

Chapter 7

Pain in Depressive Disorders

Stefan Gebhardt and Stefan Lautenbacher

7.1 Pain: A Symptom of Depression Fallen into Oblivion?

For ages pain complaints of patients suffering from depression belong to the everyday challenges of general practitioner. Typical diagnostic designations comprised ‘*dépression larvée*’ or ‘masked depression’ in the past. In some cases, depressive symptoms are masked by pain symptoms and therefore ignored by the physicians. Up to half of the patients suffering from acute depression are not diagnosed as such, possibly because they present with bodily or pain symptoms, respectively, rather than with symptoms classically known for depression. Pain ranks second, only yielding to insomnia, among the somatic and vegetative symptoms of depression and occurs in over 50 % of the patients with depression.

Thus, one might wonder why pain carries little weight in the diagnosis of depression. In recent years, pain and somatic symptoms has been considered more and more in psychiatry and psychosomatics as concomitant of depression, and has now become the status of a common comorbidity.

While there is good evidence for symptoms of depression in patients with chronic pain according to numerous studies, comparably little is known about the other ‘relation’: the role of pain in depressive disorders. To compensate for this neglect, the focus of this book chapter is laid on pain in depression. This approach appears especially worthwhile in light of the high number of affected patients and their poor prognosis compared to patients with depression but without pain.

S. Gebhardt (✉)

Department of General Psychiatry, Psychotherapy and Psychosomatics II,
Psychiatric Center Nordbaden, Heidelberger St. 1a, D-69168, Wiesloch, Germany
e-mail: stefan.gebhardt@uni-marburg.de

S. Lautenbacher

Physiological Psychology, Otto-Friedrich-University of Bamberg, Bamberg, Germany

7.2 Epidemiological Aspects

About 5–13% of the general population suffers eventually from a depressive disorder; a third hereof can be classified as chronic. The mean prevalence, according to 14 studies on pain symptoms in patients with depression, amounts to 65 % (range 15–100%; see [1]), in which musculoskeletal pain and headaches are most common. A review of 70 studies on outpatients showed a positive association between painful physical symptoms and depression [12]; some studies reported the onset of pain prior to that of depression and others found the reverse temporal relation. According to Magni et al. [34], patients suffering from chronic pain have a 2.85-fold risk of developing depression, whereas patients with depression have a 2.14-fold risk of developing pain disorders. Altogether, depression seems to predict the development of pain better than other predictors, though this relationship was found to be only moderate and potentially nonlinear.

A large cross-sectional study on 19,000 members of the general population [39] showed 43.4 % of patients with depressive disorder presenting with at least one painful physical symptom, the intensity of which was four times higher than in patients without depressive disorders. An increase in the number of depressive symptoms also increased the probability of patients suffering from pain symptoms. Interestingly, patients with depression are also suffering frequently from multilocal pain (see [1]).

In contrast, the prevalence of depressive disorders in patients suffering from chronic pain is about 40–50%; differences in epidemiologic methodology, however, lead to a great variability, with reports ranging from 1.5–100% (see [1]).

7.3 Pain Complaints on the Basis of Depression

Apart from typical symptoms like depressed mood, anhedonia and loss of interest, psychomotor retardation, concentration deficits, insomnia, loss of appetite or libido, low self-esteem and negative cognitions, depressive patients often suffer from pain, unpleasant body and pressure sensations in the head, stomach or abdomen, chest and other areas of the body [39]. Thereby, symptom clusters differ among various depression forms. Whereas young adult patients often appear strongly emotionally distressed, but do not complain of somatic symptoms, older patients with a masked depression and somatoform tendencies present nearly exclusively with somatic symptoms, which are experienced by the patients as primary cause for consulting a physician. The pain complaints lead to a high level of suffering and can become a matter of major subjective concern, consuming much of the cognitive resources. Depressive symptoms can often be experienced as less intense compared to the pain complaints, which in turn can lead the attended physician to misinterpret the nature of psychopathology. Other depressive symptoms like insomnia, lack of concentration or anhedonia are erroneously seen as directly resulting from pain, whereas their association with depression is ignored. Furthermore, subjects with major depressive disorder and comorbid painful physical symptoms are not only more likely to have atypical or melancholic features of depression, but also to show a greater overall number of other comorbid mental disorders.

7.4 Theoretical Concepts of the Connection Between Pain and Depression

There has been different models set up to explain the potential relationships between these two entities, pain and depression.

1. A depressive disorder represents a vulnerability factor and predisposition for pain as well as for its chronification. It is well known that many patients with recurrent episodes of depression for years tend to develop chronic pain. The higher risk for developing pain may be due to depression itself or due to a genetic disposition for both depression and pain. Accordingly, family studies have repeatedly shown an increased comorbidity of both conditions.
2. Chronic pain may represent a form of a specific type of depression ('masked depression'). According to the current knowledge, this appears to hold true only for a small subgroup of patients.
3. Enduring somatic complaints may represent the cause for a depression, either due to a direct emotional reaction or via a change of behavioral patterns resulting in less positive reinforcement.
4. Environmental (e.g., stress) factors may underlie both depression and pain and are able to increase the risk of the co-occurrence of pain and depression.
5. Depressed mood and pain may reflect two sides of the same coin, based on shared pathophysiology (see below).
6. More complex models comprise a dynamic component: An interactive relationship between pain complaints and depressive disorders has been assumed, in which disequilibrium in one functional system (as it is the case in chronic pain) tends to cause nonlinear changes in other functional systems (e.g., emotion regulation, stress coping or psychosocial relations) [44]. Thus, even small disturbances of the affective system may result in severe pain symptoms and vice versa. Alternatively, 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 likelihood of the common manifestation of depression and pain [41].
7. Finally, cultural influences may lead to the predominant manifestation of pain symptoms in depression, if pain as a seemingly bodily symptom is more accepted within the respective population.

7.5 Recovery Rates of Depression and Pain

Some observations have shown different short- and long-term courses of affective and pain symptoms during treatment. The improvement of mood in the course of an electroconvulsive treatment or a 3-week cognitive-behavioral therapy was not accompanied by a similar amelioration of pain [14, 27]. However, in an 8-week placebo-controlled trial on the efficacy of pregabalin in posttraumatic peripheral neuropathic pain a linear relationship of the changes in pain severity with the changes in daily function, anxiety, depression, and sleep was found [50]. In a 12-month longitudinal analysis change in pain was a strong predictor of subsequent

depression severity, and vice versa. Thus, pain and depression seem to have strong and similar effects on one another when assessed over 1 year [26].

7.6 Neurotransmitter Systems

There are several pathophysiological associations between depression and pain. On a neurochemical level both entities present as dysregulation of various neurotransmitters, especially concerning the noradrenergic and serotonergic system. In depression both neurotransmitters are supposed to play a central role in the dorsal raphe nucleus (serotonin neurons) and locus coeruleus (noradrenergic neurons) projections to the cerebral cortex and limbic system. It is assumed that depression is associated with a down-regulation of postsynaptic 5-HT_{1A} receptors [33]. In case of pain, serotonin and noradrenaline are essential in the descending inhibitory pathways from the brain stem to the dorsal horn neurons in the spinal cord (see below).

We examined the relationship between pain sensitivity and serotonergic function (measured by the neuroendocrine responsiveness to the serotonergic agent clomipramine) in 19 patients with major depression. As a result, in patients characterized by a reduced cortisol response to clomipramine, suggestive of reduced serotonergic neurotransmission, a decreased pain sensitivity was demonstrated compared to the patient group with a high neuroendocrine responsiveness [28]. Sleep deprivation therapy, which is well documented in its pro-serotonergic properties leading to short-term improvement of mood, was found to reverse pain sensitivity towards an overnight decrease of thermal pain threshold [27]. In addition, patients in the sleep deprivation group exhibited after therapy decreased basal cortisol levels and increased cortisol response to clomipramine compared to patients without sleep deprivation, which is suggestive of a normalization of serotonergic neurotransmission. These findings point to an involvement of serotonergic dysfunction underlying altered pain perception in depression.

7.7 The Role of Endocrine, Immune and Neurotrophic Factors

Monoaminergic neurons of the reticular formation are connected to the hypothalamic-pituitary-adrenal axis (HPA axis) through their abundance of glucocorticoid receptors. Prolonged stress might disrupt the glucocorticoid feedback loop, resulting in higher glucocorticoid levels, which fail in turn to deactivate the HPA axis. In consequence during chronic stress or depression, constantly high levels of glucocorticoids in the blood plasma and the resulting depletion of serotonin and noradrenaline might lead to a functional reduction of the descending pain inhibition. Thus, endocrine and neuronal mechanisms of the stress response (through the HPA-axis or the locus coeruleus) may interactively influence the intensity of pain perception.

Acute pain leads in turn to an immediate reaction of corticotrophin-releasing-hormone (CRH), proopiomelanocortin (POMC), endorphins and corticotrophin (ACTH), with ACTH activating the adrenal cortex to release cortisol. Corticoids act on the immune system and the endogenous opioid system. Opioids further modulate the release of cortisol [38]. If the output of cortisol is prolonged—as in major depression—it may damage in addition muscle, bone and neural tissue and produce the somatic basis for chronic pain. As well, sustained elevated corticoid levels may damage hippocampal neurons, particularly CA3 pyramidal neurons and may reduce hippocampal neurogenesis [11, 36]; changes in the function of the hippocampal complex may contribute to persistent pain states [49].

As well, enhanced cytokines as interleukine-6 (Il-6), C-reactive protein (CRP), tumor necrosis factor alpha (TNF-alpha), have been reported in both patients with depression and in patients with pain. Cytokines also activate CRH, which increases serum glucocorticoid levels, contributing to the conditions just described.

Further pathophysiological relations between pain and depression concern the down-regulation of neurotrophic factors. The most important is the brain-derived neurotrophic factor (BDNF), which is involved in neuroplasticity and neurogenesis, especially in the hippocampus. Another relevant neurotrophic factor is neurokinin-1 (NK-1). The neurokinin-1 receptors, mediating the action of substance P, have been found to be active in the limbic system, the raphe nuclei and the locus coeruleus. Neurokinin-1 receptor antagonists have been linked with potential antidepressant and analgesic effects, involving serotonergic, noradrenergic and hippocampal neurons. Thus, nociceptive impulses are relayed to areas of the brain, which are also involved in the formation and processing of emotions such as stress, anxiety or sadness as well as the appraisal thereof.

7.8 Neuroanatomy

Anatomical regions involved in affect regulation play also an important role in the pain system (anterior cingulate cortex, amygdala, hippocampus and thalamus) and are connected via multiple pathways to more specific pain-related structures (periaqueductal gray matter, rostral-ventromedial medulla) (see [41]). In particular, there is increasing evidence for the perspective of the amygdala as an important center for pain and its emotional component. The latero-capsular division of the central nucleus of the amygdala is hypothesized to integrate nociceptive information with polymodal information about the internal and external bodily environment. Further regions involved in both pain and emotional processing are the cerebellum, the insular cortex, the nucleus accumbens and the somatosensory cortex [9].

Additionally, areas of the brain involved in regulation of emotion and behavior are also highly abundant in opioid receptors, like the hypothalamus or the amygdala.

Furthermore, the central nervous pain mechanisms comprise cognitive (dorsolateral prefrontal cortex) and autonomic/endocrine components of processing

(e.g., hypothalamus and pituitary gland) of pain perception, which both are also of high relevance for the etiology of affective disorders.

7.9 The Importance of the Descending Pain-Inhibiting System

A reduction of sensitivity to pain has been found in patients with depressive disorders. This has been explained by pain-specific perceptual deficits rather than by affective indifference to aversive stimuli [16]. Especially the thresholds for thermal pain are higher in depressive patients (even more so apparently in female patients), albeit the thresholds for non-painful sensations like warmth, cold and vibration are only slightly affected, whereas those for ischemic pain are even reduced [5].

It is hypothesized that a diminished processing of nociceptive stimuli at spinal and subcortical stages can be made responsible for both this thermal hypoalgesia (decrease in pain sensitivity in superficial tissue) as well as an insufficient activation of descending pain-inhibiting pathways leading to an increase in pain sensitivity for deep tissue stimulation (ischemia) and in clinical pain problems [3]. In a recent study Klauenberg et al. [24] demonstrated decreased cold pain thresholds and an enhanced wind-up ratio in the quantitative sensory testing (QST) paradigm in depressive patients, indicating an increased central hyperexcitability, e.g. by deficient serotonergic inhibitory functions.

Major components of the descending pain-inhibitory system are the serotonergic raphe nuclei, the noradrenergic locus coeruleus, the rostral-ventromedial medulla and the limbic system, which exhibit, like the periaqueductal gray, a high density of opioid receptors and is therefore involved in regulation and control of affectivity. The activation of the descending pain-inhibiting pathways leads to a release of the neurotransmitters noradrenaline and serotonin from neurons within the reticular formation. This inhibits neurons in the substantia gelatinosa and spongiosa of the dorsal horn (rexed laminae I and II), whereby the somatic perceptions are suppressed. Thus, the neurons of the first and second laminae of the dorsal horn function work as a gate mechanism, depending on activating influences (gate-control-theory), which stem from non-nociceptive peripheral afferents, the descending pain-inhibiting system as well as from the endogenous opioid system.

7.10 Psychological Aspects

Both depression and chronic pain are considered as biopsychosocial phenomena, which are characterized by a dynamic interaction of biological, psychological and social factors. At least at later stages, it is functionally no longer of importance whether these factors are predispositions or consequences of the syndromes. Patients of both entities often show deficits regarding their coping strategies, recreational

possibilities and social competencies. Patients with depression and pain show more somatic anxiety, more muscular tension, more inhibition of aggression, but no significant differences in guilt compared to patients with depression without pain. Affective and bodily distress, especially depressive mood, predisposes individuals to increase attention to and more negative emotions about pain.

Negative anticipations like in depression cause a more severe experience of pain, which are associated with an elevated activity of the anterior cingulate gyrus [42]. Somatic attribution (the tendency of attributing bodily discomfort to somatic causes), contrarily to psychological attribution, has an unfavorable influence on the quality of life as well as the prognosis of depression. Interestingly, pain-related beliefs and cognitions seem to have more influence on the development and maintenance of disability and distress than pain intensity.

While psychosocial factors are surely not solely responsible for chronic pain they do play an important role in its development and exacerbation. Various psychosocial factors (like conflicts in interpersonal relations or loss of employment) and especially proneness to depression or anxiety symptoms influence and aggravate the development and intensity of pain as well as the dysfunctionality and impairment caused by it. Patients with depression suffer from dysfunctional cognitions such as catastrophizing, learned helplessness, low self-esteem, pessimistic expectations for the future or excessive self-demand, which are factors promoting the transformation of acute pain into its chronic form (see [41]). Patients with depression are known to be biased in retrieval towards more negative experiences, which favors the expectation of poor outcomes in painful conditions. Furthermore, pain is perceived more intense when it is judged as threatening and harming, which patients with depression often do. This in turn reduces the overall subjective well-being and promotes depression. Negative forms of self-image can become so rigid and dominant that the patients with depression lose the ability to surcease from them. Pain may serve as compelling evidence that no change to the better can be expected.

7.11 The Interaction Between Mood and Musculoskeletal Pain

A noteworthy mutual interaction between psychosocial and somatic symptoms, leading to pain exacerbation in depression, is the so-called 'deconditioning syndrome', resulting from the reduction of activity: abated drive may lead to physical inactivity and ultimately to deficits in muscle strength and reduction of mobility. Pain may follow because barely used and atrophied muscles are highly pain sensitive. By that, small muscle lesions are sufficient to trigger further relieving and avoidance behavior, which in turn leads to further physical deconditioning, with a vicious cycle of inactivity and pain as result. Such a deconditioning syndrome, which has often been proposed as being functionally related to chronic back pain [6], may result into a further reduction of pleasant and rewarding activities and into a maintenance or even increase of depressive symptoms. Such critical relieving

behavior is often reinforced by treatments rendering passive, for example by bed rest. On the same time pain leads to sleep dysregulation being associated with both depression and pain pathogenesis. Therefore, we consider sleep dysregulation a potential core mechanism of the link between depression and pain [30].

7.12 Therapeutical Relationship, Clinical History and Diagnostics

Prior to actual diagnostics and therapy it is necessary to establish a viable relationship between patient and therapist. This relationship should be based on empathy and allow for careful analysis of the problems as well as for the successive establishment of a 'subjective disease model', which helps to explain the treatment rationale. Interdisciplinary diagnostics require an initial anamnesis with intense investigation of the clinical history, including the sociobiographical, family, drug and substance as well as vegetative anamnesis. The pain history mainly includes the following points: localization, radiation, head's areas, intensity, attribution, character, temporal progression (rhythm), catalysts, attendant symptoms, pain-related impairment, and relevance for everyday life. An anamnesis by proxy may yield information regarding compliance or perpetuating factors. The psychopathological and physical (including neurological) findings are also indicative. The ascertainment of pain-related and more general cognitions and emotions as well as resources and subjective explanations are especially relevant for psychotherapy. For typical chronic pain syndromes such as chronic headache or chronic back pain the actual diagnostic criteria and recommendations of the according societies are used (e.g., International Headache Society).

In addition, psychometric evaluation allows for higher diagnostic objectivity. The main inventories used for severity assessment of depression are Beck's Depression Inventory (BDI/BDI-II) [4, 19] and Hamilton Rating Scale for Depression [17]. Advisable for objective classificatory diagnosis is SKID-I/II [52]. Pain intensity as the most often used pain parameter can be best and simplest quantified by Numerical Rating Scales, which show good compliance, responsiveness and usability [20]. There is no literature available for answering the question whether multidimensional tools for assessing dimensions like pain intensity and pain unpleasantness, pain such as the McGill Pain Questionnaire (MPQ) are suitable for use in patients with depression, who may have difficulties with cognitively too sophisticated and stressful tools. The same applies to otherwise widely used tools like the Multidimensional Pain Inventory (MPI), which is suitable to assess patients' coping with chronic pain. It provides a psychosocial classification system that categorizes patients into three coping styles: adaptive, dysfunctional, and interpersonally distressed, which might be styles specifically related to depression.

Some tests for the differentiation of various types of pain are also available, i.e. PainDetect [10] for neuropathic pain, however there are scarcely clinically established reliable questionnaires on diagnosing specific pain syndromes such as

different types of headache. For the emotional aspects of pain the following instruments can be used: the Pain Catastrophizing Scale (PCS) [46], the Fear of Pain Questionnaire (FPQ) [37] and the Pain Anxiety and Symptom Scale (PASS) [35]. The assessment of psychosocial impairment on various levels is best accomplished through the Pain Disability Index (PDI; [7]).

Finally, a pain-orientated physical examination including in individual cases electrophysiological methods and imaging may be of importance. These examinations for pain diagnostics, however, should be carried out with a clear rational and to a tolerable and sensible extent. Pain syndromes need to be isolated diagnostically as good as possible regarding their etiological specificity in order to initiate appropriate and evidence-based therapy.

Prevalent differential diagnoses of chronic pain apart from depressive disorders like somatoform, anxiety or personality disorders or addictions have to be ruled out. In case of patients suffering from depression or pain symptoms as a result of addiction (especially to analgesics or sedatives), detoxification and rehabilitation regimes need to be put into effect. In these cases, pain diagnostics and treatment have to be adjusted to the specific phase of addiction treatment. Pain symptoms might disappear under abstinence from psychotropic substances.

The overlap of depression, pain and somatoform disorder is becoming more and more common. A thorough classification is therefore necessary, because treatment and prognosis depend on it. However, some of these diagnostic concepts have been criticized as being too unspecific, e.g. in somatoform disorders or fibromyalgia, to be useful in differentially guiding treatment. For example, fibromyalgia comprises as core symptoms generalized musculoskeletal pain, tender points, stiffness and fatigue. Familial aggregation studies and the symptomatology suggest a (likely genetic) linkage of fibromyalgia with depression, in the sense of fibromyalgia being a depression spectrum disorder [40].

7.13 General Therapeutic Aspects

The available data on therapy effects on pain in depression are still limited. Therefore a few common sense principles for the planning of a therapy shall be given:

1. In order to prevent chronification, an early and comprehensive (pharmacological and non-pharmacological) intervention is paramount for patients suffering from depression and comorbid pain symptoms. Each barrage of nociceptive impulses on the CNS is capable of developing neurobiological pain memory traces and/or a sustained focus of attention towards pain, which in turn may lead to an increase in pain. It is important to note that many patients consult a pain specialist only after soliciting laymen and paramedical personnel for advice or after giving self-therapy a try. This is a phase when the process of chronification has often already begun. Another failure may be to refer the patients too late to multidisciplinary inpatient treatment programs, especially when pain quality or intensity has already changed and if 'red flags' as indicators for unclear or fatal

underlying diseases have been raised, which require further clarification or—in case of severe major depression—urgent treatment. However, inefficient and unnecessarily long inpatient treatment can itself promote chronification; therefore, treatment aims and duration should be carefully determined at the beginning.

2. A survey of the patient's general health status, an analysis of his/her motivation and the development of a disease model as well as of a common therapy plan should be carried out. In order to prevent too high expectancies and thereby frustration, it is necessary to outline attainable preliminary goals. A diary of pain, mood and pain cognitions, in which also attendant symptoms should be recorded, can be beneficial.
3. Pharmacotherapy has to be managed by experienced physicians, who are knowledgeable in the fields of psychiatry and pain treatment; the occurrence of drug interactions must be kept in mind and monitored.
4. If symptoms of depression predominate, these should be treated in the first place, pharmacologically with antidepressants as well as through psychotherapy, because in such cases pain often disappears during and after sufficient antidepressant therapy. Additional prescription of analgesics is indicated when a comorbid specific pain syndrome, e.g. migraine, can be diagnosed.
5. Vice versa, patients suffering primarily from pain with secondary depression symptoms might experience improvement of depression when pain has been alleviated. If pain is the leading symptom, a comprehensive initial trial with analgesics and treatment of the underlying disease—if present—(e.g., treatment for diabetes in cases of polyneuropathy) are mandatory. If need be, co-analgesics like antidepressants or anticonvulsants can be prescribed.
6. In cases where depression and chronic pain interact and aggravate each other, like in patients with immobilization or insomnia, there is risk of the development of a vicious cycle. Mediating factors of these sorts exacerbate chronification and should therefore be intensively treated during early stages of therapy.
7. Pharmacotherapy should be kept as simple and transparent as possible and should be oriented upon the interactive syndrome of pain and depression. For example: In patients suffering from pain, insomnia or depression symptoms are to be treated with antidepressants. In patients suffering from depression or with a history of a depressive disorder, medications that may induce symptoms of depression (e.g., flunarizine for the treatment of migraine) should be avoided. When prescribing opioid analgesics or benzodiazepines, the risk of addiction has to be kept in mind. Nevertheless, opioids can be helpful in individual cases of severe pain symptoms; a frequent monitoring is necessary and the application should be limited in time except for specific indications such as malignant diseases.
8. In most cases of this unresponsive comorbid condition of pain and depression, patience on behalf of both therapist and patient is called for, as correct pharmaceutical adjustment (dosage, pharmacological mechanisms or compatibility) need to be found by careful trials according to the patient's individual disposition. Therapy controls for pain, mood and mediating factor like insomnia and immobilization are indispensable.

9. Psychological factors should be addressed during planning of therapy or rehabilitation to assure optimal therapy effects. They can present as risk factor (e.g. pessimistic expectancy of therapy effects) or resilience factor (e.g. good experience in earlier trials with certain treatment strategies). This can take the form of psychotherapeutic or psychosocial support.
10. If the comorbid condition has already become chronic, psychotherapeutic, activating and social reintegrating measures should be paramount. Thereby the patient can learn that, in spite of pain or depression, he or she is able to manage part of the requirements of daily living.
11. Multimodal pain therapy with case management guided by the recommendations of interdisciplinary pain conferences, which allow for the multiprofessional discussion of the patients' problems, is necessary as soon as symptoms have become persistent.

7.14 Pharmacotherapy

Three medication classes to treat chronic pain are available: opioids, non-opioids (such NSAIDs) and adjuvant (additional) therapy including antidepressants, anti-convulsants, corticosteroids and others. However, with respect to the comorbidity of depression and pain we prefer—according to the usual psychiatric practice—the antidepressant drugs.

7.14.1 Antidepressants

Antidepressants (AD) show alleviating effects both on pain and symptoms of depression as well as on associated symptoms (such as appetite loss, sleep disturbance, etc.). The antidepressants do not only modulate neurotransmitter systems, but also opioid receptors as well as endocrine, immune and signaling-related mediators (such as TNF-alpha, STAT3, c-jun, c-fos), which are in part associated with the pain system. They also help in returning a deranged HPA axis back to equilibrium. Furthermore, ADs (especially those with both serotonergic 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 more action in the synaptic cleft of the dorsal horn neurons, but probably also in higher areas such as the rostral-ventromedial medulla, though on the latter aspect there is still a lack of studies so far. However, the specific effects of antidepressants on pain modulation, especially in cortical and subcortical areas, are not entirely understood. The enkephalin induction hypothesis suggests anti-nociceptive effect by increased enkephalin activity through antidepressant drugs as seen under doxepin. Though there are several studies about the efficacy of antidepressants on chronic pain, studies on analgesic effects of

antidepressants in patients with depressive disorders are rare. Almost all recent studies have industrial affiliations.

Tricyclic Antidepressants (TCA) are an established therapeutic option for depression, but also show analgesic effects after few days in far lower doses (amitriptyline or clomipramine between 25 and 75 mg) compared to those required for antidepressant therapy. They are therefore often used for the treatment of neuropathic pain. Amitriptyline is especially indicated for painful polyneuropathy, postherpetic neuralgia and central pain syndromes. Besides amitriptyline and clomipramine, the TCAs imipramine, doxepin, and trimipramine have also been used for therapy of chronic pain of various origins and appeared to be efficient independently from their antidepressant effects. However TCAs have many side effects such as sedation, constipation, dry mouth, urinary retention, hypotension, tachycardia or cardiovascular dysfunctions.

Selective Serotonin-Noradrenaline Reuptake Inhibitors (SSNRIs) Venlafaxine and duloxetine represent antidepressants with a dual action as a viable modern option for the treatment of depression with comorbid pain. Furthermore, they cause significantly less (e.g. anticholinergic) side effects compared to TCAs. Clinical studies have shown significant positive effects of small doses (75–225 mg/day) of venlafaxine on neuropathic pain and migraine. Duloxetine, an SSNRI with good antidepressant capabilities, is also effective in the treatment of painful diabetic neuropathy. A significant reduction of pain through doses of 60 mg/day in patients with depressive disorders compared to placebo could be shown in most studies, whereas a few studies found no effect in comparison to placebo or paroxetine (e.g., [8]). Overall, duloxetine seems to be superior in reducing pain in patients with major depression compared to other ADs.

According to a meta-analysis on physical symptoms of depression [25], both duloxetine and paroxetine are—with similar effect sizes—statistically superior to placebo in reducing pain; however, the effect sizes were small in magnitude, so that the clinical significance is still uncertain (6 studies, duloxetine versus placebo; 4 studies; paroxetine versus placebo). In another industrially sponsored meta-analysis of 11 double-blind, placebo-controlled studies, duloxetine produced significant, but small effect sizes in reducing painful symptoms (Cohen's d 0.26) and depressive symptoms (0.25) [2]. Finally, in a recent analysis excluding industrial affiliations [47] four head-to-head trials comparing effects of SSRI (paroxetine) and SSNRI (duloxetine) on pain in a total of $n = 1,095$ patients with depressive disorders were identified. However, evidence quality of these studies, which were funded by the producer of duloxetine, was rated to be only low to moderate. The pooled analysis favored paroxetine, even at higher doses, albeit not significantly and to a clinically not meaningful extent. The authors stated that no conclusions about the superiority of one of the two drugs could be currently made; they recommended that clinicians should base their decisions about the appropriate antidepressant for their individual patients on other factors such as tolerability and side effect profiles.

ADs with Selective Serotonin/Noradrenaline Reuptake Inhibition (SSRIs, SNRIs) Although being effective in pain therapy and causing little side effects, they

have mostly been found to be inferior to TCAs or newer dual action ADs, like SSNRIs or mirtazapine. Paroxetine has also been effective in relieving pain when depression is not present, e.g. in diabetic neuropathy. For note, pain symptoms or other comorbid somatic diseases are significant predictors in depressive patients for poor or delayed responses to SSRIs. Even though single studies have reported serotonergic compared to noradrenergic drugs to be superior in reducing pain, no effect of SSRIs definitely similar to those of true analgesics could be identified. In an open-label study over 9 months in patients with depressive disorders significant improvement of pain could be observed with a plateau after 1 month [15]. A randomized, double-blind study revealed a better analgesic effect of fluoxetine in patients with somatoform pain disorder when these patients suffered in addition from depression; therefore, the authors suggested that the analgesic effect may be related to an antidepressant effect [32]. Other studies were uncontrolled, of short duration (averaging 9 weeks), and used doses that were subtherapeutic for sufficient antidepressant effects. In the treatment of diabetic neuropathy, SSRIs should be reserved for patients with coexistent depression; otherwise dual-action antidepressants seem to be better agents. At higher doses, paroxetine may also act as a serotonin/noradrenaline inhibitor. Altogether, the use of SSRIs can be recommended only if pain is a symptom of the affective disorder. Interactions with monoamine oxidase inhibitors, tramadol, or triptans in causing a serotonin syndrome have to be kept in mind. Finally, there are no conclusive studies on the analgesic effect of SNRIs (reboxetin).

Mirtazapine, a noradrenergic and specific serotonergic antidepressant (NSSA), has very occasionally shown effects of relieve on pain symptoms in patients with depression. It could, however, not be established, whether the reduction of pain was due to the reduction of depressive symptoms or consequence of a specific analgesic effect. Mirtazapine is also sometimes applied for the acute treatment of pain or the prophylaxis of chronic tension-type headache. Advantages lie in its positive effects on sleep normalization. It compares favorably to the TCAs, because of its superior profile of side effects, especially regarding anticholinergic effects; To the contrary, it often causes substantial weight gain due to its action as H1-receptor blocker.

7.14.2 Other Drugs for the Management of Chronic Pain in Depressive Disorders

Anticonvulsants (especially carbamazepine, lamotrigine, gabapentine and pregabalin) are also used in the treatment of chronic pain, mainly for neuropathic and paroxysmal pain. The analgesic effect of anticonvulsants depends on the drug's inhibition of higher impulse transmission in nociceptive neurons. They also influence the receptors of the glutamate system (AMPA, kainate and NMDA). Additional benefits may be due to their primary psychopharmacological targets as mood stabilizers (carbamazepine, lamotrigine) or anxiolytic drugs (pregabalin).

Further pharmacotherapeutic options for pain management, such as steroidal anti-inflammatory drugs (NSAIDs) or opioids, are not dependent on the coexistence of depression. In the therapy of chronic pain, opioid administration following the WHO-guidelines for treatment of tumor-pain is sometimes necessary to reduce pain and increase quality of life. Interestingly, tramadol has additional effects on noradrenergic and serotonin receptors and therefore some antidepressant effects.

However, various risks need to be considered when administering analgesics. Adverse side effects may appear, e.g. medication overuse headache (previously called 'rebound headache') or NSAID-induced nephropathies and gastropathies. Though there are some hints for short-term antidepressant effects of opioids by serotonergic and noradrenergic modulation, the development of addiction is a well-known and tremendous risk of a long-term application of opioids. Furthermore, decrease of efficiency, sexual dysfunctions and depression are common in long-term treatments with opiates. It is therefore necessary to have a pain-specialist carefully monitoring the therapy. Further, 'co-analgesics' as ketamine, metamizole or corticosteroids can reduce the tolerable doses of classical analgesics.

7.15 Treatment of Migraine in Depression

The prevalent migraine in patients with depression can be treated with venlafaxine, NSAIDs, antiemetics and the migraine-specific medications triptans and dihydroergotamines. Patients have to be informed about potential transient adverse events including chest or throat tightness, flushing, heat sensations, dizziness and nausea. Patients under co-medication of SSRIs/SNRIs and triptans carry a justifiable risk of the development of a serotonin syndrome and should particularly be warned of the early symptoms in order to seek medical care in time. A co-medication of triptans with monoamine oxidase inhibitors is contraindicated. If preventative treatment of migraine is indicated, several different classes of medication can be considered: β -blockers (e.g., propranolol, atenolol), calcium-channel blockers (e.g., verapamil), anticonvulsants (e.g., topiramate, gabapentin) and TCAs (e.g., amitriptyline). TCAs are more effective than SSRIs, although associated with stronger adverse effects; there is still fewer evidence for the beneficial effect of SSNRIs in the treatment of migraine (see [23]). Therefore, in comorbid depression and chronic migraine TCAs are still the drugs of first choice. Furthermore, non-pharmacological treatments are effective in comorbid depression and migraine: e.g., lifestyle education, self-management, relaxation with biofeedback and cognitive-behavioral training (see [13]).

7.16 Treatment of Fibromyalgia and Depression

For the treatment of *fibromyalgia* the antidepressants duloxetine, milnacipran and pregabalin are labeled in the USA, whereas for TCAs, SSRIs, opioids, and gabapentin the results are too mixed to justify this classification [48]. None of all these drugs

are approved by the European Medicines Agency (EMA); consequently, off-label use is the rule in Europe.

A German meta-analysis of drug treatment in fibromyalgia [45] gives as the only recommendation—based on moderate evidence—in the case of comorbid fibromyalgia and depressive disorder or general anxiety disorder the treatment with duloxetine 60 mg/day. If fibromyalgia occurs without the other two conditions, amitriptyline 10–50 mg/day can be also recommended. This meta-analysis presents as ‘open recommendations’: pregabalin (150–450 mg/day), duloxetine (60 mg/day, also in case of absence of comorbidities) and SSRIs (fluoxetine 20–40 mg/day, paroxetine 20–40 mg/day in case of comorbid depressive or anxiety disorders).

7.17 Non-pharmaceutical Strategies for Pain Management

Psychoeducation strategies are known to be very helpful in patients with both depressive disorders as well as chronic pain syndromes. They allow—among others—for regaining control over the situation, especially if they enforce self-responsibility tasks to be conducted by the patients. Such trainings in self-management skills may lead on the long run to an increase in perceived self-efficiency, a critical factor both for positive outcomes in the treatment of depression and chronic pain.

Psychotherapy is well established for the therapy of depression, especially in the form of cognitive behavioral therapy (CBT). Similarly, the successful treatment of chronic pain also includes psychotherapeutic measures, relaxation techniques (e.g. progressive muscle relaxation, biofeedback), pain coping training, self-assurance training, conflict and stress management. Over the past few years CBT in particular has developed empirically proven concepts for the modification of cognitive schemes regarding depression, pain processing and related fields, such as somatization, and for the behavioral activation of the immobile patients. Alternatively, acceptance-based interventions such as the mindfulness-based stress reduction program and the acceptance and commitment therapy can be applied with similar effects, though more high-quality studies are needed to give clear evidence for their efficiency (see [51]).

In a meta-analysis of psychological interventions for chronic low back pain run over 22 studies cognitive-behavioral and self-regulatory treatments proved to be specifically efficacious [21]. As well, multidisciplinary approaches that included psychological components displayed positive short-term effects on pain interference and positive long-term effects on the likelihood of return to work.

Due to the fact that comorbid pain and depression often show high tendencies for chronification, the establishment of a stable therapeutic relationship is particularly crucial, in order to achieve a long-term therapeutic regime. Aims of psychological pain therapy are mainly the reduction of functional impairment and the improvement of quality of life. Complete reduction of pain, however, is often neither a realistic nor an appropriate goal. Because patients tend to have uni-causal subjective disease models, with preference for somatic explanations because of the experiences of acute pain and its treatment, psychotherapy has to open the patient’s mind

for the concept of multiple influences including psychological. The patient should thereby develop a repertoire of personal and social resources, allowing for self-managed coping in order to be no longer helpless against pain [18]. Dysfunctional cognitions can be dismantled, for example, to let the patient comprehend that resting is good for acute pain, but not indicated as ongoing behavior during chronic pain, or that physical damage, pain and impairment are often not closely connected. Most importantly, the patient can learn that—even if the pain persists—quality of life can be regained.

Other non-pharmaceutical treatments for depression with combined pain symptoms are physiotherapy and physical therapy (for example activation in case of immobilization or training of the musculoskeletal system) as well as exercise therapy (improvement of proprioception and bodily self-acceptance). Guidelines exist for specific pain syndromes. For chronic non-specific low back pain all English published guidelines recommend patient education and exercise, whereby there is no consensus about the appropriate type of exercise. Furthermore, there is a multitude of clinically established resource-oriented methods such as ergo-, art- and music-therapy, even though there are nearly no studies establishing evidence for these therapies. Active and receptive music therapy claims reduction in pain through changes in the emotional processing of pain, although the empirical evidence is still scarce.

7.18 Natural and Therapeutic Course

The course of depression with pain symptoms is predicted by various prognostic factors. Prognostically favorable are: young age, higher socio-economic status, early adequate therapeutic intervention, psychological strain and high therapy motivation of the patient, individual perspective, lack of comorbidities and acceptance of therapy. Prognostically unfavorable are: mainly somatic etiology, long durations of unemployment, external attribution of the disease, rigid concept regarding the disorder, primary/secondary/tertiary morbid gain (relief due to the symptom, social reinforcement, benefits via third parties or pensions), symptom-upholding behavior by doctors (who do not refer to psychological aspects), resignation, lack of an alternative behavioral concepts, social alienation, avoidance or extensive perseverance, tendency for somatization, addiction, deficits regarding coping strategies, relaxation techniques and social competencies (see [22, 29]). Leuchter et al. [31] found that the severity of painful symptoms is associated with other factors, such as physical illness burden, low socio-economic status, absence of private insurance, being female or from African-American or Hispanic ethnicity; after adjustment for these factors, painful symptoms have been shown to be no longer associated with poorer treatment outcomes.

If pain symptoms have been developed exclusively on the basis of a depressive disorder, they should disappear as soon as depression is remitting under antidepressant therapy or in its natural course. In two longitudinal outpatient studies

($n=500/n=3,320$) it could be shown that change in pain was a strong predictor of subsequent depression severity and, likewise, change in depression severity an equally strong predictor of subsequent pain severity [26, 43]. However, other studies found only weak associations between relief of pain and amelioration of depression.

The risk of chronification of comorbid pain and depression syndromes is high. Among others the chronification processes leads to alienation, loss of quality of life and social withdrawal. This is worsened by the patient's negatively tinted general perception, often estimating her/his situation as hopeless, which in turn often leads to a lack of compliance to the therapy regimen. An inspection focusing on benefits and disadvantages of invalidity is often necessary, so that patients can recognize the need for behavioral changes. The risk of suicide is high in patients with depression (4–15%) and should be even more increased with a comorbid pain syndrome, given that chronic pain patients show as well a high rate of attempts at suicide (5–14%). This is the final but not the entire proof that an early and intense intervention is essential for good therapy success.

Altogether, both clinics and research are getting more and more close to comorbid pain in depressive disorders. However, a differentiated management of this complex symptom cluster has to be refined and evaluated. For this reason, further studies on pathophysiological mechanisms and on clinical pathways are warranted.

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