DRUG REVIEW

Modafinil: A Review and Its Potential Use in the Treatment of Long COVID Fatigue and Neurocognitive Deficits

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Modafinil is a eugeroic agent approved for treating fatigue in narcolepsy and shift-work sleep disorder. It has been shown to have antioxidant effects preclinically and clinical efficacy in treating neurocognitive symptoms. This article describes findings from a literature review that focused on modafinil's mechanisms of action and its possible role in treating the fatigue and neurocognitive deficits of long COVID. PubMed was searched with the following key terms: "COVID-19-neuropsychiatric," "long COVID," modafinil," "modafinil-fatigue," "modafinil-inflammation," and "modafinil–antioxidant."

Coronavirus disease 2019 (COVID-19), the illness caused by severe acute respiratory syndrome–associated coronavirus type-2 (SARS-CoV-2) infection, has resulted in worldwide morbidity and mortality. Although the majority of COVID-19 infections result in mild disease, 5% of severe cases can lead to critical illness (1). A portion of recovered patients report persistent or new symptoms, even when polymerase chain reaction (PCR) test results are negative. "Long COVID" is a constellation of symptoms that includes fatigue, "brain fogginess," autonomic dysfunction, headache, loss of smell or taste, cough, depression, low-grade fevers, palpitations, dizziness, muscle pain, and joint pains. One study reported that 87% of hospitalized COVID-19 patients endorsed the persistence of at least one symptom 60 days after discharge, the most common being fatigue (53.1%) (2).

Evidence suggests a neuropsychiatric component of coronavirus infection. Among patients hospitalized for SARS and Middle East respiratory syndrome, 30% to 40% reported neuropsychiatric symptoms during the acute illness, and 10%–20% reported persistent neuropsychiatric symptoms after recovery (3). COVID-19 infections involve increased serum levels of proinflammatory cytokines, which can cross the blood-brain barrier, promoting local inflammation resulting in neurotoxicity (4). Neuroinflammation's relationship to neuropsychiatric disease and symptomatology is well established, illustrated by data demonstrating increased levels of inflammatory cytokines in depressed patients. These effects are thought to be mediated through down-regulation of monoamine neurotransmission and neurotropic factors (5).

There is limited literature regarding treatment of either the symptoms or the pathophysiology of long COVID. Established therapies targeted to the patient's presentation are currently recommended (6), and immune modulation therapies have been recommended to target the inflammatory aspect of the disease (7). Evidence shows that depressed patients with abnormally elevated inflammation are less likely to respond to classical monoamine reuptake inhibitor therapy (8). Given the inflammatory nature of COVID-19 neuropathology, one could hypothesize a similar trend among long COVID patients.

MODAFINIL: SIDE EFFECTS, DRUG INTERACTIONS, AND MECHANISMS OF ACTION

Modafinil administration has resulted in cognitive improvement in patients with attention-deficit hyperactivity disorder, major depression, and schizophrenia and in healthy populations (9), as well as decreased fatigue in patients with other medical conditions. Table 1 presents results of studies in which the effects of modafinil on fatigue and cognition were examined (10–14). Modafinil is well tolerated; the most common side effects are headache, nausea, nervousness, anxiety, and insomnia (8). Although it is a Schedule IV drug, it has a low potential for abuse because of its insolubility in water and instability at high temperatures, thus preventing its use in intravenous or inhalation forms (9). Modafinil has the potential for drug-drug interactions; it has shown reversible inhibition of CYP2C19 in human liver microsomes (8). Because selective serotonin reuptake inhibitors (SSRIs) are metabolized by CYP2C19, modafinil may increase the serum levels of escitalopram. However, there was no difference in side effects in a controlled study when either placebo or modafinil was added to an SSRI in patients with major depressive disorder and persistent fatigue (15). Modafinil has no known drug interactions with remdesivir, an antiviral approved by the Food and Drug Administration to treat COVID-19.

Mizenberg and Carter (9) reviewed modafinil's actions on neurotransmitters that likely mediate its effects on wakefulness. These consist of elevated synaptic/extracellular dopamine (DA) through inhibition of the DA active transporter; elevated synaptic/extracellular norepinephrine (NE) through interactions with alpha 1 and alpha 2 receptors; elevated extracellular glutamate in the thalamus, hypothalamus, striatum, and hippocampus through adrenergic mechanisms or through increasing the cerebral glutamate-glutamine pool; reduction of cortical GABA, possibly through

TABLE 1. Studies examining the effect of modafinil on fatigue and cognition

Study	N of subjects	Primary outcome	Results
Bivard et al., 2017 (10)	232	Fatigue, as measured by the Multidimensional Fatigue Inventory (MFI); quality of life, as measured by the Stroke Specific Quality of Life Scale (SS-QOL)[a]	Participants taking modafinil reported a significant decrease in fatigue, compared with those taking placebo (between-group MFI score difference, −7.38, 95% confidence interval [CI]=−21.76 to −2.99, p<0.001). Improved quality of life was also noted for the modafinil group vs. the placebo group (SS-QOL score, 11.81; 95% CI=2.31 to 21.31, p=0.015).
Shangyan et al., 2018 (11)	303	Fatigue, as measured by the Modified Fatigue Impact Scale (MFIS)[b] and the Fatigue Severity Scale (FSS)[c]	Modafinil was superior to placebo; the mean estimated treatment difference between the 2 groups in the MFIS score was −5.27 (95% CI=−8.51 to −2.03, p=0.001). No significant between-group difference was found in FSS scores.
Conley et al., 2016 (12)	541	Fatigue, as measured by the Brief Fatigue Inventory (BFI); depression, as measured by the Center for Epidemiological Studies–Depression Scale (CES-D) and the depression-dejection subscale of the Profile of Mood States	Among subjects with severe fatigue (BFI score ≥7), those receiving modafinil had lower depression scores, compared with a control group. Modafinil significantly moderated the relationship between baseline fatigue and CES-D total scores (p=0.04).
Rabkin et al., 2010 (13)	115	Fatigue and depression, as measured by the Clinical Global Impressions–improvement scale	Among patients with fatigue, 73% responded to modafinil and 28% responded to placebo. Modafinil did not have an effect on mood alone in the absence of improved energy. At 6 months, those still taking modafinil had more energy and fewer depressive symptoms, compared with those not taking modafinil, and only the former group showed a significant decline from baseline in their HIV RNA viral load.
Sheng et al., 2013 (14)	535	Fatigue and excessive daytime sleepiness, as measured by self-reported fatigue, the Epworth Sleepiness Scale, Multiple Sleep Latency Test, and Maintenance of Wakefulness Test	A therapeutic effect of modafinil vs. placebo on fatigue was found for patients with traumatic brain injury (TBI) (mean difference in scores on the Fatigue Severity Scale between modafinil and placebo TBI groups=−0.82, 95% CI=−1.54 to −0.11, p=0.02, I^2=0%). A beneficial effect of modafinil on fatigue was not confirmed in the pooled studies of Parkinson's disease (PD) or multiple sclerosis (MS). Modafinil demonstrated a clear beneficial effect on excessive daytime sleepiness in patients with PD (mean difference in scores on the Epworth Sleepiness Scale between modafinil and placebo PD groups=−2.45, 95% CI=−4.00 to −0.91, p=0.002, I^2=14%) but not in patients with MS or TBI. No difference was found between modafinil and placebo in patients with postpolio syndrome.

[a] Possible scores on the MFI range from 5 to 100, with higher scores indicating greater fatigue. Possible scores on the SS-QOL range from 49 to 245, with higher scores indicating better quality of life.
[b] Possible scores on the MFIS range from 0 to 84, with higher scores indicating greater fatigue.
[c] Possible scores on the Fatigue Severity Scale range from 9 to 63, with higher scores indicating greater fatigue. Possible scores on the Epworth Sleepiness Scale range from 0 to 24, with higher scores indicating greater daytime sleepiness.

adrenergic modulation of serotonergic (5HT) activity; and indirect elevation of synaptic/extracellular histamine localized to brain regions involved in wakefulness through its interactions with the NE, 5HT, and GABA systems. Modafinil has a diverse immunomodulatory profile in its therapeutic effects on preclinical models of neuroinflammatory disease states, with actions such as cytokine production impairment, T-cell recruitment and differentiation, and microglial activation (16).

Inflammation-induced reactive oxygen species damage mitochondrial membranes, allowing protons to leak and reducing ATP yield (17). Deficits in neural mitochondrial ATP production can lead to neuronal atrophy and dysfunction of neural networks involved in learning, memory, and executive function, resulting in neurocognitive symptoms, such as fatigue and executive dysfunction (17). Modafinil's inhibition of this inflammatory chain reaction may account for its favorable effects in terms of wakefulness and cognitive function in populations with neurological and psychiatric diseases associated with neuroinflammation.

MODAFINIL IN THE TREATMENT OF LONG COVID FATIGUE AND NEUROCOGNITIVE DEFICITS

A recent meta-analysis identified fatigue as the most common and "attention disorder" as the third most common syndromes associated with long COVID (18). A positron emission tomography study of COVID-19 patients found hypometabolism in a cerebral network (including the frontal cortex, anterior cingulate, insula, and caudate nucleus) that was correlated with executive dysfunction and depressive symptoms (19).

KEY POINTS/CLINICAL PEARLS

- Long COVID refers to a constellation of persistent symptoms, most commonly fatigue and "brain fog," often reported by individuals who have recovered from acute COVID-19 infection.
- Modafinil is an eugeroic agent with a favorable safety profile and a low abuse potential, which has been approved for treating fatigue in narcolepsy and shift-work sleep disorder and shown to safely treat fatigue in populations with post-stroke fatigue, multiple sclerosis, and HIV/AIDs neurocognitive dysfunction.
- Modafinil could be a safe and effective agent in treating fatigue and neurocognitive deficits in patients with long COVID.

There may be a link between acute COVID-19 infection and persistent post-infection neuropsychiatric symptoms. Excessive inflammatory cytokine release induced by initial viral infection and microglial activation disrupts neuronal mitochondrial energy metabolism, leaving neurons vulnerable to inflammatory excitotoxic factors. This process may culminate in neuronal atrophy and synaptic dysfunction. To support this, a parallel can be drawn with the findings of Rabkin et al. (13), in that persistent CNS inflammation, microglial activation, and mitochondrial toxicity are identified contributors to the development of HIV/AIDS-associated neurocognitive dysfunction (20). The evidence presented here suggests that modafinil can therapeutically act on these pathways, which possibly contributed to the symptomatic improvement shown in the trial conducted by Rabkin et al. (13). A registered clinical trial of modafinil to improve wakefulness in acutely ill COVID-19 patients is under way (NCT04751227). Used cautiously, modafinil may be an attractive candidate in treating long COVID–associated fatigue and neurocognitive deficits.

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