HUMAN PSYCHOPHARMACOLOGY
Hum Psychopharmacol Clin Exp 2004; **19**: 63–64.
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/hup.554

CASE REPORT

Recovery from chronic fatigue syndrome with modafinil

Douglas Turkington,[1] Daniel Hedwat,[1] Iain Rider[1] and Allan H. Young[2]*

[1]*Royal Victoria Infirmary, Newcastle upon Tyne, UK*
[2]*School of Neurology, Neurobiology and Psychiatry, University of Newcastle upon Tyne, UK*

Chronic fatigue syndrome (CFS) is a syndrome in which the defining symptom is marked physical and mental fatigue (Fukuda *et al.*, 1994). The aetiology and pathophysiology are as yet not determined. Treatment is often unsatisfactory, and only cognitive behavioural therapy (CBT) and graded exercise therapy (GET) have proved themselves to be of significant benefit, for some patients, in a recent systematic review (Whiting *et al.*, 2001). In terms of pharmacological treatments, the antidepressant SSRI, fluoxetine, is most commonly used, but has been shown to be of little or no benefit in treating the fatigue of CFS in randomized controlled trials (Wearden *et al.*, 1998). Clearly, more effective treatments need to be identified. Modafinil is a central nervous stimulant used in the treatment of narcolepsy. There are as yet no reports of its use in treatment of CFS. The case of a patient with severe CFS who made a good recovery with this drug is reported.

CASE REPORT

Mr C is a 33-year-old man who first presented to his GP in 1987, age 19, with a range of symptoms including severe fatigue, general malaise, generalized aches and pains and poor sleep, suggestive of an acute viral illness. During this acute illness, the patient was bedbound for 2–3 weeks. He recovered sufficiently so that he was able to begin University as planned, but relapsed and remained symptomatic for the next 13 years. Investigations revealed only past Coxsackie B virus infection, and a diagnosis of CFS was made. Over the years, Mr C's illness appeared to follow a relapsing and remitting course, leading to severe disability, the patient not being able to leave the house or to work.

Mr C first sought psychiatric help in 1990, after which courses of fluoxetine, and cognitive behavioural therapy were tried but not found helpful. Over the next decade, only prescriptions of temazepam and zopiclone, which improved Mr C's sleep, were found to be of significant benefit. In 1998, Mr C's condition reached its nadir, his condition deteriorating such that he was confined to a wheelchair, barely having the energy to sit up and feed himself, for the next 18 months. In 2000, real improvements began. Initially, symptoms of myalgia responded partially to clonazepam, and a course of modafinil, at a dose of 200 mcg mane, was successful in treating Mr C's debilitating fatigue, with energy levels improved from 20% to 60% of optimum in the space of a few months. Mr C was able to return to part-time work, and, after 13 years of illness, at last to enjoy a good quality of life.

DISCUSSION

The efficacy of the non-amphetamine based stimulant, modafinil, in the treatment of excessive daytime sleepiness (EDS) in narcolepsy, has been established in a recent radomized controlled trial (US Modafinil in Narcolepsy Multicenter Study Group, 2000). Recent trials have found evidence to suggest a possible benefit of modafinil as treatment of fatigue in the setting of Parkinson's disease (Happe *et al.*, 2001), multiple sclerosis (Rammohan *et al.*, 2002) and myasthenia gravis (MG) (Lechin *et al.*, 2000). These trials also found modafinil to be well tolerated, with few significant problems with adverse drug reactions being reported.

* Correspondence to: Prof. Allan H. Young, Department of Psychiatry, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, UK. Tel: 0191 232 5131 ext 24473. Fax: 0191 227 5108.
E-mail: a.h.young@ncl.ac.uk

Received 12 September 2003
Accepted 26 September 2003

The mechanism of action of modafinil appears to be as an α-1 adrenergic receptor agonist, and as an enhancer of excitatory glutamatergic transmission and inhibitor of inhibitory GABAergic transmission (Ferraro *et al.*, 1999). In animal studies, modafinil has been shown to increase 5-HT levels in the cortex, amygdala and dorsal raphe nucleus. The 5-HT releasing mechanism appears to differ from that of DL-fenfluramine and fluoxetine, which involve the reuptake process. The α-1 adrenoceptor agonist properties of modafinil have been used in animal studies to show a relationship between stress and selective desensitization of α-1 adrenoceptors, and the reduction of this effect by corticosteroid treatment (Stone *et al.*, 2002). In a review of the neuroendocrinology of chronic fatigue syndrome (Parker *et al.*, 2001), about one third of studies showed a reduction in baseline cortisol levels in patients with CFS, although methodological differences could account for the varying results. Reduced HPA functioning and enhanced 5-HT functioning in neuroendocrine challenge tests appeared to be a more consistent finding, although whether these changes are primary or secondary is unknown. It could be postulated that the possible therapeutic action of modafinil in CFS could be through these HPA/5-HT interfaces.

Recent research suggests that the normal safety fears in relation to amphetamine-based stimulant use (occurrence of rebound phenomenon after treatment withdrawal, and the development of tolerance and dependence with continued use) do not seem to be of concern in relation to modafinil (US Modafinil in Narcolepsy Multicenter Study Group, 2000). This would make modafinil potentially useful in CFS, where stimulants are avoided due to their potentially addictive properties. Whether patients with CFS would need to take modafinil long term needs to be established. Modafinil could be used as a short-term intervention, allowing a therapeutic window in which psychotherapeutic interventions could be applied, and dysfunctional cognitions could be challenged. Clearly, further research, in the form of long-term, double-blind, randomized controlled trials would be warranted in order to investigate the efficacy and safety of modafinil as a treatment option for CFS.

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