Specific Treatment of Residual Fatigue in Depressed Patients

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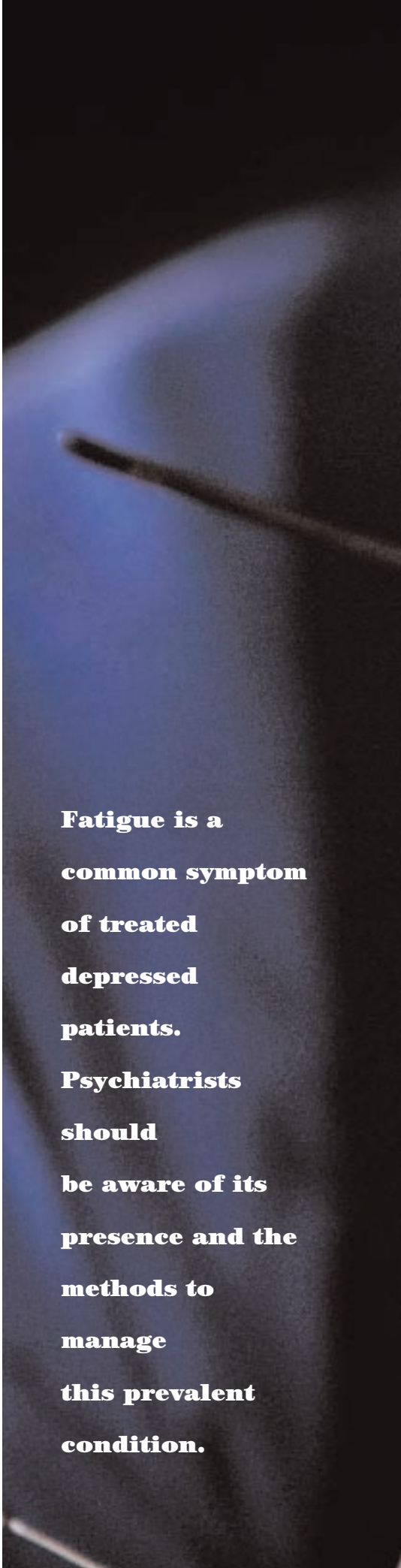

Fatigue is a common symptom of treated depressed patients. Psychiatrists should be aware of its presence and the methods to manage this prevalent condition.

INTRODUCTION

THE VAST MAJORITY OF PATIENTS WITH DEPRESSION WHO respond to treatment continue to show significant symptoms. The standard approach to this situation is switching or adding antidepressants or augmenting with other types of agents. This article ascribes to a nontraditional paradigm for the management of residual depression. In a previous publication, it has been proposed that the treatment of residual depression addresses specific symptoms.[1] Here that proposal is applied to the management of fatigue as a residual symptom in treated depressives. Due to the scarcity of studies regarding the treatment of fatigue *per se* in depression, we use information from the basic sciences and sports medicine, psychopharmacology, and the experience in the treatment of fatigue in related illnesses, e.g., somatoform disorders, chronic fatigue syndrome (CFS), fibromyalgia, or multiple sclerosis (MS). The following information helps shape some practical guidelines for the management of this significant and impairing symptom in depressive patients with a partial response to antidepressant treatment.

FATIGUE IN DAILY LIFE, PRIMARY CARE, AND DEPRESSION

Fatigue is a common complaint, not only from medical and psychiatric patients but also in the community. In the mid 20th century, a study seeking cancer-predicting signs interviewed over one million people in the US and found that 45.7 percent of women and 33.0 percent of men reported fatigue.[2] National mental health surveys in several countries agree on its high prevalence rate. The 1984 Epidemiological Catchment Area (ECA) study of the National Institutes of Health (NIH) reflected a current fatigue preva-

Table 1. CAUSES OF EDS

- Insufficient or poor quality sleep
- Psychoactive medications
  - antidepressants (paroxetine, mirtazapine, TCAs)
  - antipsychotics (clozapine, olanzapine, quetiapine, typicals)
  - antihistamines (remember OTCs)
- Sedatives and hypnotics
  - bensodiazepines and muscle relaxants
  - hypnotics (zolpidem)

lence of 6.7 percent and a lifetime prevalence of 24.4 percent;[3] in a study of the Australian Bureau of Statistics, 13.29 percent reported fatigue;[4] in a survey conducted in Great Britain by the Office of Population Censuses and Surveys, fatigue was the most common neurotic symptom with a prevalence of 27 percent.[5] Most of these people associate their fatigue with a psychological component. In a British study of over 15,000 people in the community, almost 60 percent attributed their fatigue to psychosocial or psychological causes.[6]

Fatigue is also a common complaint in primary care. Studies in primary care in North America and Europe show that 10 to 20 percent of men and 10 to 30 percent of women report significant fatigue.[7-9] The World Health Organization Multinational Primary Care Study, which was conducted in industrialized and underdeveloped countries, shows a weighted prevalence of eight percent for substantial unexplained fatigue vs. 1.7 percent for CFS.[10]

Fatigue is a common presenting symptom in depression and dysthymia. In the Depression Research in European Society (DEPRES) study, which spanned six European countries, 73 percent of people with depression reported tiredness.[11] In an Italian study of 512 patients with dysthymia without major depression, investigators found that fatigue was the most common symptom accompanying depressed mood (96% of cases).[12] Fatigue shows a strong association with the depressive syndrome. An American study, comparing depressed and nondepressed women, found that fatigue had a sensitivity of 77 percent and specificity of 84 percent for the diagnosis of major depressive disorder.[13]

Fatigue is a predictor of future depression. From a study of ECA subjects, it has been estimated that the presence of fatigue increases the chances of developing depression over the next year by 2.6 times in women and 6.8 times in men.[14] In another 13-year follow-up to the ECA from 1981 to 1994, it was found that subjects with fatigue in the 1981 interview but not in the 1994 interview had an incidence of depression 4.1 times higher than controls, and subjects with fatigue in both interviews had an incidence of depression 23.6 times higher.[15]

Table 2. MEDICAL CAUSES OF FATIGUE

- Sleep apnea
- Anemia
- Cardiac failure
- Chronic diseases, e.g., COPD
- Hypothyroidism
- Drug therapy, e.g., antihypertensives, cytokines (interferon), anticancer

Fatigue is a common symptom in treated, depressive patients, even in responders. In the DEPRES European study, 72.3 percent of men and 77.7 percent of women reported fatigue after receiving pharmacotherapy or psychotherapy for their depression.[16] In an American study, 38 percent of subjects who met criteria for response to fluoxetine still reported fatigue.[17]

POSSIBLE MECHANISMS OF FATIGUE

Fatigue is a complex concept involving both somatic information and the cognition that the intellectual or physical activity requires a higher share of the individual's energy or that the individual is less productive than usual. Probably a multiplicity of pathways and substances are related to this complex feeling, especially serotonin, dopamine, the HPA axis, and inflammatory cascades involving substances like cytokines.

Information from basic sciences and sports medicine indicates that increased serotonin in certain areas of the brain, like the lateral hypothalamus, plays a role in the genesis of central fatigue. Serotonin agonists increase fatigue, and general serotonin antagonists reduce fatigue in animal models. It has been hypothesized that serotonin may induce fatigue through inhibition of the dopaminergic system and/or through the HPA axis.[18,19]

Dopamine has long been associated with fatigue, and the most potent stimulant agents currently available are dopaminergic. Central dopamine seems

Table 3. ANTIDEPRESSANT-PSYCHOTROPIC-INDUCED FATIGUE

- SRIs (SSRIs, venlafaxine, TCAs)
  - increased serotonin seems to be a factor in central fatigue
  - if an SRI is indispensable, sertraline
- Antipsychotics
  - decreased dopamine seems to be a factor in central fatigue
- Mood stabilizers

to be related to fatigue in an inverse way to serotonin. Dopamine metabolism is enhanced during exercise in the hypothalamus and other areas of the brain, and exercise endurance is impaired after destruction of dopaminergic neurons in animal models. Clinically, fatigue, a prominent symptom in Parkinson's disease, improves with both L-dopa and bilateral deep brain stimulation.[20,21]

The association between adrenal hormones and depression has been known for decades. Though elevated cortisol secretion in depression has been an accepted truth, recent evidence seems to contradict this.[22] In any case, cortisol apparently may induce the main enzyme metabolizing tryptophan, tryptophan pyrrolase. Some inflammatory reactions involving immunologic cascades may also induce central fatigue. Fatigue is a common feature of MS, and substances associated with clinical depression and fatigue include some cytokines widely used in clinical practice (e.g., interferon).

MANAGEMENT OF RESIDUAL FATIGUE IN DEPRESSION

The management of residual fatigue in depression may be summarized in five steps:

1. Make a definitive diagnosis that it is residual fatigue.
2. Deal with contributing factors.
3. Acknowledge the importance of fatigue, establish a clear attribution, and collaboratively design a treatment plan.
4. Start graded exercise.
5. If necessary, start specific medication.

Table 4. LIFESTYLE CONTRIBUTING FACTORS TO FATIGUE

- **Sedentary lifestyle**
- **Overwork/"burnout"**
- **Drug and alcohol abuse/withdrawal (includes caffeine and nicotine)**
- **Inappropriate diet (fad diets, skipping meals)**

1. Differential diagnosis. *Excessive daytime sleepiness (EDS).* EDS may be due to insufficient or unsatisfactory sleep (including sleep apnea). Asking about sleep quality and amount (initial, middle, or late insomnia) must be part of the interview with any depressed patient. It is important also to consider hangover from hypnotics, be it over the counter (antihistaminics) or prescribed (especially zolpidem). Finally,

Table 5. COGNITIVE INTERVENTION

- **Acknowledge the fatigue, avoid minimizing it, establish attribution**
- **Reassure the patient; let him "play the sick role"**
- **Discuss stressors and patient's coping skills**
- **Challenge unhealthy cognitions**
- **Collaboratively design a treatment plan**

we must remember that many psychotropics, besides hypnotics and anxiolytics, may induce EDS. Causes of EDS are listed in Table 1.

Fatigue from medical causes. Most physical illnesses may cause fatigue. However, here we are dealing with a mental health-care population or a primary care population that is supposed to have regular medical check-ups. Thus, we only mention those medical causes of new fatigue that could be at work in an apparently healthy or stable patient. It is important to consider medications for physical conditions, like beta-blockers, antithyroid drugs, cytokines (interferon), immunosuppressants, and anti-cancer medications. Medical causes of fatigue are listed in Table 2.

Table 6. GRADED EXERCISE

- **Aerobic exercise (jogging, aerobics, biking, swimming, treadmill, walking at a brisk pace), 4 to 5 times x week**
- **Start with 5 to 15 min at a comfortable level (roughly half the maximum recorded HR), adding 1 to 3 min per week**
- **Warn patients against exceeding scheduled duration of exercise**
- **If increased fatigue, keep the same level of exercise for another week.**

Antidepressant- and psychotropic-induced fatigue. Serotonergic agents should be suspected of causing fatigue, especially if the fatigue was not present or was less marked at the beginning of treatment. It is important to keep in mind that besides SSRIs, all tricyclic antidepressants (TCAs), venlafaxine, and now duloxetine have serotonin reuptake inhibiting action. Fatigue is not an unusual complaint with anticonvulsants and is a widely known response to antipsychotics and likely related in that case to decreased dopaminergic drive but also to other mechanisms (Table 3).

2. Lifestyle factors contributing to fatigue.[23] A sedentary lifestyle with physical deconditioning is a common cause of fatigue; this will not improve easily with interventions other than exercise. Overwork also needs to be taken into account, and we must differentiate fatigue from the exhaustion caused by overwork or a hectic lifestyle that will only improve with rest. Drug and alcohol abuse are causes patients often do not volunteer, and this needs to be actively addressed. Withdrawal from nicotine, caffeine, and stimulants like cocaine

Table 7. MEDICATION MANAGEMENT

- **Switch to or add bupropion**
  - **depending on patient's profile, consider**
  - **methylphenidate (half ADHD dose or less)**
  - **modafinil 100–200mg daily (check for permanence of the effect)**
  - **l-thyroxine (25–50mcg daily)**
  - **amantadine 100mg daily or bid**
  - **selegiline 5mg daily or bid (MAOI!)**
  - **pergolide (scarce evidence)**
  - **granisetron, ondansetron (expensive, scarce evidence)**

needs to be considered. Finally, it is indispensable to ask patients in detail about their eating habits for the assessment of residual fatigue. Lifestyle factors associated with fatigue are listed in Table 4.

3. Cognitive intervention. Structured cognitive behavioral therapy (CBT) is always an option for residual depression;[24–26] however, here we are discussing a cognitive intervention to be performed by the medication prescriber and directed specifically to fatigue. This intervention in residual fatigue is, to a large extent, modeled on those for somatoform disorders, CFS, and fibromyalgia.[27–29] We acknowledge the importance of the fatigue and the impairment it causes and address patient's anxiety by establishing a causal attribution. We reassure the patient but also let him exteriorize his complaints. Jointly we design a treatment plan and recruit the patient's collaboration to change contributing factors and to follow the exercise plan (Table 5).

4. Graded exercise. Besides improving physical condition, sustained exercise may improve mood itself. Exercise is usually part of CBT protocols modified for patients with somatoform disorders, CFS, or fibromyalgia.[30,31] It is important to start with a comfortable intensity and warn patients against going over schedule, because if they get sore they are more likely to stop exercising (Table 6).

5. Pharmacological interventions. There are practically no prospective studies addressing the specific effects of medications on residual fatigue. However, the experience in treatment-resistant depression with medications like stimulants, thyroid preparations, and more recently with selegiline and modafinil, plus the increasing knowledge of the treatment of fatigue in conditions like CFS, MS, fibromyalgia, or human immunodeficiency virus (HIV) infection, allows us to extract some suggestions in this regard. Possible medication management are discussed next and are listed in Table 7.

Bupropion. This antidepressant has a unique mechanism of action that involves dopaminergic and noradrenergic actions. Clinically, it has an alerting effect and interferes with sleep if taken close to bedtime. It has also proved useful in attention deficit disorders. In depression, bupropion does not seem to affect the psychomotor performance.[32] Though we do not know of prospective studies that address its specific effect on energy in depressed patients, bupropion seems to be effective in fluoxetine-resistant CFS.[33]

SSRIs. Compatible with the proposed role for serotonin in central fatigue, these antidepressants at best seem to have no positive effect on fatigue *per se*. Paroxetine in depressed cancer patients improved depression but not fatigue.[34] Citalopram, in idiopathic chronic fatigue, showed no difference with placebo.[35] As mentioned above, one third of depressed patients who responded to fluoxetine had fatigue as a residual symptom. In a comparison with exercise in CFS, fluoxetine improved depression only, while graded exercise improved fatigue.[36] A double-blind study did not show difference among fluoxetine, paroxetine, and sertraline regarding fatigue.[37]

If an SSRI is considered indispensable in patients with marked fatigue (e.g., because of significant anxiety), some suggest that the best choice is sertraline, because of its mild dopaminergic action. Sertraline improved fatigue in depressed patients with MS, though fatigue improvement seemed to be due primarily to changes in mood.[38]

Stimulants. Stimulants have a questionable intrinsic antidepressant effect; however, they have been used as augmenting agents in depression. There is a

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patients are urgently needed, we should no

growing body of experience with stimulants to improve fatigue in medical conditions like stroke, MS, cancer, HIV infection, and in elderly patients. Recent studies include D-amphetamine in HIV and CFS and patient-controlled methylphenidate administration in cancer.[39,40] Stimulants seem better indicated for patients with medical contributors to fatigue or with significant psychomotor retardation.

Modafinil. This agent, approved for the treatment of narcolepsy, is widely used to improve alertness in other conditions. There are reports of augmentation with modafinil in partial response in depression[41] and in the treatment of fatigue in MS.[42] A relatively large placebo-controlled study of modafinil for fatigue in depression showed modafinil separating from placebo at Week 2 but not at Week 6.[43] In another study, modafinil was comparable to caffeine on alertness and performance during sleep deprivation.[44]

Amantadine and dopaminergic agents. Amantadine, an anti-Parkinsonian medication with unclear mechanism of action, has shown positive results in the fatigue of MS, but there is debate regarding the clinical significance of these findings.[45] The dopamine agonists, pergolide and cabergolide, seem to be useful as adjunct to treatment-resistant depression; pergolide, a D1 and D2 agonist, improved fatigue in Parkinson's disease patients while bromocriptine, a D2 agonist, did not.[46] Selegiline, a MAO inhibitor used in Parkinson's disease, improved vigor in CFS without showing an antidepressant effect.[47]

Thyroid hormones. Thyroid preparations have long been used as augmentation in depression treatment. There also has been permanent debate within and outside of psychiatry regarding the usefulness of giving thyroid hormones to individuals with TSH levels within the laboratory normal range. Now there is new information suggesting that hypothyroidism is a relative state. Variation of thyroid function tests within an individual over time seems to be small and much narrower than laboratory range; thus, clinically important disease might be present in individuals with normal or raised TSH concentrations.[48] In at least one study, giving l-thyroxine (50mcg) to euthyroid individuals improved depression and fatigue, especially in women, without drug-induced hyperthyroidism.[49]

Serotonin-3 receptor antagonists. These medications are mainly used as antiemetic in chemotherapy. 5-HT3 receptors are ubiquitous and present in areas that relate to depression, with high concentrations in area postrema, tractus solitarius, caudatus, nucleus accumbens, amygdala, and hippocampus. Ondansetron and tropisetron have been reportedly beneficial and well tolerated in CFS and fibromyalgia; however, a significant barrier to gaining more clinical experience is their high price.[50–52]

SUMMARY

Residual fatigue in depression not only contributes significantly to quality-of-life deterioration, but also appears to be a major risk factor for chronicity and relapse. Thus, though prospective studies on the specific treatment of residual fatigue in depressed patients are urgently needed, we should not remain passive in the interim. With a pragmatic and integral approach, our patients will benefit greatly.

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