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REVIEW ARTICLE

Atypical depression spectrum disorder – neurobiology and treatment

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Depressive syndromes are a group of heterogeneous disorders. Atypical depression (AD) with reversed vegetative signs, such as hyperphagia or hypersomnia, is traditionally neglected, demonstrated by the fact that in the most widely used depression scales, such as the Hamilton Depression Scale (HAMD), melancholic symptoms have a specific weight, while, by contrast, reversed vegetative signs are not included. However, epidemiologically and phenomenologically related disorders to AD do exist, such as somatoform disorders, neurasthenia (chronic fatigue syndrome) and fibromyalgia (FM). In this spectrum, here called the AD spectrum, instead a decrease in hypothalamus–pituitary–adrenocortical (HPA) axis activity seems to exist. This has similarities to Cushing's disease, where a suppression of central HPA system activity is accompanied by features of AD and somatization in a considerable number of patients. Opposite vegetative features might therefore be related to the opposite dysregulation of the HPA system. The psychopharmacological intervention in the AD spectrum should therefore differ from that used in typical major depression. MAO inhibitors, low-dose tricyclic antidepressants and 5-HT_3 antagonists demonstrated therapeutic efficacy, but the existing studies focused on different aspects. Hypericum extracts might be an alternative pharmacological intervention, which demonstrated therapeutic efficacy in the symptom range of the spectrum.

Keywords: atypical depression; cortisol; fibromyalgia; HPA axis; hypericum; hypocortisolism; MAO inhibitor; melancholic depression; neurasthenia; p-glycoprotein; somatoform disorders; tricyclic antidepressant

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Subtypes of depression

Major depression is an inhomogeneous group of disorders. According to DSM-IV, core symptoms have to exist, i.e. depressed mood and loss of interest and pleasure. Additional symptoms are psychomotor changes, fatigue or loss of energy, feelings of worthlessness and guilt, cognitive impairment, recurrent thoughts of death, vegetative features such as insomnia or hypersomnia, and decreased or increased appetite. A specification can be done to characterize extreme and possibly better defined syndromes, i.e. depression with melancholic features (MD), on the one hand, and with atypical features (AD), on the other (Table 1). The general picture of depression is still mainly that of the traditionally called endogenous type, which is also the form that was characterized extensively in clinical studies and with regard to its biological features. This is also reflected in the use of the Hamilton Depression Scale (17-item version), which mainly refers to melancholic features, but less to so-called atypical features, especially reversed vegetative signs, which do not add to the severity of depression characterized by this scale. This establishes a tendency to underestimate the severity of AD. This is especially problematic as this group seems to be a common form in outpatients with depression (1) and seems to have treatment implications, as summarized later.

Different definitions of AD were formulated before the definition in DSM-III was done (2). These were related to: (i) anxiety and phobic symptoms additional to depression; (ii) reversed functional shift, i.e. hypersomnia and hyperphagia; and (iii) the widest definition as 'non-endogenous'

Table 1. Atypical features specifier according to DSM IV

A. Mood reactivity (i.e. mood brightens in response to actual or potential positive events)
B. Two or more of the following features:
1 Significant weight gain or increase in appetite
2 Hypersomnia
3 Leaden paralysis (i.e. heavy, leaden feelings in arms or legs)
4 Long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) that results in significant social or occupational impairment
C. Criteria are not met for With Melancholic Features or With Catatonic Features during the same episode.

(2). Examining the correlation of the defining items one study found that the occurrence of increased sleep was related to that of weight gain, whereas other links seem to be quite weak (2). It seems therefore reasonable to focus mainly on the vegetative features.

The spectrum of atypical depressive disorders

On the basis of endocrine similarities, it has been suggested that atypical depression might be related to disorders of somatic complaints without medical explanation, such as chronic fatigue syndrome (CFS) and fibromyalgia (3,4) (Table 2). This will be discussed later. Here we want to present epidemiological data in order to find connections and differences between the different syndromes. It is, however, important to have in mind that the validity of epidemiological data are limited by the fact that comorbidity rates are highly dependent on the setting of the investigation (i.e. in-patient vs. outpatient setting). Some authors include disorders like irritable bowel syndrome, chronic pelvic pain, non-cardiac chest pain, tension headache, temporomandibular joint dysfunction, globus syndrome and multiple chemical sensitivity syndrome into this spectrum for good reasons (5). For the purpose of clarity, however, these disorders will not be discussed here in detail.

Table 2. Diagnostic criteria of chronic fatigue syndrome [after Fukuda et al. (161)]

A. Clinically evaluated, unexplained, persistent or relapsing fatigue that is of new or definite onset; is not the result of ongoing exertion; is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities *and*
Four or more of the following concurrent and persistent symptoms:
- impaired short-term memory or concentration
- sore throat
- tender cervical or axillary lymph nodes
- muscle pain
- multijoint pain without arthritis
- headaches of a new type, pattern, or severity
- unrefreshing sleep
- post-exertional malaise lasting more than 24 h

CFS and neurasthenia and their relation to depression

Comparing the characteristics of CFS with those of AD, hypersomnia, as seen in AD, is phenomenologically related to the fatigue and unrefreshing sleep seen in CFS, whereas leaden paralysis defined in AD is related to the muscle pain defined in CFS. Epidemiological studies show that about one-third of the patients with chronic fatigue currently fulfill the criteria for affective disorder, and about two-thirds fulfill the lifetime diagnosis of a major depressive episode (6,7). In another examination 55% showed irritability, 52% depressed mood and 51% anxiety (8). About half of the patients showed a high seasonality with atypical neurovegetative signs. In a study in the general population, 6.0% showed a current and 15.5% a lifetime prevalence of medically unexplained fatigue. Of these subjects, about 20% showed a lifetime prevalence of major depression. About 15% showed a present dysthymia. In this study only 0.6% of the men and 2.8% of the women had the diagnosis of a somatization disorder according to DSM-III, but when using abridged criteria as defined by Escobar et al. (9), 15% of the men and 47.5% of the women fulfilled them (10).

Neurasthenia is closely related to CFS (11,12) and both terms are often used synonymously. A longitudinal cohort study showed a strong overlap between neurasthenia and depression and anxiety, especially in subjects with a shorter duration of their complaints, and suggested that neurasthenia is equally likely to represent an early manifestation of affective disorder as it might be a consequence of it (13). Interestingly Merikangas and Angst (13) described an association of neurasthenia with irritability and sensitivity to criticism, similar to AD. Additionally somatoform symptoms like headache occurred at high frequency in this population. Another community study showed that unexplained fatigue is a major risk factor for the development of major depression (14), but that also dysphoria is predictive for the development of fatigue. A study on fatigue in patients in a primary care setting reported a prevalence of depression or somatic anxiety of 80% and a marked global dysfunction (15).

CSF and somatization

The findings from Merikangas and Angst (13) point to a diagnostic link between CFS and somatization disorder. The diagnostic criteria of the latter according to DSM-IV are listed in Table 3.

Table 3. Criteria for somatization disorder according to DSM-IV

A. A history of many physical complaints beginning before age 30 years that occur over a period of several years and result in treatment being sought or significant impairment in social, occupational, or other important areas of functioning.
B. Each of the following criteria must have been met, with individual symptoms occurring at any time during the course of the disturbance:
1. Four pain symptoms: a history of pain related to at least four different sites of functions (e.g. head, abdomen, back, joints, extremities, chest, rectum, during menstruation, during sexual intercourse, or during urination)
2. Two gastrointestinal symptoms: a history of at least two gastrointestinal symptoms other than pain (e.g. nausea, bloating, vomiting other than during pregnancy, diarrhoea, or intolerance of several different foods)
3. One sexual symptom: a history of at least one sexual or reproductive symptom other than pain (e.g. sexual indifference, erectile or ejaculatory dysfunction, irregular menses, excessive menstrual bleeding, vomiting throughout pregnancy)
4. One pseudoneurological symptom: a history of at least one symptom of deficit suggesting a neurological condition not limited to pain (conversion symptom such as impaired co-ordination or balance, paralysis or localized weakness, difficulty swallowing or lump in throat, aphonia, urinary retention, hallucinations, loss of touch or pain sensation, double vision, blindness, deafness, seizures; dissociative symptoms such as amnesia; or loss of consciousness other than fainting)
C. Either (1) or (2):
1. After appropriate investigation, each of the symptoms in criterion B cannot be fully explained by a known general medical condition or the direct effects of a substance
2. When there is a related general medical condition, the physical complaints or resulting social or occupational impairment are in excess of what would be expected from the history, physical examination, or laboratory findings
D. The symptoms are not intentionally produced of feigned.

The definition according to ICD-10 is similar with the important difference, that the age of onset is not defined in the latter catalog, but the duration has to exceed 2 years and requires the presence of two symptoms from four different functional systems. For the related but less strict definition of undifferentiated somatoform disorder according to DSM-IV, one or more physical complaints are necessary for an interval of at least 6 months. This diagnosis is therefore related to the abridged form of the somatization disorder (9). From the amount of different symptoms that are included in the diagnosis, it seems, however, that the diagnosis of somatization disorder labels a rather heterogeneous group of patients. How to define the borders of this spectrum of disorders more specifically, especially with the purpose of specifying pharmacotherapy, has to be the issue of future studies. However, a huge overlap also exists between CFS and somatization disorder with a lifetime prevalence of between 30 and 50% (6,7). Similarly, in a study which included patients with chronic pain, 85% were diagnosed as ICD-10 somatoform pain disorder and 69% as undifferentiated somatoform disorder, whereas 47% also fulfilled the diagnosis of neurasthenia (11). Somatization-like dysphoria has been reported to be predictive for the development of fatigue (14).

Somatization and depression

The relation of symptoms of somatization and depression, especially with atypical features, is well documented. For the somatization disorder a range of comorbidity from 30% (16) up to 63% for affective disorders in general in one study (17) and 84.2% in another study (18) have been reported. Interestingly, somatization disorder often leads to the development of depression, possibly as a kind of prodromal disorder (19). Additionally anxiety disorders are often present in patients with somatization (16).

The relation to AD is suggested by the finding that 79% of patients with chronic pain show a depressive disorder with about one-third of them having atypical features (20). On the other hand, patients with atypical depressive features significantly more often fulfill the criteria of somatization disorder compared with those with typical features. However, in this study, only a small number were classified as having AD. Information of how many patients fulfilled the abridged criteria is missing (21). The population from a clinical trial comparing the effect of moclobemide and fluoxetine patients with AD had significantly more somatic symptoms ($P < 0.01$) and hypochondriasis ($P < 0.01$) compared with those with typical depression (22).

Fibromyalgia

A syndrome related to both somatization disorder and CFS is fibromyalgia (FM). The most frequently used criteria today are those from the American College of Rheumatology (23) and are listed in Table 4.

With regard to epidemiological data, in one study 64% of patients meeting the criteria for CFS also met those for FM. On the other hand, however, only 18% of FM patients carried the diagnosis of CFS (24). FM and CFS patients had several symptoms in common, namely muscle pain, sleep disturbances or sleeping too much, unrefreshing sleep, difficulties concentrating and

Table 4. Criteria for fibromyalgia

1. History of widespread pain

Definition: Pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present. In this definition, shoulder and buttock pain is considered as pain for each involved side. 'Low back' pain is considered lower segment pain.

2. Pain in 11 of 18 tender point sites on digital palpation

Definition: Pain, on digital palpation, must be present in at least 11 of the following 18 sites:

Occiput: Bilateral, at the suboccipital muscle insertions
Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5–C7
Trapezius: bilateral, at the midpoint of the upper border
Supraspinatus: bilateral, at origins, above the scapula spine near the medial border
Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces
Lateral epicondyle: bilateral, 2 cm distal to the epicondyles
Gluteal: bilateral, in upper outer quadrants of buttocks in anterior fold of muscle
Greater trochanter: bilateral, posterior to the trochanteric prominence
Knee: bilateral, at the medial fat pad proximal to the joint line

Digital palpation should be performed with an approximate force of 4 kg
For a tender point to be considered 'positive', the subject must state that the palpation was painful. 'Tender' is not to be considered 'painful

gastrointestinal disturbances. This points to a syndrome extending that of a mere overlap by similarities in defining criteria. With regard to affective disorders, 68% of FM patients have a lifetime comorbidity of major depression. The actual functional impairment of these patients is related to their amount of current anxiety (25). A specific overlap of FM and AD has, however, not been examined.

Pharmacotherapy of atypical depression

In the group of AD related to the DSM-III or -IV definitions, a more favorable treatment response has been described with monoamine oxidase (MAO) inhibitors compared with tricyclic antidepressants (26,27), whereas this finding has been questioned using different definitions of 'atypicality' (28). In a placebo-controlled trial, isocarboxazid was superior to placebo in depression, anxiety and interpersonal sensitivity, especially in atypical depression with reversed vegetative features, but not in patients without these characteristics (29). The other way round, MAO inhibitors have been reported to be of favorable efficacy in AD compared with non-AD (30). The selective serotonin reuptake inhibitor (SSRI) fluoxetine seems not to be more potent in this disorder than imipramine (31), but in this study both drugs led to a higher response rate than placebo. Another study could not find a difference between fluoxetine and phenelezine. It was, however, invalidated by the small sample size (about 20 per group) and the lack of a placebo control group (32). In a trial comparing fluoxetine and moclobemide, a statistically significant superiority was found for moclobemide in the Montgomery-Asberg Depression Rating Scale (MADRS) score, the global clinical impression CGI for improvement and severity of illness, but not in the HAMD score (22). Bupropion was more effective in patients with atypical compared with 'typical' depression in a small study (33). Put together, this suggests that the phenomenological differentiation between the subgroups of depression has a biological basis.

Pharmacotherapy of the AD spectrum disorders

As a differential pharmacological response of AD seems to exist, we now want to summarize data on the pharmacotherapy of CFS, somatoform disorder and FM. We focus here on substances that have been tested at least once in placebo-controlled randomized parallel group designed trial.

MAO inhibitors

CFS and atypical depression. A randomized placebo-controlled trial using an increasing dose of phenelezine over 6 weeks in patients with CFS symptoms, but without depressed mood, revealed a significantly better outcome with the active treatment on self-reported fatigue symptoms, illness severity, mood and functional status (34). An open study showed the efficacy of moclobemide in patients with CFS in 49 patients in a trial lasting 6 weeks. However, those patients with a comorbid depressive symptomatology responded preferably to the medication (35).

Somatoform symptoms and fibromyalgia. In a randomized placebo-controlled study over 12 weeks in 130 patients comparing moclobemide, low-dose amitriptyline (25–37.5 mg/day) and placebo, both moclobemide and amitriptyline showed a significant effect over time in contrast to placebo in pain

assessment. Using a clinical impression of improvement scale, only amitriptyline had a higher response rate compared with placebo (36).

Low-dose or low-potency tricyclic antidepressants (amitriptyline, cyclobenzaprine, dothiepin, opipramol)

Somatoform symptoms and fibromyalgia. Studies on the efficacy of tricyclic antidepressants in CFS or atypical depression have not been performed to my knowledge. For FM, several studies exist. One study just mentioned above (36) revealed a superiority of amitriptyline compared with placebo in patients with FM. A further study additionally tested the efficacy of naproxen (500 mg) and the combination of amitriptyline (25 mg) and naproxen (500 mg) compared with placebo. It revealed the best outcome for amitriptyline alone after 6 weeks (37). One study showed that 50 mg of amitriptyline was superior to placebo after 9 weeks (38); another one using the same dose, however, did not show a significant efficacy (39). A study investigating the effect of 25 mg amitriptyline using a crossover design supported a positive efficacy of this drug in a 2-month trial including 22 patients (40).

Amitriptyline and the chemically related substance cyclobenzaprine were superior to placebo after 4 weeks, but not after 6 months of treatment (41). Further, cyclobenzaprine, in a trial of 40 female patients randomized to placebo or active medication (42), or in another including 120 patients in a 12-week trial (43), showed a higher efficacy compared with placebo. Interestingly, the latter study also showed a trend towards an improvement of fatigue. Similarly dothiepin (75 mg daily) showed a significant superiority to placebo, especially in the number of painful points and the subjective pain severity (44).

Somatoform disorders have successfully been treated with opipramol, an atypical tricyclic antidepressant (45). In this study, a possible interaction of the response of somatoform symptoms with the amelioration of depressive symptoms could not be ruled out.

Hypericum extract

CFS and atypical depression. Two randomized placebo-controlled studies in patients with neurotic depression or brief depressive reaction according to ICD-9 (46,47) reported a statistically significant effect of hypericum on fatigue. A study in patients with mild to moderate depression comparing the effect of hypericum extract LI 160 with fluoxetine and placebo (48) found a significant superiority of hypericum compared with fluoxetine and a trend to a superiority compared with placebo. Interestingly, a subgroup analysis including patients with reversed vegetative signs, but after the exclusion of melancholic features, found the same pattern in this subgroup with a much more pronounced effect size, but no efficacy of any drug compared with placebo in the non-atypical patients (49). Open studies demonstrated the efficacy of hypericum in seasonal affective disorder (SAD) (50–52), which is a subgroup of AD with fatigue as one main symptom. A further open study reported the efficacy of hypericum on patients with fatigue (53).

Somatoform symptoms and fibromyalgia. Recently, LI 160 demonstrated superiority to placebo in patients with somatization disorder; undifferentiated somatoform disorder or somatoform autonomic dysfunction has been demonstrated which was independent from the existence of a depressed mood (54). A randomized trial comparing hypericum extract with imipramine in mild to moderate depression showed a significant advantage of the extract over imipramine on the anxiety-somatization subscale of the Hamilton Anxiety Scale (55), possibly showing a specificity of hypericum extract on somatization. However, this effect might also be related to the different site effect profiles of the drugs. One double-blind study reported efficacy of the hypericum extract LI 160 on headache and by trend cardiac symptoms in patients with neurotic depression or brief depressive reaction (47). A further placebo-controlled trial in patients with mild depression and somatic symptoms reported descriptively strong effects of hypericum extract on headache and muscle pain compared with placebo (56). In a drug monitoring study in 3250 patients receiving LI 160, the severity of headaches, cardiac symptoms and gastrointestinal symptoms was reduced to less than 50% after 4 weeks of treatment (57). Similarly, in an open trial with 114 patients, 5 weeks' treatment with LI 160 resulted in a significant decrease in gastrointestinal complaints, headaches and heart complaints in patients with mild depressive disorder (58).

SSRI

CFS and atypical depression. Data on the efficacy of SSRIs in atypical depression have been referred to earlier, giving an inconclusive result. In CFS a double-blind placebo-controlled trial combining exercise and fluoxetine in four groups of a total of 136 patients over 24 weeks showed no significant effect of the active drug on the level of fatigue and led only to a significant improvement of

depression scores after 12 but not after 24 weeks (59). In another trial of 8 weeks' duration in 96 CFS patients, 44 additionally having depressive symptoms, no superiority of fluoxetine (20 mg) to placebo could be observed in fatigue, functional impairment, cognition and, interestingly, depression (60).

Somatoform symptoms and fibromyalgia. In a small study, 21 patients were treated with citalopram and 19 with placebo in a controlled randomized trial over 4 months. Citalopram (20–40 mg/day) had a significant effect on pain after 2 but not after 4 months of treatment, using a visual analog scale, whereas depressive symptomatology showed a significantly better outcome with citalopram compared with placebo (61). A study using citalopram in a dose of up to 40 mg daily did not show a superiority compared with placebo after 8 weeks in a trial involving 43 patients (62). A 6-week trial in 42 women with FM also could not find a difference between 20 mg fluoxetine and placebo (63). An open study comparing fluoxetine (20 mg), low-dose amitriptyline (25 mg), their combination and placebo in an crossover design showed an improvement with either medication, but favorably with the combination of both after 6 weeks (37). A recent flexible-dose study with fluoxetine (10–80 mg) in women with fibromyalgia showed efficacy of the drug over placebo after 12 weeks, paralleled by a significant effect on depression, possibly pointing to an interrelation of somatic and depressive symptoms (64). An open study using fluvoxamine up to 300 mg in somatoform disorders showed an improvement in somatoform complaints and depression in a group of 29 patients (65).

Glucocorticoids

CFS and atypical depression. An open study showed efficacy in the treatment of resistant depression accompanied by fatigue and hypocortisolism with prednisone (66). Concerning CFS, a placebo-controlled study examining the effect of fludrocortisone on a global wellness scale did not show a difference between the active medication and placebo in 50 patients per group after 9 weeks of treatment (67). Another trial over 12 weeks in 70 patients using a low dose of hydrocortisone active treatment led to a significantly greater clinical improvement in several outcome variables compared with placebo (68). Using a crossover design, comparing treatment of hydrocortisone (either 5 or 10 mg daily) with placebo for 1 month showed a significant superiority of hydrocortisone on self-reported fatigue scores. The lower dose showed better efficacy compared with the higher one (69).

Somatoform symptoms and fibromyalgia. In a crossover design including 20 patients, 15 mg prednisone per day for 14 days was not superior to placebo (70).

Benzodiazepines and related substances

CFS and atypical depression. Comparing the efficacy of moclobemide with that of diazepam in a double-blind trial showed a better efficacy of the benzodiazepine after 4 weeks as measured with the HAMD, but not after 8 weeks. This study, however, was small and not placebo-controlled (71).

Pivagabine administration (1800 mg/day) over 4 weeks in a study including 108 patients with neurasthenia for 4 weeks was superior to placebo in the CGI improvement scale (72).

Somatoform symptoms and fibromyalgia. A placebo-controlled trial in 164 patients with FM comparing bromazepam (3 mg), tenoxicam (20 mg), their combination and placebo could not demonstrate a significant superiority of any medication compared with placebo after 8 weeks (73). Zopiclone after 8 weeks in a placebo-controlled trial led to the same improvement as placebo in 33 patients with FM (74).

Immunomodulators

Atypical depression and CFS. Monthly immunglobulin infusion for 3 months did not show a superiority to placebo in a study with 99 adult patients with CFS (75) or 71 adolescent patients (76). Treatment with acyclovir for 1 week as intravenous infusions and for a further 30 days orally, compared with placebo, did not change symptoms of CFS (77).

Somatoform symptoms and fibromyalgia. In 46 patients with FM randomized for a 3-week trial with ibuprofen compared with placebo, no significant difference between the substances was revealed, especially with regard to the number of pain sites and fatigue (78). Interferon alpha administered in four different doses sublingually and compared with placebo in a 6-week trial did not differentiate the treatment groups, using the tender point index as primary efficacy variable. Only the intermediate dose of 50 IU did lead to an improvement of some secondary variables (79).

Serotoninergic agents

Atypical depression and CFS. One open label trial exists for the efficacy of the 5-HT_3-receptor antagonists in CFS. Open treatment for 15 days with 5 mg daily tropisetron ($n = 10$) or 2×8 mg

daily odansetron ($n = 10$) resulted in a significant improvement after 15 days in fatigue evaluated with a visual analog scale (80).

Somatoform symptoms and fibromyalgia. A 16-week placebo-controlled trial with 51 patients did show a superiority of the 5-HT_2 antagonist ritanserine compared with placebo with regard to the occurrence of headache and feeling more refreshed, but not in pain in general, fatigue, sleep, anxiety and tender points (81). 5- Hydroxytryptophan, in a study with 50 patients, showed a significant superiority to placebo (82).

Several studies examined the effect of the selective 5-HT_3 antagonist tropisetron in FM. A prospective multicenter double-blind study using three different doses of the selective 5-HT_3-receptor blocker tropisetron in 418 patients showed a significant superiority of the lowest dose of the active treatment (5 mg) compared with placebo on the response rate, using a visual analog scale, a pain score and the number of painful tender points as criteria. A dosage of 10 mg daily led to a trend of improvement, whereas 15 mg was similar to placebo, pointing to an inverted U-shaped dose–response curve (83). Open trials using 5 mg daily over 4 weeks also showed efficacy of this drug (84). An open trial showed that intravenous administration of 2 mg resulted in a more favorable outcome compared with 5 mg of oral administration daily (85).

Various substances

Atypical depression and CFS. A mixture of ginkgo biloba and panax ginseng was significantly superior to placebo in a 90-day trial with 65 subjects on cognitive function in patients with neurasthenia (86). Efamol marine, and commercially available essential fatty acid preparation, did not show superiority to placebo in a 3-month trial in the estimation of improvement of the patients with CFS (87). In a randomized trial in 32 patients, weekly intramuscular injection of magnesium sulfate for 6 weeks revealed a significant superiority of the active drug compared with placebo in energy levels, emotional state and pain (88).

Somatoform symptoms and fibromyalgia. S- adenosylmethionine showed an significant superiority to placebo in a 6-week trial in 44 patients with FM randomized for active treatment or placebo. In particular, pain, fatigue and mood improved (89). These findings are confirmed by double-blind crossover trial in 17 patients, partially with depressive symptoms (90). Intravenous administration in a 10-day crossover design, however, revealed no superiority to placebo (91).

A placebo-controlled study in 45 patients with FM treated for 9 months with a daily subcutaneous injection of growth hormone showed a significant superiority of active medication using the FM Impact Questionnaire and the tender point score (92).

Suggestions about the pathophysiology

If typical and atypical depression respond differentially to pharmacotherapy, biological characteristics should be differential. In fact, the outcome in depressed patients treated with nortryptiline was more favorable in patients who showed no suppression of cortisol in the dexamethasone suppression test (DST), whereas with moclobemide DST suppression was a positive predictor for response (93). Similarly the DST had a clear predictive value for the treatment with phenelezine (94). Two open studies with moclobemide, however, could not find this relation (95,96). Put together, MAO inhibitors show favorable efficacy in patients with reversed vegetative symptoms and possibly without HPA axis overactivity. In the following, we want to look closer at the endocrine changes in the atypical depression spectrum disorders in comparison to typical major depression.

Endocrine correlates of typical compared with atypical depression

Hypercortisolism has been described early in patients with MD by examining plasma as well as cerebrospinal fluid (CSF) (97–99). More disturbed sleep is strongly associated with high nocturnal ACTH and cortisol secretion (100). Weight loss is correlated with increased urinary and cerebrospinal fluid (CSF) cortisol concentration and Dex non-suppression (101–103). One study could not find this relation (104). Casper et al. (101) reported an additional correlation of weight loss with increased sleep disturbances. It therefore seems reasonable to suggest, that features like hypercortisolism and Dex non-suppression point to a specific vegetative pattern and less to depressive core symptoms (102,103).

In contrast to typically depressed patients, those with hypersomnia and hyperphagia showed no change in morning plasma cortisol and DST (105,106). In seasonal affective disorder (SAD), one special form of atypical depression, normal basal plasma ACTH and cortisol concentrations were observed, but there was a delayed and reduced ACTH response to CRH despite normal cortisol (107). These endocrine and clinical disturbances were reversed by light treatment. In a single

case of atypical depression studied longitudinally, an inverse correlation was observed between peripheral cortisol concentration and depressed mood (108). Furthermore, in a group of patients with hypersomnic winter depression, the maximal plasma cortisol level over 24 h and the cortisol amplitude were significantly reduced compared with controls (109) and the amplitude was inversely correlated to their depressed symptoms, i.e. the higher the cortisol, the better the clinical condition of the patient. The only study examining CSF-CRH levels in patients with atypical features found a decrease in CSF-CRH compared with controls (110). It has therefore been suggested that the clinical features of atypical depression are correlated with a decreased CRH-activity (111,112). Put together, this points to the complementary changes in MD and AD with respect to vegetative features and peripheral HPA axis activity.

Common biology of atypical depression spectrum disorders?

Similar to atypical depression for CFS, the hints for the reduced HPA-axis function come from reports of reduced plasma (113,114) and 24-h urine (115–117) cortisol levels, whereas one study could not find a difference in these parameters compared with controls (118). In the study of Demitrack et al. (115), the CRH concentration in the CSF group was in the same range as that of controls despite the reduced peripheral cortisol concentration, which means that an inappropriately low CRH concentration occurs as a sign of a decreased central activation of the CRH system. Additionally, at least in a subgroup of patients with CFS, the size of the adrenal gland is reduced (119), whereas it is increased in major depression (120,121), pointing to a chronically decreased or increased HPA axis activity in these disorders, respectively. One of the main differences between CFS and major depression at the receptor level seems to be the sensitivity of the glucocorticoid receptor (GR), at least when estimated peripherally. The sensitivity of lymphocytes to Dex is increased in CFS (122), whereas it is decreased in patients with depression (123). The decreased sensitivity of the GR in depression is related to a decreased ability for adaptive changes (124). In line with this finding, beta-endorphin release to social stress (125) and cortisol response to surgical stress (126) are reduced in typical depression compared with healthy subjects, possibly as a sign of reduced reagibility. In contrast, the ACTH response to hypoglycemia was enhanced accompanied by normal cortisol secretion in CSF (127,127), therefore pointing to an enhanced responsiveness of the HPA axis to acute manipulations, but also to a reduced adrenal sensitivity to ACTH, possibly as a sign of a deactivation atrophy.

Patients with FM also show low 24-h urinary cortisol secretion without a change in free plasma cortisol, combined with an increased GR capacity of leukocytes compared with controls (4). This is accompanied by an increased ACTH response to CRH administration, whereas the cortisol secretion did not differ from that of controls, which is complementary to the situation in typical depression (128). It has been suggested that this is the case due to a decreased sympathetic input to the adrenal gland (129); however, a primary adrenal insufficiency cannot be ruled out with these findings. The amplitude of the circadian cortisol changes is, however, reduced in this disorder, similar to the findings in winter depression (130, 131). The finding of a decrease of cerebrospinal fluid concentrations of serotonin, norepinephrine and dopamine in FM (132,133) strongly points to a central mechanism, especially in the view of the suggestion of the close association between the HPA axis and the norepinephrine neurotransmission (134). With regard to this hypothesis and with respect to the findings of Russell et al. (132) and Legangneux et al. (133), a suppression of the HPA axis activity and the NE-ergic neurotransmission in FM can be suggested.

Despite clinical and endocrine similarities between FM and CFS, there are some differences regarding stimulation tests. While CRH-induced ACTH release is decreased in CFS (115), it is increased in FM (4). A differential involvement of arginine-vasopressin (AVP) in both disorders has been suggested to be the reason (135). Furthermore, reports of non-suppression in the Dex test (130,136) seem to contradict the assumption of a reduced HPA axis activity in FM. For patients with FM, enhanced (128), reduced (137) and unchanged (131) ACTH responses to hypoglycaemia have been reported. In CFS, the ACTH response to this challenge was enhanced (127). These findings might be due to the heterogeneity of patients classified as CFS or FM.

There is only one study which examines patients with somatization syndrome with or without hypochondriasis according to DSM-IV (138); this reported a significant increase in salivary cortisol after waking in patients with somatization alone. No obvious explanation for this finding compared with those reported before exists.

Some of the discrepancies reported above might be related to the interference of a chronic development and disturbances in the instantaneous

regulatory abilities. This is exemplified in a study on patients with burnout syndrome, a disorder possibly related to CFS (139). Burnout was defined with the Maslach Burnout Inventory, focusing on efficiency of and motivation to work. High scores of burnout were related to chronicity and chronicity was related to a reduced salivary cortisol level after waking either under baseline conditions and after administration of Dex. The perception of high stress defined as difficulty in acute coping with stressful situations was not associated with changes in basal salivary cortisol concentration. However, high scores of stress were accompanied by higher cortisol levels after Dex administration. Interestingly, subjects scoring high on both burnout and perceived stress reported largely an increase in pain-related complaints compared with the group with only one feature and controls. Therefore, 'burnout' could be related to a generally decreased HPA axis function, whereas 'stress' could be related to a defective feedback mechanism. The issue of the duration of the disorder could additionally be of importance, as in the short term, primarily the GR receptor sensitivity or number could be increased, whereas in the long run morphological changes like an atrophy could occur, changes opposite to the hypertrophy of the pituitary and adrenal cortex observed in depression.

Another factor which might contribute to inconsistent findings could be gender differences in the neurobiology and symptomatology of affective disorders. There are some hints that atypical depression is a type mainly present in females (140). Furthermore, response to pharmacotherapy of depression differs in males and females (141). In addition, biological changes in the course of pharmacological treatment, as determined by sleep-EEG changes, differ in males and females (142). This might possibly be the basis for the finding in the same study that clinical predictors of response differ with respect to gender: higher somatic anxiety and hypochondriasis predict response to the treatment with tianeptine or paroxetine in females, but no response in males (142).

Cushing as a model for atypical depression spectrum disorders?

To further understand the biology of AD and its spectrum disorders, comparison with Cushing's disease seems to bring some insight. Some authors stress the similarity between AD and Cushing's disease, as in the latter about 50% of patients meet the diagnostic criteria of AD (143) and the symptoms improve after treatment (144). These patients resemble those with AD with regard to central HPA axis activity as they exhibit a reduced CSF CRH level during the disorder (145), which is similar to the situation in AD. The observations of the inverse relation of peripheral cortisol and mood in AD (108,109) point to a possible mechanism. As the feedback system of the HPA axis seems to be intact in AD, as reflected by Dex suppression, the finding of the inverse mood/cortisol ratio could mean that in patients with AD, an increased access of cortisol to the brain exists. In line with this assumption, in one study an increased cortisol concentration in the CSF has been demonstrated in patients with or without atypical features compared with controls (105). Patients with atypical features showed an increased ratio of CSF-cortisol/plasma-cortisol compared with controls and also with patients without atypical features of depression. A statistical analysis of these parameters has not, however, been performed in this study. This increased ratio is a sign of an increased access of cortisol to the brain, which consequently could lead to a suppression of the HPA axis. A common characteristic of all types of depression could therefore be the increased intracerebral cortisol concentration. The measurement of cortisol in the CSF in relation to CRH might clarify this assumption.

Implications for the mechanism of specific drugs

If we focus on substances effective in the whole spectrum of atypical depression disorders, the best evidence for a specific efficacy exists for MAO inhibitors. There is some good evidence for the efficacy of hypericum extracts, whereas SSRIs seem to be less effective in comparison to these drugs. Treatment with low doses of tricyclic antidepressants or with 5-HT_3 antagonists shows an efficacy in bodily complaints.

As a decrease in HPA axis activity could be a general feature in AD spectrum disorders, it seems reasonable that its activation could be related to a therapeutic efficacy. This is supported by the finding that non-pharmacological manipulations such as exercise have a therapeutic effect in fibromyalgia (146) and CFS (147), and increase HPA axis activity as measured with the Dex or Dex-CRH test (148,149). In depression in general, there is less evidence for the efficacy of exercise (150).

Successful treatment of non-melancholic depressed patients with hypericum lead to non-suppression in the Dex and Dex-CRH tests (151),

i.e. an increase in HPA system activity during a 6-week trial. Unfortunately, no data exist for the effect of MAO inhibitors on the Dex-CRH test and only one small study on the effect of MAO inhibitors on the DST (96). This study is inconclusive, however, as only a small number of patients were included, co-medication was allowed to a great extent and patients showed mainly non-suppression at the start of the study, which is untypical for AD spectrum patients. The nocturnal secretion of cortisol was, however, increased after subchronic treatment with moclobemide (152). Furthermore, the dichotomy of the action of MAO inhibitors and standard-dose tricyclic antidepressants with regard to their action on HPA axis activity has been demonstrated by their opposite influence on 5-HT-induced cortisol release in patients with depression, which was augmented after MAO inhibitors and suppressed after tricyclics (153). For tricyclic antidepressants, the dose could be of importance for a differential therapeutic efficacy; a direct comparison of the effect of this group of substances on HPA axis activity is warranted. The effect of 5-HT_3 antagonists, however, is in contrast to the assumption of a direct causal relation between HPA axis activation and clinical response in the atypical depression spectrum disorder, as they show clinical efficacy but have a rather inhibiting effect on HPA axis activity (154). A mechanism unrelated to HPA axis activity to affect somatic symptoms seems therefore also to exist.

One possible mechanism for the decreased HPA axis activity in the atypical depression spectrum disorder could be the increase in the defective function of a transport protein, p-glycoprotein, at the blood–brain barrier, which regulates the access of cortisol to the brain (155). This defect leads to an increase in intracerebral glucocorticoid concentration and to reduced peripheral HPA axis activity, as demonstrated with knockout mice (156,157). An increase in *p-gp* gene expression has been demonstrated with hypericum extract (158,159). In line with this mechanism, a decrease in intracerebral cortisol, and to a lesser extent corticosterone, concentration could be observed after subchronic treatment with hypericum extract (160). For MAO inhibitors, no direct reports exist with regard to intracerebral corticosteroids or their possible action on p-glycoprotein. This hypothesis opens up the possibility that the blood–brain barrier might be a target for drugs acting in this spectrum of disorders.

Conclusion

There is some evidence that there is a spectrum of disorders, related both phenomenologically and with respect to their neurobiology and treatment, which can be opposed to 'typical' depression. This spectrum is characterized mainly by 'reversed' vegetative signs as hypersomnia and hyperphagia, fatigue, somatic complaints without medical explanation and a mood disturbance characterized by reagibility and rejection sensitivity. A relation to hypocortisolism or at least normal suppression of cortisol by Dex has been described in some studies, but conflicting data also exist. This might be partially due to the fact that gender differences and the influence of the chronicity of the disorder are not generally taken into account. In relation to pharmacotherapy, MAO inhibitors show a well documented efficacy in this spectrum of disorders with the limitation that somatization is less well studied. Further, most of the studies were performed with irreversible MAO inhibitors, the use of which is limited due to their side-effect profile. Some evidence exists that hypericum extract could have a specific effect. As both MAO inhibitors and hypericum extract lead to an activation of HPA axis activity, the hypothesis of its inhibition in the atypical depression spectrum is supported. Trials in which gender, chronicity and HPA axis characteristics are taken into account are warranted to clarify their role in response to therapy.

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