

Invited review

Modafinil effects on cognition and emotion in schizophrenia and its neurochemical modulation in the brain

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ABSTRACT

Modafinil is a central nervous system wake promoting agent used for the treatment of excessive daytime sleeping. Its vigilance promoting properties and low abuse potential has intrigued the scientific community and has led to use it as a cognitive enhancer, before its neural functions were understood. Here, we review the effects of modafinil in human cognition and emotion and its specific actions on symptoms in patients with schizophrenia and whether these are consistently effective throughout the literature. We also performed a systematic review on the effects of modafinil on neurotransmitter signalling in different areas of the brain in order to better understand the neuro-mechanisms of its cognitive and emotional enhancing properties. A review of its effects in schizophrenia suggests that modafinil facilitates cognitive functions, with pro-mnemonic effects and problem solving improvements. Emotional processing also appears to be enhanced by the drug, although to date there are only a limited number of studies. The systematic review on the neurochemical modulation of the modafinil suggests that its mnemonic enhancing properties might be the result of glutamatergic and dopaminergic increased neuronal activation in the hippocampus and in the prefrontal cortex respectively. Other neurotransmitters were also activated by modafinil in various limbic brain areas, suggesting that the drug acts on these brain regions to influence emotional responses. These reviews seek to delineate the neuronal mechanisms by which modafinil affects cognitive and emotional function.

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Modafinil (2-[(diphenylmethyl)sulphonyl]acetamide; Fig. 1) is a central nervous system wake promoting agent with low abuse potential used for the treatment of excessive daytime sleepiness.

Modafinil was created in the late 1970s and it was proposed as an experimental treatment for narcolepsy, due to its vigilance promoting actions (Goldenberg, 1986), although other behavioural effects and mechanisms of action were largely unknown. Research over the past forty years has led to the discovery that modafinil exerts wake promoting, concentration enhancing and mnemonic effects. However, there is still limited knowledge about its neuronal mechanisms of action.

1. Introduction on the effects of modafinil in cognitive and emotional functions

1.1. Effects of modafinil on cognitive function

1.1.1. Sleeping disorders and healthy individuals

There is a large literature on narcolepsy and sleep deprived patients that has shown modafinil to enhance vigilance and attention (Gill et al., 2006; Hart et al., 2006; Wesensten et al., 2002), as one would expect, but also short-term memory (Pigeau et al., 1995), verbal flexibility (Walsh et al., 2004) and executive functions, which are cognitive control systems that manage other cognitive processes (Schwartz et al., 2004; Wesensten et al., 2005). Work on healthy individuals has shown that modafinil also enhanced executive function, including working memory, and inhibition control (i.e. being able to stop a response) (Muller et al., 2004; Randall et al., 2005; Turner et al., 2003; Sudgen et al., 2012).

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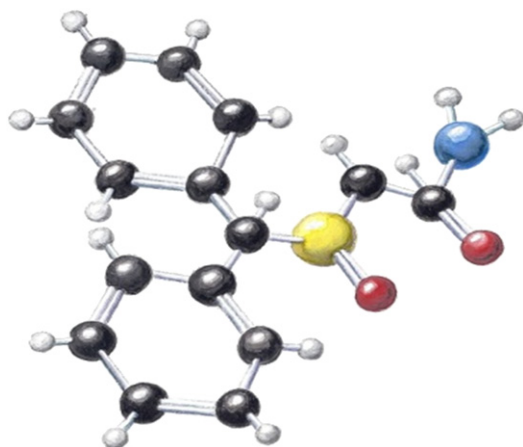


Fig. 1. Modafinil molecule structure. Drawing kindly provided by Bruno Scoriels.

1.1.2. Attention deficit hyperactivity disorder (ADHD)

Interest has grown in the potential beneficial cognitive effects of modafinil in mental disorders. Modafinil has been tested on patients with ADHD, with the hypothesis that the concentration enhancing properties of the drug might help attention deficits and hyperactivity. Several studies have shown that modafinil significantly enhanced attention functions in children with ADHD (Greenhill et al., 2006; Rugino and Copley, 2001; Rugino and Samscock, 2003; Biederman and Pliszka, 2008). Our group has shown that the drug enhanced short- and long-term memory, executive function and inhibition control in adults with ADHD (Turner et al., 2004a). Modafinil may therefore be a viable treatment for patients with ADHD; however, further chronic administration studies in patients with ADHD of the safety and efficacy of modafinil are needed.

1.1.3. Schizophrenia and psychosis

Modafinil has also been investigated as a potential candidate for treatment of cognitive deficits in schizophrenia (Morein-Zamir et al., 2007); our group has discovered that modafinil improves short- and long-term memory and cognitive flexibility in patients with chronic schizophrenia (Turner et al., 2004b). Other studies have shown that modafinil improves working memory (Rosenthal and Bryant, 2004), attention (Park et al., 2007), and inhibition control (Minzenberg et al., 2009) in schizophrenia. However, some studies have failed to find the expected cognitive enhancing properties in schizophrenia (Hunter et al., 2006; Pierre et al., 2007; Sevy et al., 2005; Spence et al., 2005), although no case of worsening of symptoms or cognitive functions have been observed in any of these studies.

Recent work has focused on first-episode psychosis, a time when deficits may be more tractable than in chronic schizophrenia, and where longer duration of untreated psychosis leads to greater severity of symptoms (Barnes et al., 2008; Marshall et al., 2005). Results indicate that modafinil enhances verbal and spatial working memory and improves accuracy in tasks measuring impulsivity (Scoriels et al., 2012). Modafinil had, however, no effect on sustained attention, attentional set-shifting, learning or fluency. The selective action of modafinil on working memory in first episode psychosis patients might have downstream effects on the key areas of social and occupational functioning.

1.2. Effects of modafinil on emotional function

1.2.1. Narcolepsy and other sleeping disorders

Modafinil's wake-promoting effects do not appear to be beneficial only for cognition, but also for emotional function. Several

studies on sleep-deprived individuals have shown that modafinil is associated with enhanced levels of mood (Pigeau et al., 1995), sense of humour (Killgore et al., 2006) and confidence (Caldwell et al., 2004). Modafinil has been shown to reverse mood disruption in individuals working on night-shifts (Hart et al., 2006) and improve the quality of life in patients suffering from shift work sleep disorder (Erman et al., 2007). Quality of life has also been improved in patients suffering from narcolepsy after treatment with modafinil, particularly in the domains of vitality and social functioning (Becker et al., 2004).

The effects of modafinil on emotional functions other than mood and affective symptoms have been evaluated only in one study in the context of sleep deprivation in healthy volunteers. Huck and colleagues have tested the ability to discriminate and label simple emotional expressions versus complex affect blends, which have been created by morphing photographs of two different affective facial expressions. For simple affective faces, neither sleep loss nor modafinil made any difference to the accuracy of judgements. In contrast, for complex emotion blends, modafinil significantly improved the ability to discriminate subtle aspects of emotion correctly relative to placebo. These findings suggest that modafinil is effective at restoring some aspects of subtle affective perception (Huck et al., 2008).

1.2.2. Healthy individuals, depression and bipolar disorders

Results are mixed with regards to the anxiogenic and anxiolytic effects of modafinil in the healthy versus mentally ill population. On one hand, Randall and colleagues have found that healthy individuals taking 100 mg of modafinil exhibited increased somatic anxiety symptoms compared to placebo or 200 mg modafinil (Randall et al., 2003). Taneja and colleagues have found a similar anxiogenic effect for modafinil administered at 400 mg daily; however, increased general mood and a significant effect on positive affect scales have also been observed (Taneja et al., 2007). Moreover, modafinil has been shown to improve symptoms of anxiety and depression in depressed (Price and Taylor, 2005) and bipolar patients (Frye et al., 2007).

1.2.3. Schizophrenia and psychosis

There are no published studies that have evaluated the effects of modafinil on affect recognition, changes of mood or other emotional functions in chronic schizophrenia. Our group has tested for the first time emotional impairments in patients with a first episode of psychosis, with tests assessing emotional face recognition, affective impulsivity, reward and punishment learning, and subjective mood changes (Scoriels et al., 2011). Modafinil improved the recognition of facial expressions for all categories of emotions and significantly so for sad faces. There were no significant effects of modafinil on subjective assessments of mood, indicating that improvements in emotional face recognition are specific to the emotional component. The improvement by modafinil of emotional discrimination may improve individual adaptation to particular emotional situations and consequent elevation of mood. Good face processing skills can promote social competence (Hooker and Park, 2002; Ihnen et al., 1998; Mueser et al., 1996) and predict later work performance and independent living in schizophrenia patients (Kee et al., 2003). In contrast, modafinil did not show any significant effects on tasks measuring emotional sensitivity to reward or punishment, or interference of emotional valence on cognitive function.

To further our knowledge on the mechanisms of action of modafinil, we performed two systematic reviews. The first review assessed the effects of modafinil in people with schizophrenia disorders and first episode psychosis, with a particular focus on its effects in cognitive and emotional functions. The second review

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