 0 to 40, 0 = no symptoms) [21], pain in PD (KPPS: 14 items with severity and frequency, scores from 0 to 168, 0 = no pain) [24], neuropathic pain (DN4: 10 items, 0–10 points, 0 = no pain) [25]. Patients completed pain diaries to register pain location and level (0–10 numerical rating scale [NRS]) for 14 days (morning and evening) before the first or second test day.

In each condition (including baseline) outcomes were assessed in the following order, after 30 min of stabilization: blinding (0–100 NRS), ongoing pain intensity (0–10 NRS), motor symptoms (Unified PD Rating Scale (UPDRS) III, 0–108 points, 0 = no symptoms) [26], and evoked pain (0–10 NRS). Hereafter, stimulation was regulated for the subsequent condition and expectations to pain intensity (0–10 NRS) were assessed immediately.

2.2.1 Outcome measures

To assess blinding, patients were asked to estimate which percentage of intensity they believed their stimulation level to be at (as determined by a 0–100 NRS, 0 = no stimulation to 100% = usual stimulation).

Pain intensity of ongoing and evoked pain was assessed using a 0–10 NRS from "no pain" to "worst imaginable pain" [27]. When evoked pain was induced, patients were asked to rate their muscle pain related to the injection once every minute until pain subsided [22].

Motor symptoms were assessed using the UPDRS-III [26] by a doctor trained in the assessment.

Expectations to ongoing and evoked pain, respectively, were evaluated on a 0–10 NRS from "no expected pain" to "worst imaginable expected pain" immediately after suggestions, or no suggestions, was given [28].

2.3 Statistical analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at Aarhus University [29,30]. Evoked pain data were coded as missing if maximum pain rating of a condition were <1. Assumptions of estimated models (below) were visually inspected using QQ-, scatter-, and box-plots as appropriate.

Individual pain profiles were visually and numerically inspected for patterns, e.g., whether high and low ongoing pain levels were associated with high and low evoked pain, respectively.

The pain trajectories for evoked pain were summarized into one value using four different methods: (1) area under curve (AUC), (2) maximum pain, (3) mean pain, and (4) total sum of pain. AUC was expected to be the most balanced summarization of pain trajectories, but as a sensitivity analysis, the other three measures were calculated to investigate if the way of summarizing pain trajectories had an important impact on the development in evoked pain across conditions. Four sets of analyses were done. To investigate if regulation of stimulation had the expected effect on ongoing pain and evoked pain (with no suggestions) and motor symptoms, random intercept piecewise linear mixed models were estimated using restricted maximum likelihood (REML). Parameters were centered at the 20% condition, a slope was estimated across downregulating stimulation from 100% through 20%, and a second slope was estimated across upregulating stimulation from 20% through 80%.

To investigate if suggestions had effects on evoked pain, five paired *t*-tests were run (one for each stimulation condition, i.e., 80, 60%, etc.) comparing evoked pain with suggestions and with no suggestions. Two paired *t*-tests were run to compare identical stimulation levels in down- and upregulating conditions with suggestions for evoked pain AUC, i.e., 80% downregulating and 80% upregulating were compared and 60% downregulating and 60% upregulating were compared.

To investigate if expected pain had an effect on evoked pain, five linear regression models were run (one for each stimulation condition) where pain was regressed on expected pain with no covariates.

To investigate if patients were successfully blinded from the current level of stimulation, a random intercept piecewise linear mixed models was estimated using REML. Specifically, reported estimation of stimulation level was subtracted from true stimulation level, producing an outcome that would be constant 0 across stimulation conditions if patients were able to perfectly guess current stimulation (and maximum 80 if they guessed perfectly incorrect). Again, parameters were centered at the 20% condition, a slope was estimated across downregulating from 100% through 20% stimulation, and a second slope was estimated across upregulating stimulation from 20% through 80%.

Across all analyses alpha level was 0.05 with no correction for family wise error rate due to the limited power of the study. All analyses were done in Stata 17.0 [31].

3 Results

The study included 24 patients with bilaterally implanted STN DBS. Two patients scored ≤24 on the MoCA (MoCA = 21 and 23) but were evaluated by a neurologist to be cognitively fit for participation. Patient characteristics are displayed in Table 1 and usual Parkinsonian medication and stimulation is displayed in Table 2. Three patients completed only one test day (two due to the strain of participating without usual medication and stimulation and one due to worsening of PD symptoms, not related to study participation). For evoked pain, 13.9% of conditions were missing, due to patients not completing the condition. In addition, 3.5% of conditions were given a rating of zero after patients having reported no evoked pain on two consecutive administrations of hypertonic saline. Twenty-two patients received Parkinsonian medication (paused during the test days) along with their DBS treatment and two patients received no Parkinsonian medication. One patient

Table 1: Clinical and demographic characteristics

	Mean (SD) or percent
Age	60.21 (5.87)
Sex	Men: 17/70.8%
	Women: 7/29.2%
Age at symptom debut	46.71 (8.15) years
Duration of PD	12.96 (5.22) years
Duration of DBS treatment	2.73 (2.23) years
Type of PD	Not informed: 4.2%
	Tremor dominant: 20%
	Hypokinetic-rigid: 25%
MoCA	25.77 (2.14)
MDI	9.35 (7.82)
KPPS	8.56 (5.04)
Type of pain	Musculoskeletal: 87.5%
	Fluctuation-related: 20.8%
	Nocturnal: 20.8%
	Oro-facial: 12.5%
	Radicular: 12.5%
	Discoloration: 8.3%
	Chronic: 4.2%
DN4	0.60 (1.10)
Baseline UPDRS (day 1)	15.55 (11.96)
Ongoing pain at baseline	1.70 (2.07)
Ongoing pain before DBS implantation	Yes: 62.5%
	No: 33.3%
	Unknown: 4.2%
Ongoing pain after DBS implantation	Yes: 41.7%
	No: 37.5%
	Unknown: 20.8%
Injection side (left/right gluteus medius muscle)	Left: 50%
	Right: 50%
Time (hours) since last dose of Parkinsonian medication before test days	Day 1: 12.70 (5.26)
	Day 2: 13.27 (4.27)

SD: standard deviation, PD: Parkinson's disease, DBS: deep brain stimulation, UPDRS: Unified Parkinson's Disease Rating Scale.

Table 2: Usual Parkinsonian medication and baseline stimulation at time of testing

ID number	LEDD	Baseline stimulation†	
		Left electrode	Right electrode
1	218	3.5	3.1
2	625	3.3	3.1
3	820	3.0	3.0
4	1,660	3.7	3.6
5	552 + 375 p.n.	3.9	3.9
6	375	2.8	2.4
7	125 p.n.	3.1	3.5
8	0	3.8	3.6
9	1,000	5.5	3.5
10	0	4.2	4.4
11	152	3.1	3.0
12	927	3.2	1.8
13	63	3.2	3.2
14	125 p.n.	5.2	2.9
15	750	2.3	3.1
16	400	2.3	2.9
17	375	3.5	3.4
18	427	2.6	3.5
19	313	2.8	2.8
20	261	3.5	3.5
21	780	3.1	3.5
22	552	3.5	3.4
23	625	4.8	3.6
24	375	3.4	3.6

LEDD: Levodopa equivalent daily dose. †Settings at baseline for left and right electrode for deep brain stimulation.

had used pain medication (400 mg ibuprofen, 1,000 mg paracetamol) in the morning of one test day but was evaluated by a neurologist to be able to experience measurable pain during the test day. Patients reported no side effects from regulation of stimulation.

3.1 Ongoing and evoked pain

None of the patients scored above the cutoff for neuropathic pain assessed with the DN4. Average KPPS score was 8.56 (SD 5.04). Six percent of patients had no pain (score = 0) and 94% of patients ranged between scores of 2 and 22 on the KPPS. Pain diaries showed that 15 patients had recurrent pain, assessed over 14 days, while two patients had reported no pain and five patients did not register their pain. The mean ongoing pain at baseline was 1.70 (2.07). Patients' individual pain profiles (raw evoked pain trajectories, ongoing pain score and location in pain diaries, KPPS score, and mean baseline ongoing pain) are presented in Appendix S1. No patterns of systematic association between ongoing and evoked pain were detected in the pain profiles.

The ways in which pain trajectories for evoked pain were summarized did not have an impact on development of evoked pain in conditions and therefore results of AUC and maximum pain are reported. Effects of stimulation (down- and upregulating) for ongoing and evoked pain are presented in Table 3. No significant effects of DBS were found on ongoing pain or evoked pain.

3.2 Verbal suggestions

Table 4 displays the differences in outcomes with suggestions and no suggestions. No significant differences with

Table 3: Effects of stimulation on motor symptoms and pain

	Coefficient	Standard error of the mean	*P* value	95% CI
UPDRS downregulating	7.327	0.444	>0.001	6.455, 8.199
UPDRS upregulating	−10.174	0.695	>0.001	−11.537, −8.811
Ongoing pain downregulating	0.117	0.106	0.269	−0.904, 0.324
Ongoing pain upregulating	−0.297	0.165	0.072	−0.621, 0.026
Evoked pain AUC downregulating	−0.779	1.389	0.575	−3.501, 1.943
Evoked pain AUC upregulating	−0.683	2.213	0.758	−5.020, 3.655
Evoked pain maximum downregulating	0.055	0.143	0.700	−0.225, 0.335
Evoked pain maximum upregulating	−0.267	0.227	0.240	−0.712, 0.179

UPDRS: Unified Parkinson's disease rating scale, AUC: area under the curve, 95% CI = 95% confidence interval. Coefficients represent the change in scores, meaning that positive scores indicate increase in scores (worsening) and negative indicate a decrease in scores (improvement). Results of random intercept piecewise linear mixed models using REML for motor and pain symptoms. Parameters were centered at the 20% condition, a slope was estimated across downregulating stimulation from 100% through 20%, and a second slope was estimated across upregulating stimulation from 20% through 80%.

suggestions and with no suggestions were detected in ongoing pain. As shown in Figure 2a, evoked pain AUC showed a difference between conditions with suggestion and with no suggestions in the expected direction, except in the 20% condition. That is, worsening of pain in downregulating conditions with suggestions and improvement of pain in upregulating conditions with suggestions. Looking at the confidence intervals, this difference showed a trend toward significance in conditions 80 down, 60 down, 60 up, and a significant effect at 80 up. For evoked pain maximum (Figure 2b) this trend was found in 60 down, 20, and 60 up. Comparison of identical stimulation levels in down- and upregulating conditions (80 down vs 80 up and 60 down vs 60 up) in AUC showed near-significant differences between 80% down (mean 36.58, SD 30.79) and 80% up (mean 23.76, SD 22.80), $t(12) = 2.12$, $p = 0.055$ and significant differences in AUC between 60% down (mean 38.75, SD 18.74) and 60% up (mean 23.32, SD 19.18), $t(13) = 3.10$, $p < 0.001$.

3.3 Motor symptoms

The UPDRS-III scores showed significant worsening in downregulating conditions and significant improvement in upregulating conditions (Table 3). No significant differences with suggestions and no suggestions were detected in the UPDRS (Table 4).

3.4 Expectations to pain

As shown in Table 5, patients' own expectations to pain levels had small to moderate effects on evoked pain. For evoked pain AUC, there was a trend in 80 down, 60 down, and 20% conditions. For evoked pain maximum, the effect was significant in 80 down and 60 down conditions and there was a trend in the 20% condition.

3.5 Blinding

Patients' own estimations of stimulation level were on average 10 points from the correct stimulation level across downregulating conditions and 10 points from the correct stimulation in upregulating conditions (Table 6).

4 Discussion

To our knowledge, this is the first study to investigate modulatory effects of suggestions and DBS on ongoing and evoked pain in PD. The study showed no effects of stimulation on ongoing or evoked pain. Patients' ongoing pain seems to be unrelated to motor symptoms, as these were affected by stimulation.

Previously, there have been reported effects of STN DBS on ongoing pain in PD [32–37]. However, these effects were tested pre- and post-implantation [10,33,34]. A study examining non-motor symptoms, found that ongoing pain intensity was not affected by whether STN DBS was on or off [38], similar to the results of the present study. In addition, previous findings indicate that in terms of chronic pain, the effect of DBS is prevalent only in the long-term [9]. This finding could be explained by DBS affecting chronic pain by improvements in features correlating with dystonic pain such as rigidity, abnormal posture,

Table 4: Differences between conditions with suggestions and with no suggestions to the effect

	Number of observations	Mean	Standard deviation	Mean difference	95% CI	P value	*T* value
Ongoing pain							
80↓ −suggestions	21	1.238	1.921	−0.452	−1.357; 0.452	0.330	−1.043
80↓ +suggestions	21	1.690	2.316				
60↓ −suggestions	21	1.857	2.220	−0.095	−1.326; 1.136	0.949	−1.161
60↓ +suggestions	21	1.952	2.252				
20 −suggestions	20	1.425	1.680	−0.325	−1.499; 0.849	0.175	−0.579
20 +suggestions	20	1.750	2.308				
60↑ −suggestions	20	1.175	1.533	−0.375	−1.130; 0.380	0.553	−1.040
60↑ +suggestions	20	1.550	1.731				
80↑ −suggestions	17	0.647	1.272	−0.176	−0.969; 0.161	0.880	−0.472
80↑ +suggestions	17	0.824	1.224				
Evoked pain AUC							
80↓ −suggestions	17	30.588	20.034	−7.950	−19.521; 3.621	0.096	−1.457
80↓ +suggestions†	17	38.538	28.510				
60↓ −suggestions	16	33.803	21.388	−6.069	−13.265; 1.127	0.701	−1.798
60↓ +suggestions‡	16	39.872	20.056				
20 −suggestions	13	34.923	20.267	5.300	−9.565; 20.165	0.702	0.777
20 +suggestions	13	29.623	18.044				
60↑ −suggestions	12	26.208	19.850	9.550	−1.945; 21.045	0.170	1.829
60↑ +suggestions‡	12	16.658	13.251				
80↑ −suggestions	9	28.189	31.459	3.689	−2.755; 10.133	>0.05	1.320
80↑ +suggestions†	9	24.500	25.864				
Evoked pain maximum							
80↓ −suggestions	17	5.829	2.324	−0.244	−1.493; 1.046	0.556	−0.373
80↓ +suggestions	17	6.053	2.655				
60↓ −suggestions	16	5.800	1.855	−0.725	−1.567; 0.117	0.513	−1.825
60↓ +suggestions	16	6.525	2.111				
20 −suggestions	13	6.115	1.816	0.462	−1.101; 2.024	0.215	0.644
20 +suggestions	13	5.654	2.609				
60↑ −suggestions	12	5.375	2.268	1.208	−0.66; 2.482	0.930	2.875
60↑ +suggestions	12	4.167	2.319				
80↑ −suggestions	9	5.524	2.439	−0.278	−1.583; 1.027	0.516	−0.491
80↑ +suggestions	9	5.522	2.044				
UPDRS							
80↓ −suggestions	21	20.143	12.093	0.810	−2.587; 4.206	0.634	0.497
80↓ +suggestions	21	19.333	12.878				
60↓ −suggestions	21	26.381	13.779	1.048	−2.738; 4.833	0.761	0.577
60↓ +suggestions	21	25.333	13.219				
20 −suggestions	20	38.650	12.402	0.400	−3.901; 4.701	0.414	0.195
20 +suggestions	20	38.250	14.075				
60↑ −suggestions	19	20.789	9.235	−3.263	−6.464; −0.063	0.282	−2.142
60↑ +suggestions	19	24.053	10.870				
80↑ −suggestions	17	14.353	9.020	−2.294	−4.995; 0.407	0.601	−1.801
80↑ +suggestions	17	16.647	8.336				

AUC: area under the curve, CI: confidence interval, UPDRS: unified Parkinson's disease rating scale.
Mean scores and mean differences for pain and motor symptoms. ↓downregulating stimulation, ↑upregulating stimulation, with suggestions (+) and with no suggestions (−) to treatment. †, ‡ conditions with suggestion and at the same stimulation intensity were directly compared (presented in Section 3).

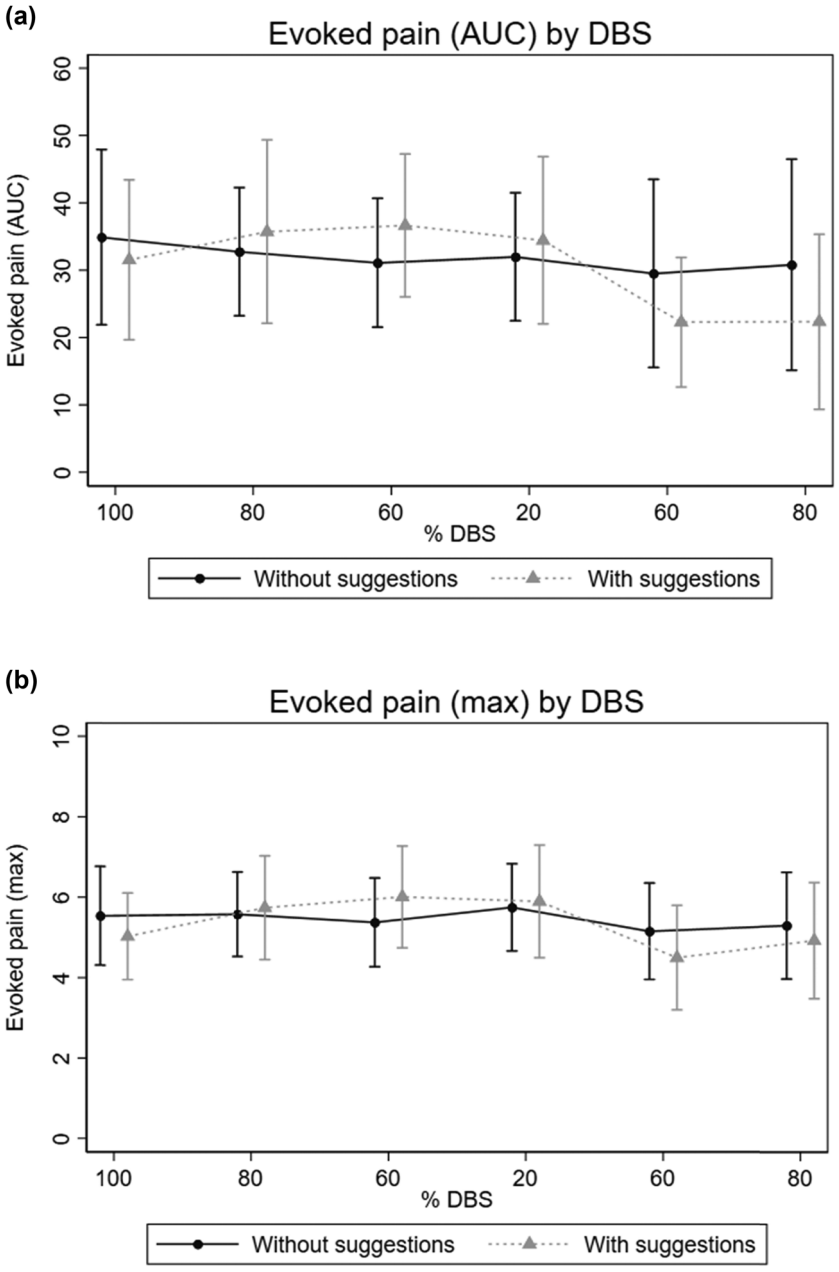

Figure 2: (a) Evoked pain: AUC and 95% confidence interval in each condition with suggestions and with no suggestions (control) to treatment effect. (b) Evoked pain: maximum pain and 95% confidence interval in each condition with suggestions and with no suggestions (control) about treatment effect.

and dyskinesias [8]. An 8-year follow-up study showed that DBS continuously relieved chronic pain, but additional chronic pain developed in 75% of patients [9]. This result may support the hypothesis that DBS has a more stable effect on chronic pain, but not necessarily related to immediate stimulation level but rather other musculoskeletal or biomechanical factors.

Hypertonic saline injections have been used and recommended as a model for acutely evoked muscular pain [22,39], but has not previously been applied in PD. This particular acutely evoked pain model was chosen for its clinical relevance, as musculoskeletal pain is prevalent in PD [4]. Restrictions of minimum baseline chronic pain was not applied in this study, as this would have run the risk injecting ceiling effects in participants reported changes in evoked pain intensity. Furthermore, in the present study, chronic pain levels were assessed using the KPPS which measures only PD-related pain. The results presented here warrant the

Table 5: Expectations' prediction of pain in conditions with suggestions to treatment

	Coefficient	Standard error of the mean	*P* value	95% CI
AUC				
80↓	4.572	2.743	0.114	−1.215; 10.360
60↓	3.664	1.844	0.064	−0.245; 7.572
20	4.370	2.348	0.084	−0.666; 9.405
60↑	2.054	2.597	0.442	−3.515; 7.623
80↑	−0.614	3.648	0.869	−8.563; 7.335
Maximum pain				
80↓	0.575	0.243	>0.05	0.063; 1.086
60↓	0.764	0.154	>0.001	0.437; 1.092
20	0.394	0.275	0.175	−0.197; 0.984
60↑	0.211	0.354	0.561	−0.548; 0.970
80↑	0.125	0.403	0.762	−0.753; 1.002

AUC: area under the curve, CI: confidence interval. ↓downregulating stimulation, ↑upregulating stimulation. Results of linear regression models (one for each stimulation condition) where evoked pain was regressed on expected pain with no covariates.

investigation of differentiated effects of suggestion on PD-related and non-PD-related chronic pain as it is quite possible that the effects of suggestion on evoked pain or pain otherwise exacerbating chronic pain could be related to whether chronic pain is related to PD or not. Patients in the present study had low levels of evoked pain and no pain was induced in 3.5% of evoked pain conditions, despite a protocol of a second injection if the first failed to evoke pain, and efforts to keep injections precise (e.g., marking of the injection site). While this is, for the purposes of this study, an incidental finding it could point to a relieving effect of DBS on musculoskeletal pain not related to expectation. Due to low evoked pain levels, the current study did not detect an effect of suggestions on intensity of evoked pain. Evoked pain levels may suggest that the patients of the study had a higher threshold for evoked pain (average evoked pain of 3.32) compared to previous studies of healthy participants. In a previous study with healthy participants, the average evoked pain by hypertonic saline at the same site was 6.8 [22]. Furthermore, no cases of absent pain induction were reported [22]. This could indicate that PD patients with DBS may have altered pain perception for muscle pain, compared to healthy controls. Of note, participants in this study were instructed to abstain from normal dopaminergic substitution on test days. The effect of suggestion on evoked pain would be considered to be partly mediated by dopamine by expectation and placebo effects. The fact that participants of this study reported evoked pain levels lower than expected compared to healthy controls could point to a non-dopaminergic pain relieving effect of DBS in PD, potentially related to the close anatomical proximity to the zona incerta, implicated in central pain syndromes [40]. The heterogeneity of this effect is in line with other findings indicating differing brain metabolic patterns in subgroups of patients experiencing pain relief after DBS compared to patients with pain which was non-responsive to DBS [41].

Additionally, altered sensory thresholds have been reported for thermal and mechanical pain with DBS [42], but not previously for evoked muscle pain. However, a design allowing for a direct comparison between the effects of DBS on evoked pain in persons with PD and healthy controls is not feasible. Conversely, future studies are required to separate, and hypothetically differentiate, the effects of DBS and dopaminergic substitution on pain and types of pain in persons with PD. Additionally, the findings presented here could suggest that saline injection is unsuited as a model of musculoskeletal pain in PD. Whether this is due to the altered sensory perception or pain-relieving effects discussed above, is a matter of future investigations.

In our study, suggestions do appear to modulate pain. Significant differences were recorded when comparing identical stimulation levels with suggestions (e.g., 60% downregulating vs 60% upregulating). Thus, at identical levels of stimulation, patients' pain was significantly worsened and improved in accordance with the suggestions they received, confirming modulatory effects of

Table 6: Effects of stimulation on blinding assessed by patients' own estimation of stimulation

	Coefficient	Standard error	*P* value	95% CI
Patients' estimation of DBS intensity downregulating	−10.399	1.312	>0.001	−12.970, −7.828
Patients' estimation of DBS intensity upregulating	10.878	2.045	>0.001	6.871, 14.886

CI: confidence interval. Investigation of blinding of patients with random intercept piecewise linear mixed models was estimated using REML. Reported estimation of stimulation level was subtracted from true stimulation level, producing an outcome that would be constant 0 across all stimulation conditions if a patient was able to perfectly guess current stimulation (and maximum 80 if they guessed perfectly incorrect).

suggestions. Significant modulatory effects of suggestions have previously been shown in studies on distinctly dopaminergic symptoms such as bradykinesia (7, 10, and 24 patients) [12,13,15]. However, a previous study of 24 patients did not find significant effects on group level on resting tremor and also did not detect any effects of suggestions on bradykinesia [16]. This was supported by another study of ten patients, which did not find effects of suggestions on tremor or rigidity but did, however, find effects on bradykinesia [14].

It has been emphasized that some patients are instantly aware when their stimulation is on [14]. Nevertheless, studies have employed research designs with stimulation on, or on and off in an attempted blinded fashion [13,14]. Such designs can be expected to include unintentional unblinding of patients, but this has not been tested. Therefore, results may, to some degree, reflect the unblinded expectations of stimulation outcomes which patients form. Importantly, the present study shows that patients can estimate their stimulation level with 10 points' error. The study was designed with this unblinding in mind and included varying intensities of stimulation. Future DBS studies should apply research designs to account for the degree of unblinding which occur in patients.

5 Conclusion

In conclusion, we report a controlled setup in which the effects of DBS and verbal suggestions on pain were investigated. Results suggest that verbal suggestions may influence effects of DBS for symptoms of pain, which are not the primary indication for implantation in PD. In addition, we found indirect indications that DBS may have reliving effects on pain in the absence of dopamine substitution. This finding, in our opinion warrants further investigation. In clinical practice this may nuance the information patients receive about the expected benefits of treatment. Furthermore, our findings corroborate previous findings that patients with DBS are not blind to stimulation settings. This should be considered when designing future studies on the effects of DBS. Future research is, additionally, warranted to clarify the relationship between the effects of DBS and dopaminergic medications on pain and types of pain in PD.

Research ethics: All subjects provided written, informed consent prior to participation. Subsequent to receiving written and oral information, patients signed a standard and pre-approved consent form. The study was carried out in accordance to the declaration of Helsinki.

Author contributions: Sophie Rosenkjær: conceptualization, investigation, writing (original draft preparation), funding acquisition, project administration. Victor Schwartz Hvingelby: investigation, writing (review, second draft and editing). Erik Lisbjerg Johnsen: investigation, resources, writing (review and editing). Mette Møller: resources, writing (review and editing). Elisa Carlino: conceptualization, writing (review and editing). Troels Staehelin Jensen: conceptualization, resources, writing (review and editing). Lene Vase: conceptualization, supervision, project administration, writing (review and editing).

Competing interests: Troels Staehelin Jensen is a Honorary Editor of Scandinavian Journal of Pain. Lene Vase is a Section Editor of Scandinavian Journal of Pain. The authors have no conflicts of interest. Study data will be made available to researchers upon request.

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Data availability: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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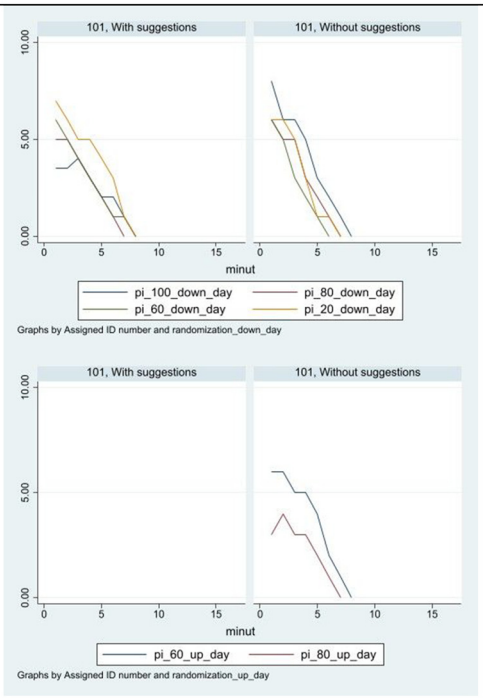
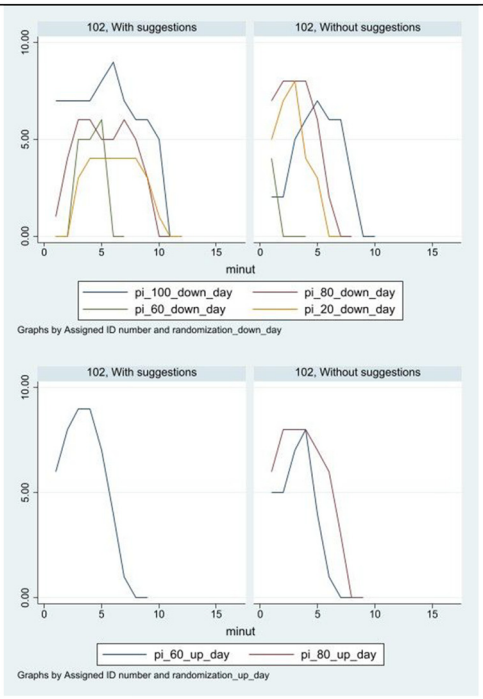
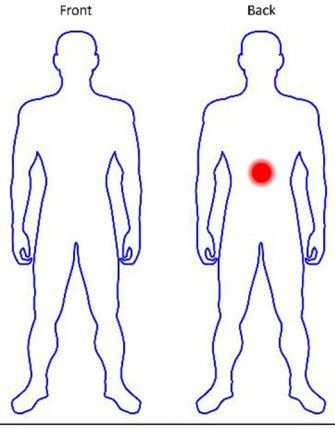
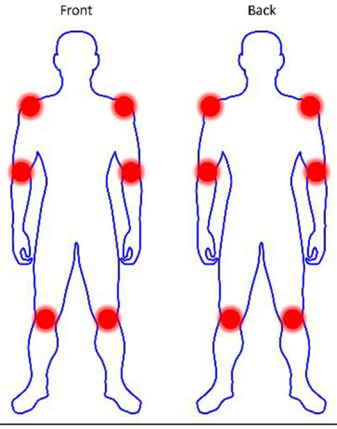
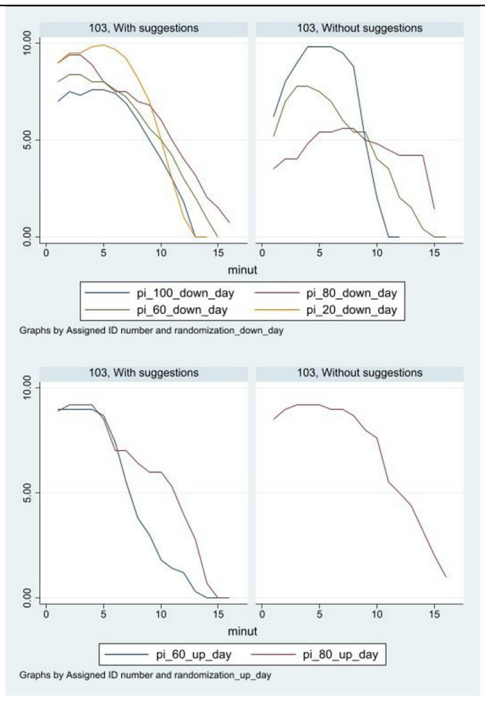
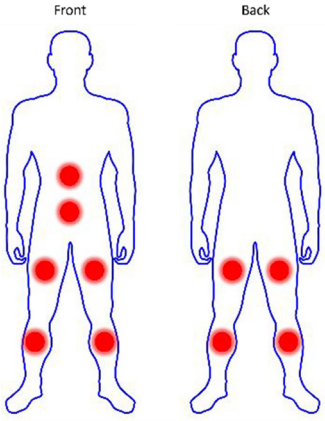
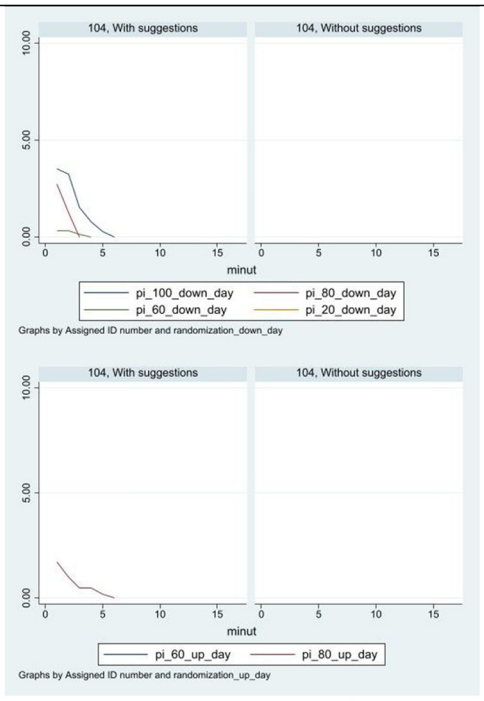
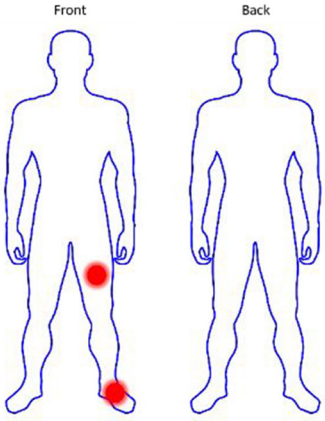
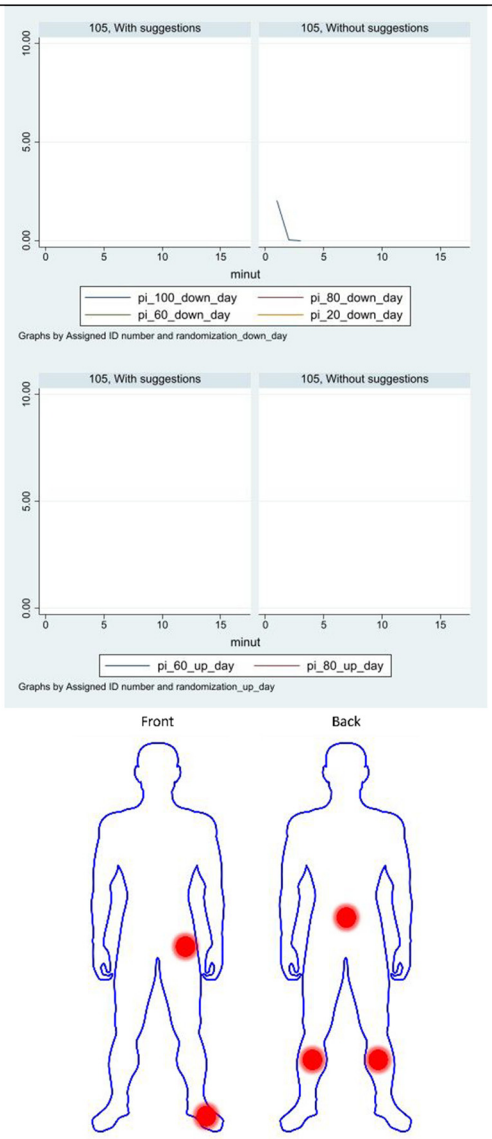
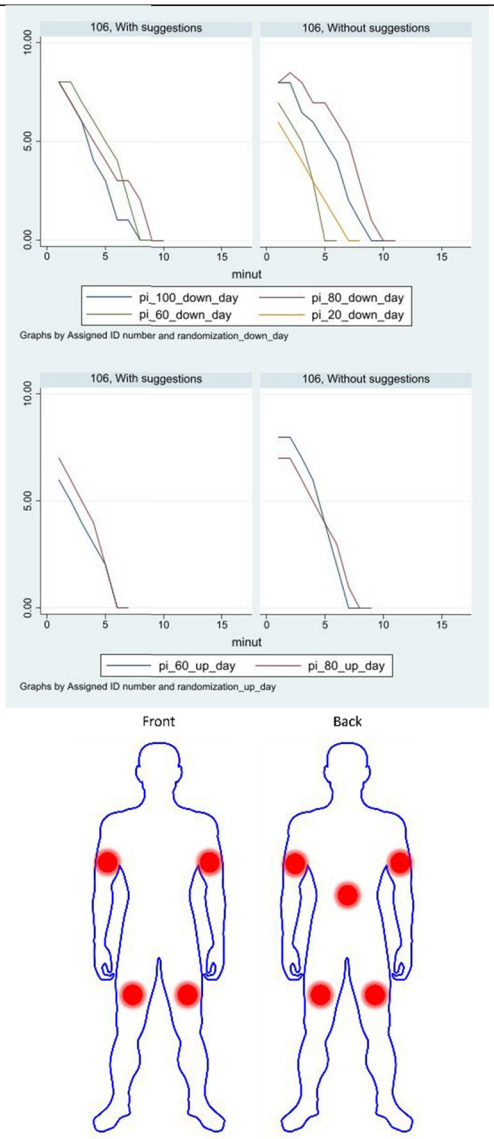
Appendix S1

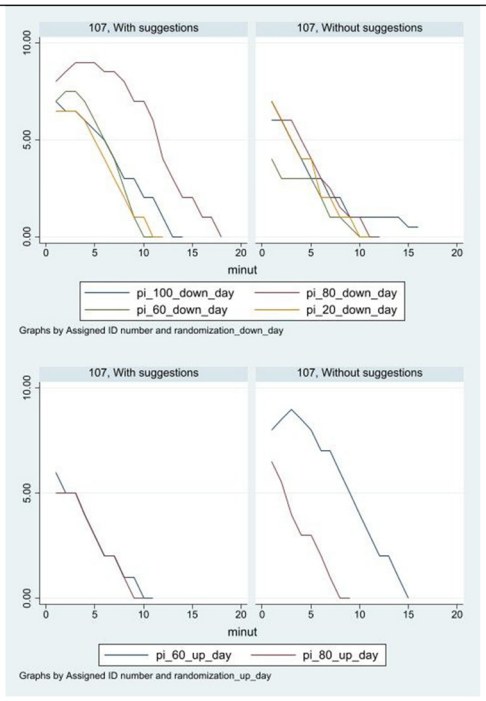
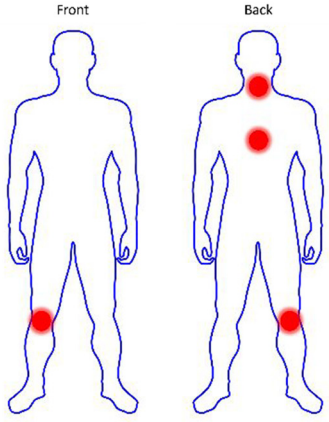
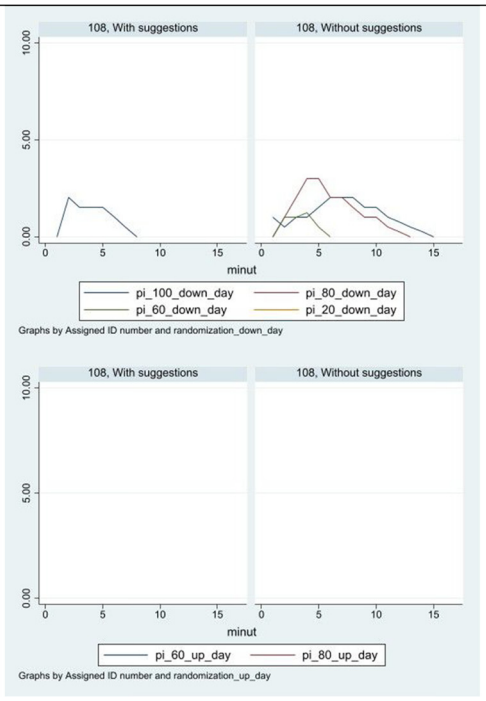
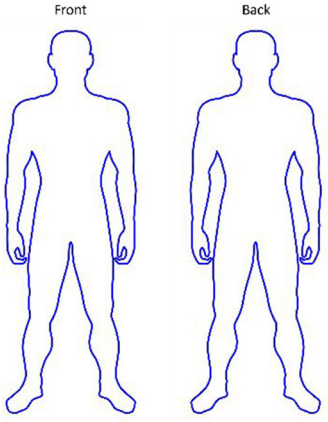
Illustration of ongoing and evoked pain profiles in each patient.

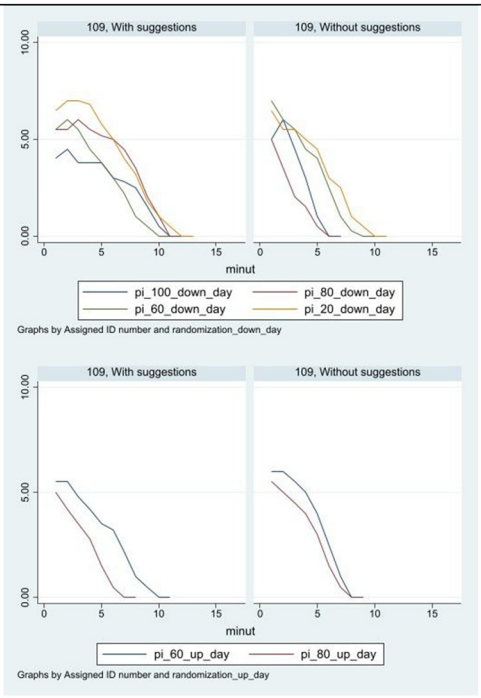
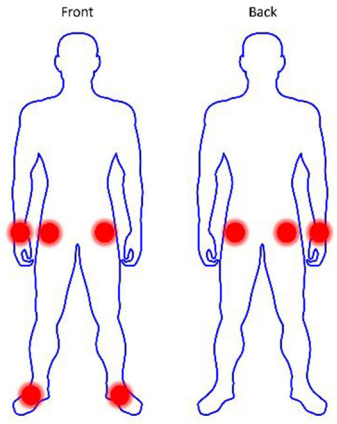
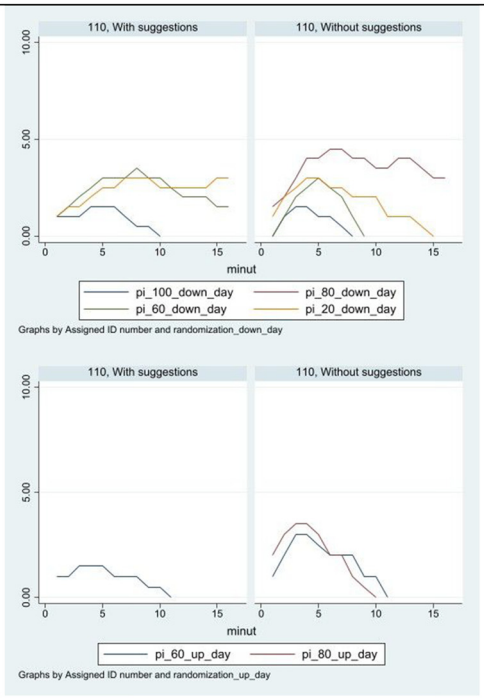
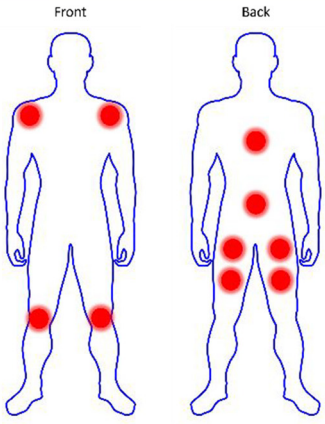
Raw pain trajectories for downregulating conditions (from 100% baseline to 80%, 60%, and 20% on the top) and upregulating conditions (coming from 20% to 60% and 80% on the bottom) and registered pain locations. All locations of pain are registered as reported in pain diaries for each patient: In case of missing pain diary or missing location, location of pain at baseline was used.

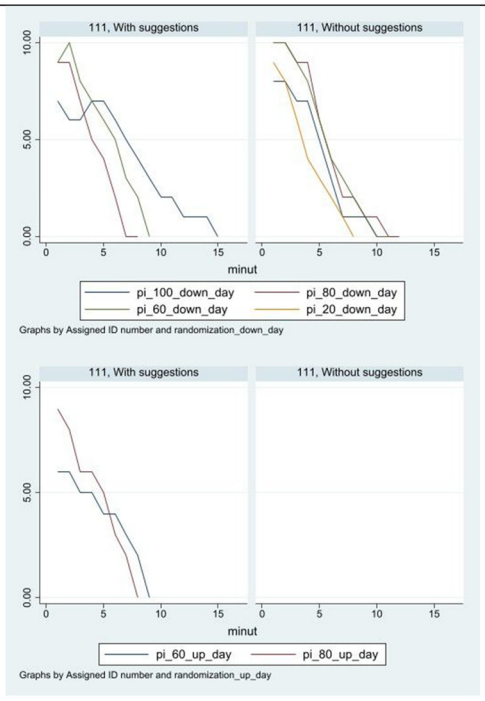
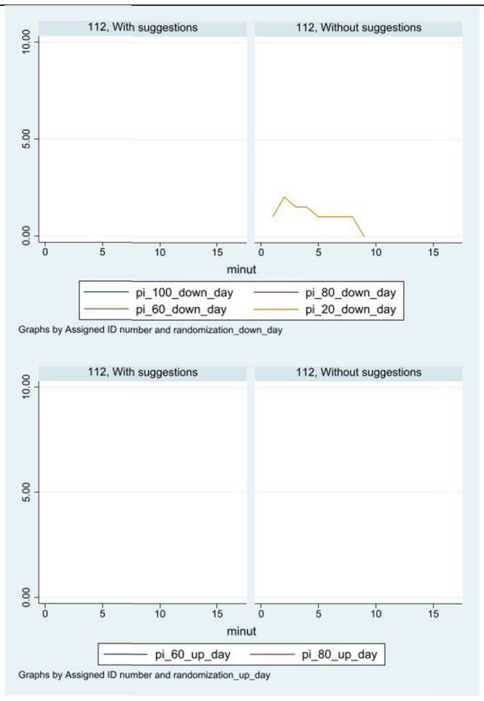
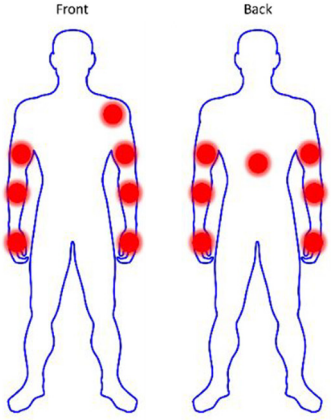
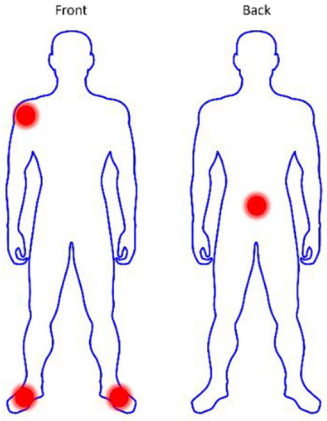
Patient 1	**Patient 2**
	
	
Pain diary, average pain score (SD): Missing KPPS score: 12 Mean baseline ongoing pain: 1.50	Pain diary, average pain score (SD): 6.08 (0.20) KPPS score: 8 Mean baseline ongoing pain: 3.50

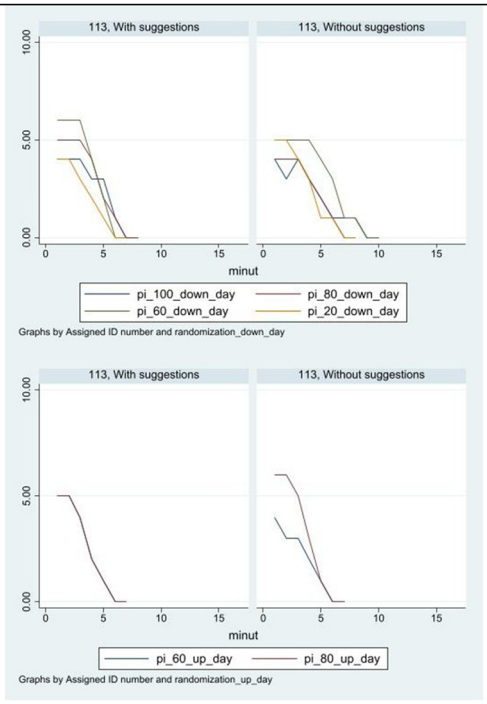
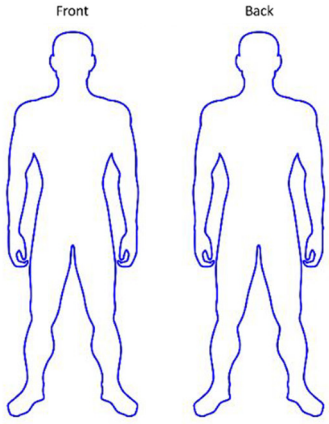
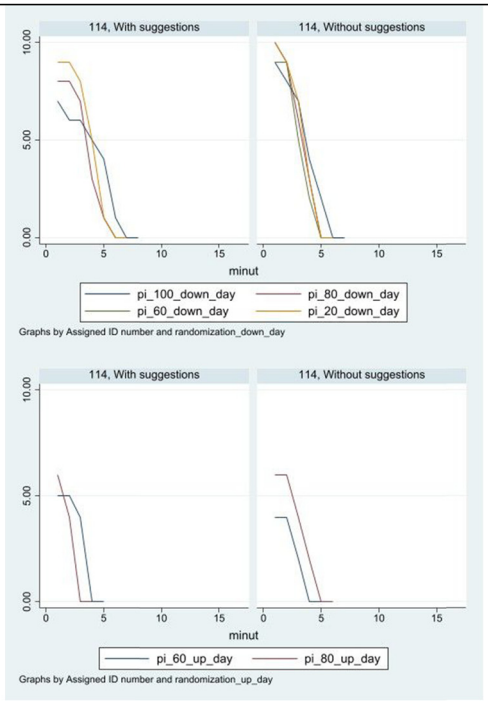
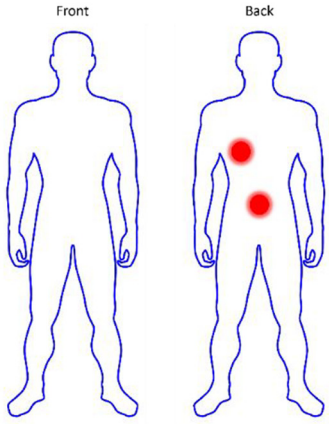
Patient 3	Patient 4
 	 
Pain diary, average pain score (SD): 4.75 (1.14) KPPS score: 22 Mean baseline ongoing pain: 5.75	Pain diary, average pain score (SD): Missing KPPS score: 8 Mean baseline ongoing pain: 1.25

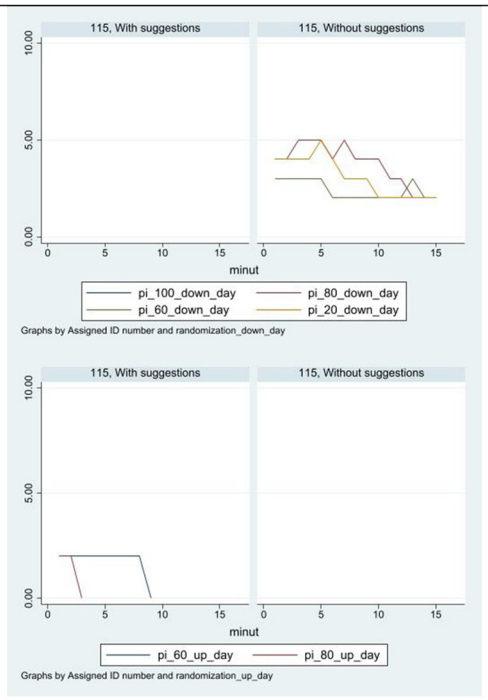
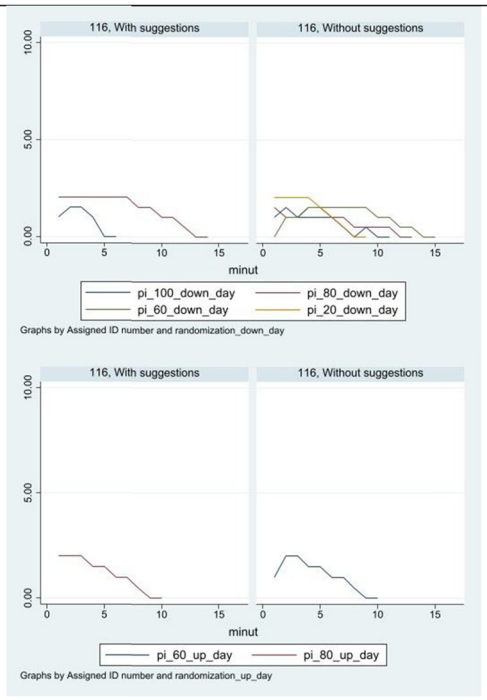
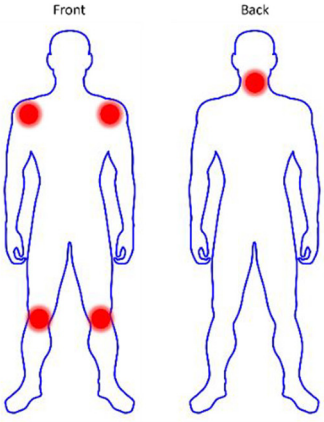
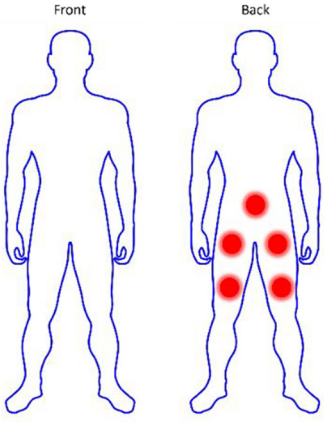
Patient 5	Patient 6
	
Pain diary, average pain score (SD): 2.13 (0.73) KPPS score: 14 Mean baseline ongoing pain:1.50	Pain diary, average pain score (SD): 2.21 (0.73) KPPS score: 12 Mean baseline ongoing pain: 0

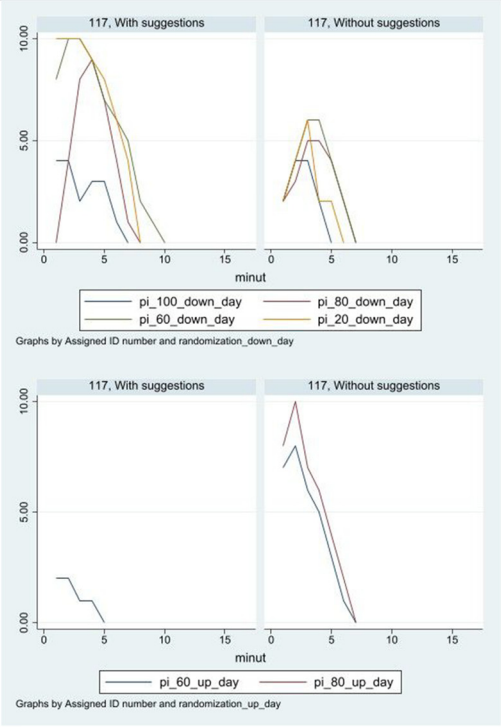
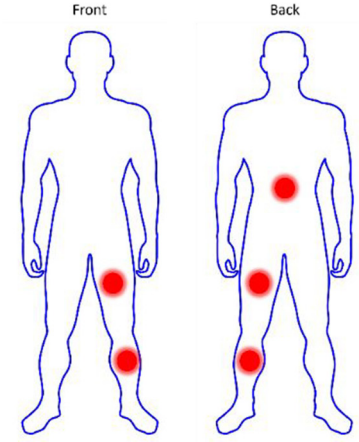
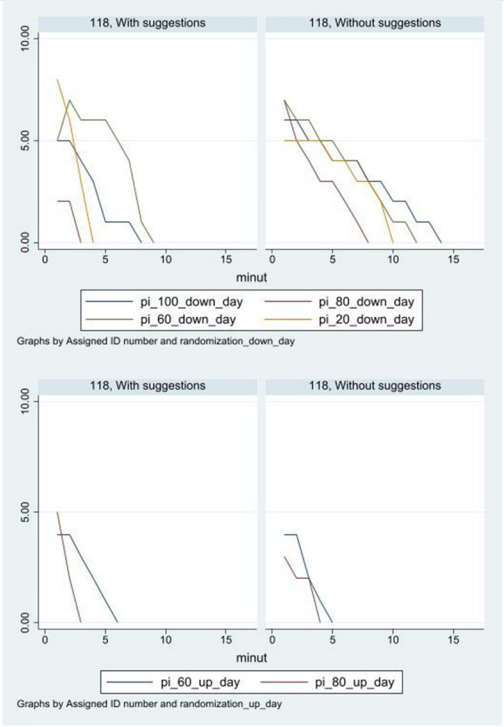
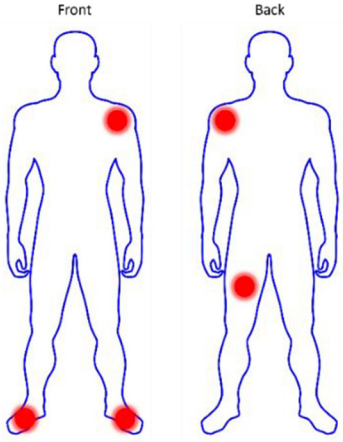
Patient 7	**Patient 8**
 	 
Pain diary, average pain score (SD): 4.45 (0.72) KPPS score: 8 Mean baseline ongoing pain: 4	Pain diary, average pain score (SD): 0 (0) KPPS score: 4 Mean baseline ongoing pain: 0

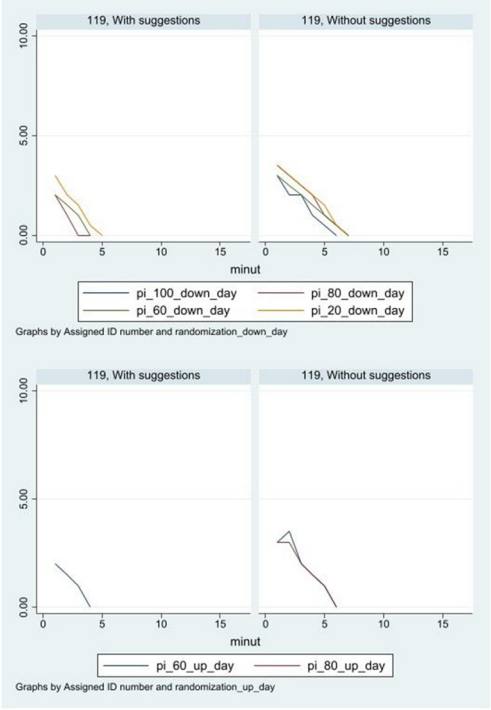
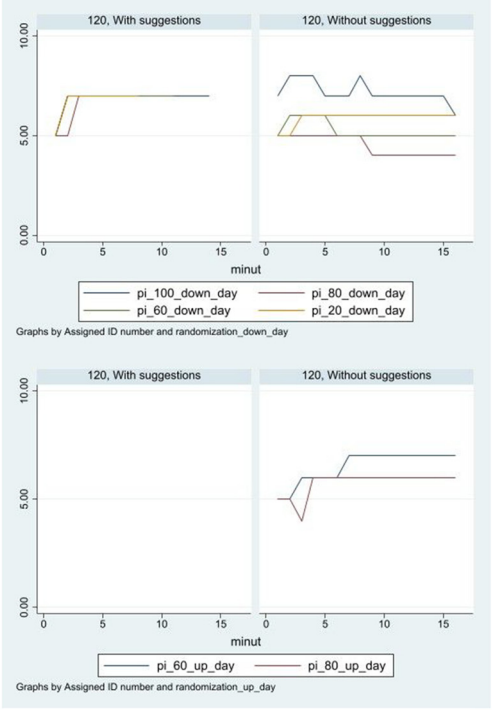
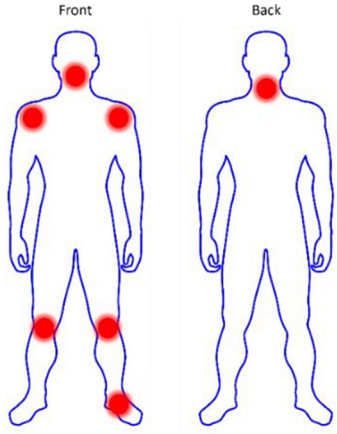
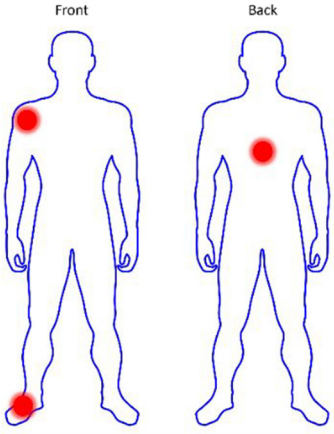
Patient 9	Patient 10
 	 
Pain diary, average pain score (SD): 3.04 (2.36) KPPS score: 3 Mean baseline ongoing pain: 0	Pain diary, average pain score (SD): 2.06 (0.94) KPPS score: 12 Mean baseline ongoing pain: 0.50

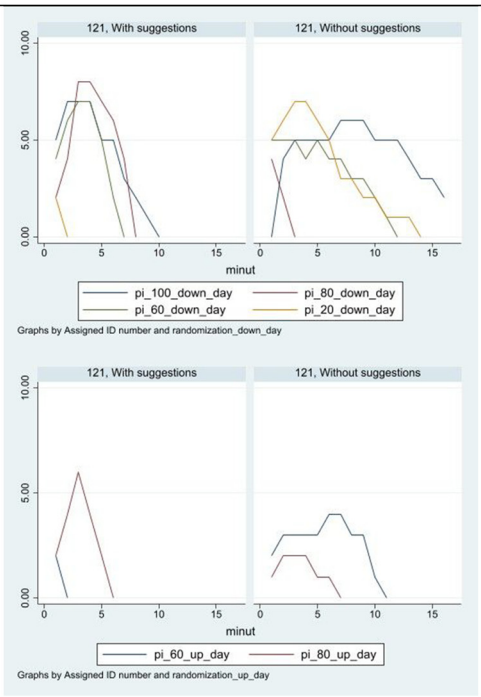
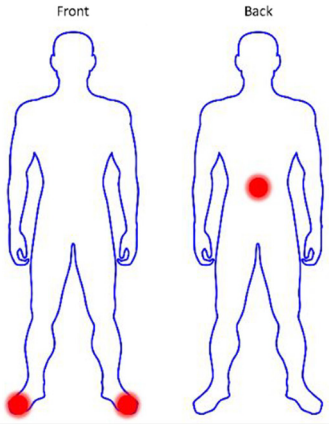
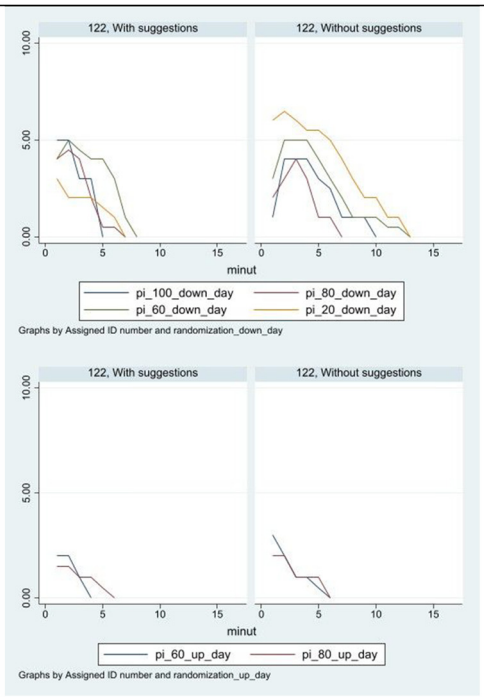
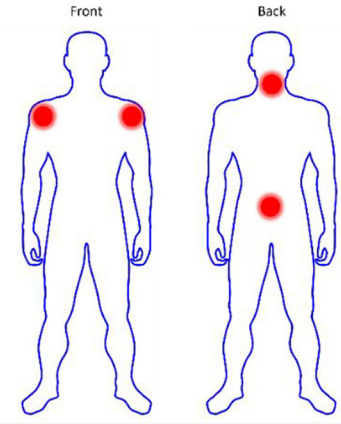
Patient 11	**Patient 12**
	
	
Pain diary, average pain score (SD): 3.50 (1.04) KPPS score: 16 Mean baseline ongoing pain: 1	Pain diary, average pain score (SD): 0.54 (4.99) KPPS score: 2 Mean baseline ongoing pain: 0

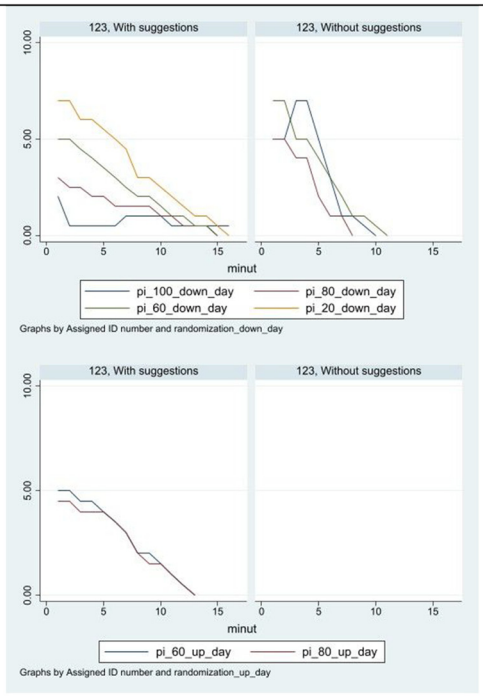
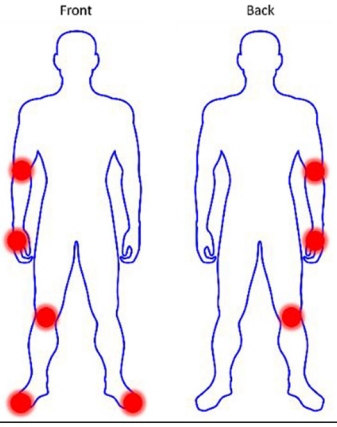
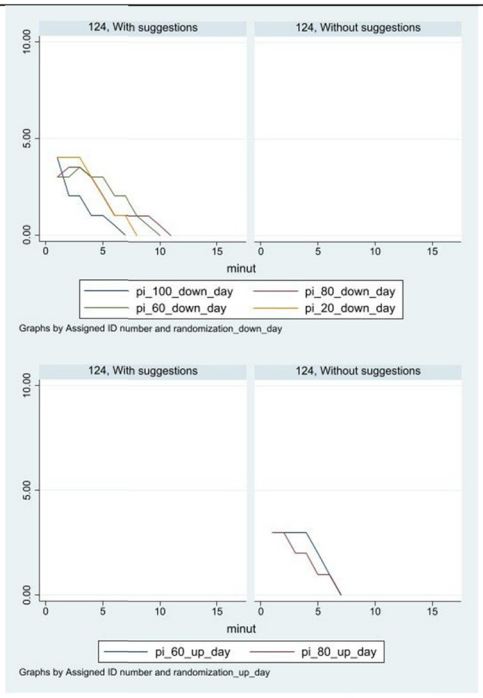
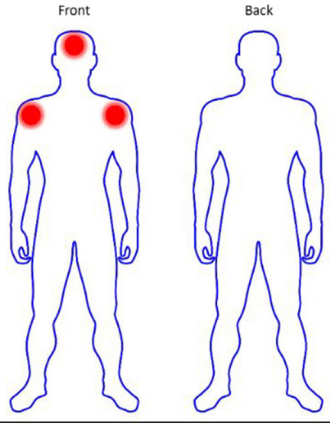
Patient 13	Patient 14
 	 
Pain diary, average pain score (SD): 0 (0) KPPS score: 0 Mean baseline ongoing pain: 0	Pain diary, average pain score (SD): 1.39 (0.68) KPPS score: 0 Mean baseline ongoing pain: 1.50

Patient 15	**Patient 16**
	
	
Pain diary, average pain score (SD): 7.43 (0.65) KPPS score: 8 Mean baseline ongoing pain: 5.00	Pain diary, average pain score (SD): 2.57 (0.58) KPPS score: 12 Mean baseline ongoing pain: 0.25

Patient 17	Patient 18
 	 
Pain diary, average pain score (SD): 4.00 (0) KPPS score: 8 Mean baseline ongoing pain: 2.00	Pain diary, average pain score (SD): 0.90 (0.55) KPPS score: 7 Mean baseline ongoing pain: 1.00

Patient 19	**Patient 20**
	
	
Pain diary, average pain score: 2.75 (0,83) King's: 12 Mean baseline ongoing pain: 1.00	Pain diary, average pain score: 6.88 (1.21) King's: 7 Mean baseline ongoing pain: 5.00

Patient 21	Patient 22
 	 
Pain diary, average pain score (SD): Missing King's: 8 Mean baseline ongoing pain: 2.00	Pain diary, average pain score (SD): Missing King's: 7 Mean baseline ongoing pain: 2.00

Patient 23	**Patient 24**
 	 
Pain diary, average pain score (SD): Missing King's: 8 Mean baseline ongoing pain: 1.00	Pain diary, average pain score: 6.79 (1.05) King's: 2 Mean baseline ongoing pain: 0