Somatoform pain disorder

Kubat, David

Master's thesis / Diplomski rad

2019

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: **University of Zagreb, School of Medicine / Sveučilište u Zagrebu, Medicinski fakultet**

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:936567

UNIVERSITY OF ZAGREB

SCHOOL OF MEDICINE

David Kubat

Somatoform pain disorder

GRADUATE THESIS

Zagreb, 2019.

This graduate thesis was made at University Department for Psychological Medicine, Clinical Hospital Centre Zagreb, and mentored by Prof. Marijana Braš, MD, PhD.

LIST OF ABBREVIATIONS

CBT- Cognitive behavior therapy

COX – Cyclooxygenase

DSM - Diagnostic and Statistical Manual of Mental Disorders

GAD - General anxiety disorder

IASP - The International Association for the study of pain

ICD - International statistical classification of diseases and related health problems

NRS - Numerical rating scales

NSAID - Non–steroidal anti–inflammatory drugs

SNRI - Serotonin and norepinephrine reuptake inhibitors

SP - Somatoform pain

SSRI - Serotonin selective reuptake inhibitors

TCA - Tricyclic antidepressants

VAS - Visual analog scales

VRS - Verbal categorical rating scales

CONTENTS

SUMMARY

Somatoform disorder is characterized by the presence of physical symptoms that would suggest a general medical condition but diagnostic procedures fail to show a general medical condition or the physical symptoms can only partly be explained by a general medical condition. In somatoform pain disorder pain is the predominant symptom. Somatoform disorder is a very common reason for visiting physicians and among the somatoform disorders somatoform pain disorder is most prevalent. Somatoform disorder has a prevalence with up to 35 % among primary physicians.[38] It is estimated to have a prevalence of 5-7% among the general population.[41] Many patients with somatoform disorders have a comorbidity with psychiatric disorders such as anxiety and depression; moreover, it has been shown that suicidal thoughts are increased in patients with somatoform pain disorders and because of this it is important to evaluate the patient's mental status.[36] The reason for one having somatoform pain disorder is today unknown, however there are a few theories, one of them is developmental theory, which is explained more in detailed. When facing a patient with pain, it is important to take into consideration something which is called total pain and not just the physical aspect of pain. The elements in total pain include physical, psychological, social, and spiritual pain.[10] The combination of these elements is believed to result in a ''total pain'' experience that is individualized and specific to each patient´s particular situation.[11]

SAŽETAK

Somatoformni poremećaj je karakteriziran prisutstvom fizičkih simptoma koji upućuju na somatsko medicinsko stanje, ali dijagnostički postupci ne uspijevaju dokazati neku tjelesnu bolest ili fizički simptomi mogu tek djelomično biti objašnjeni nekim somatskim medicinskim stanjem. U somatoformnom bolnom poremećaju,, bol je dominantan simptom. Somatoformni poremećaj je vrlo čest razlog za posjet liječnik, a somatoformni bolni poremećaj je najčešći među somatoformnim poremećajima. Somatoformni poremećaj ima učestalost od 35% među liječnicima u primarnoj zdravstvenoj zaštiti. [38] Procjenjeno je kako je učestalost u općoj populaciji od 5-7%.[41] Mnogi pacijenti sa somatoformnim poremećajem imaju komorbiditetne psihijatrijske poremećaje kao što su anksioznii depresivni poremećaji, a pokazalo se kako su kod pacijenata sa somatoformnim bolnim poremećajem istaknutije suicidalne misli te je zbog toga jako važno procjeniti njihov psihički status.[36] Uzrok nastanka somatoformnog bolnog poremećaja je do danas nepoznat, no postoji nekoliko teorija. Jedna od njih je razvojna teorija koja je detaljnije objašnjena. Kada se obrađuje pacijent s boli, važno je uzeti u obzir koncept "totalne boli", a ne samo fizičke aspekte boli. Dijelove totalne boli čine fizička, psihološka, socijalna te duhovna bol.[10] Upravo kombinacija ovih dijelova rezultira "totalnom boli", iskustvom koje je induvidualizirano te specifično za svakog pacijenta.[11]

PAIN

1.1. Definition and basic aspects

Chronic Pain is one of the most common reason for medical health care visits and affect 20% of people worldwide.[1] Although pain itself and many diseases associated with chronic pain is not life threatening, it is one of the leading cause of human suffering and disabilities.

Global burden of disease study in 2013 evaluated years lived with disability in 188 countries and found that the highest cause of years with disability was chronic back pain. Other painful conditions such as chronic neck pain were also among the most frequent causes of disability seen.[2]

According to The International Association for the Study of Pain (IASP), pain is described as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[3] Pain is subjective because it is one's own experience that determine when one has pain. We associate pain as tissue damage or potential tissue damage. It is associated with negative emotions; nobody like to feel pain. Some people experience pain without having any underlying tissue damage or other pathology. It is important to remember that activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain; pain is always a psychological state and not just a noxious stimulus.[2] Thus, it can be said that pain has several dimensions, not just tissue injury.

Indeed, chronic pain is a complex sensory and emotional experience that varies widely between people depending on the context and meaning of the pain and the psychological state of the person.[4] It is in several studies proven that cognitive and emotional factors have a significant role on one´s perception of noxious stimuli.[5] There has been imaging studies that showed that the afferent and descending pain pathway is altered by many factors unrelated to the pain stimulus itself, such as positive emotions, negative emotions and attentional state.[5]

So what is pain; is it and symptom of a disease, a syndrome or a disease by its own? This question is extensively debated in the scientific community.[6] The European Federation of IASP presented that chronic and recurrent pain is a specific health care problem, a disease in its own right.[6]

However, when looking at the classification system according to ICD-10; pain is classified based on pathophysiological mechanisms.[7] ICD-10 refers to pain attributable exclusively to an underlying pathophysiological mechanism[7] and therefore can be seen described as a symptom of another disease. The only exception here is somatoform pain disorder which can have an absence of a clear (pathophysiological) etiology. Therefore, when there is absence of clear etiology and when biological, psychological, and social factors seem to be contributing to a chronic pain presentation, ICD-10 offers the option of somatoform pain disorder.[7]

An argument to classify pain as a disease is considering the enormous global burden of this condition.

Finally, to recognize pain as a definite pathologic state would raise awareness about this neglected global health problem and promote research about new specific treatments.[7]

1.2. Nociceptive and neuropathic pain

Nociceptive pain is usually an acute type of pain and is pain generated from actual or potentially tissue-damaging injury that is transduced and transmitted via nociceptors.[8]

Nociceptors can respond to different stimuli such as chemical, mechanical or thermal and are fast or slow conducting depending on if they are myelinated or not. The A delta nociceptors are myelinated nociceptors that are large, fast-conducting fibers to thermal or high threshold mechanoreceptors. The A delta fibers are responsible for the spinal reflex withdrawal of the affected body part before the sensation of pain is felt. They are also the first in immediate sharp pain.

The other type of nociceptors are C fibers. They are smaller, unmyelinated and are located in muscle tendons, skin and body organs. They transmit dull, aching or burning sensations that are usually poorly localized and lasting longer. They can respond to mechanical, thermal and chemical stimuli.[9]

Perception is a process involved in nociception and is important for somatoform pain because in somatoform pain, the pain is perceived and felt although there might be no noxious stimuli which would cause the pain. Perception refers to interpretation of the afferent stimuli in the brain which gives rise to individual´s specific sensory experience. Perception is the conscious awareness of the pain and may be influenced by several factors such as genetics, cultural preferences, gender roles, life experience, past pain experiences, and level of health.[9]

Neuropathic pain is another type of pain defined by IASP as pain caused by a lesion or disease of the somatosensory nervous system.[3] This leads to long-term changes in pain pathway structures and abnormal processing of sensory information. Because of this abnormal processing of sensory information one can feel pain without inflammation or injury. This can lead to shooting, shock-like, burning or tingling and often felt below the level of injury, most often in legs, thighs and toes.[3] Neuropathic pain can be classified as either central or peripheral pain depending on if peripheral or central nervous system is affected.

1.3. Total pain

The concept of total pain is that each person is experiencing pain differently and on different levels. The elements in total pain include physical, psychological, social, and spiritual pain[11] which can be seen in Figure 1. The combination of these elements is believed to result in a total pain experience that is individualized and specific to each patient´s particular situation.[11]

As stated earlier, IASP states that pain is a subjective and an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Hence, pain is a subjective experience that oneself determine as painful. This is consistent with the central idea of total pain being individual and defined by physical, psychological, social, and spiritual aspects.

The understanding of pain necessarily includes an assessment of all the factors that contribute to the patient´s pain experience and not solely the underlying physical trigger.[11]

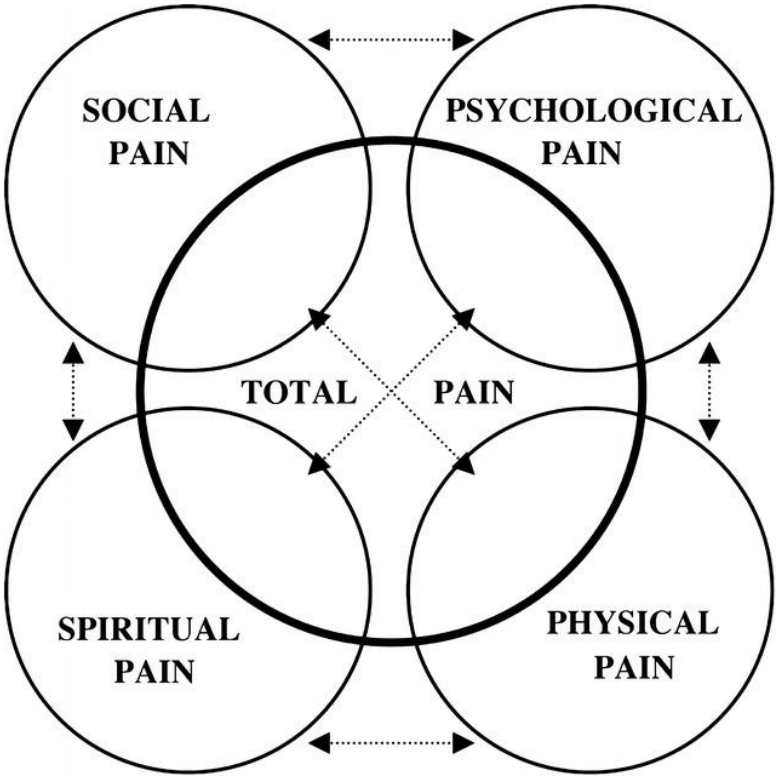

Figure 1. Elements of total pain.

Note: Adapted from Relieving total pain in an adolescent: a case report by Phenwan T, 2018. BMC Res Notes volume 11. Issue 265.[10]

1.4. Pain assessment

According to Breivik pain can be easy and straightforward when dealing with acute pain and pain as a symptom of trauma or disease. Chronic pain on the other hand is more difficult to assess.[12] One reason for this is the personal, private and subjective experience of chronic pain. What makes it harder to assess is also that patients with similar pathology may describe different types of pain or may have no pain at all. However, this determination is very important because of different treatment for different types of pain.

Meaningful assessment of chronic pain is crucial because chronic pain has a major impact on physical, emotional, cognitive function, on social and family life, and on the ability to work and secure an income.[13] Research has shown that one of the main barriers to optimal pain management is inadequate assessment. For example, some health care personnel rely on their own observations rather than directly ask patients to describe their pain. This approach does

not allow the health care personnel to adequately assess a patient´s total pain because there is no consideration of the patient´s perspective or spiritual, psychological, and social aspects.[11,14]

Pain assessment provides information regarding the severity of the condition. In addition to its diagnostic value, this information is critical for guiding treatment decisions. Repeated pain assessment should inform pain treatment in much the same way as repeated blood pressure measurement informs treatment for hypertension. Finally, pain assessment can yield clues regarding the pathophysiological mechanisms underlying the pain condition, which again can help guide treatment selection.[12]

In assessing pain, self-report is the gold standard because of pain being internal and private experience. There are several approaches for assessing pain intensity, such as verbal categorical rating scales (VRS) (e.g., Mild, Moderate, Severe), numerical rating scales (NRS) and visual analog scales (VAS) [12] seen and compared in figure 2.

NRS is the most commonly used method in clinical settings due to its ease of administration and scoring. However, in children with limited verbal abilities it might be easier use faces pain scale, which presents a series of pictures of facial expression changing with different levels of pain experience.

In NRS 0 represents “No Pain” and 10(0) represents “the Worst Possible Pain.”

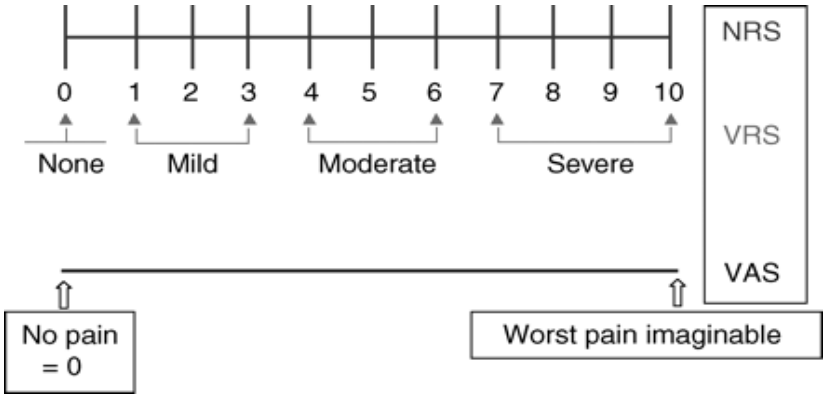

Figure 2. Correlation of NRS, VRS and VAS. Note: Adapted from assessment of pain, Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Hals EK, Kvarstein G, Stubhaug A (2008) BJA Volume 101, Issue 1. Pages 17–24.[12]

It is also very important to ask patients about temporal characteristics of their pain. This includes duration and chronicity of the pain and the temporal pattern of the pain (e.g. episodic, chronic-recurrent, constant).[12] An important issue that impacts temporal variations in pain is factors that exacerbate or ameliorate pain. These factors should be assessed as they impact interpretation of temporal changes in pain and can have diagnostic and treatment implications.

The location of pain can have obvious diagnostic implications since current diagnostic systems categorize pain conditions primarily by body site or organ system. The location and bodily extent of pain therefore also have important diagnostic and treatment implications.

1.5. Pain management

Pharmacological treatment of chronic pain should be based on analgesic ladder made from WHO; originally for managing cancer pain.[15]

This ladder is shown below in figure 3.

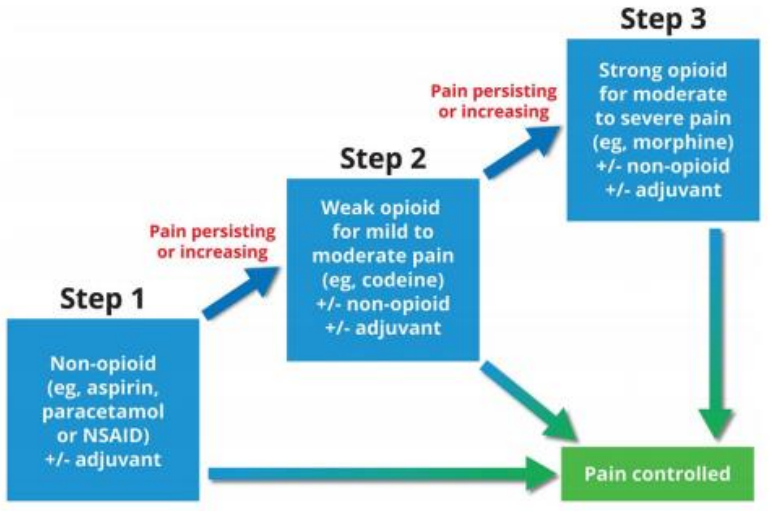

Figure 3. Analgesic ladder.

Note: Adapted from WHO guidelines for the use of analgesics in cancer pain by Ventafridda V, Saita L, Ripamonti C, De Conno F, Int J Tissue React. Volume 7. Issue 1. Pages 93–96[15]

According to this model, medications should be given orally with increasing dose and potency for managing pain relief. This model gives pain relief in up to 70- 90 % of cancer patients[16] while it provides relief in approximately 30% of patient with chronic pain without malignant disease because of side effect which limit the maximal dosage.[17] The first step of pharmacological ladder is non-opioid analgesics such as paracetamol and NSAID. NSAID act to reduce inflammation and pain by inhibition of cyclooxygenase (COX) enzymes COX-1 and COX-2. COX 1 and 2 catalyze the production two types of eicosanoids: prostaglandins and thromboxanes which have critical functions in inflammation.

The second step of the letter is to add weak opioids such as codeine and dihydrocodeine. They act on opioid receptors in CNS to attenuate the transmission of nociceptive signals.[18] Opioids mimic the effects of the body´s natural pain reducing chemicals; endorphins. Long term use has been shown to increase the risk of cardiovascular events in elderly[19] and should be used with caution.

The third step is to add strong opioids such as morphine. They are more potent in reducing pain; however, they also carry more severe side effects and as an example, respiratory depression occurs at therapeutic doses and can be fatal. Therefore, opioids must be used with caution in patients with diminished respiratory function. Oher side effects associated with chronic opioid use are nausea, constipation, cognitive impairment, sedation, and various hormonal problems.[17] Finally, the physician must be aware of that patients can develop tolerance which means that patients need to adjust and increase dosages over time in order to feel the same effect as before.[20]

Adjuvants in pain management are medicines with other pharmacological benefits than pain. This term is different than adjuvant analgesics which are drugs that has pharmacological benefits of relieving pain in certain situations. Adjuvants in the WHO ladder are for example anxiolytics, which reduce pain related anxiety; hypnotics, which help patient with pain-induced insomnia and muscle relaxants, which relieve painful spasms.[18] Adjuvants may be added at any stage of the latter depending on the individual needs.

Adjuvants analgesics on the other hand are for example TCA, SNRA which are originally anti-depressive drugs but were found to work well in neuropathic pain where opioids are often ineffective.[18] These drugs were found to have analgesic effect unrelated to their anti-depressive effect. Therefore, anti-depressants such as SNRA are often prescribed to help not only comorbid depression in chronic pain patients but also for pain relief.[18] Antiepileptic drugs such as Gabapentin and pregabalin are often used in conditions such as fibromyalgia

and neuropathic pain. Carbamazepine is effective for trigeminal neuralgia, but not other pain-conditions.[21]

Except for WHO analgesic ladder we have other treatments for pain such as interventional pain management. This involves invasive procedures such as nerve block injections, denervation surgery, implantable drug delivery systems, and nerve stimulators. They are often risky and expensive and are therefore spared until cases that do not get better with pharmacological treatment.[18]

Finally, chronic pain is as much a psychosocial problem as it is a physiological one: anxiety, depression, stress, anger, insomnia, suicide, loss of financial independence, disability, and family instability are closely associated with long term pain.[18] Pain should therefore be addressed from a multidisciplinary aspect. Multidisciplinary pain treatment is based on that pain is a combination from a physical event, recognition and appraisal of this event, affective responses to this event and environmental influences around the person with the physical event. Multidisciplinary treatment is aimed at all of these aspect at the same time.[18] Two different kind of psychological approaches often used in multidisciplinary pain programmes are cognitive–behavioral therapy and acceptance and commitment therapy.

SOMATOFORM PAIN DISORDER

2.1. Definition

The main feature of somatoform pain disorder according to the classification system ICD-10 is that there is presence of physical symptoms that would suggest a general medical condition, however there is not a general medical condition behind the complains or the physical symptoms can only partly be explained by a general medical condition.

There must not be any other mental illness that can explain the pain. In contrast to factitious disorders and malingering the patient's symptoms are real. In somatoform pain disorder, the patient is not faking the pain but is feeling real pain.

According to ICD-10, in order to diagnose one with somatoform pain disorder one must have persistent, severe, and distressing pain, which cannot be fully explained by a physiological process or a physical disorder, and which occurs in association with emotional conflict or psychosocial problems that are sufficient to allow the conclusion that they are the main causative influences. The result is usually a marked increase in support and attention, either personal or medical.[22]

2.2. Difference between DSM-5 and ICD-10 classification

ICD-10 classification of somatoform pain disorder differs a bit from the American classification DSM-5, which is included under the category called somatic symptom disorder. In this American classification, the person does not require the absence of a justified medical cause or that the symptoms are not produced intentionally. This diagnosis is made when one or more disturbing somatic symptoms are presented that alter the person's daily life. The symptoms must be accompanied by thoughts, feelings or excessive behaviors related to the symptoms that persist for more than 6 months.[23]

According to the authors of DSM-5, the previous DSM-4 criteria (which is similar to ICD 10) had overemphasized the centrality of medically unexplained symptoms. Determining that a somatic symptom is medically unexplained may not be reliable, and it may be seen as inappropriate to give an individual a mental disorder diagnosis solely because a medical cause cannot be found. Furthermore, affected patients may regard such a diagnosis that implies their physical symptoms are not 'real' as insulting.[24]

2.3. Neurobiology of somatoform pain disorder

The etiology of somatoform pain disorder is unknown, however recently the developmental theory, which is based on neurobiology has been proposed. The idea behind the developmental theory is that suboptimal early interpersonal experiences with the caregivers leads to disrupted maturation of neural circuits involved in interpersonal functioning and affect regulation by interacting with one's genetic predisposition. This finally leads to tendencies to experience distress somatically.[25]

Recent research has showed that there are common neurological substrates between interpersonal distress and attachment with somatic pain.[26] Because of this, adverse early experience that interplay with a genetic predisposition may influence the development of somatoform pain disorder due to this shared network. Altered neural dynamics of somatic distress, interpersonal distress and affect regulation increase the susceptibility of somatoform pain in adulthood.[25]

In prenatal and early postnatal life, the infant experience distress and excitement primarily somatically as higher-order affect regulation and cognition is not developed. The distress of the infant is primarily controlled by interpersonal interaction at this stage of development. These early interactions lay the foundation how the infant will regulate its distress in the future. Moreover, the infant may continue to experience and express his or her emotional

distress somatically if his or her needs are unmet, excessively stimulated, if caretaker did not learn infant how to regulate his or her affect or if constitutional predispositions interfere with the learning of self-regulatory strategies.[25] The developmental theory is summarized below in Figure 4.

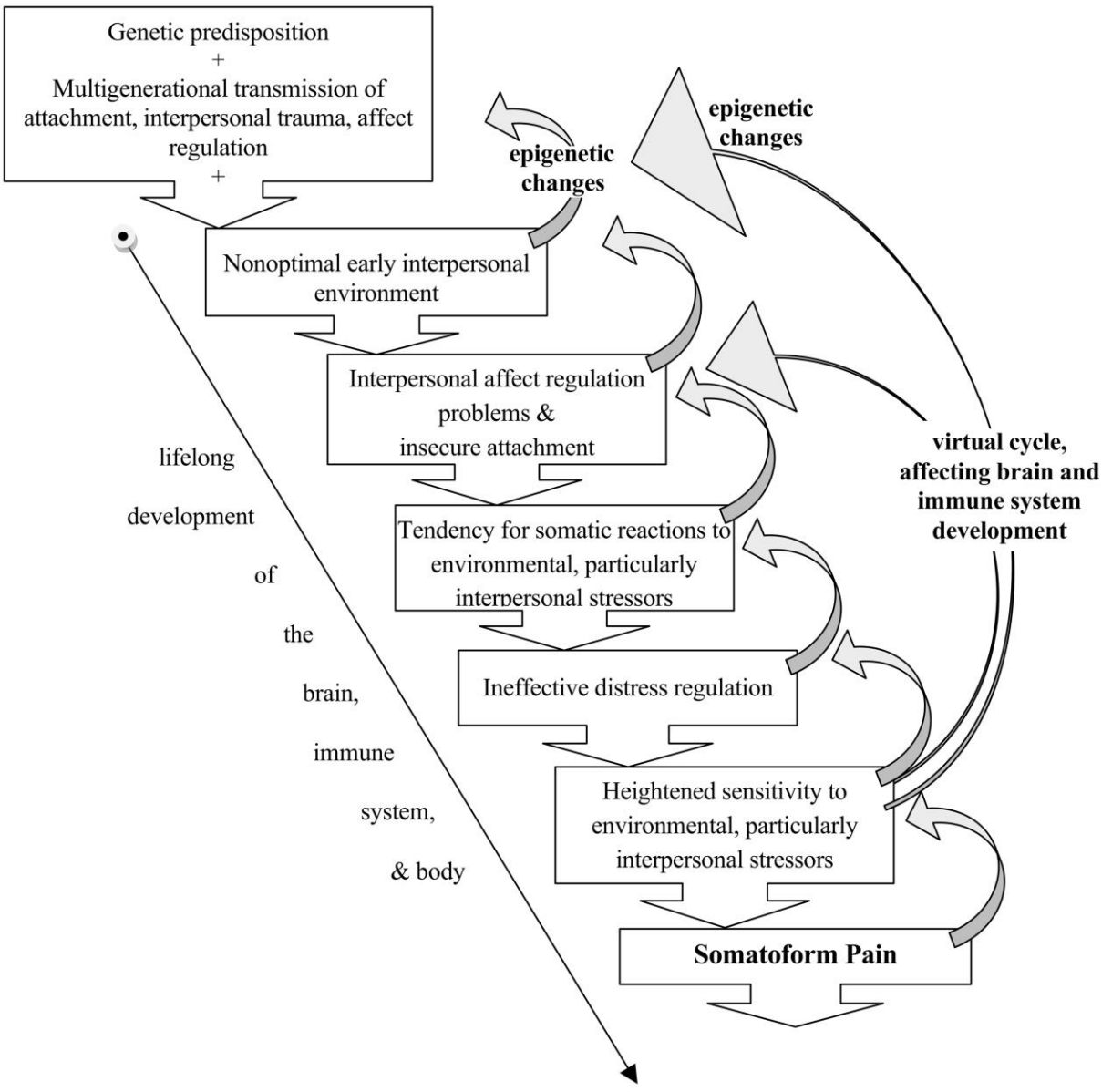

Figure 4. Developmental theory of somatoform pain.

Note: Adapted from Somatoform Pain: A developmental theory and translational research review by Landa A. Bradley S. Peterson and Brian A. Fallon, 2012 Psychosom Med. Volume 74. Issue 7. Pages 717–727.[25]

Especially important for the developmental theory is animal studies. There are animal models that show shared neural pathways between social distress and somatic pain. There was, for example a study where rats, dog pups and nonhuman primates where given opioids which decreased their separation cries. This shows that opioids played a role in both analgesia but also the reaction to social separation.[27,28, 29]

Oxytocin was also showed to affect both nociception and affiliative behaviors and infant-caregiver attachment.[30] It was also showed that the anterior cingulate cortex, which is involved in processing somatic pain is also involved in animals to produce separation vocalizations and maintenance of affiliate behaviors.[31,32]

Thus, animal studies help to support the developmental theory; that somatic pain and early attachment share neural systems and that development of these systems are compromised by non-optimal maternal-infant regulation.

It is however important to realize that this is a theory and not confirmed pathophysiology of somatoform pain and this theory might be applicable to only a subgroup of patients with somatoform pain disorder and further studies should be done to address the variability of the pathogenesis of somatoform pain disorder.

2.4. Epidemiology

In a meta-analysis on prevalence of somatoform disorders involving more than 2000 patients it was shown that point prevalence in primary care setting were 34.8%. This was established using ICD-10 criteria.[33] Among the most frequent specialties taking care of chronic somatoform patients were family practitioners (41%) followed by anesthesiologists (28%).[34]

There was also shown to be a link between sociodemographic parameters and somatoform pain. People with increased age more often reported somatoform pain. In general women were more frequent to report somatoform pain than male. Finally, lower degree education and lower household income was associated with somatoform pain.[34]

2.5. Associated conditions

It has been shown that people with somatoform disorders more frequently have depression and anxiety disorders than people without somatoform disorers.[35] It has also been shown that suicidal thoughts are increased in patients with somatoform pain disorder. In a research made

by Wiborg JF investigating the suicidal thoughts in primary health care it was shown that 37 % of all patients with somatoform pain disorder had thoughts on suicide.[36] It is thought that dysfunctional cognitive processes that are associated with the specific symptoms of patients can activate suicidal ideation, depending on the general level of stress and dispositional vulnerability of patients.[37] The research made by Wiborg JF also showed that dysfunctional illness perceptions were significantly related to active suicidal ideation independent of psychiatric comorbidity and previous suicidal behavior.[36]

There are numerous studies that show that patients with chronic pain have alterations in brain regions involved in cognitive and emotional modulation of pain and this complex interplay may explain the reason why people with long term chronic pain have increased risk to develop depression and anxiety but also why patients with cognitive distortion and psychological distress are at increased risk for developing chronic pain and central amplification of pain.[38]

2.6. Costs

In a study made in Germany, looking at the costs of somatoform pain disorder they found that in 2009, the average direct and indirect treatment costs per patient with somatoform pain disorder were 5500 €.[34] This cost was this high because of all the procedures carried out. Out of all patients with somatoform pain disorder 54 % of patients underwent x-ray examination, 25 % magnetic resonance imaging and 11 % computed tomography. In many cases these procedures were probably unnecessary because of the underlying somatoform cause of the problem. Moreover, in this study 38 % were prescribed opioids, 12 % underwent spinal nerve anesthesia for their pain; procedures probably overtreated.[34] The main challenge is to diagnose a patient with real complains of pain with somatoform pain disorder and still make the patient feel satisfied without doing excess procedures. The physician might not think that the diagnostics are necessary but do it anyways to calm the patient and make the patient feel that the doctor is taking his or her complains seriously. In other cases, physicians order the procedures in order to exclude other diseases.

If one compares the average costs of a patient that has physical complains without an adequate organic explanation with another patient where there is an adequate explanation for the physical complains, it has been shown that on average six times more money was spent on the patient without an adequate organic explanation. When we consider ambulatory care, the ratio was even higher; up to 14 times more money spent.[39]

2.7. Treatment

There are scarce studies done on psychopharmacological or psychological treatment of somatoform disorders. This might be because of the fact that patients with these conditions do not accept any other treatment than 'somatic' treatments. In fact, it may be difficult to convince them that they should be treated by a psychologist or psychiatrist. Because of this it might be hard to conduct a clinical trial within psychiatry, simply because there are not enough persons to recruit. Moreover, many affected patients have a tendency to dismiss any treatment as ineffective or even develop new symptoms after initiation of treatment.[24] Finally, pharmaceutical companies might not be interested in bringing a drug into market for somatoform disorder when it is not guaranteed that "sufficient" number of patients will take the drug and this is the reason why the number of randomized controlled studies investigating psychological and medications treatments for somatoform disorders is low, although these disorders are common and associated with considerable costs for the health care system.[24]

Treatment options include medications, particularly TCAs and SSRIs, and psychotherapy. Non-pharmacologic treatment strategies (e.g., massage, acupuncture) may also be beneficial.[40]

Among psychotherapies, CBT has the best evidence.[24] Among antidepressants SSRI antidepressants such as escitalopram, fluoxetine, and fluvoxamine have been shown to be effective in placebo-controlled trials, whereas the SNRI venlafaxine was not superior to placebo. The tricyclic anxiolytic opipramol and the neuroleptic drug levosulpiride were effective in placebo-controlled studies however, these drugs are not available in many countries.[24]

CBT is especially good method of choice in cases of both anxiety disorders and pain disorder because it has been shown to be effective in both diseases. Therefore, CBT for patients with GAD and clinically significant pain syndromes should incorporate therapy elements for both conditions.[24]

CONCLUSION

Pain is an enormous global burden that affect 20% of people worldwide and is one of the leading cause of human suffering and disabilities. Somatoform pain disorder is frequently encountered in primary physician's office and deserves more attention than received today. More research should be done in order to find definite pathophysiological processes of this disorder and to find out which treatments are best suitable for this disorder. The diagnosis and treatment of somatoform pain disorder is especially challenging because of the lack of an adequate explanation for the pain and the fact that the physician is searching for a medical condition underlying the cause of pain. Patients with somatoform pain disorder usually have psychosocial problems or emotional conflicts which are said to be the main causative influences of this disorder and the physician must always have in mind that the patient have an increased risk of other psychiatric comorbidities such as depression and anxiety.

BIOGRAPHY

I was born in Lund (Sweden) February 6th 1992. My parents came to Sweden just a few months earlier from Vojvodina; Serbia. My family speaks Hungarian at home as our origin is Hungarian. In 1994 my family moved to Stockholm and I lived my entire life here until I started medical school and moved to Zagreb six years ago. I went to primary school in Skarpnäck school until second grade and Kumla school from second grade to ninth grade. After primary school I went to IEGS; an English speaking high school in Stockholm. After high school graduation I worked two years for Attendo care taking care of elderly people and finally I enrolled to the medical program in Zagreb.

ACKNOWLEDGEMENT

Foremost I would like to express my gratitude to my mentor prof. dr. sc Marijana Braš for her support and help, as well as her personal experience and expertise during my graduate thesis writing.

Also I would like to thank the rest of my graduate committee: Prof. Veljko Đorđević , MD, PhD and prof. Dražen Begić, MD, PhD.

I would also like to express my very profound gratitude to my family and friends for providing me with support and continuous encouragement throughout the years of medical studies. This accomplishment would not have been possible without them.

REFERENCES

1. Goldberg DS, McGee. SJ (2011) Pain as a global health priority. BMC Public Health. Volume 11. Issue 770.

2. Global Burden of Disease Study 2013 collaborators. (2013) Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. Volume 386. Pages 743-800

3. Merskey H. and Bogduk N (1994) Classification of Chronic Pain. 2nd Edition. Merskey. H, Bogduk. N. IASP Task Force on Taxonomy. Seattle. IASP Press.

4. Bushnell MC, Čeko M, Low LA (2013) Cognitive and Emotional Control of Pain and Its Disruption in Chronic Pain. Nature Reviews Neuroscience. Volume 14. Issue 7. Pages 502-511.

5. Crofford LJ (2015) Psychological Aspects of Chronic Musculoskeletal Pain, Best Pract Res Clin Rheumatol. Volume 29. Issue 1. Pages 147–155.

6. Raffaeli W, Arnaudo E (2017) Pain as a disease: an overview. J Pain Res. Published online. https://www.ncbi.nlm.nih.gov/pubmed/28860855

7. Nicholas M, Vlaeyen JWS, Rief W, Barke A, Aziz Q, Benoliel R, Cohen M, Evers S, Giamberardino MA, Goebel A, Korwisi B, Perrot S, Svensson P, Wang SJ, Treede RD (2019) The IASP classification of chronic pain for ICD-11: chronic primary pain. Pain. Volume 160. Issue 1. Pages 28-37.

8. Dubin AE, Patapoutian A (2010) Nociceptors: the sensors of the pain pathway. J Clin Invest. Volume 120. Issue 11. Pages 3760–3772.

9. Ellison DL (2017) Physiology of Pain. Critical Care Nursing Clinics of North America Volume 29. Issue 4. Pages 397-406.

10. Phenwan. T (2018) Relieving total pain in an adolescent: a case report. BMC Res Notes. volume 11. Issue 265.

11. Mehta A, Chan SL (2008) Understanding of the Concept of ‘‘Total Pain’’ A Prerequisite for Pain Control. Journal of hospice and palliative nursing. Volume 10. Issue 1. Pages 26-32.

12. Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Hals EK, Kvarstein G, Stubhaug A (2008) Assessment of pain. BJA Volume 101. Issue 1. Pages 17–24.

13. Breivik H, Collett. B, Ventafridda. V, Cohen R, Gallacher D (2006) Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain. Volume 10. Issue 4. Pages 287-333.

14. Gunnarsdottir S, Donovan HS, Ward S (2003) Interventions to overcome clinician- and patient-related barriers to pain management. Nurs Clin North Am. Volume 38. Issue 3. Pages 419-434

15. Ventafridda V, Saita L, Ripamonti C, De Conno F, (1985) WHO guidelines for the use of analgesics in cancer pain. Int J Tissue React. Volume 7. Issue 1. Pages 93–96

16. World health organization (1996) Cancer relief with a guide to opioid availability. 2nd edition. Geneva, Switzerland. World health organization

17. Moore RA, McQuay HJ (2004) Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain. Volume 112. Issue 1. Pages 372–380

18. Hylands-White N, Duarte RV, Raphael JH (2017)
An overview of treatment approaches for chronic pain management. Rheumatol Int. Volume 37. Issue 1. Pages 29-42

19. Solomon DH, Rassen JA, Glynn RJ, Garneau K, Levin R, Lee J, Schneeweiss S (2010) The comparative safety of opioids for nonmalignant pain in older adults. Arch Intern Med. volume 170. Pages 1979– 1986

20. Christie MJ (2008) Cellular neuroadaptations to chronic opioids: tolerance, withdrawal and addiction. Br J Pharmacol. Volume 154. Pages 384–396

21. Rang H, Dale M, Ritter J, Flower R, Henderson G (2012) Rang & Dale’s Pharmacology, 7th edn. Elsevier, London.

22. World Health Organization. (2016). ICD-10 : international statistical classification of diseases and related health problems : tenth revision, 2016. World Health Organization.

23. Beneitez I, Nieto R (2017) Do we understand pain from a biopsychosocial perspective? A review and discussion of the usefulness of some pain terms. Volume 7. Issue 1. Pages 41-48

24. Bandelow B. (2015) Generalized Anxiety Disorder and Pain. Mod Trends Pharmacopsychiatry. Volume 30. Pages 153-165

25. Landa A, Peterson BS, Fallon BA (2012) Somatoform Pain: A developmental theory and translational research review. Psychosom Med. Volume 74. Issue 7. Pages 717–72.

26. Eisenberger NI, Lieberman MD (2004) Why rejection hurts: A common neural alarm system for physical and social pain. Trends in Cognitive Sciences. Volume 8. Issue 7. Pages 294–300.

27. Panksepp J, Herman B, Conner R, Bishop P, Scott JP. (1978) The biology of social attachments: opiates alleviate separation distress. Biological Psychiatry. Volume 1. Issue 5. Pages 607-618

28. Kehoe P, Blass EM (1986) Opioid-mediation of separation distress in 10-day-old rats: reversal of stress with maternal stimuli. Developmental Psychobiology. Volume 19. Issue 4. Pages 385–98.

29. Kalin NH, Shelton SE, Lynn DE (1995) Opiate systems in mother and infant primates coordinate intimate contact during reunion. Psychoneuroendocrinology. Volume 20. Issue 7. Pages 735–742

30. MacDonald G, Leary MR. (2005) Why Does Social Exclusion Hurt? The Relationship Between Social and Physical Pain. Psychological Bulletin. Volume 131. Issue 2. Pages 202–223.

31. Eisenberger NI, Lieberman MD. Why rejection hurts: (2004) A common neural alarm system for physical and social pain. Trends in Cognitive Sciences. Volume 8. Issue 7. Pages 294–300

32. Eisenberger NI (2006). Identifying the Neural Correlates Underlying Social Pain: Implications for Developmental Processes. Human Development. Volume 49. Issue 5. Pages 273–293

33. Haller H, Cramer H, Dobos G (2015) Somatoform Disorders and Medically Unexplained Symptoms in Primary Care A Systematic Review and Meta-analysis of Prevalence, Dtsch Arztebl Int. Volume 112. Issue 16 Pages 279–287.

34. Häuser W, Marschall U, L'hoest H, Komossa K, Henningsen P (2013) Administrative prevalence, treatment and costs of somatoform pain disorder. Analysis of data of the BARMER GEK for the years 2008-2010. Schmerz. Volume 27. Issue 4. Pages 380-386

35. Mergl R, Seidscheck I, Allgaier A.K, Möller H.J, Hegerl U, Henkel V (2007) Depressive, anxiety and somatoform disorders in primary care: prevalence and recognition. Depress Anxiety. Volume 24. Pages 185–195

36. Wiborg JF, Gieseler D, Fabisch AB, Voigt K, Lautenbach A, Löwe B (2013) Suicidality in primary care patients with somatoform disorders. Psychosom Med. Volume 75. Issue 9. Pages 800-806

37. Wenzel A, Beck AT (2008) A cognitive model of suicidal behavior: Theory and treatment. Applied and Preventive Psychology. Volume 12. Issue 4. Pages 189-201

38. Crofford L.J (2015) Chronic Pain: Where the Body Meets the Brain. Trans Am Clin Climatol Assoc. Volume 126. Pages 167–183.

39. Smith GR, Monson RA, Ray DC. (1986) Patients with multiple unexplained symptoms. Their characteristics, functional health, and health care utilization. Arch Int Med. Volume 146. Pages 69–72

40 Smith J.K, Józefowicz R.F (2012) Diagnosis and treatment of somatoform disorders Neurol Clin Pract. Volume 2. Issue 2. Pages 94–102

41. D'Souza. R, Hooten W.H (2019) Somatic Syndrome Disorders. Treasure Island (FL) StatPearls