Excessive daytime sleepiness in Parkinson’s disease: modafinil

Evidence summary: unlicensed or off-label medicine
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Key points from the evidence

Summary

Limited evidence from 4 small, short duration randomised controlled trials (RCTs; total n=89) found a statistically significant reduction in daytime sleepiness with modafinil treatment in people with Parkinson’s disease (PD) in 3 of these studies compared to placebo.

The NICE guideline on PD which was published in 2006 and is currently being updated, recommends that modafinil may be considered for excessive daytime sleepiness in people with PD. This was based on 3 of the RCTs included in this evidence summary. Since the guideline was published, it has become apparent that modafinil is associated with serious psychiatric, cardiovascular and skin adverse effects. In 2010 a safety review by the European Medicines Agency (EMA) concluded that the benefits of modafinil outweighed the risks only in the treatment of narcolepsy.

Regulatory status: off-label. This topic was prioritised because there was a high volume of requests from the NHS.
### Effectiveness

- In 2 RCTs (total n=36), 2 or 3 weeks' treatment with modafinil statistically significantly improved daytime sleepiness compared with placebo, measured using the Epworth Sleepiness Scale (ESS) score.

- Another RCT (n=40) found no statistically significant difference in improvement in ESS score after 2 weeks' treatment with modafinil compared with placebo.

- In an RCT (n=13) that focused on fatigue in PD, modafinil statistically significantly improved ESS score from baseline to week 9, but there was no statistically significant difference from baseline in the placebo group.

### Safety

- Modafinil is associated with serious psychiatric, cardiovascular and skin adverse effects; prescribers should consult the summaries of product characteristics for details of monitoring requirements.

- Following a safety review by the EMA in 2010, the licensed indications were restricted to narcolepsy only, because the benefits in the other licensed indications (treatment of excessive sleepiness in people with sleep apnoea and chronic shift work sleep disorder) were not judged to outweigh the risks.

- In addition to these adverse effects, the summaries of product characteristics for modafinil note that common adverse effects (occurring in 1–10 per 100 people) include decreased appetite, diarrhoea, nausea, anxiety, back pain, dizziness and insomnia. Headache is reported as a very common adverse event (occurring in 10 per 100 people or more).

- Some people in the RCTs included in this evidence summary experienced dizziness, diarrhoea or insomnia, but the studies were too small and of too short duration to give reliable evidence on the safety of modafinil in people with PD.

### Patient factors

- The long-term risks and benefits of modafinil for hypersomnolence in PD are not known.

- There are a limited number of treatment options for people with PD and associated excessive daytime sleepiness.

### Resource implications

- Modafinil costs between £8.69 (100 mg once daily) and £50.18 (200 mg twice daily) for 28 days treatment.
Introduction and current guidance

Parkinson's disease (PD) is a progressive neurodegenerative condition with motor and non-motor symptoms. Excessive daytime sleepiness (hypersomnolence) has been recognised as a major issue for people with PD and may have serious consequences for a person's social functioning and safety.

Specialists involved in the production of this evidence summary have suggested that excessive daytime sleepiness is often secondary to the drug treatment of Parkinson's disease, including dopamine agonists or levodopa. Recent changes to drug therapy or dose should be considered as a possible precipitant for new onset excessive daytime sleepiness. This should be assessed before considering drug interventions.

The NICE guideline on Parkinson's disease recommends that modafinil may be considered for daytime hypersomnolence in people with Parkinson's disease. This guideline is being updated, anticipated publication date April 2017.

Product overview

Modafinil is a wakefulness-promoting agent. Modafinil is licensed for the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy.

Modafinil is not licensed for treating excessive daytime sleepiness in PD and so use for this indication is off-label.

Evidence review

This evidence summary is based on the best available evidence on the use of modafinil to treat excessive daytime sleepiness in people with PD. This consists of the 3 small, short duration (4 weeks or less), placebo-controlled RCTs that informed the NICE guidance on Parkinson's disease (Adler et al. 2003, Högl et al. 2002 and Ondo et al. 2005). Another small RCT, published after the NICE guideline, focused on fatigue in PD but also reported on daytime sleepiness (Tyne et al. 2010). Recommendations from the MHRA regarding the safety of modafinil, published after the NICE guideline, are also considered.
In all the RCTs discussed in this evidence summary, daytime sleepiness was measured using the Epworth Sleepiness Scale (ESS). This self-administered questionnaire asks the person to rate the chances that they would doze or fall asleep in 8 everyday situations. The possible score ranges from 0 to 24, with a higher score signifying more sleepiness.

Of the 3 RCTs in which the effect of modafinil on excessive daytime sleepiness was the primary outcome, 2 found that modafinil 200 mg daily statistically significantly improved ESS score compared with placebo (Adler et al. 2003 and Högl et al. 2002, n=36 in total, mean improvements of 4.4 points and 2.6 points respectively). The other RCT (Ondo et al. 2005) found no statistically significant difference between modafinil 200 to 400 mg daily and placebo in change in ESS score (n=40, p=0.28). None of the studies found statistically significant differences between modafinil and placebo for any of the secondary end points, including objective measures of daytime sleepiness.

In a small, 9-week, double-blind RCT (n=13), people with fatigue associated with PD were randomised to modafinil (titrated up to 400 mg daily) or placebo (Tyne et al. 2010). The primary outcome measured in the trial was change in fatigue. Sleepiness was included as a secondary end point and assessed using the ESS score. In the modafinil group the ESS score improved by a statistically significantly amount from baseline to week 9 (median score reducing from 18 to 9, p=0.046), while the median score remained unchanged from baseline in the placebo group.

There are some important limitations to the RCTs described in this evidence summary. All were short in duration, with small numbers of participants which may have affected their statistical power to detect differences between groups. Modafinil has not been directly compared to other active treatments for excessive daytime sleepiness in PD.

Modafinil is associated with serious skin reactions (Stevens Johnson Syndrome, erythema multiforme, and toxic epidermal necrolysis), psychiatric reactions (suicidal ideation, hallucinations, delusion, aggression, psychosis, and mania) and is not recommended in people with uncontrolled hypertension or cardiac arrhythmias. A baseline electrocardiogram should be done before treatment initiation and cardiovascular function, especially blood pressure and heart rate, should be monitored regularly.

The summaries of product characteristics for modafinil state that aggression and suicidal ideation are uncommon adverse events (occurring in 1 to 10 per 1000 people). Hallucinations, psychosis and mania are rare adverse events (occurring in 1 to 10 per 10,000). The frequency of delusions, Stevens Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis cannot be estimated from the available data.
• Following an EMA safety review in 2010, the licensed indications were restricted to narcolepsy only, because the benefits in the other licensed indications (treatment of excessive sleepiness in people with sleep apnoea and chronic shift work sleep disorder) were not judged to outweigh the risks.

• The summaries of product characteristics for modafinil note that common adverse effects (occurring in 1–10 per 100 people) include decreased appetite, diarrhoea, nausea, anxiety, back pain, dizziness and insomnia. Headache is reported as a very common adverse event (occurring in 10 per 100 people or more).

• There were a limited number of adverse events reported in the trials discussed in this evidence summary, but this may be partially due to the short duration of the trials and the small numbers of participants.

Full text of evidence review.

Context and estimated impact for the NHS

The 28-day cost (excluding VAT) of modafinil ranges from £8.69 (100 mg daily) to £50.18 (200 mg twice daily) [prices taken from Drug Tariff September 2015].

Full text of context and estimated impact for the NHS.

Information for the public

A plain English summary is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with excessive daytime sleepiness associated with Parkinson's disease who are thinking about trying modafinil.
About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, but this summary is not NICE guidance.

Full evidence summary

Introduction and current guidance

The NICE guideline on Parkinson's disease (PD) was published in 2006 and is currently being updated (anticipated publication date April 2017). The guideline describes PD as a progressive neurodegenerative condition resulting from the death of the dopamine-containing cells of the substantia nigra region of the brain. Although predominantly a movement disorder, the spectrum of PD includes many non-motor problems, including sleep disturbance, which can have a major impact on quality of life.

Excessive daytime sleepiness (hypersomnolence) has been recognised as a major issue for people with PD. Excessive daytime sleepiness is defined as the inability to stay alert and awake during the major waking episodes of the day, resulting in unintended lapses into sleep (Thorpy 2012). Excessive daytime sleepiness should not be confused with fatigue, a distinct symptom discussed in some trials included in this evidence summary. Fatigue has been described as an overwhelming sense of tiredness, a lack of energy and a feeling of exhaustion (Parkinson's UK). People with excessive daytime sleepiness may fall asleep at inappropriate times during the day; whereas people with fatigue need to rest but do not generally drop off to sleep (Parkinson's UK). The relationship between sleepiness and fatigue is not well understood. Excessive daytime sleepiness may have serious consequences for a person's social functioning and safety.

Specialists involved in the production of this evidence summary have suggested that excessive daytime sleepiness is often secondary to the drug treatment of Parkinson's disease, including
dopamine agonists or levodopa. Recent changes to drug therapy or dose should be considered as a possible precipitant for new onset excessive daytime sleepiness. This should be assessed before considering drug interventions.

The NICE guideline on Parkinson's disease recommends that modafinil may be considered for excessive daytime sleepiness in people with PD.

The NICE pathway on Parkinson's disease brings together all related NICE guidance and associated products on this condition in a set of interactive topic-based diagrams.

**Product overview**

**Drug action**

Modafinil is a wakefulness-promoting agent. The precise mechanism of action of modafinil is unknown ([Modafinil Provigil 100 mg tablets summary of product characteristics](https://www.medicines.org.uk/emc/medicine/5837)).

**Regulatory status**

Modafinil is licensed for the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy ([Modafinil Provigil 100 mg tablets summary of product characteristics](https://www.medicines.org.uk/emc/medicine/5837)).

At the time the NICE guideline on Parkinson's disease was published in 2006, modafinil was also licensed for treating excessive sleepiness associated with obstructive sleep apnoea or chronic shift work sleep disorder. Since the guideline was published, it has become apparent that modafinil is associated with serious psychiatric, cardiovascular and skin adverse effects. In 2010 the EMA concluded that the benefits of modafinil outweighed the risks only in the treatment of narcolepsy, and the other licensed indications were withdrawn from modafinil's marketing authorisations ([MHRA Drug Safety Update March 2011](https://www.mhra.gov.uk/drug-safety-update/modafinil)). This is discussed further in the safety and tolerability section of the evidence review.

Modafinil is not licensed for treating excessive daytime sleepiness in PD and so its use for this indication is off-label.

NICE has published an evidence summary on another off-label use of modafinil: Fatigue in multiple sclerosis: modafinil (ESUOM 9).
In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using modafinil outside its authorised indications.

Cost

The 28-day cost (excluding VAT) of modafinil ranges from £8.69 (100 mg daily) to £50.18 (200 mg twice daily) [prices taken from Drug Tariff September 2015].

Evidence review

This evidence summary is based on the best available evidence on the use of modafinil to treat excessive daytime sleepiness in people with PD.

The NICE guideline on Parkinson's disease (published 2006) recommends that modafinil may be considered for daytime hypersomnia in people with PD. This recommendation was based on 3 small, short duration, placebo-controlled, double-blind randomised controlled trials (RCTs) and took account of the conditions for which modafinil was licensed at the time. Since the guideline was published, a further small RCT has been published that focused on fatigue in PD but also reported on sleepiness (Tyne et al. 2010). In addition, a safety review by the European Medicines Agency has led to a narrowing of the licensed indications for modafinil and additional warnings about its safety.

Clinical effectiveness

In all the RCTs discussed in this evidence summary, daytime sleepiness was measured using the Epworth Sleepiness Scale (ESS). This is a self-administered questionnaire that asks the subject to rate the chances that they would doze off or fall asleep when in 8 different situations commonly encountered in daily life. The possible score ranges from 0 to 24, with higher score signifying more sleepiness. There is no published minimal clinically important difference for ESS. In the ESS definition study (n=180), which did not include anyone with Parkinson's disease, the modal score in control participants (n=30) was 6, with scores ranging from 2 to 10. All participants with either narcolepsy or idiopathic hypersomnia had higher ESS scores than the controls (that is, greater than 10) (Johns 1991).

The 3 studies considered in the NICE guideline (Adler et al. 2003, Högl et al. 2002 and Ondo et al. 2005) were all small (n= 21, 15 and 40, respectively) and of short duration (3 weeks, 2 x 2 weeks placebo/modafinil in a crossover design and 4 weeks respectively). The mean age of the participants in all the studies was 65 years.
In the study by Adler et al. (2003), modafinil 200 mg daily for 3 weeks produced a statistically significant improvement in ESS compared with placebo. The mean ESS score in the modafinil group decreased by 3.4 points from a baseline of 17.8, whereas the mean score in the placebo group increased by 1.0 points from a baseline of 16.0 (mean difference −4.4, 95% confidence interval [CI] −8.6 to −0.2, p=0.039).

In the study by Högl et al. (2002), modafinil 100 mg daily for 1 week followed by 200 mg daily for 1 week also produced a statistically significant improvement in ESS compared with placebo. The mean ESS score in the modafinil group decreased by 3.4 points from a baseline of 13.2, whereas the mean score in the placebo group decreased by 0.8 points from a baseline of 11.8 (mean difference −2.6, p=0.011). There was no statistically significant difference between modafinil and placebo for any of the secondary end points used in Adler et al. (2003) and Högl et al. (2002), including objective measures of daytime sleepiness.

In the study by Ondo et al. (2005), modafinil 100 mg twice daily for 1 week followed by 200 mg twice daily for 3 weeks did not produce a statistically significant improvement in ESS compared with placebo. The mean ESS score in the modafinil group decreased by 2.7 points from a baseline of 15.7, whereas the mean score in the placebo group decreased by 1.5 points from a baseline of 16.0 (mean difference −1.2, p=0.28).

The full NICE guidance published in 2006 stated that while there was little evidence from RCTs of the efficacy and safety of modafinil in the treatment of daytime hypersomnolence in PD, at that time it had a product licence for use in hypersomnolence in chronic diseases. Members of the guideline development group had little experience in its use but acknowledged that modafinil can be useful in PD. At the time the NICE guideline was developed (2006) modafinil was licensed for the treatment of excessive sleepiness associated with narcolepsy, sleep apnoea and chronic shift work disorder. Following a safety review in 2010, the licensed indications for modafinil were limited to use in narcolepsy only (see section on regulatory status).

Since the NICE guideline was published, only 1 RCT has been published that reported on the effects of modafinil in people with PD and excessive daytime sleepiness (Tyne et al. 2010). The primary aim of this small double-blind, placebo-controlled RCT (n=13) was to examine the effects of modafinil on fatigue in people with PD. Sleepiness was included as a secondary end point and assessed using the ESS score. Although not an inclusion criterion, the median ESS scores at baseline (18 in the modafinil group [n=6]; 16 in the placebo group [n=7]) suggest that many of the participants had excessive daytime sleepiness. The mean age in the modafinil group (n=6) was 57 years, the mean age in the placebo group (n=7) was 61 years. The modafinil dose was increased to a maximum of 400 mg daily in increments of 100 mg each week, followed by a 5 week maintenance phase. The
mean daily modafinil dose taken by participants was not reported. The study found that in the modafinil group the ESS score was statistically significantly improved from baseline to week 9 (median score reducing from 18 to 9, \( p=0.046 \)), with no statistically significant difference observed in the placebo group (median ESS score remained at 16 from baseline to week 9).

All 4 studies recorded severity of PD using the Unified Parkinson's Disease Rating Scale (UPDRS). None of the studies reported a statistically significantly difference in UPDRS score for modafinil compared with placebo, with Adler et al. 2002 and Ondo et al. 2005 specifically reporting no difference in the motor components of UPDRS. All studies were of short duration and the long-term effect on motor symptoms is not known.

Safety and tolerability

Adverse events reported in clinical trials

Adverse events reported by participants taking modafinil in the 3 RCTs included in the NICE guideline on Parkinson's disease (Ondo et al. 2005, Adler et al. 2003 and Högl et al. 2002) included dizziness, insomnia and diarrhoea (all \( n=2 \)). In Tyne et al. 2010 adverse events reported in the modafinil group included common cold (\( n=2 \)), musculoskeletal back pain (\( n=1 \)), gastroenteritis (\( n=1 \)), anxiety (\( n=1 \)), headache (\( n=1 \)), increased blood pressure (\( n=1 \)), perioral herpes simplex (\( n=1 \)) and dry skin (\( n=1 \)).

Warning of potential serious adverse effects

In 2008, the MHRA issued a warning to prescribers about the risk of serious skin reactions (Stevens Johnson Syndrome, erythema multiforme, and toxic epidermal necrolysis) and psychiatric reactions (suicidal ideation, hallucinations, delusions, aggression, psychosis, and mania, mainly, but not exclusively, in patients with a history of psychosis, depression, or mania) in people taking modafinil.

The summaries of product characteristics for modafinil state that aggression and suicidal ideation are uncommon adverse events (occurring in 1 to 10 per 1000 people). Hallucinations, psychosis and mania are rare adverse events (occurring in 1 to 10 per 10,000). The frequency of delusions, Stevens Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis cannot be estimated from the available data.

Further to this, and following a review by the Pharmacovigilance Working Party of the Committee for Medicinal Products for Human Use (CHMP) in January 2011, the European Medicines Agency
published a statement to say that as the result of the review, the CHMP had concluded that the benefits of modafinil continue to outweigh their risks only when used for treating narcolepsy.

As a result of the EMA's review, the MHRA issued further information and advice to support the safer use of modafinil in people with narcolepsy. Modafinil is not recommended in people with uncontrolled hypertension or cardiac arrhythmias: a baseline electrocardiogram should be done before treatment initiation and cardiovascular function, especially blood pressure and heart rate, should be monitored regularly. Modafinil should be discontinued in people who develop arrhythmia or moderate to severe hypertension, and should not be restarted until the condition has been adequately evaluated and treated. Modafinil should be used with caution in patients with a history of psychosis, depression, or mania; or abuse of alcohol, drugs, or illicit substances. Such people should be monitored closely and advised to report any suspected adverse behaviours or thoughts. They should be assessed immediately and treatment stopped if appropriate. This reiterates the MHRA's previous advice about the risk of psychiatric adverse effects, and is in addition to its advice that modafinil should be discontinued at the first sign of rash and not restarted.

In addition to these adverse effects, the summaries of product characteristics for modafinil note that common adverse effects (occurring in 1–10 per 100 people) include decreased appetite, nervousness, insomnia, anxiety, depression, abnormal thinking, confusion, irritability, dizziness, somnolence, asthenia, paraesthesia, blurred vision, tachycardia, palpitations, chest pain, abdominal pain, dry mouth, dyspepsia, constipation, diarrhoea and nausea. Headache is reported as a very common adverse event (occurring in 10 per 100 people or more).

**Evidence strengths and limitations**

Limited quality evidence was found that investigated the efficacy and safety of modafinil for excessive daytime sleepiness in people with PD. Only 3 small RCTs were identified in which this was the primary focus, and these studies have limitations and gave conflicting results on the efficacy of modafinil. One further RCT was identified that reported on sleepiness in people with PD, but the primary focus of this trial was fatigue (with no statistically significant difference in the primary outcome), meaning these results should be considered exploratory.

All the studies discussed in the evidence summary used the same scale for recording excessive daytime sleepiness, the ESS. The clinical relevance of any improvements in ESS score reported in the trials is not clear, as a minimal clinically important difference in ESS has not been defined.
The 4 RCTs included in this evidence summary were small (n= 13 to 40) which may have affected the statistical power of the studies to detect differences between treatment groups. Only 1 of these RCTs reported a power calculation (Ondo et al. 2005).

All studies had a short duration (less than 9 weeks), making it difficult to assess the benefits of treatment in this chronic condition; any longer term treatment effects or adverse events could not be assessed. All studies were placebo controlled; modafinil has not been directly compared to other active treatments for excessive daytime sleepiness in PD.

Although dose adjustment was permitted in 2 RCTs (Ondo et al. 2005 and Tyne et al. 2010) the authors did not report on the mean dose that participants received, making it difficult to determine the most effective dose used.

Participants in 3 RCTs (Högl et al. 2002, Adler et al. 2003 and Ondo et al. 2005) who did not attend follow-up appointment were excluding from efficacy analysis, with approximately 10% of participants dropping out the studies. This may have biased the results, especially as the study populations were so small.

**Context and estimated impact for the NHS**

**Cost effectiveness**

No studies assessing the cost effectiveness of modafinil for excessive daytime sleepiness in PD were identified. No alternative treatments were identified.

**Current drug usage**

The NHS prescription cost analysis for England 2014 reports that approximately 74,600 community prescriptions for modafinil were dispensed in 2014, costing around £5,942,700 (net ingredient cost). The indications for these prescriptions are not provided. These data do not include hospital prescriptions.

**Information for the public**

A plain English summary is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with daytime hypersomnolence in Parkinson's disease who are thinking about trying modafinil.
Relevance to NICE guidance programmes

This use of modafinil is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

NICE has issued a clinical guideline on Parkinson's disease: diagnosis and management in primary and secondary care which is currently being updated, anticipated publication date April 2017.

References


Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

Dr Tyne has received travel and subsistence expenses from Lundbeck and Teva in the last 12 months

About this evidence summary

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