

DEPRESSION AND PAIN: OFTEN TOGETHER BUT STILL A CLINICAL CHALLENGE - A REVIEW

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SUMMARY

Depression is a common mental disorder with various symptoms and often accompanied with unexplained painful physical symptoms. Patients, especially in primary care, often present only with somatic symptoms and depressed mood is overlooked. On the other hand, psychiatrists don't pay enough attention to somatic or painful symptoms in patients with depression. The connection between depression and accompanying painful physical symptoms is not completely understood although some common neurobiological pathways are proposed. To achieve good clinical outcome all depression symptoms should be recognized and treated. In this review we focus on painful physical symptoms which could not be explained by somatic illness or the intensity can not be explained by physical disease and are attributed to somatic symptoms of depression. The aim of this review is to provide the basic necessary information for clinicians/psychiatrists on depression with painful physical symptoms, presenting the terminology, epidemiology, differential diagnostics, neurobiological background, psycho-social aspects and treatment strategies.

Key words: depression – pain - unexplained painful physical symptoms – neurobiology - treatment

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INTRODUCTION

Depression is a common mental disorder with the prevalence of 10-20% (Murray & Lopez 1996). The mortality is high and around 15% of depressed patients commit suicide (Simon & Von Korff 1998). It is estimated that by year 2020 depression will be number one disease in the world.

In patients with depression unexplained painful physical symptoms or medically unexplained pain complaints are common (Garcia-Cebrian et al. 2006). About 50% of depressed patients report pain (Katona et al. 2005). Especially in primary care setting depression is often overlooked due to physical complaints (Panzarino 1998). It is estimated that up to half of the patients with depression complain primarily of fatigue, pains and aches in muscles, joints, back, abdomen, in other organs and headache, rather than of emotional symptoms (Ohayon 2004, Schatzberg 2004, Vaccarino et al. 2008).

Different factors have been identified in depressed patients presenting only with physical symptoms: lower education, lack of psychological insight, alexithymia, severe comorbid physical illness, doctor's views on psychiatric disorders or lack of proper education, time issues, and stigma (Maj et al. 2008a). When depression symptoms are unrecognized and untreated they become worse and the outcome is poor (Sartorius 2003, Greenberg et al. 2003).

Depression and pain are still intriguing clinical topics and there are several articles reviewing this matter from different points of view, many of them focusing on analgesic properties of psychiatric medication. It has been recently proposed to raise the awareness of pain in psychiatric population in order to ease artificial boundaries separating psychiatric and

medical formulations of brain disorders (Elman et al. 2011).

The aim of this review is to provide basic relevant information for psychiatrists on painful physical symptoms which could not be explained by organic illness and are present in patients with depression as a part of somatic complaints.

TERMINOLOGY

Pain

The International Association for the Study of Pain defines pain (latin "dolor") as "an unpleasant sensation and emotional experience associated with a real or potential damage to tissue, or the equivalent of such damage" (Merskey et al. 1986). It is a complex unpleasant experience defined by sensory, emotional, social and cultural factors and is one of the most frequent complains in the primary care (Gureje et al. 1998, Stahl 2008). Pain may be classified according to site, nature or presumed mechanism. Acute pain has a protective role and warns the organism of an imminent danger, while in chronic pain central mechanisms are involved, it persists beyond its biological usefulness and compromises the quality of life (Blackburn-Munro et al. 2001).

Painful physical symptoms in depression

Major depressive disorder and anxiety disorders are often accompanied by chronic painful conditions (Gureje 2007). However there is still a lack of consistent terminology which probably reflects conceptual issues about the nature of pain and depression (Katona et al. 2005). To define pain symptoms in depressed patients

different expressions appear in the literature. Terms like “functional“, “medically unexplained“, “unexplained painful physical symptoms” or “psychosomatic” are the most commonly used (Dowrick et al. 2005, Peveler et al. 2006). In fact there are many clinical conditions where patients report pain, but there are either no symptoms of depression or depression is considered as comorbid. DSM IV classifies somatic symptoms and pain complaints without clear physical cause under the associated features of depression, while “Pain disorder” with pain being predominant focus of the clinical presentation is classified under “Somatoform disorders”, respectively (DSM IV 2000). ICD 10 follows similar diagnostic criteria; however persistent pain and fatigue, associated with somatic syndrome and fluctuating mixtures of depressive symptoms is diagnosed as “Atypical depression” (ICD 10 1992).

Differential diagnosis

Patients suffering from real chronic organic pain often become depressed. (Vossen et al. 2009, Braš et al. 2010). On the other hand, a vast majority of poorly understood painful conditions are seen in primary care and by other specialists like orthopedists, neurologists, rheumatologists or gastroenterologists under the diagnoses of chronic back pain, fibromyalgia, neuropathy, irritable bowel syndrome, and others. These functional somatic syndromes cannot always be explained by organ pathology and currently lack definitive diagnostic tests (Goldenberg, 2010). The comorbidity with depression is high; however patients under these diagnoses are seen by psychiatrists when symptoms of depression are recognized (Hennigsen et al. 2003, Fietta et al. 2007).

Other poorly defined conditions like chronic fatigue syndrome, somatoform disorders, especially persistent somatoform pain disorder, burnout, or others also sometimes present with pain complaints and depressive symptoms. It is essential to carefully examine patients' history and symptoms in order not to miss comorbid depression, and to recognize painful symptoms as a part of somatic symptoms of depression.

EPIDEMIOLOGY

The research of depression and painful physical symptoms (PPS) has been conducted in general population, and on primary and secondary (specialist) level.

General population and primary care studies

In a large cohort European study among 18,980 subjects, 4% met the criteria for major depressive disorder and among them the prevalence of at least one painful symptom was 43.3% (Ohayon 2004); in the rest of the sample 16.1% of subjects reported painful condition, respectively. Subjects with depressive symptoms and painful physical condition had a longer duration of

depression, and more often reported symptoms like fatigue, insomnia, psychomotor retardation, weight gain and severe difficulty concentrating. In the same population, 17.1% reported having at least one painful symptom; 16.5% having at least one depressive symptom and among them, one quarter had at least one painful condition. 28.5% of subjects with at least two depressive symptoms had also somatic painful complaints; and 61.9% of subjects with 8 depressive symptoms complained of painful condition. Depressive mood lasted longer in patients with painful condition (Ohayon & Schatzberg 2003).

In another study patients with depression and PPS had less favorable prognosis with only 9% of complete recovery versus 47% in patients without PPS (Geerlings et al. 2002).

In 70% of European studies on this subject patients with PPS were primarily screened for depression and a positive correlation was found in most of them. Patients with depression and PPS had more depressive symptoms, scored higher on somatic symptoms, suffered of more everyday disabilities and more frequently visited a GP (Garcia-Cebrian et al. 2006). In a study by Arnov et al. (2006) patients with major depression reported significantly higher proportion of chronic pain than those without depression (66% versus 43%). In the minority of studies patients with depression were screened for PPS and the results correlated with above mentioned studies.

In Norway 75% of patients with major depression presented with at least one non-affective complaint (Garcia-Cebrian et al. 2006). In a large Spanish study 3189 patients with unexplained chronic pain were evaluated with Visual analogue scale (VAS) and Primary Care Evaluation of Mental Disorders. Depressive symptoms were present in 80.4% of subjects (with higher prevalence in women); among them 56.2% fulfilled the criteria for major depression and 17.8% for dysthymia/mild depression, respectively. The majority of pain complaints were in neck and back (71.6%), headache (64.7%) and joints or limbs (61.3% vs 58.5%) (Aguera et al. 2010). Similar results were found in a large WHO study with 69% of patients with major depression presenting with unexplained somatic or painful symptoms. Depressed patients had the odds ratio of 3.5 in reporting unexplained somatic symptoms in comparison to non-depressed subjects (Simon et al. 1999).

Studies on secondary level and in psychiatric setting

There are few research reports on depression and pain in patients treated in psychiatry, in patients treated for pain and patients in somatic setting, like orthopedics.

In a multicenter international study STAR*D (Sequenced Treatment Alternatives to Relieve Depression) nearly 3000 patients with depression were included (Husain et al. 2007). 80% of patients with Major

depression without psychotic features complained of PPS. Clinically significant differences between patients with and those without painful symptoms were found. Patients with PPS had more severe depressive symptoms, anxious features with irritable mood, gastrointestinal problems, sympathetic nervous system arousal, lower quality of life, and poorer response to therapy with Selective Serotonin Reuptake Inhibitors (SSRIs). However, poor treatment outcome correlated also with gender, ethnicity and comorbidity (Leuchter et al. 2010).

In other studies in psychiatric setting the prevalence of PPS was 50% to 69% in depressed patients (Hartman et al. 2006). Patients with PPS were in general older and of female gender.

In patients, primarily treated for pain in so called "Pain Clinics" the prevalence of comorbid depression was 35% and 73%, respectively. However, not all studies found the connection between pain and depression (Garcia-Cebrian et al. 2006).

In general, patients with PPS have twice the probability to become depressive (Ericsson et al. 1996). Patients with PPS and depression had worse outcome and they scored higher on depression scales (Forrest & Wolkind 1974).

NEUROBIOLOGY AND PSYCHOLOGICAL FACTORS

Neurotransmitter pathways

Coexistence of depression and pain might be explained with common neurobiological pathway and psychological background. Neurotransmitters, such as glutamate, substance P, serotonin, norepinephrine, dopamine, brain-derived neurotrophic factor, and gamma-aminobutyric acid are activated in chronic pain and depression (Goldenberg 2010). The majority of data is available for serotonin (5HT) and norepinephrine (NE). They are involved in depression and are a part of brain and medulla anti-pain system (Stahl 2008, Breder & Conway 2009). Norepinephrine pathways are involved in depressed mood, apathy, loss of interest, sleep regulation, anergy, cognitive dysfunction, as well as psychomotor agitation or retardation (Stahl 2008). Serotonergic system modifies sleep and sexual behavior. Both systems are involved in numerous functions like sleep, mood, anxiety, and stress response. NE is more involved in motivation and 5HT in behavior. In endogenous analgetic system both neurotransmitters act synergistic (Kores-Plesnicar 2007). However, also dopaminergic neurotransmission is involved in depressed mood, apathy, psychomotor agitation, and cognitive functions (Stahl 2008).

Pain signals are relayed through spino-thalamic projections to thalamus and parietal cortex. From thalamus projections go to amygdala, insula, ventral striatum, hippocampus and prefrontal cortex. These projections are involved in emotional component of pain perception as well as pathophysiology of depression (Phillips et al.

2003). The perception of pain has a discriminatory (thalamo - cortical) and affective (thalamo - limbic) component.

Depression might precede the pain or pain precedes depression. It might be attributed to structural changes in genetic and receptor factors of NE and 5HT systems; however, the theory of central sensitization has been proposed (Breder & Conway 2009). Chronic pain or depression might originate from permanent opening of ionic channels in central brain structures which results in chronic overactivity of neurons. In this case, the normal physiological signals from body structures are perceived as painful (Stahl 2008).

In a study of young, untreated patients with major depressive disorder the enhanced affective response to thermal trauma was observed, with activation of amygdala, insula region and anterior cingulate cortex, and depression in activity of cortical/subcortical area for pain perception (Strigo et al. 2008). This is a supposed mechanism of high comorbidity of depression and PPS in chronic cases.

Stress, neuroendocrine factors and immune mechanisms

In animal studies, chronic pain had similar consequences as chronic stress: atrophy of hippocampus, hypertrophy of amygdala, reduction of glia in prefrontal cortex, dysfunction of dopamine projections from ventro tegmental area to accumbens (reward system) (Pittinger & Durman 2008). Similar changes were found in depression (Videbech & Ravnkilde 2004).

The emotional aspect of the pain response is encoded by corticolimbic systems (including the hypothalamic-pituitary-adrenal (HPA)) axis to encapsulate the relationship between pain, memory, and mood (Blackburn-Monro 2004). HPA axis dysfunction has been found in patients with different painful conditions, like fibromyalgia, chronic widespread pain and irritable bowel syndrome (Deak et al. 2005). On the other hand, in patients with major depression the dysfunction of HPA axis is often present and up to 50% show abnormal cortisol suppression (Merali et al. 2004).

There is a growing evidence for immune activation in depression and chronic pain (Goldenberg 2010). It has been shown that interleukin-2 or interferon caused widespread pain, fatigue and depression (Kim 2007) and proinflammatory cytokines decreased serotonin availability (Schrocksadel et al. 2006).

Psychological factors

Psychologically, early childhood trauma and catastrophic thinking contribute to depression (Anič 1996, Žunter-Nagy 1998). It has also been shown that personality and developmental traits might lead to depression and pain under stressful life events (Katona et al. 2005).

In the theory of learned pain behavior person with pain symptoms gains the attention of significant others. Such behavioral pattern is characteristic for people who gained attention in the past, had to take the adult role in the childhood or grew up with a chronically ill relative (Tyler 1986). Abused children are more often depressed in adulthood and have more somatic (and painful) complains (Arnou 2004).

THERAPY OF DEPRESSION WITH PPS

In recent years, depression and PPS have gained a lot of attention, especially with the development of newer antidepressant drugs. It is well known that early recognition and effective treatment improves the outcome and reduces therapeutic resistance and recurrence. To achieve full remission successful treatment of somatic and painful symptoms is essential. Painful symptoms might represent residual symptoms and correlate with relapse (Bair et al. 2000, Fava 2003, Greden 2003). The therapeutic options in managing painful conditions, like fibromyalgia, with antidepressants were thoroughly reviewed recently (Mohr et al. 2010), so we focus predominantly on therapeutic possibilities in depressed patients with PPS in psychiatric setting.

Pharmacotherapy

In the treatment of depression and PPS general guidelines for depression treatment apply. However some psychopharmacological drugs might be effective in relieving PPS in patients treated primarily for depression.

Antidepressants

In the past tricyclic antidepressants (TCAs) were used in patients reporting PPS or to relieve organic pain, like neuropathic pain. It was proposed that blockade of norepinephrine reuptake accounts for the analgesic effect (Max et al. 1992). They were often prescribed in patients with painful conditions but no depressive symptoms.

There is a growing body of evidence that double acting antidepressants (Selective Norepinephrine Reuptake Inhibitors - SNRIs) and dopaminergic substances have higher efficiency in relieving painful symptoms (of organic origin or unexplained) with or without depression (Fishbain 1999, Leuchter et al. 2010). Among them SNRIs (duloxetine, venlafaxine, mirtazapine, milnacipran), bupropion, and tetracyclic antidepressants as well as MAO Inhibitors are recommended (Fishbain 2009). Hypothetically such substances have anti-nociceptive effects via agonistic action on descending NE and 5HT pathways in medulla by inhibiting ascendant pain signals (the inhibition of pro-nociceptive glutamate and substance P) (Marks et al. 2009). Of these drugs, most of the data are available for duloxetine in patients with different painful

conditions like fibromyalgia, neuropathic pain or back pain, with or without comorbid depression (Mohr et al. 2010). However, most of the clinical trials do not provide results on the efficacy in relieving PPS attributed to somatic symptoms of depression. In a study in patients with depression, 50% of pain reduction was independent of the improvement of depressive symptoms which led to the conclusion that duloxetine has a direct effect on pain (Fava et al. 2004). In a 6-month non-interventional study with duloxetine 3320 patients (80% with painful symptoms, measured with Visual analogue scale) completed the trial. A 50% overall pain reduction was achieved (Schneider et al. 2011). There are some data on beneficial effect on pain of venlafaxine in patients with organic chronic pain and depression (Begre et al. 2008) or chronic pain conditions (Briley & Moret 2008), however, there is a lack of clinical trials focusing on patients with depression with PPS. There are some data that also mirtazapine reduces pain in cancer patients with mild depression (Theobald et al. 2002).

Mood stabilizers

There is a paucity of published controlled clinical trials on efficacy of mood stabilizers in depression with PPS, although antiepileptic drugs are used in pain syndromes and depression (Ettinger & Argoff 2007). Pregabalin and gabapentin, ligands of α - δ protein subunit of voltage-gated calcium channels might theoretically improve painful symptoms by down regulating calcium channels and blocking excitatory neurotransmitters (Maj et al. 2008b).

Antipsychotics, anxiolytics and analgetics

Atypical antipsychotics might have analgesic properties mainly through dopamine D2 receptors (Stahl 2008, Maj et al. 2008b). Higher central analgesia correlates with lower D2 potential. It was shown that lower receptor D2 affinity correlates with pain perception in striatum. Among second generation antipsychotics olanzapine, quetiapine, risperidone and ziparazidone have analgesic properties as well as antidepressive action.

Anxiolytic drugs have not been proven to be effective in reducing pain. Evidence of efficacy of analgesics in patients with depression is limited (Mohr et al. 2010). Caution is advised in using analgesics in patients with depression with PPS due to safety issues and tolerability/dependency potential (Marks et al. 2009).

Psycho-social interventions

Cognitive-behavioral therapy remains the most effective approach; however, emotional support, psycho-education, coping strategies and social skills training, bio-feedback, relaxation techniques, family intervention, hypnosis, moderate activity and occupational therapy are all an option (Maj et al. 2008b).

CONCLUSION

Pain and depression often present together. Research data suggest high comorbidity of depression in patients with pain of various etiology. Especially functional poorly understood disorders often present with painful symptoms. However, these patients are rarely seen by psychiatrist unless they present with comorbid depressive symptoms. It is often hard to separate symptoms attributed to depression, organic background or functional etiology. In psychiatric setting patients with typical core depressive symptoms accompanied by pain complaints that could not be explained by organic illness or attributed to other diagnoses are often seen and treated. These painful symptoms should not be overlooked, since they might affect diagnostics, treatment response and clinical outcome, especially in achieving full remission. It is important to recognize depression symptoms in patients presenting in primary care with predominantly somatic and painful symptoms and to identify painful symptoms in depressed patients by psychiatrists. The research evidence supports the common neurobiological and psycho-social background of depression and pain. Serotonin and norepinephrine pathways play an important role in depression symptoms as well as in pain and there is some clinical evidence that prescribing double-acting antidepressants might be effective. Treatment should start early and vigorously to avoid only partly remission of symptoms with unfavorable biological and psycho-social consequences.

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