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LETTER TO EDITOR

Clinical and neurocognitive changes with Modafinil in obsessive-compulsive disorder: a case report

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There are limited treatment options for co-occurring sleep disorders and obsessive-compulsive disorder (OCD). We postulated that Modafinil (Provigil) [2-{(diphenylmethyl) sulfinyl acetamide}] a non-amphetamine wakefulness-promoting agent, might be of value in patients with excessive daytime sleepiness (EDS). Randomized double-blind placebo controlled depression trials have investigated the effects of modafinil co-administered with selective serotonin re-uptake inhibitors (SSRIs) and found improvement in clinical global scores and, aside from effects on sleep and mood, modafinil has exhibited cognitive enhancing effects in some subjects (Minzenberg and Carter, 2008). In a double-blind placebo-controlled crossover challenge, Turner et al. (2004) demonstrated decreased motor impulsivity as measured on laboratory tests in adult attention-deficit/hyperactivity disorder patients treated with single doses of modafinil (100 mg and 200 mg). To date, studies examining the neuropsychological effects of treatment are rare in OCD and have generally failed to show a positive effect of SSRI treatment on cognition (Nielen and den Boer 2003). In this context, we considered a new approach for treating neurocognitive impairments in treatment-resistant OCD. Modafinil's effects on clinical symptoms and on a selected range of neurocognitive functions previously reported to be impaired in OCD (Chamberlain et al. 2005) are examined. We report the case of a patient with treatment-resistant OCD and EDS treated with adjunctive modafinil.

DW is a 33 year old unemployed man with a 13-year history of aggressive obsessions, panic anxiety, low mood, and EDS. Past treatment with dothiepin, venlafaxine, and several SSRIs had produced little benefit. A primary diagnosis of SSRI-resistant, DSM-IV OCD (defined as less than 25% improvement on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) despite adequate treatment trials) was made, with DSM-IV panic disorder and DSM-IV dysthymia as subsidiary diagnoses. His sleep schedule was chaotic, with sleeping

periods during the day, though he tended to get up at 8 am irrespectively. At initiation of modafinil, DW (right-handed, no sensory impairments) had been receiving escitalopram 40 mg for at least 12 weeks being administered unchanged throughout the trial. A single morning dose of modafinil 100 mg was prescribed and increased after three weeks to 200 mg (in two divided doses), and after four weeks to 400 mg (in two divided doses). Treatment adherence was checked verbally. Clinical assessments were performed at baseline (immediately before modafinil), at one week, and at four weeks after starting modafinil, using the Epworth Sleepiness Scale (ESS) supplemented by the patient's own sleep-report, Y-BOCS, Montgomery and Åsberg Depression Rating Scale (MADRS), Sheehan Disability Scale (SDS), Clinical Global Impression Severity scale (CGIs), State-Trait Anxiety Inventory, Locus of Control Scale (LoC) as well as the National Adult Reading Test (NART). Neurocognitive assessment was performed at baseline and following four weeks of modafinil treatment (100 mg for three weeks and 200 mg for one week). Testing comprised six selected tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition, see Table 1) on a screen, positioned approximately 60 centimeters away. According to self-report, after one and four weeks' modafinil, informants had noticed marginally improved daytime drowsiness compared to baseline. On objective tests, scores on the ESS (Baseline score (BS)=20; Week 1 (W1)=22; Week 4 (W4)=18) and the Y-BOCS (BS=22; W1=21; W4=20) also marginally improved and the SDS (BS=27; W1=24; W4=22) improved by 5 points (18%) from baseline. The CGI (BS=5; W1=5; W4=5), MADRS (BS=27; W1=25; W4=28), and LoC score (BS=16; W4=15) remained relatively unchanged. In contrast, state anxiety showed a substantial worsening by 11 points (19%) by week four (state – BS=57; W4=68; trait – BS=67; W4=68). His predicted verbal IQ score was 117 assessed by the NART. After four weeks, modafinil was increased to 400 mg. After one day

at this dose DW telephoned to report he felt agitated, paranoid, and irritable and treatment was discontinued.

Table 1 Neurocognitive performance at baseline and following four weeks of modafinil treatment, including z-scores after obtaining age-matched normative data from Cambridge Cognition. The z-scores quantify the patient's score in terms of the number of standard deviations the score is from the mean of the normative data. A negative z-score represents performance below the normative mean and a positive z-score indicates a better performance.

Variable	Baseline	Age match	Week 4	Age match
Cambridge Gambling Task				
Rational decisions (%)	86	N/A	92	N/A
Points gambled (%)	49	-0.97	67	0.55
Spatial Recognition Memory				
Recognition (%)	75	-1.10	80	-0.56
Spatial Working Memory				
Between-search errors	34	-0.98	27	-0.57
Within-search errors	0	0.53	3	-0.28
Strategy	38	-1.23	36	-0.90
Intra/Extradimensional Set Shift				
Trials to criterion: intra	7	N/A	7	N/A
Trials to criterion: extra	14	-0.89	10	-0.38
Stockings of Cambridge				
Attempts 5 moves	6	0.28	7	-0.40
Initial thinking 5 moves	4260 (ms)	0.95	5936 (ms)	0.82

Subsequent thinking 5 moves	2827 (ms)	-1.39	409 (ms)	0.57
Perfect solutions	9	-0.09	7	-1.03
Affective Go/No-Go				
Total false alarms	27	N/A	11	N/A
Reaction time	570 (ms)	N/A	585 (ms)	N/A

To our knowledge, this is the first reported case of OCD treated with modafinil. Thus, although typical of resistant OCD, there was potential for confounding effects of DW's comorbid disorders on modafinil-responses. Being open-label, the trial was also subject to confounds such as rater-bias, placebo-effects, and potential learning effects on the cognitive tasks. After modafinil treatment for 4 weeks (100-200 mg), measures of OCD (Y-BOCS), EDS (ESS), and social disability (SDS) showed small but non-substantial improvements, whereas depression (MADRS) and clinical global impression of illness severity (CGIs) failed to change, and state anxiety substantially increased. In view of the treatment-resistant nature of this case, and the short exposure to modafinil compared to conventional treatment trials, the small clinical changes in OCD symptoms are encouraging. Despite increased state anxiety, doses of modafinil up to 200 mg were reasonably well-tolerated. State anxiety is a recognized adverse effect of modafinil at clinically-effective doses although it is unclear if this effect is dose related (Minzenberg and Carter 2008). In our patient, susceptibility to increased anxiety may have been related to the comorbid panic disorder. Interestingly, in our case, modafinil dissociated state anxiety (which worsened) from OCD (which marginally improved). This study was not designed to statistically evaluate cognitive effects of modafinil. Nonetheless, DW exhibited neurocognitive deficits at baseline compared to normative data where available on several tasks, including set-shifting and mnemonic function (spatial

recognition and spatial working memory). These deficits, in general, improved following modafinil treatment. Such 'executive' domains are thought to be subserved by dissociable prefrontal cortex neurocircuitry and modulated by monoaminergic tone (Sawaguchi and Goldman-Rakic 1991). Putative cognitive improvement contrasted with the patient's subjective impression of no improvement in alertness and a worsening of state anxiety. Randomized trials comparing modafinil (≤200 mg), both as monotherapy and combined with SSRIs, with placebo and OCD patients with normal controls are indicated to clarify how far these changes are associated with the drug (and not simply learning effects) and how specific they are for OCD.

The mechanisms by which modafinil modulates clinical and neurocognitive indices have yet to be clearly delineated (Minzenberg and Carter 2008). Nevertheless, it is suggested that since each trial on the neurocognitive tasks (CANTAB, except perhaps set shifting), seems independent of its predecessors, learning effects are obviated. Also, linking the different positive effects in the cognitive tasks to specific learning effects seem unlikely as modafinil does not generally enhance associative learning (Turner et al. 2004) although it would be presumptuous to rule out learning in situations of repeated cognitive testing. However, the selective neurocognitive improvements in response accuracy (memory, set shifting), response suppression (affective stimuli) and decision-making seem more related to selective changes in behavioural sensitivity, attention and impulse control, as mediated by modafinil treatment, rather than to general learning effects.

Recently, growing evidence from translational studies questions the role of dopamine in modafinil's behavioural effects (Eagle et al. 2007). Enhancing dopamine transmission in parallel to 5-HT and/or NA activation has been proposed as a 'triple action' method to accelerate antidepressant response (Milan 2006). Our patient was taking a stable, high dose of

SSRI. Co-administration of modafinil did not improve depressive ratings and was found to worsen anxiety, paranoia, and irritability. Moreover, co-administration of dopamimetic agents and SSRIs also significantly increased extracellular dopamine levels but reduced extracellular 5-HT in rat prefrontal cortex (Weikop et al. 2007). These findings may hold relevance for our case; conceivably, adding modafinil to an SSRI such as escitalopram increased the cortical dopamine signal and thereby improved cognition, obsessions, and compulsions, but also attenuated cortical 5-HT neurotransmission, producing increased anxiety and paranoia. Further research using monoamine receptor-specific ligands may help clarify the neurochemical mechanisms underpinning modafinil's clinical and neurocognitive effects in OCD. Findings from this case study suggest that modafinil (100-200 mg) should be investigated as a candidate add-on treatment for the neurocognitive deficits associated with OCD, which likely impede everyday functioning.

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