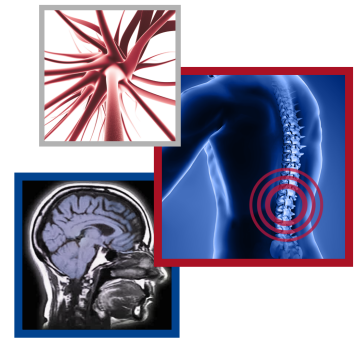
Perspective

Pain Management



The relevance of real-world data for the evaluation of neuropathic pain treatments

Ralf Baron*,[1], Gérard Mick[2,3] & Mick Serpell[4]

[1]Division of Neurological Pain Research & Therapy, Department of Neurology, Christian-Albrechts University, Kiel, Germany
[2]Pain Center, Voiron Hospital, CHU Grenoble Alpes, Grenoble, France
[3]Health, System, Process (P2S) Research Unit 4129, University of Lyon, Claude Bernard Lyon I, Lyon, France
[4]Department of Anaesthesia, University of Glasgow, Glasgow, Scotland
*Author for correspondence: r.baron@neurologie.uni-kiel.de

Practice points

- Systematic data collection in clinical practice will enable the analysis of real-world data across practices and avoid data manipulation.
- Real-word evidence can benefit both prescribers and patients by providing additional elements for the benefit-risk assessment of neuropathic pain treatments used in clinical practice.

Treatment of neuropathic pain (NP) is challenging. Interest in real-world evidence (RWE) for benefit-risk assessments of NP treatments increases given the paucity of drugs showing efficacy in randomized controlled trials and restricted labels of available medicines. To provide further context, a literature review regarding regulatory use of RWE and a clinical trial registry search for randomized controlled trials over the last 10 years was carried out. Taken together, and especially for available NP treatments, there is increasing support to consider RWE when evaluating their benefit-risk profile. Examples are provided in which RWE could be used effectively for updating the product label and informing treatment recommendations. Collected and analyzed according to state-of-the-art standards, RWE can inform treatment recommendations and product label decisions.

Plain language summary: Neuropathic pain (NP) is caused by damage to the sensory part of the nervous system and is often described as burning, throbbing or shooting pain. This condition is difficult to treat and may become chronic. Before a new treatment can be approved for use, its effectiveness and safety must be shown in controlled clinical trials. Such trials are difficult to conduct in NP and often fail. Therefore, there is increasing support for the use of real-world data (routinely collected data from e.g., patient registries, electronic medical records, health insurance claims databases) to evaluate the benefits and risks of treatments. This article presents the views of three pain specialists about the value of real-word evidence in general and specifically for the evaluation of pharmacological treatments of NP.

First draft submitted: 7 July 2022; Accepted for publication: 12 August 2022; Published online: 15 September 2022

Keywords: benefit-risk assessment • labeling guidelines • neuropathic pain • real-world evidence • treatment guidelines

Neuropathic pain (NP) is caused by a lesion or disease of the somatosensory peripheral or central nervous system [1]. Examples include postherpetic neuralgia, painful polyneuropathies, poststroke pain and others. Pain might be spontaneous (burning, throbbing and shooting pain) and/or evoked by noxious or non-noxious stimuli (allodynia and hyperalgesia) [2]. The population prevalence of chronic NP ranges between 6.9 and 10% [3]; the condition is now recognized as a separate entity in the International Classification of Diseases (ICD)-11 [4]. NP treatment is symptomatic and remains challenging, as pain is often not sufficiently relieved [5,6].

As is the case for pharmacological treatments of other conditions, traditionally, randomized controlled clinical trials (RCTs) are considered the gold standard to evaluate the benefit-risk of a new treatment for NP as they represent what is typically considered the highest level of evidence. When treatment guidelines are being developed,

Future Medicine

the level of qualifying evidence is taken into consideration for the development of final recommendations and not surprisingly, NP treatment recommendations are mostly based on the results of RCTs [7]. The international NeuPSIG guidelines for example recommend tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, and the antiepileptics pregabalin and gabapentin as first-line pharmacological treatment; second-line choices include the topical treatments with lidocaine 700 mg medicated plaster and high concentration capsaicin 179 mg (8% w/w) patch as well as tramadol [6]. However, over time, it has become increasingly difficult to show efficacy of pharmaceutical NP treatments in RCTs in NP indications [8]. We conducted two clinical trial register searches to examine if this observation stands when evaluating RCTs designed to study the efficacy of pharmaceutical treatments in NP indications and initiated over the last 10 years. The clinical trial register EudraCT was searched with the terms 'neuropathic pain', 'adult', 'Phase II and III' and 'start date 1 January 2012–21 February 2022' which resulted in 104 trials. This database was then searched for placebo-controlled RCTs (Supplementary Table 1). Of the 64 trials included, 21 are ongoing, two are UK trials (results no longer available), 13 were terminated/not initiated and 28 were completed. Only three of the completed trials reported meeting the primary efficacy end point. Searching the clinical trial register ClinicalTrials.gov using the same search terms and additionally 'older adult' and 'interventional' resulted in 183 trials which included 123 placebo-controlled RCTs (Supplementary Table 2). A total of 50 trials were completed, 21 terminated/withdrawn, 14 with unknown status and 38 active/recruiting/not yet recruiting. Table 1 lists the completed trials with primary outcome measure 'efficacy'. Four trials had a statistically significant result for the primary end point, in two trials, a statistically significant result for the primary end point was demonstrated in a subgroup of patients. Of the ten trials including pregabalin as a trial medication, two were terminated, two with unknown status, two recruiting/not yet recruiting and four were completed. One of the completed trials did not provide a statistical analysis, one was a feasibility trial and results were reported for the other two: one met the primary efficacy end point, the other did not. The results of trials as published in the registries may lead to an update of treatment guidelines and a change in the position of some drugs to first or second line as has previously occurred in France [9].

Although RCTs are regarded as the best available standard of evidence for treatment efficacy [21], the strictly standardized trial conditions (e.g., trial duration, use of pain intensity as primary outcome measure), narrowly defined patient populations resultant from strict inclusion and exclusion criteria and occasionally used surrogate trial end points do not allow the results to be generalized for the entire patient population and patient relevant clinical outcomes in a real-life practice setting [22]. Although not yet apparent for pain treatments, the nature of medications is evolving from mainly chemicals (with generally the same pharmacological target of drug action and drug–target interaction in large patient populations) to other medication types such as biologicals and cell, gene and tissue therapies (with drug-target heterogeneity, personalized medication) [23]. "*Relying (almost exclusively) on RCTs will not allow for translating the current pace of progress in the life sciences into new and better treatments for patients*" [24] and "*the RCT will need to be complemented by other methodologies to address research questions where a traditional RCT may be unfeasible or unethical*" [25]. Additionally, it is increasingly recognized that clinical practice may have evolved after initial registration of a product and no longer patented products may be used in indications that are not authorized. Therefore, the EMA has embarked on the Safe and Timely Access to Medicines of Patients initiative that supports not-for-profit organizations and academia to gather or generate sufficient evidence on the use of an established medicine in a new indication with the intent to have this new use formally authorized by a regulatory authority [26].

There has been increasing recognition of the role of real-world data (RWD) and real-world evidence (RWE) in supporting controlled assessments of the benefit-risk of available treatments. All aspects of development and use of pharmaceuticals are expected to be made more effective and efficient with the judicious use of RWD [24]. Sound methods of combining randomized and nonrandomized data not only for the assessment of safety of a treatment but also of efficacy and relative effectiveness need thus to be explored [23].

The present article presents the views of the authors regarding the value of RWE in general and specifically for the evaluation of established pharmacological treatments of NP. Following a virtual meeting held on 22 November 2021, discussions continued during the development of the manuscript and the finally adopted consensus is presented here.

Definition of RWD & RWE

Definitions of the terms RWD and RWE are still evolving. The meeting referred to the definitions published in the glossary of the European Union Innovative Medicines Initiative Get Real project; a different wording is used by the

Table 1. ClinicalTrial.gov search results – completed trials with primary outcome measure 'efficacy' (n = 49).

Trial	Primary end point	Placebo	Drug			Ref.
Trials with a statistically significant result for the primary end point (n = 4)						
NCT01536314 Preventing the development of NP postmastectomy/tumorectomy by pre-emptive or postoperative memantine administration	Pain intensity at 3 months postmastectomy (NRS 0–10) Mean ± SD	n = 20 1.3 ± 1.8	Memantine (5–20 mg/day) n = 20 0.2 ± 0.4 p = 0.017; effect size 0.76 (95% CI: 0.12, 1.4)			[10]
NCT01555983 The effect of vaporized cannabis on NP in spinal cord injury	Number of participants achieving a reduction of pain intensity of ≥30% (cross-over design, n = 42) Number needed to treat to achieve 30% pain reduction during an 8 h period vs placebo	Placebo THC	Cannabis THC 2.9% 4 (95% CI: 2.1, 5.3) p < 0.05	Cannabis THC 6.7% 3 (95% CI: 1.6, 4.2) p < 0.05		
NCT01869569 Effect of pregabalin in patients with radiotherapy related NP: a randomized, double-blind, placebo-controlled trial	Pain reduction from baseline to week 16 (NRS 0–10) Mean ± SD	n = 64 1.58 ± 1.25	Pregabalin n = 64 2.44 ± 1.52 Adjusted difference 0.87 (95% CI: 0.3, 1.44); p = 0.003			[11]
NCT02763592 Impact of 5% lidocaine medicated plaster on allodynic symptoms of localized NP after knee surgery	Time to response to treatment defined as a 30% reduction in dynamic brush-induced mechanical allodynia on the localized pain area during the chronological period extending from inclusion to 3 months	n = 12	5% lidocaine medicated plaster n = 24 p = 0.001			[12]
Trials with a statistically significant result for the primary end point in a subgroup of patients (n = 2)						
NCT01726413 A Phase II, 4-week randomized, double-blind, parallel group, placebo controlled proof of concept study to evaluate efficacy, safety and tolerability of GRC 17536 in patients with painful diabetic peripheral neuropathy	Change from baseline in mean 24 h average pain intensity at the end of dosing (week 4; NRS 0–10)	Subgroup of patients with preserved small nerve fiber function with moderate to severe pain at baseline n = 35	ISC 17536 n = 30 LS mean difference (ISC 17536 minus placebo) of -0.96 (95% CI: -1.68, -0.24); p < 0.05			[13]
NCT02318706 An Asian, Phase III, multicenter, randomized, double-blind, placebo-controlled 14-week study of DS-5565 in patients with diabetic peripheral NP followed by a 52-week open-label extension	Change in the average daily pain score from baseline to week 14 (VAS 0–10) Mean ± SD	n = 330 -1.37 ± 1.6	DS-5565 15 mg daily n = 164 -1.34 ± 1.74 p = 0.8773	DS-5565 10 mg bid n = 165 -1.47 ± 1.69 p = 0.3494	DS-5565 15 mg bid n = 165 -1.88 ± 1.88 p = 0.0027	[14]
Trials not showing a statistically significant result for the primary end point (including one proof-of-concept trial; n = 13)						
NCT01540630 A Phase IIa placebo-controlled, double-blind randomized withdrawal study to evaluate the safety and efficacy of CNV1014802 in patients with trigeminal neuralgia	Number of patients classified as treatment failure	n = 14 9 (64%)	BIIB074 n = 15 5 (33%); p = 0.0974			[15]
NCT01701362 A randomized double blind placebo controlled parallel group study of the efficacy and safety of pregabalin (bid) in subjects with post-traumatic peripheral NP	Change from baseline to week 15 in weekly mean pain scores (NRS 0–10)	n = 267	Pregabalin n = 275 Difference pregabalin vs placebo -0.22 (95% CI: -0.54, 0.1); p = 0.1823			[16]

Results are available for 19 trials; for 29 trials, results or statistical analyses were not reported; there was one feasibility trial.
LS: Least squares; NP: Neuropathic pain; NRS: Numerical rating scale; SD: Standard deviation; SE: Standard error; THC: Tetrahydrocannabinol; VAS: Visual analogue scale.

Table 1. ClinicalTrial.gov search results – completed trials with primary outcome measure 'efficacy' (n = 49) (cont.).

Trial	Primary end point	Placebo	Drug		Ref.
NCT01748695 A Phase IIa, randomized, double-blind, placebo-controlled, two-period cross-over study evaluating the safety, tolerability and efficacy of V158866 in central NP following spinal cord injury	Pain intensity after 4 weeks (NRS 0–10) (cross-over design) Mean ± SD	n = 25 5.93 ± 0.148	V158866 n = 25 5.89 ± 0.148; p = 0.834		
NCT01752322 Efficacy and safety of lidocaine 5% medicated plaster in localized chronic postoperative NP	Change from baseline in 24 h average pain intensity at week 12 (NRS 0–10) LS mean (SE) LS mean difference (SE)	n = 180 -1.47 (0.16)	Lidocaine 700 mg medicated plaster n = 179 -1.7 (0.16) -0.23 (0.23); one-sided p = 0.1533		[17]
NCT01928849 Regional anesthesia and valproate sodium for the prevention of chronic postamputation pain	Number of patients with chronic postamputation pain (S-LANSS) after 3 months or time of final adjudication assessment, up to 6 months	n = 52 37 (71.2%)	Valproic acid n = 55 36 (65.5%); p = 0.53		
NCT02065349 A Phase IIa enriched enrollment randomized withdrawal study to assess analgesic efficacy and safety of ASP8477 in subjects with peripheral NP	Change in mean of 24 h average pain intensity (NRS 0–10) Mean ± SD	n = 33 -0.11 ± 1.01	ASP8477 (40/60 mg) n = 33 -0.13 ± 1.05; one-sided p = 0.644		
NCT02365636 A Phase II, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of topically applied TV-45070 (4% and 8% w/w ointment) in patients with postherpetic neuralgia	Change from baseline to week 4 in the weekly average of the daily average NRS (0–10) pain scores Mean ± SD LS mean difference to placebo	n = 100 -1.9 ± 1.67	TV-45070 4% n = 100 -1.64 ± 1.36 0.32 (95% CI: -0.094, 0.726); p = 0.13	TV-45070 8% n = 98 -1.71 ± 1.5 0.24 (95% CI: -0.167, 0.652); p = 0.245	
NCT02490436 A randomized, crossover, placebo-controlled, double-blind, single center, Phase II study of cetuximab in patients with treatment-refractory, nonmalignant severe chronic NP	Change in average NP score (NRS 0–10) Crossover design Mean Mean difference	n = 14 0.51 (90% CI: -0.41, 1.44)	Cetuximab infusion n = 14 1.73 (90% CI: 0.8, 2.66) 1.22 (90% CI: -0.1, 2.54); p = 0.126		[18]
NCT02935608 A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of BIIB074 in subjects with NP from lumbosacral radiculopathy	Change from baseline to week 12 in the weekly average of the daily NP score on the NRS 0–10 LS mean ± SE LS mean difference to placebo	n = 142 -1.75 ± 0.181	BIIB074 (200 mg bid) n = 139 -1.5 ± 0.177 0.25 (95% CI: -0.24, 0.74) p = 0.314	BIIB074 (350 mg bid) n = 142 -1.81 ± 0.176 -0.06 (95% CI: -0.55, 0.43) p = 0.797	
NCT02957851 Equimolar mixture of oxygen and nitrous oxide (EMONO) for the treatment of peripheral NP: a randomizes, international, multicenter, placebo-controlled, phenotype-stratified Phase IIa study	Change in average pain intensity between the 7-day baseline period and the first 7-day period after last administration of treatment (NRS 0–10) Mean ± SD Adjusted effect estimate	n = 118 -1.0 ± 1.5	N_2O/O_2 50–50% equimolar mixture (EMONO) n = 103 -0.8 ± 1.3 -0.22 (95% CI: -0.59, 0.15); p = 0.25		[19]

Results are available for 19 trials; for 29 trials, results or statistical analyses were not reported; there was one feasibility trial.
LS: Least squares; NP: Neuropathic pain; NRS: Numerical rating scale; SD: Standard deviation; SE: Standard error; THC: Tetrahydrocannabinol; VAS: Visual analogue scale.

Table 1. ClinicalTrial.gov search results – completed trials with primary outcome measure 'efficacy' (n = 49) (cont.).

Trial	Primary end point	Placebo	Drug			Ref.
NCT03202979 Efficacy and safety of low doses of trazodone in patients affected by painful diabetic neuropathy: randomized, controlled, pilot study	Change from baseline of the Brief Pain Inventory Short Form item 5 '24 h average pain score' to week 8	n = 48	Trazodone (10 mg tid) n = 43	Trazodone (20 mg tid) n = 50		[20]
	Mean	-2.5	-3.1	-2.6		
	Difference to placebo		p = 0.1179	p = 0.6272		
NCT03749642 Efficacy and safety of fixed-dose combination products containing trazodone and gabapentin in patients affected by painful diabetic neuropathy: randomized, controlled, dose-finding study	Change of the average daily pain score (NRS 0–10) from baseline to day 56	n = 80	Trazodone/gabapentin (2.5/25 mg tid) n = 39	Trazodone/gabapentin (5/25 mg tid) n = 38	Trazodone/gabapentin (10/100 mg tid) n = 37	
	Mean ± SD	-2.02 ± 1.95	-2.52 ± 2.31	-2.24 ± 1.96	-2.46 ± 2.12	
	Difference to placebo, point estimate		-0.5356 (95% CI: -1.274, 0.2026); p = 0.3729	-0.2005 (95% CI: -0.9401, 0.539); p = 0.9239	-0.288 (95% CI: -1.0342, 0.4582); p = 0.8135	
NCT03865953 A Phase IIa study of the efficacy and safety of oral LAT8881 in NP	Absolute change in mean pain score (NRS 0–10) from baseline to week 4; crossover design	n = 50	LAT8881 (30 mg bid) n = 50			
	Mean ± SD	-0.74 ± 2.09	-0.87 ± 1.53			
	Mean difference		-0.14 (95% CI: -0.76, 0.49); p = 0.67			

Results are available for 19 trials; for 29 trials, results or statistical analyses were not reported; there was one feasibility trial.
LS: Least squares; NP: Neuropathic pain; NRS: Numerical rating scale; SD: Standard deviation; SE: Standard error; THC: Tetrahydrocannabinol; VAS: Visual analogue scale.

US FDA [27]. The updated Innovative Medicines Initiative glossary [28] defines RWD as follows: "*An umbrella term for data regarding the effects of health interventions (e.g., safety, effectiveness and resource use) that are not collected in the context of highly controlled randomized controlled trials. Instead, RWD can either be primary research data collected in a manner which reflects how interventions would be used in routine clinical practice or secondary research data derived from routinely collected data. Data collected include, but are not limited to, clinical and economic outcomes, patient reported outcomes and health related quality of life. RWD can be obtained from many sources including patient registries, electronic medical records and claims databases*". RWE is then defined as "*the evidence derived from the analysis and/or synthesis of RWD*". This definition is very broad and may include all investigations with the exception of RCTs and their open-label extensions.

Current trends regarding the value of RWE

RWD have traditionally been collected primarily to evaluate the safety of medicinal products following market approval. In the last decade, calls to harness the wealth of RWD as supportive evidence to RCTs for drug development and regulatory decision making regarding the efficacy of medicinal products have increased. Reasons are the limited generalizability of RCTs to clinical practice conditions, the enormous costs and the mainly short-term duration associated with this trial design, the inability to obtain adequate patient numbers for trials in rare diseases or subgroups of patients and the introduction of personalized medicine. Moreover, even in the failed RCTs (i.e., those which do not meet their primary predefined end point), there is often an identifiable group of 'responders' who benefit from treatment but is not large enough to make the mean of the test group significantly positive [29,30]. Such responder analysis might help bridge the gap between RCTs and clinical practice where personalized medicine will be practiced [30].

Regulatory authorities such as the FDA and EMA have developed strategies to develop and adopt RWE and to integrate this evidence into the decision making process [31]. Two recent articles provide a summary of the current state of RWE recommendations [32] and an overview of the approaches to generate RWE for regulatory decisions about new or expanded medication indications [33]. In 2021, the EMA published guidance on registry-based studies to improve the use of patient registries as a source of RWE [34]. The organization also recently announced the set-up of a coordination center for the development and management of a network of real-world healthcare data sources across the EU and for the conduct of scientific studies [35]. There are already a number of approvals for new drug applications and line extensions which were supported by RWE [36,37]; as an example, in 2021, the FDA approved the liver transplant drug Prograf (tacrolimus) for an additional indication based on real-world effectiveness data [38].

The authors note a shift in the scientific community toward acceptance of RWE owing to the aforementioned limitations of RCTs but also because evidence-based medicine cannot always guide clinical practice efficiently as patients and the clinical environment are often much more complex than those observed in clinical trials. More specifically in the field of NP, a condition that is particularly difficult to treat, practitioners have used existing medications to develop treatment paradigms that may have led to varying practice guidelines even within one country or region with both evidence-based guidelines and RWE-based guidelines. The shift is likely linked to the lack of RCT applicability to the local practice situation, the need for data on patient reported outcomes, increased attention to interaction between patient and physician (fostered by e.g., health pathway for NP in France), or economic reasons. Additionally, the openness of the scientific community toward RWE can be linked to the absence of new innovative treatments over the last decade for the treatment of the inherently difficult to treat NP conditions. In Europe, all currently recommended oral pharmaceutical treatments are generic (the last one [pregabalin] became generic on 21 August 2019) implying that over the last 10 years no new drugs became available (patent protection in the EU is usually 8 years followed by 2 years of market exclusivity). Moreover, there is also little hope that new innovative oral treatments will become available soon as is illustrated by our search of clinical trial registries (ClinicalTrials.gov and EudraCT). This search resulted in the identification of >100 trials initiated in the last 10 years with only very few trials being reported as successful (i.e., meeting their primary end point). It is therefore not surprising that the scientific community is considering that innovation may also come from using existing knowledge of already available treatments. These treatments are already often repurposed in practice for use in other indications than the approved ones. Last but not least, the treatment armamentarium for NP for use in clinical practice has been limited by authorities through including stronger warnings (e.g., for opioids and gabapentinoids) and through updated treatment guidance (e.g., by not recommending pregabalin any longer [9]). This may also have left clinicians with a desire to further explore alternative treatment strategies based on clinical experience and RWE.

Regarding treatments for NP conditions, authorities have typically used RWE in support of the effectiveness of non-pharmacological treatments (e.g., repetitive transcranial magnetic stimulation), but have to our knowledge not been using RWE to support the granting of new indications for pharmaceutical products. On the contrary, for pharmaceutical treatments, RWE has been used to restrict the label or to impose additional controls (e.g., in the UK on 23 September 2020, stronger warnings about the risk of dependence and addiction have been added to the patient information leaflet of opioids and gabapentin and pregabalin have become Schedule 3 drugs in the UK on 1 April 2019).

Although it seems logical to trust RWE when it comes to making safety assessments to protect the public, similar considerations could be made in order to apply the use of RWE to discuss effectiveness, so that some treatments, particularly with positive benefit-risk ratios, may be made available to address unmet medical needs of the public. This principle seems to become more acceptable as regulatory frameworks are also being set up across the globe to enable such an approach [31].

The authors are of the opinion that this trend of increasing acceptability for RWE will continue; however, this may not replace the need for evidence from RCTs for the approval of new treatments.

Challenges when carrying out RCTs for the assessments of NP treatments

Besides the already mentioned limitations of RCTs, researchers of pain trials also have to cope with a high placebo response making it difficult to demonstrate superiority of the trial medication over placebo. For peripheral NP for example, a tendency has been noted for an increasing placebo response over time resulting in a smaller effect size of medications in placebo-controlled RCTs [8,39]. The reported effect of pain medications in RCTs has traditionally been calculated as the sum of the change from baseline in pain scores with the active minus the observed change with placebo. However, it can be questioned if the old assumption that the total treatment effect is the sum of its specific effect and of 'nonspecific', or 'placebo' effect holds or whether there may be interaction between the two [40]. Assuming a true treatment effect is higher than the difference between placebo and active treatment effects, RCTs may underestimate the true effect of the investigated medication.

The findings of three trials investigating three different medications for NP treatment underline the difficulties in distinguishing active treatment effects from placebo effects in RCTs [16,17,41]. The primary efficacy analysis in a post-traumatic peripheral NP trial showed no statistically significant difference between pregabalin and placebo in change from baseline to week 15 in mean weekly pain scores [16]. Among other factors, Markman *et al.* mention a slow and continuous increase of the placebo response, which was also previously observed in some NP RCTs [39]. The different response pattern for active treatment (faster response which then levels off) in their view possibly explains the nonsignificant treatment effect of pregabalin at end point. When investigating the efficacy of topical treatments, the nature of the device also needs to be taken into account. Insufficient patient blinding was a confounding factor in a chronic pain trial (62% of patients with predominantly NP) with the high concentration capsaicin 179 mg (8% w/w) patch [41]. A high proportion of patients identified their treatment allocation because of a higher incidence of local side effects with the active patch which might have confounded treatment response. In the case of the lidocaine 700 mg medicated plaster, the plaster itself provides mechanical protection of the sensitive skin areas which is also present when placebo plasters are used. The lack of statistical significance between the lidocaine plaster and placebo treatment arms in the primary end point in a postsurgical NP trial (change in 24 h average pain intensity from baseline at week 12) might be partly explained by this [17]. Additionally, other confounders in this trial may have impacted the placebo response such as time since surgery and use of concomitant medication [17].

The nocebo effect (i.e., worsening of symptoms in a subject receiving placebo treatment) also needs to be considered when evaluating RCTs. For example, it is well known that cholesterol lowering medications may cause muscle pains. When active treatment (cholesterol lowering tablet) was replaced with placebo (tablet) in patients experiencing these side effects in a crossover trial, muscle pains continued for most of them as if the active treatment was still being received, whereas muscle pain discontinued in a third study arm in patients who did not receive a tablet [42].

Value of RWE for the evaluation of benefit-risk assessments for NP treatment

As mentioned above, placebo-controlled RCTs may underestimate the efficacy of a medication in a real-world setting. In consequence, an active treatment might not be included in treatment guidelines solely based on RCT findings, whereas RWE would allow a complementary look at the effectiveness of the medication. RWE may also

be able to support patient selection for treatments by identifying subgroups that may respond better to treatment or subgroups with particular risks or removal of risks in the product label such as restrictions for patients with hepatic or renal impairment.

There are several approaches to collecting standardized RWD on pain treatments.

ICD coding is highly used in primary care. NP was, however, not adequately represented in the previous version (ICD-10). The new ICD-11 coding for chronic NP [4] will provide new opportunities to generate RWE data on pain medications once the specific codes are available in individual countries.

In the UK, the British Pain Society discussed the collection of a set of minimum RWD for all pain medications by practitioners and patients which should not be too time consuming. Although this project was never realized, a standard data collection for individual products was initiated. These standard outcome data are generally collected locally using paper-based questionnaires and are audited by the local authorities. An example is the local collection of RWD for the high concentration capsaicin 179 mg (8% w/w) patch to keep the medication on the formulary of the Greater Glasgow & Clyde NHS. Accessibility and analysis of paper-based questionnaires is, however, more difficult than electronic data collection.

The German Pain e-Registry, a national web-based pain treatment registry developed on behalf of the German Pain Association prospectively collects data from pain patients and their pain specialists for routine purposes via the online documentation service iDocLive®. This standardized program uses validated patient reported pain questionnaires for the assessment of treatment effectiveness, safety and quality of life.

In France, an e-health application called eDOL is being developed to collect data from chronic pain patients and healthcare professionals [43]. It is supported by more than 20 university pain centers. Data are collected on all types of pain treatment irrespective of the actual pain indication they are being used for. The project is led by the ANALGESIA Institute, supported by donations from various pharma companies and academic institutions and co-financed by the EU within the framework of the European Regional Development Fund. In 2021, the third version of the tool was tested in a clinical impact study.

Recent examples of the usefulness of RWE for the evaluation of benefit-risk of various NP treatments are data from a French study using the Quebec pain registry [44] and from a German study using the German Pain eRegistry [45]. Moisset *et al.* concluded that long-term use of strong opioids is a useful treatment only for a small proportion of patients compared with antidepressants, gabapentinoids or weak opioids and should be limited to selected and carefully monitored patients [44]. Überall *et al.* showed a significantly better response and tolerability of the topical lidocaine 700 mg medicated plaster compared with tricyclic antidepressants, antiepileptics and selective serotonin-norepinephrine reuptake inhibitors in patients with localized peripheral NP unsuccessfully treated with first-line oral medications [45].

Value of RWE for regulatory decision making on label changes

Considering label changes including change in indication for a medication with already well established indications, the value of RWE depends on the specific change requested. Regarding safety, current restrictions of the use of a treatment may be re-evaluated with RWE. These data might demonstrate a safe use in a subgroup of patients previously excluded from an RCT. For example, although not investigated (or excluded from RCTs), the high concentration capsaicin 179 mg (8% w/w) patch was prescribed in routine clinical practice for NP with a facial location. Based on RWD, it could be demonstrated that this use was safe if the right precautionary measures are taken. Since the patch is already approved for peripheral NP in the EU but excluding the face because of an *a priori* safety concern, it could be sufficient to provide data regarding the safe use of the product on the face to remove the current restriction.

The narrowly defined RCT trial populations often do not allow for the inclusion of patients with comorbidities such as renal or hepatic impairment, of specific subgroups such as children and adolescents, or of treatment posology. The design is also restricted by a usually short trial duration. Effectiveness and safety signals might thus be missed and might subsequently be picked up by RWE and maybe worth considering for updating the product label.

For the demonstration of effectiveness, the sole use of RWE for approval may depend on the situation. A line extension to an indication with similar symptomology to the approved indication (e.g., an extension for the lidocaine 700 mg medicated plaster from postherpetic neuralgia to painful diabetic peripheral neuropathy or postsurgical NP) might be feasible as the pain originator resides in the periphery, whereas the extension to an unrelated indication such as chronic low back pain might require an RCT.

Inclusion of RWE in practice guidelines

Many international guidelines for NP management were developed using an evidence-based approach, in other words, evaluation of RCT findings [7]. The NeuPSIG guidelines for pharmacotherapy, for example, used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) classification for RCT evaluation of NP treatment [6]. Given regional differences in standard of care, the relevance of international guidelines on a local level is arguable.

In France, using the GRADE classification, evidence generated by multiple RCTs will always lead to treatment recommendations labeled as strong [9]. If enough RCT data are lacking, expert opinion with a consensus based on additional RWE can lead to treatment recommendations labelled as weak. The German S2k guideline for the treatment of NP [46], a guideline of the German Neurological Society (DGN), also considers the GRADE system based NeuPSIG guidelines, but also considers other evidence. German physicians are often hesitant to follow evidence-based guidelines and have a tendency to turn to practice guidelines. RWE is often rated higher by practitioners because the evidence generated is more closely linked to clinical practice. Combining evidence from RCTs, RWE and expert opinion might be the way forward for NP guideline development in Germany. In the UK, the recommendations of the National Institute for Health and Care Excellence guideline [47] while helpful, do not recommend the full range of therapies that can be and are clinically offered. For example, lidocaine 5% medicated plasters are not recommended because the trial data available was not based on their minimum standard of double-blind RCT and so was not included in their appraisal. A pragmatic approach, in other words, RCTs, simulation of data plus experience may be a good path forward.

Even if RWE is included in an NP treatment evaluation, a positive guideline recommendation might be difficult to obtain in the presence of inconclusive RCTs. Placebo-controlled RCTs of topical treatments, for example, are difficult to evaluate, not least because of the mechanisms of action of the treatment as observed in a trial with the 700 mg lidocaine medicated plaster [17]. RWE alone might not be sufficient to overcome an inconclusive traditional assessment. Nevertheless, based on the increasing availability of systematically collected RWD and the availability of RWE, the principles for developing guidelines could be revisited.

Challenges

There are a number of challenges when using RWD to generate acceptable RWE [21]. Operational and technical challenges include issues such as data access and cost, privacy obligations, data sharing and data completeness and accuracy. The main methodological challenges for RWE studies are missing data, multiple confounders and biases regarding population and data selection and physicians' choices that may be driven by patients' characteristics (e.g., age, sex and presence of depression or sleep problems), contraindications (e.g., cardiac conduction block or postural hypotension for tricyclic antidepressants and substance use disorder for opioids), cost or healthcare provider coverage and lastly patient preference. All of these can be addressed by good methodological standards. Therefore, it is important when planning and implementing RWE studies to observe a systematic approach by defining a clear and answerable research question, by selecting a fit-for-purpose data source, choosing a state-of-the-art study design, establishing a database with transparent data processing, performing appropriate statistical analyses to control bias, and reporting results in accordance with established guidelines [48].

The authors note the following specific challenges when generating RWE for NP treatment. In contrast to the concept of RCTs where the patient population is usually based on symptoms fitting the mode of action of the drug under investigation, physicians prescribe specific medications in routine medical care based on personal experience and only to patients who they think will respond to the treatment. This may precondition a positive outcome and needs to be considered as bias, even if, however, it reflects real-life conditions. Physicians might also be biased for specific treatments because of an overall positive impression. The lidocaine 700 mg medicated plaster, for example, is generally very well perceived by both physicians and patients and patient satisfaction scores are high. It is, however, difficult to link this to a specific medication effect. Nevertheless, in France and Scotland, patient satisfaction is highly regarded as valuable in evaluating treatment in clinical practice.

It may also be difficult to generalize RWE as there are differences in pain therapy in different geographical regions. Examples are different formularies across the 13 Scottish health boards and the variations in treatment patterns for localized NP in primary care across four European countries [49]. Generalization might be feasible if data collection is transparent. Methodology needs to be clearly described to allow extrapolation to the local situation. The iDocLive database for example contains data entered by pain specialists. This implies that data collected in

this database may be from the third line of patient care. It is important to clearly state this when publishing results to allow healthcare professionals from earlier lines of treatment to properly interpret the data presented.

Conclusion

There is an increasing interest in RWE to evaluate the benefit-risk profile of an available treatment in general and for available NP treatments in particular. RWE – when collected and analyzed according to state-of-the-art standards – can inform treatment recommendations and product label decisions.

Future perspective

The use of RWD as supporting evidence for traditional benefit-risk assessments of available NP treatments requires new ways of systematically collecting and analyzing RWD in order to minimize bias inherently present in clinical practice. Formalization on how to best include RWE in treatment guidelines would be welcome as would implementation of new approaches for the regulatory decision making process so that product labels can optimally reflect how these treatments should be used in clinical practice.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/pmt-2022-0057

Author contributions

All authors critically revised for important intellectual content, approved the final manuscript version and agreed to the submission.

Financial & competing interest disclosures

R Baron declares grant/research support from EU projects 'Europain' (115007), DOLORisk (633491) and IMI Paincare (777500), from German Federal Ministry of Education and Research (BMBF): Verbundprojekt: Frühdetektion von Schmerzchronifizierung (NoChro) (13GW0338C), the German Research Network on Neuropathic Pain (01EM0903) and from Pfizer Pharma GmbH, Genzyme GmbH, Grünenthal GmbH, Mundipharma Research GmbH und Co. KG., Novartis Pharma GmbH, Alnylam Pharmaceuticals Inc., Zambon GmbH, and Sanofi-Aventis Deutschland GmbH. He reports speaker fees from Pfizer Pharma GmbH, Genzyme GmbH, Grünenthal GmbH, Mundipharma, Sanofi Pasteur, Medtronic Inc. Neuromodulation, Eisai Co. Ltd., Lilly GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, Astellas Pharma GmbH, Desitin Arzneimittel GmbH, Teva GmbH, Bayer-Schering, MSD GmbH, Seqirus Australia Pty. Ltd, Novartis Pharma GmbH, TAD Pharma GmbH, Grünenthal SA Portugal, Sanofi-Aventis Deutschland GmbH, Agentur Brigitte Süss, Grünenthal Pharma AG Schweiz, Grünenthal B.V. Niederlande, Evapharma, Takeda Pharmaceuticals International AG Schweiz, Ology Medical Education Netherlands, Ever Pharma GmbH, Amicus Therapeutics GmbH, Novo Nordisk Pharma GmbH, Nanobiotix SA France and Stada Mena DWC LLC Dubai. He declares consultancy work for: Pfizer Pharma GmbH, Genzyme GmbH, Grünenthal GmbH, Mundipharma Research GmbH und Co. KG, Allergan, Sanofi Pasteur, Medtronic, Eisai, Lilly GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, Astellas Pharma GmbH, Novartis Pharma GmbH, Bristol-Myers Squibb, Biogenidec, AstraZeneca GmbH, Merck, Abbvie, Daiichi Sankyo, Glenmark Pharmaceuticals S.A., Seqirus Australia Pty. Ltd., Teva Pharmaceuticals Europe Niederlande, Teva GmbH, Genentech, Mundipharma International Ltd. UK, Astellas Pharma Ltd. UK, Galapagos NV, Kyowa Kirin GmbH, Vertex Pharmaceuticals Inc., Biotest AG, Celgene GmbH, Desitin Arzneimittel GmbH, Regeneron Pharmaceuticals Inc. USA, Theranexus DSV CEA Frankreich, Abbott Products Operations AG Schweiz, Bayer AG, Grünenthal Pharma AG Schweiz, Mundipharma Research Ltd. UK, Akcea Therapeutics Germany GmbH, Asahi Kasei Pharma Corporation, AbbVie Deutschland GmbH & Co. KG, Air Liquide Sante International Frankreich, Alnylam Germany GmbH, Lateral Pharma Pty Ltd., Hexal AG, Angelini, Janssen, SIMR Biotech Pty Ltd. Australien, Confo Therapeutics N. V. Belgium, Merz Pharmaceuticals GmbH, Neumentum Inc., F. Hoffmann-La Roche Ltd. Switzerland and AlgoTherapeutix SAS France. In the past 3 years, G Mick has received honorarium for scientific expertise from Boiron, Grünenthal, Lilly, Novartis and UPSA. MG Serpell has received honoraria from Astellas, Grünenthal, NAPP and Pfizer for speaking at meetings. His institution has received research support in the past 5 years from HTA and CSO sponsored studies and commercial sponsored studies (Pfizer, Grünenthal, Lateral Pharma Pty Ltd.) The initial virtual meeting was organized and chaired by Grünenthal GmbH, Germany. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. The sponsor paid for writing and editorial assistance (provided by Elke Grosselindemann and Birgit Brett) and for journal fees associated with the publication of this article. Grünenthal was given the opportunity to review and comment on the manuscript; however, the authors take full responsibility for the content.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. IASP. Terminology. www.iasp-pain.org/resources/terminology/
2. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol.* 9, 807–819 (2010).
3. van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: a systematic review of epidemiological studies. *Pain* 155, 654–662 (2014).
4. Scholz J, Finnerup NB, Attal N *et al.* The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. *Pain* 160, 53–59 (2019).

•• **The new ICD-11 classification for chronic neuropathic pain (NP).**

5. Dworkin RH, O'Connor AB, Backonja M *et al.* Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 132, 237–251 (2007).
6. Finnerup NB, Attal N, Haroutounian S *et al.* Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol.* 14, 162–173 (2015).
7. Deng Y, Luo L, Hu Y, Fang K, Liu J. Clinical practice guidelines for the management of neuropathic pain: a systematic review. *BMC Anesthesiol.* 16, 12 (2016).
8. Finnerup NB, Haroutounian S, Baron R *et al.* Neuropathic pain clinical trials: factors associated with decreases in estimated drug efficacy. *Pain* 159, 2339–2346 (2018).
9. Moisset X, Bouhassira D, Couturier JA *et al.* Pharmacological and non-pharmacological treatments for neuropathic pain: systematic review and French recommendations. *Rev. Neurol.* 176, 325–352 (2020).
10. Morel V, Joly D, Villatte C *et al.* Memantine before mastectomy prevents post-surgery pain: a randomized, blinded clinical trial in surgical patients. *PLOS ONE* 11, e0152741 (2016).
11. Jiang J, Li Y, Shen Q *et al.* Effect of pregabalin on radiotherapy-related neuropathic pain in patients with head and neck cancer: a randomized controlled trial. *J. Clin. Oncol.* 37, 135–143 (2019).
12. Pickering G, Voute M, Macian N, Ganry H, Pereira B. Effectiveness and safety of 5% lidocaine-medicated plaster on localized neuropathic pain after knee surgery: a randomized, double-blind controlled trial. *Pain* 160, 1186–1195 (2019).
13. Jain SM, Balamurugan R, Tandon M *et al.* Randomized, double-blind, placebo-controlled trial of ISC 17536, an oral inhibitor of transient receptor potential ankyrin 1, in patients with painful diabetic peripheral neuropathy: impact of preserved small nerve fiber function. *Pain* 163, e738–e747 (2022).
14. Kato J, Baba M, Kuroha M *et al.* Safety and efficacy of mirogabalin for peripheral neuropathic pain: pooled analysis of two pivotal Phase III studies. *Clin. Ther.* 43, 822–835.e16 (2021).
15. Zakrzewska JM, Palmer J, Morisett V *et al.* Safety and efficacy of a Nav1.7 selective sodium channel blocker in patients with trigeminal neuralgia: a double-blind, placebo-controlled, randomised withdrawal phase 2a trial. *Lancet Neurol.* 16, 291–300 (2017).
16. Markman J, Resnick M, Greenberg S *et al.* Efficacy of pregabalin in post-traumatic peripheral neuropathic pain: a randomized, double-blind, placebo-controlled phase 3 trial. *J. Neurol.* 265, 2815–2824 (2018).
17. Palladini M, Boesl I, Koenig S, Buchheister B, Attal N. Lidocaine medicated plaster, an additional potential treatment option for localized post-surgical neuropathic pain: efficacy and safety results of a randomized, placebo-controlled trial. *Curr. Med. Res. Opin.* 35, 757–766 (2019).
18. Kersten C, Cameron MG, Bailey AG *et al.* Relief of neuropathic pain through epidermal growth factor receptor inhibition: a randomized proof-of-concept trial. *Pain Med.* 20, 2495–2505 (2019).
19. Bouhassira D, Perrot S, Riant T *et al.* Safety and efficacy of an equimolar mixture of oxygen and nitrous oxide: a randomized controlled trial in patients with peripheral neuropathic pain. *Pain* 162, 1104–1115 (2021).
20. Lipone P, Ehler E, Nastaj M *et al.* Efficacy and safety of low doses of trazodone in patients affected by painful diabetic neuropathy and treated with gabapentin: a randomized controlled pilot study. *CNS Drugs* 34, 1177–1189 (2020).
21. Cave A, Kurz X, Arlett P. Real-world data for regulatory decision making: challenges and possible solutions for Europe. *Clin. Pharmacol. Ther.* 106, 36–39 (2019).
22. Dreyer NA, Hall M, Christian JB. Modernizing regulatory evidence with trials and real-world studies. *Ther. Innov. Regul. Sci.* 54, 1112–1115 (2020).
23. Eichler HG, Pignatti F, Schwarzer-Daum B *et al.* Randomized controlled trials versus real world evidence: neither magic nor myth. *Clin. Pharmacol. Ther.* 109, 1212–1218 (2021).

24. Eichler HG, Bloechl-Daum B, Broich K *et al.* Data rich, information poor: can we use electronic health records to create a learning healthcare system for pharmaceuticals? *Clin. Pharmacol. Ther.* 105, 912–922 (2019).
25. Eichler HG, Koenig F, Arlett P *et al.* Are novel, nonrandomized analytic methods fit for decision making? The need for prospective, controlled, and transparent validation. *Clin. Pharmacol. Ther.* 107, 773–779 (2020).
26. European Medicines Agency. Repurposing of authorised medicines: pilot to support not-for-profit organisations and academia. www.ema.europa.eu/en/news/repurposing-authorised-medicines-pilot-support-not-profit-organisations-academia
27. US Food and Drug Administration. Real-world evidence. www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence
28. European Union Innovative Medicines Initiative GetReal project. Glossary of definitions of common terms. www.imi-getreal.eu/Portals/1/Documents/01%20deliverables/D1.3%20-%20Revised%20GetReal%20glossary%20-%20FINAL%20updated%20version_25Oct16_webversion.pdf
29. Moore RA, Derry S, Wiffen PJ. Challenges in design and interpretation of chronic pain trials. *BJA* 111, 38–45 (2013).
30. Moore RA, Moore OA, Derry S, Peloso PM, Gammaitoni AR, Wang H. Responder analysis for pain relief and numbers needed to treat in a meta-analysis of etoricoxib osteoarthritis trials: bridging a gap between clinical trials and clinical practice. *Ann. Rheum. Dis.* 69, 374–379 (2010).
31. Li M, Chen S, Lai Y *et al.* Integrating real-world evidence in regulatory decision-making process: a systematic analysis of experiences in the US, EU, and China using a logic model. *Front. Med.* 8, 669509 (2021).
32. Jaksa A, Wu J, Jónsson P, Eichler HG, Vititoe S, Gatto NM. Organized structure of real-world evidence best practices: moving from fragmented recommendations to comprehensive guidance. *J. Comp. Eff. Res.* 10, 711–731 (2021).

- **Provides a structure for researchers and decision makers to organize the available fragmented real-world evidence recommendations.**

33. Franklin JM, Liaw KL, Iyasu S, Critchlow CW, Dreyer NA. Real-world evidence to support regulatory decision making: new or expanded medical product indications. *Pharmacoepidemiol. Drug Saf.* 30, 685–693 (2021).

- **Overview of the approaches to generate real-world evidence for regulatory decisions about new or expanded medication indications.**

34. European Medicines Agency. Guideline on registry-based studies. www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en-0.pdf
35. European Medicines Agency. Initiation of DARWIN EU® Coordination Centre advances integration of real-world evidence into assessment of medicines in the EU. www.ema.europa.eu/en/news/initiation-darwin-eur-coordination-centre-advances-integration-real-world-evidence-assessment
36. Bolislis WR, Fay M, Kühler TC. Use of real-world data for new drug applications and line extensions. *Clin. Ther.* 42, 926–938 (2020).
37. Feinberg BA, Gajra A, Zettler ME, Phillips TD, Phillips EG, Kish JK. Use of real-world evidence to support FDA approval of oncology drugs. *Value Health* 23, 1358–1365 (2020).
38. US Food and Drug Administration. FDA approves new use of transplant drug based on real-world evidence. www.fda.gov/drugs/news-events-human-drugs/fda-approves-new-use-transplant-drug-based-real-world-evidence#:~:text=FDA%20approves%20new%20use%20of%20transplant%20drug%20based%20on%20real%2Dworld%20evidence,-Share&text=Today%2C%20the%20U.S.%20Food%20and,evidence%20(RWE)%20of%20effectiveness
39. Quessy SN, Rowbotham MC. Placebo response in neuropathic pain trials. *Pain* 138, 479–483 (2008).
40. Boussageon R, Howick J, Baron R *et al.* How do they add up? The interaction between the placebo and treatment effect: a systematic review. *Br. J. Clin. Pharmacol.* doi:10.1111/bcp.15345 (2022) (Epub ahead of print).
41. Bischoff JM, Ringsted TK, Petersen M, Sommer C, Üçeyler N, Werner MU. A capsaicin (8%) patch in the treatment of severe persistent inguinal postherniorrhaphy pain: a randomized, double-blind, placebo-controlled trial. *PLOS ONE* 9, e109144 (2014).
42. Howard JP, Wood FA, Finegold JA *et al.* Side effect patterns in a crossover trial of statin, placebo, and no treatment. *J. Am. Coll. Cardiol.* 78, 1210–1222 (2021).
43. Institut Analgesia. eDOL, an e-health application. www.institut-analgesia.org/portfolio-item/edol-an-e-health-application/?lang=en
44. Moisset X, Pagé MG, Pereira B, Choinière M. Pharmacological treatments of neuropathic pain: real-life comparisons using propensity score matching. *Pain* 163, 964–974 (2022).

- **The use of pain registry data for the benefit-risk evaluation of various NP treatments.**

45. Überall MA, Bösl I, Hollanders E, Sabatschus I, Eerdekens M. Localized peripheral neuropathic pain – topical treatment with lidocaine 700 mg medicated plaster in routine clinical practice. *Pain Manag.* 12, 521–533 (2022).

- **The use of pain registry data for the benefit-risk evaluation of various NP treatments.**

46. Schlereth T. Guideline "diagnosis and non interventional therapy of neuropathic pain" of the German Society of Neurology (deutsche Gesellschaft für Neurologie). *Neurol. Res. Pract.* 2, 16 (2020).

47. National Institute for Health and Care Excellence. Neuropathic pain in adults: pharmacological management in non-specialist settings. Clinical guideline [CG173]; published: 20 November 2013; last updated: 22 September 2020. www.nice.org.uk/guidance/cg173/chapter/1-recommendations

48. Liu M, Qi Y, Wang W, Sun X. Toward a better understanding about real-world evidence. *Eur. J. Hosp. Pharm.* 29, 8–11 (2022).

49. Mick G, Serpell M, Baron R *et al.* Localised neuropathic pain in the primary care setting: a cross-sectional study of prevalence, clinical characteristics, treatment patterns, quality of life and sleep performance. *Curr. Med. Res. Opin.* 37, 293–302 (2021).