REVIEW ARTICLE

Unexplained Painful Physical Symptoms in Patients with Major Depressive Disorder: Prevalence, Pathophysiology and Management

Jan Jaracz[1] · Karolina Gattner[1] · Krystyna Jaracz[2] · Krystyna Górna[2]

Abstract Patients with major depression often report pain. In this article, we review the current literature regarding the prevalence and consequences, as well as the pathophysiology, of unexplained painful physical symptoms (UPPS) in patients with major depressive disorder (MDD). UPPS are experienced by approximately two-thirds of depressed patients. The presence of UPPS makes a correct diagnosis of depression more difficult. Moreover, UPPS are a predictor of a poor response to treatment and a more chronic course of depression. Pain, in the course of depression, also has a negative impact on functioning and quality of life. Frequent comorbidity of depression and UPPS has inspired the formulation of an hypothesis regarding a shared neurobiological mechanism of both conditions. Evidence from neuroimaging studies has shown that frontal-limbic dysfunction in depression may explain abnormal pain processing, leading to the presence of UPPS. Increased levels of proinflamatory cytokines and substance P in patients with MDD may also clarify the pathophysiology of UPPS. Finally, dysfunction of the descending serotonergic and noradrenergic pathways that normally suppress ascending sensations has been proposed as a core mechanism of UPPS. Psychological factors such as catastrophizing also play a role in both depression and chronic pain. Therefore, pharmacological treatment and/or cognitive therapy are recommended in the treatment of depression with UPPS. Some data suggest that serotonin and noradrenaline reuptake inhibitors (SNRIs) are more effective than selective serotonin reuptake inhibitors (SSRIs) in the alleviation of depression and UPPS. However, the pooled analysis of eight randomised clinical trials showed similar efficacy of duloxetine (an SNRI) and paroxetine (an SSRI) in reducing UPPS in depression. Further integrative studies examining genetic factors (e.g. polymorphisms of genes for interleukins, serotonin transporter and receptors), molecular factors (e.g. cytokines, substance P) and neuroimaging findings (e.g. functional studies during painful stimulation) might provide further explanation of the pathophysiology of UPPS in MDD and therefore facilitate the development of more effective methods of treatment.

Key Points

Unexplained painful physical symptoms (UPPS) are frequently reported by patients with all types of depression, mostly major depressive disorder (MDD), and have a disadvantageous impact on the course and clinical response to treatment.

The bulk of evidence suggests that the pathophysiology of UPPS in MDD is closely coupled with the abnormal function of brain networks involved in the regulation of both emotions and pain and other mechanisms involved in these processes such as insufficiency of descending serotonin and noradrenaline pathways and abnormal activation of proinflammatory cytokines and substance P.

Which classes of antidepressants are particularly effective in the treatment of patients with MDD and UPPS is still a matter of debate, and comparative randomised studies are therefore required.

✉ Jan Jaracz
  jjjaracz@gmail.com

1 Department of Adult Psychiatry, Poznan University of Medical Sciences, Szpitalna str 27/33, 60-572 Poznan, Poland

2 Department of Neurological and Psychiatric Nursing, Poznan University of Medical Sciences, Poznan, Poland

Mysteriously and in ways that are totally remote from natural experience, the gray drizzle of horror induced by depression takes on the quality of physical pain.
(William Styron)

1 Introduction

Pain is considered as a multidimensional experience that contains not only a sensory component but also consists of emotional, cognitive and behavioural aspects. The prevalence of chronic pain in the adult European population has been estimated as approximately 20 % [1]. Major depressive disorder (MDD) is one of the most common mental problems worldwide. As demonstrated in a cross-national study, the lifetime prevalence of major depression ranges from 1.5 to 19.0 %, with the midpoint at nearly 10 % [2]. The presence of pain in depressed subjects and depression in patients with chronic pain is higher than the separate prevalence of both conditions [3]. Depression, as a consequence of chronic pain, has attracted much attention from investigators, but much less is known about the different aspects of pain in depression.

According to the Kyoto protocol, nociception is defined as a neural process of encoding and processing noxious stimuli. Pain, in turn, is described as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or is described in terms of such damage. Nociception usually causes pain but either phenomenon can occur without the other [4].

In a substantial proportion of people, chronic pain occurs in the absence of nociceptive stimuli. The most common functional painful somatic syndromes that cannot be explained by specific organ pathology are fibromyalgia, irritable bowel syndrome and tension headaches. Unexplained painful physical symptoms (UPPS) in patients with MDD exemplify another presentation of this phenomenon. Because comorbidity of major depression and general medical conditions is relatively common, in the differential diagnosis of UPPS, pain as a result of "explained" causes should be considered.

In this paper, we report a literature review of the prevalence, pathophysiology and management of UPPS in patients with MDD.

2 The Prevalence of UPPS in Depression

The prevalence of UPPS in patients with depression has been investigated in a number of studies. In a multinational cross-sectional telephone survey of a random sample of 18,980 people from five European countries, MDD was diagnosed in 4.0 % of this population. A significant proportion of the subjects with MDD (43.4 %) reported having at least one chronic painful physical condition, i.e. four times more often than in the remaining sample [5].

A review of 14 studies published between 1957 and 2003 showed that the mean prevalence of pain symptoms in different populations of patients with depression (primary care, psychiatric outpatients and inpatients) was 65 % (range 15–100 %). The discrepancy among the results of the studies reviewed was owing to different definitions of the pain condition, and to diverse methods of assessment of pain [3]. In a cross-sectional population-based study of non-institutionalised adult populations in six European countries, the risk of reporting painful symptoms in respondents with major depression was 50 % and was almost twice as frequent as in a population without depressive symptomatology [6]. Data from the secondary analysis of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study confirmed a high prevalence of pain in 3745 depressed American outpatients. As many as 77 % of them met criteria for having pain of different aetiologies [7]. The aim of the exploratory analyses of the multinational, longitudinal, Factors Influencing Depression Endpoints Research (FINDER) study was to evaluate pain severity, and the interference of pain with daily functioning in outpatients with depression during a 6-month observation. Moderate to severe pain was defined as a score >30 mm on the visual analogue scale. In a population of 3308 patients, 56.3 % of them met this criterion at baseline [8]. The Spanish multi-centre cross-sectional study conducted by Agüera-Ortiz et al. [9] was aimed at estimating the prevalence of pain in patients with all types of DSM-IV-TR depressive disorders (mostly those with major depression and dysthymia) seen by psychiatrists in their regular practice. The patients were asked about pain symptoms at the time of the study. The presence of pain was confirmed when the intensity on the visual analogue scale was assessed as >40 mm. The location and aetiology (known and unknown) of pain were recorded. From among the 3566 patients enrolled in this study, 2107 (59.1 %) reported pain.

The studies mentioned above provide further interesting information regarding the demographic correlates of pain. Subjects with painful symptoms were more likely:

1. To be female than male [4, 8–10].
2. To have fewer years of education [10].
3. To be unemployed [4, 8, 10].
4. To be older [8, 9].

Furthermore, a relationship between baseline pain severity and some clinical features of depression has been established. Pain intensity has been correlated with:

1. Greater baseline severity of depressive symptoms [8–10].
2. The number of current medical conditions [8, 10].
3. A higher body mass index [8].
4. The severity of non-painful somatic symptoms [8].

Certain symptoms of MDD, such as anhedonia, sleep problems, loss of energy and depressed mood [9] as well as anxiety and melancholic features [10] were all associated with the severity of painful symptoms. Ohayon and Schatzberg [4] reported a correlation between chronic UPPS and other somatic symptoms of depression including change in appetite or weight, psychomotor agitation or retardation, fatigue or loss of energy, plus cognitive symptoms, namely difficulty in concentrating, thinking or making decisions.

A growing interest in pain in bipolar disorder (BD) has been noted in recent years. It has been demonstrated that chronic multi-site pain commonly co-occurs with mood disorders, particularly BD (54.8 %) [11]. A meta-analysis of 22 cross-sectional studies indicated that about one fourth of individuals with BD experienced chronic pain. In comparison to control subjects the relative risk of pain was 2.14 times higher [12].

A higher proportion of BD patients with pain was noted in another study of 641 primary care patients. Almost half of them (46 %) reported either current treatment for a pain condition or regular pain interfering with daily functioning [13].

3 Characteristics of Pain

3.1 Unexplained vs. Explained Painful Symptoms

Pain in depression may be a manifestation of a concomitant medical condition or may represent unexplained UPPS occurring mainly during a depressive episode. The proportion of patients with pain, but without a documented physical explanation for the pain, has been estimated as 42.8 % [9]. In the FINDER study, in a group of depressed patients with moderate/severe pain, 51.1 % had a current chronic medical condition, whereas one third had a current painful disease [8]. These observations suggest that painful symptoms in the course of depression constitute a group of non-homogenous phenomena challenging careful differential diagnosis.

3.2 Localisation

In the Ohayon and Schatzberg study [4], subjects with at least one of the three key depressive symptoms reported limb pain, joint/articular diseases, backache, gastrointestinal disturbances and headaches twice as frequently as subjects without depressive symptoms The most common locations of pain in out-patients with depression were the back, neck, limbs, joints, and head [9]. Usually, patients reported more than one site of pain (mean 3.7) [9]. Similar results were reported by Demeyttenaere et al. [6].

3.3 Course

More than 25 % of the participants in the STAR*D study reported that pain was present most of the time [10]. Other data also suggest that, in a significant proportion of depressed patients, the course of pain is chronic. In the Randomized Trial Investigating SSRI Treatment (ARTIST) study, the somatic symptoms of the depressed participants were monitored throughout a 9-month period of treatment with fluoxetine, sertraline or paroxetine. In comparison to core depressive symptoms and non-pain somatic complaints, pain symptoms showed the least improvement in terms of effect size [14].

More recently, De Heer et al. [15] compared the impact of current and remitted depressive, anxiety and co-morbid disorders on different aspects of pain in a large sample of individuals with depressive and/or anxiety disorders vs. normal controls. The authors found a strong association of depressive and anxiety disorders and pain. Interestingly, remission of symptoms of depression did not result in remission of pain, which was still present [15]. In another longitudinal study, after 6 months of medication with antidepressants of different classes, the proportion of patients with moderate/severe pain interfering with functioning, declined from 56.3 to 32.5 % [8]. The aim of the Netherlands Study of Depression and Anxiety (NESDA) was to examine the relationship between different courses of depressive and/or anxiety symptoms and disorders (incident, remitted and chronic) and the presence of pain during the 4-year study. The results revealed a synchrony between change in depressive and anxiety symptoms and change in pain. Moreover, in comparison to healthy controls, individuals with depressive and anxiety disorders, whether incident, remitting or chronic, had worse pain severity and a higher number of pain locations. After recovery from the disorder, pain ratings were still significantly higher than in healthy subjects [16].

3.4 Consequences of UPPS in Depression

The presence of painful symptoms has various implications on the clinical and economic aspects of depression. Pain may mask emotional symptoms of depression leading to under diagnosis, or delayed diagnosis and, in consequence, to under treatment. In patients attending family medical practices, who presented with symptoms of somatisation,

including pain, the probability of a correct diagnosis of MDD made by family physicians was lower (22 %) in comparison to those who reported mainly psychosocial problems (77 %) [17]. This effect is presumably owing to the fact that patients with depression and concomitant painful symptoms were more likely to use general medical services and were about 20 % less likely to visit a mental health specialist than patients without pain [18]. This observation was confirmed by Demyttenaere et al. who reported that respondents with MDD and UPPS had lower rates of seeking help for emotional symptoms [6].

The results of several studies provide convincing evidence that the presence of symptoms of pain at baseline is related to a worse response to antidepressants [19, 20] and a longer time to remission [10, 14, 21, 22]. In a recent paper, Fishbain and colleagues [23] presented the results of an evidence-based structured review of 17 studies investigating the relationship between the occurrence of UPPS and treatment response. They found convincing evidence linking higher pretreatment pain levels in patients with depression and pain with a lower probability of response and remission of depressive symptoms after antidepressant treatment.

The presence of pain in remission was related to the higher prevalence of subthreshold depressive symptoms which, in turn, is considered a well-established predictor of relapse of depression [24]. Consequently, patients with painful symptoms have a more chronic course of depressive and anxiety disorders [25]. Interestingly, chronic diseases (e.g. cardiometabolic, respiratory, endocrine) were not found to be associated with the risk of recurrence [24].

Evidence suggests that there is an association between the presence of several different chronic pain conditions and 12-month suicidal ideation and attempts [26]. Data from the National Comorbidity Survey Replication confirmed the independent association between some lifetime, self-reported pain and suicidal ideation, plans and attempts [27]. The results of a Korean study showed that patients with MDD and UPPS revealed significantly higher suicidal ideation, in comparison to those without pain [28]. Painful symptoms in depression also have a significant negative impact on functioning in daily activities and lead to poorer outcomes in multiple domains of health-related quality of life [8, 19].

The presence of UPPS in depression causes a greater economic burden related to lost work time and healthcare resource use, than depression alone [29]. Moreover, an additive effect of depression and UPPS on work days lost has been demonstrated [6]. Gameroff and Olson [30] estimated that the cost of medical care of patients with major depression, and at least moderate pain-related interference, was on average 2.33 times higher than that for depressed patients with little or no pain-related interference. In sum, the occurrence of UPPS in depression has a disadvantageous impact on the course and clinical response to treatment, and on some economic aspects.

4 Pathophysiology

The common coexistence of depression and pain gave rise to the formulation of a hypothesis that implies that both conditions share common pathogenic mechanisms. The first assumption refers to neuronal pathways involved in the pathogenesis of depression and the processing of pain.

4.1 Brain Networks of Depression and Pain

Functional neuroimaging gives us an opportunity to observe, in vivo, multiple cortical and subcortical structures that become active during the perception of pain. These networks consist of primary and secondary somatosensory cortices and the insular cortex, which are responsible for encoding the sensory aspects of pain, its location and duration. The anterior cingulate cortex (ACC) and insula play a role in encoding the emotional and motivational dimensions of pain perception. In addition, subcortical structures, such as the amygdala and ventral tegmental area, are also involved in the emotional and contextual aspects of pain perception. The prefrontal cortex is involved in the regulation of pain perception [31, 32]. Interestingly, activation and deactivation of selected regions have been observed without noxious stimuli during the anticipation of pain [33] and while observing other people experiencing pain [34].

Obviously, most of the components of the pain network mentioned above constitute a neural basis for other cognitive and emotional functions. Several regions that play a role in pain processing are also relevant to understanding a neural basis of depression. In short, emotion and reward processing are regulated by the amygdala and ventral striatum. The medial prefrontal cortex and ACC are involved in processing emotion and the autonomic regulation of emotion. Both the dorsolateral prefrontal cortex (DLPFC) and the ventrolateral prefrontal cortex play a role in the cognitive control of emotions by their connections to the limbic region. Disturbances of these structures and connecting pathways are responsible for the affective, motor and cognitive symptoms of depression [35]. More specifically, converging evidence suggests that frontal-limbic dysfunction may be considered as a common factor for both depression [36] and chronic pain [37].

The prefrontal cortex is involved in continuous monitoring of the external world, the maintenance of information in short-term memory and in governing efficient performance control in the presence of interfering stimuli,

as well as in the regulation of perception and the behavioural expression of pain. Moreover, it has been hypothesised that the DLPFC plays a role in "keeping pain out of mind" [38].

Accumulated evidence from neuroimaging studies has demonstrated slightly altered brain structures and functions in the frontal-limbic regions of patients with depression [39, 40] and in functional pain syndromes [41–46].

Functional brain imaging studies in depression and chronic pain also point to dysfunction of shared brain structures. Decreased brain glucose metabolism in the prefrontal cortex of depressed patients was a consistent finding in early positron emission tomography studies [47, 48] and was confirmed in more recent reports [49]. A meta-analysis of functional imaging studies in depression gave evidence of increased activity in the amygdala and medial prefrontal cortex-neural systems supporting emotion processing and reduced activity in the DLPFC, neural systems supporting the regulation of emotion, but also of pain control [50].

Abnormal function of the prefrontal cortex was also detected in chronic pain. A reduced activation of the anterior prefrontal cortex and the ACC was found in patients with rheumatoid arthritis [51]. Moreover, the role of the lateral prefrontal cortex in the pathophysiology of fibromyalgia-related hyperalgesia, in the context of catastrophizing was determined using functional magnetic resonance imaging [52]. The results of this study suggest that higher levels of catastrophizing was associated with reduced pain-anticipatory brain activity in the lateral prefrontal cortex in patients with fibromyalgia exposed to pain pressure stimuli. The authors conclude that this deficit of activation may be responsible for the hyperalgesic effect of catastrophizing. It has also been proved that activation of the DLPC is inversely correlated with a perceived intensity of pain and its related unpleasantness [38]. The regulatory role of the DLPC in pain perception is related to modulation of cortico-subcortical and cortico-cortical pathways [53].

The pattern of activation of brain structures involved in pain processing seems to be abnormal in depression. During painful heat stimulation, unmedicated depressed patients demonstrated increased activation in the right amygdala and decreased activation in periaqueducal gray matter, the ACC and prefrontal cortices, relative to non-painful stimulation. This may imply that the recruitment of pain and emotion modulatory pathways during the experience of pain in MDD are ineffective or maladaptive. Moreover, increased activation in the right anterior insular region, dorsal anterior cingulate, and right amygdala during the anticipation of painful stimuli suggest increased affective processing, which may finally lead to inefficient pain modulation in depression [54]. A question remains whether this abnormal pattern of activation is reversible during successful treatment with antidepressants. To address this issue, Lopes-Sola et al. [55] compared brain responses to painful stimulation at baseline and after 1 and 8 weeks of treatment with duloxetine in patients with MDD. The clinical response during treatment with duloxetine was associated with a significant activation reduction in regions abnormally activated at baseline, i.e. the pre-genual ACC, right prefrontal cortex and pons.

A meta-analysis of neuroimaging studies provided evidence for the functional reorganisation of the insular cortex in major depression. In depressed patients, emotion-related peaks were shifted to the dorsal anterior insula regions activated in response to physical pain in healthy subjects. This phenomenon probably explains why individuals with depression experience pain in response to non-painful stimuli [56]. Further evidence of frontal-limbic dysfunction in chronic pain states comes from positron emission tomography-ligand studies, which showed abnormal opioidergic transmission within the frontal-limbic regions in patients with chronic pain [57].

4.2 Cytokines

Cytokines are a broad class of biologically active proteins that play a central role in the immune system and in the inflammatory response to homoeostatic and harmful stimuli. Cytokines also play a key role in the generation of pain in conditions such as arthritis and, consequently, the neutralisation of cytokines may have an analgesic effect [58]. In the brain, cytokines induce deregulation of both monoamine synthesis and reuptake, leading to reduced monoamine availability [59, 60]. Reviews and meta-analyses have provided convincing evidence that, in depressed patients, serum levels of the proinflammatory cytokines interleukin-1, interleukin-6, and tumor necrosis factor (TNF)-α are elevated [61–63]. Cytokines and chemokines released in different conditions can sensitise neurons of the first pain synapse, resulting finally in the activation of neurons by innoxious signals and, furthermore, may cause central sensitisation [58, 64]. These changes can promote long-term maladaptive plasticity, resulting in persistent neuropathic pain [65, 66]. During successful treatment with antidepressants, a reduction in normal levels of cytokines was reported [67]. The relationship between proinflammatory cytokine levels and pain symptoms in patients with MDD and minor depressive disorder was evaluated by Bai et al. [68]. The authors found that the level of soluble P-selectin, but not of other proinflammatory cytokines, appeared to be a significant predictor for somatic symptoms and for pain symptoms in depression. However, we were not able to find data confirming the relationship of normalisation of cytokines levels with a reduction in painful symptoms in depressed patients.

4.3 Substance P

Neuropeptide substance P acts by binding to the neu-rokinin-1 receptor (NK-1R). Both substance P and NK-1R are widely distributed in the central nervous system, par-ticularly in the amygdala, hypothalamus, periaqueductal gray matter, locus coeruleus and parabrachial nucleus, and are co-localised with serotonin and noradrenaline neurons. Initially, substance P was considered to be the primary nociceptive transmitter in afferent sensory fibers. The presence of substance P and NK-R1 receptors in limbic regions suggests that they are also involved in the regula-tion of affective behaviour and in the neurochemical responses to stress. In major depression, elevation of sub-stance P in serum [69] and in cerebrospinal fluid [70] has been demonstrated.

The results of experimental studies suggest that NK-R1 antagonists have a similar effect on the serotonin and noradrenaline systems to that caused by antidepressants [71]. However, clinical studies provided inconsistent results. Two of them confirmed that the blockade of central NK-R1 receptors with orvepitant [72] and aprepitant [73] is an efficacious mechanism for the treatment of MDD. However, the results of Keller et al.'s study did not support the efficacy of aprepitant in MDD [74].

4.4 Neurotransmitters: Serotonin and Noradrenaline

The biochemical hypothesis of major depression posits a role of deficiency in ascending serotonin projecting from midbrain raphe and noradrenaline projecting from locus coeruleus pathways. Descending serotonin and nora-drenaline neurons communicating with the rostral ventro-medial medulla (RVM) and periaqueductal gray (PAG) have a regulatory effect on pain. Activation of descending projections causes the release of serotonin and nora-drenaline. The malfunction of these pathways observed in depression may lead to painful physical symptoms [75]. Antidepressants that act through enhancement of serotonin and/or noradrenaline neurotransmission in both ascending and descending neurons alleviate the emotional, cognitive and somatic symptoms of depression. There is growing understanding of the role of descending pain modulation and its dysregulation in chronic pain. Two reciprocally connected anatomic structures are considered to play a key role in the inhibition of pain. The first, the PAG, receives fibers from the amygdala, hypothalamus and frontal cortex. The second, the RVM, receives inputs from the thalamus, parabrachial regions and noradrenergic neurons from the locus coeruleus. Evidence suggests that descending pro-jections from the RVM increase the release of serotonin in the dorsal horn. It has also been proved that the RMV contains "on cells", which facilitate pain transmission and "off cells", which inhibit pain perception. Moreover, stimulation of the PAG and RVM in animal models causes norepinephrine release in the cerebrospinal fluid, which leads to an antinociceptive effect [32]. Recently, Ossipov et al. [76] reviewed the experimental and clinical findings providing data that empower a better understanding of the role of descending serotonergic and noradrenergic pain modulatory systems. It has been shown that descending projections from the RVM induce the release of serotonin in the spinal horns, leading to the antinociceptive effect. Furthermore, both experimental and clinical data gave evidence that stimulation of noradrenergic nuclei, PAG, and RVM cause the release of noradrenaline into the spinal cord and cause antinociception.

4.5 The Integrative Biological Hypothesis

Recently, Fasick et al. [77] on the basis of their review of the literature, have postulated that the co-occurrence of depression and chronic pain may be explained as processes occurring in the hippocampus, a brain structure that plays a role in both the processing and modification of nociceptive stimuli. The first common denominator for both conditions is an activation of proinflamatory cytokine (TNFα). This, in turn, induces activation of the hypothalamic–pituitary–adrenal (HPA) axis and reduces production of brain-derived neurotrophic factor in the hippocampus. These abnormalities were observed in both chronic pain and depression. More-over, elevated levels of brain-TNF mediate a decrease in noradrenaline release, causing inactivation of descending pain inhibitory pathways. Proinflammatory cytokines decrease glucocorticoid responsiveness leading to a loss of glucocorticoid-mediated suppression of proinflammatory cytokine production which, finally, causes a vicious cycle resulting in the overproduction of TNFα and hypercorti-solemia. The eventual consequences of these mechanisms are neuroplastic changes in the hippocampus and, finally, atrophy of the hippocampus, effects observed in both depression and in chronic pain.

4.6 Psychological factors

Catastrophizing is one important cognitive error attributed to depression. According to Sullivan et al. [78], catastrophizing is currently defined as: "an exaggerated negative mental set brought to bear during an actual or anticipated painful experience". In this case, a person predicts that all things (for example pain) are going to go wrong. The relationship between depression, pain and catastrophizing has been well documented in a large number of studies [79–82].

The authors of the Örebro Behavioral Emotion Regu-lation Model posit that emotion regulation constitutes a

central function explaining the interrelationship between chronic pain and depression. The course of both conditions is characterised by their cyclical pattern and frequent flare-ups of depressed mood and intensity of pain. A consequence of these fluctuations is catastrophic worry and anticipation of the worst possible outcome. Catastrophizing increases negative emotion and the perception of pain. When effective coping strategies are applied, the amelioration of negative mood and intensity of pain may be expected. This may protect against aggravation of symptoms. In cases in which the individual is unable to cope with flare-ups, the vicious circle mechanism starts to play a role. Here, catastrophizing causes negative effects leading to distress, pain and, in turn, to a more severe tendency to catastrophizing. The authors of this model claim that dysfunction of emotion regulation is a transdiagnostic process shared by both depression and pain [83].

5 Management

5.1 Pharmacotherapy

Because the occurrence of UPPS may impact the response to treatment and prognosis of MDD, during the initial clinical examination, and while monitoring the progress of treatment all patients should undergo a careful interview regarding the presence of pain complaints. Careful assessment may assist in the selection of effective treatment.

Wise et al. [84] proposed the following management of patients who present with UPPS and depression. In the first step, patients reporting UPPS should be assessed by physical examination and laboratory tests, making possible n hypothesis regarding the cause of pain and treatment. The important issue is to take painful symptoms seriously and to ascertain that the discomfort the patient experiences is "real pain". Next, the patients should be informed that UPPS are a common part of depressive symptomatology, and usually respond well to antidepressive drugs. Basic information about the neurobiology of depression and pain may facilitate a patient's better understanding and acceptance of the cause of symptoms.

Since their introduction in the 1960s, tricyclic antidepressants have also been used for the treatment of pain. Advances in pharmacotherapy in the last decade of the 20th century led to the introduction of new classes of antidepressants, namely selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs). These drugs, which were initially administered in the treatment of major depression, were subsequently applied in the treatment of pain syndromes. While the SNRIs appear to be effective in the treatment of chronic pain, the evidence from studies with SSRIs is inconsistent

[85]. Two recently published meta-analyses confirmed the comparable efficacy of tricyclic antidepressants and SNRIs [86, 87], in the treatment of neuropathic pain, thus certifying the recommendation of these drugs, along with gabapentin and pregabalin, as first-line treatment for this condition [88].

Functional somatic syndromes presenting with unexplained pain (i.e. fibromyalgia and irritable bowel syndrome) commonly co-occur with depression. The bulk of findings from clinical studies and their meta-analyses have provided evidence for the efficacy of amitriptyline and SNRIs in reducing pain and other symptoms of fibromyalgia [89–92]. By contrast, the authors of the Cochrane Review did not find convincing evidence for SSRIs superiority over a placebo in treating pain, fatigue and sleep problems in patients with fibromyalgia [93].

Therefore, the conviction remains that dual-action antidepressants are more effective than SSRIs in the treatment of neuropathic pain and of functional pain syndromes such as fibromyalgia. However, pain in neuropathy, fibromyalgia and other functional syndromes probably has a different neurobiological basis than that of UPPS in depression. As far as some common genetic, immune and neurohormonal mechanisms for these conditions have been postulated, one may hypothesise that specific features of a particular painful disorder are related to different contributions of these, and possibly other unique factors. This, in turn, may lead to the assumption that opinions about the superiority of dual-action antidepressants over SSRIs in reducing UPPS in depression may be unjustified.

The aim of several previous studies was to assess to what extent different classes of antidepressants are effective in reducing UPPS, along with improving other symptoms of depression. The first problem, potentially relevant for the optimisation of pharmacotherapy, is whether both noradrenergic and serotonergic drugs have favourable effects on pain in patients with MDD, and a second problem is whether dual-action antidepressants are more effective in the treatment of UPPS than selective drugs. A better understanding of these differences may be helpful in optimising the pharmacotherapy of depressed patients with UPPS.

Two randomised double-blind studies demonstrated that fluoxetine [94] and citalopram, but not reboxetine [95] have an analgesic effect in patients with somatoform pain disorder.

The results of the latter study [95] may suggest that SSRIs are superior to selective noradrenergic drugs in reducing painful symptoms. To verify this issue, we recently compared the effect of nortriptyline and escitalopram on UPPS in a randomised study of patients with MDD who participated in the Genome-based Therapeutic Drugs for Depression (GENDEP) study. Our results

provided evidence that both serotonergic and noradrenergic antidepressants are equally effective in the alleviation of UPPS in depression [96].

Assessment of the efficacy of SNRIs in the treatment of pain in MDD was the aim of several studies. The beneficial effect of venlafaxine on both depression and pain was documented in an observational, prospective study of patients with depressive symptoms and comorbid chronic pain [97], and in an 8-week study of patients with first-episode depression with painful symptoms [98]. However, the results of a recent 6-week investigation of the efficacy of 150 mg of venlafaxine in patients with comorbid depression and chronic low back pain showed that only 26.4 % of patients responded in both conditions, suggesting a weak therapeutic effect on pain [99].

Duloxetine is another potent dual-reuptake inhibitor of serotonin and NA. In the recent decade duloxetine has been widely studied in regard to its effect on UPPS. Placebo-controlled randomised studies have shown that duloxetine significantly reduces pain in depressed patients [100–102]

These observations were confirmed by a meta-analysis of 11 double-blind placebo-controlled studies [103] but not by a Spielmans' meta-analysis based on five studies of duloxetine [104]. The important issue in clinical practice is whether SSRIs, considered as a first-line treatment of depression, are as effective as SNRIs in patients with UPPS. Martinez et al. [105] conducted a multicenter, randomised, non-blinded, parallel-group 12-week trial to compare the efficacy of duloxetine with generic SSRIs (citalopram, fluoxetine, paroxetine or sertraline). Their data showed no significant differences in the depression remission rate. However, the effect of duloxetine on UPPS was significantly better, in comparison to SSRIs. The aim of several 7- to 9-week head-to-head trials was to compare the efficacy of duloxetine (40–120 mg/day) and paroxetine (20 mg/day) in depressed patients with UPPS. Two pooled analyses of these studies found no significant difference between the two drugs in the reduction of painful symptoms [106, 107]. This led Krebs et al. [107] to conclude that the current evidence from clinical trials is insufficient to speculate about the superiority of either agent over the other in the treatment of MDD with accompanying pain,

In those patients with depression who do not respond to initial treatment with SSRIs, switching to another antidepressant, preferably with another mechanism of action, is recommended. This strategy was tested in patients with MDD who reported substantial levels of pain and did not respond, or only partially responded, in the course of 6 weeks of treatment with SSRIs. The results of this study revealed that a switch to duloxetine was associated with significant improvements in painful symptoms, time in pain and interference with functioning because of pain [108]. The aim of another study was to define the optimal period

of time for switching antidepressants in depressed patients with moderate to severe pain, who had initially been treated with escitalopram. It turned out that an early switch to duloxetine in participants whose pain did not improve after 4 weeks is related to an acceleration in the reduction of pain severity and to an increase in the proportion of patients with functional remission, in comparison to patients with a conventional switch after 8 weeks [109].

The interesting issue regarding the relationship between reduction of pain severity and improvement in depressive symptoms has been addressed in several studies. Specifically, one may hypothesise that (1) the relief of pain is secondary to an improvement in the core symptoms of depression or that (2) the antidepressants have a direct effect on pain, independent from the improvement of other symptoms. Using a path analysis, Mallinckrodt et al. [110] estimated that in MDD patients treated with duloxetine, between 30 and 70 % of the observed improvement in pain severity was independent of the improvement in the emotional symptoms of depression. Using the same statistical method, Fava et al. [100] calculated that 50.6 % of the improvement in pain severity was independent of the amelioration of depressive symptoms. Taking the results of these studies together, both direct and indirect analgesic and antidepressant properties appear to be relevant for the treatment of these comorbid conditions.

Summing up, the results of the studies reviewed here do not give sufficient evidence of a better efficacy of SNRIs over SSRIs in the treatment of UPPS in MDD. Therefore, head-to-head trials comparing the antinociceptive effect of different antidepressants on UPPS are warranted

5.2 Psychological Approach

Cognitive techniques, including mindfulness practice and orienting attention away from the pain, may have a positive effect on different aspects of pain perception. Considerable evidence indicates that psychological methods, including cognitive-behavioural techniques, are useful in the treatment of both chronic pain [111–113] and depression [114].

For this reason, psychological interventions have been implemented in treatment programs for patients with comorbid depression and pain. The Stepped Care for Affective disorders and Musculoskeletal Pain (SCAMP) study was aimed at assessing the efficacy of a combined pharmacological and behavioural intervention in primary care patients with musculoskeletal pain and comorbid depression of at least moderate severity. During the first 3 months of the study, optimised antidepressant therapy was administered. This period was followed by six sessions of a pain self-management programme delivered every other week over the next 3 months (step 2). The third step of the study was a continuation phase focused on relapse

prevention. The results showed that, in patients with comorbid pain and depression, optimised antidepressant therapy augmented with pain self-management can result in substantial improvements in both depression and pain [115].

Recently, Thielke et al. [116] published the results of a year-long study of the Effectiveness of a Collaborative Approach to Pain (SEACAP). This was a collaborative care intervention study of American veterans with chronic musculoskeletal pain, applying a structured framework to educate and activate the patients, to track their symptoms and to monitor treatment adherence. The patients involved in this program were more likely to experience continued relief from depression and pain than patients treated "as usual".

6 Conclusions

Major depression is an aetiologically and symptomatically heterogeneous disorder. On the basis of their clinical presentation, several subtypes of depression have been described including psychotic, nonpsychotic, retarded and agitated, with melancholic and other atypical features. These differences of manifestation are probably related to different biological underpinnings. For example, Maes et al. [65] showed a relationship between levels of inflammatory response and melancholic features as well as of chronic fatigue in patients with major depression. Earlier observations suggest a down-regulation of the HPA axis in atypical depression and its hyperactivation in depression with melancholic features [117]. Advances in neurobiological studies could improve our understanding of the relationships between candidate genes associated with MDD, related molecular abnormalities (proinflammatory cytokines, neurotrophic factors, HPA axis dysregulation), abnormal structure/function of neural systems, and finally clinical presentation or response to treatment [34]. As stated earlier, depression with UPPS, in comparison to depression without UPPS, is characterised by a worse response to pharmacological treatment, a more chronic course and poorer functional status. It is highly probable that these clinical features are related to more specific genetic, molecular and neural abnormalities. Therefore, studies examining associations between genes (e.g. polymorphisms of genes for interleukins, serotonin transporter and receptors), molecules (e.g. cytokines, substance P) and neural systems (e.g. functional neuroimaging studies during painful stimulation) in patients with MDD and UPPS are warranted. These may lead to the application of more effective methods of treatment.

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