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REVIEW

Improving neuropathic pain treatment – by rigorous stratification from bench to bedside

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Abstract

Chronic pain is a constantly recurring and persistent illness, presenting a formidable healthcare challenge for patients and physicians alike. Current first-line analgesics offer only low-modest efficacy when averaged across populations, further contributing to this debilitating disease burden. Moreover, many recent trials for novel analgesics have not met primary efficacy endpoints, which is particularly striking considering the pharmacological advances have provided a range of highly relevant new drug targets. Heterogeneity within chronic pain cohorts is increasingly understood to play a critical role in these failures of treatment and drug discovery, with some patients deriving substantial benefits from a given intervention while it has little-to-no effect on others. As such, current treatment failures may not result from a true lack of efficacy, but rather a failure to target individuals whose pain is driven by mechanisms which it therapeutically modulates. This necessitates a move towards phenotypical stratification of patients to delineate responders and non-responders in a mechanistically driven manner. In this article, we outline a bench-to-bedside roadmap for this transition to mechanistically informed personalised pain medicine. We emphasise how the successful identification of novel analgesics is dependent on rigorous experimental design as well as the validity of models and translatability of outcome measures between the animal model and patients. Subsequently, we discuss general and specific aspects of human trial design to address heterogeneity in patient populations to increase the chance of identifying effective analgesics. Finally, we show how stratification approaches can be brought into clinical routine to the benefit of patients.

KEYWORDS
animal model, bedside testing, mechanism-based therapy, pain, quantitative sensory testing, stratification

Abbreviations: ARRIVE, Animal Research: Reporting of In Vivo Experiments; ASL, arterial spin labelling; BOLD, blood oxygen level– dependent; CMS, Chicago Medical Supply; COVID 19, Coronavirus disease 2019; CPM, conditioned pain modulation; DFNS, German Research Network on Neuropathic Pain; EQIPD, Enhancing Quality in Preclinical Design; EQUATOR, Enhancing the QUAlity and Transparency Of health Research; EU, European Union; fMRI, functional magnetic resonance imaging; IMMPACT, Initiative on Methods, Measurement and Pain Assessment in Clinical Trials; MRI, magnetic resonance imaging; NRS, numerical rating scale; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritic; PET, positron emission tomography; PROM, patient-reported outcome measure; QST, quantitative sensory testing; rs-fMRI, resting- state fMRI; sMRI, structural MRI; UK, United Kingdom; VAS, visual analogue scale; WHO, World Health Organization.

1 | INTRODUCTION

Recent data from the WHO's Global Burden of Disease Study (Vos et al., 2020) indicate that chronic pain is one of the two major causes of Years Lost to Disability worldwide, second only to mental health (Rice et al., 2016). Pain affects all corners of the globe, arising not only from diseases mostly prevalent in developing countries like leprosy (Haroun et al., 2019) but also from diabetes with an increasing frequency in tiger states in Southern America or the Middle East (Chatterjee et al., 2017), and primary pain conditions like migraine and fibromyalgia, which are reported more in the Global North (Feigin et al., 2019).

While the burden of many diseases has decreased in recent decades, pain is on the rise worldwide. This is due, in part, to medical success stories: life expectancies have increased following dramatic advances in our ability to identify, categorise and treat diseases like diabetes and cancer. At the same time, this has given rise to increasing levels of age-related disorders such as chronic pain. This is often linked to irreversible nerve damage, which can be caused by a variety of conditions or treatments, like chemotherapy, diabetes, infectious diseases and subsequent (auto-)immune responses. Moreover, a surge of new cases might currently be forming: long COVID-19 is associated with a multitude of syndromes linked to chronic pain, like chronic inflammatory or critical illness polyneuropathy. We might observe a potentially unseen wave of relatively young; otherwise, healthy patients with full life expectancy, suffer from chronic pain (Clauw et al., 2020).

One reason for the heavy global burden of pain is insufficient treatment. For neuropathic pain, the prevalence of an estimated 5–10% of the general population (van Hecke et al., 2014) and defined as pain arising from disease or injury of the nervous system (Finnerup et al., 2016), first-line treatments fail in over 50% of patients (Finnerup et al., 2015). While written almost two decades ago, the following devastating statement is still as valid as it was in 2007: 'The management of patients with chronic [pain] is complex (and response to existing treatments is often inadequate). Even with well-established medications, effectiveness is unpredictable, dosing can be complicated, analgesic onset is delayed, and side effects are common' (Dworkin et al., 2007). Given the high prevalence of chronic pain in the general population (Rice et al., 2016), this constitutes a massive unaddressed medical need.

Rather than this arising from inherently poor medications, it seems that treatments work well for some while providing little to no benefit for the remaining majority of the patients (Baron et al., 2012). With high variability of response has been shown in substances with different mechanisms of action, for example, non-steroidal anti-inflammatory drugs (Theken, 2018), opioids (Corli et al., 2019), duloxetine (Matsuoka et al., 2020) and gabapentinoids (Shaheen et al., 2022), this presents a significant challenge for interpretation of past and future trials.

A statistically insignificant treatment effect could result from a genuine lack of efficacy or substantial heterogeneity, with the benefit seen in 'responders' hidden among those who do not respond. Phenotypic stratification offers a promising opportunity to overcome this heterogeneity, allowing for clearer links between treatments and disease mechanisms. This holds promise to both improve inference from clinical trials as well as develop novel tailored treatments for subsets of the broader clinical population (Demant et al., 2014; Smith et al., 2017). This transition from treating heterogeneous groups to individual patients will be imperative to improve the success of analgesic therapy. Crucially, this move towards personalised pain medicine will require the identification, development and validation of novel biomarkers. Here, we describe past, present and future steps towards mechanistically informed neuropathic pain treatment, while providing examples from adjacent fields like nociceptive and nociplastic pain treatment where appropriate. We follow a roadmap from bench to bedside: first, we discuss current challenges in preclinical pain research, including rigour as well as pain-specific study design challenges like the need for animals to better model the clinical population and for the use of more mismatch patient-relevant outcomes and assessments. Second, we describe opportunities to improve clinical neuropathic pain research, with a focus on phenotypic stratification. Finally, we present clinical and bedside applications of stratification approaches, bringing research to patients.

2 | PRECLINICAL RESEARCH

Animal experiments have contributed considerably to our understanding of human health and disease. They are often used to identify and validate potential targets and investigate the safety and/or efficacy of interventions intended for human use. Data from preclinical trials are also used to justify the assessment of a candidate drug in clinical trials. Despite recent collaborative efforts between academic institutions and industry to develop better analgesics, only a few novel candidates have shown promise in animal models, and these have failed to demonstrate efficacy in clinical trials (Attal & Bouhassira, 2019; Borsook et al., 2014; Mao, 2012). There are many possible reasons for the disparity between the animal model and clinical trial results including the complexity and challenges of clinical trials. However, the failure to translate preclinical success to the clinic coupled with the multifaceted complexity of pain has led researchers to question the predictive validity of animal models and raised concerns regarding inadequate study design, lack of rigour and opaque reporting as potentially responsible for translational failures (Berge, 2011; Du Percie Sert & Rice, 2014; Yezierski & Hansson, 2018). To address translational challenges, preclinical systematic reviews offer a framework by which the internal and external validity can be assessed, knowledge gaps can be identified, publication bias determined, discrepancies between preclinical and clinical trial design addressed, inform 3R (replacement, reduction and refinement of animal use in research) decisions as well as generate new hypotheses for future research (Sena et al., 2014; Soliman et al., 2020). This is particularly pertinent if preclinical researchers are going to be able to follow the clinical trends towards precision medicine.

Several preclinical neuroscience systematic reviews have provided empirical evidence highlighting that inadequate methodological approaches are associated with bias, leading to an over- or underestimation of the true effect of an intervention, for example, stroke, Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis (Crossley et al., 2008; Hirst et al., 2014; Rooke et al., 2011). There is also evidence to show that studies that do not

report measures to reduce the risk of bias give higher estimates of treatment effects (Crossley et al., 2008; Hirst et al., 2014). More recently, preclinical systematic reviews in the pain field have identified similar issues. The methodological quality and transparent reporting of animal studies is an important factor when assessing the value of animal models. Systematic reviews across a range of pain research areas have demonstrated that there is scope to improve conduct and reporting standards of preclinical research (Table 1). For example, most studies do not report bias mitigations (randomisation, allocation concealment, blinded assessment of outcome, predefined animal inclusion criteria and animal exclusions) nor the methods to accurately assess the risk of bias and, therefore, the reliability of the included studies' findings (Currie et al., 2019; Soliman et al., 2021; Zhang et al., 2022). Blinding and randomisation are most frequently reported, and sample size calculations and allocation concealment are the least reported (Currie et al., 2019; Federico et al., 2020; Soliman et al., 2021; Zhang et al., 2022). The reviews do not show a consistent relationship between the reporting of methodological quality and smaller effect sizes, however, for example, Soliman et al., demonstrate larger effect sizes were reported in studies that did not report allocation concealment and sample size calculations and that both accounted for a significant proportion of heterogeneity. Thus, there is a critical need for transparency of reporting all experimental details so that the quality of research can be assessed (Sena and Macleod, 2007) and to determine the risks most pertinent to the different contexts of preclinical pain research.

2.1 | Improvement of rigour

The growing awareness of the negative repercussions of poor standards of planning, conduct and reporting of preclinical research (Ioannidis, 2005) has led to several initiatives that aim to increase the validity, reliability and reproducibility in (not only preclinical) research. Arguably the biggest change in the preclinical domain was the introduction of the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines (Du Percie Sert et al., 2020; Kilkenny et al., 2010) which have been adopted by many journals and have been integrated into the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) network of reporting guidelines. The ARRIVE guidelines provide a helpful starting point for researchers, and, when applied rigorously, lead to publications providing all information relevant for replication studies and incorporation into systematic reviews, an essential premise for more nuanced judgement of the relevance of individual findings. Their impact will depend on the uptake and accurate use, and to date, the impact of the guidelines is unclear (Hair et al., 2019).

Potentially, a more effective approach could be to assist researchers wanting to improve their work *before* reporting, when many aspects of bias can still be reduced (Henderson et al., 2013). The UK's National Centre for the study of the 3Rs has developed the experimental design assistant that can help researchers to plan rigorous experiments from the conceptual stage (Du Sert et al., 2017). The EU-funded initiative EQIPD (Enhancing Quality in Preclinical Design) has developed a quality management system and related accreditation to start an iterative discussion with researchers wanting to improve the quality of design, conduct and output of their work (Bespalov et al., 2021). These initiatives, along with the sense of community they create, are important to show researchers that improving rigour does not mean to work harder or more, but to work better.

EQIPD has also published a framework to improve rigour in the design, conduct and analysis of animal experiments (Vollert et al., 2022a) based on a systematic review of existing guidelines (Vollert, Schenker, et al., 2020b). This framework suggests that researchers can improve rigour in five domains: 1. a clear distinction between exploratory versus confirmatory research (the latter a predefined scientific hypothesis, which is statistically testable), 2. thorough pre-planning and standard operating procedures, 3. use of appropriate statistics which are meaningful for the data, 4. comprehensive randomisation and blinding at multiple stages and 5. full, open and honest documentation and reporting, linking back to the ARRIVE guidelines. This framework has just been published, but if adopted broadly could contribute to more reproducible and valid research outputs.

2.2 | Use of and lessons learned from systematic reviews

To date, preclinical pain research has been dominated by homogeneity in terms of the animal characteristics, the diseases

TABLE 1 Comparison of the prevalence of reporting of methodological quality criteria from a selection of pain-related preclinical systematic reviews.

Methodological quality criteria	Bone cancer pain (Currie et al., 2013) (%)	Chemotherapy-induced peripheral neuropathy (Currie et al., 2019) (%)	Pregabalin (Federico et al., 2020) (%)	Cannabis & Pain (Soliman et al., 2021) (%)	Burrowing (Zhang et al., 2022) (%)
Sample size calculation	0	2	4	3	38
Allocation concealment	–	1	6	4	14
Randomisation	11	28	28	32	70
Blinded assessment of outcome	31	51	33	47	43
Animal exclusions	–	18	–	14	36

modelled and the outcomes measured. Systematic reviews have demonstrated the predominance of traumatic nerve injury in male, Sprague Dawley rats with evoked limb withdrawal to noxious stimuli the most frequently used pain-associated outcome measure (Sadler et al., 2022; Soliman et al., 2021; Zhang et al., 2022). The reviews highlight common causes of reduced external validity such as how closely an animal model resembles the human condition, choice of outcome assessment and chronicity, which can impact the assessment of novel analgesic efficacy. Careful consideration should be given to the choice of species, strain, sex and age in relation to the clinical condition being modelled, as results and conclusions will be dependent on these variables. As clinical medicine moves towards stratification of patients it is necessary for animal modelling to be refined to inform that approach, and their limitations remain an important challenge. Further limitations of animal models include that they do not effectively simulate multidimensional clinical pain conditions including the complex psychological component. They also do not mimic the slow progressive and degenerative nature of many human chronic diseases, nor do they replicate the complexity of co-morbidity or polypharmacy. Therefore, clinical trials are not being informed by rigorous mechanistic preclinical studies.

2.3 | Misalignment between animal models and clinical population

The models used in preclinical pain research are not often well matched to the clinical population (Du Percie Sert & Rice, 2014; Rice et al., 2018). First, animal cohorts are genetically very similar converse to the widely heterogenous patient population. Reviews report a predominance of male, Sprague Dawley rats (Currie et al., 2019; Federico et al., 2020; Sadler et al., 2022; Soliman et al., 2021). However, within the animal population, strain, age (Pickering et al., 2006) and sex (Craft et al., 2004; Dahan et al., 2008) have been shown to impact the development and sensitivity to pain. In general, female rodents are reported to be more sensitive than males (Mogil et al., 2000). Similarly, in patients, both sex (Mogil, 2012) and ethnicity (Alabas et al., 2013) can affect pain tolerances, and response to analgesics can differ between the sexes (Niesters et al., 2010). To add, recent pain-related systematic reviews have shown that researchers predominantly use male animals (Currie et al., 2019; Federico et al., 2020; Soliman et al., 2021), which is worrisome because sex-related differences are known, and there is a higher prevalence of chronic pain conditions in women (Mills et al., 2019).

A criticism frequently levelled at pain researchers is that there is a dominance of nerve injury models (Mogil et al., 2010; Sadler et al., 2022). Nerve injury models were used to assess cannabinoid, cannabis-based medicine or endocannabinoid system modulators in 74% of the included studies, 45% in the pregabalin review (Federico et al., 2020) and 15% in burrowing review (Zhang et al., 2022). This predominance of nerve injury contrasts with the clinical situation where nerve injury only represents 9% of neuropathic pain trials included in an analysis of randomised controlled trials in a systematic review (Finnerup et al., 2015). Tailoring models to the human condition is essential and increasingly models are being developed that more closely reflect the pathophysiological condition related to patient pain, for example, disease-specific models such as herpes zoster infection (Fleetwood-Walker et al., 1999; Garry et al., 2005; Hasnie et al., 2007) and HIV and antiretroviral-associated peripheral neuropathy (Wallace, Blackbeard, Pheby, et al., 2007a; Wallace, Blackbeard, Segerdahl, et al., 2007b), diabetes (Sullivan et al., 2008) and chemotherapy-induced peripheral neuropathy (Morales & STaff, 2021).

However, there is an issue that the incidence of pain in animal models is much higher than that in patients, most of whom will not develop chronic pain. This, therefore, raises the further question as to the relevance of these models given the likely differences in the underlying pathophysiology. It highlights the potential use of naturally occurring disease models to investigate underlying mechanisms and assess the efficacy of potential analgesics (Brown et al., 2009; Clements et al., 2006; Mizisin et al., 2002).

2.4 | Outcome assessments

In clinical trials, the primary efficacy measure is usually continuous spontaneous pain, which makes it difficult to draw meaningful comparisons with preclinical studies in which reflex withdrawal responses are the most commonly assessed outcome (Rice et al., 2008). These outcomes are a measure of hypersensitivity, which are appropriate for some pain types, for example, inflammation, but not the spontaneous pain or pain associated with sensory loss. For example, neuropathic pain–associated animal models' behavioural responses are characterised by sensory gain. Whereas patients with neuropathic pain are more frequently characterised by sensory loss and spontaneous pain, sensory gain is less frequent (Maier et al., 2010; Vollert et al., 2017). Evoked limb withdrawal also presents an additional issue in that reflexes do not include the cerebral cortex in which sensory intensity is compared with prior experiences (Vierck et al., 2008). However, conditioned place preference is a paradigm that can be used to measure hypersensitivity and yield findings more relevant to the clinic due to reliance upon supraspinal processing (Vierck et al., 2008). It has also been suggested that researchers should understand how rodent behaviours are influenced by pain (Barnett, 2017) as this better captures the multidimensional nature of pain. This has led to the development of ethologically relevant behavioural outputs, for example, thigmotaxis (predator avoidance) (Hasnie et al., 2007; Huang et al., 2013; Wallace, Blackbeard, Pheby, et al., 2007a; Wallace, Blackbeard, Segerdahl, et al., 2007b; Wallace, Segerdahl, Lambert, et al., 2007c), elevated plus-maze behaviours (Roeska et al., 2009) sleep pattern disturbances (Andersen & Tufik, 2003) and place preference (Buccafusco, 2009). A recent systematic review demonstrated that burrowing (measured as the amount of substrate,

usually gravel, that is displaced from a cylinder (Deacon, 2006)) is a suitable pain-related outcome measure with decreased burrowing observed in both inflammation and nerve injury models, which is also attenuated by gabapentinoids and NSAIDs (Zhang et al., 2022). There was no correlation between mechanical evoked limb withdrawal and burrowing outcomes supporting the need for researchers to use a battery of outcome measures to assess pain-related behaviours and drug efficacy. It is important multiple assessments are used so that a broader spectrum of pain symptoms is represented. The battery of tests applied should be consistent across laboratories and studies so that meaningful comparisons can be made (Ioannidis, 2005). Assessments should include how the brain processes pain perception and related motor, autonomic and psychological responses.

2.5 | Chronicity

The duration of animal studies is usually brief (up to a few weeks) which does not adequately reproduce the impact of prolonged nociception on clinical pain. It is important that behavioural and other biological outcomes are assessed across a longer duration and multiple time points in both preclinical and clinical trials to monitor changing disease profile and pain progression. Of note, human epidemiological studies suggest that chronic pain may increase mortality risk and a recent preclinical study assessing pain behaviour over a lifetime in mice suggests that biology of importance to human chronic pain is being ignored because of the short timespans of most preclinical studies (Millecamps et al., 2022).

Preclinical and clinical studies also differ in terms of treatment dose and exposure. In preclinical studies, candidate treatments are often administered as a single, high dose, whereas in clinical trials they are given at lower doses and titrated over time (Berge, 2011). In addition, in preclinical setting drugs are often tested prophylactically or in the early stages of disease onset, which has utility for disease-modifying treatments but does not represent most clinical situations where the drugs are used in the late stages of disease once chronic pain is established (Rice & Maton, 2001).

2.6 | Forward and backward translation and stratification approaches

Animal and clinical studies are conducted concurrently providing the opportunity for both forward and backward translation. As the evidence suggests, the translation from preclinical to clinical studies can be difficult because of the inherent limitations of animal models to adequately mimic the complexity of pain states. It is also a challenge to apply precision medicine to chronic pain for which there is no known effective treatment. However, animal studies can be especially useful for providing mechanistic insights into the pathophysiology of pain as well as the pharmacology of potential therapeutics. So, how can the predictive validity of animals be improved? How can models better reproduce patients' conditions?

Advances in research methods are occurring at pace; from genetic tools to genetically modified rodents, cellular and molecular techniques including single-cell sequencing and brain imaging. There have been advances in human patients, for example, brain imaging and –omics approaches (Apkarian, 2021; Diatchenko et al., 2022) which have both revolutionised our understanding of pain. These findings, for example, of a genetic, cellular or pathway target are of limited value if the mechanism cannot be defined and tested in a model. Therefore, animal models will remain critical to advancing knowledge and offer opportunities for backward translation: the identification of novel targets from human patients to be studied in animal models is a strategy for narrowing the translation gap between bench and bedside.

2.7 | Identify group differences and increase heterogeneity

In preclinical pain research homogeneity dominates; the predominant use of male, young, healthy, Sprague Dawley rats in which nerve injury is induced and evoked limb withdrawal to mechanical and thermal stimuli measured is an extreme example of complexity reduction. It has limited utility for improving the understanding of human pain biology.

The chronic pain patient population differs because of age, sex and ethnicity, and it is necessary for preclinical studies to increasingly demonstrate the differences in cellular and molecular pathways that promote chronic pain differentially between different groups. It is also necessary for researchers not to mistakenly assume that if a therapeutic is effective in one group, it will be equally effective in another. Research targeting the mechanisms that underlie differences may have potential for the discovery of novel mechanisms and drug targets.

Increasing heterogeneity of preclinical experiments is a potential solution to remedy low reproducibility and improve generalisability of findings. Standardisation is considered the gold standard of experimental conduct because it improves the precision of outcomes. However, as discussed, using young, healthy, male, genetically similar animals, raised in the same environment means that these animals are not representative of the whole population and the findings from experiments may not be generalisable. Increasing biological variation increases the chances of finding robust effects concurrent with reducing the risk of obtaining spurious results (Voelkl et al., 2018). Increasing heterogeneity comprises of using animals of different genetic backgrounds from diverse environments, animals of different species, strain, sex and age. Recognising heterogeneity is not just necessary for reproducibility but is fundamental to reflecting the clinical heterogeneity of pain patients: the differences in terms of underlying disease, clinical presentation, pain mechanisms and different responses to treatment. Increased heterogeneity can be achieved by active and

controlled heterogeneity within a lab or by conducting multicentre experiments, which will capitalise on the natural differences between labs (Wodarski et al., 2016).

2.8 | Mechanism-targeted clinical trials

Different mechanisms promote the development of chronic pain (Denk et al., 2014) but can still result in similar phenotypes. Most clinical studies only assess phenotypes yielding a limited understanding of the underlying molecular mechanisms in patient populations. This represents a deepening knowledge gap between animal and clinical studies. This gap can be addressed by the development of technologies to define the pathophysiological mechanisms in patients coupled with expanding the range of phenotypic behaviours assessed in animal studies. For example, for neuropathic pain, the use of quantitative sensory testing (QST) may lead to improved treatment selection and improved patient outcomes (Dickenson & Patel, 2020). Rice et al. proposed that the evoked limb withdrawal outcomes could be used as sensory profiling tools, 'a sensory profile biomarker of that injury or disease model' (Rice et al., 2018). This will require the development and validation of multimodal sensory profiling tools for animal models to be able to align animal behavioural outcomes with the heterogeneity of sensory profiles of neuropathic pain patients (Baron et al., 2017; Vollert et al., 2017) and the stratification approaches required for precision medicine (Baron et al., 2012).

3 | HUMAN TRIALS

3.1 | Explaining variance in response in clinical trials

The primary outcome measure for virtually all pain trials has been change in NRS (numerical rating scale) or VAS (visual analogue scale) pain reports. There are shortcomings to using such pain scales, and more nuanced outcome measures will help aligning patient impressions with measurement as well as perceiving a more holistic picture of patients' experience (see below, on patient-reported outcomes). When using NRS or VAS, one of the key challenges in the conduct of clinical trials of pain is the inherent variance of day-to-day pain levels. Aside from the clinical relevance to patients of such fluctuations, they also increase variance in trials and, thus, decrease the chance of detecting the real effects of new treatments. Therefore, understanding sources of variance in pain—such as the pathophysiology of the individual's pain, response to placebo treatments or artefacts of trial conduct—is highly relevant for both patients and researchers alike.

Individual sources of daily fluctuation of pain are poorly understood (Schneider et al., 2012). While they have been long associated with depressive moods (Kerns et al., 1988), the directionality of causation remains unclear, with pain potentially producing or resulting from mood changes, which may also constitute a negative feedback loop. While it is not currently possible to discern individual mechanisms of pain fluctuation, it is becoming increasingly clear that high-frequency pain assessments should replace weekly averages as standard pain outcomes (Goldman et al., 2021; Schneider et al., 2018).

In clinical trials, there are additional sources of variability. Some of this might be linked to individual factors, for example, there is weak evidence for genetic predisposition to increased placebo analgesia responses (Hall et al., 2012; Vollert, Wang, et al., 2022b) or for age-influencing placebo analgesia responses in clinical trials (Vase et al., 2015). However, these effects are small in magnitude and leave most of the placebo responses unexplained. A distinction that needs to be emphasised is the difference between the placebo *effect* (a specific psycho-neurobiological phenomenon, that can be experimentally evoked) and the placebo *response* in the inert treatment arm of clinical trials. The latter includes improvement in these arms for any reason, which can result from natural history and fluctuation of disease intensity over time, regression to the mean and generally improved standard of care while participating in a trial (Finniss et al., 2010). While specific contributions are unknown and also underestimated (Lund et al., 2014), the majority of the placebo response might be because of non-specific effects rather than the placebo effect (Vollert, Cook, et al., 2020a), which, therefore, needs to be paid equal attention. It has been shown that high baseline pain inclusion criteria can increase the regression to the mean effect (Kamerman & Vollert, 2022), showing that each detail of the study design requires careful consideration when maximising sensitivity in clinical trials.

Beyond these general challenges of trial design and understanding, for chronic pain in particular, it has been discussed if a one-size-fits-all approach will be unrealistic and patients need to be stratified to find medication specific for subgroups of patients (Baron et al., 2012). Below, we will discuss three examples of stratification, neuroimaging, sensory testing and patient-reported outcomes. It should be pointed out that these are examples—there are other interesting approaches, and it seems likely that a single perfect one will not exists—but rather a composite of multiple elements might be needed in the future (Tracey et al., 2019).

3.2 | Neuroimaging to stratify

The multidimensional experience of pain ultimately emerges from spatiotemporal patterns of brain activity, within which afferent nociceptive information is modulated by cognitive factors (Kucyi & Davis, 2015; Wiech, 2016), and from which descending modulatory systems exert influence over spinal level processing (Bannister, 2019). Therefore, neuroimaging offers a potential opportunity to examine the confluence of multiple interacting mechanisms that shape the experience, chronification and alleviation of pain.

Various non-invasive imaging techniques may hold potential as diagnostic and predictive biomarkers. However, to be implementable

in clinical settings, they must not only be sufficiently sensitive but also simple, rapid and cost-effective. Thus, despite, showing promise to predict opioid analgesia (Wanigasekera et al., 2012), paradigms requiring in-scanner noxious stimulation equipment are likely not scalable. Similarly, although positron emission tomography (PET) offers molecular insights, its spatiotemporal resolution, expense, hardware demands, invasiveness and radiation exposure preclude widespread implementation (Loggia et al., 2019). Other methodologies may offer further insights but have been understudied to date: arterial spin labelling (ASL) provides a quantitative measure of regional cerebral blood flow, which is especially well suited to characterise slowly fluctuating brain signals associated with ongoing pain states (Loggia et al., 2019; Medina et al., 2021). Similarly, spinal functional magnetic resonance imaging (fMRI) may provide important insights into top-down descending modulation and its manipulation by analgesic pharmacotherapy (Tinnermann et al., 2021), although this endeavour is in its infancy and has proven to be highly technically challenging (Tinnermann et al., 2022). Paradigm-free MRI has been the most studied to date and offers clinical scalability, with MRI scanners commonplace in hospital settings and requiring no additional equipment nor experimental design. Structural MRI (sMRI) and resting-state fMRI (rs-fMRI) capture individual differences in the anatomical and functional architecture of the human brain, respectively, which can then be linked to behaviour (Finn et al., 2015). Despite their simplicity, these tools have shown initial promise to explore trait inter-individual differences emerging from supraspinal systems; pain-free rs-fMRI robustly predicts pain thresholds (Spisak et al., 2020) and baseline structural and function connectivity measures are predictive of transition from acute to chronic pain (Baliki et al., 2012; Mansour et al., 2013; Vachon-Presseau et al., 2016). Despite these successes, applications to stratified pain medicine remain scarce, and substantial additional work is required to demonstrate their value as predictive biomarkers. Moreover, it is imperative to distinguish between clinical utility and mechanistic insight, with biomarkers offering predictive value potentially doing so through aspects of brain structure or function not directly related to the mechanisms giving rise to the pain in the first place (Mouraux and Iannetti, 2018).

Chronic pain is shaped by a myriad of factors that interact over time to give rise to an individual's unique (patho)physiology (Denk et al., 2014; Fillingim, 2017). As such, no single measure of grey matter density nor functional connectivity between regions will ever capture all the variance across individuals. Indeed, a recent machine learning approach to predict high- versus low-intensity clinical pain found that including multiple imaging modalities together alongside autonomic measures produced the best performance (Lee et al., 2019). Chronic pain conditions arise from diverse aetiologies, interacting with an individual's unique personal history and genome, with treatments differentially interacting with various facets of the resultant (patho)physiology. Therefore, similar 'composite' treatment-based biomarkers will likely offer the best capacity to capture this complexity and mechanistically stratify patients (Tracey et al., 2019). Despite this, most efforts to date have focussed on a single imaging modality applied to a specific treatment and pain cohort (Tracey, 2017, 2021). The collection of both sMRI and rs-fMRI is commonplace, offering a potential foundation upon which to build more complex composite biomarkers. Development and application of additional measures, such as ASL or spinal fMRI, will likely provide complementary insights, and the utility and practical applicability of these together or in isolation within different use cases requires further exploration.

In the case of resource-intensive and side-effect-prone interventions such as ketamine for neuropathic pain, non-invasive predictive biomarkers delineating individuals who will benefit are urgently needed. Interestingly, a recent study found that while psychometric and clinical variables did not differ between ketamine responders and non-responders, both temporal summation of pain and dynamic functional connectivity at baseline correlated with subsequent pain relief (Bosma et al., 2018). Crucially, dynamic connectivity between key regions of the default mode network and descending modulatory structures was found to mediate the relationship between temporal summation and pain relief. Thus, in certain scenarios, imaging outcomes seem best placed to capture variability in treatment-related mechanisms. However, the extent to which these predictive measures constitute a disease-specific or generalisable predictor of treatment response remains unclear. For example, while microstructural diffusivity measures of the trigeminal nerve are associated with surgical outcomes in trigeminal neuralgia (Hung et al., 2017, 2019; Tohyama et al., 2018), their predictive ability is surpassed by more generic measures of grey matter surface area and thickness (Hung et al., 2021). Similarly, different baseline imaging measures relating to the insula are associated with response to pregabalin (Harris et al., 2013) and milnacipran (Schmidt-Wilcke et al., 2014). Because these studies only investigate a priori mechanisms, it is unclear to what extent similarities and differences reflect methodological choices. Data-driven approaches applied across aetiologies and treatments may help shed light on the specificity of these brain-based biomarkers.

A major limitation of fMRI is that the blood oxygen level–dependent (BOLD) signals it measures are highly abstracted from the underlying cellular and molecular mechanisms that give rise to it (Lawn et al., 2022). Essentially, the complex pharmacodynamics following drug administration is mediated through these molecular mechanisms, leaving conventional fMRI studies limited in their capacity to link (patho)physiology to pharmacotherapy (Martins et al., 2022). One approach to overcome this is to incorporate existing molecular information from PET into the analysis of rs-fMRI data, linking aberrant connectivity to underlying receptor systems. Cerebral blood flow in both post-surgical and osteoarthritic (OA) pain correlate with the spatial distribution of dopamine D2 and u-opioid receptors (Vamvakas et al., 2022). Moreover, a novel approach exploring the relationship between molecular systems and rs-fMRI demonstrated individuals with OA who responded to duloxetine had greater baseline connectivity in networks associated with the noradrenaline and serotonin transporters, while placebo responders had stronger connectivity associated with the dopamine transporter (Martins et al., 2022). This seminal work provides a template for

linking network-level dysfunction through to the molecular systems on which analgesic pharmacotherapy acts, which may prove as a useful tool for generating novel biomarkers and mechanistic stratification, although further replication and extension of this approach are required.

Despite the initial allure of neuroimaging as a window through which we can directly examine the pain experience, progress has been limited, and it offers only one part of the puzzle. The field remains in its infancy and, as with many aspects of neuroimaging, progress is hindered by costly and technical data acquisition. The increasing inclusion of baseline sMRI and rs-fMRI measures in studies exploring treatment effects offers a practicable means to begin delineating the neurobiology underlying heterogeneous treatment responses. Moreover, as the field expands, open sharing of data and collaborative consortia will be imperative to develop biomarkers within sufficiently powered samples as well as allow for out-of-sample validation. This will be crucial to move beyond solely characterising associations with treatment outcome and generate predications prospectively.

3.3 | Sensory testing for neuropathic pain

Beyond neuroimaging, one of the most comprehensive ways to gain insights into potential mechanisms of pain generation is by sensory profiling and stratification using QST. This standardised neurological assessment can assess multiple key aspects of the sensory nervous function. QST is used to quantify sensory alterations in both neuropathic and nociceptive (inflammatory) pain, although herein we focus on neuropathic pain where it has shown the most promise.

For neuropathic pain sensory phenotyping, an early success was adopting an almost gold standard. The German Research Network on Neuropathic Pain (DFNS) has developed a comprehensive protocol for QST (Rolke et al., 2006) and demonstrated that multiple labs across Europe measure comparable data (Vollert, Attal, et al., 2016a). This standardised protocol is now employed across the world, leading to a high degree of comparability of results across research groups. The DFNS protocol covers both loss of function (decreased sensitivity to painful and painless stimuli) and gain of function (painful response to non-painful stimuli or increased sensitivity to mildly painful stimuli). It has been shown that sensory profiles only change marginally (if at all) in relation to patients reporting ongoing pain (Forstenpointner et al., 2021), leading to a discussion of the relevance of QST for pain phenotyping if it cannot detect ongoing pain (Schmelz, 2021). One of the drawbacks is the focus on so-called static QST, capturing response to single stimuli, as opposed to dynamic QST, which focusses on changes in sensory reception based on multiple stimuli. Dynamic QST measures include conditioned pain modulation (CPM), seen as a human equivalent to diffuse noxious inhibitory control demonstrated in laboratory animal experiments (Le Bars et al., 1979a, 1979b; Leone & Truini, 2019), and offset analgesia, a reduction in pain perception that is disproportionately greater than expected after a small decrease in the intensity of a painful stimulus (de Broucker et al., 1990; Grill & Coghill, 2002; Yelle et al., 2008). It has been repeatedly shown that the application of a second, conditioning painful stimulus during CPM leads to decreased pain ratings of a painful primary stimulus (Locke et al., 2014) and that during a series of applications and removal of painful stimuli, an offset analgesia effect leads to reduced pain ratings (Naugle et al., 2013). Impaired descending pain modulation is discussed as a possible mechanism in the development of chronic pain (Arendt-Nielsen et al., 2010; Staud et al., 2003) and in pain chronification (Grosen et al., 2014; Yarnitsky et al., 2008). Dynamic QST measures are seen as surrogate measures of descending pain modulation, offering a means by which to stratify patients based on the functionality of top-down pain control systems, which may allow for prediction of development, chronification or treatment of pain (Kisler et al., 2019; Yarnitsky et al., 2012). It needs to be noted, however, that even in healthy individuals, descending pain modulation varies greatly (Graeff et al., 2022). Therefore, further research into the influencing factors and homogenisation of the paradigms used is required (Oono et al., 2011).

As for static QST, sensory profiles have been shown to be altered both proximal and contralaterally of neuropathic pain sites (Enax-Krumova, Attal, et al., 2021a; Enax-Krumova, Baron, et al., 2021b). They can be tentatively demonstrated for genetic variants relevant to pain processing (Sachau et al., 2021) and extreme genotypes of congenital pain (McDonnell et al., 2016), showing a basis in both normal neurophysiological and pathophysiological genetic variation. Sensory profiles are also related to patient-reported outcomes (Gierthmühlen et al., 2022; Vollert, Kramer, et al., 2016b). A large data-driven cluster analysis of over 1000 patients with peripheral neuropathic pain revealed that three distinct sensory phenotypes can be identified: one of loss of sensation, one of thermal hypersensitivity and one of mechanical hypersensitivity often combined with numbness to thermal stimuli (Baron et al., 2017), which can be used to stratify individual patients based on their sensory profile in prospective trials (Vollert et al., 2017). These phenotypes might involve differential contribution of three distinct mechanisms of pain generation: pain generated by dying fibres (possibly via disinhibition of otherwise silent pain pathways) in the 'sensory loss' phenotype, peripheral sensitization in the 'thermal hyperalgesia' phenotype and central sensitization in the 'mechanical hyperalgesia' phenotype. In support of this hypothesis, similar profiles emerge in well-defined mechanisms induced by surrogate models in healthy humans (Vollert et al., 2018). Although only few studies have been prospectively designed to test differential treatment response, the existing evidence suggests that specific treatments will be more efficient for patient groups with certain sensory patterns (Demant et al., 2014, 2015). It has also been shown that QST profiles change in response to worsening of the condition or improvement because of disease-modifying treatment (Kennedy et al., 2021). Based on these findings, the European Medicines Agency is now encouraging stratification based on sensory phenotypes for trials in neuropathic pain (European Medicines Agency, 2016). Thus, sensory profiling with QST has demonstrated multiple elements of a biomarker: differentially

responsive to treatment, linked to plausible mechanisms of disease and responsive to changes in disease (Vollert, 2022).

However, there are clear limitations to sensory profiling for pain. The mechanisms contributing to these sensory phenotypes are hypothesised, but unknown. To fully appreciate their usefulness for targeted pain treatment, uncovering peripheral and central mechanisms leading to sensory phenotypes is needed. QST as per the DFNS protocol is expensive and time-consuming and needs thorough standardisation, training and quality control (Vollert et al., 2015), and is, therefore, currently does not hold much practical clinical relevance. To achieve such, bedside sensory testing needs to be employed, and convergence between laboratory and bedside protocols has not always been given. Recently, the development of cheaper devices (Pfau et al., 2020) and simplified protocols (Bordeleau et al., 2021; Reimer et al., 2020) has helped in the alignment between laboratory QST and bedside sensory testing, which is needed for translation from hypothesis to clinical routine.

4 | CLINICAL APPLICATION

4.1 | Bedside sensory testing

To overcome the above-described limitations of the DFNS QST (time expenditure, expensive equipment, required training), bedside tools can be used, that allow simple sensory testing literally beside the patient's bed. As early as 1976, Ulf Lindblom developed an easy-to-use bedside tool that is still widely used today (Marchettini et al., 2003). The 'Lindblom roller' can be used to test a patient's perception of warmth and cold over a large skin area. Other tools followed, such as the TipTherm, also for simplified testing of thermal perception, the Neuropen, for distinguishing sharp and blunt stimuli, or more recently, a bedside device for measuring evoked pressure pain intensity (Hostrup et al., 2022).

However, these single tools can only be used to assess single pain modalities, whereas detailed information about the function of the different nerve fibre classes cannot be obtained and, thus, a comprehensive stratification of patients is not possible. Therefore, during the past 2 years, several standardised bedside QST protocols have been presented by different research groups, that capture various sensory qualities in a similar way to the 'gold standard' QST. These protocols were developed based on the DFNS QST protocol (Koulouris et al., 2020; Reimer et al., 2020; Zhu et al., 2019) or a literature review of known testing procedures (Wasan et al., 2020). While the individual sensory parameters and the devices for recording them differ between the various protocols, they are all characterised by ease of use and quick feasibility. The fact that such protocols could also be used for subgrouping of patients in the future is shown by a study of Reimer and colleagues, who developed a simple bedside protocol with 13 non-painful and painful stimuli, many of which showed good agreement with the corresponding DFNS QST parameters (Reimer et al., 2020). In addition, an assessment of sensory phenotypes based on the DFNS QST stratification (Baron et al., 2017) was developed. The authors showed that the three DFNS QST clusters can be identified by a combination of only five bedside QST parameters using four devices: An 8°C metal piece for cold perception intensity, a Q-tip for dynamic mechanical detection sensitivity, a 0.7 mm CMS hair for temporal summation, that is, single stimulus pain intensity and series stimuli pain intensity and a tuning fork for vibration threshold. In addition to the allocation to the three DFNS QST clusters, a combination of selected bedside QST parameters to assess patients with certain sensory characteristics would also be conceivable. For example, cut-off values for the detection of cold and warm perception intensity (like a cooled or heated metal piece) and for mechanical pain sensitivity (like a CMS hair or a Neuropen) could be defined to detect subgroups of patients with intact small (C- and A delta-) nerve fibres.

In addition, bedside sensory testing protocols have been developed for the assessment of CPM using, for example, a finger pressure device as tonic conditioning stimulus (Arendt-Nielsen et al., 2020). However, these protocols have so far been developed solely based on data from healthy participants (Arendt-Nielsen et al., 2020; Larsen et al., 2019) to determine their usefulness in clinical practice, they, therefore, still need to be tested in patients.

Bedside sensory testing can not only be used to identify patients' subgroups within the broad spectrum of neuropathic pain disorders in general. Another interesting approach is to develop a specific bedside protocol to identify subgroups of patients within a certain disease entity, such as osteoarthritis. As shown in previous studies, mechanisms of sensitization seem to play an important role in the chronification and amplification of pain in osteoarthritis and may predict the therapeutic outcome after total knee replacement (Imamura et al., 2008; Skou et al., 2014; Wylde et al., 2015). To implement profiling of pain mechanisms in osteoarthritis patients into clinical practice, a simple bedside tool kit was developed based on machine learning techniques (Sachau et al., 2022). For this purpose, the most accurate combination of parameters indicating sensitization was identified including not only sensory testing parameters (DFNS QST, bedside items, temporal summation, CPM) but also patient-reported outcome measures (PROMs). The most adequate bedside tool kit consisted of only three easy-to-use tests and might help to optimise mechanism-based pain therapy in osteoarthritis.

Overall, several promising bedside testing protocols have been developed in recent years, which have the potential to serve as quick and easy-to-use QST tools for broader application in clinical practice and randomised clinical trials. Whether these protocols are suitable for identifying therapy responders, however, remains to be seen in the future. For this purpose, a final validation of the individual bedside protocols and the establishment of reference values is a reasonable and necessary next step. Furthermore, a combination of sensory testing and PROM might be an interesting bedside stratification approach to overcome the limitations of QST and also take into account other aspects of pain like psychosocial comorbidities and impaired physical functioning (Sachau & Baron, 2021).

4.2 | Patient-reported outcome measures

The term 'PROMs' refers to any method, for example, questionnaire or structured interview, which can be used for assessing the state of health or the effect of a treatment/intervention from the patient's point of view without interpretation by a clinician or anyone else. Different constructs like function, quality of life or disease-specific parameters can be evaluated by use of specific PROMs (Fitzpatrick et al., 1998). Instruments for different situations are available: PROMs can aid diagnostic classification as well as characterising symptoms and assessing change during the disease. Not only can PROMs aid in clinical routine by contributing to decision-making, improving diagnostic algorithms and pain management (Boyce et al., 2014; Holmes et al., 2017; Zidarov et al., 2020), but it is also increasingly recognised that PROMs are valuable to appropriately assess treatment outcome and should, therefore, be applied in clinical trials. The most common, in fact daily, PROM for pain assessment is the routine pain intensity rating using numeric rating or visual analogue scales, while more complex tools and assessments are less broadly used. Using simple pain ratings as outcome parameters might in fact contribute to the current lack of evidence in clinical pain trials. Innovative trial designs integrating patient satisfaction as well as adequacy of treatment (Nadeau et al., 2022) measured by PROMs in addition to increasing quality of assessment by ensuring validity and reliability (Pogatzki-Zahn et al., 2019) are approaches for meeting this challenge. Furthermore, pain reduction is not the only or most important goal in the treatment of pain patients. Consideration of functionality and quality of life needs to be customary not only in clinical practice but also in clinical trials as well (Nadeau & Lawhern, 2022). For an appropriate choice of outcome parameters patient involvement in selection and development of PROMs (Staniszewska et al., 2012) should be ensured.

To increase comparability between trials and enable meta-analyses, IMMPACT (Initiative on Methods, Measurement and Pain Assessment in Clinical Trials) compiled recommendations for which PROMs should be considered when assessing chronic pain treatment (Dworkin et al., 2005), similar recommendations have been made for interdisciplinary multimodal pain therapy (Kaiser et al., 2018). These efforts enable cooperability between studies, making it easier to judge study quality and effects as well as allowing for pooled analyses.

As PROMs allow the possibility to gather information crucial in the characterisation of pain, they should not be left out in the recent efforts of investigating pain mechanisms and predicting treatment response. Psychological characteristics and patient disposition have been proven to be essential for gaging treatment success. For musculoskeletal pain, stratification based on psychosocial profiling already has been applied. It has shown that patients exhibiting pain catastrophizing, experience worse outcomes, when treated for shoulder pain (George et al., 2015) or non-specific lower back pain (Wertli et al., 2014). A thorough assessment makes it possible to adjust treatment to the patient's individual situation, beliefs, impressions and challenges.

Additionally, reported signs and symptoms may also reflect pathophysiological mechanisms. Similar to how different sensory profiles assessed by QST have shown different responses to treatment (Demant et al., 2014), using PROMs for stratification has already been shown to be promising. Patient stratification using the Neuropathic Pain Symptom Inventory showed, that the most effective combination of duloxetine and pregabalin differed dependent on the sensory phenomena and quality of pain experienced (Bouhassira et al., 2014) and was able to predict the response to botulinum toxin A (Bouhassira et al., 2021).

While stratification via QST does not take into consideration ongoing pain or spontaneous sensory phenomena (Schmelz, 2021), PROMs provide a different angle of approach for mechanism-based therapy. It is not possible to substitute one method with the other (Gierthmühlen et al., 2019, 2022). With both approaches covering each other's blind spots, a combined assessment might offer more insight (Vollert et al., 2021). Especially, with validated bedside-tools making QST more accessible, integrating this idea in future clinical trials seems feasible.

5 | CLOSING REMARKS

We have presented some major challenges and opportunities for current and future pain research and treatment. Some of the challenges are not unique to pain, for example, individual response prediction to placebo and other aspects of general clinical trial design as well as rigour and reproducibility in preclinical study conduct affect all of health research, not just pain. While focussing on specific aspects like stratification of patients and back-translation of assessments to animal models may offer exciting opportunities for advances and identification of effective treatment options, the problem remains wicked. Nonetheless, we believe that if pain researchers and treatment practitioners continue to engage in improving methodological rigour, developing new methods and technologies to focus on patient needs and patient-led outcomes, aligning animal experiments with realistic clinical scenarios, and other challenges, pain treatment will continue to improve.

AUTHOR CONTRIBUTIONS

Conceptualisation: JV; Writing – original draft: NS, DK, TL, JS, MS and JV; Writing – review and editing: NS, DK, TL, JS, MS and JV; Graphic abstract – NS and JV

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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