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Pharmacological treatment of chronic fatigue syndrome: focusing on the role of antidepressants

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Chronic fatigue syndrome (CFS) is characterized by chronic, medically unexplained fatigue associated with effort- and stress-intolerance, widespread pain, and impairment in sleep and concentration. Although this constellation of symptoms is highly prevalent in clinical practice, the pathophysiological mechanisms underlying CFS are poorly understood. Current evidence indicates similarities in symptomatology, and possibly etiology and pathogenesis, between CFS and depression. Additionally, there is significant overlap between CFS and the syndrome of fibromyalgia for which antidepressants have shown consistent efficacy. Data regarding antidepressant treatment of CFS is less copious and less uniformly positive, such that antidepressant use in CFS remains controversial. The current review aims to summarize available data related to antidepressants and other psychotropic agents in CFS to provide a platform for clinicians to make decisions in their treatment of this challenging syndrome. We identified relevant studies through a PubMed literature search with a combination of the following search terms: 'fatigue,' 'depression,' 'antidepressant,' 'etiology' (e.g., 'neurobiology,' 'neurotransmitter,' 'genetic'), 'diagnosis,' and 'treatment' (e.g., 'antidepressant' plus the specific name). In addition, studies were also identified via the reference sections of retrieved articles. The authors thoroughly reviewed major findings from the scanned literatures and eventually synthesized them, providing summary, interpretation, and future directions.

Keywords: antidepressant, chronic fatigue syndrome, depression

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1. Introduction: relationship between chronic fatigue syndrome and major depressive disorder

Fatigue has been shown to be the most common depressive symptom (38.2% prevalence) in general-practice settings [1] and the most prevalent symptom of severe major depressive episodes, particularly in women [2]. According to data from collaborative studies in six European countries (n = 1884), 73% of depressed patients reported 'feeling tired' as one of their symptoms [2]. In short, fatigue is a cardinal symptom of depression. However, many patients in clinical settings exhibit medically unexplained fatigue that is not in the context of depressive illness. In 1994, an international panel published criteria to define chronic fatigue syndrome (CFS), stipulating that CFS patients must have: i) clinically evaluated, unexplained, persistent, or relapsing chronic fatigue of least 6 months duration, which is of new or definite onset (i.e., has not been life long); ii) is not the result

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of ongoing exertion; iii) is not substantially alleviated by rest; and iv) results in substantial reduction in previous levels of occupational, educational, social, or personal activities. This fatigue was also stipulated to coexist with four out of eight potential symptoms, which include postexertional malaise lasting more than 24 h; unrefreshing sleep; impaired short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities; headaches of a new type, pattern, or severity; muscle pain; multi-joint pain without swelling or redness; sore throat; and tender cervical/axillary lymph nodes [3]. More recent publications have retained the core definition of CFS, describing it as chronic, medically unexplained fatigue, effort- and stress-intolerance, and widespread pain [4-6].

Research indicates that CFS patients are at increased risk for developing major depressive disorder (MDD) compared with non-CFS community samples [7,8], and that patients with psychiatric disorders including depression are at increased risk for developing CFS [9]. It is noteworthy that CFS patients with comorbid psychiatric diagnoses report more functional impairment than those without comorbid psychiatric illness [10,11]; in particular, anxiety and depression have been associated with poor prognosis in CFS [12].

There is extensive overlap between the clinical expression of MDD and CFS with regard to symptoms of depressed mood, personality aspects (including alexithymia), decreased energy and volition, morning fatigue, anxiety, somatization, sleep disturbance, cognitive impairment, and functional impairment [13-18].

CFS has a broad range of symptoms – involving the nervous, endocrine, and immune systems – which are similar with MDD. MDD may also lead to fatigue that cannot be explained or addressed by relevant medical examinations. It appears that high correlations between changes in depression and fatigue scores exist, even in subjects who do not meet criteria for clinical depression [19]. Hence, CFS could at least represent a subsyndromal form of MDD, or may be comorbid and overlap with MDD, although the exact direction in this relationship has not been clearly established. None the less, actually psychotropic agents, including antidepressants have been commonly used in treatment of CFS in clinical practice.

2. Why antidepressants could be justified for chronic fatigue syndrome?

The relationship between depressive symptoms and CFS may not be clearly understood, but we have at least some precedents that antidepressants may be useful in treating depressive symptoms in special conditions with known or unknown organic etiology and where there may be primary or secondary CNS involvement, for example in Parkinsontgy's disease, systemic lupus erythematosus, fibromyalgia, multiple sclerosis, and hypothyroidism that commonly manifest fatigue with psychiatric symptoms [20].

As described, depression was found to be significantly correlated with CFS severity [19]. In addition, chronically fatigued patients with a lifetime history of MDD had higher suicide-caused death rates than those without [21], and suicide is one of major causes of death in CFS patients [22]. A functional capacity in patients with CFS is usually severe and could be deteriorated in their clinical course as similar to patients with MDD [23,24]. Furthermore, CFS patients with depression were more impaired in social function than other CFS patients [25].

MDD has been also involved with alteration of inflammatory reaction, as indicated by an increased production of pro-inflammatory cytokines, such as interleukin-1-beta (IL-1β), IL-6, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ) [26,27]; antidepressants are known to have immunoregulatory effects [28,29]. A symptomatic approach might therefore be helpful, regardless of the fact that antidepressants effects are direct or indirect for treating CFS [20] under an assumption that MDD and CFS share a lot of similarities in pathogenesis as well as in symptomatologies.

Interestingly, a recent preclinical study [30] demonstrated that the tricyclic antidepressant (TCA) amitriptyline can inhibit rat mast-cell secretion and reduce intracellular levels of calcium ions, which support the hypothesis that corticotropin-releasing hormone (CRH) and other related peptides secreted by acute stress activate diencephalic mast cells, either directly or through neurotensin (NT), resulting in the release of proinflammatory cytokines that eventually contribute to CFS pathogenesis [31].

3. Antidepressant use for chronic fatigue syndrome: the evidence

Antidepressants currently approved for MDD act primarily by enhancing neurotransmission in serotonergic and noradrenergic systems, and to a lesser extent dopaminergic systems. Such medications include TCAs, selective serotonin reuptake inhibitors (SSRIs), noradrenergic and specific serotonin antagonists (NaSSas), dopamine-norepinephrine reuptake inhibitors (DNRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). Antidepressant medications have shown efficacy and tolerability in the treatment of unexplained physical symptoms such as fatigue and myalgia, although currently there are no medications (antidepressant or otherwise) approved by regulatory agencies for the indication of CFS [32,33].

According to a meta-analysis of 94 trials, TCAs and SSRIs were found to be substantially effective for treating unexplained somatic symptoms including CFS [34]. The odds ratio in this study was 3.4, and the absolute percentage difference in improvement between the antidepressant and placebo arms was 32%, yielding a number-needed-to-treat (NNT) of 3. Further analysis reveals that TCAs may be associated with a higher likelihood of efficacy than SSRIs in the treatment of unexplained painful somatic symptoms [34]. In addition, TCAs and SSRIs have demonstrated long-term

benefit (over 3 years) in a maintenance study of CFS [35]. Finally, a recent meta-analysis of TCAs, SSRIs, SNRIs, and monoamine oxidase inhibitors (MAOIs), including 1427 participants with fibromyalgia, has also suggested strong evidence for an association of antidepressants with reduction in pain, fatigue, depressed mood, and sleep disturbances, as well as improvement in health-related quality of life [36]. Data related to specific antidepressant classes studied in CFS or related disorders are detailed below.

3.1 Tricyclic antidepressants

Adequately powered placebo-controlled, randomized clinical trials (RCTs) of TCAs for CFS are still lacking. Nortriptyline 60 mg/day demonstrated benefit for depressive symptoms and fatigue [as measured by the Beck Depression Inventory (BDI) and Chronic Fatigue Symptom Checklist] in a double-blind crossover study [37]. Additionally, case reports in numerous patients support the benefit of amitriptyline and doxepin (25 – 50 mg at night) in CFS [38-40]. With regard to the treatment of fibromylagia with associated fatigue, there is a more comprehensive body of data supporting the utility of TCA. In six RCTs in fibromyalgia patients, amitriptyline 25 mg/day demonstrated therapeutic superiority to placebo on symptoms of pain, sleep, and fatigue at 6 – 8 weeks, although the benefit appeared to wane at 12 weeks [41,42]. However, whether these findings could be extended to patients with CFS is questionable.

3.2 Selective serotonin reuptake inhibitors

Although several studies have proved the tolerability of SSRIs in CFS, the efficacy of SSRIs for this syndrome remains in question. Open-label trials have shown effectiveness of SSRIs in 70% of patients with CFS, but RCTs have failed to demonstrate their efficacy.

Citalopram and escitalopram have been studied in published clinical trials in patients with CFS. In one such study [43], patients switched from placebo to citalopram 20 – 40 mg/day (n = 31) experienced statistically significant improvement at 1 month and 2 months on the primary outcome measure of the Rand Vitality Index [44]. The percentage of subjects showing substantial improvement due to treatment with citalopram was numerically higher than in a similar population treated with Siberian ginseng (n = 2, 32 vs 18%, respectively), although the difference did not reach statistical significance. In a subsequent open-label study of 16 patients with CFS [45], escitalopram 10 – 20 mg/day for up to 12 weeks yielded significant improvements in the Chalder Fatigue Scale (CFQ) [46] and the multi-dimensional Fatigue Impact Scale (FIS) [47]. Escitalopram treatment also produced significant improvement in the Hamilton Depression Rating Scale (HAM-D) and BDI, and the study did not differentiate the antidepressant effect of escitalopram from its specific efficacy against CFS.

Two RCTs of fluoxetine treatment in CFS found less favorable results. One such 8-week, placebo-controlled study [48] of fluoxetine 20 mg in CFS patients with depression (n = 44) and without depression (n = 52) failed to demonstrate benefit of fluoxetine on any outcome measure assessing fatigue, depression, psychological well-being, functional impairment, physical activity, sleep disturbances, neuropsychological functioning, social interactions, and cognitions [48]. An additional study [49] assessed efficacy and acceptability of fluoxetine 20 mg/day compared to graded exercise in a 6-month, placebo- and therapist-contact-time-controlled trial (n = 96). This study demonstrated statistically significant improvement in fatigue and functional work capacity at 12 and 26 weeks, whereas fluoxetine failed to improve such variables. Regarding depressive symptoms, fluoxetine treatment did yield significant improvement in HAM-D scores at week 12 but not at week 24.

An open-label study of sertraline in CFS demonstrated a treatment response in 65% of patients [50]; no RCTs of sertraline in CFS have been published.

In summary, data regarding the efficacy of SSRIs in CFS is mixed, perhaps reflecting inadequacy of study design, differing sample characteristics and treatment settings, and nonspecific factors such as heterogeneity in the nature of CFS and its comorbidities [43].

3.3 Serotonin–norepinephrine reuptake inhibitors

Dhir and Kulkarni have demonstrated positive effects of the SNRI venlafaxine in a rodent model of CFS induced by chronic forced swim exposure. In this recent preclinical study, venlafaxine produced a significant reduction in immobility time and reversed various behavioral, biochemical, and neurotransmitter alterations induced by chronic forced swim [51].

A report describes two CFS patients who had clinical reduction in global fatigue symptoms and immunological aberration associated with 6 weeks of treatment with venlafaxine 225 mg/day after failing to respond to a trial with an SSRI (sertraline or paroxetine) [52]. A recent case report suggests utility of duloxetine 120 mg/day in treating CFS as well [53].

Although no RCTs of SNRIs have been reported in patients with CFS, copious data support the efficacy of this class of antidepressants on multiple symptoms clusters in fibromyalgia, including fatigue. Duloxetine became the first antidepressant to be approved for the treatment of fibromyalgia by the US FDA as a result of positive short-term [54,55] and long-term [56] RCTs.

In addition, milnacipran has recently become FDA-approved for the indication of fibromylagia [32] in light of its proven efficacy in RCTs [57,58]. Considering that fibromyalgia and CFS share similarities in epidemiology, clinical symptoms, and proposed pathophysiology, further research of SNRIs in patients with CFS is warranted [59].

3.4 Noradrenergic and specific serotonin antagonist

A recent RCT [60] in CFS patients (n = 72) comparing comprehensive cognitive behavioral therapy (CCBT) to mirtazapine and placebo over 12 weeks demonstrates superiority of CCBT to the other treatments and indicates that mirtazapine is not superior to placebo on the Fatigue Scale.

The study included a mixed crossover-combination design, and at 24 weeks the treatment group initially receiving CCBT for 12 weeks followed by mirtazapine for 12 weeks showed significant improvement compared with the other treatment groups (including the group receiving mirtazapine followed by CCBT) on the Fatigue Scale and the Clinical Global Impression Scale. This study supports the notion that CFS treatment should include combination of behavioral and pharmacological therapies, with particular importance on the proper timing and sequence of therapeutic interventions [60].

3.5 Dopamine–norepinephrine reuptake inhibitor

In a small, open-label, 8-week study in patients with CFS (n = 9), 300 mg/day bupropion demonstrated a significant response for those who either could not tolerate or did not respond to fluoxetine. Bupropion also increased natural killer cell numbers, which have been suggested to be involved in the development and clinical outcomes of CFS [61]. A recent case report also supports the potential usefulness of bupropion augmentation in a patient with CFS who had partial response to the SSRI paroxetine [62].

In addition, bupropion has been suggested to have immunomodulatory effects on certain cytokines involved in the development of CFS, i.e., TNF-α [63]. Despite a paucity of well-designed RCTs of bupropion for CFS patients, the medication may have a putative role in CFS treatment as a first-line or adjunctive agent. Bupropion has a unique mechanism of action and is chemically unrelated to other antidepressants such as TCAs and SSRIs, and to other contemporary antidepressants. Bupropion enhances dopaminergic and noradrenergic neurotransmission rather than serotonergic neurotransmission, although its exact pharmacodynamic properties remain uncertain [64]; it also shares a broad range of biological properties with psychostimulants. Of note, a recent meta-analysis compared bupropion (n = 662) with SSRIs (n = 655) and placebo (n = 489) for the treatment of fatigue associated with MDD. After 6 weeks of treatment, greater improvement in fatigue scores were attributed to bupropion (-1.1 points from baseline) compared with SSRIs (-0.9 points from baseline) and placebo (-0.8 points from baseline). However, we have to consider that the observed differences of 0.2 and 0.3 favoring bupropin in comparison of bupropion with SSRIs and placebo are not sufficient to be translated into clinical practice. In a remitter analysis, it was also noted that fewer bupropion remitters experienced residual fatigue (19.5%) compared with SSRI remitters (30.2%) [64,65].

3.6 Monoamine oxidase inhibitors

A 6-week,open-label study of moclobemide at doses up to 600 mg/day in 49 patients with CFS revealed mild significant improvement in symptoms of fatigue, depression, anxiety, and somatic amplification [66]. Of note, the effects were more pronounced in patients with comorbid depression; 50% (n = 7/14) of those with comorbid MDD rated themselves as 'much better' at the end of trial, compared with only 19% (n = 6/31) of nondepressed subjects, indicating an observed difference of 31% between the two groups. A subsequent 6-week, placebo-controlled RCT of moclobemide 450 – 600 mg/day demonstrated significant superiority of moclobemide (n = 47) over placebo (n = 43) on the 'vigor' item of the Profile of Mood States (POMS) and a weak trend toward superiority on the Karnofsky Performance Index (KPI) scores [67]. Although the overall response in the moclobemide group was 51%, as measured by the subjective global impression (compared with 23% in the placebo group), this response rate was lower than the 69% observed in a previous open-label study by the same author [68]. Interestingly, subgroup analysis from the RCT suggests differential efficacy of moclobemide based on the presence of defective immune responsiveness: subjects with impaired immune responsiveness more significantly favored moclobemide over placebo, as measured by KPI scores [67].

The MAOIs phenelzine [69] and selegiline [70] also demonstrated a therapeutic effect in CFS. However, well-know adverse events such as hypertensive crisis attenuated the interest in these medications. Further study of a more recent transdermal formulation of selegiline is warranted because this delivery system significantly reduces the adverse events of the oral formulation and has been FDA-approved for the treatment of MDD [71]. **Table 1** summarizes the major findings of antidepressant trials in the treatment of patients with CFS.

4. Other psychotropic agents for chronic fatigue syndrome

The acetyl cholesterone inhibitor galantamine was studied in CFS in a large, 16-week RCT (n = 434) [72]. Galantamine failed to separate from placebo on the primary efficacy measure of Clinician Global Impression or on any of the secondary outcome measures assessing the core symptoms of CFS, including the Chalder Fatigue Rating Scale, the Fibromyalgia Impact Questionnaire, the Pittsburgh Sleep Quality Index, and a computer-based cognitive performance battery. Galantamine also failed to show superiority on changes in quality of life measured by the Nottingham Health Profile.

In a randomized-order, placebo-controlled, crossover study (n = 60) in patients with CFS, methylphenidate was found to be superior to placebo in reducing fatigue and concentration disturbance [73]. An open-label study has also shown benefit from methylphenidate in cancer-related fatigue [74] but failed to replicate its effect in an RCT [75]. A small, 6-week RCT (n = 20) demonstrated significant superiority of dexamphetamine on the Fatigue Severity Scale in patients with CFS [76]. Although stimulant medications of these types may have therapeutic benefit in CFS, at least in the short-term trial, the risks of misuse, abuse, withdrawal, and diversion should be considered.

Table 1. Summary of major findings of randomized, placebo-controlled antidepressant trials in the treatment of patients with chronic fatigue syndrome.

Studies	Medications (mg/day)	Definition of CFS	Duration (weeks)	Number (drug vs. PBO or total)	Clinical outcomes
Gracious and Wisner, 1991 [37]	NTP (40 – 60) vs. PBO	Holmes definition [82]	Not specified (less than 140 days)	Single case study (PBO-NTP-PBO-NTP)	Decrease of CFSC: from PBO Phase I (2494) to NTP Phase I (1278) and –631 decrease from PBO Phase II (1725) to NTP Phase II (not specified), approximately 95% improvement was noted in CFSC scores during the study.
Natelson *et al.*, 1996 [69]	PNZ (15) vs. PBO	Holmes definition [3,82]	6 (three 2-week blocks)	20 PBP-(PNZ or PBO)-PNZ or PBO)	FSQ, POMS, CES-D, ISS, FSS, SSC: 11 improved on PNZ in any scales, while 5 on PBO (none worse on PNZ in any scales, while 4 on PBO)
Natelson *et al.*, 1998 [70]	SRG (5 – 10) vs. PBO	Holmes definition [3,82]	6 (three 2-week blocks)	25 The first 2 weeks were a PBO phase. For the next 2 weeks, 5 mg SRG replaced 1 of the PBO, and for the final 2 weeks, subjects took 5 mg of SRG twice a day	FSQ, POMS, CES-D, ISS, FSS, SSC: 11 improved on PNZ in any scales, while 4 on PBO (1 worse on PNZ in any scales, while 6 on PBO)
Hickie *et al.*, 2000 [67]	MCB (450 – 600) vs. PBO	Lloyd definition [83]	6	47 vs. 43	Clinically global improvement: 51 vs. 33% (OR = 2.16) KPI: mean difference between two groups was 0.28 favoring MCB Vigor subscale on POMS: mean difference between two groups was 0.51 favoring MCB

ADS: Anhedonic Depression Score; BDI: Beck Depression Inventory Score; CBT: cognitive-behavioral therapy; CES-D: Centers for Epidemiological Study of Depression; CFS: Chronic fatigue syndrome; CFSC: Chronic fatigue symptom checklist; CI: Confidence interval; CTP: Citalopram; FOX: Fluoxetine; FS: Fatigue Scale; FSQ; Functional Status Questionnaire; FSS: Fatigue Severity Scale; ICD: International Statistical Classification of Diseases and Related Health Problems 10th Revised Version; ISS: Illness Severity Scale; KPI: Karnofsky Performance Index; KSS: Key Somatic Symptoms; MIR: mirtazapine; MCB: Moclobemide; NTP: Nortriptyline; OR: Odds ratio; PNZ: Phenelzine; PBO: Placebo; POMS: Profile of Mood States; RVI: Rand Vitality Index; SFS: Subjective Fatigue Score; SRG: selegiline; SSC: Symptom Severity Checklist.

Table 1. Summary of major findings of randomized, placebo-controlled antidepressant trials in the treatment of patients with chronic fatigue syndrome (continued).

Studies	Medications (mg/day)	Definition of CFS	Duration (weeks)	Number (drug vs. PBO or total)	Clinical outcomes
Hartz *et al.*, 2003 [43]	CTP (20 – 40) vs. PBO	Idiopathic fatigue	8	27	Superiority of CTP to PBO on subsets of patients with chronic fatigue measured by RVI, ADS, and KSS
Vercoulen *et al.*, 1996 [48]	FOX (20) vs. PBO	Sharpe definition [84]	8	54 vs. 53	Failed to separate from PBO on SFS and BDI scores
Wearden *et al.*, 1998 [49]	FOX (20) + Exercise (EX) vs. EX + Drug PBO vs. EX PBO + FOX vs. EX PBO + drug PBO	Sharpe definition [84]	26	136	Failed to separate of FOX from PBO on FS
Stubhaug *et al.*, 2008 [60]	MIR (24 weeks) + CBT (12 weeks) vs. PBO (24 weeks) + CBT (12 weeks) vs. CBT (12 weeks) + MIR (12 weeks) vs. CBT (12 weeks) + PBO (12 weeks): all treatments were administered in order	ICD-10 research criteria [85]	12 and 24	72	At 12 weeks, MIR failed to separate from PBO on FS At 24 weeks, CBT + MIR showed significantly more reduction in FS scores than PBO + CBT, with an observed difference of 5.5 (95% CI = 15.4 – 22), whereas MIR + CBT failed to separate from PBO + CBT

ADS: Anhedonic Depression Score; BDI: Beck Depression Inventory Score; CBT: cognitive-behavioral therapy; CES-D: Centers for Epidemiological Study of Depression; CFS: Chronic fatigue syndrome; CFSC: Chronic fatigue symptom checklist; CI: Confidence interval; CTP: Citalopram; FOX: Fluoxetine; FS: Fatigue Scale; FSQ; Functional Status Questionnaire; FSS: Fatigue Severity Scale; ICD: International Statistical Classification of Diseases and Related Health Problems 10th Revised Version; ISS: Illness Severity Scale; KPI: Karnofsky Performance Index; KSS: Key Somatic Symptoms; MIR: mirtazapine; MCB: Moclobemide; NTP: Nortriptyline; OR: Odds ratio; PNZ: Phenelzine; PBO: Placebo; POMS: Profile of Mood States; RVI: Rand Vitality Index; SFS: Subjective Fatigue Score; SRG: selegiline; SSC: Symptom Severity Checklist.

A randomized, placebo-controlled, crossover study failed to demonstrate efficacy of modafinil in patients with CFS [77]. Similarly, an RCT in patients with multiple sclerosis (MS) did not show superior efficacy of modafinil over placebo for relieving fatigue [78], although a small open-label study in patients with MS suggests that modafinil may have benefit for fatigue and sleepiness [79].

5. Conclusion

Notwithstanding considerable advances in the treatment of CFS, current evidence-based pharmacological treatments clearly provide no panacea. In particular, more research is needed concerning the long-term effects of antidepressant treatments, their generalizability to routine clinical care, and the identification of their mechanisms of treatment effects.

A practical treatment approach such as combination of pharmacological and behavioral treatments may be proposed that can be integrated in current evidence-based treatments of CFS. This treatment approach emphasizes the need to incorporate findings concerning the etio-pathogenesis of CFS into treatment, as well as tailoring treatment to individual patients [80].

6. Expert opinion

Research published to date does not support definitive conclusions about the efficacy of antidepressants or other psychotropic agents in the treatment of CFS. None the less, the data generated suggest that antidepressant medications are likely one of the proper options for addressing the core symptoms of CFS regardless of whether comorbid depression is present.

RCTs have been inconsistent in support of this notion, and much of the support for antidepressant use in CFS is derived from studies of fatigue associated with other unexplained symptoms or depression. It is not clear whether specific antidepressants or classes of antidepressant are uniquely efficacious in CFS. Unlike the body of data regarding fibromyalgia and neuropathic pain syndromes, research has not demonstrated a unique role for dual-acting (norepinephrinergic/serotonergic) agents; SSRIs are appropriate as first-line treatment and are especially tolerable. TCAs potentially induce the side effects of sedation and orthostatic hypotension, and CFS patients are prone to these risks because of their fatigue and frequent autonomic lability. TCAs might be appropriate first-line agents for a subset of patients with marked insomnia. Patients who fail to benefit from a trial with a TCA should be switched to a different antidepressant class since it has been observed that failure of a TCA trial predicts failure to respond to other TCAs [20].

Available data is limited regarding appropriate dosing strategies in the treatment of CFS. The doses of citalopram (≤ 20 mg/day) and fluoxetine (≤ 20 mg/day) used in published CFS trials were relatively low compared to most studies of MDD. Of note, studies of fibromyalgia and irritable bowel syndrome have used SSRI doses comparable to those used in MDD studies, whereas TCA doses used in research for these syndromes have been markedly lower than TCA doses in depression research [32,81]. Additionally, the duration of an adequate trial of antidepressant medication in CFS remains ambiguous. Currently available clinical trials with SSRIs were short and the usual duration of treatment was 12 weeks or less. Treatment beyond 12 weeks might show additional benefit in CFS, and hopefully further research will clarify this point.

Stimulant treatment (including modafinil) of CFS is intuitive, although available evidence does not strongly support this strategy. In their own practice, the authors have found stimulant and modafinil use to be of benefit in the treatment of CFS either as monotherapy or adjunctive with antidepressants.

Several trials proved superior efficacy for combination of pharmacological and behavioral treatment in CFS patients compared with treatment with either alone. The order of interventions may be important, and in particular, a robust response has been demonstrated with behavioral intervention followed by pharmacological treatment [60]. Hence, multimodal approach for individual patient with CFS would be proper to optimize and maximize the treatment effects.

Declaration of interest

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