Somatic symptoms in depression

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Historical conceptualizations of depression

There is a long tradition in phenomenological psychopathology that stresses basic bodily alterations as core features of depressive states. Thus, Wernicke used the term "vital feelings" to describe certain somatic symptoms occurring in affective psychoses.[1] Vital feelings refer to the close relationship of the body to the awareness of self. They determine the way we experience our body and the impression we assume our physical presence makes on other people. Vital feelings are somatic affects localized in different parts of the body. Whereas vital feelings constitute the bodily background of our normal experiences, they may move to the fore in a depressive mood. For example, depressed patients very

Both painful and nonpainful somatic symptoms essentially characterize clinical states of depressive mood. So far, this well-established psychopathological knowledge has been appreciated only insufficiently by the official diagnostic systerms of the Diagnostic and Statistical Manual of Mental Disorders, *4th edition, Text Revision* (DSM-IV TR) *and the* ICD-10 Classification of Mental and Behavioral Disorders. Clinical Descriptions and Diagnostic Guidelines (ICD-10). *From a perspective of primary care services, this unmet diagnostic need is deplorable, as the main mode of presenting a depression is by reporting somatic symptoms. This somatic form of presentation, however, significantly contributes to low rates of recognition in primary care. A diagnostic challenge may be seen in the differentiation of a depression with prevailing somatic symptoms from anxiety, somatoform disorders, and medical conditions. When somatic symptoms, particularly painful physical conditions, accompany the already debilitating psychiatric and behavioral symptoms of depression, the course of the illness may be more severe, implying a higher risk of early relapse, chronicity, suicide, or mortality due to other natural causes, the economic burden increases considerably, the functional status may be hampered heavily, and health-related quality of life may be lowered dramatically. The neurobiological underpinnings of somatic symptoms in depression may guide more promising treatment approaches.*

Dialogues Clin Neurosci. 2006;8:227-239.

Keywords: *somatic symptom; depression; neurobiology; treatment*

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often complain of a headache which is described not exactly as an ordinary pain, but more as an unbearable pressure "like a band around the head." Other disturbed vital feelings affect the chest or the abdomen, and mediate unpleasant sensations of weight, tension, heaviness, or inhibition, totally absorbing the focus of attention. In quite a similar way Dupré speaks of "coenestopathic states" which mean a distressing, qualitative change of normal physical feeling in certain areas of the body during an episode of depressive mood. It is a global loss of vitality in which all bodily parts and functions may be altered, and all their performances depressed.[2] Kurt Schneider considered these disturbances of vital feelings to be the core of cyclothymic depression. In his psychopathological assessment they were of paramount diagnostic significance in depressive illness, more or less equivalent to the first-rank symptoms in schizophrenia.[3] Huber discriminated between vital disturbances on the one hand and vegetative symptoms in depression on the other.[4] Vital disturbances refer to the vital feelings just mentioned. They comprise a loss of general vital tone of the body, a prevailing fatigue or exhaustibility, and various forms of somatic dysesthesia, typically of a static, more localized character affecting head, chest, heart region, or abdomen. All-pervasive sensations of anesthesia, stiffness, and alienation of the total body may characterize a somatopsychic depersonalization in depression which may appear as a Cotard's syndrome in its extreme form. If the vital disturbances take on a peculiar form that is difficult to describe in ordinary everyday words, Huber speaks of a "coenesthetic" depression which must be typologically differentiated from the bizarre states of coenesthetic schizophrenia. Vegetative symptoms are closely associated with these vital disturbances and coenesthesias in depression. Disturbances of sleep, appetite, and digestion are most frequent. However, there may be many other vegetative symptoms in depression such as disordered salivation, transpiration and lacrimation, cardiac arrhythmias and dyspnea, loss of libido and various sexual dysfunctions, dys- or amenorrhea, loss of or increase in body weight, decreased turgor of the skin, loss of hair, decrease in body temperature, nausea, vomiting, meteorism, dizziness, sweating, or sensations of coldness. Both vital disturbances, coenesthesias and vegetative symptoms, are typically coexistent with the well-known affective, behavioral, and cognitive symptoms of depression. With respect to the different settings of medical care, however, these psychological symptoms of depression may be masked by a dominant reporting of somatic symptoms. M. Bleuler addressed the point in his book *Depressions in Primary Care*, in 1943: *"It is a common and frequent observation that depressive patients with single somatic complaints come to the consulting room of the general practitioner, internal specialist, and even the surgeon, gynecologist, ophthalmologist, urologist and other medical specialists, and spontaneously, they only speak of somatic phenomena while concealing their state of depressive mood. They report palpitations, tightness of the chest, loss of appetite, obstipation, pollakiuria, amenorrhea and many others. Only when one looks at their psychic state does one discover that they report numerous hypochondriac ideas also in other areas, that in addition they produce depressive ideas of impoverishment and sin, that beyond that their whole stream of thoughts is inhibited, that the depression manifests itself not only in the somatic complaints reported, but in various other bodily expressions."* [5]

In spite of this long-standing psychopathological view on the somatic foundation of depressive mood, at least in moderate and severe clinical states, it is bewildering that the official psychiatric classification systems of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition *(DSM-IV)* and the *ICD-10 Classification of Mental and Behavioral Disorders. Clinical Descriptions and Diagnostic guidelines (ICD-10)* only marginally appreciate somatic symptoms as diagnostic criteria for depressive disorders while focussing on the psychological symptoms of affect and cognition. So, *DSM-IV* lists only three criteria of somatic symptoms for major depressive disorder: sleep disturbance, appetite disturbance, and fatigue or loss of energy. And correspondingly, in *ICD-10*, disturbances of sleep and appetite, loss of libido, and amenorrhea are the only somatic symptoms considered to be of diagnostic significance for major depression. Beyond this short list of predominantly vegetative symptoms, no painful physical symptoms are mentioned in either the *DSM-IV* or *ICD-10*. There seems to be a major shift in diagnostic practice, however; the second version of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision *(DSM-IV TR)* now includes new criteria referring to "excessive worry over physical health and complaints of pain (eg, headaches or joint, abdominal, or other pains)."[6] This supplement of diagnostic criteria is indicative of an again-increasing awareness of the importance of somatic symptoms in depression.

What is meant by "somatic" in somatic symptoms of depression?

In the literature there are many terms used to describe somatic symptoms in depression: somatic, somatized, physical, bodily, somatoform, painful, psychosomatic, vegetative, medically unexplained, masked, etc.[7] These diverse terms refer to different theoretical or diagnostic concepts. For states of depressive mood the neutral term "somatic" is preferred, comprising various bodily sensations that a depressed individual perceives as unpleasant or worrisome. These dysesthesias are very often localized in certain body parts or organs, or may affect the whole body in its vital condition, as in the case of fatigue or loss of energy. Several basic physical dysfunctions, such as those of sleep, appetite, or digestion, are also to be included in the term "somatic." In addition, it may be clinically relevant to differentiate between painful and nonpainful somatic symptoms of depression. From a diagnostic perspective one has to keep in mind that somatic symptoms play a significant role both in primary psychiatric disorders, first and foremost depressive and anxiety disorders, and in somatoform disorders. And in differential diagnosis, somatic symptoms must be considered as possibly even indicative of underlying somatic diseases. A diagnostic challenge may be seen in the well-known fact that depressive, anxiety, somatoform disorders, and medical conditions are frequently coexistent, or interact in the individual patient.[8-10] Regarding the assessment of somatic symptoms, Kroenke correctly points out that diagnosis very often is more approximative than precise. Presented somatic symptoms may be either clearly attributed to a distinct medical disorder or be placed into one of the following heuristic categories: somatoform disorder, another primary psychiatric disorder (often depression and/or anxiety), functional somatic syndrome (eg, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome), "symptom-only" diagnosis (eg, low back pain, idiopathic dizziness) or only partially explained by a defined medical disorder (eg, many states of chronic pain).[11]

Epidemiological studies may provide an illuminating survey of the prevalence of somatic symptoms in depressive disorders, especially those encountered in primary care, and the prognostic value of somatic symptoms regarding their development in the further course of illness.

Somatic symptoms of depressive disorders in inpatient care and primary care

In a clinical study, Hamilton reported that somatic symptoms prevailed in a great majority of depressed patients.[12] Somatic symptoms, particularly somatic anxiety and fatigue, were documented in up to 80% of a sample of 260 women and 239 men suffering from major depression. These somatic symptoms very frequently had an underlying psychopathologically relevant hypochondriasis, both in women and men. This study confirmed earlier studies showing that depressive disorders with predominantly somatic presentation were likely to be the most common form of depression, both in inpatient and outpatient care.[13,14] Hagnell and Rorsman stressed the indicative significance of somatic symptoms in depressed primary care patients regarding their risk of suicide.[15]

Epidemiological studies designed to establish prevalence figures for depressive disorders in primary care during recent years have uniformly demonstrated that depressive disorders are highly prevalent at this level of medical care.[16-19] For the great majority of depressed patients seeking professional help in the official health care system, general practitioners and internists are the decisive interface for diagnosis and treatment of depression.[20] Primary-care patients with depression very often present with somatic complaints. This seems to be more the rule than the exception worldwide.[21,22] Two of the three most common symptoms reported during a current depressive episode were somatic (tired/no energy/listless: 73%, broken sleep/decreased sleep: 63%) as shown by the European Study Society study (DEPRES II).[23] This study, however, also underlined that 65% of the depressed primary care patients suffered from a concomitant medical condition pointing to some likely difficulties in differential diagnosis. The multicenter international study (n =1146) conducted by the World Health Organization (WHO) confirmed that two thirds of the patients presented their depressive mood with somatic symptoms exclusively, and more than half complained of multiple medically unexplained somatic symptoms.[24] In another primary care study, Kirmayer et al arrived at a similar finding of patients presenting their depressive or anxiety disorders exclusively with somatic symptoms in an overwhelming majority (73%). The identified somatic symptoms were the main reason for the initial visit to the primary care physician.[25] In a US study in 573 patients with the diagnosis of major depression, two thirds (69%)

complained of general aches and pains, hinting at a close relationship between pain symptoms and depression.[26]

The diagnostic situation in primary care frequently manifests itself, however, as somewhat more complicated. Many patients present only with a single or a few somatic symptoms which remain medically unexplained and do not fulfill the affective and cognitive criteria for a discrete depressive or anxiety disorder at the end of the clinical interview. Single somatic symptoms are the primary reason for more than 50% of patients visiting a general practitioner or an outpatient clinic. In some 20% to 25%, these somatic symptoms are recurrent or chronic. Somatic symptoms that remain unexplained after a careful medical assessment generally bear a high risk for psychiatric morbidity, regardless of the type of symptoms.[27-29] Up to two thirds of these patients develop a depressive disorder in the medium term, and between 40% to 50% fulfill the criteria for an anxiety disorder.[30-33] In a cross-sectional study in 1042 primary care patients, Gerber et al investigated the differential relationship between specific somatic complaints and underlying depressive symptoms. Some somatic symptoms showed a high positive predictive value (PPV) for depression: Sleep disturbances (PPV: 61%), fatigue (PPV: 60%), three or more complaints (PPV: 56%), nonspecific musculoskeletal complaints (PPV: 43%), back pain (PPV: 39%), amplified complaints (PPV: 39%), vaguely stated complaints (PPV: 37%).[34]

Some somatic symptoms are typically covariant in the patients' complaints without having received the nosological status of a discrete medical condition. These clusters of symptoms are instead considered as functional somatic syndromes and termed according to the diagnostic standards of the various medical disciplines, eg, fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome, etc. For some authors in psychiatry these functional somatic syndromes represent typical variants of somatoform disorders. There is still a controversial dispute in the medical literature, however, as to whether to assemble all these functional somatic syndromes within one general category of somatization,[35,36] or to split them up into separate clinical entities.[37] From an empirical standpoint, it is remarkable that among these syndromes there is a significant overlap on the level of symptoms and a strong association with depressive and anxiety disorders.[38-41]

A close relationship between states of depressive mood and symptoms of pain, especially of chronic pain, has been impressively established in many empirical studies.[26,42-44] Depression and painful symptoms commonly occur together. As both conditions are highly prevalent in the general population, their frequent co-occurrence might be due to mere statistical coincidence.[45,46] From an empirical standpoint, however, the prevalence figures of coexistence are far beyond statistical expectation. In a meta-analytical survey, Bair et al demonstrated that around two thirds of all depressed patients treated in primary, secondary, and tertiary centers, both in outpatient and inpatient settings, report distressing painful somatic symptoms.[26] Conversely, the prevalence rate of major depression in patients with various pain syndromes is about 50%. There seem to be higher rates in clinical states characterized by multiple diffuse pain symptoms than by more defined types of pain. The risk of major depression is considered to be dependent on the severity, frequency, persistence, and number of pain symptoms.[47,48] From the perspective of primary care an epidemiological study assessing the predictive power of chronic pain for depressive morbidity showed that the prevalence rate of at least one chronic painful physical condition (CPPC) in the general population was 17.1%. At least one depressive symptom was present in 16.5% of subjects; 27.6% of these subjects had at least one CPPC. Major depression was diagnosed in 4% of subjects, and 43.4% of these subjects had at least one CPPC, which was 4 times more often than in subjects without depressive disorder.[49] This significant interrelationship of CPPC and depression confirmed the earlier clinical advice of Katon, suggesting that if all patients with painful physical conditions were systematically assessed regarding a possible underlying depression, some 60% of all states of depression could be detected in primary care.[50]

Generally, one has to keep in mind that, both from a cross-sectional and a longitudinal perspective, there is a relevant overlap of depressive, anxiety, and somatoform disorders, especially chronic painful physical conditions, among primary care patients presenting with medically unexplained symptoms.[51-58] It is an important clinical finding that, with an increasing number of medically unexplained symptoms, the risk of an underlying depressive disorder increases in an impressive dose-response relationship. In a study which included 1000 adults and another study comprising 500 patients with a chief complaint of somatic symptoms, the presence of any somatic symptom increased the likelihood of a mood or anxiety disorder by two- or threefold. Only 2% of patients with

no or only one somatic symptom had a mood disorder, but 60% of those patients presented nine or more somatic symptoms.[31,59] Patients with multiple medically unexplained somatic symptoms also show a greater amount of associated other psychiatric comorbidity.[60,61]

Somatic symptoms in depression and rates of diagnostic recognition within primary care

The typical form of presenting a depression in primary care is via somatization. This form of somatic presentation, however, is considered to be one of the main reasons for low rates of recognition of depression in this sector of the medical care system.[20,62] It must be acknowledged that the alarmingly low figures of diagnosed and consecutively treated depressive disorders in only 25% to 33% of affected patients found in epidemiological studies during the early 1990s have increased up to some 60%.[17,19] From a perspective of primary care, general practitioners are consulted by two groups of depressed patients who may pose a diagnostic challenge. Patients suffering from a medical condition have a frequent depressive comorbidity.[23,63] These associated depressions often remain undetected, as the diagnostic focus of the primary care physicians is led by a dominant model of somatic disease.[64] Indeed, certain somatic symptoms such as sleep disturbances, diffuse bodily pains and aches, fatigue, changes of appetite, etc, may characterize both the pathophysiological process of a discrete medical condition and a depressive disorder as well. The differential diagnosis may be difficult. The role and significance of somatic symptoms for the diagnosis of depression in medically ill patients have been a controversial issue in the scientific literature. Meanwhile, a clinically reasonable consensus has been arrived at that the *DSM-IV* criteria for major depression do not require significant modification for patients with medical comorbidities.[65-67] Somatic symptoms can positively contribute to a diagnosis if they are assessed in line with typical concomitant affective, behavioral, and cognitive symptoms of depression.[9] For a primary care physician it is important to know that at least 20% to 30% of patients with chronic medical conditions suffer from a coexisting depression.[68] It must be assumed that, even in those patients being diagnosed with an acute somatic disease for the first time, depression coexists in a significant percentage.[69] All in all, patients with medical conditions are to be considered as a risk group for nonrecognition of concomitant depression.[70] This especially applies to elderly medically ill patients.[71]

In the other major group of depressed primary care patients, the somatic symptoms complained of very often remain medically unexplained. If one focuses on the mode of presentation, about 50% of the patients report somatic symptoms exclusively, and a minor percentage of some 20% present their depressive disorder with prevailing psychological, ie, affective and cognitive symptoms.[7,21,72,73] There is not, however, a categorical split between a somatic mode of presentation on the one hand and a psychological mode on the other. Rather, a broad spectrum of transition must be assumed, and the grading of somatization has an impact on the probability of recognition of an underlying depression.[25] As a rule, primary care physicians do not recognize a depression with an individual patient better when he or she is complaining of many actual medically unexplained somatic symptoms (here they rather prefer a diagnostic standpoint of wait and see), but when the patient returns again and again to consult because of these symptoms.[74] In addition, the extent of hypochondriacal worries and health anxieties facilitate, a correct diagnosis of depression.[75,76] Patients with somatic complaints that are not explained medically in an adequate way, however, do not represent a uniform group regarding diagnostic categorization. Besides depressive disorders, which in primary care manifest themselves according to the traditional concept of an endogenous type only in minority but instead show many atypical features,[77-79] one must consider various anxiety and somatoform disorders in differential diagnosis.[60,61,80-82] Again as a rule, there exists an impressive overlap on the level of symptoms among all these diagnostic categories.[10]

Aspects facilitating somatic symptoms in depression

Many factors may contribute to the form and extent to which a depression is presented in somatic symptoms. Female gender has been confirmed to be closely associated with somatization in many studies covering differential aspects on various theoretical levels.[83] In a gender differential analysis, Silverstein draws some interesting conclusions from the epidemiological data of the National Comorbity Survey.[84,85] By dividing respondents into those who met overall criteria for major depression and exhibited fatigue, appetite, and sleep disturbances ("somatic depression") and those who met overall criteria without these somatic symptoms ("pure depression")

she demonstrated gender differences only for "somatic depression" but not for "pure depression." The higher prevalence of "somatic depression" in females was strongly associated with a high frequency of anxiety disorders. Interestingly, this type of "somatic depression" among female patients already had its onset during early adolescent years with predominantly bodily pains and aches. Wenzel et al attributed the higher prevalence of "somatic depression" in women largely to changes in appetite.[86]

Gender differences can also be found in primary care. Women consistently reported most typical somatic symptoms at least 50% more often than men. Although mental disorders, above all depressive and anxiety disorders, were found to be correlated with this mode of somatic presentation, there was also an independent female gender effect on somatic symptom reporting.[87] In a later study Jackson et al found that among primary care patients with somatic symptoms, on the whole, women were younger, more likely to report stress, endorsed more "other, currently bothersome" symptoms, were more likely to have a mental disorder, and were less likely to be satisfied with the care.[88] A greater susceptibility of women, both to psychosocial stress and somatic illness stress, was held responsible for this higher prevalence of depressive and anxiety disorders in female patients.[89] A greater vulnerability to depressive and anxiety disorders on the one hand, and a strong neurobiological association to defined functional somatic syndromes (eg, fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome) on the other may further increase the extent of this gender difference.[40,90]

The disposition both to somatization and to depressive and anxiety disorder may be intermingled in various ways. Thus, a depressive mood may trigger the immediate illness behavior to enter the medical care system and to report somatized problems caused otherwise.[91] The very high frequency of somatic anxiety symptoms in patients with major depression may be interpreted by the idea that anxiety appears to be a major source of bodily distress and consecutive hypochondriasis, thus fostering somatization behavior.[12] Indeed, specific effects of depression, panic, and somatic symptoms on illness behavior must be considered.[92] Various causal illness interpretations, a tendency to amplify somatic distress, and difficulties in identifying and communicating emotional distress, all have an impact on the form and extent of a somatic mode of presentation.[93-95] Again, regarding the course of illness, depressive and anxiety disorders following somatoform disorders may significantly contribute to the chronification and complication of the latter.[39,96]

From a perspective of etiologically relevant risk factors it is a well-established epidemiological finding that the extent and severity of early adverse events, especially manifold traumatic experiences, are tightly connected with the mental and somatic state of adults. This general disposition may be detected in a series of psychiatric disorders, as in conversion and somatization syndromes,[97-103] several chronic pain conditions,[104-106] hypochondriacal attitudes,[107] factitious disorders,[98] and depressive, anxiety, and substance disorders.[108-110] One can draw a basic conclusion from many epidemiologically designed longitudinal studies that the more a person has been exposed to severe and early trauma, the higher the risk will be that she/he will suffering from recurrent or chronic depression with pronounced suicidality, multiple medically unexplained somatic symptoms, especially chronic physical pain conditions with an onset already during adolescence or young adulthood, the more her/his psychic and somatic state as a whole will be negatively affected, and the more she/he will demonstrate abnormal illness behavior.[61,111]

Culture and society are other factors that may have an important impact on the way a depressive mood is presented in a predominantly somatic way.[25] Interestingly, the comprehensive international WHO study on depression in primary care, conducted in 12 countries on different continents, was not able to identify clear cultural influences on the somatic mode of presenting a depression. A somatic presentation was much more common at centers where patients lacked an ongoing relationship with a primary care physician than at centers where most patients had a personal physician. This variable had a robustly differentiating effect beyond the various cultural settings.[24]

Besides gender, culture, and type of patient-physician relationship, there may be many other factors influencing a more somatic mode of presentation, such as different ages in life cycle, association with medical conditions, earning a lower income, and imprisonment.[7,112]

Burden of somatic symptoms in depression

Most patients who are psychopharmacologically treated for depression fail to reach full remission.[113–114] A majority of patients may respond to antidepressants (by defin-

ition a reduction of symptoms by some 50% or more), but still suffer from residual symptoms. These residual symptoms are often somatic in nature. Symptoms of somatic anxiety and various painful conditions seem be especially common in states of incomplete remission.[115] Residual symptoms which are not treated must effectively be considered as a negative risk factor with respect to earlier relapse, and a more severe and chronic future course of illness.[116-119]

The clinical significance of somatic symptoms in depression may best be illustrated with the relationship between depression and painful physical conditions. In general, the worse the painful somatic symptoms, the more severe and the longer a depressive episode persists. In their general population-based study, Ohayon and Schatzberg found that depressed patients with chronic pain symptoms reported a longer duration of depressive mood (19.0 months) than those without chronic pain (13.3 months). In addition, a chronic physical pain condition in persons with at least one key symptom of depression was associated with an elevated rate of suicidal thoughts.[49] Fishbain considered chronic pain as a major suicide risk factor in depression.[120] Von Korff and Simon demonstrated a significant correlation between the intensity of pain symptoms and a worse outcome of depressive disorders. This worse outcome included more pain-related functional impairments, a worse state of general health, higher rates of unemployment, use of more opiates, more frequent polypharmacy, and more intensive utilization of medical services due to pain complaints.[121] Although both painful and nonpainful somatic symptoms improve with antidepressant treatment, it is the intensity and extent of pain symptoms at baseline that significantly contribute to a less favorable response to medication, and to a longer duration of treatment necessary for a satisfying result, if at all.[122-124]

If one asssembles painful and nonpainful somatic symptoms of depression into a single dimension of somatization, it is this factor that must be correlated with an impressively increased overall use of health care services, [125-127] to significant treatment nonadherence and a resulting higher risk of relapse and more chronic course of illness.[128] Again, a recurrent or chronic depression includes a higher risk of suicide[129] and an increased morbidity and mortality due to illness-inherent factors or associated natural causes.[130-132] All in all, it must be concluded that: when somatic symptoms, above all painful physical conditions, accompany the already debilitating psychiatric and behavioral symptoms of depression, the economic burden that ensues for patients and their employers increases considerably,[133-134] the functional status may be hampered signifiacantly,[135] and the health-related quality of life is lowered dramatically.[136]

Neurobiological underpinnings of somatic symptoms in depression

Various psychosocial and biological stressors may trigger a depression. Neurobiological processes underlying any depressive illness are manifold; this applies to the different somatic symptoms in particular. A strong heritable disposition, polygenetic in nature, seems to be established, but maladaptive neurobiological stress response systems already acquired by stressful and traumatic experiences during early development may play a major role in the pathophysiology of depression as well.[137] Dysfunctions in the serotonergic, noradrenergic, and dopaminergic neurotransmitter systems have been considered as relevant for quite a long time. Drawing from the neuroanatomical serotonergic tracts, starting in the midbrain raphe cell bodies and projecting to the frontal cortex, basal ganglia, limbic system, and hypothalamus on the one hand, of noradrenergic pathways originating in the locus ceruleus of the brain stem and projecting again to the same regions of the frontal cortex, limbic areas, and hypothalamus, but also uniquely to other parts of the frontal cortex and to the cerebellum on the other, Stahl stressed that deficiencies in the activity of specific pathways of serotonin and norepinephrine might account for the differential clinical phenomenology in depression. This seems to be true both for the typical psychological and somatic symptoms. Regarding somatic symptoms, especially vegetative symptoms such as changes in appetite or weight, lack of pleasure and sexual appetence, and sleep abnormalities, dysfunctional hypothalamic and sleep centers may be of paramount importance, all influenced by both serotonin and norepinephrine.[138] Fatigue, exhaustibility, or loss of energy, common distressing symptoms during a depressive episode, but also obstinate residual symptoms, may be mediated by different malfunctioning neuronal circuits that are regulated by multiple neurotransmitters.[139] Fatigue can be experienced as reduction in either mental or more physical vital feeling. Likely candidates for the neuronal structures that may mediate physical fatigue refer to brain areas regulating motor functions, such as striatum or cerebellum, but also

to certain spinal pathways transferring sensory input from the body and thus modulating the perception of physical tiredness. In addition to serotonin and norepinephrine, dopamine may be involved in this process. Mental tiredness, on the other hand, may be mediated by diffuse cortical circuits and be influenced by cholinergic, histaminergic, noradrenergic, and dopaminergic neurotransmitters. The various painful somatic symptoms in depression may essentially be associated with serotonergic and noradrenergic pathways descending from brain stem centers to the spinal cord. An imbalance in these neurotransmitters, normally serving to inhibit the sensory input from the intestines, musculoskeletal system, and other body regions, may accentuate pain sensitivity.[26,140]

As a matter of course, neither psychological nor somatic symptoms in depression can be explained by dysfunctional neurotransmitters exclusively. Many other neurobiological processes are involved in the pathophysiology of depression, such as an abnormal HPA axis with a disordered feedback mechanism of the corticotropin-releasing factor (CRF) -adrenocorticotropic hormone (ACTH) - cortisol stress response, a reduced secretion of the neuropeptide hypocretin thus contributing to a desynchronization of the sleep-wake cycle, various abnormalities in the inflammatory system with an increased production of certain proinflammatory cytokines, a resulting depletion of the serotonin system, sickness behavior and depressive mood, reduced concentrations of various neurotrophins such as brain-derived neurotropic factor (BDNF) causing impaired neuroplasticity, cell resistance, and neurogenesis.[137,141-147]

The intricate pathophysiological interplay of neuroendocrine stress response, inflammation, and neurotransmitter systems, both centrally and peripherally, may perhaps best be illustrated by the relationship between chronic pain conditions and depressive mood states (succinctly summarized in refs 148-150). In short, chronic stress evoked by chronic pain leads to a loss of negative glucocorticoid feedback in the (hypothalamic-pituitary-adrenocortical (HPA) axis and downregulation of the glucocorticoid receptors within the brain and the body periphery. Inflammation and nerve injury stimulate nociresponsive neurons within the dorsal horn of the spinal cord, and the relay of the nociceptive information ascends to the brain stem to be gated within the thalamus, prior to its cognitive appraisal within the somatosensory cortex. Monoaminergic neurons in the brain stem normally descend to the spinal cord to act as a "brake" on nociceptive transmission. During chronic pain, loss of serotonergic and noradrenergic tone in response to glucocorticoid-induced monoaminergic depletion may lead to descending inhibitory impulses to the spinal cord to effect an enhancement of pain sensation. Loss of glucocorticoid inhibition of proinflammatory cytokines leads to proliferation of peripheral inflammatory events, contributing to pain sensitization. Although acute stress may be analgesic, implying an inhibitory circuitry between the limbic and somatosensory cortices, chronic stress evoked by chronic pain, leads to downregulation of glucocorticoid-mediated activity of this inhibitory connection, causing enhanced pain perception. Similarly, although acute pain may be mood-enhancing via both sympathetic and glucocorticoid routes (implying an excitatory reciprocal link between the somatosensory and limbic cortices), chronic pain-induced downregulation of glucocorticoid modulation of this link may lead to depressed mood.

Psychopharmacological implications for the treatment of somatic symptoms in depression

Numerous trials with antidepressants have demonstrated that full remission of the psychological, and especially of the somatic, symptoms in depression can be achieved only by a minority group of depressed patients within a usual 6- to 8-week treatment period.[62,151,152] These sobering facts are reflected by a higher risk of relapse, a worse course of illness with many associated psychosocial disabilities, and a hampered health-related quality of life. Therefore, achieving a state of symptomatic remission must be a treatment goal of utmost clinical importance. Targeting both serotonin and norepinephrine in those neuronal circuits that mediate somatic symptoms is the most widely employed strategy to reduce painful and nonpainful somatic symptoms in depression.[90] In comparison with selective serotonin reuptake inhibitors, antidepressants with a dual action on both the serotonin and norepinephrine system were significantly superior in alleviating these somatic symptoms and achieving full symptomatic remission of depression. This may be a promising approach, even to treating chronic pain conditions, eg, fibromyalgia, without prevailing depressive symptoms.[153,154] This seems to have been well established in clinical trials with venlafaxine,[155-159] duloxetine,[160-163] milnacipran,[164] or mirtazapine.[165] In order to improve distressing symptoms of fatigue, the use of psychostimulants, modafinil, bupropion, or selective norepinephrine reup-

take inhibitors such as reboxetine or atomoxetine may be recommended.[166]

As a rule, psychopharmacological efforts to treat severe states of depression or states of depression with prominent somatic symptoms effectively must be guided by a perspective of a longer duration than usual. Higher dosages of a selected antidepressant have to be used very often. Sometimes shifts within or between pharmacological classes of antidepressants or an augmentation with, eg, lithium or tri-iodthyronine, are necessary to arrive at the desired aim. From a pragmatic standpoint, clinically rational algorithms may favorably guide this endeavor.[167] Finally, it must be stressed that a reasonable combination of pharmacological and psychotherapeutic approaches can improve the treatment results in many depressed patients.[168,169] ❑

Síntomas somáticos en la depresión

Estados clínicos de ánimo depresivo se caracterizan esencialmente tanto por síntomas somáticos dolorosos como no-dolorosos. Hasta el momento, este conocimiento psicopatológico bien establecido ha sido apreciado sólo insuficientemente por los sistemas diagnósticos oficiales del Texto Revisado del Manual Diagnóstico y Estadístico de los Trastornos Mentales, Cuarta Edición (DSM-IV-TR) *y de la* Clasificación Internacional de los Trastornos Mentales y del Comportamiento, Descripciones Clínicas y Guías Diagnósticas *en su décima versión* (CIE-10). *Desde la perspectiva de los servicios de atención primaria esta necesidad diagnóstica no satisfecha es lamentable, ya que el principal modo de presentación es mediante síntomas somáticos. Sin embargo, esta forma somática de presentación contribuye significativamente a reducir la frecuencia de reconocimiento en la atención primaria. Se puede encontrar un desafío diagnóstico en la diferenciación entre una depresión con síntomas somáticos predominantes y la ansiedad, los trastornos somatomorfos y las condiciones médicas. Cuando los síntomas somáticos, especialmente las condiciones físicas de dolor, acompañan a los ya debilitantes síntomas psiquiátricos y conductuales de la depresión, el curso de la enfermedad puede ser más grave, implicando un mayor riesgo de recaída precoz, cronicidad, suicidio o mortalidad debida a otras causas naturales, aumento considerable de los costos económicos, deterioro marcado del estado funcional y disminución dramática de la calidad de vida relacionada con la salud. Las bases neurobiológicas de los síntomas somáticos en la depresión pueden servir de guía para aproximaciones terapéuticas más promisorias.*

Symptômes somatiques dans la dépression

Des symptômes somatiques à la fois douloureux et non douloureux caractérisent fondamentalement le stade clinique de l'humeur dépressive. Jusqu'à présent, cette connaissance psychopathologique manifeste n'a été qu'insuffisamment évaluée par le système de diagnostic officiel, le DSM IV TR 4e édition (Diagnostic and Statistical Manual of Mental Disorders), *et l'ICD-10* (Classification of Mental and Behavioral Disorders. Clinical Descriptions and Diagnostic guidelines). *Du point de vue des services de soins primaires, l'absence de diagnostic est déplorable, la principale manifestation de la dépression étant marquée par des symptômes somatiques. Cette forme de présentation somatique est très peu diagnostiquée en soins primaires. Différencier une dépression accompagnée de symptômes somatiques dominants, de l'anxiété, de troubles somatoformes, et d'une pathologie médicale, devient un défi diagnostique. Quand des symptômes somatiques, et en particulier des troubles physiques douloureux, accompagnent les symptômes comportementaux et psychiatriques déjà invalidants de la dépression, l'évolution de la maladie peut être plus sévère, sous-entendant un plus fort risque de rechute précoce, de chronicité, de suicide ou de mortalité due à d'autres causes naturelles. La charge économique augmente considérablement, le statut fonctionnel peut être lourdement entravé, et la qualité de vie liée à la santé peut être dramatiquement abaissée. Les bases neurobiologiques des symptômes somatiques de la dépression pourraient permettre une approche du traitement plus prometteuse.*

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