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The role of eugeroics in the treatment of affective disorders

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Summary

Eugeroics are a relatively new class of wakefulness-promoting agents. The group includes adrafinil, modafinil and armodafinil. Modafinil is the most widely used and the best studied agent. Indications for the use of modafinil include the treatment of narcolepsy, shift-work sleep disorders and excessive daytime sleepiness associated with obstructive sleep apnea. Many studies show the utility of modafinil and armodafinil in the treatment of depression – both in monotherapy and as potentiation therapy if needed. Modafinil has proven to be effective in the treatment of residual symptoms of unipolar and bipolar depression such as fatigue, excessive sleepiness and some cognitive impairment. Research on armodafinil points to its effectiveness mainly in augmentation therapy of depression in the course of bipolar disorder. There are also reports on the effectiveness of eugeroics in special cases – seasonal depression, atypical depression with hyperphagia, apathy in the course of depression or as an isolated symptom, cancer-related fatigue in patients receiving chemotherapy, fatigue and excessive sleepiness in neurological diseases. Eugeroics due to their high selectivity of action in the CNS have a low addictive potential compared with other stimulants. The risk of manic switch is comparable to placebo. In general, they are well-tolerated and safe. The purpose of this paper is to review the literature on the use of eugeroics in the treatment of affective disorders.

Key words: eugeroics, modafinil, affective disorders

Introduction

Eugeroics are a group of drugs which are molecules that promote wakefulness. Adrafinil, synthesized in the mid-70s in France and used in experimental treatment of narcolepsy was a pro-molecule in this group. Modafinil is its active metabolite discovered 2 years later. It is a similar molecule, which, however, due to more promising results in animal studies has found wider use. Since the 1990s, both drugs have been consecutively introduced on the market to treat narcolepsy in France (1994), in the USA (1998) and in the UK (2002). In 2003, indications for the use of modafinil were extended to shift-work sleep disorders and excessive daytime sleepiness associated

with obstructive sleep apnea. In 2007, armodafinil – an R-enantiomer of modafinil appeared on the American market.

In addition to the originally specified indications, eugeroics were studied and introduced in the treatment of excessive sleepiness and fatigue in different medical conditions, i.a., unipolar and bipolar depression, myotonic dystrophy, ADHD, multiple sclerosis, Parkinson's disease, traumatic brain injury, cerebral palsy, post-polio syndrome, fibromyalgia, chronic fatigue syndrome, cirrhosis [1, 2]. Among non-medical indications, modafinil is used, for example, as an alternative to other psychostimulants in astronauts and soldiers, including surgeons [3, 4] who experience sleep deprivation. Armodafinil was studied for the use in fatigue caused by the change of time zones (jet lag), however, it has not been approved by the FDA (Food and Drug Administration) in this indication.

The mechanism of action of eugeroics is not fully understood, though it is known about the stimulating effects of modafinil on individual monoaminergic systems in different areas of the brain: increase in dopamine concentration in the striatum and nucleus accumbens, increase in noradrenaline concentration in the hypothalamus and serotonin concentration – in the amygdala and frontal cortex. Modafinil reduces the concentration of gamma-aminobutyric acid (GABA), which is an inhibitory neurotransmitter – this mechanism is responsible for promoting vigilance. Research on its effects on receptors and transporter systems has shown particularly important effects on the dopamine transporter (DAT) as a dopamine reuptake inhibitor (DRI). In addition, modafinil increases histamine levels in the hypothalamus, affecting the hypothalamic sleep and wakefulness system, which distinguishes it from classic stimulants such as amphetamine and methylphenidate.

Pharmacokinetics of modafinil is linear, dose – and time-dependent. Modafinil is well-absorbed from the gastrointestinal tract, achieving the highest plasma concentration after 2–4 hours post-dose and pharmacokinetic steady state up to 4 days. The elimination half-life of modafinil is approximately 14–15 hours and of the R-enantiomer of modafinil (armodafinil) is three times longer. Modafinil is metabolized mainly in the liver by the CYP3A4 subunit of cytochrome P450. It induces CYP1A2, CYP2B6 and CYP3A4 subunits, and inhibits CYP2C9 and CYP2D6. The metabolism of modafinil leads to the creation of 2 inactive metabolites: modafinil acid and modafinil sulfone. Modafinil and its metabolites are excreted through the kidneys. Adrafinil, as a modafinil precursor, has the same mechanism of action. However, it acts more slowly, requires higher doses supply due to a more complex hepatic metabolism – to modafinil and 2 above-mentioned inactive metabolites, and can potentially be more toxic.

Modafinil interacts extensively with co-administered drugs that reduce or increase its plasma levels. CYP inducers, such as carbamazepine and barbiturates, reduce modafinil plasma level. In turn, some serotonin reuptake inhibitors (fluoxetine, fluvoxamine) increase the concentration of modafinil. The effect of modafinil on the change in the concentration and efficacy of other drugs is presented in Table 1 [5].

Table 1. **Effect of modafinil on the change in the concentration and efficacy of other drugs**

Decrease in concentration	Increase in concentration
– oral contraceptives	– anticonvulsants (phenytoin, carbamazepine)
– benzodiazepines metabolized by CYP3A4 (triazolam, midazolam)	– antidepressants (tricyclics, serotonin reuptake inhibitors)
– cyclosporine	– anticoagulants (warfarin)
– some antiretrovirals (HIV protease inhibitors)	– diazepam
– statins	– propranolol
– calcium channel blockers	– omeprazole

The purpose of many studies on eugeroics was to demonstrate their usefulness in the treatment of mood and psychomotor disorders, fatigue, excessive sleepiness, and cognitive impairment.

The use of eugeroics in affective disorders – a research review

Since the occurrence of modafinil and armodafinil on the market, numerous studies on their usefulness in the treatment of unipolar an bipolar depression both from the beginning and in the treatment of some residual symptoms, were carried out. The most common residual symptoms are typical depressive symptoms, but usually less severe: depressed mood, fatigue and lack of energy, sleep and sexual disorders, anxiety or somatic symptoms (e.g., pain).

Fatigue and excessive sleepiness

Modafinil as a wakefulness-promoting agent was expected to mainly affect improvement in fatigue and lack of energy as well as excessive sleepiness. Studies described in the literature checked the usefulness of modafinil in augmentation treatment of depression with fatigue and excessive sleepiness as a drug administered from the beginning or after different periods of antidepressant and mood-stabilizing treatment alone. To assess the results, most researchers used rating scales, such as: *Hamilton Depression Rating Scale* (HAM-D) and its *Seasonal Affective Disorders Version* (SIGH-SAD), *Montgomery-Asberg Depression Rating Scale* (MADRS), *Fatigue Severity Scale* (FSS), *Brief Fatigue Inventory* (BFI), *Epworth Sleepiness Scale* (ESS), *Clinical Global Impressions Scale* (CGI), *Global Assessment of Functioning Scale* (GAF).

Since about the year 2000, studies on modafinil were limited, conducted in small groups of patients and mostly open-label. Hence, the analysis of literature by Lam et al. [6] from 2007 does not unambiguously recommend modafinil as a treatment strategy for fatigue as a residual symptom of depression and suggests the need for more double-blind, randomized, placebo-controlled trials. Nevertheless, the analysis of individual studies from before 2007 reveals similar conclusions. In most of them, the improvement in fatigue and excessive sleepiness was rapid – in the first and second

[7–9] (maximum fifth [10]) week of modafinil administration, and persisted in the following weeks. Significant improvements in the FSS and ESS scales were observed in the first weeks [7, 8, 11–13]. In the further course of therapy, the differences between modafinil and placebo became statistically insignificant about week 6 [7].

Publications starting from the year 2007 mostly concern multicentre, randomized, placebo-controlled studies on large groups of patients. The results show an important role of modafinil in improvement in terms of fatigue, comparable in unipolar an bipolar depression [14–16]. The efficacy of adjunctive modafinil was demonstrated in drug-resistant bipolar depression [17], as well as the advantage of modafinil and armodafinil over other dopaminergic stimulants (methylphenidate, lisdexamphetamine, dexamphetamine, methylamphetamine, pemoline) in both types of depression, especially in terms of effects on fatigue and excessive sleepiness and cognitive impairment [15, 18].

Atypical depression with excessive sleepiness and increased appetite

The efficacy of modafinil as monotherapy was studied in atypical depression with excessive sleepiness and increased appetite. A beneficial effect of modafinil has been reported during the 12-week open-label phase of the trial. The benefits were maintained during randomization in both groups. The authors particularly emphasized the role of modafinil in the reduction of body weight in patients with increased appetite [19].

Seasonal/winter depression

In a study of 9 patients with seasonal/winter depression, modafinil has proven to be highly effective in improving the overall functioning (measured using the SIGH-SAD, the MADRS and the HAM-D scales), and in particular vigilance in the ESS and reduction of fatigue in the FSS [20].

Major depressive disorder in somatic disorders

A large group of studies concerns the effects of modafinil on cancer-related fatigue in patients receiving chemotherapy. Conley et al. [21] studied 541 patients during chemotherapy with concomitant depression. A correlation between the severity of fatigue and the impact of modafinil on depressive symptoms was noticed – patients experiencing extreme fatigue (BFI $\geq$ 7) presented by far greater improvement in depressive symptoms.

Another important group are the patients with obstructive sleep apnea and concomitant depression or dysthymia. In a study by Krystal et al. [22] involving patients in serotonergic antidepressant monotherapy, armodafinil 200 mg daily or placebo was introduced. The authors demonstrated a significant positive impact of armodafinil on excessive sleepiness (ESS) and related improvement in overall functioning (CGI), without significant impact on depression [22].

In studies of patients with neurological disorders (Parkinson's disease – PD, multiple sclerosis – MS, post-polio syndrome – PPS, traumatic brain injury – TBI) and concomitant depression, improvements in terms of fatigue in TBI and daytime sleepiness in PD were observed. There was no therapeutic effect of modafinil on mood disorders in any of the above disorders [2].

Armodafinil in the treatment of bipolar disorder

The so far conducted multicenter, randomized controlled studies of armodafinil apply to depression in bipolar disorder type I. In augmentation armodafinil therapy (150mg daily) with already used mood-stabilizing treatment (lithium carbonate, olanzapine, valproate or risperidone), significant improvement in symptoms of major depressive disorder in the CGI and MADRS scales and in overall functioning in the GAF scale was shown. However, there were no statistically significant differences from placebo [23–26]. In the extended 6-month open-label study by the same authors on the efficacy and safety of armodafinil, further improvement in depressive symptoms and overall functioning of patients was shown [27].

Cognition disorders

Research on the effects of modafinil on cognitive functioning was conducted in different groups – healthy volunteers without sleep deprivation and patients with depression with a partial response to treatment and in remission. In a group of healthy volunteers the study by Müller et al. [3] included i.a. visuospatial and short-term maintenance of digit sequences tasks. Modafinil reduced the amount of errors in visuospatial tasks and improved short-term memory, but had no effect on attention processes [3]. In another randomized study in healthy volunteers, positive effects of modafinil on learning ability were evaluated [28]. In a pooled analysis of studies of healthy volunteers, Battleday and Brem [29] particularly emphasize the effects of modafinil on executive functions. In 35 patients with major depressive disorder with a partial response to antidepressant treatment, modafinil improved the Stroop Interference Test results, but showed no gains in other neuropsychological tests. There was no negative impact of modafinil on cognition [13]. In the latest study by Kaser et al. [30] on 60 patients with remitted depression receiving modafinil 200 mg daily, tested with a computerized neuropsychological battery CANTAB (Cambridge Neuropsychological Test Automated Battery), it has been proven that modafinil has a positive effect on working and episodic memory, but not on the planning processes and attention. In the literature, including the cited studies, the effect of modafinil on working and episodic memory was associated with noradrenergic and dopaminergic stimulation of the prefrontal cortex [3, 30, 31].

Apathy in elderly patients with depression and dementia

An increase in the dopaminergic transmission also leads to reduction of apathy. Case reports of apathy treatment with modafinil from 2007 (a patient with depression and dementia) and 2011 [32, 33] confirmed a greater effectiveness of modafinil compared with antidepressants in this disorder. Patients reported improvement of motivation and returned to their previous interests, pleasure activities and physical activity. Both articles presented elderly patients. An additional benefit of the use of modafinil in such patients is the lack of significant interactions with other medications.

Adrafinil

In the literature one can find individual reports from the 1980s till the year 2008 on adrafinil as a substance affecting cognition and behavior in animals (rodents, monkeys, Beagle dogs). Newer publications rather describe adrafinil detection methods used in forensics and sport and the use of adrafinil and its metabolites (modafinil and modafinil acid) as doping [34, 35]. To our best knowledge, there is no research on the role of adrafinil in mood disorders. Only French researchers described the positive impact of adrafinil on cognitive functioning (memory, attention and orientation) in people over the age of 50 with memory problems. However, any history of psychiatric disorders, including depression, was an exclusion criterion [36].

Table 2 shows collected results of the studies on the utility of eugeroics in the treatment of affective disorders.

Table 2. **Studies on the utility of eugeroics in the treatment of affective disorders**

Diagnosis	No.	Author/year of publication/type of the study	Symptoms	Treatment	Results/rating scales
MDD	1.	Menza et al.; 2000 [9] CRs	Fatigue and excessive sleepiness as residual symptoms	Modafinil 100–200 mg/d as augmentation therapy	Improvement in the HAM-D
	2.	DeBattista et al.; 2003 [7] Multicenter RCT	Fatigue and excessive sleepiness	Modafinil 100–400 mg/d as augmentation therapy	Improvement in the FSS and ESS, no difference from placebo in the HAM-D and the CGI-I
	3.	DeBattista et al.; 2004 [13] CS	Depressive symptoms, including fatigue, excessive sleepiness and cognitive impairment	Modafinil 100–400 mg/d as augmentation therapy	Improvement in the HAM-D, CGI-S, BDI, VASF, and the FSI, improvement in the Stroop Interference Test but not in other cognitive tests

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MDD	4.	Ninan et al.; 2004 [11] CS	Fatigue and excessive sleepiness	Modafinil 200 mg/d + SSRI	Improvement in the HAM-D, FSS and the ESS
	5.	Fava et al.; 2005 [12] Multicenter RCT	Fatigue and excessive sleepiness	Modafinil 200 mg/d + SSRI	Improvement in the HAM-D, MADRS, CGI-I, ESS, and the BFI, no difference from placebo in the FSS and the BFI (at final visits)
	6.	Vaishnavi et al.; 2006 [19] RCT	Atypical depression –excessive sleepiness, increased appetite and lack of energy	Modafinil as monotherapy	Improvement in the HAM-D, loss of weight in patients receiving modafinil, no difference from placebo in the CGI-S, BFI, ESS, FSS, and the ADDS (at final visits)
	7.	Nasr et al.; 2006 [39] CCS	Depressive symptoms, including fatigue and excessive sleepiness	Modafinil as augmentation therapy	Improvement in depressive symptoms, including fatigue and excessive sleepiness, no cases of manic switch or addiction
	8.	Fava et al.; 2007 [8] 2 RCTs analysis	Fatigue and excessive sleepiness	Modafinil 100–400 mg/d + SSRI	Improvement in the HAM-D, CGI-I, ESS, and the FSS
	9.	Dunlop et al.; 2007 [10] RCT	Fatigue and excessive sleepiness	Modafinil 200 mg/d + SSRI	Improvement in the HAM-D, no difference from placebo in the ESS
	10.	Kaser et al.; 2017 [30] RCT	Cognitive impairment in remitted depression	Modafinil 200 mg/d as augmentation therapy or monotherapy	Improvement in working and episodic memory, no difference in attention and planning
BD	11.	Menza et al.; 2000 [9] CRs	Fatigue and excessive sleepiness as residual symptoms	Modafinil 100–200 mg/d as augmentation therapy	Improvement in the HAM-D
	12.	Nasr et al.; 2006 [39] CCS	Depressive symptoms, including fatigue and excessive sleepiness	Modafinil as augmentation therapy	Improvement in depressive symptoms, including fatigue and excessive sleepiness, no cases of manic switch or addiction

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BD	13.	Frye et al.; 2007 [16] RCT	Depressive symptoms, including fatigue and excessive sleepiness	Modafinil mean dose 177 mg/d as augmentation therapy	Improvement in the IDS, greater reduction of symptoms in BD I than in BD II
	14.	Calabrese et al.; 2010 [23] Multicenter RCT	Depressive symptoms in BP I	Armodafinil 150 mg/d as augmentation in antidepressant and mood-stabilizing therapy	Improvement in the MADRS and the IDS-C30
	15.	Calabrese et al.; 2014 [24] Multicenter RCT			Improvement in the IDS-C30
	16.	Ketter et al,; 2015 [25] Multicenter RCT			Improvement in the IDS-C30 – significant differences from placebo
	17.	Frye et al.; 2015 [26] Multicenter RCT			Improvement in the IDS-C30, CGI-S and the GAF
	18.	Ketter et al.; 2016 [27] OLS (extension study)			Further improvement in depressive symptoms, safety and good tolerance of armodafinil in 6-month maintenance treatment
Seasonal/winter depression	19.	Lundt; 2004 [20] CRs (OLS)	Depressive symptoms, including fatigue and excessive sleepiness	Modafinil 100–200 mg/d as monotherapy	Improvement in the SIGH-SAD, MADRS, FSS, and the ESS
MDD in patients during ChT	20.	Conley et al.; 2016 [21] RCT	Fatigue	Modafinil 200 mg/d as monotherapy	Improvement in the CES-D, reduction of depressive symptoms in patients with extreme fatigue – BFI >=7
MDD in patients with OSA	21.	Krystal et al.; 2010 [22] RCT	Excessive daytime sleepiness	Armodafinil 200 mg/d as augmentation therapy	Improvement in the CGI-C and the ESS, improvement in sleepiness but not depression in general

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MDD/fatigue/ excessive sleepiness in neurological diseases	22.	Sheng et al.; 2013 [2] RCTs meta-analysis	Fatigue and excessive sleepiness with or without depression	Modafinil	Improvement in fatigue in TBI and in sleepiness in PD, no influence on depression in the HAM-D, BDI and the CES-D
Apathy in elderly patients	23.	Padala et al.; 2007 [32] CR	Apathy in depression and dementia	Modafinil 200 mg/d as monotherapy	Improvement in motivation, return to interests, pleasure activities and physical activity
	24.	Camargos et al.; 2011 [33] CR	Apathy, loss of motivation, interest and pleasure without depression	Modafinil 100 mg/d as monotherapy	

MDD – major depressive disorder; BD I/II – bipolar disorder type I/II; ChT – chemotherapy; OSA –obstructive sleep apnea; TBI – traumatic brain injury; PD – Parkinson's disease.

CR(s) – case report(s); RCT – randomized controlled study; CS – cohort study, CCS – case-controlled study; OLS – open-label studies

HAM-D/SIGH-SAD – Hamilton Depression Rating Scale/Seasonal Affective Disorders Version; MADRS –Montgomery-Asberg Depression Rating Scale; BDI– Beck Depression Inventory; IDS/ IDS-C30 – Inventory of Depressive Symptomatology/30-item IDS; ADDS – Atypical Depression Diagnostic Scale; CES-D – Center for Epidemiologic Studies Depression Scale; FSS – Fatigue Severity Scale; BFI – Brief Fatigue Inventory; FSI – Fatigue Symptom Inventory; VASF – Visual Analogue Scale for Fatigue; ESS – Epworth Sleepiness Scale; CGI (CGI-S/CGI-I/C) – Clinical Global Impressions Scale (CGI-I/C – improvement/change, CGI-S – severity); GAF – Global Assessment of Functioning Scale

Conclusions

The use of modafinil in the world, including in Poland, raises a number of doubts. As a consequence, the usefulness of the drug tested in research in the above-mentioned situations is not reflected in therapeutic indications registered by the EMA (European Medicines Agency) and the FDA.

Adverse effects associated with the use of eugeroics in the aforementioned literature have been reported occasionally. Mostly headaches, dizziness, nausea, dry mouth, diarrhea, and insomnia – mild to moderate, were mentioned. In general, modafinil and armodafinil were defined as well-tolerated. Between 1998 and 2007 the FDA reported 6 cases of severe cutaneous hypersensitivity reactions, including erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, and DRESS syndrome.

While using eugeroics the possibility of manic switch could seem an element of risk. In the light of the discussed studies, these concerns are not confirmed. None of them showed a relationship of eugeroics administration with sporadically occurring cases of manic, hypomanic or mixed phase switch because, if present, they were even rarer than those in the placebo group [17]. However, in the literature there are case

reports of manic episode – in a boy treated with modafinil for narcolepsy [37] and in a woman with drug-resistant depression and anhedonia in the course of bipolar disorder, where withdrawal of modafinil caused mood stabilization [38]. Given that, modafinil treatment should always be considered individually.

Another problem with the use of modafinil is fear of addiction. The cited studies highlighted the attractiveness of modafinil compared to other stimulants due to its low addictive potential. Comparisons, for example, with cocaine or amphetamine and its derivatives appear unreasonable due to the high selectivity of modafinil in the CNS (hypothalamic nuclei and the amygdala) and low dopaminergic activity in the striatum [9, 17]. Both phase switch and tolerance or addiction have not been observed even in patients with a history of substance abuse [39].

The status of modafinil in the world varies. It is a registered medicine, i.a., in dozens of European countries, in the USA, in Canada and in several Asian countries. In many countries (e.g., China, Japan, Russia) it is on the list of controlled substances alongside with amphetamine, cocaine, morphine, methylphenidate, and other stimulants. In general, it is a prescription drug registered for narcolepsy and in some countries also in shift-work sleep disorders and excessive daytime sleepiness associated with obstructive sleep apnea. According to the EMA directive from 2010, modafinil is only recommended for the treatment of narcolepsy [5]. In the light of the presented studies, eugeroics are useful in the treatment of mood disorders as monotherapy or as potentiation of antidepressant therapy. It appears that the use of modafinil in mood disorders brings the best results in short-term (up to 6 weeks) or rescue treatment. According to the authors, based on the results of research and practice, it could be possible to extend the list of indications for the use of eugeroics for those listed in Table 3.

Table 3. **Suggestions for the use of eugeroics in affective disorders**

Depressive symptoms, including residual symptoms (MDD and BD I)	Fatigue
	Lack of energy
	Excessive sleepiness
Remitted depression (MDD)	Cognitive impairment (working and episodic memory)
Atypical depression	Increased appetite
	Excessive sleepiness
Depression in somatic disorders	Fatigue (cancer during ChT, TBI)
	Excessive sleepiness (OSA, PD)
Seasonal/winter depression	
Apathy	
Patients with a history of substance addiction requiring administration of a stimulant	

MDD – major depressive disorder; BD I – bipolar disorder type I; ChT – chemotherapy; OSA – obstructive sleep apnea; TBI – traumatic brain injury; PD – Parkinson's disease.

Nevertheless, according to the principles of evidence-based medicine (EBM), eugeroics do not belong to the level I quality of evidence and level A recommendations category in these applications.

In Poland, after 10 years of modafinil presence on the market, its distribution has been withdrawn due to high price (over 1,500 PLN per month) and fruitless efforts to refund. At present, it is only possible to import modafinil preparations in individual cases, but without refund in mood disorders. In the situation of importing modafinil from Germany, the cost of a 3-month treatment is about 1,400 PLN. Patients traveling to other European countries have also the opportunity to fill Polish prescriptions at lower prices. On the other hand, frequently practiced import on one's own – for instance from the Internet – is uncertain and dangerous.

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