*International Journal of Neuropsychopharmacology* (2005), **8**, 93–105. Copyright © 2004 CINP
DOI: 10.1017/S1461145704004729

REVIEW ARTICLE

# The many faces of fatigue in major depressive disorder

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**Abstract**

Fatigue is a common complaint in the community and medical care settings. Different studies show a high comorbidity between fatigue and depressive disorder. Furthermore, fatigue is an important somatic symptom of depressive disorder and one of the main depressive presentations in primary-care medicine. Fatigue shows a slow response to antidepressant treatment and psychotherapy. Improved work performance is strongly correlated to improvement in energy. However, the assessment and treatment of fatigue in depressive disorder remains understudied. Different definitions of fatigue in depressive disorder are applied in DSM-IV and ICD-10, and depression rating scales all show a different coverage of this core depressive symptom, thereby hampering scientific research. Serotonin, norepinephrine, dopamine and histamine mediate symptoms of fatigue in depressive disorder. Although few data address the effect of antidepressants or augmentation strategies on fatigue-related symptoms, there is a pharmacological rationale for using antidepressant monotherapies, such as venlafaxine, bupropion, sertraline, fluoxetine, or augmentation of first-line treatment with stimulants or modafinil.

*Received 14 December 2003; Reviewed 28 March 2004; Revised 20 June 2004; Accepted 7 July 2004*

**Key words**: Antidepressants, depressive disorder, fatigue, modafinil, stimulants, tiredness.

## Introduction

Depression theory and practice is dominated by an emphasis on the affective and cognitive constituents of the depressive syndrome. This two-sided emphasis is reflected in the differential weight of the affective items depressed mood and loss of interest or pleasure in the definition of major depressive episode (MDE) according to DSM-IV (APA, 1994), and the view of depression as a primarily cognitive disorder. However, somatic symptoms are often the main reason for patients seeking medical care. One of these somatic symptoms, fatigue or lack of energy, will be discussed in the present paper. Although fatigue is a depressive symptom with a long history (Swindle et al., 2001), little research has focused on this variable. Findings regarding fatigue in depressive disorder mainly stem from two different sources: a research line focusing on fatigue and its psychiatric comorbidity and a research line directed towards fatigue as an important depressive symptom. The former is an expression of the huge scientific and public interest in (chronic) fatigue (Shorter, 1992), the latter being a consequence of the growing interest in depressive symptoms beyond the core depressive symptomatology.

The shifting focus towards fatigue as a primary symptom in depression has elucidated the fact that, although antidepressants have documented efficacy in relieving the affective symptoms of depression, many patients do not experience restoration of energy, at least not at the start of treatment. In major depressive disorder (MDD), fatigue may be a common residual symptom because the neurotransmitter pathways implicated in the affective symptoms are not the same pathways that seem to regulate the symptoms of fatigue. An understanding of the pathophysiology of fatigue in depression can allow practitioners to choose the pharmacological treatments most likely to relieve fatigue early in treatment.

In this paper, we review the frequency and significance of fatigue-related symptoms in MDD, followed by a discussion of the neurobiology of fatigue. We further present and describe the antidepressant

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monotherapies and augmentation strategies most likely to restore energy in depressed patients. This review will focus on fatigue as a symptom, thereby avoiding more controversial issues like chronic fatigue syndrome and neurasthenia, in which fatigue is a pivotal symptom. This approach is in line with authors who call for more research on symptoms vs. research on syndromes (Costello, 1992) and may help to disentangle the often complex comorbidities between affective and fatigue syndromes.

## Fatigue in the community and medical settings

Fatigue is a subjective symptom associated with several medical and psychiatric illnesses. It is a common complaint in the community and in primary-care settings. Different data from the Epidemiologic Catchment Area (ECA) Study shed light upon the relationship between fatigue and psychiatric disorders, in terms of current and lifetime comorbidity (Addington et al., 2001; Kroenke and Price, 1993; Walker et al., 1993). In the ECA studies fatigue is ascertained by the question: 'Has there ever been a period lasting two weeks or more when you felt tired out all the time'. Each positive response is only considered a positive symptom if the respondent told a professional about it, took medication for it, or stated that it interfered with his or her life. Walker et al. (1993) found a 6.0% prevalence of current medically unexplained fatigue in the community. Subjects with current fatigue had a significantly higher lifetime and current prevalence of major depression, dysthymia, panic disorder and somatization disorder. The higher prevalence of current major depression [odds ratio (OR) 14.7 for men, 6.3 for women] persisted even when fatigue was excluded as a criterion for the diagnosis of depression. Kroenke and Price (1993) found a 13.8% lifetime prevalence of fatigue, classified as medically unexplained or potentially due to psychiatric illness. Again, fatigue was associated with an increased lifetime risk of depression and dysthymia (OR 11.2 and 8.7 respectively). Addington et al. (2001) further prospectively explored the prevalence of fatigue and its relationship with major depression over a 13-year follow-up interval. At baseline, similar findings were made as in the study by Kroenke and Price (1993): 14.0% of individuals reporting unexplained fatigue for 2 wk or more in their lifetimes, with an 11-fold greater risk of a lifetime diagnosis of major depression compared to non-fatigued participants. Baseline depression was predictive of both recurrent/chronic fatigue (reporting fatigue in their lifetime at baseline and again sometime during the follow-up interval) and incident fatigue (reporting fatigue occurring for the first time during the follow-up interval). Participants with recurrent/chronic fatigue had a 28-fold greater risk of developing major depression than those without fatigue.

Other community-based studies, using different assessments of fatigue, have yielded similar results. Pawlikowska et al. (1994) found a 38% prevalence of substantial fatigue, as assessed with a self-rating scale. Approx. 48% of cases were fatigued for 6 months or longer, and the most common reasons cited for fatigue were psychosocial (40%). In a survey of psychiatric morbidity in Great Britain, fatigue (27% prevalence) was cited as the most common neurotic symptom (Mason and Wilkinson, 1996). Prolonged and excessive fatigue had a 13.2% prevalence in a study by Hickie et al. (2002). In 41% of cases the symptom of fatigue was clinically significant and not caused by drugs, alcohol, physical illness or injury.

Besides being a common symptom in the community, fatigue is also a highly prevalent complaint in primary-care medicine. David et al. (1990) determined the prevalence of fatigue in general practice attenders with an extensive fatigue questionnaire; 10.2% of men and 10.6% of women complained of feeling tired all or most of the time for more than a month. In a primary-care study by Cathébras et al. (1992), 13.6% of patients presented with a complaint of fatigue; in approximately half of the cases fatigue was their major reason for consultation. The rate of current major depression was 17.2% for fatigue patients vs. 8.8% for non-fatigue patients. Similar findings were made for the one-year prevalence of major depression and the rate of lifetime major depression: 20.4% vs. 11.3%, 32.3% vs. 15.7%. Different constructs of fatigue were assessed in a study of Fuhrer and Wessely (1995). The prevalence ranged between 3.7% (fatigue as a diagnosis), 7.6% (fatigue as presenting complaint) and 31.3% (symptom of fatigue/loss of energy during the preceding 2 wk). Patients with a presenting complaint of fatigue had significantly higher scores on a self-report questionnaire measuring depressive symptomatology. Furthermore, 27.2% of fatigue-complaint patients were diagnosed as depressed by their GP, and nearly 18% of patients diagnosed with depression had a presenting complaint of fatigue.

## Fatigue in MDD

Fatigue or loss of energy nearly every day is the A6 criterion – and not a core symptom – in the DSM-IV diagnosis of MDE. Furthermore, fatigue with a distinct quality is used as the B3 criterion for atypical features

specifier: leaden paralysis (heavy, leaden feelings in arms and legs). However, in the definition of depressive episode according to ICD-10 (WHO, 1992), reduced energy is described as a core feature besides depressed mood and loss of interest and enjoyment. Reduced energy is specified as leading to increased fatiguability and diminished activity, with marked tiredness after only slight effort being common.

The different wordings of 'fatigue' in DSM-IV and ICD-10 reflect its complexity and heterogeneity. This is highlighted even more by the coverage of fatigue in different depression rating scales. The Hamilton Depression Rating Scale (HDRS) covers fatigue in two different items: item 7 (work and interests) and item 13 (general somatic symptoms) (Hamilton, 1960, 1967). In the Beck Depression Inventory – II (BDI-II; Beck et al., 1996) fatigue is described by item 15 (loss of energy) and item 20 (tiredness or fatigue). Item 7 of the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979) describes lassitude as representing a difficulty getting started or slowness initiating and performing everyday activities: a construct covering both fatigue and retardation. The HDRS, BDI-II and MADRS not only differ in their coverage/wordings of fatigue but also in their perspective of observer (HDRS and MADRS being observer-rating scales, BDI-II being a self-rating scale). The importance of this perspective is made clear in a study by Gullion and Rush (1998). In a factor analysis of depressive symptoms (measured by different observer-rating and self-rating scales), the authors identified a factor 'lack of energy' which was mainly composed of self-rated items. Observer-rated items that measured fatigue loaded on a different factor 'hedonic capacity'. These results suggest different concepts of self-rated vs. observer-rated fatigue in major depression and may have implications for the measurement of fatigue in depression and antidepressant therapy.

Different studies criticize the over-evaluation of the affective/cognitive symptomatology and underline the importance of fatigue as a core depressive symptom. Buchwald and Rudick-Davis (1993) investigated the relationship between DSM-III MDE and the eight individual criterion B symptoms in cases and non-cases of MDE. Sleep disturbance (98%), loss of energy (93%) and appetite disturbance (86%) were most common in MDE. A further analysis evaluated the diagnostic efficiency of the different symptoms. Again, loss of energy was identified as a core depressive symptom. Christensen and Duncan (1995) conducted a study to determine whether energy level could be used to distinguish depressed (major depression according to DSM-III-R) from non-depressed individuals. Assessment of energy levels was done by a self-report questionnaire in depressed patients and a non-depressed control group. A discriminant function analysis using the energy measures as predictors was significant and provided a correct classification of 93% of the participants. When compared with psychosocial variables like negative cognitions and stressors, energy level proved to more effective in classifying depressed individuals. In a pan-European survey of depression in the community (Tylee et al., 1999) tiredness (73% prevalence) was identified as one of the most commonly experienced symptoms during a depressive episode.

The importance of fatigue as a core depressive symptom is even truer in some specific patient samples. Maurice-Tison et al. (1998) found fatigue/loss of energy to be the most common depressive symptom (38.2% prevalence) in general practice patients. Major depression was diagnosed in 5.9% of the total sample. In the depressed subsample fatigue was prevalent in 93.6% of cases. In a study by Suh and Gallo (1997), symptom profiles of depression (assessed by the Diagnostic Interview Schedule) among general medical service users were compared with speciality mental health service users. General medical service users were less likely to report dysphoria (OR 0.49) and worthless/sinful/guilty (OR 0.55) after holding constant the level of depression, but were more likely to report fatigue (OR 1.82). Emmons et al. (1987) examined the depressive symptom profile (assessed by an extensive self-report questionnaire) in medical and psychiatric depressed in-patients, matched in terms of total scores on the BDI. Anergy and worry were the most important symptoms differentiating depressed medical patients from depressed psychiatric patients, while suicidal ideation and loss of interest were the most important symptoms differentiating depressed psychiatric patients from depressed medical patients. Although fatigue appears to be a central component of depression in primary-care patients, tiredness (besides concurrent physical illness) is a risk factor for unrecognized depression (Tylee et al., 1993).

Many of the above-mentioned studies question the existing concept of depression and may have implications for screening guidelines and measurement of change, in which fatigue calls for a more prominent place. This is highlighted even more in studies by Moos and Cronkite (1999) and Swindle et al. (2001). Moos and Cronkite (1999) identified severe loss of energy/fatigue/tiredness, when present at intake, as a risk factor of a chronic course in a naturalistic study of unipolar depressed patients over a 10-yr period.

Swindle et al. (2001) examined the role of low energy in the relationship of depression to decreased work productivity. Depressed patients were enrolled from clinical primary-care practices in a naturalistic study of depression treatment. At baseline, tiredness/low energy was the most common depressive symptom reported by 91.3% of patients. All measures of depression, social functioning and work productivity improved from baseline to 3-month follow-up. Among different components of depressive symptoms, an energy factor was most strongly related to social functioning, absenteeism and work productivity, at baseline and at 3-month follow-up. Improved work performance was more strongly correlated to improvement in energy than to a decrease in the depressive symptoms.

Besides being a symptom of the index episode, fatigue is also prevalent in the prodromal and residual phase of major depression. Fava et al. (1990) found fatigue as one of the most common prodromal symptoms in patients with their first MDE. In a study by Nierenberg et al. (1999) residual symptoms were assessed in depressed outpatients who responded acutely to fluoxetine (20 mg/d for 8 wk). More than 80% of full responders had one or more residual symptoms of MDD: fatigue (38.8% prevalence) being one of the three most common symptoms. This slow response of fatigue during antidepressant treatment is not limited to the acute phase, as evidenced by Opdyke et al. (1996/1997). These authors studied the effect of continuation therapy (16 wk of combined nortriptyline treatment and interpersonal psychotherapy) on residual symptoms in late-life depression. Fatigue was one of the symptoms that had a slower response. Barkham et al. (1996) made similar conclusions in their investigation of dose–effect relations in time-limited psychotherapy for depression (8 or 16 sessions of either cognitive–behavioral or psychodynamic–interpersonal therapy). Of all depressive symptoms (as measured by the BDI), fatigue showed the least clinically significant change. Similarly, Kopta et al. (1994) demonstrated that the $ED_{50}$ (effective dose of psychotherapy for 50% of patients to show clinically significant change) was 17 sessions for feeling no interest and for lack of energy (compared to only five sessions for crying easily, eight sessions for hopelessness about the future, and 11 sessions for blaming yourself).

### Fatigue and the neurobiology of depression

Recent advances in neuropharmacology and neuroimaging are beginning to map the topography of symptoms in MDD (Davidson et al., 2002; Drevets, 2000, 2001; Drevets et al., 2002; Liotti et al., 2002; Mayberg et al., 1999). Different malfunctioning neuronal circuits may mediate different symptoms in MDD. Thus, the symptom of fatigue is hypothetically mediated by entirely different malfunctioning neuronal circuits than those that mediate sadness or depressed mood in MDD (Stahl et al., 2003). Furthermore, to the extent that such circuits operate independently, it may be possible to target one set of circuits successfully with antidepressant treatment but not necessarily the other (Stahl, 2003a). This may explain observations that antidepressants are often more effective for sadness and depressed mood than they are for fatigue, which is one of the most common residual symptoms in patients who respond but do not remit with antidepressant treatment (Menza et al., 2003; Nierenberg et al., 1999; Paykel, 2002; Paykel et al., 1995; Tranter et al., 2002).

The classical theory to explain depression is the 'monoamine hypothesis' which proposes that depression is related to a deficit of monoamines, particularly norepinephrine (NE) and serotonin (5-HT), at critical synapses (Schildkraut, 1965). However, this hypothesis may be a better theory for explaining the neurobiology of antidepressants than for explaining the neurobiology of the depressive symptoms (Delgado, 2000; Delgado et al., 1999, 2002; Miller et al., 1996; Moreno et al., 1999, 2000a, b). Malfunctioning of monoamine pathways has been difficult to document in depression, but the antidepressant actions of currently available drugs (i.e. their ability to reduce or eliminate depressive symptoms) are definitely linked to boosting neurotransmission in monoamine pathways (Delgado, 2000).

A new notion is evolving for the role of monoamines as regulators of many of the hypothetically malfunctioning circuits causing the symptoms associated with a MDE. Each monoamine arises from a common site in the brainstem, but is released in many projection areas throughout the brain (Berridge and Waterhouse, 2003; Dillier et al., 1978; Molliver, 1987; Oades and Halliday, 1987; Sastry and Phillis, 1977; Williams and Goldman-Rakic, 1998). Boosting monoamine actions with antidepressants in various specific sites of abnormal neuronal functioning could reduce the symptoms associated with abnormal neuronal functioning occurring in that site. Monoamine input is not necessarily deficient prior to treatment with an antidepressant. However, antidepressants that boost just one or two monoamines could reduce a whole portfolio of symptoms, since the circuits mediating those symptoms may all receive innervation from monoamine neurons.

**Table 1.** Neurobiology of components of fatigue[a]

| Component of fatigue | Site | Neurotransmitter |
|---|---|---|
| Psychomotor retardation | Cerebellum | Norepinephrine |
| | Striatum | Serotonin |
| | Caudate nucleus | Dopamine |
| Physical tiredness | Spinal cord | Norepinephrine |
| | Spinal cord | Serotonin |
| Mental fatigue | Cortex diffuse | Norepinephrine |
| | Cortex diffuse | Serotonin |
| | Cortex diffuse | Dopamine |
| | Cortex diffuse | Histamine |

[a] Gold and Chrousos (1998), Mayberg et al. (1999), Philippu and Prast (2001), Rolls (1996), Salamone et al. (2003), Stahl (2000), Stahl (2002a–c), Stahl (2003b, c), Wall and Melzack (1999).

### *Circuits for fatigue vs. circuits for depressed mood and sadness*

Functional neuroimaging studies have recently associated sadness and depressed mood with abnormal neuronal activation in the medial prefrontal cortex, including the anterior cingulate cortex and orbitofrontal cortex (Davidson et al., 2002; Drevets, 2001; Drevets et al., 2002; Levesque et al., 2003; Liotti et al., 2002; Mayberg et al., 1999). These areas not only receive innervation from serotonergic projections (from the midbrain raphe nucleus) and noradrenergic projections (from the locus coeruleus) but also from dopaminergic projections (from the ventral tegmental area) (Lidov et al., 1980; Lindval and Bjorklund, 1978; Morrison et al., 1981; Ordway et al., 2002; Steketee, 2003). Antidepressants that act on 5-HT, NE, or both, have been associated with normalization of these circuits, and presumably provide key regulatory influences on the symptoms of sadness and depressed mood (Davidson et al., 2003; Davies et al., 2003).

Despite the importance of fatigue, its neurobiological basis may be the least understood and least emphasized of all the symptoms associated with a MDE (Tylee et al., 1993). Given that fatigue can be quite generalized and also experienced as physical fatigue as well as mental fatigue, its association with specific neuronal circuits has been difficult to clarify. Nevertheless, evolving knowledge about the topography of brain functions suggests several possibilities (Table 1). Brain areas regulating motor functioning such as striatum and cerebellum are reasonable candidates for mediating physical fatigue and lack of energy that arises from the body. 5-HT and dopamine (DA) both project to striatum, and NE to cerebellum (Geyer et al., 1976; Jones and Robbins, 1992; Waterhouse et al., 1983), and these monoamine neurotransmitters in the brain areas controlling motor function may hypothetically provide regulatory influences upon the symptoms of physical fatigue (Dray, 1981; Salamone et al., 2003; Stahl, 2000). A novel hypothesis is that DA depletion in the nucleus accumbens reduces the likelihood that animals will exert effort to obtain natural stimuli such as food, suggesting that DA depletion in this area may be related to reduced motivation, psychomotor retardation, or both (Salamone et al., 2003). Sensory input from the body enters the spinal cord where serotonergic and noradrenergic descending fibres may hypothetically regulate the perception of physical tiredness (Millan, 2002; Wall and Melzack, 1999). On the other hand, diffuse cortical projections of several key neurotransmitters, especially NE, DA, acetylcholine and histamine, may all regulate the symptom of mental fatigue at the cortical level (Brown et al., 2001; Dringenberg and Vanderwolf, 1998; Racagini and Brunello, 1999; Stahl, 2002a; Tzschentke, 2001). Reduced neuronal activities in the prefrontal cortex, especially in the dorsolateral prefrontal cortex, might explain the symptom of mental fatigue in depression (MacHale et al., 2000). Decreased neuronal activity in prefrontal circuits may be associated with the sense of mental fatigue and, thus, diminished concentration, indecisiveness, diminished ability to think, and executive dysfunction (Callicott et al., 1999; Cools et al., 2002; Krawczyk, 2002; Liu et al., 2002; Rypma and D'Esposito, 1999; Salamone et al., 2003; van den Heuvel et al., 2003).

## Treating fatigue in depression

There are few data for any antidepressant that specifically address the effects on fatigue-related symptoms. Among the first-line antidepressant monotherapies, agents that increase NE, DA, or both, particularly in pathways associated with physical and mental fatigue, may be preferable for patients with prominent fatigue and lack of energy, such as those described above (Table 2) (Stahl et al., 2003). Thus, the pharmacological profiles of venlafaxine, bupropion, fluoxetine, and sertraline suggest that, of the first-line antidepressants, these agents may be most likely to relieve symptoms of fatigue in depression, but this has never been adequately studied. A retrospective analysis of seven double-blind, placebo-controlled trials of fluoxetine in depression demonstrated that fluoxetine caused significant reductions in the HDRS retardation factor [item 1 (depressed mood), item 7 (work and

**Table 2.** Potential treatments for fatigue in depression

| Drug | Neurotransmitter | Mechanism | Site |
|---|---|---|---|
| First-line monotherapies | | | |
| Fluoxetine[a] | NE | 5-$HT_{2C}$ antagonism | Cerebellum, spinal cord, frontal cortex |
| | DA | 5-$HT_{2C}$ antagonism | Caudate nucleus, frontal cortex |
| Sertraline[b] | DA | Blockade of DA transporter | Caudate nucleus |
| Venlafaxine[c] | NE | Blockade of NE transporter | Cerebellum, spinal cord, frontal cortex |
| | DA | Blockade of NE transporter | Frontal cortex |
| | | Blockade of DA transporter* | Caudate nucleus |
| Bupropion[d] | NE | Blockade of NE transporter | Cerebellum, spinal cord, frontal cortex |
| | DA | Blockade of DA transporter | Caudate nucleus |
| | | Blockade of NE transporter | Frontal cortex |
| Augmenting agents | | | |
| Stimulants[e] | NE | Blockade of NE transporter | Cerebellum, spinal cord, frontal cortex |
| | | Stimulation of NE release | Cerebellum, spinal cord, frontal cortex |
| | DA | Blockade of DA transporter | Caudate nucleus |
| | | Stimulation of DA release | Caudate nucleus, frontal cortex |
| | | Blockade of NE transporter | Frontal cortex |
| | | Stimulation of NE release | Frontal cortex |
| Modafinil[f] | HA | Unknown mechanism | Hypothalamus, frontal cortex |

5-HT, serotonin; DA, dopamine; NE, norepinephrine; HA, histamine.

* At high doses.

[a] Bymaster et al. (2002b), Di Matteo et al. (2000), Gobert et al. (2000), Ni and Miledi (1997), Stahl (1998a, b).

[b] Stahl (1998a, b).

[c] Bolden-Watson and Richelson (1993), Bymaster et al. (2002a), Muth et al. (1986), Stahl (2000), Stahl (2003b).

[d] Cooper et al. (1994), Stahl (2000).

[e] Stahl (2000).

[f] De Saint Hilaire et al. (2001), Edgar and Seidel (1997), Jasinski (2000), Jasinski and Kovacevic-Rostanovic (2000), Scammell et al. (2000).

activities), item 8 (retardation), item 14 (genital symptoms)] compared to placebo (Judge et al., 2000).

When first-line antidepressant monotherapies are not effective in the treatment of fatigue, a novel strategy is to target the neurotransmitters in the circuits that hypothetically underlie this residual symptom with a variety of augmenting strategies (Table 2) (Stahl, 2003a; Stahl et al., 2003). Augmenting agents in the past have classically included buspirone, thyroid hormone, and lithium based largely upon empirical observations (Fava and Davidson, 1996; Menza et al., 2003; Stahl, 2000). However, a new set of augmenting agents can now be added to this armamentarium.

### *NE reuptake inhibitors*

One of the best known and most frequently utilized approaches to the treatment of residual symptoms in MDD is to augment a serotonin selective reuptake inhibitor (SSRI) or a serotonin norepinephrine reuptake inhibitor (SNRI) with bupropion, a NE and DA reuptake inhibitor (Stahl, 2000). Bupropion can increase both DA and NE in the frontal cortex, as well as in other areas of the brain (Bymaster et al., 2002a; De Saint Hilaire, 2001; Li et al., 1998; Moron et al., 2002; Stahl, 2003b, c; Zhang et al., 2000). Bupropion may be effective in improving energy and fatigue (Bodkin et al., 1997), as well as executive function (Bodkin et al., 1997; Moron et al., 2002). Atomoxetine, a new NE selective reuptake inhibitor, is recently being used to augment SSRIs and SNRIs. By enhancing both NE and DA actions, both bupropion and atomoxetine could boost theoretically deficient circuits in the dorsolateral prefrontal cortex and thereby improve residual executive dysfunction in depression. By enhancing these neurotransmitters in both cortex and subcortical areas, bupropion and atomoxetine may also improve residual fatigue and loss of energy. However, no studies of this use of atomoxetine have yet been reported.

### *Modafinil*

A novel approach to increasing not only monoamine neurotransmitters but also histamine in pathways theoretically mediating residual symptoms is to administer the novel wake-promoting agent modafinil.

This drug selectively activates orexin-containing and histaminergic neurons in the hypothalamus, and releases histamine in the hypothalamus (Ishizuka et al., 2003) as well as DA and NE in the cortex (Bymaster et al., 2002a; De Saint Hilaire et al., 2001; Li et al., 1998, Zhang et al., 2000) but not notably in the nucleus accumbens (Ferraro et al., 1997). It also releases 5-HT in the cortex (Ferraro et al., 2000, 2002). This neuropharmacological profile is distinct from that of antidepressants and stimulants (Engber et al., 1998). It predicts potential actions in relieving not only sleepiness, but also fatigue and executive dysfunction in MDD. Preliminary studies do suggest that modafinil can relieve residual symptoms of sleepiness and fatigue following treatment with a variety of antidepressants in MDD (DeBattista et al., 2001, 2003, 2004; Markovitz and Wagner, 2003; Menza et al., 2000; Ninan et al., 2004). In a double-blind, 6-wk study of patients partially responsive to antidepressant treatment, modafinil augmentation significantly improved fatigue and sleepiness scores at weeks 1 and 2 respectively, compared to placebo (DeBattista et al., 2003). Differences at week 6 were not significant.

This is consistent with its known action of improving daytime sleepiness associated with a number of sleep disorders, including narcolepsy (Bastuji and Jouvet, 1988; Broughton et al., 1997), obstructive sleep apnoea (Pack et al., 2001) and shift-work sleep disorder (Roth and Roehrs, 1996). A recent study suggests that fatigue in obstructive sleep apnoea may be driven by depressive symptoms rather than by apnoea severity (Bardwell et al., 2003), so the actions of modafinil in relieving fatigue in both obstructive sleep apnoea and depression may be due to a common action on a common neurotransmitter in a common pathway. Modafinil also relieves sleepiness and fatigue in patients with myotonic dystrophy (Damian et al., 2001; MacDonald et al., 2002) and in patients with multiple sclerosis (Krupp et al., 1989), suggesting an action to reduce fatigue mediated by a common pathway that may be malfunctioning in a number of neurological and psychiatric disorders in addition to MDD.

Finally, early results suggest that modafinil may improve executive dysfunction. Although this has only been anecdotally noted in MDD, modafinil has been shown to enhance cognitive functioning in a number of potentially related conditions, from normal ageing in experimental animals (Miller et al., 2000), to normal human volunteers (Turner et al., 2003), to sleep-deprived normal volunteers (Thomas and Kwong, 2002, 2003), to both children and adults with attention deficit disorder (Rugino and Copley, 2001; Taylor and Russo, 2000). Modafinil may also improve the cognitive dysfunction and sleepiness associated with medication side-effects from antipsychotics (Makela et al., 2003) or opioids (Webster et al., 2003). To the extent that these improvements in cognitive dysfunction are due to actions in circuits that are also malfunctioning in patients with residual cognitive symptoms in MDD, modafinil may be a promising treatment option to improve cognition in such patients.

### *Stimulants*

Central nervous system (CNS) stimulants, such as amphetamine and methylphenidate, have also been used for many years to improve residual symptoms of sleepiness, fatigue and executive dysfunction in MDD. CNS stimulants not only block NE and DA reuptake but also increase the release of these two neurotransmitters by interfering with the transport of these agents into synaptic vesicles (Tanda et al., 1997; Xu et al., 2000). However, CNS stimulants can not only increase the release of DA and NE in the cortex, but also in subcortical limbic areas such as nucleus accumbens, which is responsible for the significant abuse potential of these drugs (Everitt and Wolf, 2002; Worsley et al., 2000). Clinical data have shown some positive results of adjunctive therapy with CNS stimulants for the treatment of fatigue and in medical illness (Breitbart et al., 2001; Wagner et al., 1997; Wagner and Rabkin, 2000). In a small 8-wk, double-blind, placebo-controlled trial of dextroamphetamine for fatigue and depression in men with human immunodeficiency virus (HIV), significantly more patients achieved improvement in both fatigue and mood symptoms when treated with dextroamphetine as opposed to placebo (Wagner and Rabkin, 2000). A larger placebo-controlled study of psychostimulants to treat fatigue in patients with HIV also demonstrated significant reductions of fatigue symptoms with stimulants compared to placebo (Breitbart et al., 2001). Positive results from a small, placebo-controlled trial of dexamphetamine in chronic fatigue syndrome also suggest that psychostimulants may restore energy in MDD (Olson et al., 2003). No studies have been found to examine the role of CNS stimulants as a drug treatment for executive dysfunction in depression, but given their known actions in attention deficit disorder, a positive effect upon residual symptoms of cognitive dysfunction in MDD could be expected.

## Conclusion

Fatigue is a frequent presenting symptom of MDD. Fatigue appears to be a core depressive symptom and

is classified as such in the ICD-10. However, its importance is not reflected in the DSM-IV description of MDE. Unclear coverage of fatigue in different depression rating scales and ill-defined measurement further add to this confusion and may hamper future research. Its prominent place is not limited to the acute phase but concerns the whole life-cycle of depressive disorder, fatigue being a prominent prodromal and residual symptom. Fatigue abates less frequently and more slowly than other depressive symptoms. Strangely, this relative treatment-resistance is seen with both antidepressants and psychotherapy. Fatigue is actually the symptom most strongly associated with impaired work and social functioning. Rapid relief from fatigue symptoms is, therefore, essential to achieving remission. The optimal treatment for MDD will match the patient's symptom profile with treatments that specifically target those symptoms. Thus, treatment for patients with notable physical and mental fatigue should be designed to target neurochemical dysfunctions associated with those symptoms. Although the biological basis of fatigue related to depression has not been fully established, research data demonstrate an association between deficient noradrenergic, dopaminergic, and histaminergic neurotransmission and symptoms of tiredness, low energy, and mental fatigue. Pharmacological agents that target enhancement of NE, DA, and/or histamine may, therefore, be the optimal first-line treatment for depressed patients with prominent fatigue. These include several antidepressant monotherapies, such as venlafaxine, bupropion, sertraline, and fluoxetine. In addition, augmentation of first-line treatment with stimulants or modafinil may also provide relief from fatigue symptoms.

## Acknowledgements

None.

## Statement of Interest

Koen Demyttenaere has been a consultant for, received honoraria from, or conducted clinical research supported by the following: Boehringer Ingelheim, Eli Lilly and Company, GlaxoSmithKline, Lundbeck, Organon Inc., Pfizer Inc., Pharmacia, Solvay Pharmaceuticals, Wyeth Pharmaceuticals. Jürgen De Fruyt has been a consultant for, received honoraria from, or conducted clinical research supported by the following: AstraZeneca, Eli Lilly and Company, Lundbeck, Pfizer, Pharmacia. Stephen M. Stahl has been a consultant for, received honoraria from, or conducted clinical research supported by the following: Abbott Laboratories, Asahi Kasei, AstraZeneca Pharmaceuticals, Bristol–Myers Squibb, Cephalon Inc., Cypress Bioscience, Eli Lilly and Company, Forest Laboratories, GlaxoSmithKline, Janssen Pharmaceutica, Lundbeck, Novartis Pharmaceuticals, Organon Inc., Otsuka, Pfizer Inc., Pierre Fabre, Roche, Sanofi-Synthelabo Inc., Solvay Pharmaceuticals, Sumitomo, UCB Pharma, Wyeth Pharmaceuticals and Yamanouchi.

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