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The Missing “P” in Psychiatric Training: Why is it Important to Teach Pain to Psychiatrists?

Igor Elman, MD¹, Jon-Kar Zubieta, MD, PhD², and David Borsook, MD, PhD³

¹Clinical Psychopathology Laboratory, McLean Hospital, Harvard Medical School, Boston MA

²Departments of Psychiatry and Radiology and Molecular and Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI

³P.A.I.N. Group, Department of Psychiatry, McLean Hospital and Massachusetts General Hospital, Harvard Medical School, Boston MA

Abstract

Context—Pain problems are exceedingly prevalent among psychiatric patients. Moreover, clinical impressions and neurobiological research suggest that physical and psychological aspects of pain are closely related entities. Nonetheless, remarkably few pain-related themes are presently included in psychiatric residency training.

Objective—Our objective is twofold: (1) to provide clinical and scientific rationale for psychiatric training enrichment with basic tenets of pain medicine and (2) to raise the awareness and sensitivity of clinicians, scientists and educators alike to the important yet unmet clinical and public health need.

Results—Three lines of translational research evidence, extracted from the comprehensive literature review, are presented in support of the objective. First, the neuroanatomical and functional overlap between pain and emotion/reward/motivation brain circuits suggests integration and mutual modulation of these systems. Second, psychiatric disorders are commonly associated with alterations in pain processing, whereas chronic pain may impair emotional and neurocognitive functioning. Third, pain may serve as a functional probe for unraveling pathophysiological mechanisms inherent in psychiatric morbidity given its stressful nature for the organism.

Conclusions—Pain training in psychiatry will not only contribute to deeper and more sophisticated insights into pain syndromes but also into psychiatric morbidity at large regardless of patients’ pain status. Furthermore, it will ease artificial boundaries separating psychiatric and medical formulations of brain disorders, thus fostering cross-fertilizing interactions between specialists in various disciplines entrusted with the care of pain patients.

Keywords

Pain; stress; reward; opioid; dopamine; nucleus accumbens; depression; anxiety; post-traumatic; borderline personality; comorbidity; education; interdisciplinary

Introduction

Chronic pain is a public health problem of pandemic proportions that afflicts over 70 million Americans^{1, 2} and remains the most common complaint brought to the attention of health care practitioners³. Its annual cost to the American society is staggering and is estimated to be around \$100 billion owing to medical costs and loss of earnings and productivity⁴. The current demographic trends⁵ and the tremendous shortage of pain experts⁶ forecast the need for even greater attention to pain from the medical establishment in consequence of the substantial rise in the overall proportion of geriatric population that is naturally at a heightened risk for the development of pain-related conditions⁷. Specifically, 50% of community-dwelling elders and up to 80% of nursing home residents are afflicted with chronic pain⁸. The rates of Americans over the age of 65 has increased steadily due to the rise in life expectancy and decline in fertility from 4% at the beginning of the 20th century to 12% nowadays with projected over 20% (70 million) over the next 25 years⁹. Pain is exceedingly prevalent in psychiatric samples¹⁰ and since more people will be suffering from pain so will psychiatric patients¹¹.

One of the most daunting challenges faced by psychiatric practitioners is how to distinguish and approach physical and emotional symptoms arising in the context of pain experienced by their patients. We respond to this question by proposing to integrate fundamental tenets of pain medicine within the core psychiatric residency training curriculum¹². Besides altered pain function^{13, 14}, psychiatric patients can be noncompliant with pain treatment and additionally develop co-morbid addiction to opiate analgesics¹⁵. On the other hand, chronic pain is frequently associated with anxiety and depressive symptoms¹⁶ as well as with degenerative cortical changes that may further deteriorate affective states and cognition^{17, 18}.

Sensory areas are recruited by both acute and chronic pain, but the latter is a more complex phenomenon engaging a broader stress-related neural network with emotional, motivational and cognitive components¹⁹ that converge on circuits such as the mesocorticolimbic dopaminergic and endogenous opioid, involved in salience/reward/motivational mechanisms in addition to responses to pain, more generally stressors and their regulation²⁰. With this premise of neurobiological overlap between the processing of pain and of other stressful and emotionally salient signals, the present paper considers the aspects of pain that are related to stress, reward and motivational regulation and are pertinent to psychiatric morbidity. First, we compare data on the neural mechanisms that underlie physical and emotional types of “pain”, and this comparison is taken as the basis for the assumption of overlap between these frequently related entities. Second, we summarize the mechanisms involved in the mediation of pain and analgesia, as they relate to normal processing of emotions, reward and motivation as well as their alterations encountered in psychiatric patients. The same section also covers specific background demonstrating that pain-related stimuli provide a reliable functional probe of the brain reward/salience/motivation circuitry and may thus have heuristic value for the inquiry into neurobiology of psychiatric illnesses. Next we provide specific clinical context on the association between psychiatric disorders and pain conditions. Finally, the two last sections cover psychiatrists’ training in pain medicine and the importance of this endeavor.

Physical and Emotional Pain may Represent Two sides of the Same Coin

In addition to the epidemiological association between pain and psychiatric disorders¹⁰, there are clinical, even diagnostic features of pain syndromes that point to neuropsychiatric origin. Pain’s definition by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue

damage"²¹, recognizes its multifaceted bio-psycho-social nature with causes that extend well beyond direct physical harm. This is expressed in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) as the Axis I diagnostic category of the Pain Disorder, which is encoded in three of the five diagnostic criteria, viz., A. Pain...is of sufficient severity to warrant clinical attention; B. Pain causes clinically significant distress or impairment in social, occupational, or other important areas of functioning; C. Psychological factors are judged to have an important role in the onset, severity, exacerbation or maintenance of pain²². Pain arising from physical sources is classified among the DSM-IV-TR Axis III disorders, solely reserved for medical conditions²². In the reality the distinction between Axis I and III Pain Disorders is not that obvious and both pain categories share clinical characteristics, symptom severity and functional impairment²³. Realization of such blurring of diagnostic boundaries is rooted in the lay language where the "pain" term is used interchangeably in both physical and emotional contexts²⁴.

Pain and the Brain: Implications for Emotional and Motivational Processing

Acute pain signals real or perceived tissue damage from environmental threats²⁵. Contextually, albeit not clinically similar, cancer pain is also etiologically linked to direct tissue damages due to malignancy or to surgical, chemotherapy or radiotherapy treatments^{26, 27}. Chronic non-malignant pain is not a unitary sensation evoked by a local injury, inflammation or other tissue pathology but is a complex state modulated by genetic, environmental, cognitive and emotional factors^{28, 29}. Majority of non-malignant chronic pain cases are neuropathic viz., caused by alterations in the central nervous system¹⁹. Such centralization is conceptualized as an independent neuropsychopathological disease state, occurring at the level of the spinal cord pathways and emotional/motivational circuits, respectively manifested in exaggerated response to painful (hyperalgesia) and non-painful (allodynia) stimuli in combination with negative affective states and persistent drive to eliminate pain via behavioral or pharmacological measures^{19, 30, 31}. The apparent intricate link between pain and emotions/motivations underscores the importance of dynamic interactions between these and other (e.g., neurochemical and neuroanatomical) factors for understanding of health and psychopathology (Figure 1).

Figure 2 schematically displays a somewhat representative compilation of the interactions between sensory and emotional systems with ensuing affective states and symptomatology. Evidence of such interaction is provided by functional magnetic resonance imaging (fMRI) work showing that grief-related emotional pain activates classical physical pain circuitry (e.g., periaqueductal gray, insula and the anterior cingulate cortex)³² while physical pain in humans activates reward/motivational circuits (e.g., nucleus accumbens [NAc] and ventral tegmentum [VT])³³⁻³⁵. Furthermore, acute emotional or physical pain in patients with the respective chronic conditions (i.e., complicated grief and back pain) via exposure to reminders of the deceased³² or thermal pain³⁶ robustly engages the key reward and reinforcement structure, namely the NAc. These findings suggest that emotional and physical pain may become a reinforced stimulus in some conditions (e.g., complicated grief and chronic back pain) thus providing partial explanations for their unremitting course. In a broader sense, critical for the survival mechanisms pain system, is embedded within extensive emotion/reward/motivation circuitry, representing a neural network responsible for continued existence of individuals and species via pursuit of food, water, and sex as well as via learning, decision making and adaptation to stress. Considering survival significance of social affiliations, their pleasurable acquisitions and painful losses may have evolutionarily tapped the same reward systems³⁷; an idea consistent with the reward-pain continuum hypothesis promulgated by Baruch Spinoza. A practical offshoot of the reward-aversion continuum is that pain serves as a functional probe of the brain reward and

motivational systems³³. This is an important contribution, given the paucity of reliable probes and the pivotal role played by reward and motivation in the course of psychiatric illnesses.

Co-morbidity of Pain and Psychiatric Disorders

Provided that the emotional brain circuitry abnormalities are arising in psychiatrically healthy people exposed chronic pain¹⁸, a compelling *a fortiori* argument is that propensity for pain condition is worsened by neuropsychopathology affecting the same neural structures. A model partially suited to explain this link is the diathesis-stress theory postulating preexisting sometimes subclinical traits that manifest in the form of overt psychopathology in the context of prolong pain-induced stress^{16, 38, 39}.

The list of psychiatric ailments associated with heightened pain prevalence in at least one extant epidemiological survey would stretch the entire DSM-IV-TR diagnostic range from the *Disorders Usually First Diagnosed in Infancy, Childhood or Adolescence* to *Other Conditions* that may be a *Focus of Clinical Attention*. For the purpose of the present discussion we address four common and representative syndromes, namely, the major depressive disorder (MDD), borderline personality disorder (BPD), addiction and post-traumatic stress disorder (PTSD).

Pain and MDD

Elicitation of depressed vs. happy affective states in laboratory settings respectively worsen and improves pain experience in healthy individuals and in chronic pain patients^{40, 41, 42}. Accordingly, a substantial proportion of MDD patients suffer from chronic pain⁴³, the intensity of which increases with the severity of depressive symptomatology⁴⁴. On the other hand, sustained pain leads to increased negative affective states^{45, 46} and eventually to high MDD prevalence in chronic pain patients⁴⁷ so that, in comparison to pain alone or MDD with other medical conditions, comorbid MDD-pain patients present greater severity of depressive symptoms and substantially poorer treatment outcomes⁴⁸.

In order to link MDD neuropathology and pain, painful heat stimuli were applied to the dorsal forearm of depressed patients during fMRI¹³. Among other functional alterations, depressed patients had proportionally (to depressive symptomatology) heightened right amygdala activity when anticipated and actually experienced painful stimuli¹³. Other lines of evidence supporting recursive, partly shared neural systems by MDD and pain processing include (a) serotonergic and noradrenergic pathways' involvement in mood regulation and in the control over ascending pain stimuli, explaining therapeutic pain successes of dual action serotonergic/noradrenergic reuptake inhibitors and tricyclic antidepressants⁴⁹; (b) other shared treatment modalities (e.g., transcranial magnetic or vagus nerve stimulation) and (c) abnormalities of the analgesic opioidergic system in MDD patients and the involvement of this neurotransmitter in emotion regulation⁵⁰. Taken together, these findings support the idea that MDD and pain can trigger and perpetuate each other owing to overlapping neural and emotional alterations. Therefore, assessment of pain function may provide important diagnostic and therapeutic leads in MDD, which is projected to become the second most common cause of disability after the heart disease⁵¹.

Pain and BPD

Emotion dysregulation, affective lability and impulsive behavior in BPD patients are reported to be associated with increased pain thresholds⁵² that predict dissociative symptoms and negative affect⁵³. In comparison to healthy subjects, BPD patients demonstrated enhanced opioid neurotransmission during molecular imaging with positron emission tomography⁵⁴ in conjunction with greater pain-induced fMRI signal changes in

the prefrontal cortex but lower activity in the amygdala and anterior cingulate. These are regions that interface emotion, pain and stress regulation and where the endogenous opioid system plays key modulatory roles⁵⁵. Impulsivity, a trait characterizing not only BPD patients but also those at risk for addictive disorders, was also associated with greater endogenous opioid function in similar brain regions of healthy people⁵⁶.

Pain and Addiction

Numerous epidemiological surveys documented that drug addiction (including prescription opioids) is particularly prevalent among pain patients^{16,57,58}. The mechanisms of this link are likely to be multifactorial and to involve both psychosocial and neurobiological causes⁵⁹. Among neurobiological factors, the brain reward and motivational system probably plays an important role. The mesoaccumbens dopamine pathway, extending from the VT of the midbrain to the forebrain regions such as the NAc is the crucial component of this system^{60–63}. Physiological significance of the increases in the NAc' dopamine, a common element of the rewarding effects of natural rewards as well as drugs of abuse^{64, 65}, is a subject of complementary hypotheses^{20, 66, 67} including but not limited to the subjective pleasure or "high" (reward) sought by drug users as well as motivation, appraisal of stimuli salience, stress, learning and decision making^{68–72}.

Both acute pain^{35, 73, 74} and euphorogenic drugs^{64, 65} activate dopamine transmission in the brain reward circuitry including the NAc, whereas prolonged periods of pain^{75, 76} or of drug consumption^{77–79} produce the opposite effect, accompanied by reduced motivation towards normally pleasurable stimuli^{80–83}. These findings can be interpreted in the context of the incentive motivation theory³⁴, viewing the brain reward function as comprised from core motivational and emotional processes, respectively termed 'wanting' and 'liking'. Pain- or drug-induced changes in the mesolimbic dopaminergic circuitry underlying the wanting but not liking purposes may be responsible for transforming regular wanting responses into heightened incentive salience assigned to pain or drug-related cues. Such incentive sensitization, construed as an animal homolog of human craving³⁴, may be responsible for drug seeking driven by the desire to ameliorate an inadequately treated pain (i.e., pseudo-addiction;⁸⁴) or to avoid a feared opioid withdrawal (i.e., therapeutic dependence;⁸⁵).

A closely related concept, derived from primate work, is the aberrant learning theory suggesting that learning of new rewarding or aversive experiences is encoded via interactions between tonic (baseline) and phasic spikes in dopaminergic neurons; phasic firing predicts unanticipated stimuli⁸⁶. Hence, neural adaptations to excessive dopaminergic bombardment in response to pain may lead to low signal-to-noise detection capability for natural rewards⁸⁷ along with profound overlearning of the motivational significance of cues that either predict painful episodes or are associated with painful experience⁸⁶.

The above ideas provide rich opportunities for neuropsychiatric clinicians and researchers alike to decipher seemingly elusive interactions between pain and analgesia with respect to the addiction on opioid analgesics^{88–91}. Three potential classes of interaction may (co)exist between pain and opioids, including competition, independence (i.e., additive effects) and synergism. Competition (Figure 3A) may be the most notable interaction as opioid analgesics, when administered at the adequate dose, restore the homeostatic equilibrium^{67, 92} by eliminating pain while pain offsets opioids' reinforcing properties^{89, 93}. Dependence, including tolerance and withdrawal, may nonetheless sometimes occur^{88, 94} during opioid pharmacotherapy, but it qualitatively differs from addiction by lacking the compulsive nature and loss of control^{67, 95–97}.

To our knowledge, no studies to date directly investigated whether under- or over treated pain has competitive, independent, or synergistic effects on the development of addiction.

Opioid analgesics and pain share the ability to affect extracellular dopamine concentrations in the NAc. The latter robustly activate dopaminergic neurotransmission both via inhibition of the GABA neurons⁹⁸ and by direct action at the mesocorticolimbic dopamine system and at the related structures e.g., the VT⁹⁹, the NAc¹⁰⁰ and the hypothalamus¹⁰¹. Pain likewise produces DA releases in the NAc with the involvement of the GABA-ergic mechanisms^{102, 103}. Chronic pain perpetuation and addiction development may result from the dysregulation of these systems. For instance, activation of mesolimbic dopaminergic pathways involved in motivational processing³⁵ by inadequately treated or untreated pain (Figure 3B) leads to heightened incentive salience attribution to pain and to pain-related stimuli⁸⁶. Opioid analgesics providing quick pain relief (i.e., negative reinforcement) can thus become a sensitized motivational target capturing greater attentional resources and resulting in drug craving clinically manifested in expenditure of greater behavioral effort relative to normal reinforcers to seek and to obtain opioids^{93, 104, 105}. Even though this state is viewed as pseudo- rather than genuine addiction⁸⁴, the latter features may predominate with time, giving rise to opioids' overuse in the form of ill-fated attempts to 'self-medicate' perceivably intolerable pain and pain-related anxiety⁶⁷. Such an outcome is relatively uncommon and its likelihood is increased with prior history of drug abuse, non-compliance with treatment recommendations and disability litigation^{106–108}.

Changes in the mesolimbic dopaminergic circuitry induced by opioids, taken at the doses exceeding the homeostatic need for pain alleviation (Figure 3C), may be responsible for transforming regular motivational drives into heightened incentive salience assigned to opioids or to opioid-related cues, that is to say drug craving³⁴. Additional critical aspect of opioid overuse in the context of an ongoing pain condition is the amplification of "hyperkatifeia" or negative affective states and of physical pain itself^{67, 109, 110}.

This may be a variant of cross-sensitization when exposure to one stimulus (e.g., addictive drug) increases subsequent response to itself^{111–113} and to a different stimulus (e.g., stress; ^{114–116}). Hence, a common outcome in pain patients could be generation of the 'spiraling distress cycle'⁷⁹, whereby opioid overuse provoked by the heightened pain salience produces additional deterioration in the pain^{117–20} and emotional⁶⁷ problems, leading to further opioid consumption that may eventually produce a transition from an excessive opioid use to the *bona fide* addiction. Given such an autonomous, self-sustaining feedforward loop, it is plausible that pain combined with excessive opioids brings about synergistic processes favoring addictive phenomena. In sum, safe and effective care of pain patient requires thorough understanding of the complex interplay among pain-, analgesia- and addiction-related factors.

Pain and PTSD

Anxiety syndromes are also commonly comorbid with chronic pain¹²¹. A conditioned fear and anxiety syndrome, PTSD, could be yet another example of reward/motivational circuitry involvement in the association of chronic pain and psychopathology. Several lines of evidence implicate pain in the course of PTSD. Neuroanatomically, in addition to their involvement in the pain processing^{33, 35, 122–125}, dopamine terminal fields including the NAc, amygdala and medial prefrontal cortex also play key roles in stress, aversive responses and in PTSD^{70, 126–129}. From the pathophysiological perspective, peritraumatic pain is recognized among PTSD's independent risk factors¹³⁰ while morphine analgesia reduces the severity and even prevents the appearance of PTSD symptomatology^{131–134}.

A number of mechanisms may contribute to the PTSD-pain comorbidity that carries a substantially poorer prognosis than each condition taken in isolation^{135–137}. Pain, paired with emotional trauma and its recollections, can become a conditioned stimulus that evokes fear and anxiety responses that in turn augment subjective pain perception and its neural

correlates^{138, 139} leading to additional deterioration and avoidance of pain- and trauma-related situations^{140–143}. Such a “mutual maintenance”¹⁴⁴ cycle may be evident in PTSD symptoms emergence caused by surgical pain awareness despite seemingly adequate general anesthesia or in 5% to 19% PTSD incidence surges at the 6 to 12 months follow up points in injured accidents’ survivors¹⁴⁵.

Additionally, increased central opioidergic tone^{146, 147} along with robust elevations of endogenous opiates concentrations in the cerebral spinal fluid¹⁴⁸ and in plasma¹⁴⁹, but¹⁵⁰ is a relatively consistent clinical finding in PTSD. Therefore, similar to chronic users of opioid analgesics (Figure 3C), PTSD-related exaggerated CNS opioidergic activity could contribute to the sensitized pain phenomenon potentially mediated via the amplification of the excitatory (e.g., glutamatergic) neurotransmission^{151–153}. The proposed mechanism of excessive pain occurrence could have treatment implications, as it implies prophylactic use of opioid receptor antagonists. Indeed, on the basis of the hypothesis that opioidergic mechanisms are involved in the pathophysiology and symptoms of PTSD^{146, 154, 155}, opioid antagonists have been evaluated for a potential clinical efficacy in a number of clinical trials^{147, 156, 157}. On the whole, they were safe and well tolerated and resulted in significant improvements of various aspects of PTSD symptomatology such as emotional numbing, startle response, nightmares, flashbacks, intrusive thoughts and comorbid alcoholism^{147, 156, 158}.

Pain Training in Psychiatry

Pain themes are only marginally addressed by the respective training and certification requirements set forth by the Accreditation Council for Graduate Medical Education (ACGME)¹⁵⁹ and the American Board of Psychiatry and Neurology¹⁵⁹. The former includes *Intractable Pain* among *Medical Knowledge* items but not among *Patient Care* competencies, while the latter only lists *Pain Medicine* in the section on *Psychiatric Subspecialties and Other Areas of Psychiatric Endeavors*. Psychiatrists appear to be inadequately trained in pain medicine and to consequently perceive their work with pain patients as ungratifying^{160, 161} so the present psychiatric training requirements may be suboptimal for the physicians that are uniquely poised to evaluate and treat pain patients whilst sharing responsibility with their medical colleagues for the management of mental health issues¹⁶².

Empirical data on potential benefits of increased pain training for psychiatric residents are missing. This line of inquiry may be limited by educators’ concerns that any training additions may encroach on the time honored intensive and rigorous curriculum of the critical clinical skills and knowledge base¹⁶⁰. In our opinion, far from being adverse for psychiatric education, participation in pain training may be beneficial for psychiatric residents, their patients and medical field as whole.

Pain curriculum could build upon the residents’ proficiency in neurobiology and upon the existing IASP guidelines¹⁶³. Since there are countless ways in how the training can be operationalized, a consensus concerning the adoption of various training components perhaps needs to be developed by a Committee comprised of Psychiatric Residency Training Directors and/or through the American Psychiatric Association Task Force. Following is a brief outline of possible components that may be included in the training activities.

The main objective of the first post-graduate year (PGY-1) is to shape the *physician* identity of new medical school graduates. Recent graduates accordingly spend at least four months in primary care clinical settings and so that part of their caseload requirements may include treatment and follow up of chronic pain patient(s). This clinical experience can be reinforced via didactics and direct patient care during the two months mandatory neurology rotation.

The PGY-2, focused on the foundations of physicians' identities as *psychiatrists* may include assessments of dually diagnosed pain/psychiatric patients in conjunction with psychotherapeutic¹⁶⁴ and psychopharmacological⁴⁹ strategies in the treatment of pain patients. The PGY-3 provides an opportunity to refine the previously acquired skills in more specialized settings including inpatient detoxification unit and outpatient addiction clinic. Consultation-liaison rotation in the PGY-4 could emphasize the integrative nature of pain treatment within the context of medicine at large and the distinctive role of psychiatrists in identifying and handling individual and interpersonal issues within the medical team arising in the context of challenges inherent in the care for multi-problem and at times non compliant and treatment resistant pain patients.

Why is it Important to Teach Pain to Psychiatrists?

Rather than viewing psychosocial and biological interventions as distinct therapeutic modalities, psychiatrists are exceptionally trained to conceptualize patients' care on the psychosocial-biological continuum and to shift flexibly across various parts of this spectrum among patients and treatment junctions. Thus, wide-ranging involvement of psychiatrists will invigorate essential elements of evaluation and treatment armamentarium that may be underutilized by their medical colleagues. This is a timely effort because majority of neuropathic pain is only partially responsive to opioids^{27, 165} so innovative approaches are essential for the pain field.

Psychiatrists are understandably suited to recognize and manage subtle psychological processes including expression of feelings via somatic pain complaints¹⁶⁶, defense mechanisms e.g., denial and repression vs. lie and malingering along with conscious and unconscious motivations¹⁶⁷ such as self reported pain in the face of adequate analgesia due to unwarranted anxiety about the opioid dose reduction (i.e., pseudo-opioid resistance;¹⁶⁸) or drug craving vs. pseudo-addiction⁸⁴ or therapeutic dependence⁸⁵. Additional pertinent function is the motivational enhancement¹⁶⁹ fostering compliance and active participation in pain treatment plans⁸⁰.

While multiple cognitive and behavioral strategies (e.g., cognitive restructuring, stress management and systemic desensitization) were reportedly helpful for chronic pain^{164, 170}, National Institute of Health Technology Panel assigned the highest score (i.e., strong) to the evidence regarding the effectiveness muscle relaxation¹⁷¹. Psychiatrists can become strong advocates for the utilization of cognitive and behavioral techniques by the pain field as they routinely apply them to the care of psychiatric patients. Moreover, being undisputed experts in psychopharmacology, psychiatrists can promulgate viable and non-addictive alternatives to opioids with substantial analgesic properties such as antidepressant, anticonvulsant and neuroleptic agents⁴⁹, however see¹⁷² suggesting only minor pain effect of neuroleptics). Also, psychiatrists are the most logical physicians to diagnose and treat suicidal tendencies^{1, 173} as well as mood, anxiety, psychotic and personality disorders exerting pivotal impacts on pain intensity and treatment outcomes¹⁶.

The psychiatrists' dialectical perspective¹⁷⁴ on pain alleviation while preventing, diagnosing and treating addiction to prescription opioid pain killers is addressed in the preceding sections. Additional contribution from the addiction psychiatry field may involve empirically driven treatment matching algorithms allowing provision of individualized level care according to patients needs with regard to their medical status, employment/support, drug addiction, family situation and psychiatric condition. Patient Placement Criteria by American Society of Addiction Medicine¹⁷⁵, may be adapted to pain patients^{176, 177} since they provide multidimensional assessment of severity of illness and level of function and

treatment assignment based on needs for service and level of care determination within the available treatment options.

Hence, outweighing any personal benefits for psychiatric trainees *per se*, this may be of a broader public health interest to engage psychiatrists in the care for the pain patients. Such an addendum will not only generate additional clinical expertise to evaluate and treat a large spectrum of pain-related problems, but will also help expanding the spectrum of psychiatric field to include pain as an entity rooted in numerous other specialties (to name a few: neurology, medicine, surgery and anesthesiology) and will thus advance the integration psychiatry into the mainstream medical care¹⁷⁸ and underscore the significance of attending in concert to mental and physical problems notwithstanding physicians' specialties and patients' presenting problems.

Conclusions

Chronic pain is a major problem afflicting the modern world. The coalescence of epidemiological and clinical data suggests that psychiatric patients have a predilection for a development of various pain conditions. This is at least partially due to functionally impaired neural substrates that overlap emotion, reward, motivation and pain processing. Although psychiatry is only one of many appropriate settings where pain patients can be treated, this approach has several advantages. First, psychiatry is comprehensively focused on the etiopathophysiological mind-body interactions with direct relevance to the pain syndromes. Second, neurobiological research in animal models and more recently in humans confirms a substantial degree of overlap between pain regions and brain areas implicated in core psychiatric symptoms. Third, the relationship and co-morbidity between persistent pain and psychiatric disorders has been extensively documented.

If the interactions between pain and psychiatric illnesses can be further elucidated, they might be used to screen patients at risk for the development or worsening of psychopathology (i.e., primary prevention). It may be also discovered that psychiatric patients need to be targeted for early intervention even in the presence of mild pain problems (i.e., secondary prevention). Lastly, pain medicine training could speed the introduction of other essential 'medical' topics to psychiatric curriculum that have now become timely (e.g., metabolic disturbances¹⁴). Filling in the missing "P" in elevating the psychiatrists' new role in pain patient care, teaching and research may be a substantial clinical contribution in a domain that currently offers relatively little in terms of adequate therapeutic responses.

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Figure 1. Schematic Overview of the Interface between Neurobiological and Psychological Factors Involved in Chronic Pain Experience

Several lines of evidence link pain to emotional, motivational and reward processing. At the fronto-cingulate cortical level chronic pain conditions may cause brain reorganization via glutamatergic mechanisms¹⁷⁹ including cortical thinning resulting in mild to moderate impairments in emotional and cognitive function with ensuing negative affective states and compromised decision making capacity^{12,17}. Dysphoric emotional states render pain stimuli more aversive leading to additional psychological impairments (i.e., feedforward phenomenon). With regard to subcortical systems, acute pain is associated with increased dopaminergic trafficking within mesolimbic dopaminergic pathways^{33,124}. Chronic pain exerts an opposite action by decreasing dopaminergic transmission in the same neural structures¹⁸⁰ and is accompanied by decreased motivation towards normally pleasurable stimuli⁸⁷, clinically manifested as anhedonia. Central opioidergic systems that are dysregulated in chronic pain conditions further contribute to affective disturbances.

Figure 2. Pain and Emotions (Adapted from ³³)

A: Pain produces changes in emotional states with ensuing psychiatric symptomatology and these effects are bidirectional, that is to say, negative affective states can augment the perceived intensity of pain.

B: Altered Sensation and Functional Changes in Brain Regions that subserve emotional states and cognition.

Figure 3. Schematic diagram of potential mechanisms involved in drug-related motivational changes during adequate-, under- or over-treatment of pain with opioid analgesics

(A) Pain relief owing to adequate analgesia restores homeostatic equilibrium and seldom produces addiction^{67, 92} which nonetheless may arise^{15, 88} in the context of intricate relationships among various genetic, clinical, pharmacokinetic and psychosocial factors. Dependence on opioid analgesics, including tolerance (i.e., diminution of drug's effectiveness) and resultant withdrawal^{88, 94} is a more likely outcome and it calls for a gradual and judicial dose escalation¹⁸¹. (B) Inadequately treated or untreated pain activates dopaminergic ventral striatal neurotransmission involved in motivational processing (15) leading to heightened incentive salience attribution to pain and to pain-related stimuli. Opioid analgesics is one of such stimuli that becomes a sensitized motivational target capturing greater attentional resources and leading to expenditure of greater behavioral effort relative to normal reinforcers^{93, 104, 105, 182}. Even though this state is viewed as pseudo- rather than genuine addiction⁸⁴, the latter's features may predominate with time, given the potential opioid overuse in the form of ill-fated attempts to 'self-medicate' perceivably intolerable pain and pain-related anxiety⁶⁷. (C) Similar to pain effects discussed in the preceding caption, changes in the mesolimbic dopaminergic circuitry induced by opioids, taken at the doses exceeding the homeostatic need for pain alleviation, are responsible for transforming regular motivational drives into heightened incentive salience assigned to opioids or to opioid-related cues, that is to say drug craving³⁴. Additional critical aspect of opioid overuse in the context of an ongoing pain condition is the amplification of the physical and emotional aspects of pain. The latter emotional component, recently termed "hyperkatifeia"⁶⁷, is purportedly mediated via norepinephrine and consequent corticotropin-releasing factor hypersecretion within the extended amygdala structures underlying anxiety and fear^{183, 184} namely the central nucleus of the amygdala^{185, 186} and the bed nucleus of the stria terminalis^{187–189}. Notably, such a cross-sensitization phenomenon is typical of addictive substances and entails a situation when prior exposure to one stimulus (e.g., drug) increases subsequent response to itself^{111–113, 190} and to a different stimulus (e.g., stress;^{114, 116, 189}). Hence, a common outcome in pain patients could be generation of the 'spiraling distress cycle'^{79, 191} whereby opioid overuse provoked by enhanced pain salience (see Caption B) produces additional deterioration in the pain^{117–120} and emotional⁶⁷ problems, leading to further opioid consumption that may eventually produce a transition from excessive opioid use to *bona fide* addiction