Fatigue as a core symptom in major depressive disorder: overview and the role of bupropion

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Fatigue is one of the most common symptoms found in both community and medical care settings. Fatigue may imply a prodromal or residual symptom of major depressive disorder or an adverse reaction to antidepressant treatment. Fatigue may also compromise antidepressant treatment by delaying response to antidepressants. Despite the importance of fatigue as a core depressive symptom, data specific to the effects of fatigue on pharmacological treatment are still lacking. Bupropion is an atypical antidepressant, chemically unrelated to classical agents such as tricyclic antidepressants, selective serotonin reuptake inhibitors and other contemporary antidepressants. With a pharmacological profile that involves neurotransmitter reuptake inhibition, bupropion shares a broad range of biological properties with psychostimulants. The primary action mode of bupropion involves dopaminergic and noradrenergic neurotransmissions rather than serotonergic mechanisms, although its exact pharmacodynamic properties remain uncertain. Hence, it is possible that bupropion may play a role in the treatment of fatigue-related symptoms of major depressive disorder. This paper presents a brief overview of the clinical implications and neurobiology of major depressive disorder-related fatigue, as well as the pharmacological profile of bupropion and currently available clinical data related to its treatment of fatigue-related symptoms of major depressive disorder.

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Fatigue is a subjective state of overwhelming, sustained exhaustion and decreased capacity for physical and mental work that is not relieved by rest. It is one of the most commonly encountered symptoms in both community and medical care settings [1].

Bupropion is an atypical antidepressant, chemically unrelated to tricyclic and tetracyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and other contemporary antidepressants. With a characteristic pharmacological profile that mainly involves the inhibition of neurotransmitter reuptake, bupropion shares a broad range of biological properties with psychostimulants. The primary mode of action of bupropion has been proposed to involve dopaminergic and noradrenergic neurotransmissions rather than serotonergic mechanisms, although it has not been completely understood [2–4]. Preclinical and putative clinical evidence has consistently suggested an association between some neurotransmitters, particularly dopamine and norepinephrine, and fatigue-related symptoms, while increased brain serotonin activity may possibly be associated with the early onset of fatigue [5,6]. However, few studies have investigated these relations owing to the difficulty of directly investigating human brain function and the lack of a biomarker to directly or indirectly measure fatigue [5].

This paper presents a brief overview of fatigue as associated with major depressive disorder (MDD), as well as a pharmacological profile of bupropion and currently available clinical data on its potential as a treatment for MDD-related fatigue.

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Epidemiology of fatigue

A number of epidemiologic reports have described the prevalence of fatigue in community and medical practice settings [7–16]. TABLE 1 briefly summarizes these findings.

Fatigue is a highly prevalent symptom, especially in depressive patients, being the most common depressive symptom (38.2% prevalence) in general practice settings [11]. According to data from collaborative studies in six European countries (n = 1884 depressive patients), 73% of patients reported 'feeling tired' as one of their symptoms. Of these patients, 76% complained of low mood at some point while feeling fatigued. Fatigue may be the most prevalent symptom of severe major depressive episodes and has been reported to be more prevalent in women than in men [12].

Current concept & quantification of fatigue in MDD

Although to date there is no officially accepted definition of fatigue in the context of health and illness, fatigue is generally considered to be a subjective state in which one feels tired or exhausted and in which the capacity for normal work or activity is reduced [17]. According to the Fatigue Assessment Inventory [18], fatigue should be defined as 'a sense of tiredness, lack of energy or total body give out'. The Brief Fatigue Inventory [19] describes fatigue as 'weariness or tiredness'. The lack of a clear definition of fatigue reflects its clinical complexity and heterogeneity [17]. Furthermore, there is no established biological test to confirm fatigue. For example, physical examinations may produce diagnostic information in only 2% of such patients, and laboratory investigations may reveal the cause of fatigue in approximately 5–20% of patients with chronic fatigue [20,21].

The Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV [22] imposes either depressed mood or the loss of interest or pleasure in nearly all activities (criteria A1 and A2) as essential features of a major depressive episode (MDE). However, near-daily fatigue or loss of energy is not considered an essential feature (criterion A6). Additionally, leaden paralysis (heavy, leaden feelings in the arms and legs) is subspecified as an atypical feature of MDD. By contrast, the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [23] gives fatigue-related symptoms (i.e., reduction of energy) as a core feature of MDE. This discrepancy also reflects the heterogeneity and complexity of fatigue in MDE, as does the lack of a definition of fatigue in the above sets of diagnostic criteria [24]. Nonetheless, both the DSM-IV and ICD-10 similarly use fatigue and loss of energy as

Table 1. Prevalence of fatigue in community or medical settings.*

Study	Number of subjects	Population	Prevalence	Others	Ref.
David *et al.* (1990)	611	Medical setting	10.5%, 'Feeling tired'		[7]
Walker *et al.* (1993)	18,571	Community	Current: 'spontaneous fatigue' 6.7% vs 'medically unexplained fatigue' 6.0% Lifetime: 'spontaneous fatigue' 24.4% vs 'medically unexplained fatigue' 15.5%		[8]
Kroenke and Price 1993	13,538	Community	13.8% (lifetime), 'medically unexplained fatigue'		[10]
Pawlikowska *et al.* (1994)	31,651	Community	18.3% (current), 'tired or lacking in energy'		[9]
Maurice-Tison *et al.* (1998)	2658	Medical setting	38.2% (current), 'fatigue or loss of energy' 93.6% in depressed subsample	5.9% of total sample = MDD	[11]
Tylee *et al.* (1999)	1884	Depressive patients	73%, 'tiredness'		[12]
Addington *et al.* (2001)	1741	Community	14.0% (lifetime), 'felt tired out all the time'	13 years follow-up study; 11-fold greater risk for MDD compared with non-MDD	[13]
Hickie *et al.* (2002)	1,465	Community	13.2%, 'prolonged and excessive fatigue, clinically significant and not attributed by the respondent to drugs or alcohol, physical illness or injury, not respond to rest, and lasts ≥3 months'		[14]

*A search of the studies used the key terms 'fatigue', 'epidemiology', 'depression', 'community', 'medical setting', 'primary care' and a combination of each key term on PubMed. We also used the reference lists from identified articles and reviews to find frequently cited and sufficiently powered studies: a complete coverage for the whole prevalence study was not made in this paper.
MDD: Major depressive disorder.

Table 2. Fatigue-related items in depression rating scales that are frequently used in clinical trials.

Scales	Items	Coverage and wording relative to fatigue
HAM-D	Item 7, work and activities	Described in value of 1 = thoughts and feelings of fatigue related to activities, work or hobbies
	Item 8, retardation	Slowness of thought and speech; impaired ability to concentrate; decreased motor activity
	Item 13, general somatic symptoms	Described in value of 1 = loss of energy and fatigability
Montgomery Asberg Depression Rating Scale	Item 7, lassitude	Difficulty in getting started or slowness in initiating and performing everyday activities
BDI-II	Item 15, loss of energy Item 20, tiredness or fatigability	
IDS-CR/SR	IDS-C item 20, energy/fatigability IDS-C item 23, psychomotor retardation IDS-SR item 20, energy/fatigability IDS-SR item 23, psychomotor retardation IDS-SR item 30, leaden paralysis	

BDI: Beck Depression Inventory; HAM-D: Hamilton Depression Rating Scale; IDS-CR: Inventory of Depressive Symptomatology–clinician rated; IDS-SR: Inventory of Depressive Symptomatology–self rated.

interchangeable concepts. Interestingly, the possibility that energy level can be used to distinguish depressed from nondepressed subjects has been tested in 57 subjects experiencing a current episode of MDD and a matched sample of nondepressed subjects [25]. In this study, discriminant analysis revealed that energy level correctly classified 93% of those subjects as depressed or nondepressed; the combination of energy level and other psychosocial variables failed to increase the diagnostic accuracy. Similarly, factor analysis of several depression rating scales such as the Hamilton Depression Rating Scale (HAM-D) [26], Montgomery Asberg Depression Rating Scale [27], Beck Depression Inventory (BDI)-II [28], and Inventory of Depressive Symptomatology (IDS)-clinician rated (CR)/self-rated (SR) [29] revealed lack of energy to be a primary measure of fatigue, as defined entirely by self-rated items and not by observer-rated items [24].

TABLE 2 summarizes fatigue-related items of the validated depression rating scales HAM-D, Montgomery Asberg Depression Rating Scale, BDI-II and IDS. Decreased energy, tiredness and fatigue are common symptoms of MDD (criterion A6); however, quantifying fatigue in depressed patients is extremely challenging because common scales do not have a specific quantifiable item for fatigue, as shown in TABLE 2.

For example, in the HAM-D, only item seven, which describes 'work and activities', refers to the term 'fatigue' (value of 1 = thoughts and feelings of incapacity, 'fatigue', or weakness related to activities, work or hobbies). Items eight and 13 deal with the retardation and general somatic symptoms. Such items of depression rating scales may share many similarities with the notion of fatigue. However, precise clarification of the similarities and differences awaits future studies.

The Motivation and Energy Inventory (MEI) containing 30 items [30] was recently developed to facilitate the evaluation of fatigue and lassitude in patients with MDD. The MEI was largely designed to measure three aspects: mental energy, physical energy and social motivation. Interestingly, the highest correlations were found between item 13 (general somatic symptoms) of the HAM-D and the physical energy subscale of the MEI [30]; HAM-D appeared to be closely related to the Mental Energy subscale of the MEI. This finding is not surprising, given that most of the HAM-D items relate to cognitive rather than somatic issues. The strength of the MEI is that it permits comprehensive assessment of patient vitality within clinical trials of antidepressants as well as within a wide variety of other treatment-outcome studies [30]. In fact, the responsiveness of the MEI was demonstrated in a recent randomized controlled trial for patients with fatigue-related symptoms [31]. It is also important to distinguish differences in fatigue across various medical and psychiatric disorders. In this context, the Brief Fatigue Inventory was able to discriminate differences in fatigue between dysthymia and multiple sclerosis by its sensitivity to modulated circumstances, as assessed by the situation-specific fatigue subscale [18].

Taken together, the unclear coverage and ill-defined measurement of fatigue in contemporary diagnostic criteria for MDD and depression rating scales do not allow for conclusive conceptualization and quantification of fatigue in MDD, although loss of energy is most likely in the continuum of fatigue in patients with MDD. The complementary use of depression rating scales and fatigue-specific assessment instruments will provide further information for future research.

Table 3. Causes of secondary fatigue in patients with major depressive disorder.

Category	Diseases
Cardiovascular diseases	Congestive heart failure, cardiomyopathy
Pulmonary disease	Chronic obstructive pulmonary disease, asthma
Endocrinological disease	Diabetes mellitus, Cushing syndrome, Addison's disease, hypothyroidism
Neurologic disease	Multiple sclerosis, stroke
Infectious disease	HIV, hepatitis, mononucleosis, tuberculosis
Connective tissue disease	Systemic lupus erythematosus, arthritis
Hematologic diseases	Anemia
Nutritional imbalance	
Psychological disorders	Other than major depressive disorder
Pregnancy	
Menopause	
Malignancy	Various cancers
Medication	Psychotropics, muscle relaxants, narcotics, antihypertensive agents, diuretics

Primary & secondary fatigue in MDD

The Multiple Sclerosis Council has attempted to classify primary and secondary fatigue [32]. However, the definition of the dimensions of fatigue remains in an infant state and is much more clouded in psychiatry. Overall, primary fatigue may be defined if it is directly associated with the disease process, but an understanding of many features is still unclear. Secondary fatigue is not necessarily unique to MDD; for example, fatigue may be a side effect of various medications such as antidepressants, antihypertensive agents, muscle relaxants and analgesics, or of comorbid medical conditions such as multiple sclerosis, nutritional disease, anemia, chronic respiratory diseases and psychiatric disorders. Although fatigue is highly complex, an exact differential diagnosis (i.e., primary vs secondary fatigue) according to specific causes may contribute to efficient control of the symptom [33]. Hence, a clear dimensional definition of fatigue based on the pathogenesis of fatigue in MDD and the proper rating instruments to assess this symptom should enhance and deepen our understanding of fatigue in patients with MDD. TABLE 3 summarizes the various causes of secondary fatigue in MDD.

Clinical implications of fatigue in MDD

Published studies have suggested that fatigue may be an important residual symptom of MDD. For example, data from 37 patients who completed 2–3 years of maintenance antidepressant therapy showed that complaints of physical tiredness were primarily related to residual depressive symptoms. Nierenberg and colleagues have demonstrated that approximately 80% of remitters in fluoxetine treatment (HAM-D score <8) retained one or more residual symptom of MDD [34]. Of those patients, 38.8% reported fatigue as a subthreshold or threshold residual symptom. Hence, fatigue may persist despite an adequate trial of antidepressant treatment.

In prospective studies, patients reporting unexplained fatigue for 2 weeks or more in their lifetimes had a greater risk of lifetime MDD (11- to 28-fold) than nonfatigued subjects [13,35]. In data from a WHO collaborative longitudinal study, baseline depression was found to increase the risk of developing a new onset of unexplained fatigue at 12-month follow-up, with an adjusted odds ratio of 4.15 (95% CI: 2.64–6.54) [35]. In addition, fatigue was the most potent predictor of progression to a chronic course of depression in 313 patients treated over a 10-year period [36]. Similarly, unexplained fatigue at baseline was independently associated with the development of a new episode of depression at follow-up with an adjusted odds ratio of 2.76 (95% CI: 1.32–5.78).

Given the current evidence, we may suppose that MDD and fatigue have a bidirectional relationship and would be difficult to separate from each other, which may account for the scant data on the positioning of fatigue within MDD.

Implication of the neurobiology of fatigue in MDD

Relatively little is known of the neurobiology of fatigue in MDD, compared with depressive mood or sadness [24]. Nonetheless, emerging clinical evidence suggests the involvement of the diffuse cortical area, subcortical area, thalamus, hypothalamus, pituitary, basal ganglia and brainstem in the development of fatigue-related symptoms [37,38].

In particular, the mesocorticolimbic dopamine pathway (i.e., nucleus accumbens) may be a key regulator of motivation [39]; reduced dopaminergic activity has been related to decreased motivation, anhedonia and lack of interest as part of MDD [40]. Fatigue-associated cognitive impairments are also associated with a failure to maintain adequate levels of dopaminergic transmission to the striatum and the anterior cingulate cortex [41]. In an animal study, dopamine depletion in the nucleus accumbens reduced motivation and enhanced psychomotor retardation [40]. The ventral striatum and prefrontal cortex are believed to be important dopaminergic regions involved in motivation and affect [101]. Specifically, reduced neuronal activities in the dorsolateral prefrontal cortex, well known as the executive center, may be mainly associated with fatigue-related symptoms [24,42].

Additional clinical evidence includes the frequent complaints of fatigue reported among patients with parkinsonism dopaminergic neuron degeneration [43]. Meanwhile, basal plasma levels of 3-methoxy-4-hydroxyphenylglycol were significantly reduced in patients with chronic fatigue [44].

A recent ε-methyl-para-tyrosine-induced cathecholamine deletion study reported that low central norepinephrine and fatigue may be partially correlated [45]. Clinical trials have also provided indirect evidence of norepinephrine involvement in the neurobiology of fatigue. For example desipramine (a more selective inhibitor of norepinephrine reuptake) created earlier and

Table 4. A summary of currently available randomized, double-blind trials of bupropion for the treatment of major depressive disorder that include outcome measure for fatigue-related sub-item 13 in the Hamilton Depression Rating Scale.

Study	Treatment (n)	Baseline HAM-D17 score	Baseline item 13 score	Changes in item 13 score*	Rates of fatigue resolution based on item 13 among remitters‡	Duration (weeks)	Ref.
Feighner *et al.* (1991), Study 88	BPR (n = 60) FOX (n = 60)	22.4 (2.6) 23.0 (2.9)	1.17 (0.8) 1.25 (0.8)	-0.63 (0.8) -0.63 (0.8)	27/32 (84%) 19/29 (66%)	6	[69]
Kavoussi *et al.* (1997), Study 209	BPR (n = 118) SRT (n = 116)	22.2 (3.9) 22.4 (3.7)	1.75 (0.5) 1.80 (0.4)	-1.2 (0.8) -1.3 (0.8)	60/83 (72%) 70/84 (83%)	16	[64]
Croft *et al.* (1999), Study 4001	Placebo (n = 116) BPR (n = 116) SRT (n = 116)	20.9 (3.0) 21.5 (3.2) 21.4 (3.0)	1.69 (0.5) 1.59 (0.6) 1.67 (0.5)	-0.76 (0.9) -0.97 (0.8) -0.89 (0.9)	29/48 (60%) 46/66 (70%) 39/69 (57%)	8	[65]
Coleman *et al.* (1999), Study 4002	Placebo (n = 117) BPR (n = 118) SRT (n = 109)	22.9 (4.8) 22.8 (4.7) 22.9 (4.8)	1.90 (0.3) 1.89 (0.4) 1.90 (0.3)	-1.0 (0.8) -1.2 (0.8) -1.1 (0.8)	36/51 (71%) 48/59 (81%) 41/54 (76%)	8	[66]
Weihs *et al.* (2000), Study 4003	BPR (n = 47) PRX (n = 49)	24.6 (4.2) 24.9 (4.8)	1.70 (0.5) 1.61 (0.5)	-1.2 (0.8) -1.0 (0.7)	20/23 (87%) 21/31 (68%)	6	[67]
Unpublished Study 4006	Placebo (n = 134) BPR (n = 138) FOX (n = 133)	22.3 (3.4) 23.0 (3.8) 22.5 (3.5)	1.77 (0.5) 1.86 (0.4) 1.76 (0.5)	-0.83 (0.9) -1.1 (0.9) -1.0 (0.9)	38/70 (54%) 50/68 (74%) 52/69 (75%)	8	[70]
Coleman *et al.* (2001), Study 4007	Placebo (n = 145) BPR (n = 135) FOX (n = 146)	21.8 (3.2) 22.0 (2.9) 21.8 (3.2)	1.83 (0.4) 1.86 (0.4) 1.86 (0.4)	-0.90 (0.9) -1.2 (0.8) -0.99 (0.9)	46/73 (63%) 54/71 (76%) 49/74 (66%)	8	[71]
Clayton *et al.* (2006), Study 30926	Placebo (n = 126) BPR (n = 129) ECP (n = 133)	23.3 (3.2) 23.2 (3.3) 23.3 (3.1)	1.71 (0.5) 1.78 (0.5) 1.77 (0.5)	-0.75 (0.9) -1.1 (0.8) -0.83 (0.9)	38/58 (66%) 47/65 (72% 37/64 (58%))	8	[68]
Clayton *et al.* (2006), Study 30927	Placebo (n = 130) BPR (n = 134) ECP (n = 133)	23.3 (2.7) 23.9 (3.0) 23.3 (3.2)	1.73 (0.5) 1.83 (0.4) 1.83 (0.4)	-0.70 (0.8) -0.94 (0.8) -1.0 (0.9)	30/52 (58%) 45/68 (66%) 53/73 (73%)	8	[68]
Kennedy *et al.* (2006), Study 40016	BPR (n = 66) PRX (n = 66)	21.9 (3.0) 22.3 (3.6)	1.83 (0.4) 1.85 (0.4)	-1.0 (0.9) -0.88 (0.8)	24/30 (80%) 18/29 (62%)	8	[72]

*From baseline to the end point. ‡Defined as an HAM-D17 total score ≤7 at end point. All data were proved by GlaxoSmithkline, RTP, NC. Data represent mean (standard deviation) or number (percentage).
BPR: Bupropion; ECP: Escitalopram; FOX: Fluoxetine; PRX: Paroxetine; SRT: Sertraline.

greater reductions in motor retardation versus paroxetine and a placebo [46]. Reboxetine, another selective norepinephrine reuptake inhibitor, was also found to be more beneficial than fluoxetine and a placebo in improving motivation toward action [47].

These results suggest that several neural pathways and neurotransmitters may be related in the development of fatigue in MDD, although the precise mechanism of the development of fatigue is not yet clearly understood. Comprehensive and multidimensional research, including neuropsychological, neurochemical and neuroendocrine studies as well as brain imaging methods, will facilitate our understanding of the neurobiological abnormalities and clinical implications of fatigue in MDD.

Clinical pharmacology of bupropion

Pharmacokinetics

Following oral administration, bupropion is rapidly and nearly completely absorbed along the gastrointestinal tract [48]. The maximum plasma concentration of sustained-release bupropion occurs within approximately 3 h after a 150 mg oral dose [49,50]. Plasma protein binding of bupropion is approximately 82–88% [51].

Bupropion is extensively metabolized in the liver into active metabolites including hydroxybupropion, threo-hydrobupropion and erythrohydrobupropion [52]. These metabolites undergo further biotransformation and conjugation to form meta-chlorohippuric acid, the major urinary metabolite [50].

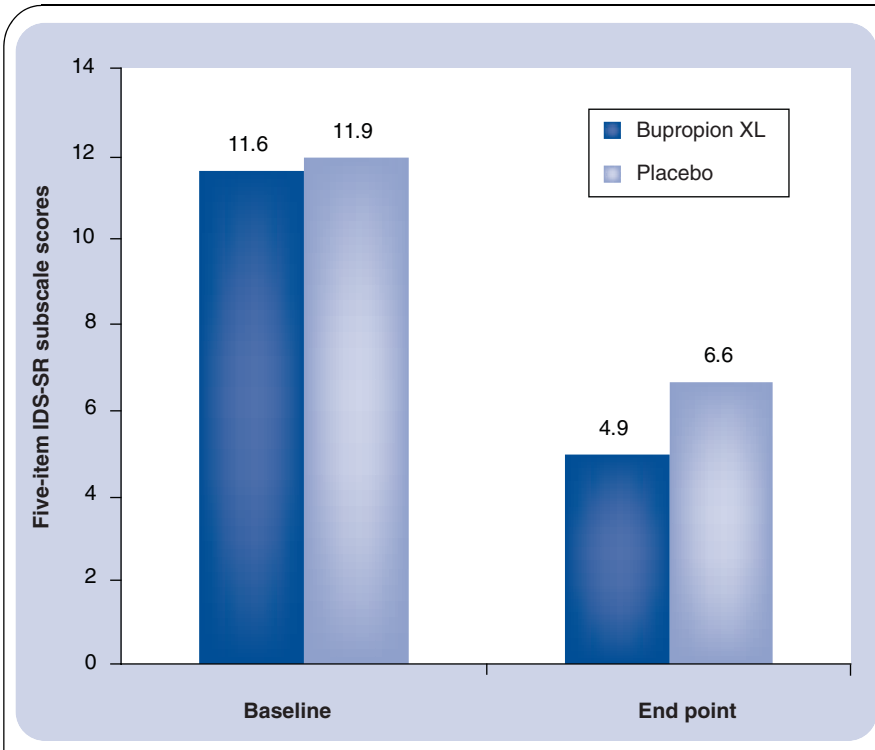

Figure 1. Changes in the scores on the five-item Inventory of Depressive Symptomatology-Self Report (IDS-SR) Energy, Pleasure, and Interest subscales.
Intent-to-treat population: bupropion n = 133; placebo, n = 137; p = 0.014.
Data from [74].

The primary cytochrome P450 (CYP) enzyme in the metabolism of bupropion to hydroxybupropion is CYP2B6 [53], with the CYP1A2, 2A6, 2C9, 2D6, 2E1 and 3A4 isoforms playing minor roles [54–56]. In addition, bupropion interacts with any drugs metabolized by CYP2D6 because of its inhibitory action on the isoenzyme [54,57,58]. A single 150 mg dose of sustained-release bupropion has a mean elimination half-life of 18–19 h [49].

Pharmacodynamics

The proposed antidepressant mechanism of bupropion is its inhibition of the neuronal uptake of noradrenaline and/or dopamine [59]. Most *in vitro* studies have found that bupropion and its metabolites do not alter serotonergic neurotransmission, either presynaptically or postsynaptically [60]. Rather, bupropion and its primary metabolite hydroxybupropion have been shown to decrease the reuptake of dopamine and norepinephrine [61]. In addition, several microdialysis studies have measured increased dopamine/norepinephrine concentrations in the nucleus accumbens and prefrontal cortex of rats after the administration of bupropion [61,62]. An examination of tissue from rat brains showed that bupropion produced greater inhibition of dopamine reuptake than noradrenaline reuptake (inhibitory concentration required to produce 50% effect: 2 vs 5 mmol/l); however, *in vivo* models show that bupropion has been a stronger inhibitor of noradrenaline than dopamine reuptake [60].

Other *in vitro* studies have shown that bupropion and its metabolites have little affinity for postsynaptic receptors, including histamine, α-adrenergic, β-adrenergic, serotonin, dopamine and acetylcholine receptors [60,61,63]. The little affinity for these postsynaptic receptors differentiates bupropion from the tricyclic antidepressants (tetracyclic antidepressants) and some contemporary antidepressants such as SSRIs [63].

Clinical data on bupropion in the treatment of MDD–related fatigue

Specific data on the effects of bupropion on fatigue-related symptoms in patients with MDD are lacking, particularly from standardized and validated psychiatric symptom measures. Recently, Papakostas and colleagues [1] conducted a pooled analysis of six randomized, double-blind clinical trials [64–68], comparing bupropion with SSRIs for treatment of sleepiness and fatigue in MDD patients. In this study, fatigue scores (defined as item 13 on the HAM-D) for bupropion (n = 662), SSRIs (escitalopram, sertraline and paroxetine; n = 655) and a placebo (n = 489) were compared. After a 6-week trial, greater improvement in fatigue scores was observed in the bupropion (-1.1; $p < 0.0001$) and SSRI groups (-0.9; $p = 0.0005$) compared with the placebo group (-0.8; $p > 0.05$). The bupropion-treatment group also had better fatigue-score improvement than the SSRI-treatment group ($p = 0.0078$). In a secondary analysis conducted with remitters (HAM-D 17, <8 at end point) after treatment with either bupropion (n = 308) or SSRI (n = 324), fewer bupropion remitters experienced residual fatigue (19.5%; n = 60/308) compared with SSRI remitters (30.2%; n = 98/324; $p < 0.002$). However, the pooled study had the following limitations: fluoxetine and citalopram were not included; treatment duration was relatively short (8–16 weeks); the primary efficacy measure used was not validated; and a publication bias may have existed [1]. Pooled analysis also has the inherent pitfall of the inclusion of heterogeneous studies. Finally, although statistically significant, the observed 0.2-point difference between bupropion and SSRIs should be considered in regard to how much relevance there is to clinical practice.

TABLE 4 summarizes the characteristics and results of all available randomized controlled trials [64–72] (total n = 10, including six studies analyzed by Papakostas and colleagues [1]) comparing bupropion with SSRIs for the treatment of MDD and including item 13 of the HAM-D 17.

A similar trend was found in a large principal component analysis study that used data from 910 outpatients who participated in randomized controlled trials of bupropion to detect

core depressive symptoms on the HAM-D; in the study, bupropion had a statistically significant benefit for cognition, psychomotor retardation and fatigue compared with a placebo ($p < 0.01$) [73].

Recently, a multicenter randomized controlled trial of bupropion XL (flexible doses: 300–450 mg/day) for patients with MDD presenting specific symptomatology of decreased energy, pleasure and interest has been completed. A total of 274 outpatients (bupropion XL group: n = 135; placebo group: n = 139) with MDD having a minimum total score of seven for general interest, energy, pleasure, sexual interest and physical energy sub-items on the IDS-SR were enrolled for the 8-week study [74]. In the study, the mean change from baseline to end point in the five-item (general interest, energy, pleasure, sexual interest and physical energy) subscale score of the IDS-SR [29] was significantly different between the bupropion XL (-6.7) and placebo (-5.3) groups ($p = 0.014$), with an observed difference of 13.3% favoring bupropion XL over the placebo. Moreover, the mean change from baseline to end point in the MEI total score [30] was also significantly higher in the bupropion XL (24.5) group than in the placebo group (17.4) ($p = 0.0127$), with an observed difference of 30.5% favoring bupropion XL over the placebo. Among existing randomized controlled trials of bupropion, this study was the first to specifically evaluate motivation and energy-related symptoms in MDD using validated psychometric rating scales. FIGURES 1 & 2 summarize the changes in the five-item IDS-SR subscale and MEI total scores.

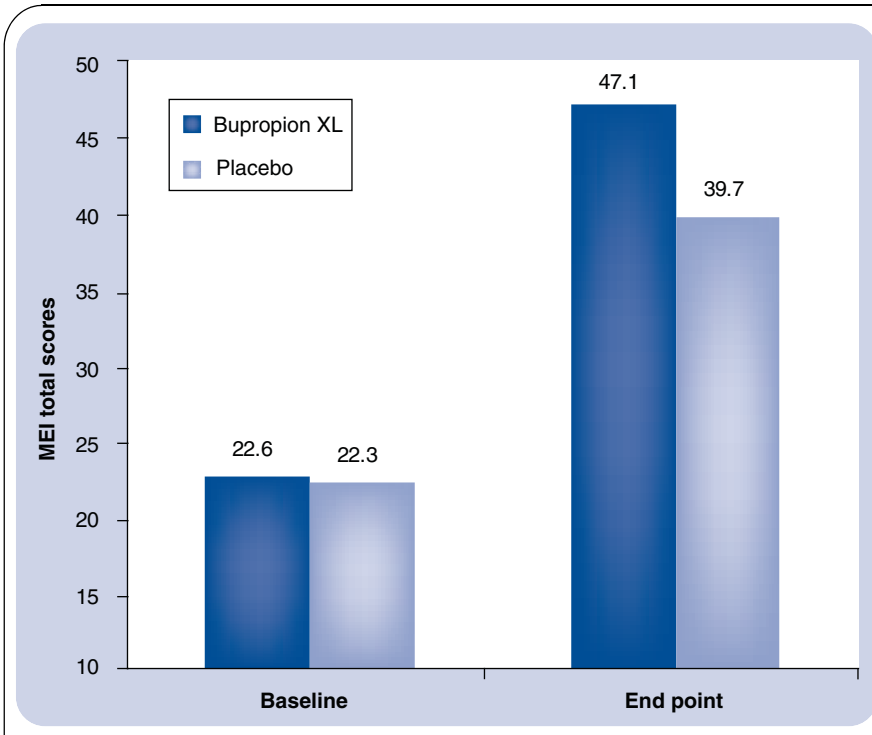

Figure 2. Changes in the scores on the Motivation and Energy Inventory (MEI) total scores.
Intent-to-treat population: bupropion, n=133; placebo, n=137; p=0.0127).
Data from [74].

Bupropion was also found to be effective as an augmentation therapy for fatigue in MDD. In a case report of patients with depression who had experienced partial symptom improvement following treatment with an SSRI but who continued to complain of either persistent or worsening fatigue, bupropion was effective and showed an early improvement within 1–2 weeks with relatively low doses (75–150 mg/day) [75].

Issues in the practical use of bupropion for MDD fatigue

Psychiatric comorbidities & hidden medical conditions

There are several medical and psychiatric conditions other than MDD that can cause fatigue. Fatigue is highly prevalent in many medical diseases, including cancer, diabetes mellitus, multiple sclerosis, chronic fatigue syndrome and fibromyalgia [76]. Conversely, subjects with current fatigue show higher lifetime and current prevalence of MDD, dysthymia, panic disorder and somatization disorder [8]. Hence, a thorough and careful clinical evaluation should precede any direct intervention.

Adequate trial

As fatigue is a common residual symptom and negatively impacts the effects of antidepressant treatment, leading to incomplete or delayed response [24], the extension of treatment duration and increase of dosage to a proper level may be prudent therapeutic options. Data from a recent randomized controlled trial indicates that bupropion XL at 300–450 mg/day may be effective and tolerable in patients with MDD presenting with fatigue-related symptoms [31], similar to the suggestion of registration clinical trials for MDD [77]. Whether higher doses of bupropion are needed for more severe cases or next step treatment option is still uncertain. Bupropion XR started to show effectiveness in treating fatigue at doses from 75 mg/day [31]. Considering the compromising effect of fatigue on antidepressants and the findings from randomized controlled trials [31], bupropion treatment of at least 8–12 weeks would be necessary for improvement in such patients, although more data are needed [34,78]. A limited study has also demonstrated early efficacy of bupropion as early as 1–2 weeks [31]. Bupropion may be used as a monotherapy or an augmentation agent.

Antidepressants other than bupropion

Antidepressants that increase norepinephrine, dopamine or both, particularly in the central pathways associated with physical and mental fatigue, may be beneficial for patients with fatigue-related symptoms [6]. In this context, the pharmacological profiles of bupropion, reboxetine, desipramine, venlafaxine,

duloxetine, fluoxetine, monoamine oxidase inhibitors (e.g., phenelzine and transdermal selegiline), and sertraline may be most pertinent for the treatment of fatigue in MDD; however, sufficient randomized controlled trial data supporting this perspective are not yet available [24].

FIGURE 3 briefly outlines the general strategies for treatment of fatigue in patients with MDD.

Adjunctive treatment

Augmentation of another potentially activating antidepressant or psychostimulant, such as methylphenidate or pemoline may be another treatment option, although currently available data are quite preliminary [24,78]. However, psychostimulants may aggravate or initiate adverse events (AEs) [79] and have abuse potential. Clinicians should prudentially use psychostimulants based on clinical information [80]. A small number of randomized controlled trials have shown a potential benefit of modafinil augmentation [81,82]. However, the formal efficacy of modafinil for fatigue and lack of energy has not yet been demonstrated [78]. Further studies are clearly needed to confirm its efficacy for MDD-related fatigue. Atomoxetine (mean dose: 42.8 mg/day) may also be considered as an adjunctive agent [83]. Currently, no available randomized controlled trial supports the augmentation of psychostimulants to bupropion in patients with MDD-related fatigue.

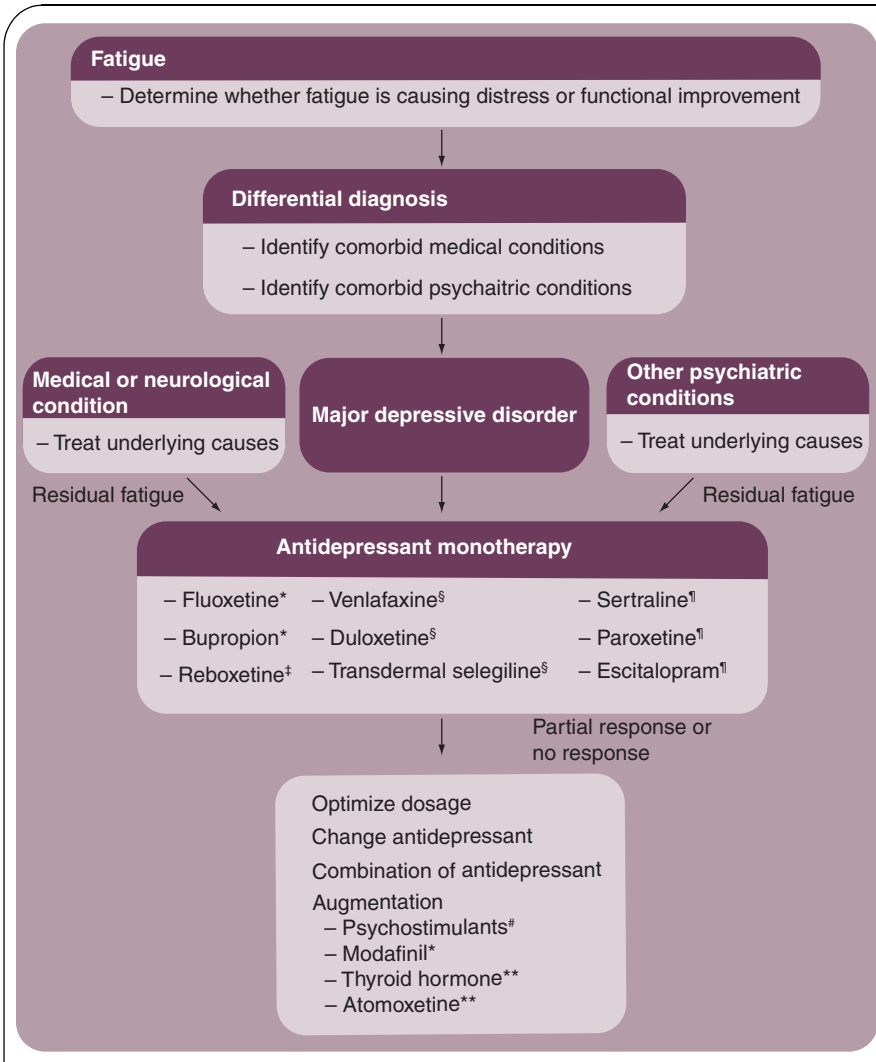

Figure 3. A suggested algorithm for treatment of fatigue in major depressive disorder. *Data from randomized, double-blind, placebo-controlled trial (randomized controlled trial); ‡Data from randomized, double-blind trial; §Potential treatment option based on action mechanism; §Data available as a class (i.e., selective serotonin reuptake inhibitors) from the results of pooled analysis of randomized, double-blind trial or as a comparator in randomized controlled trials of bupropion; #Data from randomized controlled trials for patients with HIV and chronic fatigue syndrome (dextroamphetamine, methylphenidate and pemoline) and open-label studies only in patients with MDD; **Data from open-label or case series studies.

Safety & tolerability of bupropion

Commonly observed AEs in randomized controlled trials of bupropion as treatment for MDD are headache, dry mouth, nausea and insomnia. At least 5% of patients treated with bupropion developed at least twice the placebo rates of anorexia, dry mouth, rash, sweating, tinnitus and tremor when taking bupropion 300 mg/day, and abdominal pain, agitation, anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tinnitus and urinary frequency were experienced with doses of 400 mg/day [84]. In randomized controlled trials of bupropion 300 and 400 mg/day, AEs leading to early discontinuation included nausea, agitation, headache and rash [77]. Bupropion has slightly better or at least comparable profiles in relation to weight gain, sexual dysfunction and discontinuation rate compared with SSRIs [68,85,86].

Bupropion should be contraindicated for patients with a history of seizure, cranial trauma, eating disorders or other predispositions toward seizure, and should be carefully administered to patients along with other agents lowering seizure threshold [77]. Data on immediate- and sustained-release formulations of bupropion revealed a seizure incidence of approximately 0.4 and 0.1% in patients treated at doses ranging from 300–450 and 100–300 mg/day, respectively. These percentages may exceed those of other marketed antidepressants, although direct comparative studies have not yet been conducted [77].

Although bupropion is not primarily metabolized by the CYP2D6 isoenzyme, bupropion and hydroxybupropion are weak inhibitors of CYP2D6 isoenzyme *in vitro* [84]. Hence, co-administration of bupropion with antidepressants that are metabolized by CYP2D6 isoenzyme, such as nortriptyline, imipramine, desipramine,

paroxetine, fluoxetine and sertraline, should be carefully monitored. Haloperidol, risperidone, thioridazine, β-blockers and Type 1C anti-arrhythmics should be combined with bupropion with caution [77,84].

The use of bupropion during pregnancy is rated as category C, similar to most SSRIs, except for paroxetine (category D). Bupropion has not been approved for use in pediatric patients [77].

The FDA has issued a public health advisory notice regarding worsening of depression and emergence of suicidal ideation in pediatric and adult patients being treated with ten newer antidepressants, including bupropion. Therefore, all patients treated with antidepressants should be carefully monitored for suicidal ideation and self-injury, especially at times of treatment initiation and dose increase [102].

Expert commentary & five-year view

Basic studies on the biological basis of fatigue as part of MDD are still lacking. MDD-related fatigue coexists with other MDD symptoms such as concentration difficulties and lack of motivation, and thus the precise identification of the neural basis of the fatigue would be difficult. Nonetheless, with the rapid progress of advanced neuroimaging techniques, it may be possible for future studies to detail and specify the neurobiological basis between fatigue and subsymptoms of MDD. As dopamine and norepinephrine neurotransmission have been proposed to play key roles, bupropion may be relevant as a search probe in neuroimaging research focused on the identification of the neural substrate and action mechanism for fatigue in MDD. For instance, brain activation patterns before and after administration of bupropion could be investigated by fMRI or PET methods in depressed patients with fatigue. Neurochemical research may also provide useful information about new or specific modulation factors in the regulation of fatigue in patients with MDD.

Standardized psychometric measures of fatigue for patients with MDD are lacking. Most studies have indirectly and briefly assessed fatigue using subscales of broader general health or psychopathology instruments. Although some scales are validated for the measurement of fatigue, most involve self-reported questionnaires and are not disease specific. Thus, the development of validated and objective fatigue measurements would facilitate well-designed studies in this area.

Given the current evidence of abnormalities associated with norepinephrine and/or dopamine rather than of serotonin, it is possible that antidepressants that affect norepinephrine and/or dopamine neurotransmission, such as norepinephrine and dopamine reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors and norepinephrine reuptake inhibitors, may be beneficial in the treatment of fatigue-related MDD symptoms. However, evidence supporting this hypothesis is still preliminary, and more investigation is required.

Overall, bupropion may be used as a stimulating regimen with a unique mode of action suitable for the treatment of the common and troublesome fatigue that occurs alongside other depressive symptoms in patients with MDD. Bupropion has the potential for wide use in clinical treatment of MDD-related fatigue. However, no definite conclusion about the critical role of bupropion can currently be drawn based on the quantity and quality of available clinical evidence. Furthermore, no head-to-head comparison trials have been conducted to date. Clearly, more well-designed and focused (i.e., efficacy specifically targeting fatigue and lack of energy, longer trial duration, and use of validated psychometric measures) randomized controlled trials should address this interesting issue and would provide useful and practical information regarding the pharmacological treatment of fatigue in MDD.

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Key issues

- Fatigue is a common accompanying symptom in patients with major depressive disorder (MDD), as well as the most common depressive symptom reported in general practice settings.
- MDD and fatigue are likely to have a bidirectional relationship and thus would be difficult to separate from each other, which may account for the insufficient data to date concerning clinical manifestation, timely intervention and relevant treatment options.
- Pharmacological agents targeting the neuronal pathways of dopamine and norepinephrine may help alleviate the fatigue associated with MDD.
- Bupropion appears to be potentially more beneficial in the treatment of MDD-related fatigue, compared with selective serotonin reuptake inhibitors, based on the currently available (but limited) data.
- Selective serotonin reuptake inhibitors (e.g., fluoxetine), psychostimulants and modafinil may also have potential roles in the treatment of MDD-related fatigue.

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