

Depressive Disorders and Pain: A Joint Model of Diagnosis and Treatment

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Abstract

Pain is a complex construct that is linked to neurobiological factors, mostly related to sensory pain dimensions and evaluated by somatosensory cortical and thalamic areas. But a painful stimulus is also modulated by emotional and cognitive factors, related to the emotional limbic processing of pain and to cortico-frontal evaluation and belief about pain. In this article, the authors discuss how and why pain and depression are frequently associated in clinical practice, the biological mechanisms shared by both disturbances and how this common background can explain the high comorbid incidence of depressive disorders and pain, and the rationale for treatment strategies acting on both depressive disorders and pain.

Keywords: Depression; Pain

Introduction

Pain is the most common symptom reported by any kind of medical patient and is a widespread problem in both primary medical care and specialty pain clinics or mental health settings. Pain is a complex construct that is linked to neurobiological factors, mostly related to sensory pain dimensions and evaluated by somatosensory cortical and thalamic areas. But a painful stimulus is also modulated by emotional and cognitive factors, related to the emotional limbic processing of pain and to cortico-frontal evaluation and belief about pain.

The most important biological factors related to pain include pain matrix alterations, cytokines and opioid levels, and gender. Psychological factors can be emotional disorders, such as prolonged depressive disorders, chronic anxiety and/or stress, or type of temperament and coping styles, all of which interfere with the individual functioning levels. Moreover, a social component of pain is linked to certain familial models, or to the particular culture concerning pain (for example, in medical assistance), to the social support received or perceived, and to several strengthened factors such as attention or economic costs.

In addition to its presence in physical diseases, pain is also present in several dysfunctional syndromes (fibromyalgia, irritable bowel syndrome, chronic fatigue, etc.), and is a dominant part of medically “unexplained” symptoms such as impaired concentration, sleep disturbances, fatigue and mood disorders [1]. Depressive disorders is a widespread pathology, too, and very commonly associated with chronic pain: a depressive mood, understood as relevant depressive symptoms that reduces the pain threshold and increases the emotional and cognitive perception of pain, while chronic pain first induces demoralisation, then true depression [2]. Understanding the causal relationship between pain and depression, as well as identifying common risk factors leading to both outcomes, is therefore critical to the development of prevention and treatment for these two common syndromes [3].

In this article, we discuss how and why pain and depression are frequently associated in clinical practice; which biological mechanisms are shared by both disturbances and how this common background can explain the high comorbid incidence of depressive disorders and pain; and finally, the rationale for treatment strategies acting on both depressive disorders and pain.

Comorbidity of Pain and Depressive Disorders

Depression in people with chronic pain has received greater attention from researchers and practitioners than pain symptoms

reported by depressed people, probably due to the persistence of a dualistic perspective [4]. Unfortunately, this misrecognition can induce disadvantages in the therapeutic management of patients with mood and pain comorbidity [5] and has been shown to contribute to elevated healthcare costs and a high prevalence of functional disability [6,7].

The clinical association between depressive symptoms and pain has been found in: the general population [8], community-dwelling elderly adults [9], and people with migraine [10], patients with epilepsy [11], older patients with osteoarthritis [12], people with musculoskeletal pain [13], irritable bowel syndrome [14], cancer patients [15-17] and palliative care [18]. Recently Craig et al. [19] emphasized the associations between pain, depressive mood and fatigue in a sample of 70 patients with spinal cord injury. In these patients high chronic pain had 8 times the odds of having depressive mood and 9 times the odds of having chronic fatigue [19].

The Multifaceted Processing of Pain by the Brain

The cerebral processing of pain was in the recent past subdivided into somatosensory pain processing (mainly related to the lateral thalamic nuclei), affective pain processing (linked to the insula, anterior cingulate cortex and amygdala) and the cognitive aspect of pain processing (particularly involving the prefrontal cortex, posterior parietal cortex and hippocampus) [20] (Figure 1).

These differentiations, although questionable, allow us to understand why different therapeutic approaches are needed since while the physical nociceptive component is more sensitive to analgesics, the affective component is more responsive to antidepressants. Psychotherapeutic interventions are a valid strategy with the cognitive aspects of pain, and are also effective with regard to its social or relational aspects.

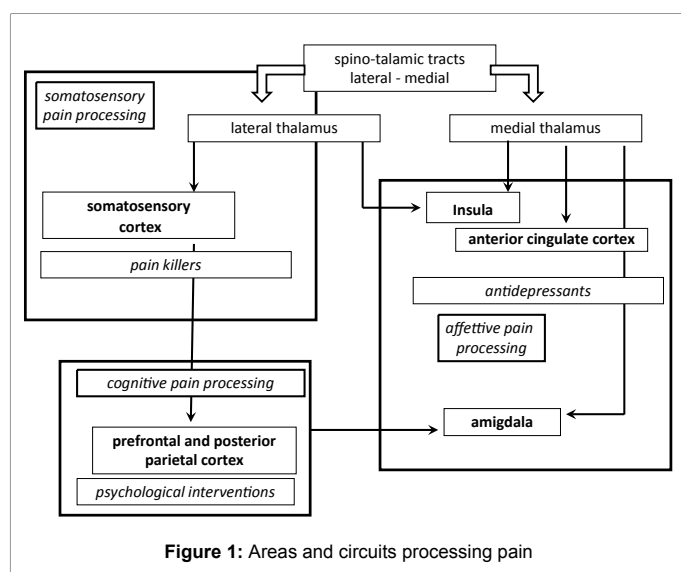
In this regard, an important construct used to explain a common pathogenic background in a group of clinically heterogeneous disorders (fibromyalgia, irritable bowel syndrome, chronic pain, migraine, etc.)

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is central sensitization. This refers to an increase of synaptic efficacy established in somatosensory neurons, for example in the dorsal horn of the spinal cord, following intense peripheral noxious stimuli. This heightened synaptic transmission leads to a reduction in the pain threshold, an amplification of pain responses and a spread of pain sensitivity to non-injured areas. The molecular mechanisms underlying central sensitization and long-term potentiation demonstrate striking similarities: the processing of such stimuli is more lasting and intense [21], particularly when the cognitive or painful stimuli are associated with a great affective reaction.

Pain sensitivity is an adaptive process affected by expectation, mood, coping, and attention. The underlying mechanisms are related to emotional experiences (e.g.: depression, loss, pain-distress) in overlapping patterns of activation, the failure of common regulatory mechanisms, direct top-down activation of the pain matrix, and changes in descending pain facilitation and inhibitory tone [22]. To this process concur both neural firing from nociceptive input and glial cell activation, contribute to this process. So psychological variables, too, contribute to pain sensitization and long-term structural changes in the pain processing regions of the brain, and this consideration is the basis of psychological treatment of pain, particularly when stress-related.

It is important to remember that in most conditions the pathophysiology of chronic pain remains elusive, but in any case such a syndrome is associated with substantial functional and structural changes, or plasticity, in a group of cortical and subcortical brain regions, often referred to as the “pain matrix”. Disease-induced plasticity can occur at both structural and functional levels and is manifested as changes in individual molecules, synapses, cellular function and network activity [23]. It is most interesting that with resolution of the pain [24], some of these CNS changes can return to a normal state.

The role of cognitive and affective components in processing pain involves relevant clinical considerations which are useful in achieving improvements in the outcomes of pain neuromodulation in patients with chronic neuropathic pain. In this way, neuromodulatory therapeutic strategies should also consider the neural mechanisms of reward valuation and appetitive motivation, such as the nucleus accumbens, ventral tegmental area, and prefrontal cortex [24].

Behavioural Constructs in Patients with Chronic Pain

Psychopathological traits are frequently associated with subjective and prolonged experience of pain and remarkably expressed in patients with comorbidity of mood alterations and pain [25,26]. These psychopathological or behavioural constructs are mainly represented by attribution styles, somatosensory amplification, illness behaviour and alexithymia.

Attribution style

Attribution style is an old construct particularly fashionable some years ago, but still valid [27,28]. It concerns to how individuals processes their symptoms, relating them to environmental events (normalising attributional style), rather than to a psychological status (psychological attributional style) or to a physical background only (somatic attributional style). This last style is predictive of the number of obscure somatic complaints, particularly pain, which patients refer to the doctor. Attribution styles, and consequent illness behaviour, are also determined by the culture and organisation of the health service itself [26]. It has been proven that psychoeducational intervention aimed at modifying attribution style (e.g. changing the patient’s opinion that becoming sedentary is not inevitable with aging), can trigger behaviour modification, e.g. improve walking levels and quality of life in sedentary older adults [29].

Somatosensory amplification

Somatosensory amplification is the tendency to experience somatic sensations as intense, noxious and disturbing. It is linked to bodily hyper-vigilance, to focusing on weak and infrequent sensations and considering the most visceral and somatic sensations as abnormal [30,31]. This amplification, which can exacerbate and intensify the experience of somatic sensations, is often present in older patients [2] and also contributes to several illnesses such as fibromyalgia [32], tension headache [33], angina pectoris [34] and myofascial pain [35].

Illness behaviour

Illness behaviour refers to behaviours that individuals engage in once they believe that they are ill. Research focusing on attendance rates as a form of illness behaviour suggests that somatisation is associated with high levels of health care utilisation; there is a complex relationship between somatic symptoms and underlying cognitions/illness behaviours [26]. A recent study measuring illness behaviour in 278 patients with systemic sclerosis demonstrated a significant negative relationship between these behaviours and physical and mental quality of life, such as pain and symptoms of depression [36].

Alexithymia

Alexithymia is a term used in psychosomatic medicine to refer to the inability for some individuals to verbally describe their emotional problems, refer to a condition where individuals cannot verbally describe their emotional problems but express them somatically?

A recent study evaluating 271 patients with chronic pain confirmed the importance of alexithymia in increasing pain and depressive disorders in several disturbances: depressive disorders and pain scores were significantly higher in the alexithymic group than in the non-alexithymic group, and depression was the main factor in pain conditions of alexithymic chronic pain patients [37]. Moreover in another work that we performed with myofascial pain patient emerged a higher prevalence of depressive and anxiety symptoms associated with a higher prevalence of alexithymia and expression-in modality to cope with anger [38]. In our experience, too, with regard to the role of

alexithymia in fibromyalgic patients, we found that alexithymic traits were present in 20% of the patients and contributed significantly to pain perception levels and a lower quality of life [39]. More recently, some authors have introduced the concept of "secondary alexithymia" to describe patients with a chronic disease such as cancer or chronic pain, who, focus on the somatic background of the illness, develop an alexithymic style in social relationships [26]. The problem of alexithymia in cancer patients demonstrates conflicting results because of the methodological problems of several studies, as confirmed by a review of the literature carried out by De Vries et al. [40]. However, several possible links emerge between alexithymia and the immune system, quality of life, and depression. Recent progress in neuroimaging has provided important information regarding emotional experience in alexithymia: these patients show amplified activity in areas considered to be involved in physical sensation, and also an increase in hormonal arousal responses during visceral pain, associated with greater activity of the insula, anterior cingulate cortex, and midbrain [41].

Pain catastrophizing (PC)

Pain catastrophizing is the tendency to ruminate on pain sensations, to feel helpless about pain and to magnify beliefs and feelings toward the painful situation? Several models of pain catastrophizing have been proposed, including attention-bias, schema-activation, communal-coping and appraisal [42]. PC behavior, communicated by patients with persistent pain (information senders) to caregiver (information receivers) is sometimes dysfunctional communication and over time, much of a patient's exhibition of pain behavior (eg. facial expression of pain, verbalization) can lead to a loss of support by the caregiver [43]. Catastrophizing is also a strong predictor of negative pain-related outcomes, such as clinical pain intensity, and physical disability [44,45]. A recent prospective study shows that the PC score can significantly vary in the menstrual cycle, thus demonstrating an important hormonal modulation [46].

Pain catastrophizing is placed in a balanced conceptual model in which such psychological vulnerability has to face an opposite process of adaptation to chronic pain, such as pain acceptance and other positive psychological resources, which are predictive of enhanced pain coping and resilience to pain [47].

Another emotional dimension of pain, often neglected until a few years ago, is spiritual pain, which is certainly associated with the expression of the symptom, with coping and quality of life. An evaluation of one hundred advanced cancer patients showed that patients with spiritual pain reported that it contributed adversely and significantly ($P < 0.001$) to their emotional and physical symptoms, including pain [48,49]. Existential suffering and deep personal anguish at the end of life are some of the most debilitating conditions that occur in patients who are dying [50], and both are strictly related to pain. Unfortunately, the aspect of spirituality is often neglected: of 29 instruments identified as appropriate for use in palliative care, only 15 included items on spirituality [51]. Similarly, in 1,117 original articles published between 1994 and 1998, only 70 articles (6.3%) included spiritual or religious variables [52].

In this respect, physicians must become sensitive to end-of-life issues in order to employ the necessary multidisciplinary approach to provide the highest quality end-of-life care for patients and their families [53]. In our own experience, from the second year on, our medical students are taught aspects of End-of-Life Care education in order to improve future students' attitudes toward dying patients [54].

About measures of spirituality, which deal with two of its main

components (faith/religious beliefs and meaning/spiritual well-being) psychotherapeutic intervention for spiritual suffering (meaning-centred group psychotherapy) is proposed by Breitbart [55].

The Broad Spectrum of Chronic Pain

The temporal relationship between pain and mood is still unclear. It is certainly plausible that either syndrome may lead to the other: an individual who feels pain may subsequently become depressed, and depressed patients are more likely to develop pain symptoms. Depression can be an immediate consequence of pain, but the prolonged duration of pain certainly has a greater impact on a person's social and emotional functioning. From this point of view, physicians should consider several aspects (biological, psychic and social) together when making a clinical diagnosis and, most of all, when they have to prescribe a tailored treatment strategy for a patient with chronic pain [2].

It is not possible to evaluate and treat chronic pain without considering psychological and social functioning. The physical aspects of pain, concerning pain onset, location, quality, intensity, duration and aggravating-alleviating factors are the most commonly considered clinical features, since they represent the target of biological (physical or pharmacological) treatments.

Not all assessment scales are valid instruments to differentiate the individual components of pain (biological, psychic, cognitive and social) and, consequently, to evaluate the treatments' effectiveness on each pain component.

Pain is without doubt an individual experience: as a consequence, its cognitive, emotional and relational components must always be taken into consideration. A pharmacological approach limited to pain killers can sometimes be inadequate, with a poor therapeutic response. This can induce the clinician to increase the dosage, giving rise to more side effects without clinical outcome advantages. In several patients, a wider diagnostic approach, also evaluating possible emotional and/or cognitive interference with pain, allows, if necessary, more tailored interventions (with other classes of drugs such as antidepressants, or with non-pharmacological treatments) in order to enlarge the treatment's analgesic spectrum.

Cognitive Aspects of Pain

Cognitive aspects of pain are mainly represented by the patient's evaluation, expectations and the meaning that a patient attributes to his/her pain. These aspects are strictly related to previous experiences and personal coping styles.

The prefrontal cortex, posterior parietal cortex and hippocampus are considered the main areas involved in cognitive evaluation of the painful stimulus and, therefore, also in its emotional significance.

It is now well known that pain and memory can share similar mechanisms: the long-term potentiation (LTP) is a synaptic substrate for memory and learning present in the cerebral cortex and related to a long-lasting highly localised increase in synaptic strength [21]. LTP in nociceptive pathways is linked to hyperalgesia, through both neuronal and glial cellular mechanisms, contributing to pain amplification following trauma, inflammation, and nerve injury. Spinal LTP can be also induced by abrupt opioid withdrawal, making it a possible mechanism of some forms of opioid-induced hyperalgesia [56]. On the other hand, preventing LTP induction can reduce pain amplification [57]. In the same way, Prakash and Golwala [58] stressed that memories are stable once stored: older memories are more resilient to damage than recent memories [58]. Therefore, chronic pain ought to

be prevented as early as possible in order to avoid “pain memory” from being established.

Sensory experiences are also highly related to the interactions between expectations and incoming sensory information. Using combined pain-rating scales and fMRI techniques, Koyama et al. [59] observed that brain activation is more related to the intensity of expected pain than to the real intensity of the noxious stimuli. When awaited pain was manipulated, expectations of decreased pain can reduce both the subjective experience of pain and the activation of pain-related brain regions, such as the primary somatosensory cortex, insular cortex and anterior cingulate cortex [59]. In other words, it is evident that positive expectations can reduce the severity of pain perception. It is well known that hypnotic suggestions can reduce pain perception: Rainville et al. [60] demonstrated that hypnosis does not work on the somatosensory cortex, but acts on the affective component of peripheral body pain perception, located within the anterior cingulate. These findings provide direct experimental evidence that frontal lobe limbic activity in humans is linked to the effect of pain.

The fundamental aspect of placebo or nocebo effects is closely connected to the problem of expectation. From the fundamental study of Levine and Gordon [61] published in *Nature* in 1984, it is well known that the placebo effect on pain is linked to the unconscious self-activation of the opioid endogenous system, as confirmed by the blockade of the analgesic effect in placebo responders using naloxone (a potent antagonist on opioid receptors). More recently, several studies have demonstrated how patients' expectations influence placebo activity: patients with Parkinson's disease, for instance, will, after placebo administration, obtain an improvement in motor performance [62], through activation of dopaminergic systems. Placebo and nocebo effects are factors that strongly influence pain perception and their neural basis for endogenous pain modulation is now better identified [63]. The fact that the non-pharmacological component of any analgesic response can also be ascribed to the placebo effect is very important: for a pain killer, as for any other drug, the patient's expectation of the drug's effectiveness can increase (placebo effect) or decrease (nocebo effect) the analgesic pharmacological efficacy [2].

Of the brain modulatory networks, the hippocampal region is important for amplifying pain experiences during nocebo or increased anxiety, while the nucleus accumbens shows a bidirectional response of both opioid and dopamine release that produces either placebo (increased release) or nocebo (decreased release) effects [63]. In particular, the dopamine release from nucleus accumbens induced by placebo analgesia is mainly related to expectation of analgesia [64].

Related to this concept is the question whether Alzheimer patients' pain perception differs from that of other subjects of the same age. In fact, Alzheimer disease patients showed a weaker placebo component in response to the analgesic treatment when reduced connectivity of the prefrontal lobes was present. Remarkably, the loss of these placebo-related mechanisms also reduced treatment efficacy [65].

A most intriguing aspect is that physicians, too, are involved in sharing pain and relief with the patient: recent data show an activation of the physician's brain during patient-physician interaction, including the right ventrolateral and dorsolateral prefrontal cortices. Moreover the physician's ability to adopt the patients' perspective is correlated with increased brain activations in the rostral anterior cingulate cortex. Jensen et al. suggest that physician treatment involves neural representations of treatment expectation, reward processing and empathy, paired with increased activation in attention-related structures [66].

Emotional Aspects of Pain

The most important emotional aspects of pain are anxiety, depressed mood and chronic stress.

Anxiety

Anxiety intervenes mainly in the modulation of acute pain, but is also implicated in chronic pain states. Anxiety disorders are the most prevalent type of mental disorder, frequently co-occurring with various medical conditions, and associated with higher health care costs [67]. Nevertheless, despite their prevalence, anxiety disorders often go unrecognized in pain care facilities, because of the overlap of anxiety and mood symptoms, and also due to the frequent presence of unexplained physical symptoms, associated with medical disorder, but related to an emotional pathogenesis [68].

Depressive disorders

Depressive disorders is also a widespread pathology very frequently associated with chronic pain in a vicious circle: depressive mood reduces the pain threshold and increases, emotionally and cognitively, the pain perception, while chronic pain first induces demoralisation, then true depression [2].

In the clinical practice, it is important to consider that a significant relationship between mood symptoms and pain is not limited to severe pain levels, but can be also present in patients with low pain score levels [69].

Pain affect is very important, but largely ignored in pain studies, primarily due to the lack of validated animal models: a strategy to understand pain affect could be the use of conditioning principles or operant behaviours (such as conditioned place preference, avoidance, escape from noxious stimulus, and analgesic drug self-administration) to indirectly reveal the affective condition of pain, when combined with traditional reflex-based pain measurements in future studies of pain [70].

The relationship between mood and pain is also confirmed by recent considerations on the removal (or offset) of pain and relief. Franklin and colleagues recently demonstrated, with psychophysiological measures that were specific to negative (startle eye blink reactivity) and positive valence (startle post auricular reactivity), that pain offset simultaneously stimulates positive affect and diminishes negative affect for at least several seconds. These findings confirm the affective nature of relief and provide insight into why people engage in both normal and abnormal behaviours associated with relief [71]. Another relevant relationship links pain and chronic fatigue was demonstrated by the literally review of Meeus et al. [72] that sub lined the chronic fatigue syndrome (CFS) as a debilitating condition that is characterized by persistent and relapsing fatigue, lasting at least six months, not resolved by rest, causing a marked reduction of working activity, and exacerbated by minimal physical exercise [72]. Pain and chronic fatigue syndrome have different response to rehabilitative treatments in a recent study of Bourke et al. [73] in the PACE trial. This study compared the adaptive pacing therapy and the graded exercise therapy, the results showed that both treatments were of efficacy compared to more passive forms of rehabilitation [73].

Stress and Pain

Pain induces stress, and stress induces pain. Chronic stress is strictly related to pain with multiple mechanisms, both biological and psychological: in this way chronic stress can foster pain, but pain in itself can act as a stress. From this point of view, the relationship

between stress and pain has a great implication for clinical practice and provides a strong rationale for assessing and treating pain from a bio-psycho-social perspective [74].

One of the major biological components of the link between stress and pain is hyperactivity of the hypothalamus-pituitary-adrenal (HPA) axis (with resultant hypercortisolism), which is also one of the most replicated physiological abnormalities seen in patients with major depression. Such hyperactivity starts with overproduction of the corticotrophin releasing hormone (CRH) which is released from the paraventricular nucleus (PVN) of the hypothalamus. In turn, CRH drives production of the adrenocorticotrophic hormone (ACTH) and the subsequent release of glucocorticoids (i.e. cortisol in primates, corticosterone in rodents) from the adrenal glands [75]. It is strictly linked to the hypothesis of “glucocorticoid resistance”: in major depression, the increased levels of glucocorticoid hormones are conceptualized as driven by an impairment in GR function (glucocorticoid resistance), and therefore as a “compensatory” mechanism [76]. Moreover, it is important to remember that CRH is not only a “stress hormone” but also a neuromodulator outside the HPA axis: for example, endogenous activation of CRF1 receptors in an arthritis pain model contributes to amygdala hyperactivity and pain-related behaviours [77]. It is most interesting that non-pain-related activation of CRF1 receptors in amygdala can also trigger pain-responses in normal animals, suggesting that conditions of increased amygdala CRF levels, for example stress-related, can contribute to pain in the absence of tissue pathology or disease state [77]. In contrast CRH is also involved in stress-induced analgesia (SIA): exogenous CRH mimics stress effects on pain sensitivity and causes an analgesic effect, probably mediated by a non-opioid mechanism associated with endogenous glucocorticoids released in response to central CRF administration [78]. Finally, most intriguing from the clinical and therapeutic point of view, is the observation that the frequent co-occurrence of pain, depression, and fatigue observed among cancer patients is underpinned by stress hormones that act as a common mechanism for this cluster of symptoms. In 104 advanced cancer patients, HPA activation (indicated by plasma levels of cortisol and adrenocorticotrophic hormone) and SNS activation (indicated by plasma epinephrine and norepinephrine) show that shared variance between hormone levels predicted shared variance between PDF symptoms [79].

Finally, in most patients, stress, pain and depression (alone or together) lead to an excessive release of the CRH, ACTH and glucocorticoids. Consequently, a sympathetic over-activity, also linked to an increase of vasopressin (AVP) [80], combined with diminished parasympathetic tone, contributes to immune activation and release of proinflammatory cytokines (e.g. TNF- α , IL-1, IL-6) from macrophages and other immune cells. Elevated mediators of the inflammatory response, combined with excessive sympathetic tone, may contribute to activation of microglia and astroglia. Activated microglia exchange signals with astrocytes and nociceptive neurons, amplifying pain-related transmission of glutamate (Glu), substance P (SP), adenosine triphosphate (ATP), brain-derived neurotrophic factor (BDNF), pro-inflammatory cytokines (IL-1, IL-6, IL-8, TNF- α), nitrogen oxide (NO) and prostaglandins (PGs) [73].

Nevertheless, other studies report that conditions of chronic pain, fatigue, fibromyalgia and a typical depressive disorders (characterised by symptoms such as increased sleep or appetite, leaden legs, sensitivity to rejection in relationships) are characterized not by hypercortisolism, but by decreased cortisol production and release, both at baseline and in response to a variety of stressors [75].

Briefly, some studies suggest that HPA activity can be diminished in chronic pain but increased in depression: experimental data on chronic low back pain patients confirm that chronic pain appears to be associated with low cortisol secretion [81]. Interestingly, a number of studies have also demonstrated that manipulating the GR function with both agonists and antagonists has an antidepressant effect and, indeed, that other drugs targeting the HPA axis and cortisol secretion - even drugs with opposite effects on the HPA axis - have antidepressant effects. These studies do not support the notion that cortisol has ‘negative’ effects on the brain. On the contrary, this paper concludes that a lack of the ‘positive’ effects of cortisol on the brain, because of glucocorticoid resistance, is likely to be involved in the pathogenesis of depression [81].

In other words, HPA axis hyperactivity and inflammation might be part of the same pathophysiological process: HPA axis hyperactivity is a marker of glucocorticoid resistance, related to an ineffective action of glucocorticoid hormones on target tissues, which could lead to immune activation; and, equally, inflammation could stimulate HPA axis activity via both direct action of cytokines on the brain and by inducing glucocorticoid resistance [82].

In this regard, and from the therapeutic point of view, it is most important to remember that through their activity on transmitters, antidepressants ameliorate HPA axis hyperactivity. Such therapeutic action is mediated, at least in part, by restoring the GR function, and is consistent with studies showing that a decreased GR function contributes to HPA axis hyperactivity and to the development of depressive symptoms [83]. In this way, antidepressants increase the GR function, thus leading to the resolution of glucocorticoid resistance [84].

In other words, chronic pain is often equated with chronic stress, but the relationship between chronic pain and HPA axis activity is still poorly understood: experimental data from patients with chronic pain syndrome (CPS) show that this pathology is associated with a degree of hypocortisolemia, particularly in male patients [85].

Other clinical data, from human experimental studies, confirm that relative hypocortisolism, which may be regarded as a neuroendocrinological correlate of chronic stress, may be a characteristic of some functional pain syndromes [86]. The same dualistic phenomenon concerning hypo/hyper cortisolism is present with other stress-related systems: for example, pain and social stress can increase plasma levels of endocannabinoids and the latter can demonstrate both beneficial (cardioprotection, vasodilatation) and negative effects (vasoconstriction), respectively mediated by CB2-mediated anti-inflammatory effects and CB1-mediated metabolic changes [87].

A most important fact is that early-life stress induces persistent elevation of IL-6, hyperalgesia, and susceptibility to chronic muscle pain, which appears by exposure to stress in adults. This probably depends on an interaction between adrenal catecholamines and proinflammatory cytokines at muscle nociceptor level [88]. As a matter of fact, childhood adversities are associated with abnormal glucocorticoid signaling within the HPA axis and the development of functional pain disorders in adulthood, such as irritable bowel syndrome (IBS) and fibromyalgia (FM) [89], as also confirmed by experimental studies with selective CRF receptor 1 [90].

Resilience is an important moderator of both pain and stress: a study concerning eighty-four subjects evaluated with the Resilience Scale for Adults (RSA) demonstrated that individuals scoring high on

the RSA reported less pain and stress and that this protection was more pronounced for the high-stress group [91].

The Common Biological Background of Mood and Pain

The frequent association between pain and depressed mood can be explained by a vicious emotional and social pathogenic circle, but also by a common biological background that is, at the same time, involved in the modulation both of painful and emotional experience. Considerations from biological and neuroimaging areas confirm this overlap between pain and mood [2].

Neurotransmitters

It is well known that a decrease of serotonin (5HT), norepinephrine (NE) and/or dopamine (DA), particularly in limbic areas, is a historical pathogenic hypothesis of depressive disorders. But if this reduction occurs also in the areas involved in the Descendent Inhibitory System, such as the Periaqueductal Griseum (PAG), the same neurotransmitter deficit induces an increase in pain (Table 1).

A large body of research, including animal and human studies, has confirmed the crucial role of the serotonin (5-HT) system in the regulation of nociception and chronic pain-related behaviours. On the other hand, some data disagree about the inhibitory or facilitator influence from descending 5-HT-spinal receptor system in acute and persistent pain [92]. More recently, experimental animal studies have explained individual variability to serotonergic treatments: 5HT induces variable effects depending on the physiological or pathophysiological status of the animal. This has notably been observed with 5-HT₇ receptor agonists who exert a pro-nociceptive action in healthy rats but alleviate hyperalgesia, consecutive to nerve lesion, in neuropathic animals [93].

The involvement of the dopaminergic system in pain and mood control is complex: the serotonin system signals a large class of stimuli that are intrinsically aversive (eg. stress or pain), while the dopaminergic system signals a large class of stimuli that are intrinsically appetitive (e.g. pleasure or sweetness) [94].

Pain and reward are actually opposite but interacting processes: recent pain and reward research fields point to extensive similarities in the anatomical substrates of painful and pleasant sensations and the role of the opioid and dopamine systems in modulating both pain and pleasure is now well known [95]. From the psycho-neurobiological point of view, the orbito-frontal cortex and opioids play an important role in hedonic experience, and the ventral striatum and dopamine predominantly process motivation for reward. On the basis of neuroimaging studies, Becker et al. hypothesize that the orbitofrontal cortex and opioids are responsible for pain modulation by hedonic experience, while the ventral striatum and dopamine mediate motivational effects on pain [96]. In this way, pain relief can act as a reward mechanism that leads to operant learning, which, in turn, can affect pain sensitivity. Unfortunately, investigations into pain-reward interactions are scarce [96] and also complex, because of the number of genes and associated polymorphisms that impact pain tolerance and or sensitivity [97].

The relevance of the noradrenergic system in pain and mood modulation is also strongly documented, and has been for a long time: the use of herbal noradrenergic reuptake inhibitors for pain dates back at least to the Crusades, where St. John's Wort, whose active moieties include hypericum, a noradrenergic reuptake inhibitor, was used both to treat battle wounds and depression [98].

System	Mood	Pain
Neurotransmitters	5HT/NE/DA hp	Descending inhibitor system
Hormones	HPA/HPG/HPT hp	HPA/ neurosteroids
Immune system	Cytokines and mood	Cytokines and pain
Neurotrophism	Hippocampal shrinkage	Pain matrix alterations

Table 1: Biological mechanisms shared by depressive disorders and pain

It is well known that the noradrenergic system is a component of the descending inhibitory pathways [13], through projections from noradrenergic neurons in locus coeruleus and activation of inhibitory α_2 -adrenergic receptors in lamina II of the dorsal horn [99].

Moreover, most clinically available noradrenergic reuptake inhibitors, including TCAs, not only work on the reuptake of other neurotransmitters (like serotonin), but also have multiple other actions involved in analgesia, such as an activity on sodium channel blockade, on the opioid and cannabinoid system, on adenosine, and other receptors [100]. Noradrenergic agents are far more effective in chronic pain states than acute pain states: this statement suggests a shift toward noradrenergic-mediated pain pathways following nerve injury [101,102].

Cytokines

An increase of pro-inflammatory cytokines can be related, directly and indirectly, to both depressive disorders and pain.

The participation of cytokines in neurogenic inflammation, peripheral and central sensitization and hyperalgesia is well documented, and a disproportion of pro-inflammatory and anti-inflammatory cytokines is known to be a contributory cause of pain and pain behaviour. Moreover, cytokines are able to perpetuate a vicious circle between local inflammation and systemic pain behaviour, for example, sickness behaviour [103]. Cytokines also sensitise nociceptive signalling in the peripheral and central nervous systems [104]. In conditions of chronic widespread pain (CWP), the tenderness related to muscle pain depends on increased peripheral and/or central nervous system responsiveness to peripheral stimuli, which can be either noxious (hyperalgesia) or non-noxious (allodynia). Cytokines seem to play an important role in sensitising deep tissue nociceptors of CWP patients, and the combination of peripheral impulse input and increased central pain sensitivity may be responsible for widespread chronic pain disorders [105].

Neuroimaging studies also support the relationship between inflammatory states and depressive disorders. Using functional magnetic resonance imaging (fMRI) with rheumatoid arthritis (RA) patients, Schweinhardt et al. [106] suggest that the medial prefrontal cortex (MPFC) plays an important role in mediating the relationship between depressive symptoms and clinical pain severity in RA, possibly by engaging brain areas important for affective and self-relevant processing.

Concerning the central modulation of pain, an important advance in pain research is the remarks that not only neurons are involved in the aetiology of chronic pain: activated microglia contributes to pain states, through the production of pro-inflammatory cytokines, chemokines and extracellular proteases [107]. The pronociceptive role of microglia in conditions of neuropathic and postoperative pain and opioid tolerance is well known: the activation of spinal cord microglia after nerve injury, surgical incision and chronic opioid exposure increases the synthesis and release of the neurotrophin brain-derived neurotrophic factor and the pro-inflammatory cytokines interleukin-1 β , interleukin-6, and tumor necrosis factor- α . These microglia-released mediators increase the excitability of dorsal horn neurons,

contributing to central sensitization, partly via the suppression of inhibitory synaptic transmission [108].

Immune system pathways are able to activate cross-talk with the brain, influencing behaviour: in fact, cytokine signaling in the brain is known to regulate important brain functions, including neurotransmitter metabolism, neuroendocrine function, and synaptic plasticity, as well as the neural circuitry of mood [109]. During depressive disorder episodes increased levels of pro-inflammatory eicosanoids, cytokines and acute-phase proteins have been noted. Furthermore, there is prospective longitudinal evidence for the emergence of mood symptoms in response to chronic immune-inflammatory activation [110]. Elevated immune-inflammatory signaling is therefore a relevant mechanism to the pathogenesis of mood disorders [111,112], as also confirmed by the fact that adjunctive treatment with anti-inflammatory agents can sometimes increase the therapeutic efficacy of antidepressants [113]. Another well-known confirmation of the direct relationship between inflammation and mood is the possibility to induce depressive disorders in patients with risk factors (such as mainly high baseline levels of interleukin 6, history of major depression) during the use of interferon therapies [114].

The pro-inflammatory cytokines (mainly IL2, IL6, TNF α) can interfere with mood in several ways: through the increase of CRH and global activation of the HPA axis; by glucocorticoid resistance due to a decrease of GR expression; by a reduction of T3; by the excitotoxicity due to the glutamate increase at microglial and astroglial level. A most intriguing mechanism is the activity on the metabolic enzyme indoleamine 2,3-dioxygenase (IDO) which breaks down tryptophan into kynurenine: an increase of pro-inflammatory cytokines up-regulates IDO, thus moving the tryptophan from the serotonin pathway to the kynurenine pathway, and reducing 5HT production with consequent depressive disorders [115], mainly concerning, in animal models, anhedonia and anxiety-like behaviors [116].

Another very interesting overlap between depressive disorders and pain is the simultaneous presence of insomnia, chronic pain, and depression. Overlapping mechanisms in the central nervous system suggest common neurobiological substrates that may underlie the development and interplay of these disorders. A role of altered mesolimbic dopaminergic function in the promotion of arousal, pain sensitivity, and mood disturbance has been suggested [117]. Other authors assume that the common background can be represented by a pro-inflammatory cytokine increase. Cytokines, such as TNF α and IL1 β , play an important role in sleep regulation: in normal humans and in multiple disease states, plasma levels of TNF α covary with EEG slow wave activity (SWA) and

sleep propensity. Many of the symptoms induced by sleep loss, for example, sleepiness, fatigue, poor cognition, and enhanced sensitivity to pain (all symptoms present in sickness behaviour) are elicited by injecting exogenous TNF α or IL1 β [118]. The relevance of sleep alterations observed in depressed patients is similarly well known [119].

Another important issue is the interaction between pro-inflammatory cytokines and the neurotrophin brain-derived neurotrophic factor (BDNF), in both depressive disorders and pain.

It is well known, according to the neurotrophic hypothesis of depression, that neuronal plasticity plays an important role in recovery from depression and that antidepressant drugs can increase the expression of several molecules associated with the neurotrophin BDNF and its receptor TrkB [120]. On the other hand, depressive disorders, particularly when long lasting and severe, are associated with reduced volumes of the hippocampus and prefrontal cortex [121].

Cytokines can actually decrease the BDNF and interfere with TrkB receptor signaling, which may adversely influence neurogenesis and neuroplasticity. This phenomenon is observed both during the inflammatory cytokine increase after stress [122] and after exogenous administration: for example, the administration of IFN α [123], as well as other inflammatory cytokines [124], decreases systemic BDNF levels in humans. Inflammatory cytokines also influence BDNF receptor (TrkB) phosphorylation, thereby further interfering with BDNF signaling [125]. From the clinical point of view, altered BDNF levels in fibromyalgia syndrome suggest that BDNF is involved in the sensitization process, probably through its effects on neuronal plasticity [126].

An important area of debate concerns the discrepancies between neurotrophic factors with regard to their activity on mood and pain. Nowadays it is well known that neurons are not the only cell type involved in the aetiology of chronic pain and that microglia-neuron interaction is strictly involved in the pathobiology of neuropathic pain [127]. Spinal microglia is activated by peripheral nerve injury and this activation induces changes in dorsal horn neurons which, in turn, initiate the mechanism of central sensitization. Several neuropeptides, cytokines, chemokines and neuro-transmitters have been implicated in this process, but it is probable that the main information transfer between activated microglia and neurons is due to the BDNF. In other words, microglial-derived BDNF can mediate central sensitization in lamina I by attenuating inhibitory synaptic transmission [128]. Moreover, the activation of the P2X4 receptor subtype, expressed by microglia, drives the release of BDNF, which causes disinhibition of pain-transmitting spinal lamina I neurons, thus representing a critical microglia-neuron signaling molecule that gates aberrant nociceptive processing in the spinal cord [129].

In support of the role of BDNF in pain, there is a body of studies concerning different animal models of neuropathic pain [130] and the fact that neurotrophins can act as mediators of acupuncture effects on the central nervous system (CNS) [131].

Another noteworthy aspect, concerning the relationship between mood and pain, is the clinical observation that pain could be a symptom of depression. Depressive disorders is related to a spectrum of symptoms including affection (dysphoric mood, irritability, loss of interest and pleasure), cognition (impaired memory, concentration and decision-making, cognitive distortion), behaviour (coping styles and psychomotor changes) and also somatic symptoms, such as alterations in appetite, weight, sleep patterns, sexual desire, increased fatigue, and chronic pain (headaches, back pain, visceral pain, etc.) [68].

The Social Component of Pain

The social aspects of pain are a complex theme related to the cultural context and situations surrounding the patient. Considering that pain can also be a strong social signal and can induce secondary advantages, it is important to view the patient in his/her relationship to others and in his/her social context.

In rodents, social defeat experiences, such as low maternal care, social isolation, or sexual restraint, can cause an increase in the nociceptive threshold. This can be related to both chronic stress and to reduced opioid activity [132]. On the other hand, experimental and clinical evidence has shown that chronic stress plays an important role in the onset and/or exacerbation of symptoms of functional gastrointestinal disorders: a mouse model of chronic psychosocial stress confirmed that mice exposed to psychosocial stress developed visceral hyperalgesia [133].

Research findings also show that negative early experiences, such as poor maternal care, interact with genetic factors to influence the functioning of the stress system. Interpersonal affect regulation between infant and caregiver is crucial for the optimal development of these brain circuits. Aberrant development of this shared neural system during infancy, childhood or adolescence may therefore increase sensitivity to physical and social pain and to problems with their regulation in adulthood [134]. Moreover, emerging evidence suggests that experiences of social pain, i.e. the painful feelings associated with social disconnection, rely on some of the same neurobiological substrates that underlie experiences of physical pain: in other words, physical and social pains share some of the same neurobiological substrates.

Campbell et al. [135] evaluate the relationships between the perceived partner responses to the patient's pain behaviour and outcomes of pain. Patients demonstrated a reduction of pain intensity when partners had solicitous responses, except patients who were depressed. In this way, depressive symptoms are important in negatively modulating the efficacy of the perceived partner reactions, demonstrating the relevance of social context and mood on pain [136].

Another important aspect in the comprehension of social pain is the relationship between empathy and pain. Empathy, the ability to share the feelings of other people, can also modulate the intensity of pain shared with others. Previous human imaging studies, focusing on empathy for others' pain, have consistently shown activations in regions also involved in the direct pain experience, particularly the anterior insula and anterior and mid-cingulate cortex [130]. Moreover, physiological resonance between individuals is also considered a biological construct linked to empathy: activation of the HPA and sympatho-adrenomedullary axes can be present during an aversive state induced by the stress of another person, and the cortisol response of observers may increase with trait empathy [137].

Gender and pain

Gender exerts an important role in pain responses, in both biological and psychological dimensions. In a large recent meta-analysis, Alabas et al. [138] found that individuals who considered themselves more masculine and less sensitive to pain than typical men, showed higher pain thresholds and tolerances. Gender stereotypes specific to pain scales showed stronger associations with sex differences in pain sensitivity response than in masculine and feminine personality trait scales [138].

It is debatable whether the higher depression rate in women mediate sex differences in pain perception, while the role of anxiety is ambiguous. Cognitive and social factors appear to partly explain some sex-related differences [139]. From the biological point of view, the involvement of hormonal and physiological factors is under discussion: it is hypothesized that temporal summation, allodynia, and secondary hyperalgesia may be more pronounced in women than in men [140]. The evidence to support less efficient endogenous pain inhibitory systems in women is mixed and does not necessarily apply to all pain modalities [141].

On the other hand, there is a substantial body of epidemiological and clinical evidence suggesting that the sex hormones, particularly estradiol and progesterone, play a role in pain. This statement is confirmed by functional imaging techniques [142].

A sex difference in pain modulation through widespread noxious inhibitory controls (DNIC) was upheld in a systematic review carried

out by Popescu et al. the DNIC seems to be significantly more efficient in males than females (mean female/male ratio=0.54) [141].

An intriguing argument is the relationship of the key role of neurosteroids in pain modulation: these compounds control the development and plasticity of the nervous system, and both endogenous and synthetic steroids play a crucial role in the neurobiological processes involved in pain sensation [143]. Moreover, there is strong evidence of sex steroid-based differences in pain perception. A steroid-based pharmacological mechanism of chronic pain can also be postulated to partially explain the analgesic activity of several antidepressants and atypical antipsychotics [144].

Consequently, with the previous considerations on the social aspects of pain, several psychosocial interventions are proposed to reduce pain, particularly in patients with cancer. A recent meta-analysis carried-out by Sheinfeld Gorin et al. [145] demonstrated that psychosocial interventions had medium-size effects on both pain severity and interference, supporting the need for systematic implementation of quality-controlled psychosocial interventions as part of a multimodal approach to the management of pain in patients with cancer [145].

To conclude this section, it is also important to remember that there are important ethnic differences in pain and, consequently, in pain management: for example, the experience of pain can differentially activate stress-related physiological responses across various ethnic groups, and members of different ethnic groups may use differing coping strategies in managing pain complaints. Underestimating these components may facilitate the persistence of elevated levels of pain-related suffering in individuals from ethnic minority backgrounds [146].

Therapeutic Approaches to Pain

The multifaceted treatment of pain is due to a complex pain pathogenesis involving biological, psychological, cognitive and social factors, so the choice of pain treatment for a patient has to deal with different pain components (physical, emotional, cognitive, and relational). In this way, most treatments can integrate pharmacological and non-pharmacological interventions.

In addition, within the pharmacological choice, the physician has to evaluate which class of analgesic will be most effective with a given patient, considering the different, but usually synergistic, pharmacodynamic activities of each class. From this point of view, analgesics, antidepressants and anticonvulsants frequently have to be associated to obtain complete remission of pain, particularly when it is comorbid with emotional aspects such as chronic stress, anxiety and depressive disorders.

When the emotional, cognitive or social pain component is relevant in a given patient, non-pharmacological interventions such as a psycho-educational or psycho-therapeutic project must also be associated with the analgesic prescription.

Neuropsychopharmacological approaches to pain

The pharmacological treatment of pain is based on several classes of drugs that can be chosen according to pain severity and WHO guidelines [147]: non-steroidal anti-inflammatory drugs (NSAIDs), weak opioids and strong ones. All these classes can, if necessary, be associated with the so-called "adjuvants", a wide class of pharmacological compounds, mainly antidepressants, anticonvulsants, and steroids.

The choice of an analgesic or anticonvulsant compound is

outside the purpose of this paper and we therefore focus on the use of antidepressants.

In the presence of emotional disorders associated with pain (anxiety, mood depressive disorders depression, chronic stress), the first class of choice among the adjuvants are antidepressants (ADs). ADs are drugs with a broad spectrum of clinical activities, acting on depressive disorders, anxiety, chronic stress and pain.

ADs relieve pain through several different mechanisms; the important fact is that pain relief is obtained with the same biological mechanisms involved in depressive disorders [2].

Dysregulation of NE and 5HT is associated with depressive disorders and pain, so normalisation of such neurotransmitter levels can act on both symptomatology, particularly when comorbid. As far as pain is concerned, a 5HT and NE increase induces potentiation of the endogenous opioid system of the periaqueductal griseum and, at the same time, increases the inhibitory activity of serotonergic and noradrenergic descending pathways operating at the spinal cord gate control. This double mechanism of action is confirmed by the fact that to block antidepressant analgesic activity, both a naloxone blockade of opioid systems and the use of ondansetron, which blocks the serotonergic activity of 5HT₃ receptors, are needed [148].

Transmitter activity, particularly on serotonin (5HT) and norepinephrine (NE), is strictly involved in the fast and direct pain mitigating effect, which is mainly linked to the inhibition of rapid reuptake, with a consequent almost immediate increase of neurotransmitters at the synaptic level. This direct action appears in the first hours after administration of antidepressants and can also be present with low dosages. Such a mechanism is completely independent of the AD's effect on mood. The indirect antidepressant pain mitigating effect, on the other hand, appears later, with improvement of the depressed mood after 3-4 weeks of treatment at full dosages. This activity, related to an increase of the threshold for pain (which is reduced by depressive disorders) is achieved when ADs normalize mood through complex mechanisms (receptor down-regulation, HPA normalization, etc.) involved in the slow antidepressant's activity [2].

Another mechanism of action that ADs exert on both mood and pain is the reduction of cytokine pro-inflammatory activity, through an increase of anti-inflammatory cytokines. High cytokine levels actually correlate with depressive disorders, cognitive dysfunction, pain and stress levels [149]. This result is obtained in several ways: ADs counteract CRH activation (and consequently the secondary HPA response to hyperproduction of cytokines), IDO induction (and secondary tryptophan depletion with reduced 5HT availability) and contribute to the production of anti-inflammatory cytokines [150].

Interactions between antidepressants and analgesics

An intriguing consideration therapeutically linking pain and depressive disorders is that analgesics and antidepressants both act on the structures regulating mood and pain. The main example is the similarities between tramadol and venlafaxine: both drugs are racemic, demonstrate a methoxyphenyl-, an N,N-dimethylamino- and a hydroxycyclohexyl group in each compound, and present a comparable topographical display for recognition by common receptor sites. Both tramadol and venlafaxine are metabolised by the P450 2D6 system, which produces an active o-desmethyl metabolite. The side effects are similar: nausea, headache and dizziness. Tramadol can actually be considered a venlafaxine derivative [151]. Of great importance in clinical practice, particularly with elderly people, is the observation that the contemporary use of tramadol and serotonergic drugs can induce

a serotonergic syndrome characterised by cognitive and emotional symptoms such as confusion and delirium [152].

Moreover, when associated with serotonergic antidepressants (such as SSRIs or SNRIs), several opioids (fentanyl, oxycodone, methadone, etc.) can, in predisposed patients, favour the appearance of a serotonergic syndrome [153]. Reducing GABAergic inhibition, opioids induce an increase of 5HT release, which, when associated with an increased availability of serotonin produced by SSRIs or SNRIs, can cause a serotonergic syndrome [154].

In the same way, it is important to remember that part of the analgesic mechanism of opioids is related to their agonistic antidepressant-like effect on delta-opioid receptors [155].

In addition, with regard to the similarities between antidepressants and analgesics, also conventional pain therapy (such as opiates, NSAIDs) shows a significant effect on (HPA) axis function: ACTH and cortisol blood levels decreased in all subjects taking opiates or NSAIDs to treat pain. These changes also showed significant correlation with psychological features of the subjects, depending on age and sex [156].

Psychological interventions against pain

Psychotherapies: Cognitive and emotional components of pain widely justify the psychotherapeutic approach to pain perception. Recently, Wiech et al. [157], examining the effect of the presentation of a religious image on pain perception in religious and agnostic subjects, were able to show a decrease in subjective pain perception in the religious subjects, correlated with the activation of the right ventrolateral prefrontal cortex (VLPFC). This study shows the impact of mental state, faith and belief on the processing of physical stimuli; the authors consider that the reduction of pain perception was due to a reappraisal of the negative experience of pain through the religious belief. Reformulating the significance of an event and reinterpreting its meaning is also the principal aim of any psychotherapeutic intervention. A number of psychotherapeutic and adjunctive techniques, such as cognitive behavioural therapy (CBT), dynamically oriented therapy, hypnosis, relaxation training, supportive psychotherapy and behaviour therapy, can be employed to address the psychological and social features associated with and contributing to pain. These are not mutually exclusive interventions but complement each other to effectively address different patients' needs and produce relief [158]. Psychotherapies differ with regard to their approach, perspectives and goals. CBT, for instance, focuses on the patient's belief system related to problematic behaviours and is often used to modify cognitive strategies and reduce excessive problematic pain-associated behaviours, thus reducing pain perception.

In this way, Kashikar-Zuck et al. [159] recently confirmed CBT effectiveness in pain coping, catastrophizing, and coping efficacy, also in children and adolescents with juvenile fibromyalgia. In a dynamically oriented therapy, on the other hand, the therapist focuses on integrating and interpreting the material brought forth by the patient in order for the patient to gain insight into its origin and to readjust behavioural recurring patterns. These therapies are designed to bring about fundamental emotional and cognitive changes and address relationship difficulties. In our experience, a brief psychodynamic approach (Brief Adlerian Psychodynamic Psychotherapy, BAPP) is effective in oncological pain, also in elderly patients. B-APP, usually combined with psychopharmacological treatments, demonstrates a further significant ($p < 0.01$) reduction of pain perception and depressive disorders (assessed through the Visual Analogue Scale and Hospital Anxiety and Depression Scale) and a

further significant ($p < 0.005$) increase of Fighting Spirit and Fatalism coping styles (assessed through the Mini Mental Adjusted to Cancer Scale), compared to pharmacological treatment alone [159]. It is widely demonstrated that combined antalgic therapies (analgesics, antidepressants, anticonvulsants, hypnosis, physical interventions, and psychotherapies) are more effective than each treatment alone [160,161]. Based on the fact that, on the one hand, cancer-related pain may result not only from changes in the peripheral nervous system but also from changes in cortical activity over time and, on the other hand, that cortical reorganization by neuroplasticity may be used to manage pain symptoms, Prinsloo et al. proposed a brain-computer interface as a learning paradigm to augment neuroplasticity for pain management [162].

Lifestyle-oriented treatments: The pain components related to cognition and social aspects are sensitive to interventions that include patient education, and aerobic or other physical exercise, often integrated in a CBT. These non-pharmacological treatments, in particular exercise and CBT (cognitive-behaviour therapy), have yielded effect sizes and cost-benefit ratios comparable to medications, particularly in the fibromyalgia context [162].

For example, fibromyalgia patients frequently use alternative therapies, strongly indicating both their dissatisfaction with, and the substantial ineffectiveness of, traditional medical therapy, especially pharmacological treatments. Physical therapies, rehabilitation and alternative therapies are generally perceived to be more “natural”, to have fewer adverse effects and, in some way, to be more effective [163].

The most efficacious non-pharmacological approaches seem to be those with a focus on changing unhelpful beliefs/attitudes and activities associated with the illness. Other non-pharmacological interventions may benefit specific individuals (eg, massage, nutritional approaches), but to date do not demonstrate sufficient evidence from randomized controlled trials to establish their efficacy [164]. Noteworthy is the fact that exercise leads to changes in serum BDNF levels: this association highlights the importance of exercise in FMS and other chronic pain conditions [165].

Such interventions are not only proposed for fibromyalgia patients: Sabiston et al. [166] demonstrated, in a group of 145 survivors of breast cancer, that physical activity was a significant ($P < 0.01$) partial mediator of the relationship between pain and depression, and between pain and positive affect [166]. In this way, participation in physical activity is one pathway whereby pain influences mental health. Consequently, survivors of breast cancer should be helped to increase their level of physical activity to improve their mental health. Other authors, too, support the relevance of physical activity as a safe, cost-free, non-pharmacological way of managing pain, particularly through a reduction of anxiety and depression, an improvement of physical capacity, and an increase of functioning and independence [167]. Of clinical interest is the possibility of using a brief, 10-minute exercise protocol on pain, mood, and perceived exertion as carried-out with patients admitted to a Chronic Pain Rehabilitation Program (CPRP): such a brief exercise protocol was associated with self-reports of immediate antidepressant and anxiolytic effects and, after the 3-week CPRP, self-reports in perceived exertion also decreased. Unfortunately, this brief exercise was not found to have an acute analgesic effect [168]. Other systematic reviews of the literature [169] and meta-analysis support the benefits of physical activity for patients with cancer and cancer survivors, because exercise is associated with reduced pain and fatigue and improvements in quality of life [170].

Non-Pharmacological activity within a pharmacological treatment

An important bridge linking pharmacological and psychological treatment is the fact that both the pharmacodynamic and pharmacokinetic properties and the emotional aspects of the patient contribute to the effectiveness of a given drug. This consideration is strictly related to the placebo paradigm and mainly involves the patient's expectations concerning a given treatment.

According to these statements, when an individual assumes a pharmacological treatment, a nonpharmacological effect can be added to (placebo effect) or subtracted from (nocebo effect) the pharmacodynamic activity of the drug, based on personal expectations of the effectiveness of the drug in it. This fact is well demonstrated by several studies [171] the important role of expectations in modulating pain and analgesia is demonstrated by the decreased effectiveness of the drug when the patient is completely unaware that a medical therapy is being carried out

(hidden therapies) [172]. To eliminate a patient's expectations, drugs are administered through covert infusions by computer-controlled machines. In this paradigm of drug administration, a patient does not know that any analgesic is being injected, so does not expect anything. In post-operative pain, it was found that a hidden injection of different painkillers, such as morphine, buprenorphine, tramadol, ketorolac and metamizol, is significantly less effective than an open one, when the patients know that a pain reduction will occur.

Conclusions

Depression and pain are two mutually influencing aspects to be constantly monitored in any patient. The emotional and social components of the pain experience may strongly influence the intensity and length of pain, and these components must be carefully considered in the diagnosis and management of pain, especially with respect to treatment outcome.

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