Novel treatment (new drug/intervention; established drug/procedure in new situation)

Apathy syndrome treated successfully with modafinil

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Summary

The treatment of apathy is often complicated and difficult. The authors present a case of apathy syndrome that was treated successfully with modafinil. An 87-year-old widowed Brazilian woman presented with loss of interest and pleasure in activities. Her level of apathy, as evaluated by the Brazilian care giver version of the apathy scale, was 25 (a score higher than 18 points is associated with an apathy syndrome). No diagnosis of depression or sleep disorder was noted. After 2 years with many different antidepressants, modafinil treatment was started at 100 mg/day. One month after the initiation of modafinil therapy, the patient reported feeling more motivation, and she also returned to her favorite physical activity, which was swimming (400 m/day). Apathy scale revealed an improvement (18 points). Actigraphic analysis was performed, and no sleep disturbances were noted before or after treatment. Modafinil may be a promising option in the treatment of apathy.

BACKGROUND

The symptom of apathy appears to be common in various medical disorders, such as dementias, Parkinson's disease, stroke, cardiovascular diseases, traumatic brain injury and others.¹ However, apathy syndrome is defined as a syndrome of primary motivational loss; that is, the loss of motivation is not attributable to emotional distress, intellectual impairment, or a diminished level of consciousness.² There are studies that propose that apathy differs from depression, affecting separate regions of the brain,³ though diminished interest, psychomotor retardation, fatigue/hypersomnia, and a lack of insight are common to both apathy and depression.⁴

The treatment of apathy is often guided by the comorbidities shown by the patient: acetylcholinesterase inhibitors are the preferred agents for use in patients with Alzheimer's disease and apathy; dopaminergic agents for patients with Parkinson's disease and apathy; and stimulating antidepressants for patients with depression and apathy.¹ Nevertheless, the treatment of apathy syndrome is difficult. Drugs such as methylphenidate⁵ and bupropion⁶ have been used for the treatment of apathy, with good results.

In this paper, we present a case of the successful treatment of apathy syndrome with the psychostimulant modafinil.

CASE PRESENTATION

An 87-year-old widowed Brazilian woman was evaluated for the first time in 2007; her husband had died 2 months previously. She was miserable and had lost her appetite. She had lost approximately 5 kg in body weight (10% of her previous weight), presented with insomnia and lack of motivation, and cried easily. She showed a loss of interest and pleasure in activities such as dining out or visiting her family. Her past medical history was remarkable for mild gastro-oesophageal reflux disease and hyperlipidaemia. Her medications included lansoprazole 30 mg/day, domperidone 20 mg/day, atorvastatin 10 mg/day, calcium

500 mg/day, and cloxazolam 2 mg at night (for 2 months). She had no history of diabetes, smoking, alcohol consumption, hypertension, thyroidopathy or psychiatric disorders. She had stopped taking physical exercise since the death of her husband. The weight loss was investigated and no significant abnormalities on gastrointestinal endoscopy or in the complete blood count and hepatic and lipid panels were shown. Levels of vitamin B12, folate and 25-OH-vitamin D were normal. The patient scored 09 on a 30-item geriatric depression scale (a score higher than 10 points is associated with depression).⁷ Despite her recent widowhood, the patient was treated with citalopram 20 mg/day and the dose of cloxazolam was decreased to 0.5 mg at night and was discontinued after one week. Two months later, her weight had not increased and she presented the same complaints. Her medication was changed to escitalopram 10 mg/day and, on evaluation at 2 months, the patient reported an improvement in appetite and had regained 2.0 kg of the lost weight. She continued to express a lack of initiative, effort, interest, and motivation, and the dose of escitalopram was increased to 20 mg/day and atorvastatin was discontinued, without improvement being shown. A new blood panel was performed and the results were normal (haematocrit=43.4%; haemoglobin=14.9 g/dl; leucocyte count=7.600 mm³; alanine transaminase=21 U/l; aspartate aminotransferase=18 U/l; creatinine=0.90 mg/dl; amylase=78 U/l; lipase=51.0 U/l; ferritin=51.0 ng/ml; thyroid-stimulating hormone=1.11 UI/ml; blood glucose=92 mg/dl; serum protein electrophoresis=normal; albumin=4.22 g/dl and globulin=2.58 g/dl; fecal occult blood test=negative; stool analysis=negative for parasites). On evaluation 1 year after first presentation, the patient had stopped using antidepressants for 3 months, without improvement in her symptoms. Venlafaxine 75 mg/day was started, and also produced no improvement in the patient's condition. Finally, 2 years later, desvenlafaxine 50 mg/day was tried, and resulted in a weak response. On that occasion, the blood level of 25-OH vitamin D was low (17.5 ng/dl; reference range: 20–56 ng/ml) and

vitamin D supplementation was started at 10,000 IU/day for 15 days.

The patient's level of apathy, as evaluated by the Brazilian care giver version of the Apathy Scale, was 25. This version has good comprehensibility, the results correlate strongly with standardised measures of apathy and functional activities of daily living, and the instrument has been validated in Portuguese. Scores range from 0 to 42, and a score higher than 18 points is associated with apathy syndrome.⁸

TREATMENT

Modafinil was started at 100 mg/day and treatment with desvenlafaxine 50 mg/day was maintained. No significant sleep disorder was observed 6 days after the start of modafinil treatment, when compared with 6 days before (actigraphic analysis). There was also no difference in the patient's score on the Epworth Sleepiness Scale before and after modafinil therapy (4 points/4 points).⁹

OUTCOME AND FOLLOW-UP

One month after initiation of modafinil, the patient reported feeling more motivation, and she had returned to her favorite physical activity, swimming (400 m/day). Family members and caregivers reported improvement in the patient's daily activities. Her score on the Apathy Scale had improved to 18 points. The patient did not report any adverse effects of modafinil and continued the treatment until 3 months later, when she forgot to buy the drug. After four weeks, the symptoms had returned. Modafinil was started again, followed by an improvement in symptoms. The patient has used modafinil for 8 months without any complications.

DISCUSSION

Apathy syndrome and depression are difficult to differentiate, and often apathy is treated as an aspect of depression. In fact, apathy may become a more prominent feature of depression in older age groups, when compared with younger patients.¹⁰ In the case reported herein, the symptoms presented did not fulfil the criteria of major depression, and the score on the depression scale was low. Separate quantification of apathy syndrome and depression can be made possible by carefully selecting rating scales.¹ In our case, we have some reason to believe that apathy is not a consequence of depression, other diseases or medications: we waited around 2 years after patient had used antidepressants without improvement, before using modafinil; although atorvastatin and clonazepam can be associated with apathy, our patient stopped using these drugs and no improvement was observed; under evaluation for 1 year, the patient stopped using antidepressants for 3 months, without improvement in apathy symptoms; moreover, vitamin D supplementation was done at 10,000 IU/day (150,000 UI) before modafinil treatment, without improvement as well.

The treatment of apathy syndrome is often complicated and difficult, and reports such as this can help in practice. Methylphenidate has been the drug used most commonly in such cases, and results in improvement in apathy, but it can precipitate agitation, sinus tachycardia, delirium, and insomnia.⁵ To our knowledge, there is only one report of

the use of modafinil in a patient with apathy syndrome: a 78-year-old man with dementia and depression who was also experiencing apathy and used 200 mg/day of modafinil with significant improvement in apathy.¹¹ Our patient did not have dementia or depression and had used many antidepressants for the treatment of her apathy without result. In fact, some studies have associated the use of antidepressants with apathy, but our patient had a period without the use of antidepressants during which her condition did not improve.¹²

Psychostimulants have been used for the treatment of fatigue, to promote alertness and wakefulness, and for the treatment of attention-deficit hyperactivity disorder (ADHD) and narcolepsy. Modafinil was approved for use in ADHD and has been reported to be useful in other disorders, such as excessive sleepiness, fatigue and impaired cognition. Modafinil reduces excessive sleepiness and the severity of illness in all three disorders for which it has been approved by the Food and Drug Administration, namely, narcolepsy, shiftwork sleep disorder, and obstructive sleep apnoea with residual excessive sleepiness despite the optimal use of continuous positive airway pressure.¹³ The mechanism of action of modafinil is not clear. Some studies suggest that its action is related to many pathways, notably the dopaminergic and GABAergic systems.¹³

Taneja and colleagues evaluated normal healthy volunteers to determine how treatment with modafinil affects mood. Modafinil, as compared with placebo, decreased the general mood scores for calmness and increased the scores for energised, concentrated, over-alert and quick-witted behaviours.¹⁴

A systematic review was conducted to evaluate the evidence that relates the use of modafinil and methylphenidate to measures of emotional, cognitive or motivational parameters, specifically mood, wakefulness, motivation, attention, concentration, memory, learning and executive functions in healthy individuals. Substantial heterogeneity was observed among studies. Modafinil had some positive, though moderate, effects in enhancing attention in individuals who were not sleep deprived. No effect was found on memory, mood or motivation.¹⁵ The authors recommended further studies of modafinil, because the demand for drugs such as modafinil has been growing as a result of the pressure exerted on people in modern societies to live and work in situations that often disregard their biological rhythms.

In the majority of the studies, the use of modafinil was well tolerated. The adverse effects cited were headache, dizziness, gastrointestinal complaints, tachycardia and palpitations, nervousness, restlessness, and sleep disturbances, and, especially in studies with non sleep-deprived individuals, insomnia.¹⁵ These effects were not observed in our patient. Maser and colleagues reported a case of orofacial dyskinesia induced by modafinil in a 74-year-old man with refractory bipolar depression who had been treated with 200 mg/day.¹⁶

Modafinil is a useful option in the treatment of apathy syndrome in the older patients. In this case, the drug was introduced at a dose of 100 mg/day, the maintenance dose was 50 mg/day, and the patient showed significant improvement. Modafinil's efficacy and safety in the treatment of apathy syndrome must be assessed in controlled studies.

Learning points

- ▶ The treatment of apathy syndrome is often complicated and difficult in older patients.
- ▶ A differential diagnosis must be made, mainly with depression.
- ▶ Modafinil may be a promising option in the treatment of apathy syndrome.

Competing interests None.

Patient consent Obtained.

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