Modafinil Therapy for Apathy in an Elderly Patient

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Apathy is the most common behavioral problem associated with Alzheimer’s dementia, affecting 70–90% of patients in various stages of dementia. It presents as lack of motivation, initiative, and persistence. Apathy has profound consequences for both patients and caregivers. The presence of apathy in Alzheimer’s dementia is linked to deficits in activities of daily living and functional decline, as well as to a greater anterior cingulate neurofibrillary tangle burden and the presence of ApoE epsilon4 allele. Apathy also serves as a behavioral marker for rapidly progressing dementia, with greater decline in cognitive, functional, and emotional impairment. Thus, prompt recognition and treatment of apathy are crucial. Apathy and depression are independent entities with some overlapping characteristics. Landes et al. identified symptoms of apathy that do not overlap with depression. Self-criticism and negative outlook for the future are common in depressed individuals, who instead show a lack of concern. Some of the overlap could be explained by involvement of the frontal subcortical circuits in both diseases. Several studies have identified patients with “pure apathy” with no depression after assessing for both conditions in a variety of illnesses.

Treatment of depression may not alleviate apathy; furthermore, some of the common treatment options for depression, such as selective serotonin-reuptake inhibitors (SSRIs), may induce apathy. Several agents, such as amantadine, amphetamine, bromocriptine, bupropion, methylphenidate, and selegiline, have been used for the treatment of apathy, with mixed results. This is the first report of use of modafinil for treatment of apathy. Modafinil is a novel vigilance-promoting agent pharmacologically distinct from stimulants. Modafinil’s increased dopaminergic transmission is thought to help alleviate apathy. Due to its relative lack of drug interactions, modafinil is a good alternative for elderly patients, who often receive multiple medications. Apathy improved significantly after treatment with modafinil in this patient. To the best of our knowledge, as of January 22, 2007, this is the first report of modafinil treatment of apathy syndrome.

CONCLUSIONS: Modafinil may be useful in treating apathy syndrome. Its role in the treatment of apathy requires further testing in clinical trials.

KEY WORDS: apathy, modafinil.


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contribution from cytochrome P450 pathways. It is a mild inhibitor of CYP2C19 and inducer of CYP1A2, 2B6, and 3A4. Due to its relative lack of drug interactions, modafinil is a good alternative for elderly patients, who often receive multiple medications.

Case Report

A 78-year-old man with a remote history of depression presented to our clinic with an increase in depressive symptoms and lack of motivation during the previous year despite being treated with the SSRI escitalopram 20 mg for the entire duration. The depressive symptoms included inability to make decisions, hopelessness, a sense of worthlessness, guilt feelings, low energy levels, weight loss, daytime sleepiness, and insomnia.

The patient scored 8 on a 15 item geriatric depression scale. In addition, over the previous 2 years, he had experienced memory problems with gradual onset but steady progression. The deficits included short-term memory, misplacement of items, repetitiveness, word finding difficulty, and disorientation. He scored 26/30 on the Folstein’s Mini-Mental State Examination (with deficits in serial 7s, recall, and copying), 10/28 on the short Blessed scale, 11/13 on long-term memory, 3/4 on abstractions, and 1/2 on judgment.

The family history was positive for Alzheimer’s dementia in his mother, who died at the age of 84 years. The patient’s medical history included skin cancer, osteoarthritis, and hypercholesterolemia. He lived with his wife of 54 years, who was very supportive of him. Reversible causes of dementia were ruled out. A computed tomography scan of his head showed moderate bilateral frontal lobe and mild cerebellar atrophy and mild bilateral periventricular white matter changes. In addition to escitalopram, he was also being treated with simvastatin 20 mg/day, salsalate 1500 mg twice daily, donepezil 10 mg/day, and buspirone 15 mg twice daily.

Escitalopram was discontinued and mirtazapine was started. On evaluation at 1 month, the patient reported improvement in appetite and had regained 3.2 kg of lost weight. He scored 5 on the 15 item geriatric depression scale. He continued to express lack of initiative and motivation. His apathy as evaluated by Marin’s apathy scale was 59. This 18 item scale assesses apathy in behavioral, cognitive, and emotional domains over the previous 4 weeks. Scores range from 18 to 72, with higher scores indicating greater apathy. Modafinil was started at 50 mg and titrated to 200 mg/day over 4 weeks.

Four weeks after initiation of modafinil, the patient reported feeling more motivation. He had taken up reading more of the mystery books that he liked, he resumed writing letters to servicemen in Iraq, and he was also noted to be spending more time with his grandchildren. Evaluation of apathy and its subdomains at 10 weeks revealed significant improvement (Table 1). The patient did not report any adverse effects with modafinil and continues to be treated with it.

Discussion

Indirect evidence suggests the role of the dopamine receptor system in the etiology of apathy. Long-length fibers of the dopamine system arising from the ventral tegmental area and projecting to the ventral striatum and prefrontal cortex have been implicated in motivation. The anterior cingulate cortex, which receives dense dopamine innervations from the ventral tegmental area, appears to be of importance in motivation and reward. Lesions of the anterior cingulate cortex have been associated with apathy and amotivation. Stimulants such as methylphenidate have been used in the treatment of apathy, further consolidating the role of the dopamine receptor system in apathy. In our patient, his response to modafinil could be explained by its dopaminergic activity.

Our patient’s resolution of depression with mirtazapine therapy was not associated with improvement in apathy. This is supported by other studies confirming that apathy and depression may be different entities needing different treatments. Furthermore, SSRIs have been noted to cause apathy; however, discontinuation of escitalopram in this case did not automatically result in resolution of apathy.

Modafinil has been used as an augmenting agent for treatment of depression with prominent symptoms of excessive sleepiness and fatigue. In a 6 week open-label study, modafinil use in combination with fluoxetine or paroxetine enhanced the symptom benefit in patients with major depressive disorder. In the same study, the onset of action of the SSRIs was enhanced with the addition of

<table>
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<th>Time</th>
<th>Apathy Evaluation Scale</th>
<th>Motivation</th>
<th>Novelty</th>
<th>Persistence</th>
<th>Geriatric Depression Scale</th>
<th>Mini-Mental State Examination</th>
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modafinil. In another study, modafinil augmentation of SSRI treatment for depression relieved excessive sleepiness, reduced fatigue, and improved mood. In that case report, modafinil was essentially used as an augmenting agent with mirtazapine. Because modafinil was not administered as monotherapy, it cannot be ruled out that some interaction between modafinil and mirtazapine could be responsible for the changes in apathy.

Although several case reports have reported improvement of apathy with dopaminergic agents, few have specifically assessed for apathy as a syndrome. Chatterjee and Fahn reported improvement of apathy in an 82-year-old patient with Parkinson’s disease. Depression was successfully treated with paroxetine, but apathy persisted. Methylphenidate was started at 5 mg twice daily and an improvement was noted within the first week. Jansen et al. reported 2 patients with chronic apathy accompanied by dementia. Methylphenidate was administered at 5 mg twice daily, resulting in one patient reporting significant improvement in apathy, while the other was unable to complete the rating scale. Our team has reported a case of successful resolution of apathy with methylphenidate independent of change in depression. The Apathy Evaluation Scale and Hamilton Depression scale were used in evaluation of the patients. Although the apathy resolved, the depression ratings were unchanged.

In this case report, we used Marin’s Apathy Evaluation Scale, which was developed specifically to assess apathy and differentiate it from depression. It is available in clinician-rated, self-rated, and informant versions. It has good internal consistency (coefficient α > 0.86) and test–retest reliability (r > 0.76). Clinician-rated and self-rated versions have been shown to differentiate apathy from depression.

No adverse reactions were reported by our patient, suggesting relative lack of drug interactions with modafinil. This makes modafinil an attractive option as an augmentation agent in elderly patients who are receiving polypharmacy. Although this patient did not experience any adverse effects, close monitoring for adverse effects is necessary in elderly patients with dementia. The most common adverse effects reported with the use of modafinil are headaches (13%), nervousness (8%), and nausea (5%) in long-term studies for the treatment of excessive daytime sleepiness associated with narcolepsy. More studies are needed in patients with dementia.

Conclusions

Apathy is a common behavioral problem that often goes undiagnosed and untreated. Modafinil may be useful in the treatment of the apathy syndrome. Relative lack of drug interactions makes this an attractive choice for patients taking multiple medications. Modafinil’s role in the treatment of apathy syndrome must be assessed in systematic studies.

References

EXTRACTO

OBJETIVO: La apatía es un trastorno común del comportamiento que a menudo es confundido con la depresión. La apatía se diferencia de la depresión en la sintomatología, presentación clínica, y opciones terapéuticas. Los inhibidores de la recapitación de serotonina, un tratamiento habitual de la depresión, pueden producir un incremento de la apatía. La apatía tiene un significativo impacto en el estatus funcional de los pacientes y en los resultados de los tratamientos. Por tanto es crucial identificar terapias específicas de la apatía. Nuestro objetivo es presentar un caso de tratamiento con éxito de un síndrome de apatía con modafinilo. En lo que alcanza nuestro conocimiento, este es la primera comunicación sobre tratamiento de síndrome de apatía con modafinilo.

RESUMEN DEL CASO: Se trata de un varón de 78 años con demencia y depresión cuya apatía no respondía a los antidepresivos. El modafinilo, un nuevo medicamento que mejora el estado de alerta, farmacológicamente diferente de los estimulantes, se empleó con éxito para tratar la apatía. La apatía se valoró utilizando la Escala de Evaluación de Apatía (Apathy Evaluation Scale) desarrollada específicamente para identificar la apatía y distinguirla de la depresión.

DISCUSIÓN: En la etiología de la apatía, están implicados los déficit en el sistema de receptores de dopamina. El aumento de la transmisión dopaminérgica que produce el modafinilo puede ayudar a aliviar la apatía. Debido a la relativa ausencia de interacciones, el modafinilo es una buena alternativa para los ancianos que a menudo reciben múltiples tratamientos. La apatía mejoró significativamente en este paciente.

CONCLUSIONES: El modafinilo puede ser útil en el tratamiento del síndrome de apatía. Para establecer su lugar en el tratamiento de la apatía, es necesario realizar ensayos clínicos al respecto.

Juan del Arco

RÉSUMÉ

OBJECTIF: L’apathie représente un trouble de comportement qui est souvent mal interprété pour la dépression. La symptomatologie, la présentation clinique, et les options thérapeutiques sont différentes pour l’apathie et la dépression. Les inhibiteurs de la recapitulation de la sérotonine, un traitement fréquemment prescrit dans la dépression, sont connus pour causer ou augmenter l’apathie. L’apathie représente un facteur important pour le patient au niveau fonctionnel et des résultats thérapeutiques. Il s’avère donc important de trouver un traitement spécifique pour l’apathie. L’objectif de cet article est de présenter un patient avec apathie qui a été traité avec le modafinil.

RÉSUMÉ DU CAS: Un homme de 78 ans avec démence et dépression chez qui l’apathie n’avait pas répondu aux antidépresseurs. Le modafinil, un psychostimulant, a été utilisé pour traiter l’apathie chez ce patient. L’échelle d’évaluation d’apathie a été utilisée pour poser un diagnostic d’apathie chez ce patient. Cette échelle a été développée spécifiquement pour différencier la dépression de l’apathie.

DISCUSSION: Des déficits au niveau du système dopaminergique sont impliqués dans l’étiologie de l’apathie. Le modafinil augmenterait la transmission dopaminergique ce qui expliquerait son action au niveau de l’apathie. Ce médicament provoque peu d’interactions médicamenteuses et représente une alternative intéressante chez les personnes âgées. Chez ce patient, l’apathie s’est nettement améliorée suite au traitement avec le modafinil.

CONCLUSIONS: Le modafinil s’avère un médicament intéressant dans le traitement de l’apathie. Des études cliniques sont nécessaires pour identifier son rôle dans le traitement de l’apathie.

Louise Mallet