Pathophysiology of the Acute Pain Chronification and the Possibilities of Its Prediction and Prevention

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Abbreviations

3 PM	Predictive, preventive, and personalized medicine
4-HNE	4-hydroxynonenal
CGRP	Calcitonin gene related peptide
CNS	Central nervous system
CVS	Cardiovascular system
DHA	Docosahexaenoic acid
DNA	Deoxyribonucleic acid
EPA	Eicosapentaenoic acid
EPMA	European association for predictive, preventive, and personalized medicine
ERAS	Enhanced recovery after surgery
GIT	Gastrointestinal tract
hs-CRP	High sensitivity C-reactive protein
IASP	International association for the study of pain
IL	Interleukin
LLLT	Low level laser light therapy
MDA	Malondialdehyde
MMP-9	Matrix metalloproteinase 9
MnSOD	Manganese superoxide dismutase
Na^+	Sodium ion

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NGAL	Neutrophil gelatinase-associated lipocalin
NMDA	N-methyl-D-aspartate
NS	Nervous system
NSAIDs	Nonsteroidal anti-inflammatory drugs
PBMT	Photobiomodulation therapy
PPPM	Predictive, preventive, and personalized medicine
PUFA	Polyunsaturated fatty acids
RNA	Ribonucleic acid
RPCQ	Risk of pain chronification questionnaire
SHS	Suboptimal health status
SIRT3	Sirtuin 3
SNRIs	Serotonin norepinephrine reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
TCA	Tricyclic antidepressants
TENS	Transcutaneous electrical nerve stimulation
TNF-α	tumor necrosis factor alpha
TNF-β	tumor necrosis factor beta
TRPV	Transient receptor potential V channel
UGT	Urogenital tract
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor

1 Educational Background

1.1 Pain

Pain is defined by the International Association for the Study of Pain (IASP) as: "An unpleasant emotional and sensory experience that is associated with, or described as, potential or actual tissue damage. Pain is always subjective".

Pain is a complex sensation, processed by branched, hierarchically arranged neural networks in several cortical and subcortical centers of the brain (the so-called Pain Matrix as a specialized part of the "Neuromatrix") [1–5].

Pain is a subjective perception, each person perceives it individually. It arises during the development of an individual on the basis of repeated experience with pain, with its individual experience and reaction to it. The onset of pain takes place in four basic phases, described in detail by the American neurosurgeon Loeser in 1982. In the so-called **the conceptual model of pain** (Fig. 1) recognizes the phase of nociception (somatic component), pain (sensory component), suffering (affective component), and the phase of subsequent painful behavior (behavioral component) [6].

Acute pain is a symptom, it is a part of many pathological conditions, and diseases. Its role is primarily protective, the pain has a positive, warning meaning for a living organism. Its physiological significance lies in the fact that in the event of an

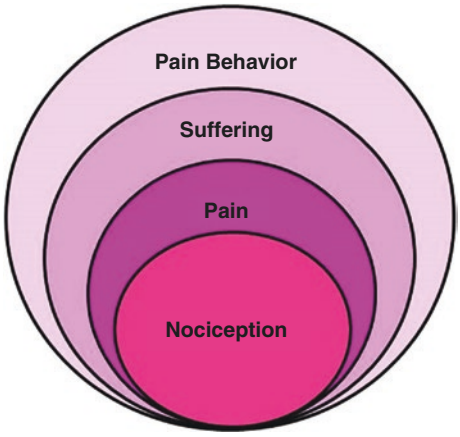

Fig. 1 Biopsychosocial model of chronic pain, Loeser's conceptual model of pain [9]

acute threat, it draws attention to the need to eliminate the cause of the damage to the organism and seek help. It is part of an archetypal attack-escape threat. Acute pain is associated with the activation of a symptomatic nervous autonomic system that responds to a "stress response" to the extent of the intensity of the stimulus and the condition of the nervous system. However, if its intensity is too strong, its metabolic, neurogenic, and immunological changes can seriously damage the patient's health. Acute pain usually lasts as long as the cause of its occurrence, respectively the healing time of the damaged tissue that causes the pain [1]. It usually does not exceed 6 weeks, but it can be considered acute for a maximum of 3–6 months [7].

Chronic pain is more difficult to define, or more precisely several aspects are needed to define it. The most commonly used time point of view defines chronic pain as lasting longer than 3–6 months. In this context, the Doyen of systematic pain treatment prof. John J. Bonica suggested that chronic pain should be defined as "pain that persists for more than one month after the end of a normal healing period, or is associated with a pathological process that causes it to persist or recur for months to years" [8]. Although a certain period of time is required for the onset of chronic pain (i.e., the transition from acute to chronic pain, chronification), the emphasis on time is inaccurate and simplistic in its definition [1]. A similar, often used characteristic of chronic pain, such as "pain lasting longer than the expected healing time" [9], says nothing about its pathophysiological nature.

The distinction between acute and chronic pain is based not only on the time factor, but also on other differences [10]. The fundamental differences defining chronic pain in contrast to acute pain are therefore not only in its symptomatology (especially its duration, its nature, psychological changes, etc.), but especially in the evolving pathophysiological changes. Nervous system accompanied by typical "painful behavior." Chronic pain is a separate disease with complicated aetiology, pathophysiology, and symptoms. Even for the polymorbid patient, it often becomes the most important source of impaired quality of life and suffering. It is the understanding of the manifestations and dynamics of changes in the painful behavior of the patient who can decisively clarify the presence of chronic pain. In some cases,

the presence of nociception, a painful afferent from the damaged area, is not even necessary. At the same time, the phases of the conceptual model can develop in the opposite order towards the somatisation of subjective experience of mental suffering and pain [7]. As we can see in Fig. 1, in the case of chronic pain, a nociception recedes into the background and affective, cognitive, evaluative, and behavioral aspects that interact with each other, become more important [11].

The transition from acute pain to chronic, the so-called **Pain chronification** is a serious and relatively common medical condition in which patients suffer from pain for an extended period of time that exceeds the time normally expected to treat the condition. The fundamental differences defining chronic pain versus acute pain are not only in its symptomatology, but especially in the developing pathophysiological changes in the nervous system (NS), which can be described by the term "sensitization." By this term we mean a kind of "sensitization" of the nervous system, i.e., its excessive sensitivity to stimuli and at the same time its excessive reactivity. It expresses an increased response to the supply of information from the environment, which is able to overwhelm, disrupt, and eventually disable the pain inhibitory mechanisms. This process is very dynamic, evolves over time and involves a number of pathological restructuring changes in the nervous system in its metabolism, function, and structure (the so-called **pathological neuroplastic changes**), which can lead to dysfunction and in extreme to failure of transmission and modulation nociceptive systems.

Chronic pain is often referred to as "**pathological**" but also as "**dysfunctional" pain**. It is the understanding of the manifestations and dynamics of changes in the painful behavior of the suffering patient that can decisively clarify the presence of chronic pain. Thus, chronic pain meets the criteria for progressive central nervous system (CNS) dysfunction with the development of pathological neuroplastic changes at the level of axons, synaptic connections, receptor complexes, neurotransmitter function, etc., and can be understood as central neurogenic pain. According to the International Association for the Study of Pain (IASP) [12], chronic pain is defined as "pain of no apparent biological value that persists after the normal expected time of tissue healing (which is usually 3 months)" [13, 14].

Unlike an acute pain, **chronic pain is a complex disease** of both central and peripheral NS with polymorphic symptoms and persistent suffering. In the process of **chronifying of acute pain**, it is important to gradually change the significance of individual **components of pain**. Raudenská states that in chronic pain, nociception relatively recedes and affective, cognitive, evaluative, and behavioral aspects, which, together with somatic ones, interact with each other gradually become more important [11]:

1. **In the somatic component**, chronic pain is characterized over time by varying intensity, localization, nature of pain (prickly, dull, burning, etc.), lowered threshold for shortening of skeletal muscles (especially neck muscles, trapezoid muscles, and others) and their failure to respond to physical release techniques, various visceral symptoms of increased sympathetic tension (cardiac, digestive) and many others.

2. **In the psychological component**, chronic pain is often manifested by insomnia, mood disorders (anxiety, depression.), anhedonia, loss of appetite, weight disproportion, loss of libido, loss of interests, energy, increased fatigue, power reduction, lack of concentration, etc. The emotional component of pain is characterized by anger, fear, anxiety, or a sad, pessimistic mood with feelings of hopelessness, that the treatment will last for the rest of life.
3. **The cognitive component** of chronic pain is represented by ideas about the origin and maintenance of pain, views on treatment and its evaluation, feelings of possible guilt (own or others), subjective feelings of inperformance, use and effect of coping strategies and more.
4. **The behavioral component** is characterized by painful behavior. We can define it as a set of psychic phenomena, subjectively felt by the sufferer himself/herself, i.e., as their experience of the situation with the subsequent and reaction to them. Objectively, then, painful behavior can be perceived as an observable activity, i.e., a specific physical activity [11]. Individual aspects of painful behavior (motor, emotional, cognitive, physiological) form a system, the components of which interact with each other. Typical painful behaviors may include limiting or avoiding activity, lying during the day, taking protective and relieving attitudes, muscle tension, grimacing, sighing, seeking social support, drug abuse, re-seeking medical care, re-hospitalizations, coercion financial and social benefits, etc. [15].

2 General Conditions Stimulating Chronic Pain

In the diagnosis and treatment of chronic pain, unfortunately, physicians usually do not know exactly what causes the chronification of acute pain in their patients. A better understanding of these processes is therefore of great importance for the prediction and subsequent prevention of pain chronification and is fully in line with the position of European Association for Predictive, Preventive, and Personalized Medicine (EPMA) in the field of PPPM [1, 16–18].

Several factors play an important role in the process of transition from acute—normal pain to chronic—pathological pain. Among them, not only the intensity and duration of acute pain dominate, but also the gradual failure of the hitherto functional segmental, descending and supraspinal pain inhibitory system.

At least **two conditions must be present for the onset of chronic pain**, which can in principle be divided into peripheral and central. Must be present:

1. Sufficiently long-term and intensive nociceptive afferent of pain impulses from the area of damage to the CNS (peripheral cause of chronic pain).
2. Predisposed, "latent" situation of sensitization of CNS structures (central cause of chronic pain).
   (a) **The persistence of pain pulse transmission** from the periphery to the Pain matrix can have several causes:
      - **Wrong diagnosis of the cause of pain** through the fault of healthcare professionals, where the source of pain is not remedied at all and the

patient is being treated for a completely different diagnosis. It can also be a delayed treatment or a poorly chosen treatment of a known cause. However, one of the most common reasons in this area is that with current treatments we are not able to causally eliminate the source of the patient's pain, i.e., we cannot cure the patient. Of course, this cannot be a reason why, even in the acute stage of the disease, we should not at least try to alleviate his pain and suffering.

- it is also quite often **patient's non-cooperation with the health care system**, e.g., such as ignoring the symptoms of the disease, not finding adequate help, not accepting the recommended treatment, etc.

(b) **Disruption of central pain processing** is the second, central condition for pain chronification. Under normal, physiological conditions, the CNS effectively filters excessive painful afferents in the event of severe acute pain, thus preventing the possibility of impairing the normal functioning of the nociceptive nervous system. However, the CNS may be in a state of disturbance of the dynamic balance of its activity, which is conditioned by disturbance of the action (synthesis, action, degradation) of neurotransmitters with the predominance of the influence of excitatory molecules over inhibitory ones. In particular, the CNS (even before an obvious harmful stimulus) may be at some degree initially very discreet "hyperexcitated," which in the clinic may not yet show significant physical or mental symptoms. Rather, we can observe only slight **signs of irritation** in the patient, both **psychological**, such as nervousness, irritability, lacrimosity, insomnia, anergy, concentration problems, etc. and on the other hand, where with a careful history and examination we can register the **physical** persistence of shortening of the neck (or other) muscles, a reduced pain threshold, but also sensory sensations (hypersensitivity to sounds, light, etc.). Various manifestations of **vegetative imbalance** are also present, such as oppression, palpitations, hypertensive disease (often drug-resistant), dyskinesia of digestive tract—including irritable bowel syndrome and reflux disease, sweating, peripheral congestion disorders, and many other manifestations of sympathetic tone predominance.

The reasons for this sensitive setting of the nervous system can be various, but in principle (as we have mentioned above) it is probably a relative predominance of secretion of excitatory neurotransmitters over inhibitory, respectively reduced synthesis of inhibitory neurotransmitters in the synaptic cleft. However, this hypersensitive, neurasthenic setting may be somewhat innate, constitutive in the patient.

At present, chronic pain is understood as a **biopsychosocial phenomenon**, as a result of the interaction between physiological, emotional, motivational, and cognitive processes. For chronic pain, the question often arises as to whether the pain is somatic or psychogenic. The dualistic model of the origin of pain is as follows: pain arises from nociception (i.e., primary tissue damage) or suffering (primary psychological damage). Both forms of pain are related to stress. During life, a number of

minor stressful events also affect a person, which can contribute to the onset and maintenance of pain [11].

3 Stressful Situations as a Cause of Chronic Pain

Based on clinical experience more than 30 years of pain medicine practice we can assume that the diffuse disturbance of neurotransmitters levels described above is caused by a chronic, sufficiently intense and long-lasting stress situation, or also by acute, very intense stress. In patients with chronic pain, we most often encounter the following **stressful situations** in practice (see also Fig. 2):

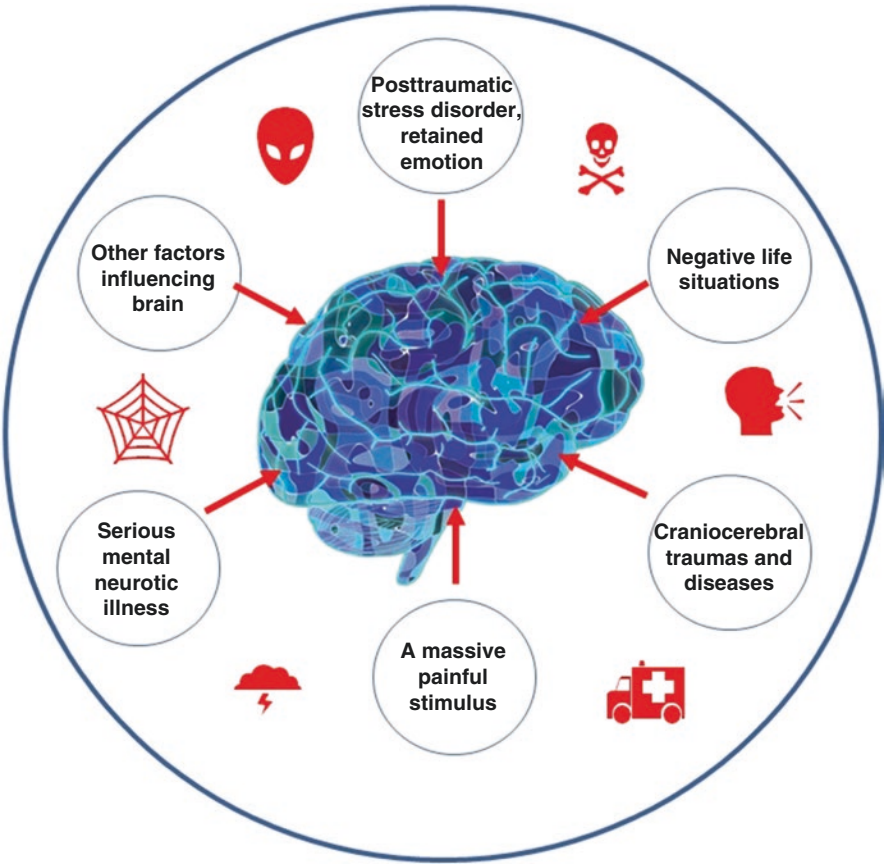

Fig. 2 An outline of particular stressful situations which may contribute to the nervous system sensitization and development of chronic pain. Not essentially all factors are named in the figure but the idea is more clear using this visualization. Our thanks go to Geralt Altmann from Pixabay for sharing his picture of the brain under Pixabay licence at the site https://pixabay.com/sk/illustrations/mozog-biol%c3%b3gia-abstraktn%c3%a9-veda-951874/

1. **Chronic post-traumatic stress disorder** is a condition in which the integration of a traumatic experience into other everyday experiences fails [19]. These are persistent **uncompensated psychotraumas** from the patient's past, usually after surviving serious life situations such as the death of a loved one, divorce, long-term suffering with a violent partner, but also sexual and other parental abuse, car accidents, natural disasters and wars and many other hardships. These often persist displaced in the patient's subconscious, usually in the form of unprocessed experiences and **retained emotions** [20] which are probably the cause of the gradually emerging imbalance of neurotransmitters at the expense of inhibitory substances (poetically called "hormones of happiness").
2. In most patients with whom we encounter in everyday pain medicine practice, the dominant etiological factors of chronic pain appear to be **less intense, but long-lasting negative life situations**. These are situations that come with everyday life and can be encountered by anyone. They do not always have the features of serious "psychotrauma," but rather they are life-uncomfortable and disruptive to the well-being and happiness of a person. Most often we can encounter long-term discomfort in the home or work environment, dissatisfaction with the social situation, the consequences of neighborhood disputes, underestimation and misunderstanding by the environment, but also chronic physical overload, burnout, e.g., for teachers, health professionals, etc.
3. **Craniocerebral traumas and diseases** with the development of chronic post-concussion syndrome as a result of either mild brain injury (coma, concussion) in about 5% of patients, or more often severe contusion brain injuries (brain contusion), or other brain damage, e.g., after a sudden stroke, brain surgery, encephalitis, etc. The result may be the development of similar chronic diffuse biochemical, metabolic brain damage, and somatic, cognitive, and psychological symptoms [21].
4. **A massive painful stimulus** of sufficient intensity and duration, usually associated with severe traumatic devastating injury, such as limb loss, etc.
5. **Serious conditions of mental illnesses**, poorly responding, even resistant to adequate psychiatric treatment, the most common anxiety-depressive mood disorders, generalized anxiety disorder, etc.

The common denominator of the above conditions is the **stress stimulus of excessive intensity**, which acts on the central nervous system. Subsequently, the **disruption of the dynamic balance of excitatory and inhibitory neurotransmitter levels** arises and further deepens with a reduction in the production of inhibitory mediators and an increase in excitatory mediators. The reason may be the need for the neuromatrix, often for a long time (months and years) to calm, suppress or inhibit stress-induced excessive irritation of the brain, which is a very metabolically demanding process. The result can be a significant decrease, even depletion of stocks of building materials and energy reserves for the synthesis of the necessary receptor complexes, neurotransmitters and other membrane and cytosolic structures of neurons with inhibitory function. Subsequent progressive irritation affects the sensitive and motor functions of the nervous system, including the vegetative system (with a predominance of sympathetic activity) and the associated hormonal imbalance.

However, these observations would deserve further, more detailed clinical research, as there is not enough relevant data in the literature and the situation may in fact be different. Such a status of patient's health can be easily described as being far from optimal yet we suppose that it can be reversible under early preventive and truly personalized measures. That is why we see the potential of combination of the tools for suboptimal health status assessment [22–25], and tools for determination of chronic pain predisposition as suggested further.

Based on the above information, we can imagine the **process of chronification of pain** in such a way that practically the entire nervous system is latently sensitized, excited and ready, waiting for a suitable trigger moment. It can also be, for example, a physiological pain in an uncomplicated operation, injury, or disease with a normal course. Although the intensity of this initiating pain may not be significant, it is sufficient that it is relatively excessive to overwhelm a poorly functioning nociceptive (transmission, perceptual, and modulatory) system, which can then relatively quickly (during several weeks) to develop a state of sensitization. This begins the process of developing changes that lead to chronic pain.

4 Stages of Chronic Pain

According to the above model of acute pain chronification, we can distinguish the following three stages in the development of chronic pain [1, 4, 18]:

1. **Latent stage**, the stage of neuromatrix sensitization in which the conditions for the development of chronic pain are already prepared, non-specific symptoms of sensitization of NS are present, but the pain is not yet present.
2. **Prodromal stage**, at the beginning of which the initiating normal painful stimulus (operation, injury, painful illness) is intense enough to overcome the disturbed pain inhibitory mechanisms, which starts a cascade of further progression of functional and structural changes nociceptive system. The present pain persists despite the healing of its cause, it intensifies, pain begins to limit the affected person's activities, the first signs of modified pain behavior appear.
3. **Manifested stage** is characterized by more or less fully developed symptoms of chronic pain with an individual combination of somatic and psychological symptoms with painful behavior, in the somatic area the pain usually manifests in a weakened area or system of the body (the so-called locus minoris resistentiae).

5 The Most Common Clinical Characteristics of Chronic Pain

Chronic pain is manifested by a set of symptoms on a somatic, mental, and social level. In clinical practice, we usually meet them with each patient in an individual combination. However, some symptoms are present in most patients, some of which we have already mentioned in the previous text.

At the **somatic level**, we often observe easier shortening of skeletal muscles, predominantly in the neck, trapezoid muscles, reduced pain threshold, but also sensory sensations (hypersensitivity to sounds, light, and other), as well as imbalance of the **autonomic nervous system** and subsequently also the functions of the visceral organs of the gastrointestinal tract (GIT), urogenital tract (UGT), cardiovascular system (CVS), etc. (in terms of excitation, spasms), e.g., palpitations, hypertension, GIT dyskinesia—including reflux disease and irritable bowel syndrome, sweating, peripheral circulatory disorders, and many more. It is also common not to respond to standard medical procedures (e.g., to appropriately selected analgesics) and to a paradoxical worsening of pain after therapy (e.g., after well-indicated physical therapy, prehabilitation, rehabilitation, etc.).

In the **psychological field**, patients with chronic pain regularly encounter various degrees of mood disorders, especially in the form of anxiety-depressive disorder, which itself can further worsen the experience of chronic pain. We also see a wide range of emotional changes, such as various fears, phobias, anger and aggression, a negative worldview and hopelessness, but also panic, psychosensitive irritability, self-blame, catastrophic tendencies, sleep disorders, anergy, etc. The patient's personality type (e.g., hypochondriac, neurotic, anxiety, and others) can also affect pain perception and experience.

In the **social field**, chronic pain significantly affects the patient's life, especially by limiting his work, social and cultural habits. On the contrary, the patient's social environment can significantly affect his attitude to experience chronic pain. Chronic patients often use their suffering for personal gain in the company of their loved ones. The so-called Rentier syndrome in an effort to obtain inadequate relief and financial benefits. It is well known that there are significantly fewer patients with chronic pain from the environment of managers and self-employed people with higher education than in the group of unemployed and with lower education.

6 Pathological Processes in Chronic Pain: Nervous System Sensitization

Chronic pain is characterized not only by its duration, but above all by clinical characteristics resulting from a complex of dynamic pathophysiological changes in the nervous system. These pathological changes in function and later in structure not only characterize chronic pain, but it also directly creates and provides its maintenance and progression. The preconditions for the development of changes in the nervous system, which characterized chronic pain, are, in particular, persistent nociceptive transmission, which may precede or immediately follow the gradual development of **sensitization of the nervous system**. It is mainly based on the development of pathological neuroplastic changes in Pain Matrix.

Pathological changes in various neuronal nociceptive structures relate initially to functional and later also to structural neuroplasticity. Changes in functional

plasticity are at the molecular, synaptic and cellular levels up to changes in the function of the neural network, when more cell groups respond synchronously to harmful stimuli by increasing the generation of impulses by the spinal neural network with the emergence of the so-called **wind-up phenomenon**. Changes in structural plasticity are manifested mainly by an increase in the size and density of synaptic spines. The neural axons can respond to persistent nociceptive activity in two ways: by sprouting and producing of new connections (sprouting), or by degeneration. Neurocytes, which can also proliferate (e.g., microglia and astrocytes) or atrophy (e.g., loss of inhibitory interneurons), react similarly [1, 26].

Peripheral tissue damage or nerve injury often leads to various conditions of pathological pain, such as spontaneous pain, hyperalgesia, and allodynia, which can persist for years to decades after the healing of the injured tissues has ended. Although peripheral neuronal mechanisms (such as nociceptor sensitization and neuroma formation) also contribute to the development and maintenance of pathological pain, current evidence also points to an important role for changes in central neuronal functions [14]. Due to the processes of central sensitization, harmful stimuli can cause chronic pain, respectively misinterpretation of harmless stimuli (secondary hyperalgesia and allodynia).

Thus, the **pathological neuroplastic changes** associated with chronic pain affect to some extent all structures of both peripheral and central nervous system, especially synaptic connections, receptor membrane complexes, neurotransmitters production, as well as changes in the shape and number of neuronal axons and dendrites. Chronic irritation of nociceptive pathways mainly results in changes in the functional sensitization of membrane ion channels with subsequent gene expression (C-fos gene) and changes in the function of perisynaptic region receptors (their types, structures, affinities) and neurotransmitter levels (e.g., increased substance P synthesis, calcitonin gene related peptide—CGRP—on Aβ fibers and neurons of dorsal spinal horns). The penetration of Aβ fibers into the gelatinous substance and the formation of synaptic connections to C fibers in this area, the expansion of neuronal reception areas and the extinction of inhibitory interneurons occur. The pain is chronifying [27, 28].

As a result of these dysregulating neuroplastic changes, **NS sensitization** (represented by the "wind-up" phenomenon), functional and anatomical changes in the neural structures of the pain pathway with impaired pain transmission and inhibition and long-term changes in neuronal functions arise. The most important changes in neuronal functions in the chronification of pain include increased sensitivity and neuronal excitability of the afferent part of spinal neurons, decreased activity of inhibitory mechanisms facilitating painful transmission, increased excitability of posterior root ganglion cells, but also the development of ectopic activity on damaged or neuroplastic altered neurons and glia activation. In the clinical picture, these changes condition the development of the mentioned allodynia, hyperalgesia, spontaneous pain, and hyperpathia (with an increased response to painful stimuli).

7 Potential Markers for the Prediction and Prevention of Chronic Pain in the Context of Suboptimal Health Status

On the basis of our long-term clinical experience with Chronic Pain Management, as well as published global clinical research [1, 4, 18, 29], we can assume that chronic pain conditions are most common due to chronic, sufficiently intense, individual and long-lasting stressful situations and influencing factors as outlined in Fig. 2. These factors, together with a set of clinical signs of sensitization, as discussed further, can serve as **specific predictors** of pain chronification from the point of view of PPPM, as well as objects of interest in targeted prevention in specific individuals. Here again we want to emphasize the important relation between pain chronification and **suboptimal health status** (SHS). According to the definition the SHS is a physical state between health and disease, and is characterized by the perception of health complaints, general weakness, low energy, decline in vitality within a period of 3 months and it is regarded as a subclinical, reversible stage of chronic disease [22–25]. We suggest that particular conditions for pain chronification may very well be understood as belonging or creating the conditions for suboptimal health status and should be taken into consideration in a complex application of PPPM principles in future healthcare as we outline in the other chapter dealing with "prehabilitation" as a practical application of prediction, prevention and personalized attitude in a hospital.

Just as in the case of SHS, the most basic method for assessing individual patient assumptions for pain chronology is a form of well-designed **questionnaire**, combined with substantiated theoretical and practical **diagnostic methods**. The chronic post-traumatic stress disorder mentioned above can serve as an example of such a condition, but also the less intense, but long-lasting negative life situations, which make life-uncomfortable, reduce the level of well-being and happiness of a person. We must also mention the recent global preventive measures taken to combat the COVID-19 pandemic, which undoubtedly also cause mental, social, and physical stress. We reiterate that craniocerebral trauma with chronic post-seizure syndrome is also a common cause of CNS sensitization. In these cases, it is not only a brain and spinal cord injury, but also other brain damage, e.g., sudden stroke, encephalitis, intoxication, and other CNS disorders.

8 Clinical Symptoms of CNS Sensitization

An essential element of primary and secondary prevention, as well as of the treatment of chronic pain, is the identification of the presence of individual clinical signs of CNS sensitization. The most important of them are as follows:

1. facilitated skeletal (neck) muscle shortening,
2. the absence of objective findings despite polymorphic subjective difficulties,

3. manifestations of excessive sympathicotonia—hypertensive disease and/or tachycardia unresponsive to pharmacotherapy, spasms, and imbalance of gastrointestinal motility,
4. failure to respond to standard medical procedures,
5. paradoxical deterioration after rehabilitation and after invasive therapeutic procedures,
6. polymodal pharmacotherapy intolerance,
7. chronic fatigue syndrome,
8. excessive meteosensitivity,
9. condition after craniocerebral trauma of the CNS—of both, less serious nature (fall on the back), and of serious nature (head injury, brain surgery, coma, contusion, acute stroke, etc.)
10. reporting "whole body pain",
11. lacrimosity,
12. sleep disorders,
13. depressive—anxiety disorder,
14. rating your pain intensity on a 10-point Visual Analogue Scale (VAS) as "10 or more";
15. neurasthenic behavior,
16. persistent dissatisfaction with current treatment,
17. consequences of serious negative life situations (psychotraumas),
18. discomfort and dissatisfaction at home (broken relationships, loneliness, etc.)
19. discomfort and dissatisfaction at work (burnout, bullying),
20. purposeful action with an effort for material or social benefits from the present disease (the so-called Rentier syndrome).

9 Laboratory and Epigenetic Markers of Chronic Pain Can Complement the Markers of Nervous System Sensitization

Although older studies found that **biochemical markers** are not specific for chronic pain [30, 31], the more recent publications summarize quite a lot of interesting and promising markers like, among others, in urine it is methylmalonic acid, xanthurenic acid, homocystein, matrix metalloproteinases MMP-9, also neutrophil gelatinase-associated lipocalin (NGAL), vascular endothelial growth factor (VEGF), in serum there are pro inflammatory cytokines such as interleukines (IL-4, IL-6, IL-8, IL-10, IL-17, IL-21), tumor necrosis factor alpha (TNF-α), hs-CRP, in blood the level of T_H17 lymphocytes, in cerebrospinal fluid it is arginin vasopressin, somatostatin, tumor necrosis factor beta (TNF-β), endotelin 3, and other [32–34].

While many of the mentioned markers correlate with severity of pain and inflammation rather than with the predictive potential, and, as generally known, prolonged inflammation can cause various chronic painful disorders [34], still the early determination of their levels before the surgery, or medical procedure, may very well be combined with the information about potential neural system sensitization in the

particular patient. And it may as well be combined with assessment of the suboptimal health status which takes into consideration also a psychological status that is affected by the same external factors, for example, long-lasting stressful situations that may cause neural sensitisation [22, 24, 25].

Moreover, some of these biochemical markers, many of them related to the diet and lifestyle, are routinely measured in the clinical labs and offer a possibility for targeted preventive actions within the process of prehabilitation which can further be supported by nutrition profiling that would include particular markers. Among such markers that can be relatively easily monitored in the clinical laboratory there are: vitamin D, vitamin B12, vitamin B6, coenzyme Q10, glutathione, homocysteine, n-3 PUFA (linoleic acid, EPA, DHA), zinc, selenium, magnesium, 4-hydroxynonenal (4-HNE), malondialdehyde (MDA), whose early determination prior to the planned surgery can contribute to the prediction of pain chronification as well as it can help in personalized therapy and monitoring after the surgical/medical procedure undergone by the patient [32, 34–37].

There are also studies which link chronic pain to the **epigenetic factors** influencing particular methylation sites at concrete regions of human DNA [38]. Other studies show that DNA methylation markers in T cells could serve as "predictors" of pain sensitivity and potentially chronic pain [39]. This kind of analysis, however, is rather complicated for being implemented in the routine processes of healthcare at the current state of the technology in the vast majority of hospital laboratories. Although the predictive potential for pain chronification on the basis of specific epi/genetic analyses (DNA methylation, histone acetylation, mi RNA, etc.) is, undoubtedly, very high, we don't expect that these tests will become a routine in the near future so that we propose more feasible way of pain chronification prediction which would proceed from the specific questionnaire with combination of measurement of biochemical markers. Moreover, the very factors (see Fig. 2) which the questionnaire is focused on to identify, may contribute to chronification of pain via changing particular genes' expression [38] thus causing pain hypersensitivity in the patient who may possibly be early identified on the basis of well-designed predictive questionnaire.

10 Role of Mitochondrial Health in Prediction of Chronic Pain

In the context of another chapter of this book dedicated particularly to the mitochondrial health and its role for PPPM/3 PM here we want to emphasize the interrelations between the topics. The mitochondrial dysfunction has been linked to chronic pain through several mechanisms mediated via mitochondrial electron transport chain, mitochondrial permeability transition pore, apoptotic pathways, calcium homeostasis, reactive oxygen species. It was suggested that mitochondrial energy generating system and mitochondrial reactive oxygen species play important roles in the pathogenesis of chronic pain [40, 41]. We want to stress that monitoring of mitochondrial health may serve as yet another marker since the improper

function of mitochondria in the cells of a patient indicate that there is the potential for pain chronification. Moreover, this knowledge provides the tools and strategies for personalized therapies and interventions based on dietary supplements. Antioxidants such as vitamin C and vitamin E show additive antinociceptive (pain reducing) effects after peripheral nerve injury [34, 35].

Numerous studies have also reported that polyphenols, biologically active phytochemicals with flavonoids being among them, have antioxidant and anti-inflammatory properties and ability to activate sirtuin 3 (SIRT3), a mitochondrial protein directly or indirectly controlling antioxidant enzymes such as manganese superoxide dismutase (MnSOD). Other findings also demonstrate that restoring mitochondrial functions and protecting activity of sirtuin 3 by natural antioxidants such as mentioned polyphenols, could be beneficial during oxidative-stress-induced allodynia and hyperalgesia. Besides, re-establishing the activity of SIRT3 by polyphenolic fractions of particular plant extracts may serve as a new target in therapeutic intervention for the management and rehabilitation of pain-suffering patients [36, 42, 43].

11 Role of Microbiome in the Personalized Prediction and Prevention of Pain Chronification

Although this topic goes far beyond the scope of our chapter, we cannot omit yet another possibility for complex intervention in the case of predicting and preventing chronic pain through the particular mechanisms of the gut–brain axis. The studies show various links between pain, inflammation, immunity, and gastrointestinal microbiota. Thus preventive action in pain chronification may also lead, in parallel to other preventive actions, to supporting healthy microbiome via well-designed personalized diet based on the analysis of nutritional status and patient's gut microbiome [34, 37, 44–47]. Such an attitude is well in agreement with prehabilitation process, as discussed in the particular chapter of this book, and with practical application of PPPM in the procedures of future healthcare.

12 Standard Prevention of Chronic Pain

By understanding the pathophysiological characteristics of the pain chronification process, we are able to identify this condition in the patient and recognize risk factors for each stage of chronic pain. As a result, we are able to identify and apply at each stage an individually selected combination of preventive and therapeutic approaches to minimize suffering associated with chronic pain and subsequently to mitigate the socio-economic impact of chronic pain.

In clinical practice, we can distinguish two types of **chronic pain prevention**:

1. **primary prevention**: it is an effort to prevent the development of chronic pain, i.e., that the chronification process of acute pain does not even start. As these

measures should be performed at the latent or early prodromal stage of chronification, they are non-standard for the pain specialists and rather concern the work of general practitioners and specialists in the treatment of acute pain in individual specialties. In any case, they relate to the influence of the peripheral component of pain, which can be influenced by effective preemptive and postoperative analgesia, infiltration of the surgical incision, etc., as well as the central component of pain, when it is necessary to identify or predict or therapeutic procedures, planned operation, etc.

2. **secondary prevention**: it is aimed primarily at reducing the spectrum and reducing the intensity of progression of chronic pain symptoms, as well as alleviating the consequences and complications of the manifest stage of chronic pain. This is already mostly in the hands of the pain specialists.

13 Chronic Pain Pharmacotherapy Algorithm

The success of the treatment of chronic pain lies in understanding the pathophysiological changes associated with sensitization of the nervous system and in deploying the right combination of drugs individually for the patient. When striving for complexity and purposefulness of the therapeutic procedure, it is necessary to influence the central and peripheral component of chronic pain and at the same time to time the individual therapeutic steps correctly. This process of complex treatment of chronic pain is structurally illustrated by the so-called **Chronic pain pharmacotherapy algorithm**, which emphasizes the need to combine pharmacists from different groups influencing several levels of the nervous system that are involved in the development of pain [1]:

1. **Stimulation of damaged and failing central pain inhibition.** In pain medicine practice, it is often necessary firstly to stimulate and stabilize impaired pain inhibition mechanisms (segmental, descending, and central), usually by using an appropriate antidepressant (from the group of Tricyclic antidepressants (TCA), Selective serotonin reuptake inhibitors (SSRIs), and Serotonin norepinephrine reuptake inhibitors (SNRIs)), administered for a long time (on average 1 year) in a low dose once a day, but also transcutaneous electrical nerve stimulation (TENS), but also others.
2. **Stabilization of the present CNS sensitization.** N-methyl-D-aspartate (NMDA) receptor antagonists (e.g., ketamine, nonsteroidal anti-inflammatory drugs—NSAIDs), transient receptor potential V channel (TRPV) agonists (capsaicin) and potassium channels (flupirtine), as well as antidepressants (TCAs, SSRIs, SNRIs) as an antinociceptives or “antisensitising” drugs, that stimulate central inhibitory mechanisms, or opioids, anxiolytics, neuroleptics, calcium channel blockers and many others. There is, too, possible to use some non-pharmacological procedures (such as psychotherapy, autogenous training, targeted motivation, TENS), and others.

3. **Reduction of nociceptive peripheral afferentation.** In addition to strengthening the central component of pain, we must also secure the reduction of excessive nociceptive afferentation from the periphery in different ways. This is either.
   (a) by reducing the generation of pain impulses (the so-called pain generator) either by **controlling sterile inflammation** at the site of tissue damage by applying anti-inflammatory drugs (NSAIDs, corticoids) or,
   (b) by trying to **reduce ectopic excitation** by anticonvulsants (pregabalin, gabapentin, carbamazepine) and on the one hand,
   (c) by **reducing painful transmission** by applying regional anesthesia techniques at the level of the spinal cord, nervous plexus, and peripheral nerves (by local anesthetics in the role of Na^+ channel blockers).

   Depending on the patient's condition, we can apply them either at the same time as the pharmacotherapy is started, or only after the effect of this treatment. In clinical practice, it is really interesting to see how a few hours of limiting the supply of painful impulses coming from the point of origin to the spinal cord can allow to reconstruct segmental and supraspinal "defense" (inhibitory mechanisms) of the central nervous system with consequent improvement in patient pain and suffering.
4. **Ensuring current analgesia.** In addition to the above-mentioned therapeutic interventions, we strive to ethically ensure quality up-to-date analgesia according to the principles of the analgesic ladder with the application of non-opioid and opioid analgesics, adjuvant drugs, non-pharmacological procedures, etc.

14 Suggested Strategy for Prevention of Chronic Pain from the PPPM Point of View: Creating a Questionnaire as a Research Tool for Pain Chronification Prediction and Its Relation to the Assessment of the Suboptimal Health State and the Possibilities of Photobiomodulation Therapy in Management of Chronic Pain

In the previous text we hypothesized that the above spectrum of pathognomonic symptoms, typical of the presence of CNS sensitization and usually leading to chronic pain, can be used to predict the risk of pain chronification in the context of PPPM as well as in the context of established SHS assessment. Based on these assumptions, we believe that from a PPPM perspective, these symptoms may serve as specific predictors of pain chronification. The most basic method for assessing the patient's individual assumptions for pain chronification is the form of a suitably designed **questionnaire**, combined with substantiated theoretical and practical scientific diagnostic methods.

Creating a questionnaire as a sophisticated research tool is a relatively complex professional activity, but even so, it is the most frequent research method in biomedical research. Questionnaire research is a good choice as it provides us with a

wide range of information from a large number of respondents and may very well extend the information potentially acquired by analyzing particular biomarkers of chronic pain, inflammation, malnutrition, and SHS.

In addition to the prediction of pain chronification, from the PPPM/3 PM point of view we must emphasize also preventive therapy and management of chronic pain by particular diet as outlined in the literature [34, 36, 37, 42, 43] and non-phamacological interventions using modern photobiomodulation therapy (PBMT), formerly known as low level laser light therapy (LLLT) [48] which has effect on the mitochondrial processes, apoptosis, inflammation, and other which may be linked to pain at different levels [49–53].

15 Risk of Pain Chronification Questionnaire

The questionnaire we are currently working on is named "**Risk of Pain Chronification Questionnaire**" (RPCQ). It is designed the way that will allow a patient to fill it him/herself—usually before the first, initial algesiological examination. Thematically, it touches the level of somatic or unspecified mental attributes. It further examines the anxiety and depression of the patient. The topics of questions complement each other in order to achieve the main goal—to detect risk factors, predictors of pain chronification, or to reveal the occurrence of predictive factors that can detect and especially quantify the risk of transition of acute pain to chronic. The scoring system identifies the degree of **risk of pain chronification**. Based on the total score obtained, we will be able to determine the degree of risk of acute pain chronification (ranging from none to clearly present signs of chronic pain). The questionnaire is currently undergoing the validation process in our hospital and will be published to share the experience with worldwide scientific community.

16 Practical Significance of the Questionnaire for the Prehabilitation Processes in the Future Healthcare Set Up in the Context of PPPM

The questionnaire has two potential benefits. On one hand, it is the detection of the degree of sensitization in the patient, the detection of risk factors that could lead to the process of transition from acute pain to chronic pain but eventually it can reveal the presence of chronic pain as the disease itself, if not properly and early managed ahead of the medical procedure.

The second important significance of this questionnaire lies in the fact that it is able to detect the risk of surgery failure due to the existence of CNS irritation and sensitisation in the preoperative period. In clinical practice, we sometimes encounter a situation where, despite the standard preoperative and perioperative course, the result of the operation did not turn out well. The patient is dissatisfied, constantly complaining of pain in the surgical wound, suffers from insomnia, mood disorders, and develops persistent postoperative pain. This situation leads to various misunderstandings between the surgeon and the patient, and it is usually the patient who ends

up with, at best, being labeled as "maladapted patient." Thus, the key question is not if we can, even in the preoperative period, predict whether and in whom such a postoperative complication can occur but rather how we should do it the most feasible and effective way to prevent it from happening.

In the field of planned surgical procedures in the preoperative and perioperative period—the use of the concept of **Enhanced Recovery After Surgery** (ERAS) [54] is known in healthcare. ERAS is a multimodal perioperative care designed to achieve early recovery in patients undergoing major surgery. ERAS represents a paradigm shift in perioperative care in two directions. First, it re-examines traditional practices and, where necessary, replaces them with evidence-based best practices. Second, it is complex in its scope and covers all areas of the patient's pathway through the surgical process which is well in an agreement with complex attitude of PPPM.

It is known that the key factors that keep patients in the hospital after surgery and prevent them from rapidly returning home, include the need for parenteral analgesia or the need for intravenous fluids, e.g., in intestinal dysfunction. Central elements of the ERAS pathway address these key factors and help elucidate how they interact to influence a patient's recovery. In addition, ERAS provides advice to all those present and involved in the perioperative care process and helps them work as a well-coordinated team in providing the best care. ERAS minimizes the occurrence of complications, leads to a faster recovery, shortens the hospital stay. It consists of various interventions, whether preoperative, perioperative or postoperative.

In the context of the principles and visions of PPPM/3 PM it is very important to emphasize the role of the preoperative period that is essential for preoperative optimization and prehabilitation—the common intention is compensation of comorbidities. In the field of prehabilitation, particular approaches are implemented that are crucial for the best outcome of the medical procedure. For example, well prepared patient (prehabilitated) should undergo evaluation of the nutritional status and consequent improvement of this status on the basis of particular laboratory tests if necessary. Furthermore, it is psychological grounding, suboptimal health status assessment, pain chronification questionnaire, and other evaluations of the factors having influence on the particular medical procedure. The essence is that it is no longer possible to achieve the optimal functional capacity of the patient or his/her optimal psychological/physical/nutritional status postoperatively, which is too late, and only 40% of patients regain their initial functional status postoperatively.

And it is in this preoperative period, within ERAS and prehabilitation that the immense potential of the well-designed questionnaire that is currently, as described above, being under validation process in our hospital, and its predictive power will rise even more in synergy with the suboptimal health status assessment [22–25] In practice, the patient pre-operatively completes a questionnaire, which is then evaluated by an ERAS specialist.

- If none or the first risk level (level 0 or 1) of pain chronification is detected, prehabilitation continues, the operation is recommended to the patient.
- If a low risk of chronification (level 2) is detected after completing the questionnaire, the patient must undergo a psychological examination and, based on the

psychological examination, the operation is recommended or postponed—then the patient must undergo a psychological intervention.
– If, after completing and evaluating the questionnaire, the third or fourth risk degree of chronification is classified (i.e., high risk of chronification or chronic pain is present)—the operation is postponed, psychological examination follows and the patient's sensitization must be treated.

We anticipate the completion of the validation process for predicting the risk of pain chronification by the end of 2022. After the validation, we plan to apply it in the clinical practice of several workplaces of pain specialists, surgeons, general practitioners and other specialists, especially within the ERAS system. Expected benefits of the questionnaire implementation for prediction of pain chronification in clinical practice we plan to share through scientific publications and we also plan to share the experience and facilitate implementation of PPPM in the hospital environment in cooperation with other institutions worldwide.

17 Conclusion and Recommendations

The need for determination of risk factors or predictors that support and/or describe the process of pain chronification follows from our long-term experience in daily routine practice in the field of Pain medicine as well as it is emerging from the scientific knowledge accumulated to date.

Nervous system sensitization plays a key role in the transition from acute to chronic pain. The occurrence of certain factors, predictors, is clearly associated with the phenomenon of pain chronification. Recognizing, identifying, and using them as predictive markers plays a key role in preventing chronic pain as well as providing targeted and personalized treatment. Therefore, the detection of these factors, which are directly related to the phenomenon of pain chronification, plays a key role not only in pain medicine but also in the practical implementation of the concept of predictive, preventive, and personalized medicine, where by detecting these factors we can prevent suffering from pain and reduce the risks of surgery or other medical procedures.

In the context of the main topic of the whole publication, "PPPM from Bench to Bedside," here we propose that the strategies of suboptimal health status assessment, prehabilitation procedures that include nutrition profiles assessment, mitochondrial health, and assessment of the health status for pain chronification prediction should all be combined into one complex attitude under the PPPM/3 PM strategy in the future system of healthcare worldwide. In our hospital we are working on the practical implementation of all particular attitudes benefiting primarily our individual patients as well as the whole society. An international collaboration may substantially speed up the process and catalyze the essential changes that are needed to transform the current systems of healthcare into the new, perspective, sustainable, science-and-common-sense-based system of future healthcare.

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