A Review of the Effects of Modafinil on Cognition in Schizophrenia

Sharon Morein-Zamir[1,2,3]**, Danielle C. Turner**[3,4]**, and Barbara J. Sahakian**[2,3]

[2]Department of Psychiatry, University of Cambridge School of Clinical Medicine, Box 189, Addenbrooke's Hospital, Cambridge CB2 2QQ, U.K.; [3]Behavioural and Clinical Neuroscience Institute, University of Cambridge, Downing Site, Cambridge CB2 3EB, U.K.; [4]Department of Clinical Neurosciences, School of Clinical Medicine, University of Cambridge, U.K.

Modafinil, a wake-promoting agent believed to operate via the hypocretin/orexin system, has a similar clinical profile to that of conventional, dopaminergic stimulants but different biochemical and pharmacological properties. There is increasing interest in the use of modafinil to improve cognition in schizophrenia as well as in other disorders such as attention-deficit/hyperactivity disorder. Recent research has focused on enhancing cognition in patients with schizophrenia because of the association between cognitive performance and functional outcome. Initial findings indicate that modafinil may lead to better executive functioning and attentional performance in patients with schizophrenia. The results further suggest that patient characteristics such as overall current cognitive functioning levels, genetic polymorphisms, and medication status may be important mediators for the effectiveness of modafinil, allowing for future treatment to be targeted to those most likely to benefit. Currently, further research is required to address the potential benefits and risks of chronic administration of modafinil to patients with schizophrenia.

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Cognition in Schizophrenia

In recent years, the cognitive and motivational impairments, seen in schizophrenia, have been determined to be one of the main causes of the profound and persistent disability typically produced by the disorder.[1] Although psychotic symptoms may improve following treatment, a range of cognitive deficits will often persist.[2,3] The disability resulting from cognitive deficits has recently been considered to have a greater impact on long-term functioning than the delusions and hallucinations.[4,5] Addressing long-term outcome is vital because schizophrenia is considered the single most important cause of chronic psychiatric disability.[6] Increasing evidence now indicates that cognitive dysfunction in schizophrenia is associated both with impaired functional outcomes such as occupational limitations, social dysfunction, and impairment in independent living[7–9] and with a reduction in subjective outcomes such as self-reported satisfaction with life and self-esteem.[10] For example, cognitive flexibility as measured by the Wisconsin Card Sorting Test (WCST), has been related to community outcome in schizophrenia[4,11,12] and response to psychological intervention.[13] Moreover, improvements in WCST performance have been associated with increased social competence and improvements in verbal memory with increased acquisition of psychosocial skills.[14] Given the growing support for the important role of cognitive deficits in influencing functional outcome, the cognitive deficits themselves are now being viewed as treatment targets.[1,15]

Cognitive impairments in schizophrenia are most clearly defined in terms of performance deficits on objective neuropsychological tests. Cognitive deficits have been documented at illness onset[16,17] and persist for most of the patient's life without periods of spontaneous remission. In fact, cognitive impairments may even precede the development of psychotic symptoms.[18,19] Significant impairment is highly prevalent in schizophrenia, with 1 study estimating 90% of patients having clinically meaningful deficits.[20] Nevertheless, there is evidence suggesting that some patients with schizophrenia are neuropsychologically normal.[20,21] One possible explanation is provided by evidence suggesting that cognitive performance tends to be more related to negative symptoms.[8,22] Another likely explanation is that while some test performance scores fall within the normal range, these scores do not reflect the patients' predicted or premorbid intellectual abilities, which should actually be higher than normal.[23]

Neuropsychological performance in patients with schizophrenia encompasses performance difficulties across a broad range of cognitive domains, with selective deficits existing against a background of general dysfunction.[24] Deficits in executive functions incorporating cognitive flexibility and attentional set shifting, working

[1]To whom correspondence should be addressed; tel: +44-1223-767035; fax: +44-1223-336968; e-mail: sm658@cam.ac.uk.

memory, and planning have been widely reported,[25–28] together with impairments in language, memory, and visuospatial and motor tests.[16,24,29,30] Executive functions incorporate the ability to plan and monitor one's behavior, set goals, and utilize feedback. These functions are particularly sensitive to prefrontal damage and accordingly the prefrontal cortex has been implicated in the pathogenesis of schizophrenia.[31] Difficulties in executive functioning can further result in problems with sustained, selective, and focussed attention and the use of social cues to modulate behavior. It is impairments in executive functions that are increasingly receiving attention in schizophrenia due to the potential to improve social, functional, and adaptive outcome.[32] The WCST, measuring cognitive flexibility, is one of the most common tests of executive function demonstrating impairments in schizophrenia.[33,34] It is important to note though that because the cognitive impairment in schizophrenia is reflected by a broad range of performance deficits, a single test is not sufficient to adequately assess impairment. Rather, multiple measures are required to characterize the overall cognitive profile of the disorder.[35]

Psychopharmacological Treatment for Impaired Cognition in Schizophrenia

It has been suggested that even small improvements in cognition may be clinically relevant to schizophrenia.[35] Improved cognition can also benefit levels of medication compliance and lead to a decrease in the burden placed on relatives and caregivers.[9] Although the potential public health benefit from the development of pharmacological treatments is substantial, current treatment for the improvement of cognitive disabilities in schizophrenia is limited.

While the extent of improvement by psychopharmacological treatments may be restricted due to brain structural abnormalities and problems in neural connectivity in schizophrenia, such treatments may also lead to the more efficient use of the existing neural systems.[8] Stimulants, such as methylphenidate and amphetamine, have been used in the treatment of schizophrenia, primarily in an attempt to address prominent negative symptoms[36] but often with unavoidable side effects. Methylphenidate has also been reported to benefit cognitive functioning in schizophrenia.[35] One study reported that amphetamine administration led to significant improvement in WCST performance in a group of patients maintained on haloperidol.[37,38] Increased regional cerebral blood flow was also found during the WCST in the left dorsolateral prefrontal cortex (DLPFC) of patients who received amphetamine. However, the administration of stimulants, which directly or indirectly enhance dopaminergic function, has been reported to lead to exacerbation or reemergence of positive symptoms.[39] For example, psychostimulants have been reported to increase thought disorder in patients with schizophrenia[40] and redundant responding on a verbal fluency test.[41]

The standard pharmacological approach to treat the positive and negative symptoms of schizophrenia has had a limited impact on neurocognitive deficits, with the older antipsychotics associated with inconsistent or minimal long-term improvements.[42,43] It has been suggested that the newer antipsychotic medications have an increased cognitive benefit compared with the old antipsychotics,[44,45] but this suggestion has been challenged.[46] Moreover, many of the cognitive deficits seen in schizophrenia do not normalize with these drugs, and their long-term efficacy on cognition remains unclear.[2,32,47–49] Likewise, the cognitive effects of atypical drugs may depend on the genetic polymorphisms related to dopamine function.[50,51] The marked effects of first- and second-generation neuroleptics on the psychotic symptoms together with the generally much smaller cognitive effects suggest that the antipsychotic medications act on different neural systems from those that underlie the cognitive impairments.[8]

Modafinil in Schizophrenia

In recent years, modafinil (Provigil), a wake-promoting agent, has emerged as a possible agent to improve cognition in schizophrenia as an add-on to antipsychotic medications. Modafinil is licensed for the treatment of narcolepsy and has largely replaced the use of traditional stimulants such as methylphenidate in this disorder.[52] Modafinil was initially reported to be administered to schizophrenia patients in order to reduce the fatigue and sedation induced by antipsychotic medications[53,54] in accordance with its potential for reduction of fatigue in other disorders such as multiple sclerosis[55] and depression.[56,57] The application of modafinil to schizophrenia has sparked much interest because the biochemical and pharmacological properties have been differentiated from those of amphetamines.[58,59] Modafinil has demonstrated functional specificity on sleep regulation and circadian rhythms[60,61] and has less potential for abuse and less peripheral and central side effects than amphetamine.[62–64]

Despite considerable research, the precise mechanism of action for modafinil is still unclear. Modafinil is thought to act in part as a hypocretin/orexin agonist with excitatory effects on the locus coeruleus adrenergic neurons.[65–67] For instance, Fos protein immunohistochemistry has demonstrated that hypocretin/orexin neurons are activated after modafinil administration, suggesting that some properties of modafinil might be mediated by the neuropeptide.[68,69] Hypocretin/orexin neurons are believed to play a role in many domains including vigilance states, arousal, emotion, reward function and motivation, drug addiction, feeding, and regulation of sleep and wakefulness.[70] Additional evidence suggests that modafinil might be acting via a similar mechanism to

that of hypocretin/orexin to promote histamine release.[71,72]

Recent studies indicate that modafinil appears to have complex and widespread effects throughout the brain, likely involving multiple neurochemical systems.[73] For example, in animal experiments, behavioral effects of modafinil are antagonized by noradrenergic drugs but not by a dopamine antagonist.[74–76]

Studies investigating the effects of modafinil on non–sleep-deprived healthy volunteers have suggested that it has significant cognitive enhancing capabilities.[77–79] The charting of the cognitive effects of modafinil on healthy volunteers is clinically relevant because it provides insight into its neuropsychological effects, free from the confounds of any underlying pathology. Turner et al[77] reported that in addition to self-accounts of increased alertness and attentiveness, compared with placebo, modafinil improved performance on neuropsychological tests of visual memory, verbal working memory, spatial planning, and response inhibition. At the same time, modafinil resulted in slowed latencies in visual memory and spatial planning tasks that corroborated the improvement in inhibiting prepotent responses, indicating a reduction in impulsive responding.[77] Additional results converge with these findings that modafinil leads to improvements in reaction time, vigilance, and working memory in normal adults[79–81] though some exceptions have been reported.[82] Modafinil has also been found to produce a strikingly similar pattern of cognitive changes in a group of adults with attention-deficit/hyperactivity disorder (ADHD), improvements on tests of visual memory, digit span, spatial planning, and response inhibition with concomitant slowing relating to reduced impulsivity.[83] The effect of improved response inhibition observed following modafinil in healthy volunteers and ADHD patients was similar to that seen with methylphenidate in these groups.[84,85] At the same time, some differences were also noted, eg, spatial working memory was found to improve following methylphenidate but not modafinil.[85] Importantly, no impairment of performance relative to placebo was noted following modafinil in any of the cognitive domains tested, in contrast to methylphenidate.[77] In sum, the pharmacological studies indicate that modafinil has some similar cognitive effects to those of conventional stimulants such as methylphenidate,[77,83–85] but at the same time, has a distinct pharmacological mode of action that appears to limit the side effects commonly experienced with traditional dopaminergic stimulants. Consequently, the use of modafinil to ameliorate cognitive impairment in schizophrenia is now being explored.

Several studies have shown promising preliminary results in clinical domains when modafinil was added to antipsychotic treatment regiments.[86,87] A randomized, double-blind crossover study of 18 patients reported significantly greater motor activity when patients were administered a single 100-mg dose of modafinil compared with placebo.[86] In a 4-week open-label trial, 9 patients with schizophrenia received up to 200 mg of modafinil daily and experienced significant improvement in global functioning and improved overall clinical condition and self-reported quality of life.[87] This latter study also demonstrated some improvement in the letter-number sequencing subtest of the Wechsler Adult Intelligence Scale (WAIS), supporting the notion that modafinil can improve cognition in schizophrenia.

Clear support for cognitive enhancement of modafinil in schizophrenia was provided in a double-blind, crossover design with 20 chronic stable patients with schizophrenia.[77] A 200-mg dose of modafinil was found to lead to enhanced performance in several domains of cognition. The patients were administered a broad battery of cognitive tasks, including tests of verbal and visual memory, working memory and planning, attentional set shifting, and response inhibition. Each patient undertook parallel versions of the battery on 2 separate occasions, once on placebo and once on modafinil, with the order randomized. Results showed improved performance on modafinil for short-term verbal memory span as measured by the WAIS digit span test, and trends toward improved visual memory and spatial planning, as measured by delayed pattern recognition memory and the one-touch Tower of London spatial planning task, respectively. These results are consistent with previous studies with modafinil in healthy volunteers and ADHD where significant improvement in pattern recognition memory and the Tower of London spatial planning task.[77,83] When administering modafinil to schizophrenia patients, a slowing of response latencies was also noted on the spatial planning task, although, in contrast to the previous studies using modafinil in healthy volunteers and adults with ADHD, no direct change in the response-inhibition task was noted.

Importantly, there was significant improvement on modafinil in cognitive flexibility in schizophrenia as measured by the 3-dimensional attentional set-shifting test, which provides a componential analysis of the WCST and has previously been shown to be sensitive to frontal lobe dysfunction.[88] Patients with schizophrenia are known to experience significant impairments when performing the attentional set-shifting task.[26,27,89,90] The finding of improvement of attentional set shifting by modafinil provides the first demonstration of improved cognitive flexibility in patients with schizophrenia using adjunctive pharmacological therapy.[77,83] This improvement in attentional set shifting with modafinil is particularly important for several reasons. First, attentional set shifting is severely impaired in schizophrenia and may serve as a useful index of cognitive deterioration in schizophrenia. Second, even modest improvements in attentional set shifting, as measured by the WCST, have been proposed to enable patients to organize themselves sufficiently to allow for independent living.[35]

The finding of improved short-term memory dovetails with a recent functional imaging study that reported enhanced activation in the anterior cingulate cortex with modafinil during a 2-back working memory task.[91] Previously, it has been found that the anterior cingulate is involved in a wide range of executive functions.[92] Using a randomized, double-blind design, 17 patients with schizophrenia were administered 100 mg of modafinil and placebo on 2 separate days and performed the task while undergoing functional magnetic resonance imaging (fMRI). Although there was no significant group-level effect, those who exhibited the greater anterior cingulate cortex response also exhibited the greater performance enhancement in working memory. The authors concluded that the beneficial effects of modafinil may have been restricted to a subset of their patients who had more impaired executive function and suggested that the type of antipsychotic medication may interact with the influence of modafinil.[91] The former conclusion converges with the finding that the effects of modafinil on working memory were most pronounced in healthy young adults whose performance was most impaired.[80] It may also be that a more robust improvement would have been seen had a dose of 200 mg of modafinil, rather than 100 mg, been used.

In a follow-up study by the same group, also employing fMRI and a subset of 12 of the patients, an association between modafinil and another area of the prefrontal cortex was reported.[93] In this study, the patients generated sequences of taps that were required to be at irregular rates. The degree of irregularity in such a task has previously been shown to be associated with greater activation of the left DLPFC. This irregularity, or temporal variability, has been interpreted as a measure of cognitive control with greater variability indicating better control. Again, no significant group-level effects were noted, in part due to the large variability between participants. However, levels of activation in the left DLPFC together with baseline executive function (letter fluency scores) predicted the improvement in behavioral performance seen following modafinil. Thus, the authors of the study asserted that modafinil may be most effective in those patients with a notable impairment in executive function.

It has been proposed that the cognitive effects of modafinil may result from the increase of control over impulsivity, thus playing a similar role to that of other stimulants such as methylphenidate.[77,83,94] In contrast to conventional stimulants, modafinil also leads to a slowing of response latencies in tasks such as planning in addition to enhancing performance accuracy on numerous tasks.[83,94] This slowing is thought to reflect the deliberation required during active planning rather than a general speeding because response speed overall is not affected by modafinil compared with placebo.[83] Theories of reflection propose that performance can be impaired due to a deficit in utilizing available information before making a decision.[95] In accordance, patients with schizophrenia tend to plan their actions less in advance and have less sophisticated planning strategies, both of which characterize frontal lobe dysfunction.[28,96,97] Hence, it would appear that with modafinil patients become less impulsive possibly allowing them to better plan their actions and utilize more sophisticated strategies.

However, the results are not clear-cut because a recent report examining the effects of modafinil on 20 schizophrenia patients over 8 weeks did not find significant effects of modafinil on cognitive function, fatigue, or symptomatology.[98] In this double-blind, placebo-controlled study, patients were assigned to either placebo or modafinil and neuropsychological testing, encompassing tests of attention and concentration, memory, working memory, and executive function (as assessed by fluency), was carried out at the beginning and at the end of the 8-week period. However, as the authors of that article acknowledge, the study may have suffered from insufficient power due to the small number of subjects in each group together with differences in baseline performances between the 2 groups, potentially accounting for at least some of the results.[99] The use of suboptimal or low doses (eg, 100 mg) of the drug due to safety concerns may also have led to weaker or null findings.[91]

To date, the literature examining the administration of modafinil to schizophrenia patients has generally suggested some improvements in cognition. In particular, enhancements are noted in the domains most impaired in patients with chronic schizophrenia with primarily negative symptoms, encompassing frontal lobe function and including cognitive flexibility and control, spatial planning, working memory, and short-term memory.[91,93,94]

One important point surfacing from existing research has been the possibility that only specific subgroups of patients may benefit from modafinil-related cognitive enhancement. Studies to date have focused on patients with chronic schizophrenia exhibiting primarily negative symptoms. In part, this is due to the relative feasibility of testing such patients as compared with patients with florid positive symptoms but also due to the cognitive deficits being experienced in this group that could potentially be improved. Moreover, given that there have been reports of modafinil exacerbating positive symptoms in some individuals with schizophrenia,[87,98,100,101] it would seem inadvisable to administer the drug to patients experiencing such symptoms.

Current studies further suggest that it is the patients with relatively intact intelligence levels but who still experience significant executive function impairment that may be likely to benefit from modafinil. For example, Turner et al[94] focused on a group of chronic patients with schizophrenia who were either living independently or in sheltered accommodation and with a premorbid National Adult Reading Test IQ measurement in the range of 100–126. It was thought that a group of such

high-functioning patients might be the best group to target because they were likely to show improvement in functional outcome from pharmacological enhancement. It may be the case that patients require a minimum level of cognitive reserve[102] in order to benefit from the administration of modafinil. Although suggestive, further studies are required to ascertain whether such findings could result from regression toward the mean, ceiling effects on some tasks, or the enrollment of relatively few participants. Future studies could address such issues directly by contrasting the effects of modafinil on patients with schizophrenia who experience differing degrees of cognitive impairment relative to average or above premorbid intelligence levels.

Existing research also suggests that the influence of modafinil could potentially be modulated by concomitant neuroleptics medication. Spence et al[91] reported that the greatest cognitive and physiological responses to modafinil tended to be in patients receiving "typical" neuroleptic medication. They suggested that because typical and atypical drugs differ in their affinity to the $5HT_{2A}$ receptor, and the effects of modafinil may be modulated by the serotonergic system, atypical antipsychotic treatment might constrain the effects of modafinil. It remains unknown at present whether different types of atypical antipsychotic drugs may interact differentially with modafinil. Nevertheless, cognitive enhancement was still seen in the study of Turner et al[94] where most patients were on atypical antipsychotic medication. In any case, medication status could be a further potential variable influencing the effects of modafinil. To summarize, the patients who may potentially benefit from modafinil require further characterization.

A further point arising from recent research is the need to conduct larger scale studies investigating not only the potential importance of individual differences but also the influence of modafinil during long-term chronic administration. While the wake-promoting effects of modafinil do not wane over time, there is almost no data in regard to its cognitive efficacy over such time spans in neither healthy nor patient populations. While cognitive impairments have been found to be relatively constant over time in schizophrenia,[103,104] it is currently unknown whether cognitive improvements would demonstrate similar stability. At present, several large-scale studies examining the effects of modafinil on schizophrenia are underway. Three such studies have been sponsored by the National Institute of Mental Health (NIMH) in the United States (http://clincialtrials.gov/ct/). The first is currently recruiting for a randomized, double-blind, placebo-controlled study to examine the effects of modafinil on brain function based on catechol-*O*-methyltranserase (COMT) genotype (http://www.clinicaltrials.gov/ct/search?term = nct00057707). The second study aims to use fMRI and electrophysiology to examine the effects of modafinil on cognitive context processing (http://

www.clinicaltrials.gov/ct/show/NCT00423943?order = 1). A third study targeting patients with attentional impairments, aims to examine the effect of modafinil as an adjunctive to second-generation antipsychotics (http://www.clinicaltrials.gov/ct/show/NCT00314639?order = 1).

A final yet important issue is the safety and tolerability of modafinil in schizophrenia, particularly when taken chronically. Numerous studies have reported that modafinil was well tolerated in their samples of patients with schizophrenia.[93,94,99] Often only mild side effects are reported including headaches, insomnia and dry mouth.[98] Nevertheless, while most patients appear to tolerate the drug well, several cases have been reported where patients who received modafinil suffered from psychotic relapse or worsening of already existing psychotic symptoms.[87,98] These reports have primarily included patients receiving chronic administration although there is 1 report of a single patient undergoing psychotic relapse 4 days after a single dose.[91] The concern for safety may also limit the use of effective dosage levels (eg, 100—vs 200 mg). More definitive evidence regarding the safety and tolerability of modafinil will eventually be provided by the use of meta-analysis as well as by large-scale studies, such as the ongoing NIMH sponsored clinical trials.

Recently, armodafinil has been investigated for its effective wake-promoting effects. Modafinil as a racemic compound contains equal amounts of R-modafinil and S-modafinil. Armodafinil, as the R-enantiomer, has been shown to have a longer half-life than modafinil and the proportion of circulating R-modafinil can be as much as 3 times greater than that of circulating S-modafinil.[105] It has been reasoned that most of the therapeutic benefits of racemic modafinil could be attributed to armodafinil and accordingly armodafinil has been shown to improve wakefulness and memory functioning in obstructive sleep apnea/hypopnea syndrome.[106,107] It remains to be seen whether armodafinil will be found to be more effective than modafinil in improving cognition in healthy participants or groups such as schizophrenia.

Conclusions

The use of modafinil to improve cognition in schizophrenia as well as other disorders such as ADHD has shown promising initial findings. While the studies to date have been limited by the small number of participants and have focused primarily on short-term rather than chronic administration, several consistent results have begun to emerge. Among these are the potential of modafinil for improving executive functioning and attentional performance in patients, which would appear to have direct implications on their day-to-day functioning. Moreover, current studies suggest that patient characteristics such as overall cognitive functioning levels and genetic polymorphisms may be important mediators for the effectiveness of modafinil allowing for future treatment to target those

most likely to benefit from it. Finally, it is likely that benefits of drugs that improve cognition will be further enhanced by nonpharmacological approaches such as psychological therapies and neurocognitive activation.[102] This combination may be crucial for promoting substantial improvements in objective and subjective functional outcome.

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