OPINION

The DABBEC Phenotyping System: towards a mechanistic understanding of CP/CPPS

Stephen A. Allsop, Derek J. Erstad, Karolina Brook, Salman F. Bhai, Jeffrey M. Cohen and Jordan D. Dimitrakoff

Abstract | There is an urgent need to elucidate the mechanistic basis of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), as the current methods of symptom-based diagnosis and treatment have failed. Here, we propose a phenotyping system that bridges the gap between the symptom-based diagnosis and treatment of the present and the mechanistic approach of the future. Our phenotyping system uses the Chronic Prostatitis Collaborative Research Network (CPCRN)-recommended algorithm in combination with the NIH Chronic Prostatitis Symptom Index (NIH-CPSI) as a basis for diagnosis, while incorporating novel domains for quantitative assessment and stratification of CP/CPPS patients. We believe this novel system will serve to help advance our understanding of the roles of the patient's genome and proteome in the etiology of CP/CPPS. We predict that, as we begin to understand the mechanistic basis of CP/CPPS pathology and progression, we will develop specific treatments that will aim to cure the disease, rather than merely quell the symptoms.

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Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a clinical condition presenting as chronic pelvic pain for 3 months within a 6-month period, with a variable degree of urinary and sexual dysfunction in the absence of any identifiable pathology.[1] CP/CPPS is the most frequent urological diagnosis in men under the age of 50 years. Population-based surveys estimate the prevalence of CP/CPPS-like symptoms to be 6–12%,[2] accounting for 8% of urological visits and 1% of primary care visits in the USA. The direct costs of care approach $6,500 per patient per year.[3] The quality of life of CP/CPPS patients is consistently worse than that of patients with congestive heart failure, diabetes or Crohn's disease.[4]

The single clinical entity known as CP/CPPS is, in reality, a heterogeneous condition, both in terms of its clinical manifestations and its underlying mechanisms. At least three lines of evidence highlight this heterogeneity in CP/CPPS. First, the clinical presentation varies between patients and, even in the same patient, symptoms fluctuate over time.[5] Second, different etiological mechanisms (such as infection, inflammation and nerve damage) might account for the observed pathology in the same patient and between patients.[6] This presents a major challenge in defining the pathophysiology of CP/CPPS, which in turn presents a unique challenge in diagnosis and treatment. Finally, CP/CPPS symptoms overlap with those of irritable bowel syndrome (IBS), fibromyalgia, chronic fatigue syndrome, and other chronic pain disorders.[7] The combination of these three factors creates considerable complexity in administering effective therapies for the alleviation of CP/CPPS symptoms.

The purpose of this article is threefold: first, we critically review existing knowledge on the diagnosis of CP/CPPS and propose our original phenotyping system; second, we evaluate several key contributing factors in CP/CPPS and propose a mechanistic roadmap for diagnosing and treating this condition; and third, we discuss existing obstacles in the design of clinical trials in CP/CPPS, and propose two novel study designs that we believe should be applied in the future.

Competing interests
The authors declare no competing interests.

Evaluation of CP/CPPS diagnosis

The NIH-CPSI

In light of the increasing perception of CP/CPPS as a symptom-based diagnosis of exclusion, in 1999 the NIH/NIDDK sponsored the Chronic Prostatitis Collaborative Research Network (CPCRN), which developed the NIH Chronic Prostatitis Symptom Index (NIH-CPSI).[8] The NIH-CPSI is a psychometrically validated index of symptoms and quality of life impact in men with CP/CPPS. The NIH-CPSI serves as the current criterion standard for the diagnosis of CP/CPPS, while providing a standardized outcome measure for CP/CPPS treatment efficacy.

Subsequently, the CPCRN used the NIH-CPSI to evaluate the efficacy and safety of antibiotics[9] and α-blockers,[10] two commonly prescribed groups of medications in patients with CP/CPPS. Neither of the therapies was shown to be superior to placebo—an observation that could be explained by patient selection, a lack of clarity over optimal dosing, and the short duration of therapy. However, it is also plausible that the outcomes of these randomized controlled trials reflect the fact that, while the NIH-CPSI captures a wide spectrum of clinical manifestations of CP/CPPS, it does not provide detailed mechanistic information. For example, two patients may present clinically with identical symptoms of chronic pelvic pain and be diagnosed with CP/CPPS on the basis of the NIH-CPSI. In the first patient, the pain could result from local inflammation caused by prostate infection, autoimmunity, or physical trauma. In the second patient, the pain might result either from a decreased pain threshold of the peripheral sensory nerve endings or from amplification of the pain perception within the central nervous system (CNS), known as central sensitization. Although the causative factors and pathogenetic mechanisms underlying the symptom (pain) in these two patients are quite different, they would be indistinguishable on the basis of the NIH-CPSI. Thus, although the NIH-CPSI allows the right patients to be captured (ensuring homogeneity), enrolling patients in clinical trials purely on the basis of their NIH-CPSI status might introduce even more heterogeneity to the study population.

Box 1 | DPS vs UPOINT

In the UPOINT system, one of the designated domains is "tenderness of skeletal muscles". While tenderness in the skeletal muscles is an important clinical distinction in CP/CPPS, it is a symptom that represents the final common pathway for numerous possible mechanisms (e.g. inflammation, infection, autoimmunity, nerve and muscle injury). The UPOINT system categorizes CP/CPPS patients with this symptom of muscle tenderness into a single mechanistic domain.

Contrarily, the DPS categorizes patients in a manner that does not rely on different symptom domains. Taking the initial symptom—tenderness of skeletal muscles—the DPS attempts to dissect the underlying mechanisms that shape the symptom perception. In addition, DPS provides a phenotypic framework that can drive clinical research focused on the mechanisms leading to the presentation of these different symptoms and provide a basis for adequate treatment.

Abbreviations: CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome; DPS, DABBEC Phenotyping System.

Theoretically, in the above example, even though the first patient would benefit from local therapies, the second patient would be more likely to respond to centrally acting analgesics.

MAPPing systemic aspects of CP/CPPS

Recognizing the need to reassess the scientific approach to CP/CPPS, the NIDDK initiated the Multidisciplinary Approach to Pelvic Pain (MAPP) Network in 2008. The MAPP consortium is a unique interdisciplinary 'systems biology' effort aimed at providing novel insights into CP/CPPS pathogenesis from the molecular to the population level. MAPP studies will hopefully provide the scientific foundation for establishing the CP/CPPS phenotypes and enhancing its diagnosis (through biomarker discovery) and management (through mechanistically driven trials).

UPOINT: an alternative approach

In 2009, Shoskes and Nickel[11,12] proposed UPOINT, a novel questionnaire instrument that captures six CP/CPPS symptom domains: urological, psychosocial, organ-specific, infection, neurological and tenderness of skeletal muscles. UPOINT is predicated on the hypothesis that "each domain has been clinically defined, linked to specific mechanisms of symptom production or propagation, and associated with specific therapy".[11]

In a nonblinded prospective trial design, Shoskes *et al.*[13] administered UPOINT-directed multimodal therapy (α-blockers or antimuscarinic agents for urinary symptoms; quercetin for organ-specific symptoms; physical therapy for tenderness) to 100 patients with CP/CPPS. With a median follow-up duration of 50 weeks, 84% of patients reported at least a 6-point decrease in NIH-CPSI total score, the standard for a clinically significant response in CP/CPPS trials. However, as acknowledged by the authors, regression to the mean, the unknown optimal duration of therapy and the placebo effect limit the generalizability of these results.[13] Importantly, UPOINT is limited by the strength of correlation between symptoms and disease mechanisms, and provides little improvement in mechanistically driven treatment outcomes when compared to the NIH-CPSI. Lastly, as a single physician examined and diagnosed all the patients, the UPOINT study has the risk of having a biased cohort. Commendably, however, UPOINT recognizes and seeks to address the heterogeneity present in patients with CP/CPPS (Box 1).

The DABBEC Phenotyping System

We propose the DABBEC (Dimitrakoff, Allsop, Brook, Bhai, Erstad and Cohen) Phenotyping System (DPS) (Box 1) as a clinically useful method for phenotyping patients, designing clinical trials, and evaluating the efficacy of mechanistically driven treatments for CP/CPPS. This system incorporates a view of CP/CPPS as both a localized and systemic condition. The DPS consists of four scoring domains: the NIH-CPSI, localized-versus-systemic (LvS), hypothalamic–pituitary–adrenal axis/sympathetic nervous system (HPA/SNS), and CYP21A2 phenotype.

Following a clinical diagnosis of CP/CPPS, as recommended by the CPCRN guidelines,[14,15] we suggest that clinicians administer questionnaire instruments to assess the patient's constitutional, psychological and cognitive symptom domains. This symptom domain phenotyping will be helpful in identifying comorbidities, such as depression, anxiety and catastrophizing—conditions that are highly prevalent in patients with CP/CPPS. We recommend that such patients receive multimodal therapy in the context of multidisciplinary teams of psychologists, neurologists and internists.

Box 2 | The DABBEC Phenotyping System

NIH-CPSI

Pain score

- (0–7): **1**
- (8–14): **2**
- (15–21): **3**

Quality of life score

- (0–4): **0**
- (5–8): **1**
- (9–12): **2**

Urinary score

- (0–3): **0**
- (4–7): **1**
- (8–10): **2**

LvS

Localized (pelvic) disease: **10**

Systemic disease: **20**

HPA/SNS

Low score: **1**

Medium score: **2**

High score: **3**

CYP21A2

CYP21A2 deficiency: **A**

No CYP21A2 deficiency: **B**

The DABBEC Phenotyping System subscores (bold) for each of the first three domains (NIH–CPSI, LvS and HPA/SNS) are added to give the total score (maximum 30), with the A or B for CYP21A2 phenotype added for further categorization of patients. Abbreviations: HPA/SNS, hypothalamic–pituitary–adrenal axis/sympathetic nervous system; LvS, localized versus systemic disease; NIH-CPSI, NIH Chronic Prostatitis Symptom Index.

NIH-CPSI and LvS domains

As a first step in the DPS, patients complete the NIH-CPSI and receive an NIH-CPSI subscore that would fit into the larger scoring system we are proposing (Box 2). Second, we propose a model for CP/CPPS that includes two main modes of presentation: localized (pelvic) disease, caused by an inciting event, such as infection, inflammation or trauma, which results in peripheral sensitization; and systemic disease due to central sensitization and amplification of pain perception (Box 2). While we describe both forms separately, it should be noted that the localized form can evolve into a systemic condition, and, at the same time, the systemic condition might manifest as a primary event with initial presentation in

the pelvic (prostate) area (that is, the prostate pain might appear in the context of pain in the gut or musculoskeletal pain, rather than being an isolated symptom).

In the localized mode of presentation, CP/CPPS is initiated by an inciting event, which may result from multiple etiological mechanisms such as infection, inflammation, autoimmunity, dysfunctional voiding, physical trauma or nerve damage.[6] Importantly, each inciting event causes local tissue inflammation, which may or may not resolve over time. This inflammation induces changes in tissue pH and the neuronal chemical milieu, resulting in a phenotypic switch in nociceptive (pain-sensing) neurons. The phenotypic switch is characterized by changes in signaling pathways and gene expression that lead to a decreased threshold for nociceptor nerve firing. Allodynia, a symptom resulting from aberrant nociceptive signaling in response to stimuli that would not normally induce pain, is frequently observed in patients at this stage.[16–18]

Peripheral sensitization, a hallmark of this form of the disease, is actually a common transient process following local trauma.[19] However, in CP/CPPS, peripheral sensitization often persists after resolution of the inciting event, with patients continuing to experience extreme sensitivity to pain in the absence of any detectable stimulus. Peripheral sensitization underlies hyperalgesia, in which a normally painful stimulus is perceived as extremely painful, and allodynia. This is a result of continued exposure of nociceptors to inflammatory and other cellular signals that cause the cell to be more sensitive to these stimuli.[18] Essentially, a combination of stimuli that would previously not cause depolarization of a nociceptor may cause a pain response after the peripheral sensitization process takes place.[18] In the case of repeated inflammatory signals, this may occur because of an overproduction of TRPV1 receptors, which are activated in response to cell stress and begin a signaling cascade. Activation of TRPV1 can cause more TRPV1 to be placed in the membrane by a PI3K–SRC kinase pathway that phosphorylates and activates TRPV1.[20]

In its systemic mode of presentation, CP/CPPS symptoms occur in the context of a 'central pain syndrome', similar to fibromyalgia. This mode can also develop as a result of the first mode, which starts with local tissue inflammation and peripherally sensitized neurons inducing retrograde signaling in centrally acting nociceptive neurons in the dorsal horn of the spinal cord. This signaling results in changes in gene expression in centrally acting neurons, leading to increased neurotransmission of pain signals to and within the cortex. The end result is a central pain syndrome, or amplification of pain within the CNS. At this point, removing the trigger of peripheral sensitization (the prostate) does not result in symptom alleviation. Central sensitization can present in the context of a genetic predisposition, and will often present with systemic pain symptoms along the lines of fibromyalgia. Historically, such patients have been difficult to treat with antibiotics and α-blockers or with local therapies (such as transurethral resection of the prostate), as the underlying pathology is within the CNS.

The novelty of the DPS is that it provides a conceptual framework that takes into account both the localized and systemic modes of presentation. However, one of the major challenges in the clinical approach to treating CP/CPPS patients is differentiating between localized or systemic disease, a distinction that is crucial to implementing appropriate treatment. One potential approach to this problem could be to apply a lidocaine test, which has been tried in patients with painful bladder syndrome/interstitial cystitis (PBS/IC).[21] This test would utilize a lidocaine cream to numb the urethra and the urethral part of the prostate. Persistence of pain (negative outcome) would suggest a central pain syndrome. In the DPS scoring system, localized disease would receive a domain score of 10, while centralized pain (that is, systemic disease) would receive a domain score of 20.

HPA/SNS domain

The third aspect of our system evaluates hypothalamic–pituitary–adrenal (HPA) axis function and dysregulation. The rationale for this assessment is based on pre-existing evidence for HPA axis dysfunction in CP/CPPS patients.[22] Anderson *et al.*[22] reported that men with CP/CPPS have increased adrenal sensitivity and produce 30% less adrenocorticotropic hormone compared to healthy controls, indicative of a possible CNS adjustment. The authors proposed that chronic stress, as seen in CP/CPPS, "selectively targets brain circuits responsible for integration of psychogenic stimuli, resulting in altered HPA axis responsiveness." While the true magnitude of HPA axis dysfunction in CP/CPPS remains unknown, research in patients with PBS/IC, a related condition in women, has provided promising insights into the possible roles of the HPA in CP/CPPS. Lutgendorf *et al.*[23] showed that women with PBS/IC who had high cortisol levels in the morning experienced less pain and urinary urgency during the early part of the day; however, women with low morning cortisol were 12.8 times more likely to experience symptoms compared to those with high cortisol levels. In concert with data from Anderson and colleagues,[22] these findings suggest that levels of cortisol, a key player in the HPA axis, is an important aspect of PBS/IC.[23] These data, in conjunction with the observed HPA axis dysfunction in CP/CPPS patients, suggest that the HPA axis could offer unique therapeutic opportunities. Thus, our phenotyping system seeks to evaluate HPA axis function in patients with CP/CPPS.

One possible way to evaluate HPA axis function is by using the allostatic load, a measure of "the physiological cost of making long-term adaptive shifts across a broad range of systems to match internal functioning to environmental demand."[24,25] In our phenotyping system, allostatic load will be used as a global metric of HPA axis function in CP/CPPS patients. Measuring allostatic load serves a dual purpose in our system: as it also reflects psychological stress and depression[25]—which are not uncommon comorbidities in patients with CP/CPPS—the allostatic load can, therefore, be influenced by both physiological and psychological stress associated with this disease. One standard measure for the allostatic load score is a composite score determined by the quantification of multiple neurotransmitters, neuropeptides and hormones that are involved in the regulation of reward, fear conditioning and social behavior. We propose using the HPA/SNS evaluation to assess the patient's allostatic load score as part of our phenotyping system. The patient would receive a subscore of 1, 2 or 3 depending on the results of their evaluation (Box 2).

CYP21A2 domain

The finding of altered HPA axis function in CP/CPPS prompted us to study the levels of different hormones along the HPA axis in CP/CPPS patients. The results of this study suggested that the enzyme CYP21A2 may be associated with CP/CPPS symptom severity in a subset of patients.[26] CYP21A2 converts progesterone, via 11-deoxycorticosterone, to corticosterone, and 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol

Box 3 | Candidate genes for future studies in CP/CPPS

BHLHE22
Mutations in this gene lead to a loss of inhibitory interneurons in the dorsal horn that regulate the perception of itch. *BHLHE22* may also have a role in controlling sensitivity to pain.[30]

COMT
Involved in the perception of pain stimuli. Mutations in *COMT* result in a predisposition to chronic pain conditions, such as fibromyalgia and temporomandibular joint disorder.[28]

GCH1
Contributes to the pain response, and is involved in regulating pain sensitivity and persistence. *GCH1* haplotype has been shown to be protective for the development of peripheral neuropathic and inflammatory pain.[29]

Abbreviation: CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome.

(11-DOC). Precursor:product ratios for progesterone:corticosterone and 17-OHP:11-DOC were found to be significantly elevated in CP/CPPS patients compared to controls. The accumulation of 17-OHP and progesterone proximal to CYP21A2, and the decrease of corticosterone and 11-DOC distal to CYP21A2, implies a CYP21A2 deficiency in these patients. Interestingly enough, the observed biochemical signature found in the CP/CPPS patients in this study is similar to that seen in nonclassic congenital adrenal hyperplasia (CAH). Anecdotal observations have demonstrated that a small subset of patients with nonclassic CAH benefit from cortisol treatment. This is accompanied by the fact that patients with the related classic form of CAH, with elevated levels of 17-OHP, achieve complete resolution of their symptoms following treatment with cortisol.[27]

In light of these data, we propose using a combined genomic and quantitative proteomic approach to evaluating CYP21A2 abnormalities in CP/CPPS patients, as CYP21A2 deficiency is potentially amenable to corticosteroid treatment. In addition, identifying even a single mechanism that allows subphenotyping of CP/CPPS patients into a mechanistically defined group that can be targeted for a therapeutic intervention would provide a major breakthrough in our understanding of this condition. In the DPS, the patient would be assigned the letter A or B (denoting the presence or absence of a CYP21A2 deficiency, respectively) to represent their CYP21A2 phenotype status (Box 2).

Overview

The DPS provides a unique way of quantifying various components of CP/CPPS. Within the LvS contexts, the severity of disease is directly reflected by the NIH-CPSI score. As discussed above, this questionnaire is currently the primary means of quantifying symptom severity in CP/CPPS; however, it is limited in its scope. Our system provides a forward-looking analysis of CP/CPPS by incorporating the NIH-CPSI while also including other aspects of diagnosis (LvS, HPA/SNS and CYP21A2) that we believe are critical to the multifaceted etiology of this disease. Furthermore, the DPS also allows the physician to look within the scoring system at particular domain scores to further stratify patients. For instance, a patient with high pain and quality of life scores but a low HPA/SNS evaluation would not score as highly as a patient who had the same pain and quality of life issues but also had a high HPA/SNS score. The usefulness of our scoring system as a progressive means to aid in the long-term phenotyping plan for CP/CPPS is discussed in the following sections.

A vision for the future of CP/CPPS

The DPS represents the first generation of this novel approach to CP/CPPS phenotyping. While we envision that our system will form a basis for the clinical management of CP/CPPS, we believe that the future of CP/CPPS diagnosis lies in a thorough understanding of the underlying mechanisms of CP/CPPS pathogenesis. Thus, basic and clinical research will form the basis of evidence-based diagnosis and management in patients with CP/CPPS. Here, we propose the novel use of several genomic and imaging approaches, previously implicated or studied in other chronic pain syndromes, which will provide a higher level of specificity to CP/CPPS diagnosis.

Genomics

The genetic basis of CP/CPPS remains elusive. While the optimal approach to unraveling the underlying genetic mechanisms is unclear, two possible approaches are genome-wide association studies and candidate gene studies. To date, no genome-wide association studies have been performed in CP/CPPS. Although candidate gene studies provide a somewhat limited view of diseases in general, we feel that this is the most promising start for establishing the mechanistic basis of CP/CPPS. Based on existing studies, promising gene candidates include *CYP21A2*,[26] *COMT*,[28] *GCH1*,[29] and *BHLHE22* (also known as *BHLHB5*).[30]

Additionally, evaluating patients for mutations in specific genes implicated in CP/CPPS (*CYP21A2*)[26] and general pain processing and sensitization (*COMT*,[28] *GCH1*,[29] and *BHLHE22*[30]) might help uncover hidden phenotypes that, although homogeneous in terms of their resulting symptoms, have different underlying mechanisms and will respond to targeted therapeutic approaches (Box 3). We believe that future studies will identify additional biomarkers, provide validation to existing biomarkers, and elucidate additional pathogenetic mechanisms in CP/CPPS.

For example, as outlined in the previous section, *CYP21A2* is one of the candidate genes that are of particular interest to us. However, the question remains as to what role *CYP21A2* could have in contributing to the symptoms seen in CP/CPPS patients. One possible mechanism relates to pre-existing evidence that steroid hormones and their precursors produced in the adrenal glands can cross the blood–brain barrier and exert various actions on the central and peripheral nervous systems.[31] Thus, increased levels of steroids (progesterone, 17-OHP, androstenedione and testosterone) resulting from CYP21A2 deficiency might modulate neurotransmitter binding sites or receptors, including calcium channels and $GABA_A$, NMDA and P2X receptors.[32] This, in turn, could result in changes in pain perception. We believe that generating knowledge of the key genetic factors involved in the etiology and progression of CP/CPPS will be essential to the development and testing of mechanism-based treatment modalities.

Imaging

As discussed previously, a fundamental question in the evaluation of patients with CP/CPPS is whether they have end-organ disease or a central pain syndrome (localized versus systemic disease). We propose the use of pelvic floor functional MRI (fMRI) for distinguishing between those two possibilities.[33] This imaging modality,

in combination with brain fMRI or brain magnetic resonance spectroscopy (MRS), might provide intriguing insights into disease mechanisms.[34]

Brain fMRI presents a unique opportunity for phenotyping, as previous studies in other chronic pain conditions have demonstrated abnormal cortical thickness and white and gray matter composition in pain-processing centers.[35] Although some of these centers universally respond to pain, others are variably altered by somatic and visceral pain experiences.[36] One intriguing hypothesis is that a unique pattern might be identified that can distinguish between patients with CP/CPPS only, CP/CPPS and fibromyalgia and CP/CPPS and IBS. Fibromyalgia induces changes in the primary somatosensory cortex, while IBS results in changes in the posterior insula and other areas with a stronger visceral component.[37] An fMRI study presented at the 2009 American Urological Association meeting demonstrated that the pain experienced by CP/CPPS patients has a unique temporal variability property, distinct from that seen in patients with chronic back pain or postherpetic neuralgia.[38] The investigators in this study reported that the associated brain activity was primarily located in the bilateral anterior insula and anterior cingulate.[39]

Many patients with CP/CPPS report the onset of their symptoms following infection, inflammation or other exposures such as trauma or voiding dysfunction. While information from the patient history is useful in establishing the onset and progression of symptoms, owing to the lack of a unique signature, it does not allow for 'staging' of CP/CPPS. Although staging has been universally effective in conquering cancer, the lack of understanding of the onset of peripheral and central sensitization has precluded the establishment of a staging system for CP/CPPS. We believe that advanced imaging methods, such as pelvic floor and brain fMRI, can provide a unique bridge to disease staging in CP/CPPS. Establishing a universal staging system will provide the uniform language and system of communication between different working groups in terms of the natural history of the disease, progression, and treatment outcomes in clinical trials of CP/CPPS treatments.

Another strength of the DPS is that it provides the opportunity to match fMRI patterns, as well as specific genes, with certain score ranges. The DPS supports this concept of staging by offering a quantitative designation that links LvS disease to fMRI results. The DPS has a maximum total score of 30 points; scores below 20 represent localized disease, and could be correlated with a specific fMRI pattern, while scores above 20 represent systemic disease and could correlate with a different fMRI pattern. This same concept can also be used in genotyping. For example, a mutation in one of the implicated genes discussed above could correlate with a particular score. This type of analysis puts the data in a context that would link specific fMRI patterns or genetic signatures with the different stages of the disease, providing another step in the direction of mechanistic understanding.

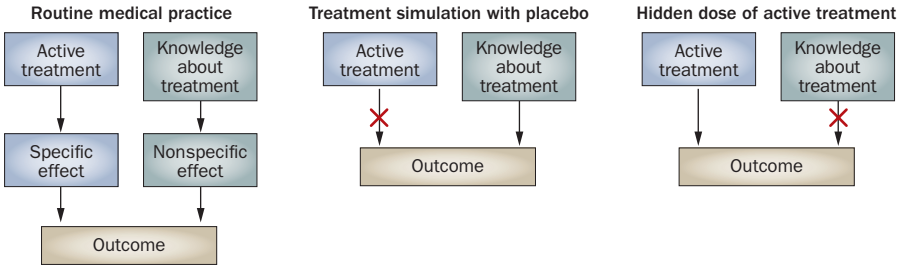

Figure 1 | The open-hidden study design. In this experimental approach, a treatment is given in a routine manner, in which the psychosocial context surrounding treatment administration is present (open treatment), and also in a hidden manner, in which the treatment is given without the patient's knowledge. In the case of a drug intervention, the open treatment mimics normal clinical care; the clinician injects a drug in full view of the patient with verbal and contextual interactions. For the hidden treatment, the drug is infused by a computer pump in the absence of the clinician and the therapeutic context. Patients receiving hidden treatment are aware that at some stage they will receive a drug, but they do not experience the expectation component or other contextual factors surrounding the treatment. Because the hidden administration removes the psychosocial context of treatment, the placebo component is defined as the difference in outcome between open and hidden treatments, although no placebo is given. Adapted from Colloca, L. *et al. Lancet Neurol.* **3**, 679–684 (2004), with permission from Elsevier.[44]

Clinical trials: past and future

As noted above, heterogeneity, fluctuation of symptoms over time and overlap with other chronic pain disorders present unique challenges in the design and execution of clinical trials in CP/CPPS. Part of the solution lies in our proposed phenotyping system, which will allow the elucidation of the mechanisms that underlie symptoms in individual patients. Beyond this, several epidemiological factors can explain the lack of treatment efficacy in previous randomized controlled trials conducted by the CPCRN, such as patient selection, lack of clarity over optimal dosing, and the duration of therapy.

To overcome these challenges, we recommend two novel clinical study approaches for CP/CPPS: the open-hidden study design and the delayed-start design.

The open-hidden study design

Although the placebo effect is poorly understood in CP/CPPS, evidence suggests that it may have an important role in treatment outcomes.[40,41] The open-hidden study design is a way of assessing the contribution of the placebo effect (Figure 1) that has been used in other pain conditions, and holds promise for the design of clinical trials in CP/CPPS.

This study design could improve CP/CPPS treatment guidelines in a manner similar to that discussed by Finniss *et al.*[41] In this paper, the authors refer to an open-hidden study design used to show that proglumide, a cholecystokinin antagonist, was more effective than placebo in reducing postoperative pain, while placebo was more effective than no treatment.[42] These results suggest that proglumide acts effectively on pain pathways, producing specific effects, while placebo activates placebo analgesic mechanisms through expectation pathways, producing nonspecific effects. However, a 'hidden' injection of proglumide (administered without the knowledge of the patient) had no analgesic effect, revealing that proglumide achieves a response by interacting with and enhancing placebo mechanisms (expectation pathways), not by acting on independent pain pathways. Proglumide, therefore, is only effective when combined with placebo mechanisms inherent to the clinical encounter.[42]

Standard clinical trials, such as those conducted by the CPCRN, only compare the response to placebo with the response to active intervention, with no interpretation of the interaction between the two. Thus,

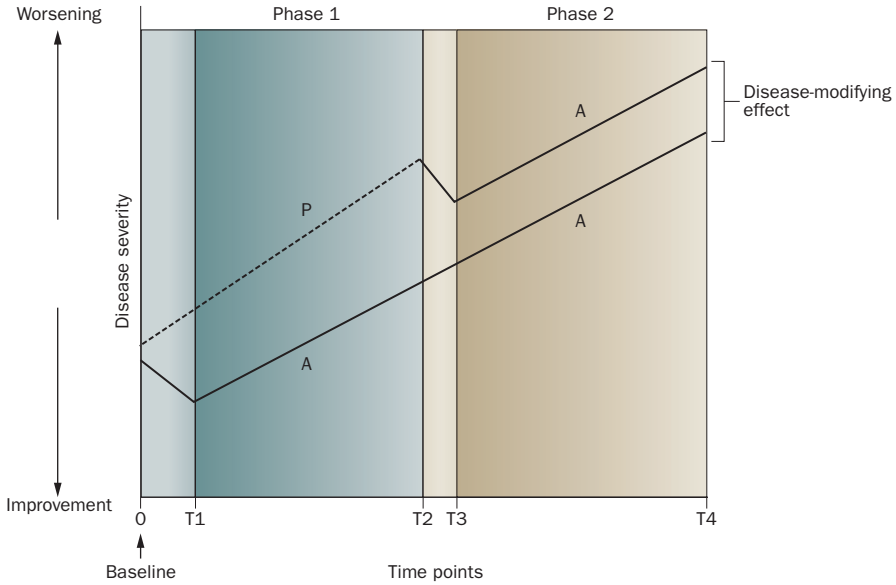

Figure 2 | The delayed-start study design. In phase 1, patients are randomly assigned to receive either active treatment (A) or placebo (P) from baseline to T2. The 0–T1 period reflects transitory responses to the initiation of study agents, which is usually not included in analysis. The effect of the treatment on symptoms and a possible indication of its disease-modifying effect are recorded during the T1–T2 period. In phase 2 (T2–T4), all patients receive the active treatment. Again, the T2–T3 period reflects transitory responses. T3–T4 data reflect the disease-modifying effects of the treatment. The difference between the P–A and A–A curves at T4 indicates the disease-modifying effect, and the difference in the slopes of P–A and A–A during the T3–T4 period reflects the maintenance of the disease-modifying effect during phase 2. Adapted, with permission, from D'Agostino, R. B. Sr. *N. Engl. J. Med.* **361**, 1304–1306 (2009).[43]

they are unable to determine whether active intervention has specific effects on symptoms or merely enhances any nonspecific effects. The open-hidden study design will help answer the question "is the intervention alleviating the symptoms of CP/CPPS because of the implicated mechanism of action (biologic effect) or because of the activation of expectation pathways (placebo effect)?" An understanding of this relationship in chronic pain conditions such as CP/CPPS is vital to improving treatment outcomes.

The delayed-start study design

When treating chronic diseases, it is often difficult to separate positive short-term effects on symptoms from an actual change in disease progression. As with the placebo effect, evaluation of the disease-modifying effects of CP/CPPS treatments is necessary to advance our understanding of the available treatments.

To address this issue, we propose the delayed-start study design (Figure 2).[43] This approach divides the clinical trial into two phases. In phase 1, patients are assigned to either the active treatment or the placebo group. Patients in the treatment group receive the treatment and are followed for a determined period of time, at the end of which the effects of the treatment on symptoms can be observed. In phase 2 of the trial, patients in both the treatment and placebo group receive treatment, allowing the study group to analyze the disease-modifying effects of the treatment.

This clinical trial design presents a number of challenges that require both an extensive knowledge of CP/CPPS and complex statistical measures to overcome. However, the delayed-start study design is optimal for determining the disease-modifying effects of treatments for CP/CPPS. This type of knowledge would greatly facilitate the development of innovative practice guidelines, as well as inform future research.

Conclusions

To address the fundamental problem of mechanistic heterogeneity in CP/CPPS, we propose the DPS as a bridge between the symptom-based medicine that has been practiced in the past and the mechanism-based medicine that is necessary for more-effective treatment. We have discussed ways in which the DPS will be used to aid future studies of CP/CPPS while providing a current diagnostic tool that utilizes measures that are already available. As a step towards our improved mechanistic understanding, we suggest certain genes that may have a role in CP/CPPS etiology and progression. In addition, we present the novel idea of staging in CP/CPPS and the use of fMRI to distinguish between localized and systemic disease. Lastly, we have addressed problems in current clinical trial design, and encourage the use of the open-hidden and delayed-start trial designs to advance our understanding of CP/CPPS treatment outcomes.

*Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA (**S. A. Allsop, D. J. Erstad, K. Brook, S. F. Bhai, J. M. Cohen, J. D. Dimitrakoff**).*

Correspondence to: J. D. Dimitrakoff
jdimitra@bidmc.harvard.edu

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All authors contributed equally to researching data for the article, discussing its content, writing and review/editing of the manuscript before publication.