Off-Label Drug Uses

Modafinil: Parkinson Disease–Related Somnolence

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This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts*, a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@ku.edu.

BACKGROUND

Excessive daytime sleepiness (EDS) is a common nonmotor symptom of Parkinson disease (PD), affecting up to 50% of patients.^{1–3} In addition, some dopaminergic medications used to treat PD have been associated with significant sleep attacks, posing potential hazards to patients during activities of daily living (eg, driving). Modafinil promotes wakefulness via improvement in dopaminergic transmission; but, unlike other psychostimulants, modafinil does not appear to affect the extrapyramidal motor system and thus may be a useful alternative in the management of excessive daytime sleepiness in PD patients.

PATIENT POPULATION

Adults with PD.

DOSAGE AND DURATION

Initial dose: 100 to 200 mg once daily in the morning or 100 mg twice daily (morning and lunch). Dose may be titrated by 100 mg weekly to effect or maximum dose: 400 mg/day (in divided doses). Treatment duration ranged from 2 to 8 weeks in controlled trials and up to 8 months in case reports.

RESULTS

The use of modafinil in the treatment of PD-related somnolence has been studied in several small

controlled trials enrolling fewer than 100 Parkinson patients, demonstrating conflicting results.^{4–7} Data from open trials and case reports suggest limited benefit.^{8–11} Several national and international guidelines state that modafinil should be considered in the management of PD-related somnolence, recognizing that evidence is conflicting with improvement noted in subjective sleep ratings but inconsistent or no benefit observed in objective sleep parameters.^{2,3,12,13} Evaluating the same published clinical data, the Scottish Intercollegiate Guidelines Network does not recommend the use of modafinil in the management of excessive daytime sleepiness.¹⁴

Guidelines

American Academy of Neurology

The American Academy of Neurology (AAN) guidelines on the management of nonmotor symptoms of PD recommend that modafinil should be considered for patients to improve subjective perception of EDS. This recommendation is based on the review of 3 controlled trials^{4–6} that demonstrated effectiveness in improving patient perception of wakefulness without actual improvement in objective sleep measurements. These guidelines also state that there is insufficient evidence to support or refute a safety benefit in patients with PD with EDS who engage in activities where sleepiness poses a potential danger (eg, driving).¹²

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American Academy of Sleep

The American Academy of Sleep (AASM) practice parameters for the treatment of narcolepsy and other hypersomnias of central origins recommend that the use of modafinil may be effective in the treatment of EDS due to PD based on conflicting data from 3 trials^{4,6,8} and committee consensus. This recommendation is presented as an option, defined as a patient-care strategy that reflects uncertain clinical use and implies either inconclusive or conflicting evidence or conflicting expert opinion. The conclusion on the use of modafinil was based on conflicting data regarding the impact on subjective and objective measurements of sleep.²

Parkinson Society of Canada

The Canadian guidelines on PD¹³ state that modafinil may be considered for use in hypersomnolence associated with PD. This recommendation is based on formal consensus or expert opinion. Review of conflicting data from 3 controlled trials⁴⁻⁶ was described.

European Federation of Neurological Society

The European Federation of Neurological Society (EFNS) evidence-based review of the management of PD recommends that modafinil may be added to other measures in the management of daytime somnolence and sudden onset of sleep attacks. Other management techniques include the assessment of nocturnal sleep disturbances; improvement of nocturnal sleep by reducing akinesia, tremor, and urinary frequency; recommendation to stop driving, reduce/discontinue sedative drugs; decrease dopaminergic drugs (mainly dopamine agonists); and consider a switch to other dopamine agonists as all dopaminergic drugs may induce daytime somnolence. The addition of other wake-promoting agents such as methylphenidate may be also considered.³

Scottish Intercollegiate Guidelines Network

The Scottish Intercollegiate Guidelines Network (SIGN) guidelines regarding the management of PD suggest that the treatment of excessive daytime sleepiness should focus on the determination of a reversible factor (eg, depression, poor sleep hygiene, drugs). Based on the data from 3 controlled trials,⁴⁻⁶ the guidelines did not recommend the use of modafinil in the management of EDS. It should be noted that the same trials were evaluated in other clinical guidelines.

Controlled Trials

An additional controlled trial has been published after most guidelines were issued. A small double-blinded, placebo-controlled trial evaluated the effect of modafinil on PD-related fatigue in 19 adult patients and also included somnolence measurements in its methodology. Patients received either modafinil (100 mg twice daily) or placebo for 2 months. Fatigue was measured via alternate finger tapping, Multidimensional Fatigue Inventory scale, depression scale, and Epworth Sleepiness Scale (ESS). Three subjects in the modafinil group withdrew due to adverse events (hematuria, memory loss, loss of balance, urinary frequency, soft stool and flatulence, early awakening) and were not included in the analysis. At the end of 2 months, individuals had a significantly higher tapping frequency than they did at baseline (185 vs 197 strikes/min; $P < .05$). They also had less fatigability in finger tapping and lower but not significant reduction in ESS scores (8.3 vs 6.0; $P < .12$). The authors concluded that although physical fatigability may be improved, objective measurements of symptoms may not be affected.⁷

Noncontrolled Trial

An additional open-label trial has been published after most guidelines were issued. In an open-label trial, 10 institutionalized elderly patients (at least 70 years old; mean age: 79.7 years) with PD and EDS received modafinil for 3 weeks. Initial doses were 100 mg in the morning for 1 week followed by 100 mg twice daily (morning and lunch) for the next 2 weeks. All patients had a greater than 10 score on the ESS. The mean ESS scores at 3 weeks was significantly reduced when compared to baseline levels (10.6 vs 12.7, respectively; $P < .001$). Global assessment scores and appetite were also improved. No adverse events or changes in weight were observed.⁹

SAFETY

This is a limited safety profile. Refer to package labeling for complete prescribing information (eg, Warnings/Precautions, Adverse Reactions, Drug Interactions).

Adverse events related to modafinil therapy have been headache, dry mouth, dizziness, back pain, and generalized pruritus. In some reports, symptoms have decreased when dosages were reduced.⁸

Guidelines have noted that the benefit risk ratio for the use of modafinil in the management of PD-related EDS is not well documented because of the small numbers of patients treated in published trials.²

THERAPY CONSIDERATIONS

The use of modafinil in the treatment of PD-related somnolence has been studied in controlled and noncontrolled settings with conflicting results. Several national and international guidelines recommend that modafinil should be considered in the management of PD-related somnolence, recognizing that evidence is conflicting with improvement noted in subjective sleep ratings but inconsistent or no benefit observed in objective sleep parameters. Evaluating the same published clinical data, the SIGN does not recommend the use of modafinil in the management of PD-related excessive daytime sleepiness.

REFERENCES

1. Knie B, Mitra MT, Logishetty K, Chaudhuri KR. Excessive daytime sleepiness in patients with Parkinson's disease. *CNS Drugs*. 2011; 25(3):203-212.
2. Morgenthaler TI, Kapur VK, Brown T, et al; Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep*. 2007;30(12):1705-1711.
3. Ferreira JJ, Katzenschlager R, Bloem BR, et al. Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson's disease. *Eur J Neurol*. 2013;20(1):5-15.
4. Hogl B, Saletu M, Brandauer E, et al. Modafinil for the treatment of daytime sleepiness in Parkinson's disease: A double-blind, randomized, crossover, placebo-controlled polygraphic trial. *Sleep*. 2002;25:905-909.
5. Adler CH, Caviness JN, Hentz JG, Lind M, Tiede J. Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. *Mov Disord*. 2003;18:287-293.
6. Ondo WG, Fayle R, Atassi F, Jankovic J. Modafinil for daytime somnolence in Parkinson's disease: Double blind, placebo controlled parallel trial. *J Neurol Neurosurg Psychiatry*. 2005; 76(12):1636-1639.
7. Lou JS, Dimitrova DM, Park BS, Johnson SC, Eaton R, Arnold G, Nutt JG. Using modafinil to treat fatigue in Parkinson disease: A double-blind, placebo-controlled pilot study. *Clin Neuropharmacol*. 2009;32(6):305-310.
8. Nieves AV, Lang AE. Treatment of excessive daytime sleepiness in patients with Parkinson's disease with modafinil. *Clin Neuropharmacol*. 2002;25:111-114.
9. Lökk J. Daytime sleepiness in elderly Parkinson's disease patients and treatment with the psychostimulant modafinil: A preliminary study. *Neuropsychiatr Dis Treat*. 2010;6:93-97.
10. Rabinstein A, Shulman LM, Weiner WJ. Modafinil for the treatment of excessive daytime sleepiness in Parkinson's disease: A case report. *Parkinsonism Relat Disord*. 2001;7:287-288.
11. Happe S, Pirker W, Sauter C, Klosch G, Zeitlhofer J. Successful treatment of excessive daytime sleepiness in Parkinson's disease with modafinil. *J Neurol*. 2001;248:632-634.
12. Zesiewicz TA, Sullivan KL, Arnulf I, Chaudhuri KR, Morgan JC, Gronseth GS, Miyasaki J, Iverson DJ, Weiner WJ; Quality Standards Subcommittee of the American Academy of Neurology. Practice Parameter: Treatment of nonmotor symptoms of Parkinson disease: Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2010; 74(11):924-931.
13. Grimes D, Gordon J, Snelgrove B, et al; Canadian Neurological Sciences Federation. Canadian guidelines on Parkinson's disease. *Can J Neurol Sci*. 2012;39(4 Suppl 4):S1-30.
14. Scottish Intercollegiate Guidelines Network. *Diagnosis and Pharmacological Management of Parkinson's Disease. A National Clinical Guideline*. Edinburgh: SIGN; January 2010. ■