Bulletin 113 | October 2015

PrescQIPP Community Interest Company

Modafinil: Restrictions on indications and evidence for off-label uses

Almost £2.7 million is spent annually on modafinil in England (ePACT February to April 2015). QIPP projects in this area focus on reducing prescribing of modafinil for cost and safety reasons. This is by adhering to licensed indications and current guidance.

Recommendations

- Limit prescribing of modafinil to the treatment of excessive sleepiness associated with narcolepsy in adults, with or without cataplexy (the only licensed indication in the UK).[1] This is due to lack of evidence on safety and efficacy in other (off-label) conditions.
- Only prescribe modafinil in patients where a diagnosis of narcolepsy has been made by a specialist in accordance with diagnostic criteria. Prescribing according to an agreed shared care guideline (SCG) is advised – a locally adaptable PrescQIPP SCG template is available at: http://www.prescqipp.info/resources/viewcategory/383-modafinil
- Review modafinil prescribing and monitor for the potential risk of serious adverse drug reactions (ADRs), for example: cardiovascular (CV) symptoms (hypertension and cardiac arrhythmias), psychiatric disorders (suicidal-ideation, mania and hallucinations), skin and multi-organ hypersensitivity reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis).[2]
- Review inappropriate off-label prescribing for:
  - Fatigue in Multiple Sclerosis (MS),[2,3] Parkinson's disease (PD),[4-6] depression,[4] post-stroke[7] and lung cancer[8]
  - Apathy in Alzheimer's disease[9]
  - Adjunctive therapy in schizophrenia[10]
  - Management of Attention Deficit Hyperactivity Disorder (ADHD)[4,11]
  - Misuse (cognitive enhancement)[12]
  - Chronic fatigue syndrome.[4]
- The General Medical Council (GMC) good practice in prescribing guidance states that doctors should be satisfied there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy, taking full responsibility for prescribing an unlicensed medicine (including off-label use), for overseeing the patient's care, monitoring plus any follow-up treatment.[13]
- Manage fatigue in MS by assessing and offering treatment for anxiety, depression and difficulty in sleeping. Evaluate potentially contributing co-existing medical problems, such as anaemia or thyroid disease. Consider mindfulness-based training, cognitive behavioural therapy (CBT) or fatigue management. Advise people that aerobic, balance and stretching exercises including yoga may be helpful.[14]
- Check for reversible causes of fatigue in PD such as depression, poor sleep hygiene and drugs associated with altered sleep pattern.[5] For sleep disturbance at night, review all medications and avoid (where possible) any drugs that may affect sleep or alertness, or may interact with other medication (e.g. selegiline, antihistamines, H_2 antagonists, antipsychotics and sedatives).[6]

Background

Modafinil was first marketed in Europe in 1992 as an oral 'wakefulness-promoting' agent acting on the central nervous system (CNS).[1,15] Its precise mode of action is unknown, but involvement of dopamine and norepinephrine is most likely.[2,15] Modafinil is only indicated for the treatment of excessive sleepiness in adults with narcolepsy, with or without cataplexy.[1]

Modafinil can cause serious adverse effects including psychiatric disorders (such as suicidal-ideation, mania and hallucinations) cardiovascular symptoms (such as hypertension and cardiac arrhythmias) and serious skin and multi-organ hypersensitivity reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis). In January 2011, the European Medicines Agency (EMA) concluded that benefits of modafinil only outweighed risks when used to treat narcolepsy. They asked manufacturers to implement measures to minimise risks: informing healthcare professionals of latest product information changes, setting-up studies investigating cardiovascular and dermatological safety of modafinil. The EMA noted that modafinil was often used for non-indicated conditions (off-label use), so asked those companies to carry out further studies including a 'drug utilisation study' to investigate why GPs prescribe modafinil.[15]

National guidance

The EMA found that risks outweighed benefits in clinical trials for all indications other than narcolepsy, so concluded that these should be withdrawn from the marketing authorisations.[15] Therefore modafinil should no longer be used to treat excessive sleepiness from:

- Obstructive sleep apnoea[15,16]
- Shift-work sleep disorder[15,16]
- Idiopathic hypersomnia.[15]

Doctors should also be aware of the safety profile of modafinil and monitor patients appropriately.[15] The MHRA advised upon contraindications, cautions for use, monitoring requirements during treatment and criteria for stopping modafinil treatment:

- **Contraindications:** uncontrolled hypertension or cardiac arrhythmias, children up to 18 years old, women who are pregnant or breastfeeding.
- **Cautions**: patients with a history of psychosis, depression, mania, abuse of alcohol, drugs or illicit substances. Monitor these patients closely and report any suspected adverse behaviours or thoughts. Assess patients immediately and stop treatment if appropriate.
- **Monitoring**: perform baseline electrocardiogram before starting treatment, with specialists further evaluating patients with abnormal findings before modafinil can be started.
- **Stopping**: modafinil is no longer indicated in shift-worker sleep disorder or obstructive sleep apnoea, these patients can stop modafinil at any time.[1] Also stop treatment if the expected outcomes are not achieved.

The NICE Clinical Knowledge Summary (CKS) does not recommend the use of modafinil in primary care for the management of chronic shift work disorder, because it is not licensed in this condition. Although modafinil has a low potential for dependence, the risk of dependence with long-term use cannot be excluded therefore it should be used with caution.[17,18] Dexamfetamine and methylphenidate are also used to treat narcolepsy, an unlicensed indication for these drugs.[18]

There is no NICE Clinical Guideline (CG) for narcolepsy. In April 2013, NICE published an 'Evidence Summary: Unlicensed or Off-label Medicine' ESUOM9: Fatigue in multiple sclerosis: modafinil (further details in evidence base section on the following page).[2]

Evidence base

Range of uses for modafinil

A Drug Safety Research Unit performed a small observational study (n=1096) using modified prescription-event monitoring in primary care from July 2004 to August 2005. The authors found the ten most frequent prescribing indications for modafinil.[19] These are shown in table 1 adapted from the original paper.

Table 1: Ten most frequent prescribing indications for modafinil[19]

Order of frequency	Indication	Percentage of prescribing
1	Narcolepsy	24.5%
2	Lassitude	24.2%
3	MS	13.4%
4	Obstructive sleep apnoea/hypopnoea syndrome	10.3%
5	Drowsiness	6.8%
6	Sedation	3.2%
7	Chronic fatigue syndrome	2.6%
8	PD	1.6%
9	Insomnia	1.3%
10	Shift-work sleep disorder	0.9%

The authors' conclusions were that their study provides important additional safety data on modafinil in 'real world' use, including those where the prescribing indication is outside the terms of the licence. A significant number of women of childbearing potential had not been started on appropriate contraceptives prior to starting modafinil. This resulted in three women becoming pregnant: One spontaneous abortion, followed by another pregnancy in the same woman resulting in therapeutic termination, one ectopic pregnancy, and one live birth with left lower lid entropion, which subsequently corrected itself (accidental pregnancy with modafinil stopped in the first trimester). The majority of ADRs reported within the first month of modafinil treatment had previously been documented (by manufacturers): headache/migraine, nausea/vomiting, dizziness, palpitations. Also a number of serious events, including psychosis occurred at the higher dose only. Causality assessments were performed on targeted events, confirming the potential of modafinil to induce certain types of ADRs in individual patients including cardiac and psychiatric events.[19]

The Canadian Agency for Drugs and Technologies in Health (CADTH) reviewed the clinical safety and efficacy of modafinil in 2012 for sleep disorders and fatigue secondary to MS. The review notes that modafinil has also been tested in a number of off-label conditions such as fatigue in MS, PD or depression, cocaine addiction, and attention deficit hyperactivity disorder (ADHD).[3]

Evidence for various off-label conditions

1. Fatigue in MS

A NICE ESUOM in 2013 reviewed the information for modafinil to treat fatigue in MS. Fatigue in MS may be directly related to the disease, or can be secondary to a number of non-disease factors. If fatigue is disrupting the individual's life then consider the possibility of depression, or other factors such as

chronic pain or poor nutrition. No studies were identified on the cost-effectiveness of modafinil for treating fatigue in MS. The key points from the evidence were:

- Modafinil is not licensed for treating fatigue in MS. Therefore this is an off-label use of this medication. It is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using modafinil outside of its authorised indications.
- Two small placebo-controlled randomised controlled trials (RCTs) did not find any statistically significant evidence that modafinil improved fatigue in adults with MS (of any disease pattern).
- The RCTs did not provide any evidence of longer-term safety and efficacy of modafinil for treating fatigue in MS.
- No serious adverse effects of modafinil were reported in either RCT, but common adverse effects were observed in both trials.
- No other drugs have marketing authorisation for MS-related fatigue, although off-label amantadine may also be considered.[2]

The CADTH Rapid Response Report of 2012, on clinical safety and efficacy of modafinil, focussed on sleep disorders and fatigue secondary to MS. Modafinil has a different pharmacologic profile to other stimulants used in sleep disorders, namely methylphenidate or amphetamines. No conclusions can be drawn on the efficacy of modafinil compared to methylphenidate or amphetamines due to the absence of head-to-head clinical trials. Relative to placebo, modafinil was associated with improvements in sleepiness and some domains of health-related quality of life, in patients with narcolepsy however, the clinical importance is unclear. No clear benefit was found with modafinil in patients with MS related fatigue. The available data were insufficient to draw conclusions on the safety of modafinil in patients with sleep disorders or MS. Also the studies assessed short term efficacy only (≤5 to 12 weeks). Some studies detected statistically significant differences between modafinil and placebo however, the clinical importance of these findings is not clear.[3]

A systematic review of the treatment of fatigue in MS published in 2008 (and later assessed by the Centre for Reviews and Dissemination (CRD) assessed studies looking at both pharmacological interventions and psychosocial/physiological interventions for the treatment of fatigue in MS. Pharmacological interventions assessed included modafinil compared with placebo. Results reported mixed evidence of effectiveness for pharmacological interventions for fatigue in participants with MS (10 studies across all pharmacological interventions). Five of these studies reported adverse events occurring during the study period. The authors concluded that there was limited evidence-based advice for people with MS to help management of fatigue using pharmacological or psychosocial approaches. More methodologically rigorous research was recommended. The CRD assessment of this review was that there was limited evidence of pharmacological or psychosocial/psychological approaches in the management of fatigue for people with MS. Also more robust research across the broad range of interventions was needed (particularly energy conservation). The CRD felt that the authors' appropriately discussed the limitations of the evidence and that their cautious conclusions appeared reasonable, but were based on a number of small and quite variable poor-quality studies.[20]

The NICE CG on management of MS in primary and secondary care says assess and offer treatment to people with MS who have fatigue due to anxiety, depression, difficulty in sleeping and any potential medical problems such as anaemia or thyroid disease. Consider mindfulness-based training, CBT or fatigue management. Advise people that aerobic, balance and stretching exercises including yoga may be helpful in treating MS-related fatigue.[14]

2. Sleep apnoea or shift-worker sleep disorder

A recent Cochrane Database Systematic Review of pharmacological interventions for sleepiness and sleep disturbances caused by shift work, included 15 RCTs (n=718). One trial assessed the effect of modafinil. It increased alertness and reduced sleepiness to some extent in employees suffering from shift-work sleep disorder, but was associated with adverse events. The review concluded that more and

better quality trials on the beneficial effects, adverse effects and costs of all pharmacological agents inducing sleep or promoting alertness in shift-workers (both with and without a diagnosis of shift work sleep disorder) and systematic reviews of their adverse effects are needed.[21] In 2010 the EMA recommended that modafinil use should be restricted to treat sleepiness associated with narcolepsy only and should no longer be used for the treatment of excessive sleepiness associated with obstructive sleep apnoea, or chronic shift-work sleep disorder.[16]

3. Chronic fatigue syndrome

An evidence-based review on approved and investigational uses of modafinil in 2008 found that trials for various conditions, including cognition in chronic fatigue syndrome provided inconsistent results; all studies had extremely small sample sizes. Modafinil cannot be recommended for this condition until definitive data become available.[4]

4. Fatigue in PD

Daytime hypersomnolence affects up to 50% of people with PD. Sudden onset of sleep is caused by dopamine agonists.[17] NICE CG35 on PD states that modafinil may be considered for daytime hypersomnolence, but this was published in 2006.[6] The advice in August 2010 to restrict use of modafinil to treat sleepiness associated with narcolepsy only, supersedes the recommendation in NICE CG35. This is being updated and the revised CG35 is due for publication in October 2016.[22] Scottish Intercollegiate Guidelines Network (SIGN) guidance on diagnosis and management of PD states that modafinil and melatonin are not recommended for the management of excessive daytime sleepiness (EDS) associated with PD. Management of EDS should centre on finding a reversible cause such as depression, poor sleep hygiene and drugs associated with altered sleep pattern.[5] For night-time sleep disturbance, review all medication and avoid (where possible) any drugs that may affect sleep or alertness, or may interact with other medication (e.g. selegeline, antihistamines, H2 antagonists, antipsychotics and sedatives).[6] An evidence-based review in 2008 on approved and investigational uses of modafinil states that trials for excessive sleepiness in various conditions, including PD provided inconsistent results; all studies had extremely small sample sizes. Modafinil cannot be recommended for this condition until definitive data become available.[4]

5. Fatigue in depression

An evidence-based review on approved and investigational uses of modafinil in 2008 found a substantial placebo effect on outcomes such as fatigue in various patients, including major depressive disorder. However it did not provide any benefit greater than placebo.[4]

The CRD assessed a meta-analysis (Goss et al, 2013) with six RCTs (910 patients), published in the Journal of Clinical Psychiatry. Goss et al concluded that the evidence supported use of adjunctive modafinil for the safe treatment of depression and fatigue, in patients with unipolar or bipolar depression. However, the evidence base was small and of unclear quality. Treatment duration was short-term across all trials. The authors acknowledged the considerable heterogeneity, with significant variability in terms of patient and trial characteristics. Addition of further trials may affect the results. The CRD assessment concluded that it was unclear how the statistically significant results translated into clinical significance, given that the confidence intervals suggested that the effects were only just statistically significant. The limitations and uncertainties surrounding the evidence suggest that the author's original conclusions may not be reliable.[23]

6. Post-stroke fatigue

The 2010 SIGN guidance on management of patients with stroke stated modafinil has been studied in post-stroke fatigue, but there is insufficient evidence to support its use. Patients should be screened for depression.[7] The SIGN statement is partly based on a 2008 review (Annoni et al) which states that post-stroke fatigue occurs in around 50% of patients and is frequent (30%) even after minor strokes. It can last for more than one year after the event and is different to usual fatigue. There are few studies but treatment may include: low-intensity training, cognitive therapy, treatment of associated depression, wakefulness-promoting agents like modafinil, correction of risk factors (depression, attentional impairment, inactivity, sleep apnoea, alcohol, being overweight) and adaption of activities.[24]

7. Schizophrenia

SIGN guidance on schizophrenia published in 2013 stated a review of generally poor quality studies found conflicting evidence for modafinil as augmentation of antipsychotics, in people with schizophrenia. There is insufficient consistent evidence on which to base a recommendation for modafinil as adjunctive therapy in schizophrenia. Modafinil is not licensed as adjunctive therapy for people with schizophrenia.[10] An evidence-based review on approved and investigational uses of modafinil in 2008 found a substantial placebo effect on outcomes such as fatigue in various patients, including schizophrenia. However, it did not provide any benefit greater than placebo.[4]

8. Apathy in Alzheimer's disease

A small (n=23), short-term (8 weeks) RCT of modafinil for the treatment of apathy in mild to moderate Alzheimer's disease concluded that the addition of modafinil to standard treatment (acetylcholinesterase inhibitors) did not result in significant additional reductions in apathy, or improvements in Activities of Daily Living (ADL) functioning. Larger studies with more statistical power are needed to confirm the absence of significant effects.[9]

9. Fatigue in lung cancer

An RCT with 208 patients compared modafinil to placebo, in the treatment of fatigue in non-small-cell lung cancer (NSCLC). The study was carried out in 24 hospitals across the UK. The conclusion was that modafinil had no effect on cancer-related fatigue and should not be prescribed outside a clinical trial setting. Its use was associated with a clinically significant placebo effect. The authors advise that simply allocating the time within a clinical consultation to acknowledge and discuss fatigue, may benefit the many patients experiencing this distressing symptom.[8]

10. ADHD management

A qualitative review of 43 short term studies reporting ADRs from ADHD medication, found a large number of children dropped out of studies due to serious ADRs. The authors state that as ADHD medications are prescribed for long-term treatment, there is a need for long-term safety studies. Also greater transparency about ADRs from the pharmaceutical companies is required.[25] The NICE CG on diagnosis and management of ADHD in children and young people was updated in March 2013. It states that the use of medication unlicensed for ADHD (including modafinil) should only be considered in the context of tertiary services.[26] The 2009 SIGN guidance on ADHD states that the limitations on the use of modafinil due to adverse effects and the lack of clinical experience prohibit a recommendation for use.[11]

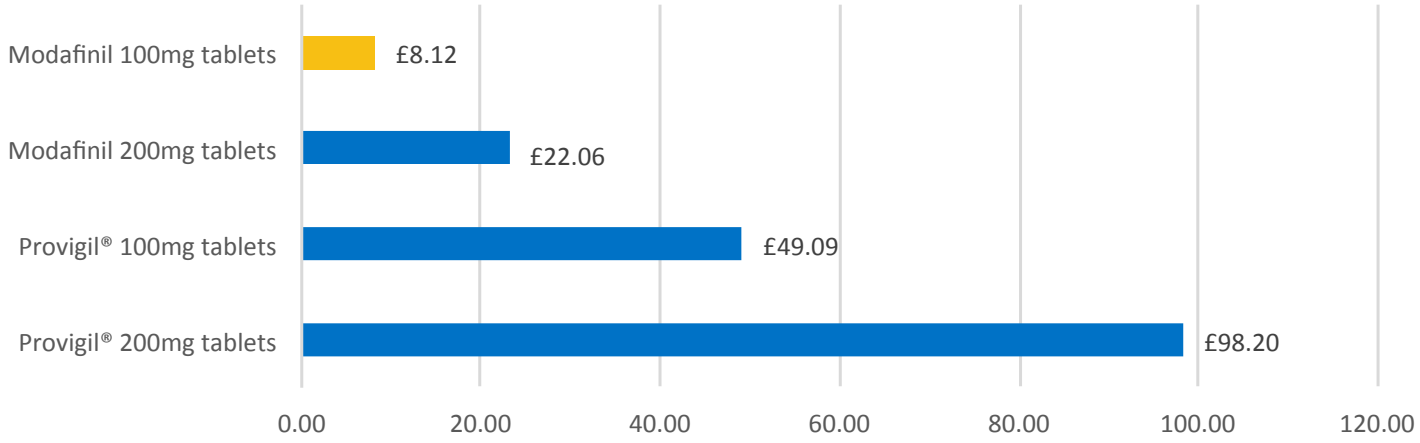
Cognitive enhancement

Several research reports indicate that a significant number of healthy individuals have used modafinil off-label. This is with the intention of improving cognitive functioning, e.g. boosting academic or job performance. Trials in healthy volunteers have failed to find cognitive enhancing effects of modafinil. In a small RCT with 64 healthy volunteers, the principle outcome measures were response latencies in the Hayling Sentence Completion Test (HSCT) for modafinil compared to placebo. The investigators concluded that participants given modafinil were significantly slower in the performance of the task overall. This finding is consistent with previous research in patients with ADHD and healthy volunteers, indicating that modafinil slows response time during cognitive tasks. The lack of improvement in performance accuracy on the HSCT after taking modafinil extends previous research on healthy volunteers that also failed to find cognitive enhancing effects of modafinil on several neuropsychological tasks. The authors suggest future studies should investigate effects of modafinil with testing procedures involving cognitive flexibility, language retrieval and creativity. Also tasks in demanding environments where this drug is often used. In summary, the current study shows that modafinil increases the latency of response to the HSCT without improving accuracy of the task.[12]

Cost

Chart 1 below shows costs for 28 days treatment (one daily dose). The usual pack size for all items shown is 30 tablets, but costs have been adjusted to 28 days. Generic modafinil 100mg tablets are the preferred option of all items in the chart at £11.82 for 30 tablets,[27] which is £22.06 for 28 days of treatment at the lowest dose of 200mg daily. Higher doses will be more costly.

Chart 1. Cost comparison of generic modafinil with Provigil® 28 days[27,28]



The current spend on modafinil in England is over £2.7 million (ePACT February to April 2015. **If prescribing of modafinil reduced by 50%, this would save more than £1.3 million over 12 months. This equates to £2,408 per 100,000 patients.** In addition, the average number of prescriptions for 60 tablets or more is 31% (range 0% to 63%). This could indicate patients on higher doses that should be reviewed.

Summary

- Review modafinil prescribing in off-label conditions to reduce the risk of serious ADRs (CV, skin and multi-organ hypersensitivity reactions).[2] Only prescribe in patients with a diagnosis of narcolepsy made by a specialist, according to an agreed shared care guideline (SCG) - see separate PrescQIPP SCG template at www.prescqipp.info/. Switch from Provigil® to generic modafinil.
- Insufficient evidence exists on efficacy and safety for prescribing in off-label conditions including fatigue in: MS, PD, depression, post-stroke and lung cancer; apathy in Alzheimer's disease, adjunct in schizophrenia, chronic fatigue syndrome, management of ADHD.
- Manage fatigue in MS by offering treatment for anxiety, depression, difficulty in sleeping, anaemia or thyroid disease as required. Consider mindfulness-based training, CBT or fatigue management. Advise that aerobic, balance and stretching exercises/yoga may be helpful.[14] Check for reversible causes of fatigue in PD, such as depression, poor sleep hygiene and drugs associated with altered sleep pattern.[5]
- If the prescriber considers it essential to try modafinil there must be a treatment plan agreed with the patient, including stopping criteria if ADRs occur or desired outcome is not achieved.
- Reducing modafinil prescribing to 50% of current levels would save more than £1.3 million over 12 months. This could potentially be achieved by prescribing for the licensed indication only which has the best evidence for safety and efficacy, rather than off-label indications. Also prescribing generic modafinil 100mg tablets (instead of generic 200mg or branded Provigil®) would enhance savings.

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Additional PrescQIPP resources

 Briefing

 Data pack

 Patient letters, audit

Available here: http://www.prescqipp.info/resources/viewcategory/383-modafinil

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