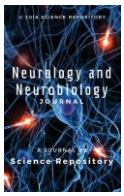

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The neurobiology of depression and the dilemma of pain treatment

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HPA - hypothalamic-pituitary-adrenal axis
SSRI - selective serotonin-noradrenaline reuptake inhibitors
SSNRI - selective serotonin reuptake inhibitors
TCA - tri-/tetracyclic antidepressants

ABSTRACT

Pain is a known side symptom of a depressive disorder. A recent meta-analysis suggests strongly that treatment of comorbid pain in primary depressive disorders is a treatment of the depressive disorder itself. This seems to be mostly independent of the treatment method. However, it is essential that the depressive disorder is treated successfully.

For the individual patient, this means that the choice of antidepressant is based on the individual effect/side effect profile, not on a supposedly better analgesic effect of antidepressants. As well, psychotherapeutic strategies and complementary therapies, such as music therapy, are highly recommended depending on the individual case. The improvement of the affective system leads to the normalization of the pain system resulting in a relief of pain. Of course, this does not preclude additional suitable analgesic therapy, which in turn may have effects on depression.

Although this approach seems to be strongly evident, it is hardly implemented in practice. A number of obstacles seem to interfere with the establishment of appropriate general and individual therapeutic strategies and lead to a dilemma in pain management of depressive patients: research and publication bias, obstacles in areas of expertise and professionals' interests as well as in psychopathology itself are discussed in this paper.

Introduction

Though depressive symptoms in patients with chronic pain are often reported, the occurrence of pain in depressive disorders is neglected, both in research and in clinical practice. However, it is not a small minority of patients with a rare disease constellation. 5-13% of the general population suffer from a depressive disorder, a third hereof can be classified as chronic and 40-75% of patients with depressive disorders suffer from pain symptoms [1-3]. Furthermore, patients presenting with pain as a symptom, have worse prognoses and therefore implicating a strong use of medical health services [4]. Thus, this topic is of particularly high clinical relevance involving besides neurologic and somatic disciplines, psychosomatic and psychotherapeutic areas.

Up to half of patients suffering from acute depression are not diagnosed as such, possibly because they present with physical or pain symptoms, respectively, rather than with signs classically known for depression. Symptom clusters differ among various depression forms. Whereas young adult patients often appear strongly emotionally distressed, but do not complain of somatic symptoms, the masked depression with

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somatizing tendencies shows nearly exclusively somatic symptoms, which are considered by patients as primary cause for consulting a physician. Depressive symptoms can often be experienced as less intense compared to the pain complaints, which in turn can lead the attending physician to misinterpret the nature of psychopathology. Other depressive symptoms like insomnia, lack of concentration or anhedonia are erroneously seen as resulting directly from pain, whereas their association with depression is ignored [3].

One big problem is that patients with pain symptoms and depression often do not get the right treatment. Since every doctor, no matter which specialization, is familiar with the topic of pain, it is always in his or her own area of expertise, be it orthopedics, surgery, internal medicine, neurology or others, that an appropriate therapy is attempted. Valuable time is lost, which would allow adequate therapy.

The association of both pain and depression

A positive association between painful physical symptoms and depression is well known, whereby some studies reported the onset of pain prior to that of depression and others found the reverse temporal relation [5]. Depression seems to predict the development of pain better than other predictors [6]. The relationship between depression and pain might underlie different models:

1) a mutual causation
2) a bi-directional relationship between pain complaint and depressive disorders: a disequilibrium in one functional system tends to cause nonlinear changes in other functional systems
3) third party factors might underlie both depression and pain, such as genetic aspects; or attachment aspects which have an impact on emotional processes as well as on the pain processing system via the cortisol system [14]
4) depressed mood and physical pain can reflect two sides of the same coin, e.g. based in neurobiology [7, 8]. Both depression and pain can be modeled as an accumulation of allostatic load, which is responsible for greater vulnerability and in turn for an increased common likelihood of the manifestation of depression or pain syndromes [9]
5) From a philosophical point of view, depression could also be viewed as a further developed cortical of the archaic pain system (subcortical / spinal) through the added consciousness.

Neurobiological aspects

A numerous of single finding on both depression and pain exist and are often overlapping. In an overview the relevant neurobiological aspects are described [3].

Anatomic regions of affect regulation (anterior cingulate cortex, amygdala, hippocampus and thalamus) being connected with pain-related structures (periaqueductal gray matter, rostral-ventromedial medulla), or being highly abundant in opioid receptors (hypothalamus, amygdala) and regions involved in both sources of information (cerebellum, insular cortex, nucleus accumbens, somatosensory cortex, dorsolateral prefrontal cortex, hypothalamus and pituitary gland)

Neurochemical dysregulations of various neurotransmitters, concerning the noradrenergic and especially the serotonergic system [10]. Experimentally higher pain thresholds were found, but simultaneously elevated clinical pain symptoms. This constellation was attributed to a diminished processing of nociceptive stimuli at spinal and subcortical stages being responsible for both a decreased pain sensitivity in superficial tissue as well as an insufficient activation of the descending pain-inhibitory system leading to an increase of pain sensitivity for deep tissue stimulation and therefore clinical pain problems [11,12].

Endocrinological dysregulations of the hypothalamic-pituitary-adrenal axis (HPA axis) resulting in higher glucocorticoid levels and depletion of serotonin and noradrenaline and therefore in a functional reduction of the descending pain-inhibition and in damage of muscle (leading to chronic pain), bone and neural tissue, especially of the hippocampus [13]. As well, enhancement of cytokines and downregulation of neurotrophic factors are involved in both depression and pain.

Genetic aspects: There are very interesting links between genetic predisposition, epigenetics, psychosocial development, including attachment aspects, to the manifest experience of depression and pain. Particularly impressive is the studies of Meaney and colleagues that suggested that the maternal care behavior changes time-stable DNA methylation at the promoter sequence of the glucocorticoid receptor gene influencing resilience in adulthood and probably therefore the vulnerability for several mental disorders such as affective disorders [14]. The enormous wealth of psychological findings on depression and pain (see overview) could be epiphenomena of a neurobiological basis or integrating interacting mechanisms [3].

Pharmacological treatment strategies

Antidepressants show alleviating effects both for depressive and pain symptoms. Not only do the antidepressants modulate neurotransmitter systems, but also opioid receptors as well as endocrine, immune and signaling-related mediators, which are in part associated with the pain system and help in returning a deranged HPA axis back to equilibrium [15-17]. Furthermore, antidepressants (especially those with both serotoninergic and noradrenergic qualities) normalize the insufficiently active descending pain-inhibiting tracts by increasing the availability of both serotonin and noradrenaline in these top-down modulatory circuits with the most evidence for synaptic cleft at the dorsal horn neurons, but probably also in higher areas such as the rostral-ventromedial medulla as well as by their neuroplastic effects [18-20].

A large meta-analysis on the effectiveness of different antidepressant classes to alleviate pain in depressed patients was performed [21]. It could be shown that the analgesic effects of different antidepressant classes (selective serotonin-noradrenaline reuptake inhibitors (SSNRI), selective serotonin reuptake inhibitors (SSRI) and tri-/tetracyclic antidepressants (TCA)) can be interpreted as largely equivalent. As well a strong positive correlation between their effectiveness on the mood and their positive effect for pain relief of the patients was found indicating a close relationship of antidepressant treatment effects and pain relief. Interestingly, of 14 SSNRI studies all but one and four of the six included studies which assessed SSRI effects are connected with industrial

affiliations [22-26]. In contrast, only one study of all the placebo- and non-placebo-controlled TCA studies had industrial affiliations [27].

Further pharmacological strategies involve anticonvulsants used in the treatment of chronic pain, mainly for neuropathic and paroxysmal pain or pharmaceutical options which refer to exclusively pain symptoms, such as non-steroidal anti-inflammatory drugs or opioids as well as "co-analgesics" as ketamine and corticosteroids [28]. However, pharmacological treatments on depression, pain and function are not impressive [29].

Non-pharmacological treatment strategies

In clinical practice, the very intensive use of non-pharmacological strategies for pain symptoms of depressive patients is standard and now indispensable. These include in particular psychological approaches, such as cognitive-behavioral psychotherapy, specialized pain-focused approaches, schema therapy, trauma therapy, psychodynamic therapies with object-relationship-theoretical and attachment-oriented approaches, mindfulness and acceptance and commitment therapy, and others (see [3]).

Other non-pharmaceutical treatments for depression with combined pain symptoms are physiotherapy and physical therapy (for example immobilization or training of the musculoskeletal system), exercise therapy (improvement of proprioception and self-acceptance). Furthermore, there is a multitude of clinically established resource-oriented methods such as ergo-, art- and music-therapy, even though there are practically no evidence-based evaluation studies regarding these therapies for patients with depression and pain. Active and receptive music therapy show reduction in pain through the emotional dimension of chronic pain, however empirical evidence is still low due to a lack of studies [30, 31]. In our own work we were able to identify the reduction of a simulated chronic pain in depressed patients when music was used in an experimental setting [32].

Further strategies, such as chemo-, radio-, hormone- and neurosurgical therapies, are applied if the pain is in the foreground. The evidence for transcutaneous electric nerve stimulation (TENS), despite its popular use, is still low [33]. The repetitive transcranial magnetic stimulation (rTMS) might be another treatment perspective for concurrent pain and depressive symptoms [34].

Overall, it is striking how small the evidence is in terms of practical application studies of such non-pharmaceutical strategies if compared to the multitude of pharmaceutical studies, which are often associated with the industry.

Stumbling blocks

There is no question that patients with depression and pain symptoms are severely handicapped by a terrifying number of obstacles in their therapy and are - not least because of these - exposed to a high risk of a long-term deterioration of their illness. Some of these obstacles are named here:

Research: Due to industrial affiliations and the corresponding availability of financial resources, pharmaceutical studies are conducted much more frequently and to a much greater extent than non-pharmaceutical studies. As a result, it seems that pharmaceutical methods are much more helpful than other methods (such as inpatient psychotherapy), or that some agents are more helpful than others. For example, there are a lot of studies on drugs, but nearly no studies on music therapy (which has a high impact in these patients); as well, there are many studies on duloxetine, whereas far fewer studies have been done on TCA, although TCA are often applied in patients with pain.

Publication: On the one hand studies with industrial affiliations have much more possibilities to succeed in a publication than independent studies. For example, the financial resources enable perfect study designs, and the journals enjoy a good reputation when reporting on pharmacological innovations. On the other hand, research with no or negative results is known to have a very low probability of being able to succeed in a publication than research with significant findings.

Areas of expertise: Pain is the medicine topic par excellence. Every discipline within medicine claims this topic in its own way. An interdisciplinary exchange is still seen reluctant, maybe due to unspoken reasons of competition. Thus, it happens that patients who urgently need to be referred for long-term psychosomatic therapy are assigned to an operation or an otherwise supposedly specialist treatment. It is not uncommon for patients with chronic pain to undergo psychosomatic rehabilitation treatment after a number of unsuccessful surgeries, but little is achieved psychosomatically as the help should have taken place earlier. The transfer into a specific psychosomatic therapy is often only for damage limitation and "acceptance therapy", but no more for the actual improvement of the pain, which would have been possible on a psychosomatic level, if a timely assignment had been made.

Professionals' interests: Neither psychosomatics, nor psychotherapy, behavioral medicine or behavioral therapy, etc. have a sufficient influence in the medical professional society, which would lead to be taken seriously for effective therapy. This is because only professionals, i.e., Psychosomatic or psychotherapists themselves, can judge professionally their field of expertise. Even large-scale studies on the treatment of pain in depression can only be carried out once the infrastructure for such studies has been established. However, this is only possible if this topic can also be assigned as an area primarily related to the psychosomatic field. Interestingly, there seems to be a negative feedback-loop: Since psychosomatics is not yet fully accepted in the large fields of pain medicine, psychosomatics does not even have the self-image for it. And that is exactly why psychosomatics will continue to be hired behind.

Psychopathology: Patients with pain in depression often show a very passive attitude. They show social withdrawal and are more willing to endure the pain than to take steps forward, which often reflects an individual functionality. Nevertheless, the nature of this syndrome is diametrically opposed to an independent commitment to the needs of patients. Also, they tend to passively take a hopeful drug and trust in the physician rather than practice activity and self-efficacy, what in turn is a disturbance-maintaining behavior. Physicians themselves are flattered to possibly be able to help with their art and respond to this relationship offer. They prescribe medication without transferring the patients to

long-term psychotherapy or psychosomatic therapy. The desire for pharmacotherapy comes through more than other procedures that can be much more helpful and sustainable in the long term. Interest associations of patients with pain and depression are therefore rather rare, so there is also a patients' lobby bias.

Conclusion

Treatment of pain in primary depressive disorders is a treatment of the depressive disorder itself. This seems to be mostly independent of the method, e.g. which class of antidepressant or psychotherapeutic method. It is only essential that the depressive disorder is treated successfully. The improvement of the affective system leads to the normalization of the pain system resulting in a relief of pain. This seems to be evident for everybody, but the opposite is usually the case in clinical practice. Physicians still refrain from planning an individual successful antidepressant treatment but continue to choose medicines which are supposed to be effective on pain according to industrial studies. It is crucial to cause a remission of the depression, by whatever means. So, it would be important that - when drugs are used - they have as little side effects as possible for the patient and at the same time develop a good antidepressant effect. The main focus here is on the antidepressant treatment, not on the pain treatment. But other treatment strategies – especially psychotherapy or familiar methods, such as music therapy – should be applied, if a sustained remission of depression can be suspected in the individual case.

Not infrequently, patients with pain and depressive mood are still treated only pain-focused and no antidepressant strategies are used, let alone a somato-mental disorder model developed together with the patient in order to derive corresponding behavior modifications. In psychosomatic inpatient treatments does this first causal approach usually take place. However, until the patients come to this point, the disease is often already advanced. It is particularly interesting that the professional world revolves around the same own axis and - whether for economic reasons, whether from solidarization phenomena – clinicians do not dare to advance necessary steps in favor of the affected patients: on an individual-clinical level, as well as at research and health policy level. Despite these obstacles, guidelines that result from literary views and experience are useful and should be developed. We have already proposed first guidelines. After publication of the meta-analyis here are some further important keynotes for the treatment of patients with primary depressive disorders and comorbid pain symptoms:

1. Careful diagnostics, addressing both somatic and psychosocial factors, may allow for therapy specifically directed towards pain at an early stage.
2. Treatment of the pain symptoms is not necessary, but especially a treatment of depression, which may not necessarily be just on a medication basis
3. The effectiveness of the treatment of depression is decisive, not certain antidepressant substance groups. For the individual patient, this means that the choice of antidepressant is based on the individual effect / side effect profile, not on a supposedly better analgesic effect.
4. Of course, this does not preclude additional suitable analgesic therapy, which in turn may have effects on depression.
5. With the reduction of depressive symptoms, a normalization of the pain system can be expected.

Conflicts of interest

The author declares no conflict of interest

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