[12] Mylius V, Engau I, Teepker M, Stiasny-Kolster K, Schepelmann K, Oertel WH, Lautenbacher S, Moller JC. Pain sensitivity and descending inhibition of pain in Parkinson's disease. J Neurol Neurosurg Psychiatry 2009;80:24–8.
[13] Mylius V, Moller JC, Bohlhalter S, Ciampi de Andrade D, Perez Lloret S. Diagnosis and management of pain in Parkinson's disease: a new approach. Drugs Aging 2021;38:559–77.
[14] Mylius V, Perez Lloret S, Cury RG, Teixeira MJ, Barbosa VR, Barbosa ER, Moreira LI, Listik C, Fernandes AM, de Lacerda Veiga D, Barbour J, Hollenstein N, Oechsner M, Walch J, Brugger F, Hagele-Link S, Beer S, Rizos A, Chaudhuri KR, Bouhassira D, Lefaucheur JP, Timmermann L, Gonzenbach R, Kagi G, Moller JC, Ciampi de Andrade D. The Parkinson disease pain classification system: results from an international mechanism-based classification approach. PAIN 2021;162:1201–10.
[15] Nolano M, Provitera V, Estraneo A, Selim MM, Caporaso G, Stancanelli A, Saltalamacchia AM, Lanzillo B, Santoro L. Sensory deficit in Parkinson's disease: evidence of a cutaneous denervation. Brain 2008;131:1903–11.
[16] Quinn NP, Koller WC, Lang AE, Marsden CD. Painful Parkinson's disease. Lancet 1986;1:1366–9.

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Response to Mylius et al.

Letter to Editor:

We thank Mylius et al. for showing interest in our work[8] and for providing an interesting discussion on mechanistically stratifying Parkinson disease (PD)-related pain using the recently developed PD-Pain Classification System (PD-PCS). Here, we further address the role of dopamine as well as the move towards mechanism-based treatment for pain in individuals with PD.

1. Dopamine in Parkinson disease pain

Dopamine clearly plays a crucial role in PD pain, and pain is a major feature of nonmotor fluctuations.[14,17] However, mechanistic evidence to date is neither entirely consistent nor sufficient to characterise its precise contributions. Two recent meta-analyses showed partially normalised pain thresholds in "on" vs "off" states, albeit with significant heterogeneity between studies.[18,19] The fact that dopaminergic drugs only diminished, but not normalised, pain thresholds suggests the involvement of nondopaminergic mechanisms. Indeed, the contribution of nondopaminergic systems in pathophysiology of PD is well documented.[6,11,12] PD subtypes have been defined by the nonmotor symptoms dominating their clinical presentations, with each postulated to be associated with the impairment of specific neurotransmitter system(s): cholinergic, noradrenergic, serotonergic, and mixed (nigrostriatal and extrastriatal) dopaminergic.[15,16,20]

Pain is a multidimensional experience. Studies to date predominantly assess pain thresholds, which measure only one of these aspects and do not strongly engage the emotional and aversive facets of pain. Moreover, they do not reflect clinically relevant pain states experienced by patients with PD.[1] Thus, although we agree with Mylius et al. that optimising dopaminergic treatment should be the first step before considering additional interventions, this treatment strategy is, by definition, not aiming to target interventions to mechanism-stratified patients. Indeed, in their article delineating PD pain into nociceptive, neuropathic, and nociplastic, Marques et al. specifically state that they "voluntarily chose not to include in our definition of [parkinsonian central pain] the response to dopaminergic treatment as it seems to be inconsistent and cannot be used as a discriminatory criterion."[9]

2. Mechanism-based treatment of Parkinson disease pain

Although the classification-based approach used by Mylius et al. using the PD-PCS makes an important contribution, its ability to target treatments to mechanisms remains speculative, even if designed with a treatment-oriented approach.[10] Furthermore, the utility of the addition of nociplastic pain beyond existing neuropathic and nociceptive pain has yet to be demonstrated. Moreover, the aspects of pain it captures have already been included in previous classifications[2,5] and are part of the King's Pain Parkinson's Scale (KPPS); an in-depth and patient-orientated classification of PD-related pain.[1] The KPPS is also increasingly used in clinical trials as an outcome measure and may serve as a means to assess treatment outcomes in subgroups of patients.[7,22]

The PD-PCS also does not address pain in the prodromal "premotor" state, despite a large multicentre study finding that 46% of de novo drug-naive PD patients reported pain to have been present in the 2 to 10 years before the onset of motor symptoms.[13] Furthermore, it also fails to characterise nondopaminergic pain, despite nondopaminergic pharmacotherapy offering promising opportunities for future analgesic intervention, with several clinical trials testing analgesic efficacy of cannabinoids (CAN-PDP; EudraCT ID: 2019-003623-37), MAO-B inhibitors (SUCCESS; ClinicalTrials.gov ID: NCT03994328), and opiates (OXYDOPA; ClinicalTrials.gov ID: NCT02601586) currently being in progress or setup.

In its current form, the PD-PCS may lack sufficient granularity to meaningfully stratify patients and further substratification beyond nociceptive, neuropathic, and nociplastic pain may be warranted. Crucially, additional progress may require defining neurobiologically distinct mechanisms beyond psychometry. True mechanistic stratification requires basic science studies delineating psychophysical, electrophysiological, or neuroimaging phenotypes. This is already an ongoing process for other types of chronic pain, with progress to date largely coming from psychophysical means of stratification.[4] For example, quantitative sensory testing can stratify superior responders to oxcarbazepine in patients with peripheral neuropathy,[3] and conditioned pain modulation can target duloxetine to patients suffering from painful diabetic neuropathy with malfunctioning descending pain modulation.[21] Such studies conducted using mechanism-based stratification— using psychometrics, psychophysics, imaging, or a combined approach—will be crucial to building an evidence base for stratified treatment responses in PD pain.

Mechanism-based stratification has shown promise in other chronic pain disease states. The PD-PCS offers an interesting step towards pain classification. However, patient phenotyping-

based strategies supporting clinically relevant neurobiological pathways and outcome measures are also required.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Acknowledgements

Mr Timothy Lawn is in receipt of a PhD studentship funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King''s College London. The authors acknowledge funds from the European Union's Horizon 2020 research and innovation programme "TOBeATPAIN" under the Marie Skłodowska-Curie grant agreement No 764860. The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

References

[1] Chaudhuri KR, Rizos A, Trenkwalder C, Rascol O, Pal S, Martino D, Carroll C, Paviour D, Falup-Pecurariu C, Kessel B, Silverdale M, Todorova A, Sauerbier A, Odin P, Antonini A, Martinez-Martin P; EUROPAR and the IPMDS Non Motor PD Study Group. King's Parkinson's disease pain scale, the first scale for pain in PD: an international validation. Mov Disord 2015; 30:1623–31.

[2] Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurol 2009;8:464–74.

[3] Demant DT, Lund K, Vollert J, Maier C, Segerdahl M, Finnerup NB, Jensen TS, Sindrup SH. The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: a randomised, double-blind, placebo-controlled phenotype-stratified study. PAIN 2014;155: 2263–73.

[4] Edwards RR, Dworkin RH, Turk DC, Angst MS, Dionne R, Freeman R, Hansson P, Haroutounian S, Arendt-Nielsen L, Attal N, Baron R, Brell J, Bujanover S, Burke LB, Carr D, Chappell AS, Cowan P, Etropolski M, Fillingim RB, Gewandter JS, Katz NP, Kopecky EA, Markman JD, Nomikos G, Porter L, Rappaport BA, Rice ASC, Scavone JM, Scholz J, Simon LS, Smith SM, Tobias J, Tockarshewsky T, Veasley C, Versavel M, Wasan AD, Wen W, Yarnitsky D. Patient phenotyping in clinical trials of chronic pain treatments: IMMPACT recommendations. PAIN 2016;157: 1851–71.

[5] Ford B. Pain in Parkinson's disease. Mov Disord 2010;25:S98–S103.

[6] Freitas ME, Fox SH. Nondopaminergic treatments for Parkinson's disease: current and future prospects. Neurodegener Dis Manag 2016;6:249–68.

[7] Geroin C, Di Vico IA, Squintani G, Segatti A, Bovi T, Tinazzi M. Effects of safinamide on pain in Parkinson's disease with motor fluctuations: an exploratory study. J Neural Transm 2020;127:1143–52.

[8] Lawn T, Aman Y, Rukavina K, Lampretsas GS, Howard M, Ballard C, Chaudhuri KR, Malcangio M. Pain in the neurodegenerating brain insights into pharmacotherapy for Alzheimer's disease and Parkinson's disease. PAIN 2021;162:999–1006.

[9] Marques A, Attal N, Bouhassira D, Moisset X, Cantagrel N, Rascol O, Durif F, Brefel-Courbon C. How to diagnose parkinsonian central pain? Parkinsonism Relat Disord 2019;64:50–3.

[10] Mylius V, Lloret SP, Cury RG, Teixeira MJ, Barbosa VR, Barbosa ER, Moreira LI, Listik C, Fernandes AM, de Lacerda Veiga D, Barbour J, Hollenstein N, Oechsner M, Walch J, Brugger F, Hägele-Link S, Beer S, Rizos A, Chaudhuri KR, Bouhassira D, Lefaucheur J-P, Timmermann L, Gonzenbach R, Kägi G, Möller JC, Ciampi de Andrade D. The Parkinson disease pain classification system: results from an international mechanism-based classification approach. PAIN 2021;162:1201.

[11] Park A, Stacy M. Non-motor symptoms in Parkinson's disease. J Neurol 2009;256:293–8.

[12] Politis M, Niccolini F. Serotonin in Parkinson's disease. Behav Brain Res 2015;277:136–45.

[13] Pont-Sunyer C, Hotter A, Gaig C, Seppi K, Compta Y, Katzenschlager R, Mas N, Hofeneder D, Brücke T, Bayés A, Wenzel K, Infante J, Zach H, Pirker W, Posada IJ, Álvarez R, Ispierto L, De Fàbregues O, Callén A, Palasí A, Aguilar M, Martí MJ, Valldeoriola F, Salamero M, Poewe W, Tolosa E. The onset of nonmotor symptoms in Parkinson's disease (the onset pd study). Mov Disord 2015;30:229–37.

[14] Rukavina K, Leta V, Sportelli C, Buhidma Y, Duty S, Malcangio M, Ray Chaudhuri K. Pain in Parkinson's disease: new concepts in pathogenesis and treatment. Curr Opin Neurol 2019;32:579–88.

[15] Sauerbier A, Jenner P, Todorova A, Chaudhuri KR. Non motor subtypes and Parkinson's disease. Park Relat Disord 2016;22:S41–6.

[16] Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. Nat Rev Neurosci 2017;18:435–50.

[17] Storch A, Schneider CB, Wolz M, Stürwald Y, Nebe A, Odin P, Mahler A, Fuchs G, Jost WH, Chaudhuri KR, Koch R, Reichmann H, Ebersbach G. Nonmotor fluctuations in Parkinson disease: severity and correlation with motor complications. Neurology 2013;80:800–9.

[18] Sung S, Vijiaratnam N, Chan DWC, Farrell M, Evans AH. Parkinson disease: a systemic review of pain sensitivities and its association with clinical pain and response to dopaminergic stimulation. J Neurol Sci 2018;395:172–206.

[19] Thompson T, Gallop K, Correll CU, Carvalho AF, Veronese N, Wright E, Stubbs B. Pain perception in Parkinson's disease: a systematic review and meta-analysis of experimental studies. Ageing Res Rev 2017;35: 74–86.

[20] Titova N, Chaudhuri KR. Personalized medicine in Parkinson's disease: time to be precise. Mov Disord 2017;32:1147–54.

[21] Yarnitsky D, Granot M, Nahman-Averbuch H, Khamaisi M, Granovsky Y. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. PAIN 2012;153:1193–8.

[22] Yu SW, Lin SH, Tsai CC, Chaudhuri KR, Huang YC, Chen YS, Yeh BY, Wu YR, Wang JJ. Acupuncture effect and mechanism for treating pain in patients with Parkinson's disease. Front Neurol 2019; 10:1114.

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Pain management in older adults: facts to consider

Letter to the Editor:

The recent article published in *PAIN*® explains many underlying patient-related barriers (especially addiction, severity of pain, and insufficient pain relief) related to the use of opioid analgesics in cancer pain management in the United States between 2002 and 2020.[7] However, despite the increased prevalence of poorly managed cancer-related chronic pain in the elderly, analgesic dosing for this population was not clearly defined. Cohen and colleagues mentioned in *The Lancet* that opioids are not a first-line treatment for chronic pain management,[1] because of tolerance and adverse behavioral effects, without considering dose optimization and the therapeutic window of alternative analgesics. For example, nonsteroidal anti-inflammatory drugs prescribed before opioids also show analgesic tolerance and adverse effects on major organs, including the liver, kidney, and gastrointestinal tract (bleeding).[9] Exercise, physical activities, healthy lifestyle, good sleep, and nonpharmacological management can provide psychological relief from chronic pain, but their effectiveness in managing chronic pain remains poorly defined.[3]