Parkinson's Disease Pain Classification System (PD-PCS)

Step 1 Classification of PD-related pain

1. **The close temporal relationship** of pain onset with the disease onset may reflect the first motor symptoms in PD patients.[6]
2. **In off-condition** (low dopaminergic level), pain can be associated with wearing-off and/or end-of-dose akinesia (early morning or nocturnal akinesia and/or akinesia related with medication intake), paroxysmal off-stage (unrelated to medication intake), or off-dystonia (often in the early morning).[3,7,10,14,19]
3. **In on-condition** (high dopaminergic level) mainly choreatic dyskinesia is present. Choreatic dyskinesia is usually perceived as a non-painful symptom, but dyskinetic movements may become painful in case of additional pathological conditions (e.g. osteoarthritis). Choreatic dyskinesia includes peak-on, plateau and biphasic dyskinesia, with the latter occurring at intermediate dopaminergic levels. On-dyskinesia, i.e., especially biphasic dyskinesia, can also manifest as painful dystonia in some cases. Rarely, both choreatic and dystonic biphasic dyskinesia may occur simultaneously.[10,14]
4. **The fluctuation with the dopaminergic state** may give another additional hint for an association between pain and PD. Thus, the positive effects of any antiparkinsonian treatment on pain should be included.[2,19]

Step 2 Three main mechanistic descriptors for PD-related pain:

1. **Neuropathic pain:** It is defined as pain caused by a lesion or disease of the somatosensory nervous system.[17] In the PD-PCS classification system neuropathic pain is deemed present when the DN-4 is scored positive, irrespective of the presence of deep tissue tenderness of pain at palpation as describe bellow.[1]
2. **Nociceptive pain:** pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.[9] It includes cases of musculoskeletal pain due to motor status fluctuations such as off-period pain (morning pain, wearing off pain, beginning of dose pain, end of dose pain), as well as many painful dystonic spasms (early morning dystonia, off period dystonia, beginning of dose dystonia, end of dose dystonia) as well as peak of dose pain.[14] The myofascial pain syndrome, coat hanger headache and localized (shoulder) or regional pain syndromes are included here. By definition, instances when joint, fascia, tendons or muscle palpation is painful or tender, it is considered that nociceptive information or being conveyed by the activation of nociceptors (C- or group IV unmyelinated fibers from skin or deep tissues, respectively). Quite frequently there is a large area of secondary mechanical hyperalgesia around the painful area, which is due to central sensitization of the painful stimulus and likely to be modulated by the dopamine status of the patient.[18] It impacts the perception of pain due to changes in sensory thresholds.[5,12]
3. **Nociplastic pain:** Pain that arises from altered nociception despite no clear evidence of tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.[11] In the hierarchical definition of pain proposed by the IASP and used in the PD-

PCS, nociplastic pain is present when pain is not neuropathic neither nociceptive (DN4 is negative, being <4/10).[9] In clinical practice PD pains considered as nociplastic include instances of clear hyper/hypodopaminergic fluctuations with non-motor neuro-psychiatric manifestations predominate the clinical picture and where pain is frequently not the main complain, but instead, it is part of richer and more complex clinical presentation where one frequently faces crises or flares of profuse sweating, dysphoria, feelings of inner restlessness, motor agitation, wandering, with pain frequently present at the abdomen, with deep location or in the face, or, in some instances ill localized and rapidly moving location.[15] In most cases patients with PD nociplastic pain can be classified as having dopaminergic agonist withdraw syndrome,[13] dopamine dysregulation syndrome,[4] and other neuropsychiatric manifestations of dopaminergic levels where pain exists as part of a broader and more complex clinical picture, being rarely the sole complaint of the individual.[16] We also classified leg motor restlessness and non-motor OFF here,[2,8] when the neuropathic component is not dominant. Nociplastic pain is considered to occur due to the hyperactivation of the nociceptive system, which is not triggered by the peripheral nociceptors, but instead, is caused by an imbalance of the pain (and mood) top-down modulatory systems.[11]

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Table e1: Frequency of responses in the DN4 concerning the pain mechanisms at the first visit (n=159)

	Nociceptive pain (n=87)	Neuropathic pain (n=25)	Nociplastic pain (n=35)	p-value
Burning pain	37 (43%)	16 (64%)	8 (23%)	<0.01
Painful cold	11 (13%)	8 (32%)	5 (14%)	0.06
Electric shocks	12 (14%)	6 (24%)	6 (17%)	0.47
Tingling	25 (29%)	23 (92%)	15 (43%)	<0.01
Pins and needles	29 (34%)	21 (84%)	9 (26%)	<0.01
Numbness	28 (33%)	20 (80%)	11 (31%)	<0.01
Itching	13 (15%)	8 (32%)	2 (6%)	0.02
Hypoesthesia				
to touch	18 (21%)	14 (56%)	4 (11%)	<0.01
to pinprick	14 (16%)	16 (64%)	1 (3%)	<0.01
Pain provoked or				
increased by brushing	3 (3%)	7 (28%)	0 (0%)	<0.01
DN4 Total	2.2±2.0	5.6±1.8	1.7±1.9	<0.01
DNA ≥ 4	17 (20%)	24 (96%)	6 (17%)	<0.01

Table e2: Regions affected by types of PD-related pain

	Nociceptive (n=87)	Neuropathic (n=25)	Nociplastic (n=35)	p-value
Number of affected regions	4.8±5.2	8.5±5.8	10.1±8.9	<0.01*
Body segment				
Head	11 (14%)	5 (25%)	4 (15%)	0.58
Trunk	38 (47%)	8 (40%)	7 (27%)	0.04*
Lower back	34 (42%)	8 (40%)	8 (31%)	0.22
Upper limbs	25 (31%)	9 (45%)	19 (73%)	0.03*
Lower limbs	32 (40%)	14 (70%)	21 (81%)	0.03*

Number of affected regions is shown as means ± standard deviation. Data was analyzed by chi-squared or ANOVA tests.

PD: Parkinson's Disease.

Table e3: Differences in patients'characteristics according to the type of PD-related pain

	PD unrelated pain (n=38)	Nociceptive (n=75)	Neuropathic (n=16)	Nociplastic (n=23)	Overall p-value
Males	27 (71%)	47 (63%)	8 (50%)	13 (57%)	0.45
Age	69.4±10.9	63.0±11.2	64.3±14.7	66.6±10.7	0.04
Right-handed	37 (97%)	74 (99%)	16 (100%)	22 (96%)	0.74
Married	28 (74%)	51 (68%)	11 (69%)	16 (70%)	0.94
Employed	5 (13%)	7 (9%)	0 (0%)	0 (0%)	0.17
PD duration	9.3±7.7	10.5±7.9	12.3±9.0	9.9±6.0	0.59
MDS-UPDRS-III	35.3±14.9	35.8±14.7	44.0±18.4	32.7±15.1	0.15
MDS-UPDRS-IV	3.8±4.0	7.1±4.3	7.7±5.0	5.9±4.9	0.01
LIDs	8 (21%)	39 (53%)*	9 (60%)*	8 (35%)	<0.01
WOQ-9 score	2.8±2.2	5.4±2.3*	6.3±2.2*	5.1±2.7*	<0.01
Clock score	2.7±1.3	2.9±1.6	2.9±1.7	2.7±1.5	0.80
PDQ-8 score	18.1±19.1	30.6±22.3	37.4±24.6	27.9±27.2	0.02
HADS-A score	5.0±3.5	8.0±3.8*	9.6±4.3*	7.8±4.4*	<0.01
HADS-D score	5.4±4.1	8.1±4.5*	9.9±5.1*	7.0±4.0	<0.01
BPI worst pain score	6.9±2.6	7.5±2.3	8.3±1.5	5.9±3.5	0.03
BPI weakest pain score	1.1±1.6	2.1±2.4	2.1±1.7	0.9±1.9	<0.01
BPI average pain score	4.3±2.1	5.4±2.2	6.4±1.6*	4.7±3.2	0.03

Pain score now	1.5±2.3	3.4±2.9*	4.9±3.0*	2.5±3.0	<0.01
MPQ sensory	10.5±8.2	14.0±6.4	19.0±7.7*	11.1±9.2	<0.01
MPQ affective	3.5±4.3	5.6±4.1	6.6±4.6*	4.6±4.5	0.05
MPQ total	14.1±12.0	19.7±9.5*	25.5±12.0*	15.7±13.1	<0.01

Means ± standard deviation are shown. Comparisons were performed by chi-sq or ANOVA tests (* $p<0.05$ vs PD-unrelated pain, post-hoc tests adjusted for multiple comparisons). Patients with mixed pain (i.e. pain in more than one domain with severity scores within ±20% range) or other PD-related pains were excluded (n=7).

PD: Parkinson's Disease; MDS-UPDRS-III: Movement Disorders Society Revision of the Unified Parkinson's Disease Rating Scale part III; MDS-UPDRS-IV: Movement Disorders Society Revision of the Unified Parkinson's Disease Rating Scale part IV; LIDs: levodopa-induced dyskinesia; WOQ-9: Wearing-off questionnaire-9; PDQ-8: Quality of life in Parkinson's Disease questionnaire; HADS-A: Hospital Anxiety and Depression scale - Anxiety subscore; HADS-D: Hospital Anxiety and Depression scale – depression subscore; BPI: Brief Pain Inventory; MPQ: McGill Pain Questionnaire.

Table e4: PD-PCS assessment according to PDQ-8

	<8 (n=39) Low	9-16 (n=36) Intermediate	17-41 (n=40) High	>42 (n=44) Very high	Overall p-value
Number of PD related pains	1.6±0.9	2.0±1.0	1.3±0.7	1.3±0.4	<0.01
PD-unrelated pain	12 (33)	10 (28)	5 (13)	8 (18)	0.12
Nociceptive pain related to PD	13 (33)	22 (61)	28 (70)	24 (55)	<0.01
Score	11.4±21.0	18.5±20.6	27.9±29.9	27.3±30.6	0.02
Neuropathic pain related to PD	3 (8)	5 (14)	7 (18)	10 (23)	0.29
Score	4.6±18.4	4.9±13.6	7.7±20.1	11.3±22.5	0.34
Nociplastic pain related to PD	14 (36)	8 (22)	4 (10)	9 (20)	0.05
Score	6.5±15.0	3.9±9.8	2.7±11.9	11.3±23.7	0.07
PD-PCS total score	20.5±30.0	27.4±27.3	39.4±32.3	49.9±37.6	<0.01

Means ± standard deviation are shown. Comparisons were performed by chi-squared or ANOVA tests.

PD-PCS: Parkinson's Disease - Pain Classification System.