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Patient phenotyping in clinical trials of chronic pain treatments: IMMPACT recommendations

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Abstract

There is tremendous inter-patient variability in the response to analgesic therapy (even for efficacious treatments), which can be the source of great frustration in clinical practice. This has led to calls for “precision medicine”, or personalized pain therapeutics (i.e., empirically-based algorithms that determine the optimal treatments, or treatment combinations, for individual patients) that would presumably improve both the clinical care of patients with pain, and the success rates for putative analgesic drugs in Phase 2 and 3 clinical trials. However, before implementing this approach, the characteristics of individual patients or subgroups of patients that increase or decrease the response to a specific treatment need to be identified. The challenge is to identify the measurable phenotypic characteristics of patients that are most predictive of individual variation in analgesic treatment outcomes, and the measurement tools that are best suited to evaluate these characteristics. In this article, we present evidence on the most promising of these phenotypic characteristics for use in future research, including psychosocial factors, symptom characteristics, sleep patterns, responses to noxious stimulation, endogenous pain-modulatory processes, and response to pharmacologic challenge. We provide evidence-based recommendations for core phenotyping domains and recommend measures of each domain.

Keywords

Phenotype; Central Pain Modulation; Neuropathic; Quantitative Sensory Testing; Psychosocial; Sleep

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Introduction

Persistent pain is a serious therapeutic challenge and a public health epidemic; it is estimated to affect over 100 million American adults at any given time, is among the leading global causes of reduced quality of life [1], and carries direct and indirect costs of over 600 billion dollars annually in the U.S. alone [102]. Patients are treated with a wide range of interventions, with analgesic medications among the most common treatments. However, long-term administration of analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) and opioids involves risks of organ damage, overdose, and in some cases drug dependence and misuse syndromes [32;33;133;136;188]. Such findings have stimulated intensive efforts to direct specific treatments to those patients who will demonstrate the most favorable risk-benefit profiles (i.e., those who are most likely to experience meaningful analgesia and improvements in function, and least likely to experience serious side effects).

As has long been recognized, inter-patient variability in analgesic outcomes (even for efficacious treatments) is impressively broad, and can be the source of significant frustration in clinical trials as well as clinical practice [9;74;77]. Numerous large, high-quality, randomized, controlled trials (RCTs) of drugs for many chronic pain conditions have produced negative findings despite encouraging results from preclinical and early clinical studies. However, rather than a stark lack of efficacy, such results may indicate the presence of substantial patient heterogeneity, which obscures positive outcomes in certain subgroups of the study cohort. That is, within a diagnostic category (e.g., post-herpetic neuralgia (PHN), fibromyalgia (FM), osteoarthritis), multiple pain mechanisms and outcome-relevant patient characteristics may be active to varying degrees in different patients, leading to marked inter-subject variation in treatment effects. This variability in phenotypic presentation of different pain syndromes is found to be greater between patients than between different pain syndromes [e.g. 10;16;17], indicating that mechanistic etiologies and subsequent successful treatment are likely to be based at the level of the individual rather than at the level of the disease. In contrast to preclinical studies that focus on selective pharmacologic blockade of a single identified nociceptive mechanism, studies designed to facilitate phenotyping in clinical practice may need to assess (separately and in combination) numerous, multidimensional, potential contributors to the experience of pain. Collectively, this state of affairs has led to calls for personalized, or tailored pain therapeutics, also termed precision medicine [16;74;202]. Precision, or personalized treatment approaches in pain medicine will presumably improve both clinical care of patients with persistent pain, and the success rates for putative analgesic drugs in Phase 2 and 3 RCTs (e.g., trialists could perform baseline phenotyping, and enrich the subsequent trial by selectively enrolling patients with phenotypes that are most likely to respond to the active agent being studied). A cornerstone of this approach is that the characteristics which render an individual patient, or subgroup of patients, more responsive to a specific treatment need to be identified [44]. Similar profiling, or subgrouping, efforts are currently underway in other arenas of medicine as well; for example, this recent statement from a review of “individualized prediction of treatment effects” in the management of cardiovascular disease could easily have been drawn directly from the world of analgesic clinical trials:

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> "The single estimate of effect provided in trials is an average group-level estimate, implicitly considering that every patient has an average risk, and the same average response to treatment. However, individual patients vary greatly in characteristics that affect the absolute benefit they will receive from treatment. Some will benefit more than average while others do not benefit or may even be harmed. Current practice is to administer the same treatment to a wide range of patients who are all presumed to resemble the 'mean' patient behind the single point estimate of treatment effect. However, there are no average patients, and there is a wide range of treatment effects in individual patients."[238], p. 837.

As noted in a recent review [74], this treatment by patient interaction is only one source of variability in observed RCT responses (others include within-patient variation over time), but it is clearly an important source of variability and potential negative impact on assay sensitivity. A challenging issue, and ongoing point of debate, is what measurable phenotypic characteristics of patients are most predictive of inter-patient variability in analgesic treatment outcomes, and what measurement approaches are best suited to evaluate these characteristics. Although a great deal is known about the predictors of persistent pain and disability, less is known about the phenotypes that predict the *responses* to pain treatment, and we cannot assume that these factors, or factor combinations, are the same. Indeed, the absence of a unified conceptual model of pan phenotypes constitutes an important limitation within the field. We define phenotype as "The ensemble of observable characteristics displayed by an organism", and note that while some definitions of phenotyping include the assessment of genetic features of an organism, we focus here exclusively on patient self-reported characteristics (e.g., psychosocial functioning), patient-reported symptoms (e.g., sleep disruption, neuropathic pain symptoms), and patients' verbal or behavioral responses to standardized provocation (e.g., quantitative sensory testing (QST), which involves administration of precisely calibrated somatosensory stimuli). This necessarily limits the scope of the present review, and we realize that as our knowledge of the mechanisms underpinning the development and maintenance of chronic pain continues to grow, the importance of additional phenotypes may well become clearer. For example, neuroimaging-based markers of central sensitization provide crucial mechanistic and prognostic information regarding inter-individual variability among patients with a variety of chronic pain syndromes (e.g., chronic pelvic/abdominal pain [37]), and a recent functional MRI (fMRI) study of resting state connectivity revealed that pre-treatment assessment of brain connectivity phenotypes among patients with fibromyalgia was associated with subsequent response to oral analgesic medications and to placebo [211]. We also recognize that all of the phenotypes discussed in the present review are shaped by genetic factors, as noted in recent reviews of the pain genetics literature [69;128], but a comprehensive treatment of pain genetics is beyond the scope of this article. See Table 1 for an index of the phenotypic domains covered here, as well as examples of specific measures.

1. Methods

In June 2013, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), a consortium of individual from academia, government agencies (e.g., the U.S. Food and Drug Administration (FDA), National Institute on Drug Abuse, and

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Substance Abuse and Mental Health Services Administration), pharmaceutical companies, and patient advocacy and research organizations, convened a 2-day meeting with the aim of developing recommendations for the domains and specific measures that should be applied in patient phenotyping for Phase 2 and 3 analgesic clinical trials. Much of the evidence base derives from trials of analgesic medications, but these recommendations are envisioned as being generally applicable to non-pharmacologic trials as well. Meeting participants were selected for their international expertise in research, administration, policy, and clinical care related to measuring individual differences in patients with pain and/or conducting clinical trials. The meeting was intended to derive general recommendations that would be broadly applicable to numerous chronic pain conditions and treatment modalities; as a consequence, the composition of the meeting reflected a broad representation of relevant disciplines and perspectives (e.g., anesthesiologists, neurologists, rheumatologists, psychologists, basic scientists, neuropathic pain experts, musculoskeletal pain experts, visceral pain experts), from a number of countries, while limiting the overall meeting size in order to promote fruitful and efficient discussion.

A set of background articles was circulated prior to the meeting to ensure that participants were familiar with relevant issues. In addition, background lectures were presented by several of the authors of this article (M. A., R. D., R. E., R. F., P. H., S. H.) that covered a broad range of relevant clinical research design issues. After the meeting, additional literature searches were conducted, reviewed, and incorporated into the summary of the discussions and recommendations. Electronic versions of the manuscript were circulated to all authors and iteratively revised based upon their input. Final agreement on the recommendations presented in this article was achieved through discussion at the meeting and iterative review of the draft manuscript by all of the authors. The final version of the manuscript was approved by all authors.

2. General considerations

Phase 2 and 3 RCTs assessing analgesics have traditionally been designed to demonstrate analgesic efficacy relative to placebo or an active comparator. However, such trials also represent a valuable opportunity to implement phenotyping methodologies that could promote rapid advances in the identification of patient subgroups, and, subsequently, individualized pain management.

There are multiple benefits to developing a unified and standardized evidence-based set of recommendations for Phase 2 and 3 trial phenotyping. Such benefits include the eventual refinement and standardized operational definition of a detailed pain taxonomy (which may cross current anatomically- and etiologically-based diagnostic boundaries [90]), the potential for pooling phenotypic and outcomes data across studies in order to achieve enhanced power for subgroup analysis, and the advancement of a science of personalized pain management (i.e., by helping pain researchers to prioritize phenotyping targets from the nearly-limitless array of potential contributors to inter-patient variability in treatment outcomes). A recently-proposed evidence-based, multidimensional approach to classifying chronic pain disorders has highlighted the momentum in the field away from traditional anatomically-based clinical diagnosis [90]; this proposed taxonomy includes a dimension incorporating phenotypic

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neurobiological and psychosocial mechanisms, risk factors, and protective factors. Moreover, by identifying gaps in the evidence regarding prediction of pain trial outcomes, we believe that the present review will highlight important avenues for future pain research. Similar to prior IMMPACT meetings charged with developing recommendations for the use of specific measures in analgesic RCTs [75], presenters and meeting participants used a variety of criteria in evaluating potential phenotyping domains and instruments. These included: [1] appropriateness of measure content; [2] reliability; [3] validity; [4] interpretability; [5] precision of scores; [6] respondent and administrator acceptability; and [7] respondent and administrator burden and feasibility. In addition, a central guiding criterion was [8] published evidence of predictive utility in one or more analgesic clinical trials (preferably RCTs, though the participants also considered evidence from longitudinal cohort studies).

Throughout the remainder of the manuscript, when considering evidence of an association between phenotype and outcome in longitudinal treatment studies, we distinguish between 2 broad classes of effects. First, general predictive effects involve studies in which the phenotypic characteristic in question is either examined only within a single treatment group – as is often the case in prospective cohort studies of multidisciplinary pain management programs, for example- or is similarly associated with the outcomes from multiple treatments, potentially including placebo treatments. Second, treatment effect modification refers to findings in which a phenotypic characteristic is differentially associated with outcomes in different study treatment arms. Such effect modification findings are also sometimes referred to as moderation (with the variables in question termed “moderator” variables [18;245]), and we use these terms interchangeably. This category of findings (i.e., treatment effect modification, or moderation) is far more conducive [than general predictive effects] to enhancing the assay sensitivity of analgesic trials, which relies on maximizing the separation between improvement in the active treatment group and that in the placebo group [74;77;78]. For example, some evidence suggests that for many analgesic RCTs, a higher intensity of baseline pain is associated with an elevated probability of response to both active agent and placebo [9;76;78]; in this case, increasing the mean baseline pain intensity is unlikely to improve assay sensitivity. However, in the case of analgesic trials in patients with neuropathic pain conditions such as painful diabetic neuropathy and persistent post-surgical pain, more intense pain at baseline has been selectively associated with greater improvement in the active treatment arm vs. placebo [78;272]. Such findings highlight the sometimes selective nature of phenotyping effects and suggest, for these particular conditions, setting a trial entry criterion requiring a minimum pain intensity that is at least moderate in magnitude could increase power [or reduce the required sample size] by enhancing the effect size for the agent being studied.

Recent reviews have recommended careful attention to trial characteristics that might enhance assay sensitivity by, for example, reducing the magnitude of placebo effects [77]. Here we are concerned not with design features such as the length of the study, but with patient characteristics that might be selectively or differentially associated with greater responses to specific active treatment agents, or with reduced responsiveness to placebo treatments. Given that the mechanisms underlying placebo analgesia appear to differ from the analgesic effects produced by active agents such as opioids [8;23], it seems plausible that

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certain phenotypic characteristics might predict responses to one of those categories of treatment and not the other. Such a phenotype could then be employed as part of the selection criteria for a Phase 2 or 3 RCT in order to maximize the estimated standardized effect size (i.e., the difference between the treatment and placebo group mean responses, divided by the standard deviation of the outcome variable) of the trial. Note that many of the patient-level characteristics studied here are likely to be generally predictive of outcomes in a variety of diagnostic groups (e.g., neuropathic pain conditions, musculoskeletal pain, visceral pain), though in some cases individual variables may offer more selective predictive value for specific treatments in particular chronic pain conditions. Collectively, a number of variables have been used to characterize or phenotype patients with a broad array of chronic pain diagnoses; these phenotyping variables include psychosocial factors, pain qualities and other symptom characteristics, sleep patterns, responses to noxious stimulation, endogenous pain-modulatory processes, and response to pharmacologic challenge. The following sections of the manuscript elaborate on phenotypic characteristics that have been studied as potential contributors to the assay sensitivity of putative pain-reducing treatments (see Tables 1 and 2 for a summary of the recommended phenotyping measures).

In conducting this review, it is not our intention to criticize the existing pain RCT literature. Because of the enormous number of extraneous, uncontrolled (and potentially uncontrollable) factors that impact outcomes in analgesic RCTs, clinical trials examining group means in large numbers of subjects have been necessary to answer the straightforward question of whether there is a causal relationship between an intervention and an outcome. This approach has been crucial in identifying a number of medications [and, more generally, classes of medications] that, on average, produce significant benefit over placebo. We hope that this manuscript will offer useful suggestions for further advancing the field by assisting investigators in selecting self-report phenotyping measures that have potential for influencing the outcomes of specific analgesic treatments. In general, this area of knowledge is not sufficiently mature to permit firm recommendations regarding patient selection at this point; rather, we offer suggestions for future trials intended to inform the field and eventually lead to such specific recommendations.

3. Phenotypic domains

4.1. Psychosocial factors

The overlap between affective disturbance and chronic pain is widely recognized [103;231]. Across numerous studies, patients with a variety of chronically painful conditions generally have a several-fold increase in the risk of being diagnosed with a mood disorder. Longitudinal research also supports a strong bidirectional link between mood disorders and persistent pain; the development of an enduring pain condition confers a substantially increased risk for the subsequent diagnosis of an affective disorder, while psychosocial variables such as depression, anxiety, and distress are among the most potent and robust predictors of the transition from acute to chronic pain, especially musculoskeletal pain [82;157;175]. Some evidence also suggests that high levels of negative affect and pain-specific distress are associated with reduced benefit from a variety of potentially pain-reducing treatments [82;249;250]. This evidence is almost entirely from “general prediction”

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studies, that is, those studies that prospectively or retrospectively predict treatment responses in active treatment groups but not differences vs. placebo or another active treatment. A number of relevant studies in this area involve studies of inter-patient variability in pain trajectories following surgery. Recent findings related to persistent pain after joint replacement highlight the importance of assessing mental health, or psychosocial functioning, pre-operatively [72;115;244], as patients with higher baseline levels of anxiety and depression report less benefit, more complications, and poorer function for years after total knee or total hip replacement.

One important note: before proceeding to recommend specific measures, we find it prudent to echo the sentiments of recent reviews that note that characterizing domains of variables as “psychological” or “psychosocial” refers principally to the method of assessment rather than the presumed underlying pathophysiologic mechanism that drives pain-related outcomes [69]. For example, constructs such as somatic awareness, and pain-related catastrophizing may partly reflect altered peripheral and central nervous system processing of sensory stimuli; these “psychological” features of patients are often significantly correlated with measures of somatosensory amplification on quantitative sensory testing (QST).

Collectively, while instruments assessing depression, anxiety, and distress have most often appeared as outcome measures in the pain RCT literature [75;228–230], emerging evidence suggests that pre-treatment phenotyping of these patient symptoms can have important predictive effects [82]. On the basis of a review of the literature of measures of emotional functioning used in phenotyping participants in analgesic trials, the Hospital Anxiety and Depression Scale (HADS) can be recommended as a core phenotyping measure for assessing general negative affect (see the background materials for IMMPACT-XVI at http://www.immpact.org/index.html). The HADS is a 14-item self-report questionnaire designed to assess symptoms of anxiety and depression in those with medical illness. It has well-established reliability and validity in the assessment of symptoms of depression and emotional distress, and it has been used in numerous clinical trials [180;218]. It does not include somatic symptoms, such as fatigue and sleeplessness, which may otherwise be attributable to physical illness and it has been standardized among large community samples. It has also been validated in several medical illness populations with good sensitivity and specificity for predicting DSM-IV major depression or generalized anxiety disorder diagnoses. Depending on the needs of the study and the degree of specificity required, HADS scores can be used to provide separate indices of anxious and depressive symptomatology [210], or a total HADS score may be used as an index of overall negative affect [130;250;251]. There has, however, been some debate regarding the independence of the anxiety and depression subscales and the factor structure of the HADS [180].

Importantly, several trials of opioid analgesics have noted that elevated pre-treatment scores on the HADS are associated with reduced opioid analgesic benefit [130;248;249] within the active treatment group. In addition, higher baseline HADS scores also predicted higher rates of medication misuse [248], an important outcome to consider in Phase 2 and 3 trials of opioid analgesics. To date, the observed associations between baseline HADS scores and analgesic outcomes have been limited to the category of general predictive effects (e.g., no study has yet shown that pre-treatment HADS scores influence responses to an active agent

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but not placebo). Such findings are important, of course, and provide valuable information that is directly relevant to the clinical care setting (in which medications are not administered in a randomized, blinded fashion); however, definitive conclusions about the potential for HADS scores to influence RCT assay sensitivity must await the results of effect-modification analyses. Issues of sample size also need to be considered, as many trials are not powered specifically to evaluate subgroup- or phenotype-specific outcomes. In the meantime, it is noteworthy that the predictive associations of HADS scores with pain-related outcomes extend beyond trials of opioid analgesics [29;48;142;234;250], though not all trials have shown a predictive effect of baseline HADS scores on pain treatment outcomes. For example, among patients with FM randomized to pregabalin [5], patients with high HADS scores benefitted as much as patients with lower HADS scores, suggesting that affective phenotypes may present drug-specific patterns of association (e.g., high levels of distress may be prospectively associated with reduced opioid analgesia, but may have no impact on responses to other classes of medication).

The HADS is, of course, not the only psychometrically sound and widely used measure of emotional distress. Additional instruments such as the Depression, Anxiety, and Positive Outlook Scale (DAPOS; [195]), the Patient Health Questionnaire [7], the Generalized Anxiety Disorder 7-item Scale [174], or the Center for Epidemiological Studies – Depression scale (CES-D) are also likely to offer good phenotyping potential. The CES-D, a well-validated 20-item measure of depressive symptomatology, has been highly regarded by pain researchers, in part on the basis of its relative brevity, wide international use, and utility as a core measure in prospective studies of the transition from acute to chronic low back pain (LBP) [194]. Additional consideration should be afforded to the NIH-supported Patient-Reported Outcomes Measurement Information System (PROMIS) and the NIH Toolbox, a multidimensional set of brief measures assessing cognitive, emotional, motor and sensory function across the lifespan. While still early in their developmental trajectory as phenotyping instruments, and while designed predominantly as outcome measures, they appear to be potentially valuable additions to the existing assessment tools [49]. PROMIS pools self-report items tapping domains of physical, mental, and social health, into item banks and then uses item response theory and computer adaptive testing methods to provide precise measurement of individual symptom clusters, including domains of negative affect [192;193]. To date, very few prospective studies of treatment for long-term pain have used a PROMIS scale as a phenotyping measure, though published protocols from some current trials suggest that PROMIS measures are beginning to be applied in these contexts (e.g., a trial of spinal manipulation for low back pain: [262]). One recent observational cohort study of patients with LBP treated with epidural steroid injections reported that high basal levels of PROMIS-assessed negative affect were associated with reduced analgesic benefit, consistent with the previously-cited HADS literature [139].

In addition to measures of general negative affect, pain-specific cognitive and emotional processes have demonstrated importance in shaping pain outcomes and treatment responses. Catastrophizing is a pain-specific psychosocial construct comprised of cognitive and emotional processes such as helplessness, pessimism, rumination about pain-related symptoms, and magnification of pain reports [82]. While catastrophizing positively correlates with general measures of negative affect such as depressive symptoms and

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anxiety, it also shows a unique and specific influence on pain-related outcomes [82;145;196]. Retrospective survey studies in patients with musculoskeletal pain have indicated that catastrophizing often emerges as one of the most important pre-treatment variables predicting surgical outcomes [154;213], and a risk factor that impairs the effectiveness of pain-relieving interventions [123;138]. Multiple RCTs in various neuropathic and musculoskeletal pain conditions have shown that pain patients with high pre-treatment catastrophizing report less benefit from topical analgesics [165], cortisone [163], an oral acetaminophen and tramadol combination [209], and psychosocial treatments such as cognitive behavioral therapy (CBT) [68;232], though few of these studies tested for treatment effect modification. A recent study of patients with persistent temporomandibular joint pain, randomized to 6 weeks of either standard care or CBT and followed for 12 months, confirmed the long-term predictive effects of catastrophizing [158]. Patients with high levels of pre-treatment catastrophizing, and those whose catastrophizing scores did not change after treatment, were significantly more likely to be non-responders at 1 year follow-up. Finally, while many of the above studies involve general outcome prediction, a recent RCT of transcutaneous electrical nerve stimulation (TENS) for post-operative pain reported strong effect-modification findings [200]. Patients (n=317) undergoing joint replacement surgery were randomized to receive TENS, placebo TENS, or standard care (no TENS) for 6 weeks. Those in the TENS group with high baseline catastrophizing scores showed less pain reduction and reduced range of motion at 6 weeks. In contrast, there was no predictive effect of catastrophizing in the other two groups (i.e., those receiving placebo or standard care treatment).

When assessing catastrophizing, we recommend the use of the Pain Catastrophizing Scale (PCS [225]), a 13-item, well-validated, self-report measure of catastrophic thinking associated with pain [82]. The PCS has 3 subscales (Magnification, Rumination, Helplessness), has good psychometric properties in pain patients and pain-free controls [237], is the most commonly used measure of pain-related catastrophizing, and has been applied in samples of patients with neuropathic pain, musculoskeletal pain, visceral pain, and cancer-related pain.

Additional psychosocial factors for consideration—Expectations are a crucial component of placebo responses, but they also strongly influence the outcomes of active treatments, from surgery [101;273] to opioid analgesics [26] to complementary and alternative medicine [CAM] approaches such as acupuncture [259]. A recent analysis of multiple large acupuncture trials reveals that both patient and clinical expectations for treatment success are potent predictors of response [258;259]; we recommend that these be considered as phenotypic measures in clinical trials. Though many of the published studies of expectations use single-item assessments, multidimensional scales such as the Stanford Expectations of Treatment Scale [270] may have the strongest psychometric properties. It is important to note that we are not recommending the manipulation of subject expectations, but rather their assessment as a potential contributor to trial outcomes and assay sensitivity.

Measures of somatization, somatic focus, or somatic awareness assess important phenotypic characteristics, particularly for patients with chronic pain conditions such as FM or temporomandibular joint disorders (TMD) [69;91;92]. Findings from the Orofacial Pain:

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Prospective Evaluation and Risk Assessment (OPPERA) study, a large, high-quality, multi-site prospective cohort study of the development of TMD, suggest that measures of somatic focus (e.g., the somatization subscale of the Symptom Checklist -90, and the Pennebaker Inventory of Limbic Languidness, PILL) are among the strongest psychosocial predictors of the subsequent development of TMD [91]. At present, there is a paucity of data from Phase 2 and 3 analgesic RCTs pertaining to the use of somatization measures as phenotyping tools for the purpose of improving assay sensitivity in pain clinical trials, but we recommend considering the inclusion of such measures in a baseline phenotyping assessment. Collectively, while such factors have traditionally been most frequently studied in patients with chronic widespread or idiopathic pain disorders, abundant evidence also suggests their importance in shaping pain-related outcomes [including the transition from acute to chronic pain] for neuropathic pain conditions such as PHN [73;140] or burning mouth syndrome [208].

Finally, several studies suggest that the outcomes of various multidisciplinary or surgical treatments can be predicted by baseline assessment of neuropsychological measures that assess working memory, cognitive processing speed, and attention. [13;110]. Although we know of no Phase 2 or 3 analgesic trials demonstrating similar predictive effects, the inclusion of such cognitive phenotyping measures may be considered in future work in this area. We should also note that the present article is only one in a long line of studies and classification systems that have suggested phenotyping, or clustering, patients on the basis of psychosocial characteristics, with the eventual goal of predicting treatment responses or other pain-related outcomes (e.g., disability) [24;25;45;132]. Such efforts include measurement tools such as the West Haven-Yale Multidimensional Pain Inventory (MPI, [144]), which yields empirically validated subgroups of patients [206], the Örebro Musculoskeletal Pain Screening Questionnaire [31;156], which clusters patients according to their risk for developing persistent pain, the Treatment Outcomes in Pain Survey - Short Form (S-TOPS, [117]), which phenotypes multiple physical and emotional pain-related domains, the STarT back tool, designed as a primary care screening instrument, which predicts recovery from acute back pain [124;257], as well as models such as the fear-avoidance model [59;246], and the avoidance-endurance model [120;121]. The comparison (and perhaps eventual integration) of these measures and models is unfortunately beyond the scope of the present work, but it is noteworthy that essentially all of these classification systems lean heavily on the assessment of negative affective symptoms (e.g., depression, anxiety, distress] and maladaptive pain-related cognitions [e.g., catastrophizing) [205].

4.2. Pain variability and pain qualities

There has recently been a great deal of interest in using electronic tools to perform real-time and more frequent assessment of pain than has traditionally been accomplished using assessment methods that require respondents to report retrospectively on pain levels over periods of time such as a week or month [172;214]. As most pain conditions fluctuate spontaneously, sometimes over very short time scales, diary-based methods that record frequent current pain ratings have come into vogue, sometimes replacing recall-based questionnaires that query subjects about “usual” or “typical” or “average” pain levels. Prior IMMPACT reports have recommended further research on these real-time data capture

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methodologies for potential use as outcome measures in analgesic trials [77]. The use of such methods also offers phenotyping opportunities, as patients differ widely in the degree of temporal variability in their ratings of pain intensity. To date, several RCTs have assessed baseline within-subject pain variability as a phenotypic predictor of trial outcomes in patients with musculoskeletal pain [e.g., [119] as well as neuropathic pain [89].

In an early study of patients with FM, pain variability was stable over time (that is, each subject tended to exhibit a characteristic degree of variability in pain intensity ratings that tended to remain the same over the course of the study, even if his or her mean pain intensity level changed), and individuals with greater variability were more likely to be classified as placebo responders [but were not more likely to respond to milnacipran, the active agent] [119]. Similar findings (i.e., greater response to placebo, but not active treatment, among subjects with high baseline pain variability) are evident in RCTs in clinical trials of PHN and painful diabetic peripheral neuropathy (DPN [89]). Such effect-modification results might suggest that subjects with high pre-treatment variability in pain intensity could be excluded from RCTs in order to minimize placebo responses and maximize assay sensitivity. Additionally, a recent analysis of pooled data from 4 double-blind, randomized controlled trials on the efficacy of topical capsaicin 8% versus an active control (capsaicin 0.04%) found that, despite the very different capsaicin concentrations, higher baseline pain variability was strongly associated with better responses in both groups [166]. Collectively, while the limited research and conflicting findings prohibit firm recommendations about the use of pain variability as an inclusion or exclusion criterion for RCTs, we recommend considering an index of temporal variability in pain intensity as part of the baseline phenotyping of trial participants.

Other aspects of patient-reported pain symptoms are also potentially important targets of phenotyping. In this manuscript we leave aside consideration of patients' average baseline pain intensity, as this topic has been treated extensively in prior IMMPACT reviews [75;77;78;80]. However, as the complex nature of pain symptomatology is increasingly recognized, there has been a rapid increase in the number of questionnaires that measure an array of pain quality descriptors (e.g., "burning", "shooting", "aching") [79;134;155]. Two of these scales in particular include a wide range of the most-commonly used descriptors in samples of patients with pain, the revised Short Form McGill Pain Questionnaire (SF MPQ-2) and the Pain Quality Assessment Scale (PQAS). Both measures are brief, psychometrically sound, and well-validated in multiple neuropathic and non-neuropathic patient samples [79;134;159;186]. Moreover, one recent PQAS study of effect modification in a sample of patients with neuropathic pain found that a number of PQAS items, assessed at baseline, were associated with response to pregabalin [but not with response to placebo] in an RCT [99]. In particular, patients who rated their pain as paroxysmal, deep, electrical, and radiating [along with several other descriptors] reported greater analgesic benefit from pregabalin [but there was no association with placebo benefits], highlighting the potential predictive benefits of comprehensively phenotyping patients' self-report of pain qualities. Similarly, in an effect modification study of individual differences in analgesic responses to intravenous lidocaine treatment, patients with a particular pain quality phenotype on the short form MPQ (i.e., those reporting their pain as "heavy") were disproportionately likely to obtain good analgesic responses [47], but this phenotype did not influence placebo

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responses. Collectively, on the basis of these initial effect modification findings, we recommend the use of either the PQAS or the SF-MPQ-2 for a brief but comprehensive self-report evaluation of pain qualities.

Neuropathic pain symptom reporting instruments—Other self-report instruments targeting descriptions of pain types or pain qualities have been designed specifically to screen for and assess neuropathic pain, defined by an International Association for the Study of Pain publication as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” [135]. Neuropathic pain may affect up to 10% of the general population [239] and is a common target of Phase 2 and 3 analgesic trials. A review by the European Federation of Neurological Societies noted that the lack of specificity of instruments [for identifying neuropathic pain] such as the original McGill questionnaire has led to the development and validation of a number of largely self-report screening tools with improved sensitivity and specificity for identifying the presence of a neuropathic pain condition [60;61]. As summarized by Haanpaa et al. [112], measures such as the Leeds assessment of neuropathic symptoms and signs (LANSS), Douleur neuropathique en 4 questions (DN4), and painDETECT questionnaire are generally relatively effective [often showing adequate sensitivities and specificities for identifying neuropathic pain], convenient, brief methods for assessing the presence and symptomatology of neuropathic pain conditions [97;113;116;233]. However, we should note that recent reviews have identified some limitations in the reliability and validity of these measures, especially in the cross-cultural adaptations of the questionnaires as well as their trans-diagnostic specificity for identifying neuropathic pain. For diagnostic purposes, self-report screening instruments should not replace a comprehensive clinical examination [169].

While the screening tools described above have most often been used either as screening measures in epidemiologic studies or as outcome measures in clinical trials, Attal and colleagues [9] have recently observed that a potentially more important contribution relates to phenotypic profiling to enhance therapeutic prediction. The examination of neuropathic symptom patterns with assessment tools permits the classification of patients into subgroups (e.g., those with vs. without mechanical allodynia), with the assumption that these subgroups have different underlying pain mechanisms and hence will respond differentially to interventions with varying mechanisms of action. Because these assessment methods capture various pain descriptors and qualities of neuropathic pain, they also can be used to characterize patients’ sensory abnormalities. Some tools such as the Neuropathic Pain Symptom Inventory (NPSI) have been specifically validated for this purpose. So far, the NPSI and painDETECT have been most extensively used in neuropathic pain studies to subgroup patients according to their pattern of sensory abnormalities [10;17;21;97;148;160]. These studies used a hierarchical cluster analysis or factor analysis to identify prevalent patterns or dimensions of sensory symptoms that occur commonly among patients with a variety of neuropathic pain conditions, including DPN, PHN, central pain syndromes, and painful radiculopathy. It is noteworthy that the painDETECT (and other similar instruments) has been used to subtype not just patients with neuropathic pain but also individuals with chronic musculoskeletal pain conditions such as fibromyalgia [148], osteoarthritis [171], axial low back pain [95], and persistent post-traumatic pelvic pain [105]. To date, almost no

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Phase 2 and 3 trials appear to have used prospective phenotyping as an inclusion criterion (for an exception, see [19;20]), consistent with the relative infancy of this field. However, several encouraging trials that use post-hoc clustering of patients have appeared in the literature over the past several years.

In a Phase 3 trial of tapentadol for chronic low back pain, painDETECT and the NPSI were used to phenotype neuropathic pain symptoms at baseline, and some differentially large improvements were observed on several quality of life subscales among the group identified as likely having a neuropathic component to their pain [223]. Even more recently, a pooled post-hoc analysis (assessing potential effect modification findings) was done with baseline NPSI data from four large Phase 3 trials of pregabalin [97]. Cluster analysis produced subgroups of patients with specific patterns of neuropathic pain symptoms, and several of the NPSI-identified subgroups had greater pain improvement after taking pregabalin than did those who took placebo. Interestingly, a randomized, double-blind comparison of pregabalin and duloxetine in patients with diabetic neuropathic pain suggested that the cluster of patients with the lowest baseline NPSI scores (i.e., the least neuropathic pain symptoms) responded better to duloxetine than to pregabalin ($p=.002$ for the comparison of 8-week pain reduction), while the cluster with the highest baseline NPSI scores reported equivalent benefit from the two medications [35]. This type of effect-modification evidence is particularly tantalizing in the context of neuropathic pain, which almost certainly involves multiple mechanisms and broad inter-patient variability. At least one trial has also investigated the predictive effects of specific NPSI dimensions in an effect modification analysis [67]. This RCT of the sodium channel blocker oxcarbazepine in patients with peripheral neuropathic pain noted that the subgroup of patients reporting “paroxsymal” and “burning” pain symptoms on the NPSI at baseline showed significantly better pain reduction with oxcarbazepine than placebo ($p=.002$ for the interaction of baseline phenotype with treatment [67]). Finally, a Phase 3 trial of prolonged release (PR) tapentadol (in which patients with a positive initial response to tapentadol PR were randomized to continuation of tapentadol PR or to tapentadol PR plus pregabalin) in patients with chronic low back pain used neuropathic symptom profiling as an inclusion criterion. Only patients with a painDETECT score of 13 or above were enrolled; outcome analyses suggested strong improvements in painDETECT and NPSI scores in patients treated with tapentadol PR and with tapentadol PR plus pregabalin [19;20].

Additional evidence for the potential benefits of these phenotyping measures derives from a recent retrospective study (general prediction) of outcomes following dorsal root entry zone (DREZ) lesioning [114]; patients with the highest baseline painDETECT scores reported the worst long-term outcomes. Moreover, data from a large uncontrolled general prediction study of high-concentration capsaicin patches showed that higher baseline painDETECT scores were associated with greater pain reduction after 12 weeks of treatment in patients with chronic neuropathic pain [126]. Collectively, these findings strongly suggest that specific neuropathic pain phenotypes may be associated with differential responses to varying analgesic treatments. Patients with the greatest degree of pre-treatment neuropathic pain symptoms might respond best to pregabalin, or topical capsaicin treatment, whereas those reporting the least baseline neuropathic symptoms might benefit most from duloxetine, for example, as in [35]. Such conclusions are presently tentative at best, and require

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replication and additional head-to-head comparisons of active treatments. Some of these neuropathic pain measures have been developed and tested for use in particular diagnostic groups of patients. In the domain of chronic back pain, the Standardized Evaluation of Pain (StEP), which consists of 6 interview questions and 10 physical tests, has been used to evaluate the neuropathic components of spinal pain and to distinguish axial LBP from back pain with signs of a radiculopathy [212]. Indeed, StEP has recently been applied as part of a screening neurological examination to evaluate participant eligibility in an RCT focused on patients with radiculopathy-related neuropathic pain [187]. Other validated tools such as the Michigan Neuropathy Screening Instrument are also increasingly used to assess specific neuropathic conditions (e.g., distal peripheral neuropathy in diabetes) [34].

Given the generally positive evidence for their validity, their ease of use, and their reasonable sensitivity and specificity, use of the NPSI and/or painDETECT is recommended for screening for neuropathic pain phenotypes or characterizing/subgrouping sensory profiles of neuropathic pain patients. In samples of LBP patients, the StEP could be considered to identify radicular pain, though painDETECT and NPSI have been more widely used to phenotype neuropathic LBP in Phase 2 and 3 trials [19;20;223]. It is important to note that these recommended phenotypic measures assess constructs that overlap with other domains as well. Self-report of neuropathic pain symptoms on screening measures correlates with QST findings [97], catastrophizing [125], sleep disruption, and measures of emotional distress [12;34]. It is presently unclear precisely how all of these potentially inter-related phenotyping measures might be studied as predictors of analgesic outcomes in a single trial; we strongly encourage additional clinical studies in this area.

4.3. Sleep and Fatigue

Experimental, clinical, and epidemiologic studies have suggested that sleep disruption or deprivation has a variety of negative effects within the general population and in pain-specific samples, including: enhanced pain sensitivity, reduced pain inhibition, elevated chronic pain severity and disability, and an increase in the frequency and impact of daily musculoskeletal pains [81;93;183]. In longitudinal studies, individuals with sleep disturbance are at elevated long-term risk for developing clinically-relevant pain, especially persistent musculoskeletal pain, and most researchers in the field have concluded that pain and sleep disruption exhibit reciprocal, bi-directional influences [93]. It is also clear that insomnia and its associated symptoms are a major contributor to poor pain-related quality of life; an IMMPACT survey found that trouble falling asleep, trouble staying asleep, and feeling tired, are 3 of the top 10 importance-rated domains for individuals with persistent pain [230].

While it has become clear that sleep and pain often improve together [70], the presence of concurrent changes over the course of treatment does not necessarily imply that pretreatment sleep phenotype predicts analgesic outcomes in a RCT. However, several interventional studies have provided general evidence for such an association. Among patients with chronic orofacial pain undergoing multidisciplinary pain management, participants with poorer sleep and more fatigue were less likely to be treatment responders at follow-up [110]. It is also noteworthy that in pre-clinical studies, sleep-deprived animals derive reduced analgesic

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benefit from opioids and at least one controlled human study has shown similar effects, with fatigued/"sleepy" participants showing no effect of codeine on pain thresholds, in contrast to non-sleepy subjects [224]. Interestingly, a post-hoc analysis of data pooled from 16 placebo-controlled trials of pregabalin in patients with neuropathic pain conditions (i.e., DPN or PHN) revealed that, among thousands of patients, one of the best predictors of pregabalin-associated pain reduction was a high degree of sleep disruption at baseline [242;243]. This small set of apparently disparate findings again suggests that phenotypic measures of sleep disturbance are likely to have treatment-specific predictive effects (e.g., patients with severe insomnia may benefit most from pregabalin and least from opioids). This is a fertile area for future research, as multiple reviews suggest that assessment of sleep-related factors may provide important predictive phenotypic information about individual patients with an array of acute and persistent pain conditions [93;96].

For assessing sleep when phenotyping patients in clinical trials, self-report instruments such as the Pittsburgh Sleep Quality Index (PSQI)[39] and the Insomnia Severity Index (ISI)[22] can be recommended. These are widely used instruments with good psychometric properties that have been validated in individuals with chronic pain disorders [221]. The PSQI and ISI have well-established cut-off criteria demarcating good from poor sleep and clinical insomnia, and these have been validated in a variety of neuropathic and musculoskeletal pain samples [93]. An "objective" measurement of sleep may also be considered, as a patient's self-report may differ from polysomnography- or actigraphy-derived indices, especially in patients with persistent pain [184]. Wrist actigraphs provide a 24-hour measure of motor activity that decreases sharply during sleep. They are convenient and unobtrusive, and are increasingly being used in sleep and pain research, showing prospective associations with post-surgical pain [261] and with daily variation in long-term pain [181].

In addition to indices of sleep, a measure of fatigue should be administered; as noted by the Outcome Measures in Rheumatology (OMERACT) group, simple visual analog scales and several multi-item measures such as the Multidimensional Fatigue Inventory (MFI) show good reliability and validity and have been widely recommended for use as outcome measures [147]. These would be a reasonable choice for phenotyping fatigue; the MFI in particular has been used in multiple pharmacologic treatment studies of patients with chronic pain [6;170]. Sleep disruption and fatigue often co-occur within symptom clusters in the context of a variety of persistent pain conditions [176;241], but to date, no published studies appear to have examined pre-treatment fatigue phenotypes as predictors of analgesic outcomes.

4.4. Quantitative sensory testing (QST) and sensory profiling

QST refers to a set of psychophysical methods used to quantify somatosensory function. It is based on measurements (using standardized response scales) of responses to calibrated, graded, innocuous, or noxious stimuli (generally mechanical or thermal) and represents an extension and refinement of the bedside clinical examination of the sensory system. QST has been used for decades in a variety of research settings, often for the purpose of diagnosing and monitoring sensory neuropathies and pain disorders, as well as for the investigation of pain mechanisms, the characterization of somatosensory profiles in various pain disorders,

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and the elucidation of individual differences in pain sensitivity and pain modulation [4;15;15;62;161;190;203;204]. QST allows the assessment of specific sensory modalities that correspond to distinct receptors, peripheral nerve fibers, and their corresponding central nervous system pathways which are common to many persistent pain conditions. It has been most widely utilized for testing of cutaneous sensations, but it has also been adapted to test sensations from deep tissue and viscera, allowing broad application to an array of pain conditions [4]. QST may be used to quantify and monitor the presence and severity of either positive sensory phenomena (e.g., allodynia and hyperalgesia] or negative sensory phenomena [e.g., hypoesthesia and hypoalgesia). Collectively, the past 20 years have witnessed a veritable explosion of QST research, with large annual increases in the number of peer-reviewed QST publications appearing on PubMed [27].

A handful of recent, large studies have applied QST to patients with a variety of pain syndromes [often neuropathic pain conditions] in order to examine sensory profiles or subgroups [97;106;161]. Many of these studies use the German Research Network on Neuropathic Pain (DFNS) testing protocol, which is highly standardized and reliable [104;191;203;204], and which includes the assessment of a broad variety of parameters, such as detection thresholds for thermal and mechanical stimuli, pain thresholds, temporal summation of mechanical noxious stimuli, and dynamic mechanical allodynia.

In general, the recent “profiling” studies of large groups of neuropathic pain patients have determined that: [1] the vast majority of subjects exhibit at least 1 sensory abnormality on QST [17], which is expected, given that many diagnostic criteria require positive or negative sensory symptoms/signs [2] every somatosensory abnormality occurs with a non-zero frequency across every pain condition studied to date, and [3] no particular QST profile is unique to a given pain diagnosis [17;97;106;161]. These observed “trans-etiological” patterns of sensory symptoms and deficits may reflect separate but overlapping pain mechanisms, which may eventually be a fruitful target for specific therapeutic approaches.

In addition to its utilization for characterizing and profiling, QST has also been applied in a number of predictive contexts. Pre-operative individual differences in pain sensitivity and somatosensory function have shown prospective associations with acute and chronic post-operative pain in studies of postsurgical pain across a number of procedures from amputation to cesarean section to bunionectomy [109;143]. Such findings highlight the potential value of QST in these settings (e.g., patients with a particular QST profile might experience reduced risk for persistent post-operative pain if managed with particular pre-, peri- or post-operative analgesic regimens), but it is presently unclear whether these results can be applied to the realm of Phase 2 and 3 RCTs in patients with persistent pain. In the context of other conditions such as DPN and chemotherapy-induced neuropathy, QST has proven itself to be a sensitive predictor of clinical deterioration (e.g., the development of foot ulcers in diabetic patients) or the worsening of neuropathy [15].

To date, relatively few Phase 2 and 3 analgesic RCTs have utilized baseline phenotyping by QST to predict treatment response. However, some promising findings are emerging [9;17] from the handful of recent, diverse neuropathic pain trials recently examining pre-treatment QST responses as predictors of response to therapy. These predictive studies are founded on

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the concept that if sensory symptom profiles reflect pain mechanisms, then patients with different sensory response characteristics are likely to respond differentially to particular treatments, allowing (eventually) the tailoring of mechanism-targeted treatments to individual patient phenotypes [16;202].

QST was used in a study of patients with traumatic nerve injury and PHN who were treated with botulinum toxin. A good outcome (i.e., a significant reduction in spontaneous pain and dynamic mechanical allodynia) correlated with the preservation of cutaneous thermosensation, documented by low warm and heat pain thresholds at baseline [201]. Similar predictive results were observed in a study of motor cortex stimulation among patients with chronic neuropathic pain (e.g., trigeminal neuralgia, post-stroke pain) [71]. Participants with preserved thermal thresholds reported the largest percentage pain relief from motor cortex stimulation. Suggestive evidence that certain treatments are most effective in the context of thermal hyperalgesia has also come from a recent case report in which QST was performed in a patient with bilateral at-level pain following a spinal cord injury [256]. On the right side of the body, the patient exhibited preserved thermosensation, and some evidence of cold hyperalgesia, while on the left side, there was a prominent loss of thermal and mechanical sensation. Interestingly, pregabalin treatment was highly effective for at-level pain on the right side but not the left side, suggesting a selective effectiveness for pain mediated by hypersensitivity processes.

Other trials have reported parallel results when considering mechanical, rather than thermal, QST measures. Among patients with PHN, those with mechanical allodynia had a better outcome with intravenous lidocaine than with placebo [14], a finding (i.e., better response to active treatment among those with mechanical allodynia or hyperalgesia) that has been reproduced among patients with spinal cord injury pain treated with lamotrigine [94], and patients with HIV neuropathy treated with pregabalin [215]. A recent investigation in patients with chronic visceral pain confirms that pre-treatment hyperalgesia (in this case, hyperalgesia to cutaneous electrical stimulation) in the painful area was associated with better analgesic responses to pregabalin [185]. No associations were detected with the magnitude of placebo analgesia, though other reports have described a general predictive capacity for QST-derived pain responses. For example, a recent RCT revealed that cold hyperalgesia was among the most potent predictors of placebo responses among patients with unilateral lateral epicondylalgia [57].

To date, the majority of the positive findings involving QST-assessed phenotypes have been identified in post-hoc analyses. However, some recent trials have begun to incorporate pre-specified phenotypic hypotheses into their study designs. For example, a 2014 RCT of oxcarbazepine showed effect modification using elements of the multimodal DFNS QST paradigm [67]. At baseline, patients were phenotyped with the DFNS paradigm into “irritable nociceptor” [i.e., those with sensory gain, relative to reference data, on mechanical and/or thermal testing] and “nonirritable nociceptor” groups. The irritable nociceptor group derived substantially greater benefit from oxcarbazepine than their counterparts in the nonirritable nociceptor group, with no differences in placebo effects, which were minimal in both groups. The number needed to treat [NNT] for 50% pain relief was 3.9 in the irritable nociceptor group, compared with an NNT of 13 in the remainder of the sample [67].

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Together, these studies highlight the potential for tailoring specific treatments to particular subgroups of patients with differing sensory profiles, and suggest that agents affecting sodium and calcium channels may exert their largest analgesic effects among neuropathic pain patients who exhibit the greatest degree of hyperalgesia and allodynia in the painful area. Such a conclusion may only apply to systemic administration of these medications, as studies of topical lidocaine have yielded inconsistent results [122;252]. Similarly, recent trials of topical capsaicin have noted varying patters of response, with one study reporting that patients without allodynia and hyperalgesia responded best to high-concentration topical capsaicin treatment [141], while another found that the presence of cold and pinprick hyperalgesia at baseline was predictive of a better analgesic response to 8% capsaicin [162].

Studies of other treatments, in contrast, have occasionally reported that the least pain-sensitive, and most pain-tolerant, patients are most likely to benefit from multidisciplinary pain treatments [83;107], and to derive the largest analgesic effects from oral opioid medications [84;88;127] and implantable devices [41]. Among these predictive studies, the diversity in QST methods, patient samples, and applied treatments makes it difficult to draw conclusions at present regarding which patient subtypes/profiles are most likely to respond to a specific intervention. This has led to calls for the careful standardization and integration of QST methods into multicenter clinical trials, which would subsequently allow reliable post-hoc analysis of QST-derived predictors of response [9;17].

For Phase 2 trials, the DFNS QST battery can be recommended, when circumstances permit (one limiting factor is time, with the full battery taking 1–3 hours to administer, depending on the number of body regions tested, [203]), with the possibility to add supplemental QST measures (e.g., suprathreshold measures of response, capsaicin challenge, conditioned pain modulation - see below). For Phase 3 trials, it is recommended that the DFNS battery be considered, taking into account that implementation will be challenging in large multicenter trials. A desirable alternative for Phase 3 trials, or large multicenter Phase 2 trials, would be a “bedside” QST assessment, such as that recently reported in 3 large RCTS by Freeman and colleagues [97]. Pre-treatment phenotyping with such methods has yielded evidence of effect modification in multiple RCTs [67;97;215]. Recent reviews have called for increased application and study of such brief, bedside QST protocols, which do not require specialized equipment, and which may be feasible additions to large multicenter trials [15;27;62]. In addition, trial-to-trial variability of many QST responses is greater among patients with chronic pain than pain-free controls [263]. Such variability should be examined as a potentially influential phenotypic factor (in much the same way that day-to-day variation in clinical pain intensity may be an important predictive variable, see section 4.2).

4.5. Conditioned pain modulation [CPM] and other indices of pain modulation

In addition to standard QST measures of pain and sensory thresholds, there has also been a good deal of interest in phenotyping individual variability in endogenous pain-modulatory processes [108;153]. Pain-facilitation is often assessed using temporal summation methods, and endogenous pain inhibition has been most commonly measured by applying Diffuse Noxious Inhibitory Control (DNIC) paradigms to humans. DNIC is a physiological counter-irritation phenomenon described over 30 years ago in animals [149–151]. A noxious

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stimulus applied to one body region can reduce spinal neuronal responses to a heterotopically-applied second noxious stimulus, often of a different modality. In humans, this “pain inhibits pain” phenomenon is now termed Conditioned Pain Modulation (CPM) and is measured psychophysically [264;265]. Currently, the CPM concept is best viewed as the net effect of various facilitating and inhibiting systems exerting their activity at spinal or supraspinal levels. In most CPM paradigms, a phasic noxious stimulus is applied both alone and in conjunction with a tonic noxious conditioning stimulus applied to a distant body site, with the pain response to the phasic stimulus expected to be reduced when applied concurrently with the tonic noxious stimulus. CPM appears to depend, at least in part, on opioid-mediated supraspinal mechanisms [222] and may also involve serotonergic and noradrenergic pathways [268;269]. It varies widely in magnitude across individuals and is a sensitive measure of deficits in pain modulation in fibromyalgia and a variety of persistent pain disorders [240] including long-term post-surgical pain [36;85;267].

Because pain is modulated by monoaminergic descending pathways [some of which appear to be involved in CPM], it seems logical to assume that patients who differ in pre-treatment CPM might respond differentially to medications acting on these targets. Yarnitsky and colleagues postulated that patients showing decrements in CPM should benefit more from serotonin-noradrenaline re-uptake inhibitors (SNRIs), which augment descending inhibition by spinal monoamine reuptake inhibition, than patients whose CPM appears to be functioning effectively [269]. They examined CPM in patients with DPN who were treated with duloxetine and found that CPM predicted the drug’s efficacy; patients with less efficient pre-treatment CPM derived substantial pain relief from duloxetine, while those with efficient baseline CPM did not benefit. Further, for the low CPM group, duloxetine-related changes in pain intensity paralleled changes in CPM. The study did not include a placebo group and so it was not possible to examine whether CPM was a treatment effect modifier for duloxetine.

A more recent RCT, this one a placebo-controlled trial of tapentadol, focused on treatment-related changes in CPM [179]. Twenty-four patients with DPN were randomized to receive either sustained-release tapentadol or placebo for 4 weeks. At baseline these patients did not demonstrate a significant CPM response, but patients randomized to tapentadol subsequently developed significant CPM, the magnitude of which corresponded to the degree and temporal course of patients’ reduction in their neuropathic pain. Other studies in NSAID-treated patients have similarly revealed predictive relationships between baseline CPM and analgesic outcomes, with a higher magnitude of pre-treatment CPM predicting more pain relief in an open-label, general prediction study of a topical NSAID [58]. Studies of non-pharmacologic analgesic interventions such as exercise also suggest significant associations between the magnitude of CPM and the magnitude of exercise-induced hypoalgesia (EIH) [152;236].

Interestingly, CPM may be somewhat specific in its treatment-predictive capacity; in contrast to the SNRI findings, a recent RCT in patients with chronic pancreatitis suggested that pre-treatment CPM was not associated with the analgesic effectiveness of pregabalin [185] and was in turn unaffected by subsequent pregabalin treatment [38]. Such specificity is expected, given the overlap between CPM mechanisms and SNRI mechanisms [269].

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Accordingly, the committee recommends consideration of the inclusion of a measure of CPM in Phase 2 and 3 analgesic trials, where pharmacologically appropriate. While there are dozens of published methods for assessing CPM [198;240], we recommend if possible implementing a version of the paradigm employed by Yarnitsky and colleagues [269], in which a hot water bath was used as a conditioning stimulus and an individually-tailored noxious contact thermal stimulus was used as the concurrent test stimulus. However, the availability of the required testing equipment may be limited, and use of alternative paradigms may be desirable or necessary, as noted in a recent review [266].

Psychophysical assessment of pain facilitation is most often assessed using temporal summation paradigms, which involve applying a series of identical noxious stimuli and measuring the increase in the percept of pain intensity [4]. Individuals differ broadly in their degree of temporal summation, and many groups of patients with persistent pain exhibit increased temporal summation relative to controls [268]. Temporal summation of pain can be reduced by a variety of analgesic treatments, from ketamine [3] to spinal cord stimulation [87] to acupuncture [271] to exercise [235]. Recent studies of post-operative pain have highlighted the potential prognostic value of temporal summation for predicting the development of persistent post-operative pain [189] and for profiling patients with various chronic pain syndromes including osteoarthritis and atypical odontalgia [86;197]. However, no Phase 2 or 3 studies to date have evaluated the prospective predictive effects of temporal summation phenotypes on treatment outcomes.

Finally, offset analgesia is a pain-modulatory process that has recently been used to profile patients with persistent pain [178]. The phenomenon of offset analgesia is characterized by a disproportionately large decrease in perceived pain intensity following a relatively small decrease in noxious stimulus intensity. While offset analgesia is classified as an endogenous pain-inhibitory process, it is distinct from CPM [146], which suggests its potential utility as a unique pain-modulatory phenotyping measure. Offset analgesia is impaired (i.e., the magnitude of the decrease in perceived pain intensity is lower than expected) in patients with chronic neuropathic pain [177–179], and is unaffected by ketamine, tapentadol, or oral opioids [167;177–179]. To date, as with temporal summation, offset analgesia has not been studied as a general predictor or effect modifier in any Phase 2 or 3 trials.

4.6. Response to pharmacologic challenge

Although rarely studied in the context of Phase 2 and 3 clinical trials, valuable phenotypic information may be derived from careful assessment of a patient's response to a pharmacologic challenge. Here we omit consideration of those studies in which early response to a medication (e.g., at 2 weeks after initiating treatment) predicts long-term analgesic responses to that medication during a lengthy, sustained, treatment period. This phenomenon is well-documented [137;247] and is obviously clinically valuable, but it does not advance the goal of performing pre-treatment phenotyping in order to select patients with good responses to a particular intervention.

A series of studies has examined the use of an intravenous infusion paradigm to predict the subsequent analgesic response to an oral analogue of the same drug class. As noted in a 2009 review of these studies [53]:

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> "The rationale behind use of intravenous infusion tests is that they can quickly predict those patients who will respond to a subsequent course of oral medication, thereby eliminating the time and expense of a lengthy oral medication trial and reducing the risks of adverse effects associated with ineffective drug treatment. An infusion test can serve as a prognostic tool for a treatment associated with significant risk, such as implantable analgesic devices or oral opioid therapy. In these situations, a screening test with a high specificity and positive predictive value may prevent patients unlikely to respond to a high-risk therapy from receiving an unwarranted treatment. Intravenous infusion tests can also provide valuable information when the definitive treatment provides considerable relief to only a small subset of patients."

Overall, this review reported evidence for the potential predictive benefits of IV lidocaine and IV ketamine tests.

Several prior randomized trials in neuropathic pain patients have reported that responses to acute IV lidocaine infusion are positively associated with the degree of analgesia obtained by mexiletine treatment [14;207]. Similar findings were evident in open-label studies or retrospective chart reviews [46;227]. Several other trials have used a low-dose IV ketamine probe to predict subsequent responses to dextromethorphan [54]. A series of open-label, general prediction studies by Cohen and colleagues has suggested that response to an IV ketamine infusion is a significant predictor of intermediate-term relief with subsequent dextromethorphan treatment in patients with neuropathic pain [52], FM [55], and patients showing signs of opioid tolerance [56]. For example, in Cohen et al. [56], 0.1 mg/kg of ketamine was administered IV over seven minutes, followed by a course of several months of oral dextromethorphan treatment. There was a strong association between short-term [measured over the course of minutes] pain relief with IV ketamine, and subsequent pain relief with dextromethorphan over the course of several months' follow-up ($r = .54$, $p < 0.001$).

While the use of IV opioid infusions to predict long-term analgesic responses to oral opioid therapy is highly appealing [111], the limited extant data are mixed [53]. Two open-label trials of oral morphine [11] and transdermal fentanyl [65;66] in a small number of patients with neuropathic pain have observed a moderate correlation between the acute analgesic effects of an IV opioid and the subsequent intermediate- or long-term analgesic effects of sustained treatment with that same opioid. However, a similarly-designed small study in patients with phantom limb pain failed to detect a significant correlation between IV morphine's analgesic effects and patients' longer-term analgesic responses to a course of oral morphine treatment [129]. Finally, an IV phentolamine test in neuropathic pain did not predict the analgesic response to transdermal clonidine [40;63]. Taken together, it is difficult to provide definite estimates of the positive and negative predictive value of examined infusion paradigms as the number of studies and prospectively evaluated patients was small, heterogeneous pain conditions were explored, different study protocols were used, and variable criteria were applied to infer analgesic efficacy. The authors note here that the prognostic benefits of any acute, IV pharmacologic challenge are likely to be medication-specific, and in addition may be confounded by sensory cues or adverse effects (e.g., nausea)

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associated with infusion of active medication but not placebo. In general, crossover RCTs involving multiple active treatments have tended to show no relationship between the degree of analgesia achieved by agents with different mechanisms of action (e.g., no association between morphine and nortriptyline analgesia in [199], and no overlap in the variability in response to amitriptyline and maprotiline [254] among patients with PHN).

More recent studies used pharmacological testing to predict subsequent responses to non-analogue drug classes. Responses to topical lidocaine have been demonstrated to predict the subsequent response to high-concentration topical capsaicin [166]. In a 12-week RCT of high-concentration topical capsaicin for PHN, prior to application of the capsaicin patch, patients received a brief administration of a local anesthetic cream (lidocaine 4%) on the affected area. The local anesthetic was used to mask the burning pain associated with the placement of the capsaicin patch, but when considered as a "challenge" it produced broad phenotypic variability in patient responses, which was prospectively associated with long-term capsaicin treatment response. Those whose PHN pain was alleviated with the topical anesthetic had a roughly 3-fold increase in the probability of being classified as a capsaicin responder over the course of the 12-week trial. Capsaicin has also been used as a means to identify the effective dose of specific analgesic agents [260], as well as a pharmacologic probe of local nociceptor function. For example, in a randomized, placebo-controlled trial of topical clonidine in patients with painful diabetic neuropathy, sensory profiles were assessed during screening with a topical capsaicin challenge [42]. The increase in spontaneous pain after cutaneous capsaicin application was used as a phenotypic indicator of nociceptor function at baseline. While in the full sample, the primary endpoint (pain reduction) did not differ significantly between the clonidine and placebo groups, when patients were stratified post hoc according to their capsaicin response, clonidine significantly reduced pain in a subgroup of patients who rated the topical capsaicin challenge as painful. Moreover, the magnitude of separation between the clonidine- and placebo-treated patients became more pronounced with increasing capsaicin ratings, demonstrating evidence of effect modification. As the authors note, such findings "suggest that the analgesic effect of clonidine depends on the presence of functional capsaicin-responsive nociceptors in the skin, and raises the broader issue that neuropathic pain treatments may be guided by results of sensory testing" [42]. In addition to assessing spontaneous pain following topical capsaicin, direct measurement of local neurovascular response to capsaicin is also possible using methods such as laser Doppler imaging, which may provide valuable phenotypic information distinct from self-reported pain [118]. Overall, we recommend the consideration of specific pharmacologic challenge in applicable RCTs; for example, if mexiletine is an active agent being studied in patients with neuropathic pain, multiple RCTs have suggested that the results of an acute IV lidocaine challenge may be predictive in this context. However, given the relative scarcity of data, the small size of most published trials, and the potential risks associated with the infusion of some agents (e.g., ketamine), it is not possible to propose firm recommendations at this time.

5. Conclusions

To date, phenotypic profiling in clinical trials has predominantly focused on characterizing the effects of treatments on an array of pain-related symptoms and signs. Recent years,

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though, have witnessed a growing interest in predictive phenotyping [9;17;41;69]; there appears to be great potential to advance the goal of tailored, or personalized, pain treatment. The tremendous heterogeneity among patients with persistent pain, and the disappointing, negative results of many analgesic trials may be harbingers of a future in which patients are comprehensively phenotyped (in addition to being diagnosed), then are managed according to an empirically-supported algorithm that matches those patient profiles to the optimal combination of treatments. As an intermediate step to such “deep” phenotyping, we hope that our present recommendations may help investigators to select the most promising phenotyping measures for use in Phase 2 and 3 analgesic trials (see Tables 1 and 2). An additional potential benefit to human phenotyping studies has been highlighted by recent commentaries in this area that have called for back-translation of specific phenotypes (e.g., QST-based sensory profiling) into animal research, which would allow more precise characterization of the pathophysiologic mechanisms that characterize specific subgroups of patients [16]. Such work would have the potential to facilitate the identification of new drug targets, which could then be investigated using phenotype-tailored investigation of treatment outcomes.

Balanced against the benefits of phenotyping are the associated costs of additional assessment, as well as obstacles to the implementation of phenotyping protocols. These are rarely discussed in the scientific literature, but important barriers may include: considerable costs of implementing phenotyping methods, training investigators, and maintaining phenotyping data in a multi-center trial, concerns that identification of treatment-responsive subgroups may lead to narrow regulatory approval (e.g., the case of BiDil: [226]), pragmatic considerations regarding the difficulties of administering, scoring, and interpreting phenotyping measures in clinical practice settings, and inadequate power to detect subgroup effects. In addition, limited research evaluating the temporal stability of some of the recommended phenotypes is available, and we know relatively little about the natural history of these phenotypic characteristics. We hope that ongoing open discussion of these issues may facilitate the design of future analgesic trials.

We appreciate that a substantial proportion of the studies cited in this article were performed in samples of patients with neuropathic pain, which, despite a substantial prevalence [239], is not the most commonly-experienced type of pain in the general population. Neuropathic pain is frequently studied in Phase 2 and 3 trials of analgesics, probably at least in part because it is presumed to be easier to identify a “pain mechanism” to target for a condition like PHN than for a condition such as nonspecific, axial, low back pain [100;255]. In addition, some have reported that placebo effects may be lower in magnitude in RCTs for some neuropathic pain than for musculoskeletal pain conditions [2;50], and this may have enhanced the appeal of testing putative analgesic compounds in Phase 2 and 3 trials in patients with neuropathic pain. However, the phenotyping approach described here is presumed to be relatively general, and applicable to numerous types of persistent pain conditions, including those traditionally classified as neuropathic, musculoskeletal, or inflammatory. For example, QST phenotyping is increasingly being applied in OA, and multiple recent studies have suggested that indices of central pain modulation such as temporal summation are important predictors of OA treatment outcomes, especially joint replacement outcomes [189;216;217]. Similar findings are evident in studies of chronic LBP,

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as QST-assessed indices of pain sensitivity and pain modulation show significant prospective associations with pain intensity and disability following treatment [182]. Moreover, psychosocial factors such as depression, anxiety, distress, and catastrophizing appear to have fairly general effects, as these variables have been prospectively associated in recent studies with: greater physical disability and reduced treatment response among RA patients treated with steroids [168], chronic back pain patients undergoing acupuncture [28], chronic neck pain patients treated with radiofrequency lesioning or facet blocks [219;220], chronic pelvic pain patients undergoing surgery [131], whiplash patients managed with multimodal rehabilitation [51], primary care patients experiencing back pain [173], orofacial pain patents receiving injection therapies [164], Fibromyalgia patients enrolled in an exercise program [43], IBS patients undergoing CBT [30], neck pain patients treated with manual therapy [64], and many other combinations of non-neuropathic chronic pain with a variety of treatment approaches.

Overall, it is clear that many factors, not all of them captured by the sort of phenotyping recommended here (e.g., genetic variation), may contribute to inter-individual variability in analgesic outcomes. Perfect, or near-perfect, prediction of an individual patient's response to a given treatment appears at present to be an unattainable goal. However, the findings outlined in the present review, some of which have derived support from multiple studies (e.g., patients with relatively higher baseline levels of neuropathic symptoms on self-report measures, compared to those with lower levels, appear to benefit most from pregabalin), indicate that there are reasonable grounds for proceeding with additional phenotyping work in Phase 2 and 3 trials. A healthy degree of skepticism is warranted, of course, given the absence of replication of most findings as well as the retrospective nature of most results to date, but we believe that this area of work shows substantial promise. Large trials, meta-analyses, or pooled data sets, that include multi-modal phenotypic assessments [e.g., 67;97, which include both QST and self-report measures of neuropathic pain] are likely to provide the most informative and actionable results, and we encourage investigators to publish comprehensive, patient-level phenotyping data. In addition, while the vast majority of the studies cited here have evaluated pain intensity as the primary outcome, numerous surveys have noted that treatment-related improvements in a variety of domains (e.g., sleep, mood, activity level) are important to patients with chronic pain [230]. It may be that differing phenotypic factors are relatively more or less important in shaping differing domains of outcomes, suggesting that outcome-specific phenotyping may be necessary. While the present report focuses on "subjectively measured" phenotypes, more objectively measured patient characteristics (e.g., MRI or other imaging findings, neurophysiological studies) are also likely to play an important predictive role. Moreover, crossover designs, as well as trials that include head-to-head comparisons of active agents [e.g.,35] may provide the most rapid advances in the development of tailored, mechanism-based treatment algorithms. Other recent reviews, while noting that multi-period crossover trials have rarely been conducted in the pain literature, have called for such studies in order to examine treatment-by-patient interactions [74]. It is our hope that combining such designs with comprehensive, multimodal, pre-treatment phenotyping may move the field further toward the eventual goal of providing empirically-based, personalized pain medicine.

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Table 1

Core phenotyping domains and recommended measures.

Domain	Recommended Measure(s)	Description
Psychosocial	Hospital Anxiety and Depression Scale (HADS)	14 items, 7 assessing depressive symptoms, 7 assessing anxiety symptoms. Total score can be used as a measure of global negative affect (180).
	Pain Catastrophizing Scale (PCS)	13 items, comprising 3 inter-correlated subscales: Magnification, Rumination, and Helplessness. The PCS is well-validated in patient and healthy samples, and is the most-commonly used measure of pain catastrophizing in the field (225).
	PROMIS Subscales	A set of patient-reported health status measures that provide information about physical, mental/emotional, and social wellbeing. The measures can be administered in a variety of formats (e.g., using computerized adaptive testing) (49).
	Consider: SCL-90 Somatization Scale and/or PILL	
Pain Qualities	Variability in Pain Intensity	Generally assessed using daily diary methodologies, with computation of the degree of variability across time for individual patients (89).
	Short Form McGill Pain Questionnaire 2 (SF-MPQ-2)	A revision of the widely-used MPQ, which assessed sensory, affective, and cognitive/evaluative pain descriptors. The SF-MPQ-2 has 22 items assessing a variety of pain qualities (79).
	Pain Quality Assessment Scale (PQAS)	20 items evaluating neuropathic and non-neuropathic pain qualities (e.g., hot, sharp, shooting) (253).
	painDETECT	9-Item instrument to assess the neuropathic components of pain. Scores identify respondents as either “likely”, “unlikely”, or uncertain in terms of the probability of having neuropathic pain. It has good sensitivity, specificity, and positive predictive value in identifying neuropathic pain (98).
	Neuropathic Pain Symptom Inventory (NPSI)	12-item measure that queries respondents about the degree of neuropathic pain symptoms (e.g., “Does your pain feel like electric shocks?”) over the past 24 hours. It has good sensitivity, specificity, and positive predictive value in identifying neuropathic pain (10).
Sleep	Pittsburgh Sleep Quality Index (PSQI)	Well-validated 19-item measure assessing sleep quality and sleep disruption over the past month (Buysse, Reynolds et al., 1989).
	Insomnia Severity Index (ISI)	7-item scale assessing the severity and impact of insomnia symptoms over the prior 2 weeks (22).
	Consider: Wrist actigraphy and a fatigue VAS or the MFI	
Quantitative Sensory Testing (QST)	DFNS testing battery, when applicable	Includes detection and pain thresholds for thermal and mechanical stimuli, allodynia, temporal summation, etc. (104;161;203)
	Consider: Freeman et al., “bedside” QST battery	
Conditioned Pain Modulation (CPM)	Yarnitsky et al. thermal CPM testing paradigm	Change in pain intensity of a phasic contact heat stimulus during hand immersion in painfully hot water (269).
Pharmacologic Challenge	No general recommendations	

CPM= Conditioned Pain Modulation; DFNS= German Research Network on Neuropathic Pain (translated); HADS= Hospital Anxiety and Depression Scale; ISI= Insomnia Severity Index; LBP= Low Back Pain; MFI= Multidimensional Fatigue Inventory; NPSI= Neuropathic Pain Symptom Inventory; PCS= Pain Catastrophizing Scale; PILL= Pennebaker Inventory of Limbic Languidness; PROMIS= Patient Reported Outcomes Measurement Information System; PQAS= Pain Quality Assessment Scale; PSQI= Pittsburgh Sleep Quality Index; QST= Quantitative

Sensory Testing; SCL= Symptom Checklist; SF-MPQ= Short Form McGill Pain Questionnaire; StEP= Standardized Evaluation of Pain; VAS= Visual Analog Scale

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Table 2

Selected supporting studies.

Measure/Author	Sample Size	Methodology	Prediction Type	Results
HADS Jamison et al., 2012	N=268 opioid-using patients with chronic LBP	12-week RCT: ER Hydromorphone vs. Placebo	Some elements of effect modification analyses	Patients with high baseline HADS scores were more likely to drop out; those with moderate-high HADS scores had higher pain and disability ratings (i.e., less analgesic benefit) during hydromorphone treatment.
Wasan et al., 2009	N=86 patients with chronic axial pain undergoing Medial Branch Blocks	Prospective cohort study with 1-month follow-up.	General prediction	Patients with high baseline HADS scores were less likely to obtain significant pain relief (10% vs. 45% in the low HADS group) at 1 month follow-up.
PCS Rakel et al., 2014	N=317 patients undergoing total knee replacement randomized to TENS, placebo TENS, or standard care	RCT with 6-week follow-up	Effect modification	In the TENS groups, patients with higher PCS scores had more pain and less range of motion at 6 weeks. No associations between PCS and pain outcomes were observed in the other groups.
PROMIS Karp et al., 2014	N= 159 LBP patients treated with epidural steroid injections	Observational cohort study with 1-month and 3-month follow-up.	General prediction	A number of PROMIS subscales were assessed, including those for negative affect, sleep, pain behavior and pain interference (these were used as outcomes). Negative affect and sleep prospectively predicted more pain and dysfunction at 3 months.
SF-MPQ 2 Carroll et al.,, 2010	N=71 patients with “suspected neuropathic pain”	Within-subjects trial of pain relief with saline infusion compared to IV lidocaine infusion.	Effect modification	Patients describing their pain as “heavy” at baseline experience greater pain relief from IV lidocaine but do not differ in placebo pain relief.
PQAS Gammaitoni et al., 2013	N=99 patients with peripheral neuropathic pain, treated with pregabalin in an enriched enrollment randomized withdrawal design (EERW).	EERW trial with 3-week treatment period following titration.	Effect modification	Higher scores on the PQAS “Paroxysmal Pain” and “Deep Pain” scales were associated with better response to pregabalin, but were unassociated with placebo responses.
painDETECT Hober et al., 2014	N=822 patients with neuropathic pain	12 weeks of treatment with 8% capsaicin patches (high-concentration topical capsaicin).	General prediction	High baseline scores (>18) predicted more pain reduction (~24% pain reduction) relative to low (<13) scores (~13% pain reduction).
NPSI Bouhassira et al., 2014	N=804 patients with painful diabetic neuropathy	RCT of duloxetine (60mg) vs. pregabalin (300mg) monotherapy, with non-responders randomized to either high-dose monotherapy or combination therapy	Effect modification	The cluster of patients with the lowest NPSI scores had the largest separation favoring duloxetine over pregabalin when comparing monotherapies.
Sleep Vinik et al., 2014	N= 4,527 patients with DPN or PHN, pooled from 16 RCTs	Data was pooled from 16 randomized, placebo-controlled trials of pregabalin in patients with PHN or DPN. Sleep disturbance was measured using a 0–10 self-report item on Daily Sleep Interference.	Effect modification	Across studies, PHN and DPN patients with severe sleep disruption at baseline derived substantially more pain reduction from pregabalin than placebo (p’s< .001).
QST Demant et al., 2014		Crossover RCT of 6 weeks oxcarbazepine (up to	Effect modification	Patients with “irritable nociceptors” (i.e., sensory gain on at least some

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	N=97 patients with peripheral neuropathic pain	2,400mg; mean daily dose ~1,800 mg) vs. 6 weeks placebo. Patients phenotyped at baseline using a bedside version of the DFNS protocol.		measures of thermal and mechanical QST) had a better response to oxcarbazepine. No group differences in placebo responses.
Simpson et al., 2010	N= 302 patients with painful HIV-associated neuropathy.	RCT of pregabalin (mean dose 386 mg) vs. placebo with 2 weeks dose adjustment, 12 weeks maintenance, and an optional 3-month open-label extension.	Effect modification	Patients with the most mechanosensitivity to pinprick at baseline had good pain reduction with pregabalin (p= .01) while low-to-moderate sensitivity subjects had no pain reduction (p= .87). No effects on placebo analgesia.
CPM Yarnitsky et al., 2012	N= 30 patients with DPN	Treatment with 1 week of placebo followed by 1 week of duloxetine 30mg, then 4 weeks of duloxetine 60mg.	Some elements of effect modification analyses	Patients with worse CPM at baseline got the most reduction in pain with duloxetine treatment. A greater increase in CPM correlated with more pain reduction as well.
Niesters et al., 2014	N= 24 patients with DPN	Randomization to 4 weeks of tapentadol SR (mean daily dose = 433mg) vs. placebo. CPM Methods: test stimulus= heat pain, conditioning stimulus = cold pressor.	Effect modification	On average, patients did not show CPM at baseline. Those randomized to tapentadol SR developed CPM, those randomized to placebo did not. Larger magnitude of CPM increase correlated with greater pain reduction.

CPM= Conditioned Pain Modulation; DFNS= German Research Network on Neuropathic Pain (translated); DPN= Diabetic Painful Neuropathy; EERW= Enriched Enrollment Randomized Withdrawal; ER= Extended Release; HADS= Hospital Anxiety and Depression Scale; HIV= Human Immunodeficiency Virus; ISI= Insomnia Severity Index; IV= Intravenous; LBP= Low Back Pain; NPSI= Neuropathic Pain Symptom Inventory; PCS= Pain Catastrophizing Scale; PHN= Post-Herpetic Neuralgia; PILL= Pennebaker Inventory of Limbic Languidness; PROMIS= Patient Reported Outcomes Measurement Information System; PQAS= Pain Quality Assessment Scale; PSQI= Pittsburgh Sleep Quality Index; QST= Quantitative Sensory Testing; RCT= Randomized Controlled Trial; SF-MPQ= Short Form McGill Pain Questionnaire; StEP= Standardized Evaluation of Pain; TENS= Transcutaneous Electrical Nerve Stimulation