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Editorial: Neuropathic Pain

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Neuropathic pain (NP) arises from direct injury or disease affecting the somatosensory system and remains a substantial unmet clinical challenge [1]. Traditional pharmacotherapy often provides inadequate relief, fueling exploration into mechanism-based diagnostics and therapies. The papers in this special issue collectively advance understanding across three domains: diagnostic measures, mechanistic targets, and interventional strategies.

Quantitative assessment of small-fiber dysfunction

Berfelo et al. [2] investigated the utility of intra-epidermal electrical stimulation (IES) to assess nociceptive detection thresholds (NDT) and evoked potentials (EPs) in diabetic patients with (DMp) and without (DM) painful neuropathy. Their results demonstrated significant alterations in NDT and EP responses among patients with painful neuropathy, suggesting that IES-derived electrophysiological parameters can objectively capture small-fiber dysfunction. These findings support the use of IES as a valuable adjunctive tool in the diagnostic evaluation of painful diabetic polyneuropathy, offering a more precise and quantifiable assessment of sensory fiber impairment.

Mechanistic foundations supporting targeted treatment

Sigma-1 receptor in diabetic neuropathy

Peng et al. [3] conducted a comprehensive review of preclinical and early clinical studies implicating sigma-1 receptors (S1R)—endoplasmic reticulum-resident chaperones that modulate ion channel function and excitotoxic signaling—in the pathogenesis of painful diabetic neuropathy. They emphasize the relevance of endogenous ligands, such as neurosteroids (e.g., progesterone, DHEA) and hallucinogens (e.g., DMT), in modulating S1R activity. The authors propose that selective antagonism of S1R may reduce pathological neuronal excitability while preserving neuroprotective mechanisms, highlighting these receptors as promising targets for translational research. Accumulating evidence underscores the critical role of S1R in modulating pain perception and transmission [4–6].

Mechanism-based treatment framework

Demartini et al. [7] advocate for a stratified therapeutic approach to NP, grounded in the identification of its underlying pathophysiological mechanisms—namely, peripheral deafferentation, central sensitization, or ectopic neuronal activity. By aligning specific mechanisms with corresponding targeted interventions, such as sodium channel blockers for neuronal hyperexcitability, ion channel modulators for ectopic discharges, and neuromodulation techniques for central dysrhythmias, the authors provide a compelling framework for personalized, mechanism-based management strategies aimed at enhancing treatment efficacy and clinical outcomes in NP patients.

Novel pharmacological candidates

1,4-naphthoquinones

Kozlovskiy et al. [8] investigated the pharmacological properties of two synthetic 1,4-naphthoquinones (1,4-NQs) (U-286 and U-548), demonstrating their antagonistic activity at P_2X_7 receptors. In vitro, both compounds significantly inhibited ATP-induced pore formation in macrophages and neuronal cells. In vivo, U-286 produced a marked anti-inflammatory effect, reducing carrageenan-induced inflammation by over 70% within four hours. These results support the potential of 1,4-NQs as dual anti-nociceptive and anti-inflammatory agents, meriting further pharmacodynamic and mechanistic evaluation.

Psychedelics and neuroplasticity

Yasin et al. [9] reviewed current preclinical and clinical evidence on the potential role of serotonergic psychedelics, such as psilocybin and lysergic acid diethylamide (LSD), in the management of refractory chronic pain. They suggest that these compounds exert analgesic effects through 5-HT_{2A} receptor activation, modulation of neuroinflammation, and enhancement of synaptic plasticity and cortical reorganization. Despite these promising mechanisms, the authors emphasize the need for rigorous clinical trials to establish optimal dosing, safety parameters, and long-term therapeutic efficacy.

Interventional and device-based therapies

Matejowsky et al. [10] present a comprehensive review of interventional strategies for managing refractory NP, encompassing spinal cord stimulation (SCS), intrathecal drug delivery systems (IDDS), peripheral nerve stimulation, and various ablative or destructive procedures. The authors synthesize evidence indicating that SCS and IDDS offer superior analgesic outcomes compared to conventional systemic pharmacotherapy, particularly in patients with treatment-resistant NP. They underscore the critical role of appropriate patient selection, interdisciplinary management, and systematic long-term outcome monitoring in maximizing therapeutic benefit. Safety remains a central concern in interventional pain management, and this is especially pertinent in the NP population, where invasive techniques carry specific risks and must be carefully balanced against potential benefits [11].

This integrative, mechanism-targeted approach aligns with current clinical paradigms that prioritize individualized treatment strategies based on precise diagnostic phenotyping. However, the field still faces a major challenge in the rigorous validation of existing assessment tools. Addressing this gap, one study in this special issue validated the Chinese version of the painDETECT questionnaire, confirming its strong reliability, internal consistency, and discriminative accuracy for identifying NP. These findings support its clinical applicability as a culturally adapted screening instrument for Chinese-speaking populations [12]. Given that painDETECT is among the most widely utilized tools for the diagnosis of NP in both clinical and research contexts, its robust cross-cultural validation is of particular significance [13–15].

Challenges and future directions

Despite substantial advances in the understanding and management of NP, several significant challenges remain unresolved. Translational research must effectively bridge the gap between preclinical discoveries

and clinical implementation. For example, while IES offers promising objective measures of small-fiber function, normative reference data and validation across a range of NP phenotypes are essential for its broader clinical adoption. Similarly, the therapeutic potential of S1R modulators must be confirmed through clinical trials employing patient-centered endpoints to establish both efficacy and safety. Neuroplasticity-based treatments, particularly serotonergic psychedelics, show emerging promise but require rigorous randomized controlled trials with standardized protocols and long-term follow-up to determine their clinical utility. In parallel, the incorporation of neuromodulatory interventions such as SCS and IDDS into clinical practice necessitates additional high-quality evidence regarding their long-term effectiveness, cost-efficiency, appropriate patient selection criteria, and safety profile. Furthermore, while mechanism-based treatment algorithms offer a rational framework for individualized care, prospective validation in real-world settings is imperative to substantiate their clinical applicability and optimize treatment outcomes in diverse patient populations.

Conclusion

The collective works presented in this special issue constitute a multi-dimensional advance in NP research. By integrating objective diagnostics, mechanism-based therapies, novel pharmacological modalities, and refined interventional techniques, they mark a substantial step toward personalized, effective, and durable NP management. Future efforts should prioritize rigorous clinical validation, multidisciplinary care models, and dynamic patient stratification to fully translate these insights into improved clinical outcomes.

Abbreviations

1,4-NQs: 1,4-naphthoquinones

EPs: evoked potentials

IDDS: intrathecal drug delivery systems

IES: intra-epidermal electrical stimulation

NDT: nociceptive detection thresholds

NP: neuropathic pain

S1R: sigma-1 receptors

SCS: spinal cord stimulation

Declarations

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Author contributions

GV, GF, AAAA, and MLGL: Writing—original draft, Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

Giustino Varrassi, President of the Fondazione Paolo Procacci and the Associate Editor and Guest Editor of Exploration of Neuroscience, had no involvement in the decision-making or the review process of this manuscript. The other authors declare that they have no conflicts of interest.

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References

1. Bouhassira D. Neuropathic pain: Definition, assessment and epidemiology. Rev Neurol (Paris). 2019; 175:16–25. [DOI] [PubMed]
2. Berfelo T, Krabbenbos IP, van den Berg B, Gefferie SR, Buitenweg JR. Observing nociceptive detection thresholds and evoked potentials in diabetic patients with and without painful neuropathy. Explor Neurosci. 2024;3:493–507. [DOI]
3. Peng Y, Zhang Q, Chen S. Sigma-1 receptor as an emerging target for painful diabetic neuropathy—a review. Explor Neurosci. 2025;4:100680. [DOI]
4. Pergolizzi J, Varrassi G, Coleman M, Breve F, Christo DK, Christo PJ, et al. The Sigma Enigma: A Narrative Review of Sigma Receptors. Cureus. 2023;15:e35756. [DOI] [PubMed] [PMC]
5. Pergolizzi J Jr, Varrassi G. The Emerging Role of Sigma Receptors in Pain Medicine. Cureus. 2023;15: e42626. [DOI] [PubMed] [PMC]
6. Urits I, Borchart M, Hasegawa M, Kochanski J, Orhurhu V, Viswanath O. An Update of Current Cannabis-Based Pharmaceuticals in Pain Medicine. Pain Ther. 2019;8:41–51. [DOI] [PubMed] [PMC]
7. Demartini L, Bonezzi C. Neuropathic pain: proposal of a mechanism-based treatment. Explor Neurosci. 2025;4:100686. [DOI]
8. Kozlovskiy S, Pislyagin E, Menchinskaya E, Chingizova E, Sabutski Y, Polonik S, et al. Antinociceptive effect and anti-inflammatory activity of 1, 4-naphthoquinones in mice. Explor Neurosci. 2024;3:39–50. [DOI]
9. Yasin B, Mehta S, Tewfik G, Bekker A. Psychedelics as novel therapeutic agents for chronic pain: mechanisms and future perspectives. Explor Neurosci. 2024;3:418–33. [DOI]
10. Matejowsky HG, Kataria S, Spillers NJ, O'Quin CC, Barrie S, Ahmadzadeh S, et al. Interventional procedures for refractory neuropathic pain. Explor Neurosci. 2023;2:276–86. [DOI]
11. Pastrak M, Visnjevac O, Visnjevac T, Ma F, Abd-Elsayed A. Safety of Conventional and Pulsed Radiofrequency Lesions of the Dorsal Root Entry Zone Complex (DREZC) for Interventional Pain Management: A Systematic Review. Pain Ther. 2022;11:411–45. [DOI] [PubMed] [PMC]
12. Leung H, Ip JWY, Lam JMK, Lee GKW, Li CCF, Li R, et al. Validation and cultural adaption of the neuropathic pain screening questionnaire painDETECT in Chinese. Explor Neurosci. 2024;3:219–30. [DOI]

13. Nikaido T, Tabata S, Shiosakai K, Nakatani T, Sakoda H. Safety and Efficacy of Mirogabalin in Lumbar Spinal Stenosis Patients with Peripheral Neuropathic Pain on NSAIDs: Post Hoc Analysis of the MiroTAS Study. Pain Ther. 2025;14:1293–310. [DOI] [PubMed]
14. Überall MA, Simanski C, Zellnig M, Eerdekens M, Engelen S, Heine M, et al. Progressive Response of Repeated Treatment with High-Concentration (179 mg) Capsaicin Patch in Peripheral Neuropathic Pain After Surgical or Traumatic Nerve Injury: Findings from the 12-Month German CASPAR Registry Study. Pain Ther. 2025;14:1399–416. [DOI] [PubMed]
15. Ahmed MS, Varrassi G, Hadjiconstanti D, Zis P. The Diagnosis and Management of Meralgia Paresthetica: A Narrative Review. Pain Ther. 2025;14:103–19. [DOI] [PubMed] [PMC]