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RESEARCH ARTICLE

Off-label pharmacological treatment for neuropathic pain: A Delphi study by the Spanish Pain Society Neuropathic Pain Task Force

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Abstract

Objectives: The use of off-label pharmacotherapies for neuropathic pain (NP) is growing relating to the many unmet needs of patients. However, clinical guidelines fail to address it, and the available evidence is sparse and fragmented. We arranged a formal expert consensus to address this controversial issue and provide some guidance on judicious use.

Methods: A two-round standard Delphi survey that involved pain clinic specialists with experience in the research and management of NP was done over an ad hoc 40-item questionnaire prepared by the authors. Consensus on each statement was defined as at least either 80% endorsement or rejection after the second round.

Results: Forty-three and thirty-seven panelists participated in the first and second round, respectively. Consensus was reached in 34 out of 40 statements. Endorsed alternatives for unresponsive patients include non-gabapentinoid antiepileptics (oxcarbazepine and eslicarbazepine), venlafaxine, intravenous lidocaine (when doses can be optimized), and some vaporized cannabinoids (under appropriate surveillance). In addition, lacosamide, low-dose naltrexone, propofol, or ketamine could prove beneficial if subjected to more research. Other options were rejected, and there was controversy about the usefulness of topical preparations.

Discussion: For patients who do not respond to standard NP treatments, some other viable pharmacological options can be attempted before advancing to other therapeutic stages. This may help patients who are reluctant to or have some contraindication for interventional therapies.

KEYWORDS
Delphi Technique, intractable pain, neuralgia, off-label use, review

INTRODUCTION

Neuropathic pain (NP) arises as a direct consequence of a lesion or disease affecting the somatosensory system at central and/or peripheral levels.[1] A best estimate of population prevalence of pain with neuropathic characteristics is likely to lie between 6.9% and 10%.[2] A number of conditions such as diabetes, shingles, spinal cord injury, stroke, multiple sclerosis, cancer, human immunodeficiency virus infection, radiculopathy, and traumatic or surgical nerve injuries can cause it.[3] Generally chronic and severe, very unpleasant and disabling,[4,5] it exerts a substantial impact on patients' lives, healthcare resources, and society.[4,6–8] Due to its complex pathophysiology and heterogeneity, the correspondence between etiology, underlying mechanisms and clinical manifestations is usually limited,[9] which poses numerous therapeutic challenges.[10] The wide diversity of agents and procedures required to treat it[11,12] and the overall modest response to drug therapy[12] further complicate treatment. To make things worse, there has been little progress in NP pharmacotherapy in the last decade, which has not seen any major innovation in the body of related scientific evidence. Moreover, relevant research has further compounded this situation by revealing that the efficacy of current mainstream pharmacological approaches is lower than anticipated.[13]

In this milieu of widespread disappointing outcomes and unmet needs, the clinical use of off-label single or combined pharmacotherapies and invasive interventions

for NP is expanding (eg,[14,15]). However, the available information is highly fragmented and usually focused on individual agents or conditions. A number of concerns surround off-label therapies as well due to the sparse efficacy data, the eventual need for pain phenotyping that is not readily available in the routine practice and the potential for side effects.[15,16] Additionally, despite the guidelines acknowledging the potential of (un)approved combination therapies, they do not provide detailed accounts on specific arrangements and indications because of the lack of dedicated studies.[17,18] Consequently, clinicians often found themselves without the necessary evidence or guidance to base their practices and offer alternatives to patients enduring persistent pain.[19]

Nonetheless, there seems to be room for improvement. Despite the efforts to develop a more rational therapeutic approach,[20] many patients do not receive appropriate treatment for their pain,[19] and inadequately treated NP, rather than refractoriness per se, has been found to be responsible for unsuccessful outcomes.[11] To guide clinicians and help optimize current resources until new relevant developments emerge, the Spanish Pain Society (*Sociedad Española del Dolor, SED for its acronym in Spanish*) has been sponsoring reviews and recommendations for the management of NP, including the use of off-label drug therapies,[21,22] combination therapies,[17,22] and interventional procedures. Within this context, the present article regards an ongoing initiative launched to contextualize current therapeutic practices for NP, aiming to compensate for the inevitable lag of clinical guidelines.[23–25] In particular, the SED NP Task Force involved pain experts throughout Spain in a Delphi study to enable researchers to: (a) assess the off-label pharmacological management of NP, (b) clarify, organize and align opinions on criteria for the initiation of such therapy, and (c) provide a framework for reducing empiricism and promoting its judicious use. The outcomes are the focus of this paper. A complementary Delphi study on the role of interventional management for NP was also undertaken, which results are provided in a separate article.[26]

METHODS

Questionnaire

This study was based on an ad hoc 40-item instrument (Table 1) prepared by the study coordinators as described in the Supplementary Material.

The Delphi technique

We used the standard Delphi technique, which is a highly structured method of group interaction in which

TABLE 1 Description of the Delphi survey questionnaire

(A) Antiepileptics
1. Although oxcarbazepine is not approved for trigeminal neuralgia, it is a useful drug with moderate evidence support and generally a better tolerability profile than carbamazepine, but it is important to monitor the hyponatremia that it can cause
2. We recommend a therapeutic assay with oxcarbazepine in patients refractory or intolerant to carbamazepine
3. Eslicarbazepine has cleaner pharmacokinetics than carbamazepine, which translates into a more favorable side-effect profile, particularly concerning hyponatremia. Therefore, despite the available evidence is particularly limited, therapeutic assays are granted in patients with poor tolerability or refractory
4. Lacosamide is an anticonvulsant that works by blocking sodium channels, and there are studies supporting its use for NP
5. Lacosamide is effective to improve allodynia and hyperalgesia
6. Lacosamide at maximum doses of 400 mg/day may be a suitable therapeutic option in patients who do not respond to other therapies
7. We discourage the use of levetiracetam for NP
(B) Antidepressants and antipsychotics
8. Although there are studies with atypical antipsychotics in animal models of NP, their value has not been established in human pathology
9. The summary of product characteristics of duloxetine only includes the indication for diabetic NP and the clinical guidelines consider it a first-line treatment for NP. It was shown to be effective for post-chemotherapy polyneuropathy, and as such we also recommend it as a first-line treatment for this pathology
10. Venlafaxine was shown to be useful in several NP conditions (in particular, diabetic neuropathy and other polyneuropathies). We recommend it for these pathologies when there is no response to approved treatments
11. Unlike duloxetine and venlafaxine, desvenlafaxine has no evidence of efficacy for NP
(C) Anesthetics
12. The intravenous lidocaine infusion is beneficial for NP treatment, which is usually refractory to therapies that are more traditional
13. Several central and peripheral NP pathologies can potentially be treated with lidocaine (post-stroke pain, post-herpetic neuralgia, diabetic neuropathy, CRPS, etc.)
14. (Intravenous lidocaine) doses are not clearly established but some studies suggest doses between 3 and 5 mg/kg. Lower and repeated doses could have similar and maintained effects
15. Despite sparse evidence, the addition of magnesium at doses of about 1 gram may improve the analgesic efficacy of lidocaine. Consequently, we recommend that it be considered in patients who do not respond to lidocaine alone
16. In addition to propofol's regulatory mechanism of action over some neurotransmitters such as glutamate, there are potential antihyperalgesic effects on type 2 angiotensin receptors specifically related to nociceptive mechanisms

TABLE 1 (Continued)

17.	Ketamine has multiple mechanisms of action and therapeutic targets explaining both the analgesic effects as well as potential side effects, among which psychotic bouts or hypertension and tachycardia stand out
18.	Ketamine treatment for NP requires monitoring liver function and ruling out psychiatric history prior to onset
19.	Sevoflurane has been used and shown to be potentially effective for the topical treatment of cutaneous venous ulcers; more studies should be carried out to show its efficacy in other NP models
(D) Topical preparations	
20.	Capsaicin patches for phantom limb pain should be applied on the stump since painful stumps are commonly mistaken as phantom limbs
21.	There is no comparative evidence between the effects of capsaicin 8% patches and lidocaine 5% dressings or their combination for NP. However, the studies of capsaicin patches are more robust and show greater efficacy than for lidocaine dressings
22.	No evidence from controlled trials supports the use of capsaicin patches for the treatment of radiculopathies. Furthermore, given the low degree of penetration, its potential effectiveness is dubious
23.	There are studies and non-controlled case reports from several authors suggesting that capsaicin 8% is effective for the treatment of facial trigeminal pain
24.	There are some reports of comparative efficacy between topical gallium maltolate and opioids. Conversely, we are not aware of any related report about topical phenytoin
25.	No experience with lidocaine patches or topical capsaicin iontophoresis is available, but with some local anesthetic
26.	Publications in pediatric CRPS report the use of capsaicin 8% patches, like in adults
27.	There are 1-year capsaicin papers published, but we have experience of good tolerability when used for periods longer than 3 years
(E) Cannabinoids	
28.	Experimental data in laboratory and animal models show that cannabinoids are a valid alternative in NP treatment
29.	Cannabinoids have weak recommendations for use and moderate quality of evidence. They achieve small pain reductions, with latency periods, and must be administered in combination with other analgesics
30.	Some societies have recommended their use as second- or third-line therapies, yet with considerable precautions and indication limitations
31.	The combination of low THC (<12.5%) and high CBD concentrations seems to exert improved analgesic effects, but yet no studies have evaluated pharmacological products based on such a combination
32.	Best analgesic effects are achieved via the vaporized route of administration. The effect is small by oral route. The smoked route is discouraged
33.	Sativex, the only cannabinoid-based treatment currently available in Spain, has shown analgesic benefits for central pain associated with multiple sclerosis, plexus avulsion injury, NP following a peripheral lesion and diabetic neuropathy
34.	Neither long-term side effects nor the risk of addiction have been characterized, but short-term effects are mild to moderate, the most serious being the acute cognitive (particularly over memory at high doses)
35.	We do not recommend their use in patients under 25 years of age, in pregnant women, or in patients with cardiovascular or respiratory diseases, psychosis or substance abuse history
(F) Other agents	
36.	Blockage of TLR4 receptors by low-dose naltrexone is a putative mechanism of action explaining its efficacy for refractory NP at doses below 6 mg
37.	Although there is no clear evidence supporting the efficacy of low-dose naltrexone for NP, we recommend assaying it in patients refractory to other therapies given its potential efficacy and proven safety
38.	Low-dose naltrexone dose schedule should be individualized, although the average effective dose is about 4 mg/day
39.	The clinical therapeutic guidelines do not yet recommend anesthetic agents that act by blocking NMDA receptors within the nervous system due to lack of evidence
40.	Amantadine has been used as an anti-influenza and antiparkinsonian agent, but there is not enough evidence to use it to treat pain and the mechanism of action is unknown

Note: There was consensus on accepting the statements in shaded rows. There was no consensus on rejecting any statement.

Abbreviations: CBD, cannabidiol; CRPS, complex regional pain syndrome; NMDA, *N*-methyl-D-aspartate; NP, neuropathic pain; THC, tetrahydrocannabinol; TLR4, toll-like receptor 4.

members (or panelists) usually interact via questionnaires and receive feedback through facilitators. It is frequently used in medical research as a survey method to gain consensus.[27] In this case, we used a pre-specified 2-round process without any physical meeting to preserve participants' anonymity and allow free expression of opinions while providing them the opportunity to see and comment upon other members' responses.

Respondents' agreement was sought on whether individual statements were well supported by evidence, or they could be used to guide or recommend therapeutic strategies. Since this study focused on therapy decisions, a high level of agreement was fixed a priori to recognize consensus on accepting (≥80% endorsement) or rejecting (≤20% endorsement) the statements. Responses from the first round were collated and used to create personalized questionnaires for the second round that included the same statements (no items were dropped) together with both the individual panelist's rating and the ratings from the entire panel. Respondents could re-rate the statements, either providing the same rating as before or a modified rating in consideration of those from the other participants. A one-month term was allowed to answer the first round in early 2020. Then the personalized questionnaires for the second round were prepared, which was completed within 6 months from study inception (Figure 1). The

process took longer than expected because of disruption caused by the coronavirus pandemic. Panelists' withdrawal between the rounds (see the Results) may relate to this issue. We followed the recommendations for the conduct and reporting of studies using the Delphi technique in health care research.[28] The appropriate checklist is included in the supplemental Table S2.

The Clinical Research Ethics Committee of a Spanish Hospital approved the final study protocol. All panelists provided a written consent to participate. The research was carried out under the Spanish laws for the protection of personal data.

Development of the study questionnaire

The Delphi survey was based on a questionnaire that included a series of statements that the panelists had to rate on 5-point Likert scales of agreement (from 0 = strongly disagree to 4 = strongly agree). This is the most common format in Delphi studies for attempting consensus.[28] The study coordinators, who were members of the SED NP Task Force, developed it using the available scientific literature and their personal clinical experience. For this purpose, a literature search on the pharmacotherapy of NP was done in PubMed, Google Scholar, Web of Science, and Scopus from January 1, 2012 onwards using the following keywords (either alone or combined): "neuropathic", "pain", "neuralgia", "drug", "agent", "therapy", "pharmacotherapy", "pharmacotherapies", "antiepileptics", "anticonvulsants", "antidepressant(s)", "antidepressive(s)", "antidepression", "antipsychotic(s)", "lidocaine(e)", "lignocaine(e)", "naltrexon(e)", "an(a)esthetics", "anesthesiology", "an(a)esthetize", "n methylaspartate", "nmda", "cannabinoid(s)", "topical(s)", and "topically". The questionnaire was prepared in two stages. The first was a generation stage in which each member proposed candidate items individually, which were collated into a preliminary draft version that contained 96 items. These items were generated in consideration of the most commonly used off-label drugs by the panelists to treat NP, understood as those used for unapproved indications or in unapproved age groups, dosages, or routes of administration.[29] Drug selection

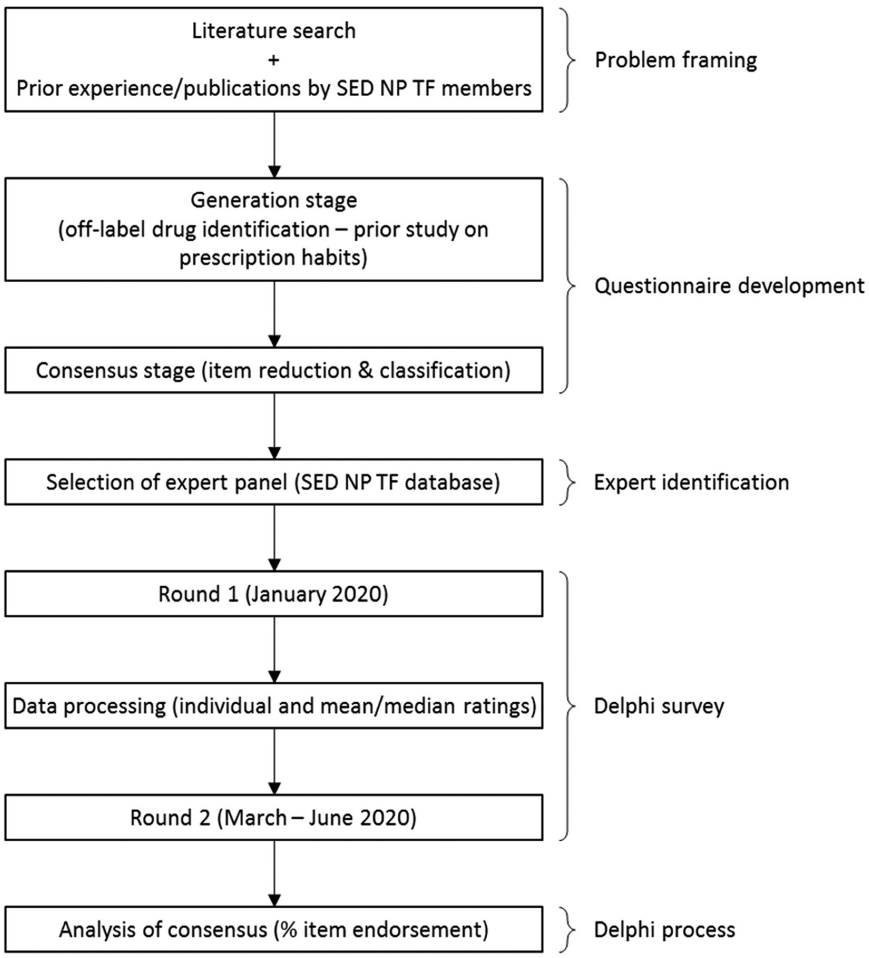

FIGURE 1 Flow chart of the Delphi study

was based on a previous study by the authors about the prescription habits of pain clinicians in Spain.[22] The second stage involved a consensus development process in which consecutive rounds were carried out to narrow down the number of items and agree on their final wording (Figure 1). The final version had 40 statements grouped into 6 sections (antiepileptics, antidepressants and antipsychotics, anesthetics, topical preparations, cannabinoids, and other agents) that were defined by affinity criteria and groups according to classical drug classifications.[30] To make the survey easier to follow, create, and complete, the study coordinators divided the survey into the smallest number of possible sections. Statements that belonged to one of the classic drug classifications were grouped. For the statements that did not fit or could not be grouped, some kind of affinity was performed to match them. Antipsychotics and antidepressants were gathered together. Statements for ketamine and lidocaine were grouped by affinity, under the "anesthetics" title, with sevoflurane and propofol. Otherwise, the survey would have had several more sections, resulting in a greater possibility of unfinished questionnaires.

Participants

Experts on neuropathic pain research and management were identified through a database run by the SED NP Task Force of pain clinic specialists. They were selected based on their clinical (interests, experience, workloads, etc.) rather than academic (h-index, volume of citations, etc.) expertise. They were approached by email with an invitation to participate. It was planned to involve about 50 members. In total, 103 candidates were contacted, of whom 50 agreed to participate. A set of scientific evidence collated beforehand by the study coordinators was circulated among them at least 4 weeks before the start of the Delphi process. This set included full texts of relevant articles, monographs obtained upon request to pharmaceutical companies, and extracts of published literature and results of preclinical and clinical studies prepared specifically for the present research. The panelists used the available evidence and their own clinical expertise to answer the survey.

Statistical analysis

Means, medians, interquartile ranges as well as absolute and relative frequencies were calculated for the scores of each individual item after the first round. These statistics were provided, together with the individual item ratings, to all panelists before the second round. The same descriptive statistics were calculated after the second round to generate the results.

RESULTS

In total, 43 and 37 panelists participated in the first and second rounds, respectively. The drop in participation is attributed to panel attrition between the two rounds. In the first round, panelists only agreed on 22 out of 40 statements (55.0%). The sections on antidepressants and antipsychotics, intravenous lidocaine and naltrexone, and topical preparations were the most controversial (Figure S1). However, the level of agreement was much higher in the second round, expanding to 34 out of 40 statements (85.0%, Table 1). Nonetheless, the topical preparations remained contentious; 3 out of 6 unsupported statements belonged to this section (Figure S2). The consensus was always on accepting statements; none was rejected unanimously (Figure 2, Figures S1 and S2).

Antiepileptics

Survey items focused on drugs such as carbamazepine, oxcarbazepine, eslicarbazepine, and lacosamide, which are either listed as last-line choices or disregarded by clinical guidelines. There was agreement that oxcarbazepine may still be useful when carbamazepine fails for uncontrolled pain, and particularly for trigeminal neuralgia, yet its hyponatremic potential should be scrutinized. Moreover, despite the evidence available so far being limited, panelists agreed that eslicarbazepine may still be used, and possibly better tolerated, in these situations (Figure 2A, items 1 to 3). Although the evidence is inconclusive, lacosamide at intermediate doses was also deemed as an additional resource when other drugs fail (Figure 2A, items 4 to 6). In contrast, the use of levetiracetam was discouraged (Figure 2A, item 7). Agreement on antiepileptic drugs was clear; consensus was reached in the first round for all statements except for levetiracetam.

Antidepressants and antipsychotics

The survey included few questions regarding these drugs and all focused on the serotonin-norepinephrine reuptake inhibitors duloxetine, venlafaxine, and desvenlafaxine. Panelists agreed that duloxetine is useful in treating diabetic neuropathy, but they also endorsed it for chemotherapy-induced peripheral neuropathy. Consensus was also reached that venlafaxine has proven to be effective in some NP conditions, in particular diabetic neuropathy, and other polyneuropathies, so that it may be used when there is no response to listed treatments (Figure 2B, items 9 and 10). Conversely, the opinions were almost evenly divided about desvenlafaxine, with one half opposing the other on whether there is enough evidence to support its use in NP (Figure 2B,

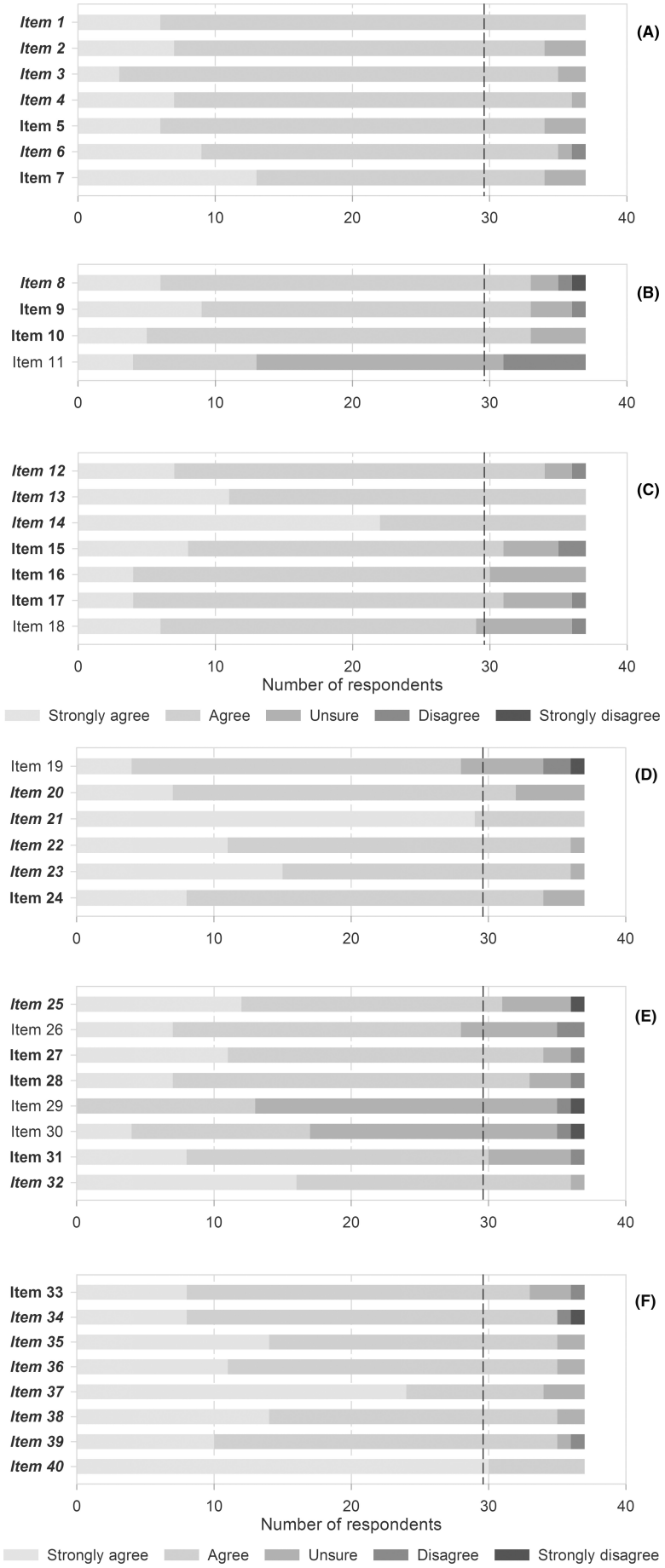

FIGURE 2 Agreement after 2 rounds with items about off-label use of drugs for NP. (A) Antiepileptics, (B) Antidepressants and antipsychotics, (C) Anesthetics, (D) Topical preparations, (E) Cannabinoids, (F) Other agents. See Table 1 for a description of the items. Italics and bold letters indicate the items (statements) for which consensus was reached in the first and second rounds, respectively. NP, Neuropathic pain. The vertical black dashed line indicates the predefined threshold to recognize consensus on accepting the statements (>80% of respondents). There was no consensus to reject any item.

item 11). Consensus on these statements was moderate; it was only reached after the second round for duloxetine and venlafaxine and was not attained for desvenlafaxine. Nearly all panelists agreed, already from the first round, that atypical antipsychotics are unhelpful for NP (Figure 2B, item 8).

Anesthetics

There was considerable agreement that intravenous lidocaine is a suitable treatment for several peripheral and central NP conditions (particularly those related to diabetes, trauma, and cerebrovascular disease) that do not respond to more conventional therapies. All panelists also agreed that doses should be discrete and low (below 3 mg/kg) but repeated to maintain efficacy (Figure 2C, items 12 to 14). Though in the second round, they also agreed that adding magnesium to the infusion could boost the analgesic effect when there is insufficient response to lidocaine alone (Figure 2C, item 15).

There was consensus that propofol has antinociceptive and antihyperalgesic effects by acting on angiotensin type 2 receptors (Figure 2C, item 16) already from the first round. Consensus was also wide on the analgesic properties of ketamine through varied mechanisms of action that are in turn linked to noteworthy side effects such as psychiatric symptoms, hypertension, and hepatotoxicity. Hepatic function and psychiatric antecedents and symptoms should be assessed and monitored during ketamine treatment of NP (Figure 2C, items 17 and 18). Sevoflurane can alleviate pain associated with chronic venous ulcers and could be further evaluated in other NP conditions in the experts' view (Figure 2C, item 19).

Topical preparations

There was consensus that capsaicin patches could be used to treat phantom limb pain given its relationship with stump pain or hypersensitivity (Figure 2D, item 20), and that they are safe (for any peripheral NP condition) for long-term use (over 3 years, Figure 2D, item 27), and in children (Figure 2D, item 26). In the second round, panelists also agreed that, although sparse, there is evidence supporting the use of capsaicin patches for trigeminal neuralgia (Figure 2D, item 23) but not for radiculopathies (Figure 2D, item 22).

This section concentrated most of the disputed items, as consensus was not reached in three out of eight items. These referred to the lack of comparative studies between lidocaine plasters and capsaicin patches or their association (Figure 2D, item 21), the lack of evidence about the effects of topical phenytoin and iontophoretic delivery of lidocaine and capsaicin (Figure 2D, items 24 and 25), and the existence of some evidence about the antalgic properties of gallium maltolate (Figure 2D, item 24).

Cannabinoids

Consensus was easily achieved in all statements (Figure 2E). The wording was in general cautious yet allowing that cannabinoids may have some role in the treatment of NP. Panelists agreed that these drugs should be used with caution as second- or third-line therapies (item 30), that modest pain reductions should be expected so they should probably be combined with other analgesics (item 29), that the vaporized form is preferred (item 32), and that the best analgesic effect is achieved with the combination of low tetrahydrocannabinol and high cannabidiol doses despite there still being no studies of any pharmaceutical product with this combination (item 31). There was also consensus that there has been a somewhat positive experience with the single cannabinoid medicinal product currently licensed in Spain in some NP conditions, including diabetic neuropathies, peripheral neural lesions, plexus avulsion, and multiple sclerosis pain (item 33). Lastly, it was agreed that short-term side effects are in general well tolerated, the acute effects on memory being the most relevant (item 34), and that long-term effects and addiction potential are, on the other hand, still largely unknown (item 34). Also, cannabinoids should not be used in pregnant women, patients under 25 years of age, those with a history of psychosis or substance abuse, or current cardiovascular or respiratory diseases (item 35). The consensus that preclinical evidence supports the use of cannabinoids for NP (item 28) was not reached until the second round.

Other agents

In the second round, there was agreement that blocking of toll-like receptors 4 (TLR4) by low-dose naltrexone may be a safe and valid choice for refractory patients. Consensus was nearly reached that the dose should be about 4 mg/day (Figure 2F, items 36 to 38). On the other hand, panelists found that the evidence to pursue

the development of amantadine for NP is insufficient (Figure 2F, item 40). In contrast, there was no consensus that clinical guidelines do not recommend NMDA antagonists due to insufficient evidence (Figure 2F, item 39).

DISCUSSION

The present Delphi study combined the available evidence with the most recently informed experts' opinion based on their understanding and own clinical experience to provide a critical appraisal of pharmacotherapeutic alternatives for NP beyond first- and second-line therapies regarded by current clinical guidelines. The results support the use of off-label drug treatments within certain limits and respecting some criteria. Some emergent themes that may have immediate clinical implications concern the use of non-gabapentinoid antiepileptics, the antidepressant venlafaxine, intravenous lidocaine, and a certain combination of cannabinoids (Table 2). In addition, promising preliminary results justify further research on lacosamide, low-dose naltrexone, propofol, ketamine, and topical sevoflurane or high-concentration capsaicin (Table 2). Until the repertoire of clinical guidelines can be expanded with new evidence or drugs, our results might provide some guidance to treating physicians who feel off-label therapeutic attempts would help in any of the numerous troublesome NP cases.

TABLE 2 Key research points

(A) Implications for routine clinical practice
a. Therapeutic trials with the non-gabapentinoid antiepileptics oxcarbazepine and eslicarbazepine (particularly for trigeminal neuralgia) or the antidepressants venlafaxine (for diabetic neuropathy and other neuropathies) and duloxetine (for chemotherapy-induced peripheral neuropathy) as second- or third-line options are warranted, as they may relieve some unresponsive patients
a. Repeated, short intravenous lidocaine infusions may benefit some patients with NP related to diabetes, trauma, or cerebrovascular disease, provided that the times and doses can be personalized for the individual patient
a. Modest improvements could be achieved with an authorized vaporized combination of low-dose tetrahydrocannabinol and high-dose cannabidiol in patients with varied NP conditions, such as diabetic neuropathies, peripheral neural lesions, plexus avulsion or multiple sclerosis, who can be reliably monitored and followed-up
(B) Implications for future clinical research
a. Lacosamide, low-dose naltrexone, propofol, and ketamine have peculiar mechanisms of action that may represent new therapeutic avenues that deserve further study
a. Positive results could be expected in future studies of topical sevoflurane to alleviate chronic venous ulcer pain and high-concentration capsaicin patches for phantom limb pain and complex regional pain syndromes

Antiepileptic drugs have various effects at excitatory and inhibitory synapses that may reduce NP generation and transmission, for example by decreasing sodium and calcium influx, enhancing gamma aminobutyric acid release and effect, or diminishing glutamate transmission.[31] Gabapentinoids selectively bind to presynaptic voltage-gated calcium channels inhibiting the release of excitatory neurotransmitters and are included as first-line treatment for some NP indications in most clinical guidelines, particularly post herpetic neuralgia and peripheral diabetic neuropathy.[32] However, their growing use is surrounded by both efficacy and safety concerns,[15,33,34] and alternatives are being sought. Despite the traditional evidence that oxcarbazepine, among other antiepileptics, has little or no efficacy for NP,[35] there was agreement that it should still be considered, together with eslicarbazepine, as a potential resource in difficult situations. The potential of lacosamide for NP attracted attention shortly after being launched, but it soon fell out of favor.[36] Nevertheless, the idea of a modest efficacy was never abandoned,[12,35] and there is now a renewed interest in it. The reasons include its distinct mechanism of action over sodium channels and its potential to revert some molecular changes associated with states of chronic pain.[37] In general, the view of the panelists is that antiepileptics other than gabapentinoids can achieve good results in some patients and thus deserve therapeutic trials. Otherwise, extensive phenotypic typing, that is not available in the everyday clinical practice, would be required.[16]

Duloxetine has been especially recommended and is in fact approved for the treatment of diabetic neuropathy.[38] However, there is evidence that it may also improve chemotherapy-induced peripheral neuropathy.[39–41] The latter fact, which panelists have endorsed, is of clinical relevance given the lack of effective alternatives for this condition.[40,41] Venlafaxine has shown activity against some NP conditions, but was found to be insufficient to be acknowledged by the clinical guidelines.[42] Notwithstanding, a more recent review uncovered more studies showing superiority over placebo and suggested that despite the fact that venlafaxine did not perform better than other active medications, it may benefit some patients who have not responded to them.[43] Although the published evidence on desvenlafaxine for NP is actually small, a considerable portion of panelists did not concur. This opinion might have been influenced by a Spanish review that highlighted some potential benefits.[44] Tricyclic antidepressants were not included in this survey because they are already authorized for the treatment of NP.

There was an almost immediate agreement that atypical antipsychotics have no role in NP. Apart from a single review and the references cited therein that show some promising results with olanzapine,[45] there is virtually no data to this respect in the literature.

There are reports on the safety and efficacy of repeated intravenous lidocaine 3–5 mg/kg 30-minute

infusions in reducing pain intensity in certain NP conditions,[46–48] but they have been played down as they were neither long-lasting nor followed by meaningful functional improvements.[46,49] Notwithstanding, the panelists noted that analgesic efficacy could be maintained if repeatedly dosed at small amounts. This opinion together with further directions suggested by recent reviews[49] should stimulate future trials about indications, timing, infusion periods, and magnesium supplementation to establish the role of intravenous lidocaine in NP.

The potential of low-dose naltrexone to treat NP relates to the modulatory glial effects delivered through blockade of TLR4.[50] The TLR4 can be over-expressed in NP and bind endogenous molecules released by injured tissues to induce a proinflammatory response.[51] There are promising pre-clinical and preliminary clinical evidences suggesting that it is a valuable treatment for NP that does not respond to other medications.[52] Thus, more clinical research on this topic seems to be justified.

The antinociceptive and neuroprotective effects of anesthetics are an emerging area of anesthesiology. Propofol can decrease the in vitro expression of the dorsal root ganglion neurons type 2 angiotensin receptors (AT2)[53] that have been identified as novel therapeutic targets for peripheral NP.[54] A selective AT2 inhibitor reduced pain intensity in patients with diabetic neuropathy or post-herpetic neuralgia, although amid safety concerns.[55] Propofol may thus be a safest alternative in this new therapeutic avenue, which the survey panelists acknowledged. They also agreed that ketamine is another anesthetic with therapeutic potential for NP. In a systematic review of NMDA antagonists for treatment of NP, ketamine was the drug with the highest number of positive studies, but the authors noted that more insight is necessary on the clinical use of these drugs for NP.[56] It has also been effective in a number of non-randomized studies, and seems to be best suited when central sensitization mechanisms are predominant or for patients with opioid-related issues.[57] Dosing schemes should be further investigated.[57] Although the evidence on the benefits of both sevoflurane and amantadine for the treatment of NP is very limited,[56,58] the panelists deemed that the former, but not the latter, deserves further research. This divergent criterion might relate to the reverse item formulation: the statement on sevoflurane was "positive" while that on amantadine was "negative" (Table 1), impelling panelists to agree to opposite declarations (acquiescence bias).[59]

Topical agents are typically considered second-line therapies for some peripheral NP conditions,[60] particularly post-herpetic neuralgia, diabetic neuropathy, HIV neuropathy, and post-traumatic/surgical pain.[61–63] However, despite there being only anecdotal evidence in other NP conditions, the experts agreed that capsaicin patches can also be used for post-amputation pain regardless of whether it is phantom limb or stump pain, as they are related and often mixed up,[64,65] for facial trigeminal pain,[66–69] as well as for complex regional pain syndrome in children.[70] In contrast, even when there is also some favorable evidence,[71] they endorsed the statement that capsaicin patches should not be used for radiculopathies. As mentioned, the negative formulation of the latter item might have predisposed panelists' opinions. There was also unanimous agreement that their clinical experience supports the long-term safety of these patches despite the lack of published evidence on this aspect and the concern for potential toxic effects on epidermal nerve fibers.[12]

Consensus was not possible in three statements, suggesting that topical analgesia for NP is a contentious area. Panelists disagreed that there is no evidence (meaning some considered there is) on the relative merits of capsaicin patches compared to lidocaine dressings, their iontophoretic delivery, or the effects of topical phenytoin. However, to our knowledge, there is only one head-to-head published comparison between topical lidocaine and capsaicin that was released even after this survey took place,[72] and a few recent reports on topical phenytoin by a single group of investigators.[73–76] Some data are available on lidocaine iontophoresis, but not with the patch galenic form, for which there is only a handful of preclinical experiments.[77]

The legalization of cannabis for medicinal use has attracted considerable attention in recent years because of their potential for treating chronic pain conditions. However, the reviews of the available literature on the issue have come to partially divergent conclusions.[78] In general, the evidence suggests that cannabis-based medicines may be reasonably considered for chronic NP.[79] However, there are outstanding issues that need further elucidation, for instance which active ingredients to use and in what proportion, and the best dosing strategies or suited NP conditions.[80] The European Pain Federation has published a position paper that shed some light on this,[79] with which the panelists agreed on four points: (1) that these medicines have established beneficial yet modest effects, (2) that they should be considered as third-line therapy, (3) that the burden of side-effects is favorable provided that appropriate cautions and surveillance are adopted, and (4) that they have some contraindications. Indeed, this study provided some guidance on other issues. Particularly, the most suitable combination is that of low-dose tetrahydrocannabinol and high-dose cannabidiol, and also that vaporized delivery is the preferred mode of administration. Recent evidence published after the present survey was completed[81] does not challenge these views.

The spectrum of off-label alternatives evaluated was limited by the number and content of the statements included in the survey. Although the construction process of the questionnaire was inclusive and based on the interventions commonly used by panelists to treat NP, item reduction steps might have undermined dissenting opinions if they tended to be ignored for the sake of reaching

a consensus.[82] This structural bias may also affect the Delphi consensus process itself, since the feedback between rounds could encourage panelists to agree with choices that have a favored majority. Nevertheless, some methodological strengths safeguard the integrity of this research, including the pre-definition of objectives, consensus criteria, and number of rounds, or the inability to modify, drop, add or combine items between rounds by either the study coordinators or panelists.[83] The survey had both, positive (declarations about the existence of evidence) and negative (about the absence of evidence) statements. Thus, it is possible that panelists' responses have been influenced by prior views of the coordinators who prepared the questionnaire because of the aforementioned acquiescence bias.[59] Neither the questionnaire nor the results were subjected to external validation, which might impair the study representativeness. The limited literature on off-label pharmacotherapies for NP makes it hard to derive convincing conclusions even after experts have arrived at a wide consensus. Salient topics might be used to guide some clinical decisions and future research about promising alternatives.

CONCLUSIONS

Using a Delphi technique and a review, we have found that when there is no adequate response to approved pharmacotherapies for the management of NP, some alternatives remain before resorting to interventional therapies. Some may be readily applicable to clinical practice while others should first undergo further research. The former includes replacing or augmenting therapies with oxcarbazepine, eslicarbazepine, venlafaxine, intravenous lidocaine – after some trial and appraisal – or, under adequate surveillance, a particular combination of tetrahydrocannabinol and cannabidiol. Among the latter, lacosamide, low-dose naltrexone, propofol, and ketamine are potential new treatments that deserve more scrutiny. This information may help reluctant patients or in case of contraindications for invasive interventions. The authors do not intend to replace current therapeutic guidelines, deem that off-label drug use should be contained and acknowledge that the management of NP often requires a comprehensive multidisciplinary therapeutic approach.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

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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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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