

NEUROBIOLOGICAL AND CLINICAL RELATIONSHIP BETWEEN PSYCHIATRIC DISORDERS AND CHRONIC PAIN

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SUMMARY

Pain is one of the most ubiquitous problems of today's world, its impact being far-reaching. Current conceptualizations of pain medicine adopt a bio-psycho-social perspective. In this model, pain is best described as an interactive, psycho-physiological behavioral pattern that cannot be divided into independent psycho-social and physical components. Neurophysiologic substrates of the pain experience can be broken down into the pain transmission elements emanating from peripheral, spinal, and supra-spinal processes. There are many complex mechanisms involved in pain processing within the central nervous system, being influenced by genetics, interaction of neurotransmitters and their receptors, and pain-augmenting and pain-inhibiting neural circuits. The patient's emotional experiences, beliefs and expectations may determine the outcome of treatment, and are fully emphasized in the focus of treatment interventions. There are several common psychiatric disorders accompanying and complicating the experience of pain that warrant clinical attention and that can be the focus of psychiatric treatment. These include depression, anxiety, sleep disorders, somatoform disorders, substance-related disorders and personality disorders.

Complex and disabling pain conditions often require comprehensive pain treatment programs, involving interdisciplinary and multimodal treatment approaches.

There are many roles that the psychiatrist can perform in the assessment and treatment of the patients with pain, individually tailored to meet the specific needs of the patient.

Rational poly-pharmacy is of a high importance in the treatment of patients with chronic pain, with antidepressants and anticonvulsants contributing as the important adjuvant analgesic agents.

Key words: *pain - drug therapy – comorbidity - psychiatric disorders – psychotherapy - Liaison psychiatrist*

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INTRODUCTION

Modern medical research and clinical practice have been increasingly pointing to possible mechanisms of interconnections of physical and psychological health and in sickness, or the process of which at the same time events in our mind affect the body processes or psychological events result in the appropriate emotional and mental states. Intensive development of neuroscience and new methods to show the living brain led to the re-integration of neuroscience and psychosomatic research, the possibility of identifying mechanisms of interdependence between mind and body and the origin of disease. Chronic pain is a psychosomatic disorder with physical, mental, social and spiritual components as well as one of the best examples of the interconnectedness of body and mind in clinical medicine. In the United States this decade is declared "Decade of control and pain research" and almost every day we witness new neurobiological and pharmacotherapy knowledge about this complex phenomenon (Keefe et al. 2004). Contemporary findings suggest that understanding the brain is critical and indispensable component of pain research in order to explain the ways in which psychological, behavioral and social factors influence pain disorder, which is the way to the optimal therapeutic approach. Recent studies indicate the paths of information from the brain to the target organ through the "system of information transfer", which

includes endocrine, immune and autonomic nervous system. Studies of the brain in chronic pain play an important role in the rapid development of "personalized medicine" in chronic pain patients because the information on the structure and function of the brain in patients with pain disorders could help in predicting response to specific therapeutic interventions (pharmacological and psychotherapeutic). This approach will help in better understanding of psychosomatic concepts and their acceptance in medicine in general. According to the type, pain is divided into somatic, visceral, and neuropathic. Today, along with fever, pulse, blood pressure and breathing frequency, pain is considered the fifth vital sign. Pain is the most common reason for which the patient seeks for help, is associated with numerous medical and surgical conditions, and under certain circumstances, becomes a disease itself (Bouckoms 1999). Despite the many available medications and other therapeutic methods, for many of the chronic pain patients pain remains their unwanted and painful daily companion, for a variety of different reasons. The definition of pain by the International Association for the Study of Pain (IASP) is as follows: "Pain is noticeably uncomfortable and emotional experience associated with actual or potential tissue damage, or described at the time of such damage (Keefe et al. 2004). It has already been mentioned in the definition that the pain is always subjective, and the experience pain depends on many factors, which can be

divided into physiological, psychological and social. Psychological aspects of pain are highly complex neuropsychological phenomenon, but refer to those higher-level functioning of the CNS that create the perception of pain, including emotional and cognitive aspects of pain and behaviors associated with the experience of pain. It turned out that the psychological factors that increase the pain are catastrophic thinking about pain, anxiety and fear associated with pain and helplessness, and factors that reduce the pain are self-efficacy of self-reliance and self-esteem, strategies to cope with pain (coping), readiness for change and acceptance of problem (Keefe et al. 2004).

The pain therefore appears without known injury to tissue or pathophysiological causes, mostly due to psychological reasons, although there is no way that this objective is different than the experience of pain caused by tissue injury. Activity induced in the nociceptors and nociceptive pain pathways are not pain, but are nociception, and pain perception is formed in the CNS as a very complex phenomenon. Pathophysiology of acute pain is fairly clear, but chronic pain is still a great enigma, and includes a number of neurotransmitters (GABA, glutamate, NA, serotonin, neurokinin 1, NO, substance P, glycine, opioids, etc.). A state of chronic pain associated with "central sensitization", where a constant activation of peripheral pain neurons in the pain affects „neuroplasticity depending on activity“. In analytical terms, the pain is explained by chronic frustration in meeting needs, is an integral part of the experience in early childhood, and plays an important role in the development of interpersonal relationships, particularly with family members. It is associated with "being loved" and "be punished", and with a sense of guilt (Bouckoms 1999).

Contemporary conceptualization of pain have accepted biopsychosocial perspective, and the interaction of biological, psychological and social factors. Today there is a number of multidisciplinary programs and protocols for treating patients with chronic pain, in which the liaison psychiatrist has an important place. The primary goal of the multidisciplinary treatment is to improve the patient's level of functioning, while reducing the frequency and intensity of pain, and increase quality of life. Regardless of specialization, the team should consist of professionals who understand biopsychosocial model of chronic pain and whose assessment will not be limited only to a narrow specialist interests.

CHRONIC PAIN AND PSYCHIATRIC DISORDERS

In clinical practice, there is significant interconnection of pain and psychiatric disorders, and pain is a possible symptom in almost all psychiatric disorders. A large number of patients with chronic pain has some of the associated psychiatric diagnosis. Modern psychiatric classification have introduced pain disorder as a separate entity. Thus, ICD-10 differs

persistent somatoform pain disorder (F45.4) as part of somatoform disorders and permanent personality changes due to chronic pain (62.8 F - personality syndrome with chronic pain).

DSM-IV has introduced the category of pain disorders as one of five somatoform disorders, and also describes the chronic pain syndrome. A significant number of patients with chronic pain also develops a chronic pain syndrome, which is manifested in intense pain, suffering, pronounced changes in behavior, decreased activity, sleep disorder, anxiety, depression, suicidal ideas, social withdrawal, irritability, fatigue, cognitive difficulties, impaired sexual activities, hopelessness, helplessness and avoiding behavior.

Depression and chronic pain

Contemporary literature increasingly points to the connection between depression and chronic pain, both at the neurobiological and at the clinical level, and only the modern classification represent an attempt to formal diagnostic taxonomy. The Roman emperor and philosopher Marcus Aurelius wrote: "Untreated pain destroys us." Platnew stressed that physical complaints are an integral part of the depressive syndrome, and Montassut used the term depression larvee (masked depression) and cenestopathie for aberational bodily sensations in mental disorders, including pain (Keefe et al. 2004).

Pain has an important role in the complex of symptoms known as depression. Depression is much more common in patients with chronic pain than in the general population, as confirmed by numerous studies. On the other hand, among the vegetative and somatic symptoms of depression, the pain is in second place, immediately after the insomnia. There are studies that support the thesis that pain causes depression because of the current depressive episode which start after the beginning of pain. However, many patients with chronic pain often have episodes of depression for years, before the pain. There is the assumption that the depression in patients with chronic pain is a manifestation of personality, which is the result of early developmental conflicts, guilt, anger, and masochism. From this perspective, chronic pain is a symptom of depression (von Knorring et al. 1983). Psychoanalytic theory emphasizes the parallelism between mental and physical pain, being able to move from first to second. Pain can be a conversion symptoms that prevents the development of more serious depression. Behavioral theories suggest that patients with chronic pain change their behavior and therefore have less positive reinforcement, becoming depressed, a cognitive point of cognitive distortions. Sociological theories suggest that in many cultures the pain is more tolerable than the symptoms of depression, thus the depression manifests itself with chronic pain. Hypotheses about the interconnectedness of chronic pain and depression is common today, explained by the biochemical

characteristics, such as inclusion and noradrenergic and serotonergic system of hypercorticism and subnormal suppression of creating of cortisol in response to dexamethasone (Atkinson et al. 2004). The presence of depression worsens other medical illnesses, interfere with the therapy and increases the negative impact on quality of life in patients with higher pain intensity, longer duration of pain, reduced life control, use of passive coping strategies, and intensive behavioral changes. Patients with long-term chronic pain have more suicidal ideas, thoughts and attempts.

Anxiety

Anxiety, like fear and pain, has a warning and adaptive role to some extent, when otherwise useful symptoms start to turn into disorder. As the two bodily alarms, pain and anxiety are strongly linked, so activities that reduce anxiety can dramatically reduce the pain and anxiety in people, and analgesic treatment might reduce the anxiety that has intensified the pain (Symreng & Fishman 2004). Correlation of pain, anxiety and affective quality of pain recognized even Aristotle, who said that the pain was "out of sensations and passions of the soul within." In patients with chronic pain the entire spectrum of anxiety disorders is present. They all have a higher prevalence than in the general population, including generalized anxiety disorder, adjustment disorder with anxiety symptoms, forced-obsessed disorder, agoraphobia, panic disorder, PTSD and other psychological mechanisms connection between anxiety and chronic pain are not fully understood, and there are several different models of causality. The usual components of anxiety in patients with chronic pain are tendency to hypervigilance and catastrophic behaviour, reinforcing the perception of pain in patients. Pain and anxiety strongly influence behavior in pain. There are also a number of hypotheses about the biological mechanisms of this association, which include a variety of ways and neurotransmitters (monoamines, GABA, glutamate, adenosine, cannabinoids, numerous neuropeptides, hormones, neurokinins, cytokines), and there is great overlap between those involved in anxiety and chronic pain. New methods of brain imaging showed a large overlap of activities of certain regions of the brain in anxiety and chronic pain (Symreng & Fishman 2004). In addition to somatosensory and autonomic (neurovegetative) system, the experience of pain includes the structures that determine the emotional and cognitive functions of humans. Traditionally, the perception of pain has been questioned as a sensory-processing area in primary and secondary somatosensory cortex and posterior parietal cortex. The introduction of functional neuroimaging it is clear that there are other CNS structures (prefrontal cortex, anterior insula, premotor area and striatum) activated by painful stimuli. Particularly interesting is the function of intralaminar nuclei, which apart from forwarding nociceptive cortex stimulation to cortex also affect the autonomic functions

and emotion (the projection to the anterior cingulate gyrus and amygdala). In these places are intertwined functions of fear and pain. Chronic stress disorder, which causes increased and prolonged sense of fear, further stimulates structures that characterize the pain affectively, and possibly modifies them structurally. Also, stress and neuroendocrine disorders that accompany them, lead to disorders of memory, probably due to dysfunction of the hippocampus. Long lasting painful conditions lead to particular clinical syndrome that can cause mental disorders. Also, certain mental disorders can have chronic pain as a leading symptom. That is why the last few years there have been numerous studies about the relationship between PTSD (post traumatic stress disorder) and chronic pain. Clinical practice and research suggests that chronic pain and PTSD often appear together, a negative interaction with the course, outcome and treatment of each. Recent studies indicate intense pain as the direct cause of PTSD, and the unbearable pain of a traumatic experience (Otis et al. 2003).

There are more numerous genetic research studies on traumatic experiences and pain (Diatchenko et al. 2005, Nackley et al. 2007, Zubieta et al. 2003). It is believed that chronic stress disorder has a similar form of the occurrence as the acute stressful stimuli, as well as chronic neuropathic pain to peripheral painful stimuli. In both cases, hypersensitivity occurs, changing the perception of the world and causing a reaction also on non-nociceptive stimulus. This causes a possible mutual occurrence of these disorders. Timely identification and therapeutic intervention in these disorders may modify chronic state of disorders and affect the outcome of treatment.

Fibromyalgia

Fibromyalgia syndrome (FM) is one of the most common chronic pain syndromes in a population and a significant public health problem, although often undiagnosed and unsuccessfully treated. Fibromyalgia is a syndrome that causes spontaneous diffuse pain that lasts longer than three months, and spread along spine or in one or more of the four quadrants of the body. The pain may provoke digital palpation in 11 of 18 typical "pain points". It is defined as a painful condition of muscle and fibrous tissue and functional psychosomatic disorder. Sensory perception helps the body in coping with risk, which is particularly clear in the sensation of acute pain. However, the neuronal pathways of pain can become dysfunctional, leading to chronic poor adaptability of diseased conditions, such as FM. Although not the primary cause, psychological and social factors may affect the FM in three ways: they can make an individual more sensitive to FM, may have a role as triggers in the beginning of a FM, and can affect the severity and worsening of the disease. Psychological assessment of patients and characteristics of FM, as well as different therapeutic methods in treatment, is primarily based on an assessment of the main symptoms

such as pain, sleep disorders, anxiety, depression and quality of life. FM is a separate psychiatric disorder and a significant number of patients with FM-om show no clinical psychiatric disorder. The most common psychiatric disorders are depressive disorder and posttraumatic stress disorder and other anxiety disorders, and it is known that they are linked with the intensity and severity of symptoms of FM. Patients with FM commonly suffer from sleep disturbances, particularly with nocturnal myoclonus. A significant number of patients with FM are hypersensitive to external stimulation, and overly anxious to the sensation of pain (generalized hypervigilance). Studies show a large number of patients with FM having a history of emotional and physical abuse, usually by a family member or partner, which leads to the conclusion about the impact of PTSD symptoms on the development of FM, which is confirmed by neuroscience findings on the connection between these two disorders.

Substance abuse

The prevalence of substance abuse in patients with chronic pain is higher than in the general population. A significant number of patients in pain treatment centers have prescribed drugs that may lead to the development of tolerance and addiction, so it is very important to educate patients. There is a need for good psychiatric patient's history in terms of previous experiences of abuse substances, and continuous monitoring of patients. A person who has already once been dependent, e.g. to tranquilizers, has a higher risk to develop dependence on opiates. Increased risk is known also for the patients who were physically or sexually abused in childhood, and patients with certain psychiatric disorders. Key criteria for the disorder dependence on drugs in patients with chronic pain is the loss of control in drug therapy, excessive preoccupation despite adequate analgesia, and the consequences of excessive medication.

However, it is important to stress that it is patients who have a history of addictive behavior having an increased prevalence of chronic pain, which may sometimes, just because of the fear of addiction, be inadequately treated, with the further stigmatization of patients.

Psychosocial aspect of pain in cancer patients

Pain in cancer patients is a complex phenomenon that involves the whole personality, and numerous research and clinical experience suggest that pain is much more intense and more frequent in cancer patients with psychiatric comorbidity. The changing nature of cancer pain requires constant evaluation and frequently changing therapeutic strategies. The interaction of pain with other symptoms in the disease (fatigue, weakness, nausea, vomiting, constipation, decreased cognitive function) increases the negative effect of the pain, and thus creates a vicious circle that is very difficult to treat

successfully. In particular, one discusses the connection between cancer, depression and pain (Worz 2003). Depression is associated with poor control of pain, worse cooperation and reduced desire for long-term therapy. Since the uncontrolled pain is extremely important risk factor for suicide, it is highly important to recognize and promptly treat depressive disorders, which are also one of the biggest determinants of suicidal ideas in cancer patients. Research indicates that the treatment of cancer pain very often does not include these psychological variables, and that insufficient use of psychopharmacological and psychotherapeutic interventions are important reasons of inadequate treatment. Factors that influence the patient to inadequate pain treatment have been: poor knowledge of pain, poor pain control, communication deficits on the pain and fear of dependence on drugs.

Liaison Psychiatrist in patients with chronic pain

Multidisciplinary treatment of patients with chronic pain is unimaginable without a psychiatrist, because that would mean ignoring one dimension of the chronic pain. Liaison psychiatrist has to help other members of the team in understanding the psychological dimensions of pain in each patient, and to educate other health professionals about specific therapeutic interventions that they may implement later on their own. In the assessment of patients it is extremely important to conduct good psychiatric interviews during one or more meetings. The following steps are to create a conceptualization of the case and determine treatment plan. Diaries of pain are important elements of the estimates are, just as self instruments, evaluation of the experience of disease and behaviors associated with pain. It is also important to analyze the response to disease and chronic pain by others, and the impact of chronic pain on work, family and social functioning of patients (Braš et al. 2006). The relationship between patient and therapist that is based on partnership, trust and empathy is extremely important in ensuring safe and effective treatment. In the treatment of pain one tries to use a natural influence on the transmission of pain impulses. A number of drugs is administered to affect the amplification of endogenous inhibition of synaptic transfer of pain information. In analgesia one attempts to use also the possibility of influence to interrupt painful stimuli. However, the analgesia can and must act at the highest level of integration, at the level of the cortex, ie at the level of perception of pain impulses. The most potent and least known place of modulation of pain impulses is certainly brain.

Psychotherapy intervention

Psychological control of pain is defined as the modification of the psychological pain processing, including supraspinal mechanisms that change the excitation / attention, perception / memory and emotion / cognition. The progress of noninvasive brain imaging

technique offers immense possibilities for studying the functional presentation of these systems and the effects of psychotherapy on the same nociceptive and painful experiences. In patients with chronic pain require a careful evaluation of indications for psychotherapeutic intervention.

Psychodynamic approach to patients with chronic pain emphasizes the importance of individual differences in patients on the basis of their development, intrapsychological conflicts, interpersonal differences and inability to adapt to chronic illness. Psychodynamic psychotherapy emphasizes the need to search for unconscious conflict that contributes to and supports the development of psychological disorders therapeutic alliance with the therapist. Cognitive-behavioral therapy (CBT) in treating patients with chronic pain is applied individually and in groups, and there are defined protocols for patients with certain types of chronic pain, or to solve a particular problem. There is an increased use of cognitive, behavioral, and cognitive-behavioral techniques. Psychoeducation is an extremely important part of treating patients with chronic pain, being particularly suitable because it can be implemented at all levels (individual, group / through a multimedia presentation), and by all health professionals. It is a process through which informs the patient about chronic pain, its treatment and prevention of relapse. During psychoeducation patient can gradually take control of the situation, and learns skills to maintain that control. Biofeedback, relaxation techniques and medical hypnosis are very common components in the treatment of patients with chronic pain, share common features, and are often combined. All these techniques emphasize the active involvement of patients in treatment and their personal responsibility in this process.

Psychopharmacotherapy chronic pain

In patients with chronic pain, collaboration psychiatrist will apply psychopharmacological treatment either as adjuvant (additional) analgesic therapy, or as a specific therapy for the treatment of psychiatric comorbidity. Some psychopharmacs have been proved as analgesics, and there is a need for deep knowledge regarding their optimal prescribing, particularly in combination with analgesics, where possible unpleasant interactions can be expected. Compliance to drug therapy (compliance) is an important issue for a large number of patients with chronic pain, particularly the problem of properly taking opioid medications. Medications may have a number of meanings to the patient, and proper understanding of the psychotherapeutic intervention can contribute to better patient compliance. The treatment of psychiatric comorbidity disorders includes indicated drugs, but one must be extra careful of their safety and tolerability. This is especially due to the fact that patients with chronic pain are often elderly, with the already present serious somatic illness, and often take a number other drugs with possible adverse interactions (Braš 2009).

Generally, the drugs used to treat chronic pain are divided into three major groups: non-opioids (such as aspirin and other NSAID's), opiate and other drugs (natural and synthesized) and adjuvant (additional) therapy, which includes antidepressants, anticonvulsants, anxiolytics, corticosteroids, antihistamines, etc.

Antidepressants

The term "adjuvant analgesics," describes those psychotropic drugs whose primary indication is not pain. However, they act as analgesics in certain conditions, in addition to treatment of psychiatric comorbidity. Psychotropic drugs as adjuvant therapy are becoming increasingly important group of drugs, useful in the possible reduction in dose of opioids and other analgesics, but also because of their proven efficacy in certain painful entities, particularly in neuropathic pain and fibromyalgia. Neurobiology of pain suggests the potential efficacy of antidepressants in the treatment of chronic pain. Analgesic effect of antidepressants is due to blockade of reuptake of serotonin and norepinephrine, thus increasing their level, thereby enhancing the activation of descending inhibitory neurons. Today, many other mechanisms that generate antinociceptive effect are known (Leo & Barkin 2003). In addition to effects on the pain paths, comorbid psychiatric disorders may worsen the perception of pain, interfere with the ways of coping and cause additional morbidity. This is why antidepressants reduce pain being a symptom of PTSD or depression, as well as reduce depression if it is caused by pain. Antidepressants reduce other symptoms associated with chronic pain (appetite, sleep, etc), which significantly contribute to overall distress, psychological morbidity and physical disability (Braš 2009). Tricyclic antidepressants (TCA) are often used for neuropathic pain but have many side effects such as sedation, constipation, dry mouth, urinary retention, postural hypotension, tachycardia, cardiovascular side effects, etc. Analgesic effect of TCA is independent of the presence of depression, it occurs at lower doses, with the earlier onset of action. Although selective serotonin reuptake inhibitors (SSRIs) are generally better tolerated and safer than TCAs, they are not as effective in eliminating chronic pain as a TCA, and their use makes sense only if the pain is a symptom of the disorder. It is necessary to pay attention to possible interactions with SSRIs and MAO inhibitors, tramadol, or triptan in order not to develop a central serotonin syndrome. Chronic pain syndromes accompanied by depression are much more effectively cured with antidepressants with a dual effect on noradrenergic and serotonergic receptors. This has an explanation in the pathophysiology of pain, as these transmitters are important both in the pathogenesis of depression and in the pain perception, due to the descending control of pain. Thus, for example, venlafaxin is promising for patients with pain and depression, or PTSD, and has led to a significant reduction of pain in patients with diabetic

polyneuropathy and migraines. Duloxetine, which is a dual antidepressant well balanced in all doses, is effective in relieving chronic pain, in same doses as in the treatment of depression. Mirtazapine (NASS) has shown efficacy in the treatment of phantom pain and sleep disorders. As a potential antagonist of 5-HT₂ and 5-HT₃ serotonin receptors it has a potential as adjuvant analgesic and antiemetic, while as the H₁-receptor blocker it acts sedative and stimulates appetite. Efficacy of Mirtazapine in tension chronic headaches, as well as in fibromyalgia, has been demonstrated. Bupropion (dopamine reuptake inhibitor and NA) has a good analgesic potential of a unique profile of possible side effects, and is proved to be effective in reducing fatigue in cancer patients. Modulators of serotonin (trazodone, nefazodone) are useful in treating insomnia with a pronounced analgesic effect (7.15). It is also very interesting to assess the effects of tramadol analgesics. In addition to opioid effect it has effects on noradrenergic and serotonin receptors, and there are studies on its possible antidepressant effect, with certain similarities to venlafaxine.

Anticonvulsants

Some anticonvulsants also have analgesic effects for certain categories of neuropathic pain, and are useful in treating some psychiatric disorders. Today, in the treatment of chronic pain the focus is on so-called „rational polypharmacy“. Integrated psychiatric treatment, in other words pharmacotherapy with psychotherapeutic interventions, faster and better recovery is achieved, there is a lower rate of deterioration, and the cost of treatment is reduced. In the modern world there is a common practice assessment and treatment of anesthesiologist and psychiatrist ("joint clinic"). This represents the acceptance of the unity of body and soul, and natural acceptance of the nature of pain and his physical and psychological components.

CONCLUSION

In the treatment of patients with chronic pain psychological / psychiatric aspects have an important place in all phases of treatment, with an important role in research and education. The best approach in treating patients with chronic pain is certainly the multidisciplinary, with a detailed, joint assessment of the patient, the formulation of the case and determining the therapeutic plan. Quality of interactions between health professionals and patients, and education of professionals about biopsychosocial approach, communication skills, psychological interventions and

continuing care should be present in all the clinics for the treatment of pain.

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