A review of modafinil and armodafinil as add-on therapy in antipsychotic-treated patients with schizophrenia

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Ther Adv Psychopharmacol

[2012] 2(3) 115–125

DOI: 10.1177/

2045125312441815

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Abstract: Schizophrenia is characterized by reality distortion, psychomotor poverty and cognitive disturbances. These characteristics contribute to a lesser social functioning and lower quality of life in patients with schizophrenia. It has been suggested that modafinil and its isomer armodafinil as an add-on strategy to antipsychotic treatment in patients with schizophrenia may improve cognitive functioning, attenuate fatigue, inactiveness and other negative functions as well as weight gain. In this paper we review the literature relevant to the question of whether modafinil and armodafinil are beneficial as add-on therapy in antipsychotic-treated patients with schizophrenia. A total of 15 articles were included in this review; of the 15 articles, 10 were randomized controlled trials (RCTs). Evidence for the use of modafinil or armodafinil as add-on therapy to antipsychotic drugs to alleviate fatigue, sleepiness and inactivity is inconclusive. One cohort study and one out of two single-dose crossover RCTs in which modafinil addition was studied could demonstrate a positive effect. All five RCTs of modafinil (three RCTs) and armodafinil (two RCTs) addition with a longer study duration could not demonstrate a positive effect. With respect to cognitive disturbances, animal models of cognitive deficits show clear improvements with modafinil. In RCTs with a treatment duration of 4 weeks or more, however, no positive effect could be demonstrated on cognitive functioning with modafinil and armodafinil addition. Yet, four single-dose crossover RCTs of modafinil addition show significant positive effects on executive functioning, verbal memory span, visual memory, working memory, spatial planning, slowing in latency, impulse control and recognition of faces expressing sadness and sadness misattribution in the context of disgust recognition. The addition of modafinil or armodafinil to an antipsychotic regime, despite theoretical and preclinical considerations, has not been proved to enhance cognitive function, attenuate fatigue, enhance activity, improve negative symptoms and reduce weight in patients with schizophrenia.

Keywords: armodafinil, cognitive disturbances, fatigue, inactiveness, modafinil, schizophrenia

Introduction

Schizophrenia is characterized by reality distortion, psychomotor poverty and cognitive disturbances [Ross *et al.* 2006]. Antipsychotics are effective against symptoms of reality distortion, but less effective against negative symptoms, such as fatigue and inactivity, and cognitive decline [Salimi *et al.* 2009]. Yet, the latter symptoms are major factors contributing to lesser social functioning [Mohamed *et al.* 2008] and lower quality of life in patients with schizophrenia [Eack and Newhill, 2007]. They are thought to be secondary to the

disease, but may also be due to or be aggravated by the antipsychotic regime [Hill *et al.* 2008; Leucht *et al.* 2009]. Sedation, for example, is a well-known side effect of clozapine and quetiapine [Leucht *et al.* 2009].

In the search for a treatment for negative symptoms and cognitive disturbances in patients with schizophrenia, diverse add-on strategies have been suggested, such as D-cycloserine, glycine [Tuominen *et al.* 2005], paroxetine, fluoxetine [Sepehry *et al.* 2007] and methylphenidate

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[Burke and Sebastian, 1993]. Modafinil is studied in schizophrenia, since on theoretical and preclinical grounds modafinil could have the potential to relieve negative and cognitive symptoms [Dawson *et al.* 2010; Pedersen *et al.* 2009]. Modafinil is registered for the treatment of several sleep disorders associated with excessive daytime sleepiness, including narcolepsy, obstructive sleep apnoea and shift work sleep disorder [Valentino and Foldvary-Schaefer, 2007].

The working mechanism is not fully understood. Modafinil has affinity for the dopamine transporter in the striatum and norepinephrine transporter in the thalamus [Madras *et al.* 2006]. At doses used in clinical settings modafinil may exert a significant inhibition of both catecholamine transporters [Hermant *et al.* 1991]. This contributes to the promotion of wakefulness by modafinil. Modafinil administration leads to significantly elevated extracellular dopamine [Wisor *et al.* 2001], norepinephrine [de Saint Hilaire *et al.* 2001], serotonin [de Saint Hilaire *et al.* 2001], glutamate [Ferraro *et al.* 1997] and histamine [Ishizuka *et al.* 2003], and decreased gamma-aminobutyric acid (GABA) levels [Ferraro *et al.* 1997]. The elevation of neurotransmitters is more prominent in the neocortex than in subcortical areas [de Saint Hilaire *et al.* 2001]. Dopamine levels are mainly increased in the prefrontal cortex [de Saint Hilaire *et al.* 2001] and the caudate nucleus [Wisor *et al.* 2001]. Dopamine elevation is thought to be partly responsible for modafinil effects on wakefulness [Wisor *et al.* 2001] and activity [Young *et al.* 2011]. Stimulants, such as amphetamine, can evoke or enhance positive symptoms in patients with schizophrenia [Curran *et al.* 2004]. As modafinil lacks many of the behavioural and neurochemical effects of amphetamine [Minzenberg and Carter, 2008], it may therefore not evoke or enhance positive symptoms. Norepinephrine is elevated by modafinil in the prefrontal cortex and rostromedial hypothalamus [de Saint Hilaire *et al.* 2001]. It potentiates the norepinephrine-induced inhibition of sleep-promoting neurons in the ventrolateral preoptic nucleus [Gallopín *et al.* 2004].

Cognitive and behavioural effects of modafinil are likely to be primarily a function of changes in monoamine activity. Arousal and activity promoting effects of modafinil are probably largely due to its effects on catecholamine systems [Minzenberg and Carter, 2008]. Modafinil addition to antipsychotic treatment could ameliorate cognitive performance [Turner *et al.* 2004],

inactiveness [Farrow *et al.* 2006] and induce weight reduction [Henderson *et al.* 2005]. By increasing activity, modafinil could decrease the bodyweight of schizophrenia patients. Weight gain often observed in schizophrenic patients is most probably due to the side effects of antipsychotic drugs and is a risk factor for the development of metabolic syndrome [Meyer *et al.* 2008]. If modafinil is effective in all of these respects, this would imply a great health benefit for many patients treated with antipsychotics.

Recently an isomer of modafinil, armodafinil, has also been studied in patients with schizophrenia [Kane *et al.* 2010]. Compared with modafinil, armodafinil produces higher plasma concentrations, whereas elimination half-life is comparable [Darwish *et al.* 2010].

In this paper we review all of the available literature to investigate whether modafinil and armodafinil are able to enhance cognitive function, attenuate fatigue, enhance activity and reduce weight in patients with schizophrenia treated with antipsychotic drugs. In addition, for clinical practice, doses and tolerability are discussed.

Methods

A literature search was performed in Pubmed® (National Library of Medicine) and Embase Psychiatry® (Winspirls) from 1972 to March 2011 with the following search terms: ((modafinil) OR (armodafinil)) AND (schizophrenia) in the title and/or abstract. References cited in the papers were also checked for relevant articles.

The inclusion criterion was that the article covered the subject of modafinil or armodafinil addition in schizophrenia. We excluded reviews, case reports and studies that did not meet the inclusion criteria.

Results

A total of 52 papers were found, of which 37 were excluded. Of the excluded articles 36 did not meet the inclusion criteria and 1 article was excluded because modafinil was administered to patients with diverse, but not separately presented, psychiatric disorders. So, 15 articles were included in this review: 5 were randomized placebo-controlled trials (RCTs), 5 were crossover RCTs, 1 was a cohort study and 4 were animal studies (the human trials are presented in Tables 1 and 2).

Table 1. Overview of trials of modafinil and armodafinil as add-on therapy in patients with schizophrenia considering fatigue and/or cognitive functioning with a duration of 4 weeks or more.

Reference	Drug	Design	N	Duration of treatment	(Mean) dosage	Fatigue/sleepiness/activity	Cognitive functioning	Cognitive testing battery
Freudenreich <i>et al.</i> [2009]	Modafinil	RCT	37	8 weeks	250 mg	–	–	DS-CPT, GPM, HVLT, LCF, NAART, TMT, WAIS-III LNS, WCST, WMS-III FFPS.
Sevy <i>et al.</i> [2005]	Modafinil	RCT	24	8 weeks	200 mg	–	–	COWAT, CPT-IP, DMST, LNS, ODRT, RAVLT.
Pierre <i>et al.</i> [2007]	Modafinil	RCT	20	8 weeks	180 mg	–	–	CVLT, DS-CPT, TMT-B.
Rosenthal and Bryant [2004]	Modafinil	Prospective cohort	10	4 weeks	200 mg	+	+	WAIS-III LNS
Bobo <i>et al.</i> [2011]	Armodafinil	RCT	60	6 weeks	150mg	–	–	CPT-IP, CPT-flanker, WCST, COWAT, ACT, CFT, FMT, STDT, ANS DS-FWD, DS-BKWD, PEAT, SWMT.
Kane <i>et al.</i> [2010]	Armodafinil	RCT	60	4 weeks	(4 groups: placebo, 50 mg, 100 mg and 200 mg)	–	–	MATRICES

+ = significant effect of modafinil on symptom

– = no significant effect of modafinil on symptom

ACT= Auditory Cononant Trigram

ANS= Auditory Number Sequencing

CFT= category fluency test

COWAT= the Controlled Oral Word Association Test

CPT-IP= The Continuous Performance test, identical Pairs version

CPT-flanker= Continuous Performance Test, Flanker version

CVLT= the California Verbal Learning Test

DMST= the Delayed Match to Sample Task

DS-CPT = the Degraded Stimulus Continuous Performance Test

DS-FWD, DS-BKWD= Digit Span (forward,backward)

FMT= face memory test

GPM = Grooved Pegboard model.

HVLT = the Hopkins Verbal Learning Test

LCF = the Letter and Category Fluency

LNS = the letter-number span

MATRICES= Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery

NAART = the North American Adult Reading Test

ODRT= the Oculomotor Delayed Response Test

PEAT= Penn's Emotional Acuity Test

RAVLT= the Rey Auditory Verbal Learning Test

STDT= Strategic Target Detection Test

SWMT= Spatial Working Memory Test

TMT= the Trail-Making Test

TMT-B = the trail-Making Test B

WAIS-III LNS = the Letter-Number Sequencing subtest of the Wechsler Adult Intelligence Scale-Third Edition

WCST = the Wisconsin Card Sorting Test

WMS-III FFPS = the Faces and family pictures subtests of the Wechsler Memory Scale-III

Table 2. Overview of one-dose trials on modafinil as add-on therapy in patients with schizophrenia considering fatigue and/or cognitive functioning.

Reference	Design	N	Dosage of modafinil	Fatigue/sleepiness/activity	Cognitive functioning	Cognitive testing battery
Turner <i>et al.</i> [2004]	Crossover RCT	20	200 mg	–	+	PRM, DMTS, SWM, SSP, IDED, NTOL, WAIS DS, STOP
Spence <i>et al.</i> [2005]	Crossover RCT	19	100 mg	?	+	2-back
Farrow <i>et al.</i> [2006]	Crossover RCT	18	100 mg	+	?	Not tested
Hunter <i>et al.</i> [2006]	Crossover RCT	12	100 mg	?	+	MAE LF
Scoriels <i>et al.</i> [2011]	Crossover RCT	40*	200 mg	?	+	ERT, BFRT, RPLT, AGN

+ = significant effect of modafinil on symptoms
 – = no significant effect of modafinil on symptoms
 ? = not studied
 * $n = 40$ patients with first episode psychosis, this sample consisted of $n = 28$ schizophrenia, $n = 2$ schizoaffective disorder, $n = 6$ bipolar disorder, $n = 2$ depressive psychosis.
 AGN= the CANTAB Affective Go-No-Go Task
 2-back = the working memory task "2-back"
 BFRT= the Benton Facial Recognition Test
 DMTS = the Delayed Matching to Sample task
 ERT = the emotion recognition task
 IDED = the attentional set-shifting task
 MAE LF= the Multilingual Aphasia Examination: letter fluency task
 NTOL= the One-touch Tower of London spatial planning task
 PRM = the Pattern Recognition Memory task
 RPLT= the Reward and Punishment Learning Test.
 SSP= the spatial span task
 STOP = the stop-signal task
 SWM = the Spatial Working Memory task
 WAIS DS= the digit span from the Wechsler Adult Intelligence Scale

Results of the studies were critically appraised, considering the magnitude of the effects and the quality of the data.

Fatigue, sleepiness and activity levels

Several case reports on modafinil as add-on therapy to antipsychotic drugs revealed positive effects on sleep duration [Maleka *et al.* 2003], willingness to participate in activities [Maleka *et al.* 2003] and fatigue [DeQuardo, 2004].

The RCTs considering fatigue, sleepiness and activity levels, in which a single dose of modafinil was administrated, show conflicting results. The RCT conducted by Farrow and colleagues demonstrated a prominent and significant effect of a single dose of 100 mg modafinil on activity levels in patients with schizophrenia [Farrow *et al.* 2006]. Activity was measured using an Actiwatch

(a wrist worn device containing an accelerometer) for 20 hours following modafinil or placebo administration. Compared with the placebo group, patients with modafinil showed significantly more motor activity. Mean motor activity after receiving placebo was 120.8, SD 56.8, and after receiving modafinil 135.1, SD 59.3. The average increase in motor activity was 12%. The study also showed a significant negative correlation between the avolition score of the Scale for the Assessment of Negative Symptoms (SANS) and Actiwatch-measured motor activity in the placebo group, whereas there was no such correlation in the modafinil group.

In the crossover RCT by Turner and colleagues the study duration of each condition was one day [Turner *et al.* 2004]. In the modafinil condition a dose of 200 mg was administered. No significant differences were found between the placebo and

modafinil groups with respect to fatigue measured on a visual analogue scale.

Studies of modafinil addition with a duration of treatment of 4 weeks or more all did not produce significant results, except for a prospective cohort study, which reported a significant attenuation of fatigue after modafinil addition [Rosenthal and Bryant, 2004].

Pierre and colleagues conducted an 8-week RCT study in a total of 20 patients [Pierre *et al.* 2007]. Mean modafinil dose was 180 mg/day. They found a nonsignificant reduction in self-reported sleep duration of 0.3 hours during the night and 0.9 hours during the daytime.

The RCT conducted by Freudenreich and colleagues revealed no significant influence of modafinil, with a mean dose of 250 mg/day, on the measures of daytime sleepiness and fatigue on the Epworth Sleepiness Scale (ESS) and the Fatigue Severity Scale (FSS) [Freudenreich *et al.* 2009]. A total of 37 patients were included in this 8-week study. A limitation of the study was that only a few of the included patients were impaired by fatigue. One could argue that modafinil only benefits patients with substantial fatigue complaints. As a matter of fact, the baseline mean FSS score of the placebo group was significantly higher than that of the modafinil group.

The study by Sevy and colleagues included patients with a severity score of at least 4 on the fatigue component of the Clinical Global Impressions (CGI), which means that they were moderately ill [Sevy *et al.* 2005]. The modafinil dose was limited to 200 mg/day and the study duration was 8 weeks. There was an overall reduction in fatigue in both the placebo and modafinil group that did not differ between the groups. Unfortunately, also in this study the baseline FSS score of the placebo group was significantly higher (50.6) than that of the modafinil-treated group (39.7).

Two RCTs of armodafinil addition in patients with schizophrenia treated with antipsychotic drugs show similar results on fatigue and sleepiness. The study by Kane and colleagues included 60 patients in a 4-week RCT [Kane *et al.* 2010]. The 60 patients were assigned into four conditions: a placebo condition, and three conditions with different study dosages of armodafinil, 50 mg/day, 100 mg/day and 200 mg/day. The ESS scores were not significantly reduced in the

armodafinil conditions compared with the placebo condition. Bobo and colleagues conducted a 6-week RCT of 150 mg armodafinil addition in 60 antipsychotic-treated patients with schizophrenia or schizoaffective disorder [Bobo *et al.* 2011]. ESS and FSS score changes did not differ significantly in the armodafinil condition compared with the placebo condition.

The evidence on modafinil and armodafinil as an effective add-on therapy to antipsychotic drugs to treat fatigue, sleepiness and inactivity is inconclusive.

In the reviewed studies the sample sizes were small. Moreover, inclusion criteria, dose of modafinil and armodafinil, study duration and assessment instruments differed substantially between the different studies.

Cognitive functioning

Do modafinil and/or armodafinil ameliorate cognitive functions in patients suffering from schizophrenia?

The main cognitive disabilities in patients with schizophrenia are deficits in executive functioning. A test for executive function is the attentional set shifting (intradimensional–extradimensional [ID/ED]) task. Administration of subchronic phencyclidine (PCP) to rats is used as an animal model for executive functioning deficits in schizophrenia. When PCP was administered to rats an ID/ED shift deficit was induced and when these rats were treated with modafinil, the ID/ED shift deficit improved significantly [Dawson *et al.* 2010; Goetghebeur and Dias, 2009; Pedersen *et al.* 2009]. Neuroimaging showed that acute modafinil treatment effectively reversed distinct PCP-induced alterations in overt cerebral metabolism in the anterior prefrontal cortex, the retrosplenial cortex and the medial prefrontal cortex (layer 1). In the latter region, modafinil caused hypermetabolism [Dawson *et al.* 2010]. Redrobe and colleagues used the same animal model for executive functioning deficits [Redrobe *et al.* 2010]. Subchronic PCP treatment of rats induced a significant memory impairment in the novel object recognition task (NOR). A significant improvement of visual learning and recognition processing was found in modafinil treated rats.

Single-dose RCTs in humans all show significant positive results on cognitive functioning when

modafinil is given to antipsychotic-treated patients with schizophrenia.

In the crossover RCT by Turner and colleagues, 20 patients received a single dose of 200 mg modafinil and were tested 2 hours post-drug-administration for approximately 2 hours [Turner *et al.* 2004]. Modafinil significantly improved visual memory as measured by the Pattern Recognition Memory task (PRM) and tended to improve accuracy on the delayed version of this task. Modafinil also significantly improved short-term digit memory in both forward and backwards score as well as on executive functioning. Executive functioning improved significantly as measured with the ID/ED task. Spatial planning improved on the One-touch Tower of London spatial planning task (NTOL) and latency increased. This increase in latency might be explained by an impulsivity reducing effect of modafinil.

In the crossover RCT by Spence and colleagues, 19 schizophrenia patients with prominent negative symptomatology underwent functional magnetic resonance imaging (fMRI) scanning, 2 hours after administration of 100 mg modafinil, while executing a working memory task [Spence *et al.* 2005]. In the modafinil group the working memory task performance was better. This improvement in working memory task achievement was associated with significantly greater activation in the anterior cingulate cortex in the modafinil group. The anterior cingulate cortex signal and performance change was most significant in the patients receiving typical antipsychotics, which suggests that patients receiving typical antipsychotics are more likely to benefit from modafinil treatment for cognitive deficiencies than patients receiving atypical antipsychotics. The improvement of working memory performance was demonstrated in those patients with worse performance on a verbal fluency task at initial assessment.

Hunter and colleagues conducted a crossover RCT fMRI study in which they showed a greater effect of modafinil in individuals with worse pre-existing executive function in terms of left dorsolateral prefrontal cortex activation and behavioural task performance [Hunter *et al.* 2006]. The executive function was measured using the letter fluency task of the Multilingual Aphasia Examination, an executive task known to implicate the left prefrontal cortex. *Post hoc* placebo coefficient of variation was negatively

correlated with both change in activation and change in coefficient of variation. Modafinil caused an increase in dorsolateral prefrontal cortex activation during purposeful modulation of motor activity in time.

Scoriels and colleagues conducted a single-dose crossover RCT in 40 patients with first episode psychosis [Scoriels *et al.* 2011]. The modafinil dose in this study was 200 mg. Recognition of faces expressing sadness and sadness misattribution in the context of disgust recognition improved significantly in the modafinil condition. Diagnoses of the participants were not uniform: 28 patients were diagnosed with schizophrenia, 2 with schizoaffective disorder, 2 with depressive psychosis and 6 with bipolar disorder.

The modafinil addition studies with a study duration of 4 weeks or more were not able to reproduce these significant results, with the exception of the prospective cohort study of Rosenthal and Bryant [Rosenthal and Bryant, 2004]. They assessed working memory, attention and sequencing ability in 10 patients with schizophrenia. Modafinil improved cognitive function with a significant mean improvement of 1.1 on the raw score and 1.3 on the scaled score of the WAIS-III LNS after 4 weeks on modafinil addition treatment.

Sevy and colleagues could not demonstrate positive effects of modafinil addition on cognitive functioning in their RCT conducted in 24 patients [Sevy *et al.* 2005]. Their cognitive test battery assessed sustained attention and vigilance, attention and concentration, spatial working memory, nonverbal working memory, executive functioning and immediate and delayed recall.

In the RCT by Pierre and colleagues in 20 patients, no significant differences in neurocognitive test scores were found [Pierre *et al.* 2007]. In this study visual attention and task switching, verbal memory and sustained attention and vigilance were measured.

Freudenreich and coworkers conducted a RCT in 37 patients [Freudenreich *et al.* 2009]. Premorbid intelligence, sustained attention and vigilance, working memory, secondary verbal memory, visual memory, executive function, problem solving, set shifting, semantic fluency and psychomotor speed were assessed. They found no influence of modafinil on any of these cognitive domains.

The two armodafinil addition studies of Kane and colleagues and Bobo and coworkers with a duration of treatment of respectively 4 and 6 weeks, did not show significant improvement in cognitive functioning in antipsychotic-treated schizophrenia patients [Kane *et al.* 2010; Bobo *et al.* 2011]. Kane's group used the measurement and treatment research to improve cognition in schizophrenia consensus cognitive battery (MATRICS). Bobo's group also used a broad cognitive testing battery.

In conclusion, four animal model studies of cognitive deficits showed significant improvements with modafinil [Dawson *et al.* 2010; Goetghebuer and Dias, 2009; Pedersen *et al.* 2009; Redrobe *et al.* 2010]. In humans, four single-dose crossover RCTs showed significant positive effects of modafinil on executive functioning, verbal memory span, visual and working memory, spatial planning, slowing in latency, impulse control and recognition of faces expressing sadness and sadness misattribution in the context of disgust recognition [Hunter *et al.* 2006; Scoriels *et al.* 2011; Spence *et al.* 2005; Turner *et al.* 2004]. fMRI studies revealed the involvement of the dorsolateral prefrontal cortex and the anterior cingulate cortex in improvement of cognitive deficits in schizophrenia by a single-dose administration of modafinil [Spence *et al.* 2005; Hunter *et al.* 2006]. A cohort study showed improvements in working memory, attention and sequencing ability [Rosenthal and Bryant, 2004]. But none of RCTs with a longer duration of treatment considering modafinil [Freudenreich *et al.* 2009; Pierre *et al.* 2007; Sevy *et al.* 2005] and armodafinil [Bobo *et al.* 2011; Kane *et al.* 2010] could demonstrate significant improvement of cognitive functioning in patients with schizophrenia.

Weight reduction

One RCT study investigated whether or not modafinil treatment produces weight loss. A total of 20 patients were included in an 8-week study. Mean modafinil dosage was 180 mg/day. Modafinil indeed resulted in weight loss (−2.9 lb), while placebo did not (+0.8 lb), but the difference was not statistically significant [Pierre *et al.* 2007]. After this study another RCT was conducted, in which not only weight, but also heart rate, temperature and blood pressure, nutrition intake, blood glucose, insulin, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol and triglycerides were considered. A total of 35

patients on clozapine were included in an 8-week study. The mean modafinil dosage was 250 mg/day. No statistically significant results were found either. A possible benefit of modafinil for weight loss and body mass index (BMI) were found with effect sizes of 0.62 and 0.61, respectively. Mean weight loss was 0.84 kg in the modafinil group compared with a 0.01 kg weight gain in the placebo group. Nonsignificant results in favour of the modafinil group were a lower caloric intake, a decreased total cholesterol and insulin resistance measures. On the other hand HDL, LDL and triglyceride changes and glucose measures were not in favour of the modafinil group [Henderson *et al.* 2011].

The RCT of armodafinil addition in antipsychotic-treated patients with schizophrenia by Bobo and colleagues could not demonstrate clinically relevant changes from baseline in body weight and metabolic laboratory studies [Bobo *et al.* 2011].

Tolerability

Overall, modafinil was well tolerated. However, several studies report that modafinil worsened psychosis in some patients [Aggarwal *et al.* 2009; Narendan *et al.* 2002; Rosenthal and Bryant, 2004; Spence *et al.* 2005; Sevy *et al.* 2005]. One case of hypomania was reported that occurred after addition of modafinil in order to counteract the clozapine-induced sedation in a patient with schizophrenia [Ozer and Demir, 2010].

DeQuardo reported that clozapine toxicity was induced by adding 300 mg modafinil to clozapine [DeQuardo, 2002]. Remarkable is that this increase in serum level occurred 112 days after adding modafinil to clozapine. Fischer and Weiner reported a case in which clozapine levels were lowered by modafinil [Fischer and Weiner, 2008]. DeQuardo poses the inhibition by modafinil of hepatic metabolism involving isoenzyme cytochrome P450 2C19 activity [Robertson *et al.* 2000] is involved [DeQuardo, 2002]. Since clozapine is metabolized partially by isoenzyme cytochrome P450 2C19 [Baldessarini and Frankenburg, 1991], the lowering of clozapine levels after adding modafinil, as reported by Fischer and Weiner, can be explained by modafinil induction of hepatic metabolism by isoenzyme cytochrome P450 1A2 [Robertson *et al.* 2000]. Isoenzyme cytochrome P450 1A2 is also involved in the hepatic metabolism of clozapine [Pirmohamed *et al.* 1995].

Agitation, insomnia and dry mouth were mentioned as side effects observed after modafinil administration in the study of Sevy and colleagues [Sevy *et al.* 2005]. Turner and colleagues reported no effects of modafinil on systolic blood pressure, diastolic blood pressure or heart rate [Turner *et al.* 2004].

Armodafinil was also generally well tolerated in both conducted RCTs. Reported side effects of armodafinil in by schizophrenia patients included diarrhoea, headache, muscle spasms, dizziness, dry mouth, insomnia, folliculitis, hostility and restlessness [Kane *et al.* 2010]. In the RCT of Bobo and colleagues the auditory hallucinations of one patient in the armodafinil group worsened [Bobo *et al.* 2011].

Dosage

Dosages of modafinil in the studies varied from 100 to 300 mg/day. The dosages usually started at 100 mg and were raised to 200 mg if modafinil was tolerated. Mean dosages reported by the RCT of Freudenreich and colleagues was 250 mg modafinil a day [Freudenreich *et al.* 2009], and by the RCT of Pierre and colleagues was 180 mg [Pierre *et al.* 2007].

Dosages of armodafinil ranged from 50 to 200 mg/day [Bobo *et al.* 2011; Kane *et al.* 2010].

Discussion

Evidence for the use of modafinil and armodafinil as add-on therapy to antipsychotic drugs to alleviate fatigue, sleepiness and inactivity is inconclusive. One cohort study and one out of two single-dose crossover RCTs in which modafinil addition was studied could demonstrate a positive effect. All five RCTs of modafinil (3 RCTs) and armodafinil (2 RCTs) addition with a longer study duration could not demonstrate a positive effect.

With respect to cognitive disturbances, animal models of cognitive deficits show clear improvements by modafinil. In RCTs with a study duration of 4 weeks or more, however, no positive effect could be demonstrated on cognitive functioning by modafinil or armodafinil addition. Yet, four single-dose crossover RCTs on modafinil addition show significant positive effects on executive functioning, verbal memory span, visual memory, working memory, spatial planning, slowing in latency, impulse control and recognition

of faces expressing sadness and sadness misattribution in the context of disgust recognition. Moreover, a cohort study of modafinil addition shows improvements in working memory, attention and sequencing ability. fMRI studies reveal the involvement of the dorsolateral prefrontal cortex and the anterior cingulate cortex in the modafinil-induced improvement of cognitive deficits in schizophrenia.

All studies discussed in this review had small sample sizes, which makes them vulnerable for type II errors. Possibly due to the small sample sizes the positive outcomes did not reach the level of statistical significance.

Positive effects of modafinil on cognition and fatigue are best demonstrated in patients with poor pre-existing functioning. Evidence for this hypothesis is provided by research in both animal and human studies [Hunter *et al.* 2006; McFadden *et al.* 2010]. Since most studies did not exclude relatively good functioning patients, the effect of modafinil might be underestimated (ceiling effect). Whether this could also account for armodafinil is unclear.

The antipsychotic drugs used in the reviewed studies differed, even within the study populations. Modafinil and armodafinil might exert different effects when added to typical or atypical antipsychotic drugs. Modafinil may particularly improve cognitive functioning in patients using typical antipsychotic drugs [Spence *et al.* 2005], while effects of modafinil on activity and fatigue might be stronger in patients using atypical antipsychotic drugs, since atypical drugs have more sedative side effects.

Effect measurements differed between the accounted studies, which makes a comparison difficult and for some studies even impossible. Some studies use subjective measurements, others a small subset of cognitive tests, that do not cover all cognitive deficits in schizophrenia. To be able to fully assess the usefulness of modafinil and armodafinil as add-on therapy in schizophrenia, measurement instruments used to assess cognitive function have to be more uniform.

Modafinil and armodafinil dosage and duration of treatment and follow up differ widely.

The defined daily dosage of modafinil for narcolepsy is 300 mg/day. It could be that a

lower dosage causes only small effect sizes or is ineffective.

Whether modafinil and armodafinil can establish weight loss in patients with antipsychotic-induced overweight is unclear. If so, weight reduction may be caused by an increase in activity or by an unknown other mechanism. When modafinil and armodafinil produce weight loss, it would therefore be interesting to investigate whether or not weight reduction is more pronounced in inactive patients who become more active with modafinil and armodafinil than in active patients with no activity increase in response to the substance. The risk of worsening of psychotic symptoms and, in the case of clozapine use, a rise of clozapine serum levels must be taken into account when the addition of modafinil is considered.

For future research, uniformity in treatment dosage, treatment duration, antipsychotic drug and outcome measurements is recommended.

To assess effects on fatigue, sleepiness and activity-level of modafinil or armodafinil as add-on therapy to antipsychotic drug treatment in patients with schizophrenia, we would suggest an 8-week RCT in patients with high scores on the FSS with a baseline activity measurement using a wrist worn accelerometer during the week preceding and the last week of modafinil or armodafinil add-on treatment, and a baseline and 8-week measurement of FSS scores. To assess effects of modafinil or armodafinil on cognitive functioning in patients with schizophrenia, we would suggest an 8-week RCT in patients with initially high SANS scores. With baseline and 8-week assessment of cognitive functioning using a large cognitive testing battery which includes the North American Adult Reading Test (NAART), the Degraded Stimulus Continuous Performance Test (DS-CPT), the Hopkins Verbal Learning Test (HVLIT), the Faces and family pictures subtests from the Wechsler Memory Scale-III (WMS-III), the Wisconsin Card Sorting Test (WCST), the Trail-Making Test, the Letter-Number Sequencing subtest (WAIS-III), the Letter and Category Fluency (LCF) and the Grooved Pegboard model. Both in large study populations including subgroups of atypical and typical antipsychotic drug treated patients, we suggest using a study treatment regime of 200–300 mg of modafinil, or 50–200mg of armodafinil, depending on tolerability in the individual patient.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

Acknowledgements

We like to acknowledge the staff of our library department for their help.

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