

# Mood and Anxiety Disorders as Early Manifestations of Medical Illness: A Systematic Review

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## Key Words

Medical illness · Prodrome · Anxiety · Irritability · Depression · Mania · Affective disorders

## Abstract

**Background:** Affective disturbances involving alterations of mood, anxiety and irritability may be early symptoms of medical illnesses. The aim of this paper was to provide a systematic review of the literature with qualitative data synthesis. **Methods:** MEDLINE, PsycINFO, EMBASE, Cochrane, and ISI Web of Science were systematically searched from inception to February 2014. Search terms were ‘prodrome/early symptom’, combined using the Boolean ‘AND’ operator with ‘anxiety/depression/mania/hypomania/irritability/irritable mood/hostility’, combined with the Boolean ‘AND’ operator with ‘medical illness/medical disorder’. PRISMA guidelines were followed. **Results:** A total of 21 studies met the inclusion criteria and were analyzed. Depression was found to be the most common affective prodrome of medical disorders and was consistently reported in Cushing’s syndrome, hypothyroidism, hyperparathyroidism, pancreatic and lung cancer, myocardial infarction, Wilson’s disease, and AIDS. Mania, anxiety and irritability were less frequent. **Conclusions:** Physicians may not pursue medical workup of cases that appear

to be psychiatric in nature. They should be alerted that disturbances in mood, anxiety and irritability may antedate the appearance of a medical disorder. © 2014 S. Karger AG, Basel

## Introduction

Affective disturbances involving alterations of mood, anxiety and irritability may be early symptoms of medical illnesses [1, 2] as well as of psychiatric disorders [3, 4]. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [5] suggests that in certain cases manic, depressive and anxiety symptoms may be linked to medical conditions and identifies ‘bipolar and related disorder due to another medical condition’, ‘depressive disorder due to another medical condition’ and ‘anxiety disorder due to another medical condition’ as diagnostic categories. It specifies that a depressive state may appear in the course of the medical illness often preceding its major symptoms and that a manic or hypomanic picture may occur during the initial presentation of the medical condition (within 1 month) [5]. The DSM-5 provides examples of medical conditions that may be associated with mood and anxiety disturbances but not a list of med-

ical disorders characterized by affective prodromes. Further, it does not list irritability as a disturbance that may be due to a physical condition, despite its common presence in medical settings [6, 7].

In 1994, Fava et al. [2] reviewed the literature and reported the known affective prodromes of medical illness in the form of an editorial. No update has been carried out and no systematic reviews have been conducted since then. Such knowledge, however, may entail considerable clinical value in the diagnostic process in medical settings. It may also provide interesting insights into the pathophysiology of affective disturbances.

## Methods

### *Eligibility Criteria*

Eligible articles included English-language papers published in peer review journals reporting data on affective prodromes of medical illness. Papers on dementia and Alzheimer's disease were excluded because of the strong interaction between affective prodromes and cognitive symptoms.

### *Information Sources and Search*

MEDLINE, PsycINFO, EMBASE, Cochrane, and ISI Web of Science were systematically searched from inception to February 2014. In addition, a manual search for reference lists from all articles selected and for any relevant reviews was done. Search terms were 'prodrome/early symptom', combined using the Boolean 'AND' operator with 'anxiety/depression/mania/hypomania/irritability/irritable mood/hostility', combined with the Boolean 'AND' operator with 'medical illness/medical disorder' (for details of the search strategy used for MEDLINE, see online suppl. appendix; for all online suppl. material, see [www.karger.com/doi/10.1159/000367913](http://www.karger.com/doi/10.1159/000367913)).

### *Study Selection, Data Collection Process and Data Items*

Titles and abstracts were screened by one of the authors (F.C.). Articles appearing potentially relevant were retrieved and two authors (F.C. and G.A.F.) independently assessed each of the full reports. Disagreements were resolved by consensus among these primary raters and the senior investigator (N.S.).

### *Summary Measures*

The search strings, the list of relevant reviews, the data coding, and the quality criteria that were used can be requested from the corresponding author. PRISMA guidelines were followed [8].

## Results

### *Selection of Articles and Study Characteristics*

The search of MEDLINE, PsycINFO, EMBASE, Cochrane, and ISI Web of Science databases provided a total of 11,030 citations; the manual search provided 3,327 citations.

As a whole, 14,357 citations were considered. After reviewing the abstracts to exclude those which clearly did not meet the criteria, 203 remained. Of these, 182 were excluded: 107 studies did not meet the inclusion criteria and 1 was a duplicate; thus, 74 case reports were considered separately. A total of 21 studies met the inclusion criteria and were surveyed in the present systematic review (for details, see online suppl. table 1). No unpublished relevant studies were obtained (for flow diagram of the search, see online suppl. fig. 1).

Since the numerous case reports were deemed to provide additional clinical information, details of 70 of the 74 found (4 were not included because it was not possible to retrieve the full text) are summarized in online supplementary table 2.

Mood disorders (depression, mania, anxiety, irritability) as early manifestations of medical illness, as summarized in table 1, are reported below.

### *Depression*

Depressive symptoms are frequently encountered in the medically ill. However, only a limited number of patients suffer from a major depressive disorder according to DSM criteria, that is, depressed mood associated with loss of interest or pleasure, appetite changes, sleep disturbances, psychomotor retardation or agitation, fatigue, feelings of worthlessness and guilt, and suicidal thoughts. Physical illness may play a causative role by inducing structural brain damage (e.g. stroke) or altering neurotransmitter mechanisms (e.g. Cushing's syndrome). In some instances, stressful life events may be a contributing factor to the onset of disease manifesting with depression (e.g. hyperthyroidism) [9].

### *Endocrine Disease*

Depression is the most common psychiatric manifestation of Cushing's syndrome, occurring in more than half of the patients, as reported by studies that used a standardized assessment [10]. About a quarter of patients reported a major depressive disorder either immediately before or at the onset of illness [11–13]. Depression also appeared in the prodromal phase of Graves' disease in 14% of patients [11]. Of 250 consecutive patients referred to a psychiatric hospital for depression and anergia, 20 (8%) were found to have some degree of hypothyroidism [14, 15]. In 25 patients with mild primary hyperparathyroidism [16], depression (52%), fatigue (68%), forgetfulness (76%), decreased concentration (72%), uneasiness (60%), and sleeplessness (56%) were found. In this group, psychiatric symptoms did not significantly improve after parathyroidectomy [16].

**Table 1.** Early manifestations of medical illness

Medical illness	Clinical characteristics
<i>Endocrine diseases</i>	
Cushing's syndrome	Major depression, often melancholic subtype; common symptoms: irritability and emotional lability, change in appetite or weight, loss of energy, change in sleep, anhedonia, psychomotor retardation or agitation, decreased concentration, suicidal thoughts [11–13]
Hypothyroidism	Depression, anergia [14, 15]
Primary hyperparathyroidism	Depression, tiredness, forgetfulness, decreased concentration, uneasiness, sleeplessness [16] Irritability [16]
<i>Neurological diseases</i>	
Multiple sclerosis	Major depressive disorder, dysthymia [17]
Meningiomas	Major depressive disorder and/or anxiety [18]
Parkinson's disease	Major depression and anxiety [19–21]
<i>Malignancies</i>	
Pancreatic cancer	Depression described as 'loss of ambition', 'loss of push' or 'lack of go', anxiety, insomnia, decreased appetite and weight loss, premonition or foreboding of having cancer [23–26] Restlessness, agitation, anxiety [24] Irritability [24]
Lung cancer	Depression [27, 28] Anxiety [28]
Gastric cancer	Irritability [24]
<i>Miscellaneous</i>	
Myocardial infarction	Major depressive disorder, demoralization [30, 31] Somatic anxiety, generalized anxiety, panic, agoraphobia [31] Irritability [31]
Wilson's disease	Depression [29] Mania: increased talkativeness, restlessness, marked mood changes [29] Anxiety [29] Irritability and aggression [29]
AIDS	Somatic and nonsomatic symptoms of depression (sadness, anhedonia, low mood) [34]

### Neurological Disease

Byatt et al. [17] found that 75% of their subjects with multiple sclerosis reported a delay in multiple sclerosis diagnosis due to symptoms of major depressive disorder. Such a delay is clinically significant because it may postpone the treatment, increase the disease burden and disability and lower the quality of life. Depressive illness was also observed as a presentation of meningioma [18]. The psychiatric symptoms were the only initial manifestations in about 20% of the cases occurring in the fifth decade of life. Thus, such patients should be investigated by brain imaging studies even though there are no neurological signs or symptoms [18]. Some authors found that major depression may precede the diagnosis of Parkinson's disease [19–21]. Depressive symptoms were present in the year before the initial evaluation of 37%

of patients with a subsequent diagnosis of Parkinson's disease [19]. A higher prevalence of depression occurred in women than in men and depressive symptoms were usually moderate in intensity [20]. Patients with major depression antedating Parkinson's disease were younger and had significantly fewer Parkinson's disease signs than those without a history of depression, even though the duration of parkinsonism was comparable [20]. In another study, depression and anxiety were observed in 47% of patients in the 10-year period before the diagnosis of Parkinson's disease and in 25% of controls [21].

### Malignancies

In 1931, depression, anxiety, insomnia, and weight loss were described for the first time as earliest manifestations of pancreatic cancer [22]. Later, several studies con-

firmed depression as a prodrome of this disease [23–26]. Depressive symptoms occurred as first symptoms in about 38–45% of patients with carcinoma of the pancreas, while anxiety in the prodromal phase was observed in about 12% [24]. Usually, these patients are in old age and have minimal clinical findings and signs. Depression was described as ‘loss of ambition’, ‘loss of push’, ‘lack of go’, and the individuals expressed a kind of premonition or foreboding of having cancer [23]. Symptoms of a major depressive illness may also precede the diagnosis of lung cancer [27, 28]. About 16% of lung cancer patients had symptoms of a major depressive illness at the time they first presented to the hospital [27]. Similarly, 12% had symptoms of serious depression at their first presentation to chest specialists [28].

#### Miscellaneous

About 42% of patients with Wilson’s disease had depression as an early manifestation of the illness and these symptoms were severe enough to warrant psychiatric intervention in almost half of them before the diagnosis of Wilson’s disease was made [29]. Depression was found to precede the onset of myocardial infarction [30, 31]. In particular, 23% of the patients enrolled by Carney et al. [30] met DSM-III-R [32] criteria for a major depressive episode which occurred at least 2 weeks before the acute event. In another investigation [31], depressed mood was found to occur in the 6 months preceding a diagnosis of myocardial infarction in 49% of the patients. Of these, 17% had a major depressive disorder according to the DSM-IV [33]. Depressive symptoms were observed before the diagnosis of AIDS in the longitudinal study run by Lyketsos et al. [34]. They reported an increase in the mean score of both somatic and nonsomatic self-rated depressive symptoms starting 1.5 years before a diagnosis of clinical AIDS and continuing thereafter.

#### Case Reports

In case reports, depression was found to be a prodrome of a subsequent medical disorder such as the following: hypothyroidism [35], hyperthyroidism [36–42], hypoparathyroidism [43], hyperparathyroidism [44–46], hyperprolactinemia [47], Addison’s disease [48–50], pheochromocytoma [51], brain tumors [52–56], Parkinson’s disease [57], lymphoma of the central nervous system [58], normal pressure hydrocephalus [59], limbic encephalitis [60], meningoencephalitis [61], carcinoma of the pancreas [62–67], mitochondrial disorder [68–72], and multiple sclerosis [73–75] (online suppl. table 2). The case reports suggest that ‘thyroid melancholics’ are gener-

ally older, appear ill with weight loss and do not demonstrate the usual signs and symptoms of Graves’ disease [36, 38]. They also suggest that, when affective prodromes antedate multiple sclerosis, the clinician can be helped in formulating the correct diagnosis by a history of recurrent or episodic emotional disability, the failure to achieve positive results with usually effective psychotherapeutic and/or pharmacological treatments, a vague history of transient sensory or motor disturbances which may be attributed to various innocuous causes, and the presence of subtle neurological signs on thorough examination [73–75].

#### Mania

Several medical illnesses may trigger a manic episode, that is, a distinct period of abnormally and persistently elevated and expansive mood with symptoms such as grandiosity, decreased need to sleep, distractibility, increase in goal-directed activity, excessive involvement in pleasurable activities, pressure to keep talking, and flight of ideas. However, increased talkativeness, restlessness and significant mood changes, characterized by cheerfulness and occasional irritability, were specifically assessed as prodromes only in Wilson’s disease [29] (table 1).

#### Case Reports

In case reports, mania could antedate the onset of hypothyroidism [76–81], hyperthyroidism [41], brain tumors [52, 82, 83], venous angioma of the frontal lobe [84], hydrocephalus [85, 86], multiple sclerosis [87, 88], herpes simplex encephalitis [60, 89], meningeal cryptococcosis [90], Wilson’s disease [91], and mitochondrial disorder [72] (online suppl. table 2).

#### Anxiety

Anxiety, a fearful anticipation of an imminent but intangible danger, may be related to a number of medical disorders. It may occur as recurrent, prominent attacks or as generalized anxiety. Illnesses with anxiety as a prodromal syndrome are listed in table 1.

Increased anxiety has been observed in the prodromal phase of Wilson’s disease, even though only in 12.5% of cases [29]. Jacobsson and Ottosson [24] described excessive anxiety in about 12% of patients with a later diagnosis of pancreatic cancer. Anxiety may be the early manifestation of lung cancer in about 10% of patients presenting for the first time to a chest specialist [28]. Somatic anxiety (38%), generalized anxiety (17%), panic (14%), and agoraphobia (12%) were found in the 6-month period before myocardial infarction [31].

## Case Reports

Anxiety was found to be an early manifestation of meningioma [92, 93]. Together with depression, it can antedate Addison's disease [48]. Panic with or without agoraphobia and agoraphobia without panic may precede the diagnosis of hyperthyroidism [38, 41, 42, 94]. Panic attacks and anxiety could be the early manifestations of hypoparathyroidism [95], hypoglycemia [96], pheochromocytoma [51, 97], brain tumors [52, 54–56], temporal lobe epilepsy [98, 99], and mitochondrial disorders [69, 72]. In pancreatic cancer, restlessness, agitation and anxiety were the most common symptoms [100], together with frank panic attacks and generalized anxiety [101, 102] (online suppl. table 2).

## Irritability

Irritability is a feeling state characterized by reduced control over temper, which usually results in irascible verbal or behavioral outbursts, although the mood may be present without observed manifestation [6, 7, 103]. The experience of irritability is always unpleasant for the individual and the overt manifestation lacks the cathartic effect of justified outbursts of anger. Irritability is a mood state which may be independent of depression and anxiety [103] but can be symptomatic of several psychiatric disorders [6, 104] and a prodromal symptom of major depression [3, 4].

Irritability was found to precede the diagnosis of incidentally detected mild primary hyperparathyroidism in 48% of patients [16]. It seemed not to improve after parathyroidectomy, but 50% of the patients reported an improvement in general health perceptions [16]. Irritability was prodromal also in about 44% of gastric cancer cases and in about 30% of pancreatic cancer patients [24]. Irritability and aggression were described to precede a diagnosis of Wilson's disease [29]. Finally, irritability was observed in 56% of subjects in the 6 months before the occurrence of a myocardial infarction [31] (for details of clinical features, see table 1).

## Case Reports

Irritability could be an early manifestation of hyperthyroidism [37], Addison's disease [105], brain tumors [52, 55], left temporal meningioma [92], and multiple sclerosis [73, 87]. A case record of the Massachusetts General Hospital contains a striking illustration of a man who entered the hospital complaining of abdominal pain, headache, irritability, and nervousness and later had a diagnosis of cancer of the pancreas [106] (online suppl. table 2).

## Discussion

The findings of this systematic review should alert the physician that mood and anxiety disorders and irritability may antedate the appearance of the overt manifestations of a medical condition. Depression was found to be the most common affective prodrome of medical disorders and was consistently reported in Cushing's syndrome, hypothyroidism, hyperparathyroidism, pancreatic and lung cancer, myocardial infarction, Wilson's disease, and AIDS. Anxiety and irritability may occur in conjunction with depression, but were less frequent on their own. Mania was not found to be consistently associated with specific medical disorders other than Wilson's disease [91]. The occurrence of affective prodromes should be particularly suspected in patients having an onset of mania later than the expected age and when standard psychiatric treatments do not lead to an improvement in psychological symptoms. In fact, affective symptoms due to a medical illness tend not to fully respond to antidepressant drugs, even when properly administered [107, 108], but rather to the proper treatment of the underlying medical disorder. Indeed, many patients dismissed as suffering from a mood or anxiety disorder, with an adequate follow-up, may later present with a medical illness responsible at least in part for it [109]. In a study [110], about 50% of psychiatric patients who suffered from medical conditions remained undiagnosed as to the underlying physical disorders; primary care physicians failed to diagnose the physical illness in 32% of cases and psychiatrists in 48%, even though having a psychiatric disorder may be associated with an increased risk of medical illness (e.g. breast cancer) [111]. Primary care physicians may not pursue a medical workup of cases that appear to be overtly psychiatric in nature; similarly, patients having had previous psychiatric treatment may prejudice the clinical judgment of the physician [112]. Psychiatrists who miss the correct medical diagnosis may have the opinion that the patient's somatic condition is not their concern, may fail to think of nonpsychiatric reasons for the patient's complaints [112] or may not have at hand the adequate diagnostic instruments. For instance, some neurological diseases start with psychiatric manifestations and for this reason they are often misdiagnosed. A paradigmatic example is multiple sclerosis. As Lemere [113] pointed out, it 'may present itself as a psychiatric problem for [...] years before the neurologic disease becomes manifest [...]; patients are misdiagnosed as having a neurosis'.

Assuming that the clinicians have the tools and the knowledge to suspect a causative medical illness in affec-

tive disorders, the question of how far to go into screening for the medical illness still remains an open one. An early investigation on depression and thyroid disease [114] suggested that all depressed patients should be screened for signs, symptoms and specific risk factors for hypo- and hyperthyroidism, but that routine testing was not indicated. This means that the amount of medical workup should be related to the features of affective disorders (e.g. age of onset, resistance to treatment, atypical presentation) and to family and personal history.

The presence of psychiatric manifestations early in the course of a medical disorder may determine major prognostic and therapeutic differences among patients who otherwise seem to be deceptively similar since they share the same medical diagnosis. For instance, in all disease phases of Cushing's syndrome, affective disorders may interfere with quality of life and social functioning, increase health care utilization and reduce compliance, and are associated with higher mortality [10]. In particular, patients with the pituitary-dependent form (Cushing's disease) and depression were found to suffer from a more severe form of illness, both in terms of cortisol production and clinical presentation, compared to those without depression [115, 116]. Some characteristics of depression in Cushing's syndrome may have pathophysiological implications for the melancholic and atypical subtypes of depression in psychiatry in relation to degrees of HPA axis activation [117]. Interestingly, the clin-

ical observation of resistance to antidepressant drugs of early symptoms of major depression in Cushing's syndrome and its responsiveness to inhibitors of steroid production paved the way for the use of these latter drugs in psychiatry [10].

The main limitation of the present systematic review is that populations, methods and instruments, as well as outcome definitions, were very different across studies. Due to this limitation, no meta-analysis was conducted. Consequently, artefact variance such as sampling and measurement errors could not be accounted for. Moreover, the majority of the studies included had a retrospective design. Longitudinal studies are warmly encouraged.

In conclusion, a limited number of medical diseases appear to be consistently associated with the occurrence of early mood and anxiety disturbances. They should be considered in the diagnostic workup of patients who present with psychiatric disturbances, particularly when they appear to be refractory to standard psychiatric treatments.

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