Cambridgeshire & Peterborough Integrated Care System

NHS Cambridgeshire & Peterborough

Shared Care Guideline: Modafinil

Excessive sleepiness associated with narcolepsy and cataplexy

Contents

Executive Summary

- **Narcolepsy is a chronic, debilitating, life-long neurological disease characterised initially by excessive daytime sleepiness (EDS) in all patients.**
- Narcolepsy usually progresses to include cataplexy (sudden loss of muscle tone), sleep paralysis, hypnagogic hallucinations and fragmented nocturnal sleep.
- **Modafinil** is the first-line pharmacological agent of choice for patients presenting with EDS as their most troublesome symptom. (EFNS, 2011) (AASM, 2014).
- Modafinil is licensed in adults over 18 years, initially 200mg daily, *either* in 2 divided doses morning and at noon *or* as a single dose in the morning, dose is adjusted according to response to 200mg to 400mg in 2 divided doses or as a single dose.
- For elderly patients initiate treatment dose at 100mg daily. (BNF online).
- Exceptionally patients will need doses of 600mg to 800mg in divided doses to manage their EDS symptoms (off-licence).
- Patients will be initiated with a 4-week supply of tablets from the Royal Papworth Hospital Pharmacy Department.
- Patients will be reviewed at Royal Papworth Hospital Out-Patient Clinic for treatment response prior to a decision been made as to whether treatment is to be continued and monitored by G.P. in primary care under a shared care guideline.
- The responsibilities of the hospital specialist, primary care clinician and patient for this Shared Care Guideline can be found within this document.
- Before consenting to treatment, people of childbearing potential must be informed of the risk of teratogenicity.
- People of childbearing potential should be advised of the need to be on suitable contraception prior to initiation of modafinil (oral contraceptives are NOT a suitable method).

Sharing of care depends on communication between the specialist, primary care clinician and the patient or their parent/carer. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The doctor/healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

1. Scope

This guideline provides information relating to Modafinil and outlines the responsibilities of the primary care clinician and the Respiratory Support and Sleep Centre at Royal Papworth Hospital NHS Trust in the prescribing and monitoring of this medicine.

2. Aim

To provide clear and concise information to primary care clinicians in order that their patients with narcolepsy receive on-going safe and effective care using evidence-based medicine, following evaluation by our Sleep Medicine Consultants and their team.

3. Introduction

- Narcolepsy occurs in 1 in 2500 subjects and is a chronic, debilitating, life-long neurological disease characterised initially by excessive daytime sleepiness during the second and third decades of life.
- Narcolepsy usually progresses to include cataplexy (sudden loss of muscle tone), sleep paralysis, hypnagogic hallucinations and fragmented nocturnal sleep. Excessive, uncontrollable daytime sleepiness is experienced by all patients with narcolepsy, and is usually treated with stimulants and/or modafinil during the day to help keep patients awake.
- Amphetamines and their derivatives have the disadvantage of being generalised central nervous system stimulants so that patients develop a range of autonomic side-effects as well as motor hyper-activity and a sense of euphoria. Tachycardia, hypertension and excessive sweating are all common problems. Amphetamines also have several drug interactions. Tolerance develops in around one-third of patients and drug abuse is common because of the euphoriant action.
- Modafinil is not an amphetamine and is much more selective in its action within the brain. It works on the sleep-wake centres, probably in or close to the hypothalamus, to switch the balance in favour of wakefulness. It increases alertness during the day but does not cause any autonomic side-effects and has little effect on mood or hyperactivity.
- Modafinil should only be used in patients who have had a complete evaluation of their excessive sleepiness and in whom a diagnosis of narcolepsy has been made in accordance with diagnostic criteria. Such an evaluation usually consists of, in addition to the patient's history, sleep measurement testing in a laboratory setting and exclusion of other possible causes of the observed hypersomnia

4. Abbreviations

EDS Excessive Daytime Sleepiness.

5. Dose and Administration

- Modafinil is usually given as a once daily dose on waking or twice daily with the second dose between 12 midday and 2 pm. In this situation two-thirds to three-quarters of the total daily dose is normally given on waking and the remainder in the middle of the day. Modafinil has little effect on sleep if it is taken early in the day but if it is taken later on may lead to insomnia.
- The initial dose, is usually 200 mg daily, increasing gradually to 400 mg daily and exceptionally to 600 to 800 mg daily if this is required to achieve a satisfactory level of alertness.

- Doses above 400 mg are unlicensed. Daytime alertness improves 1 to 2 hours after ingestion and the peak blood level is reached 2 to 4 hours later. Peak levels could be delayed by up to one hour if taken with food. Tablets should be swallowed whole with a little water.

Dose in the elderly:

- It is recommended that patients over the age of 65 years should commence on a dose of 100 mg daily in view of expected compromise in renal or hepatic clearance as a result of advanced age. A maximum dose of 400 mg daily should only be used in absence of either renal or hepatic impairment.

Dose in hepatic and renal impairment:

- Modafinil is metabolised in the liver to modafinil acid and modafinil sulphone, both of which are inactive. 90% of the drug is excreted through the kidneys in these forms and 10% as unchanged modafinil. There is inadequate information to determine the safety and efficacy of dosing in patients with renal impairment. The dose needs to be halved in the presence of severe liver or renal impairment (<10ml/min) (i.e. 100 to 200 mg daily).

Availability:

- Modafinil is available generically as 100 mg and 200mg tablets.

6. Adverse Effects

Very common (≥ 1 in 10)

- **Headache** (affecting approximately 21% of patients. This is usually mild or moderate, dose dependent and disappears within a few days).

Common (≥ 1 in 100 and < 1 in 10)

- Includes dizziness, dry mouth, nausea, diarrhoea, abdominal pain and blurred vision, chest pain, tachycardia, palpitations, vasodilatation, constipation, nervousness, insomnia, anxiety, depression, somnolence, confusion, paraesthesia, decreased appetite, asthenia, abnormal thinking, nervousness, confusion, irritability, dyspepsia, agitation, aggression and abnormal liver function tests (dose related increases in alkaline phosphatase and gamma glutamyl transferase have been observed).

Less common (≥ 1 in 1000 and < 1 in 100)

- Includes abnormal ECG, hypertension, hypotension, bradycardia, arrhythmia, weight changes, pharyngitis, sinusitis, eosinophilia, leucopenia, hypercholesterolaemia, hyperglycaemia, diabetes mellitus, increased appetite, sleep disorder, emotional lability, decreased libido, hostility, depersonalisation, personality disorder, abnormal dreams, agitation, aggression, suicidal ideation, psychomotor hyperactivity, dyskinesia, hypertonia, hyperkinesia, amnesia, migraine, tremor, vertigo, CNS stimulation, hypoaesthesia, incoordination, movement disorder, speech disorder, taste perversion, abnormal vision, dry eyes, extrasystoles, arrythmia, bradycardia, flatulence, reflux, vomiting, dysphagia, glossitis, mouth ulcers, sweating, rash,

acne, pruritis, back pain, neck pain, myalgia, myasthenia, leg cramps, arthralgia, twitch, abnormal urine, urine frequency, menstrual disorder, peripheral oedema, thirst, minor allergic reactions.

Rare (≥ 1 in 10000 and < 1 in 1000)

- Serious rash, including Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis and Drug Rash with Eosinophilia and Systemic Symptoms. **Modafinil should be discontinued at the first sign of rash and not re-started (SPC).**
- *Psychiatric disorders* - patients should be monitored for the development of *de novo* or exacerbation of pre-existing psychiatric disorders (including anxiety, suicide-related behaviour, psychotic or manic symptoms, depression, aggressive or hostile behaviour, insomnia or substance abuse) at every adjustment of dose and then regularly during treatment. If important psychiatric symptoms develop in association with modafinil treatment, **modafinil should be discontinued and not re-started.**
- *Multi-organ hypersensitivity* reaction has occurred in close temporal association to the initiation of modafinil. There are no factors that are known to predict the risk of occurrence or the severity of multi-organ hypersensitivity reactions associated with modafinil. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations included myocarditis, hepatitis, liver function test abnormalities, haematological abnormalities (e.g., eosinophilia, leukopenia, thrombocytopenia), pruritus, and asthenia. If a multi-organ hypersensitivity reaction is suspected, **modafinil should be discontinued and not re-started.**

7. Cautions

- *Cardiovascular risks* - an ECG will be performed by the hospital in all patients before Modafinil treatment is initiated. Patients with abnormal findings should receive further specialist evaluation and treatment before Modafinil treatment is considered.
- Blood pressure and heart rate should be regularly monitored in patients receiving modafinil. Modafinil should be discontinued in patients who develop arrhythmia or moderate to severe hypertension (>140/90mmHg, or 150/90mm/hg for patients >80 years) and not restarted until the condition has been adequately evaluated and treated.
- Modafinil tablets are not recommended in patients with a history of left ventricular hypertrophy or cor pulmonale and in patients with mitral valve prolapse who have experienced the mitral valve prolapse syndrome when previously receiving CNS stimulants. This syndrome may present with ischaemic ECG changes, chest pain or arrhythmia.
- **As Modafinil promotes wakefulness, caution should be paid to signs of insomnia.**
- Modafinil should not be used in children aged less than 18 years old because of safety and efficacy concerns.
- Caution should also be exercised in administering modafinil to patients with a history of alcohol, drug or illicit substance abuse due to the potential for dependence.

- **Patients with abnormal levels of sleepiness who take modafinil should be advised that their level of wakefulness may not return to normal. Patients with excessive sleepiness, including those taking modafinil should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or any other potentially dangerous activity Undesirable effects such as blurred vision or dizziness might also affect ability to drive.**

8. Contraindications

- Modafinil is contraindicated for use during pregnancy and lactation, in children and in patients with uncontrolled moderate to severe hypertension or arrhythmia.
- Modafinil is contraindicated in patients with a known hypersensitivity to modafinil or any constituents of the tablets including lactose). As modafinil tablets contain lactose they should not be used in patients with rare hereditary problems of galactose intolerance, the total lactase deficiency, or glucose-galactose malabsorption.

9. Interactions

- Anticonvulsants:
  Co-administration of potent inducers of CYP activity, such as carbamazepine and phenobarbital, could reduce the plasma levels of modafinil. Due to a possible inhibition of CYP2C19 by modafinil and suppression of CYP2C9 the clearance of phenytoin may be decreased when modafinil is administered concomitantly. Patients should be monitored for signs of phenytoin toxicity, and repeated measurements of phenytoin plasma levels may be appropriate upon initiation or discontinuation of treatment with modafinil.
- Steroidal contraceptives:
  The effectiveness of steroidal contraceptives may be impaired due to induction of CYP3A4/5 by modafinil. Alternative or concomitant methods of contraception are required for patients treated with modafinil. Suitable long-term methods are copper intrauterine devices, levonorgestrel-releasing intrauterine devices, and depot progestogen-only injections. Adequate contraception will require continuation of these methods for two months after stopping modafinil.

  For emergency contraception, if a copper IUD is not suitable, a double dose of oral levonorgestrel emergency contraception is advised.

- Antidepressants:
  A number of tricyclic antidepressants and selective serotonin reuptake inhibitors are largely metabolised by CYP2D6. In patients deficient in CYP2D6 (approximately 10% of a Caucasian population) a normally ancillary metabolic pathway involving CYP2C19 becomes more important. As modafinil may inhibit CYP2C19, lower doses of antidepressants may be required in such patients.

- Anticoagulants:
  Due to possible suppression of CYP2C9 by modafinil the clearance of warfarin may be decreased when modafinil is administered concomitantly. Prothrombin times should be monitored regularly during the first 2 months of modafinil use and after changes in modafinil dosage.

- **Other medicines that are largely eliminated via CYP2C19 such as diazepam, propranolol, omeprazole may have reduced clearance.**

- **Also to consider are drugs metabolised by CYP1A2, 2B6 and 3A4/5 where modafinil** has been observed in human hepatocytes, which were it to occur in vivo, could decrease the blood levels of drugs metabolised by these enzymes, thereby possibly decreasing their therapeutic effectiveness. Results from clinical interaction studies suggest that the largest effects may be on substrates of CYP3A4/5 that undergo significant pre-systemic elimination, particularly via CYP3A enzymes in the gastrointestinal tract. Examples include ciclosporin, HIV-protease inhibitors, buspirone, triazolam, midazolam and most of the calcium channel blockers and statins. In a case report, a 50% reduction in ciclosporin concentration was observed in a patient receiving ciclosporin in whom concurrent treatment with modafinil was initiated.

Further information about dose and administration, adverse effects, cautions, contraindications and interactions can be found in the Summary of Product Characteristics for Modafinil Provigil 100 mg Tablets.

10. Monitoring Standards & Actions to take in the event of abnormal test results/ symptoms

- Blood levels of modafinil are not required.
- Tachycardia and hypertension are potential adverse effects. Modafinil should not be prescribed if the diastolic blood pressure is 100 mmHg or greater before treatment. The blood pressure should be monitored in hypertensive patients.
- Liver function tests are also found to be abnormal in 1 to 10% of patients (dose related increases in alkaline phosphatase and gamma glutamyl tranferase have been observed).
- Patients should be advised that modafinil is not a replacement for sleep and good sleep hygiene should be maintained. Steps to ensure good sleep hygiene may include a review of caffeine intake.

11. Shared Care Responsibilities

a. Hospital specialist:

- Send a letter to the primary care clinician requesting shared care for the patient including details of baseline monitoring undertaken.
- Inform the primary care clinician after each clinic attendance if there is any change to treatment or monitoring.
- Inform the primary care clinician of patients who do not attend clinic appointments. and the action plan (e.g. for repeat DNAs and no contact from patient request the primary care clinician to signpost patient to clinic instead of issuing repeat medication).
- To provide any advice to the patient/carer when requested.

- For people of childbearing potential, the specialist must:
  - Discuss therapeutic options for managing excessive sleepiness associated with narcolepsy and involve the patient in selecting the best therapeutic option based on evaluation of the individual's circumstances.
  - Ensure understanding of the teratogenic risks and the measures needed to minimise these risks, clearly state the need to avoid pregnancy, and provide supporting documentation (e.g.: a copy of the product's patient information leaflet).
  - Ensure that patient is using a suitable form of contraception prior to initiating modafinil.
- Confirm through discussion with the patient their non-pregnant status. If there are doubts, then ask the patient to take a pregnancy test before the first prescription is issued. (Note pregnancy tests may not detect an early pregnancy that has occurred after unprotected intercourse in the preceding 3 weeks so may need to be repeated).
  - Obtain the patient's/carer's assurance that they are using a suitable form of contraception before the first prescription is issued. If the patient declines to use suitable contraception, then request a compelling argument for choosing not to use contraception based on zero pregnancy risk (eg physiological, personal beliefs, sexual orientation). If the specialist is satisfied, then they can initiate the prescription. If not convinced they should decline to prescribe modafinil, explain why and discuss alternative treatment options.
  - Document in the medical notes that the above actions have been taken.
- Ensure Baseline ECG, blood pressure, and liver and renal function is taken before the initial prescription is given.

b. Primary Care Clinicians:

- Agreement to shared care guideline by the primary care clinician.
- Report any adverse events to the hospital specialist, where appropriate.
- Request advice from the hospital specialist when necessary.
- For people of childbearing potential the primary care clinician must:
  - Monitor compliance with contraception and contraceptive advice throughout treatment with modafinil and for 2 months afterwards. As a guide, pregnancy prevention advice should be repeated on an annual basis.
  - Respond promptly to communication from the patient regarding potential breaches in contraceptive cover/self-assigned zero pregnancy risk. Conduct pregnancy testing and refer to specialist if required.
  - Refer patients wishing to become pregnant to the specialist.
- Monitor blood pressure and heart rate regularly whilst on treatment and discontinue in patients who develop arrhythmia or moderate to severe hypertension and refer patient back to specialist.
- Monitor liver function test and renal function and contact hospital specialist if concerned regarding dosage adjustments.
- Monitor for any adverse effects and refer back to hospital specialist if concerned.
- For patients taking warfarin, concomitantly, Prothrombin times should be monitored regularly during the first 2 months of modafinil use and after changes in modafinil dosage.

c. Patient or parent/carer:

- Report to the hospital specialist or primary care clinician if they do not have a clear understanding of their treatment.
- Patients must not exceed the recommended dose.
- Patients must attend their scheduled clinic and blood test appointments (where relevant).
- Must inform other clinical staff that they are receiving treatment.
- Report any adverse effects to the hospital specialist or primary care clinician.
- People of childbearing potential must:
  - Agree to abide by the requirement to use suitable contraception OR provide compelling basis for being considered at zero risk of pregnancy.
  - Contact the primary care clinician immediately if they suspect there has been a problem with the contraception or if they may be pregnant, OR if there has been *any* change in their circumstances such that they might no longer be considered at zero risk of pregnancy.
  - Inform the primary care clinician if they wish to plan a pregnancy so that a referral can be made to the specialist to discuss alternative treatment options for excessive sleepiness associated with narcolepsy.
  - Continue suitable contraception for two months after the cessation of modafinil.

12. Contact numbers for advice and support

Royal Papworth Hospital NHS Foundation Trust - Respiratory Medicine Department

Specialist	**Post**	**Telephone**
Dr Nick Oscroft	Consultant Sleep Physician and Clinical Lead for Modafinil Shared Care	01223 639474
Dr Mike Davies	Consultant Sleep Physician	01223 639472
Dr Martina Mason	Consultant Sleep Physician	01223 639473
Dr Tim Quinell	Consultant Sleep Physician	01223 639475
Dr Ian Smith	Consultant Sleep Physician	01223 639476
Dr Dariusz Wozniak	Consultant Sleep Physician	01223 639477
Duncan Grady	Thoracic Directorate Pharmacist	01223 638179 or 01223638 000 and ask for pager 845
Pharmacy Department	Non-Urgent Medicines Information for Clinicians engaging in Modafinil Shared Care	01223 638179
Medicines Helpline	Non-urgent Medicines Information for Patients receiving Modafinil via a shared care agreement	01223 638777 (answerphone)

13. Equality and Diversity Statement

This document complies with the Papworth Hospital NHS Foundation Trust service Equality and Diversity statement.

14. Disclaimer

It is your responsibility to check that this printed out copy is the most recent issue of this document.

15. Document ratification details

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The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics.

Appendix 1: Shared Care Request Letter (Specialist to Primary Care Prescriber)

Dear [insert Primary Care Prescriber's name]
Patient name: [insert patient's name]
Date of birth: [insert date of birth]
NHS Number: [insert NHS Number]
Diagnosis: [insert diagnosis]

As per the agreed Cambridgeshire and Peterborough Joint Prescribing Group shared care guidance for modafinil for the treatment of excessive sleepiness associated with narcolepsy this patient is now suitable for prescribing to move to primary care.

The patient fulfils criteria for shared care, and I am therefore requesting your agreement to participate in shared care. Where baseline investigations are set out in the shared care protocol, I have carried these out.

I can confirm that the following has happened with regard to this treatment:

Criteria	**Specialist to complete**
The patient has been initiated on this therapy and has been on an optimised dose for the following period of time:	[insert time period]
Baseline investigation and monitoring as set out in the shared care documents have been completed and were satisfactory	Yes / No (delete as appropriate)
The condition being treated has a predictable course of progression and the patient can be suitably maintained by primary care	Yes / No (delete as appropriate)
The risks and benefits of treatment have been explained to the patient	Yes / No (delete as appropriate)
The roles of the specialist/specialist team/ Primary Care Prescriber / Patient and pharmacist have been explained and agreed	Yes / No (delete as appropriate)
The patient has agreed to this shared care arrangement, understands the need for ongoing monitoring, and has agreed to attend all necessary appointments	Yes / No (delete as appropriate)
I have enclosed a copy of the shared care guideline which covers this treatment/the SCP can be found here (insert electronic/ web link)	Yes / No (delete as appropriate)
I have included with the letter copies of the information the patient has received	Yes / No (delete as appropriate)
I have provided the patient with sufficient medication to last until	[insert date]
I have arranged a follow up with this patient in the following timescale	[insert timescale]

Treatment was started on [insert date started] and the current dose is [insert dose and frequency].

[insert/delete as applicable] For people of child bearing potential, I have counselled about pregnancy and contraception, that the effectiveness of some contraceptives may be impaired by modafinil, and this may reduce effectiveness. The patient is using an effective, alternative and/or concomitant methods of contraception as recommended and is aware that this should be continued for two months after stopping modafinil.

If you agree, please undertake monitoring and treatment from [insert date] NB: date must be at least 1 month from initiation of treatment.

The next monitoring is due on [insert date] and should be continued in line with the shared care guideline.

Yours sincerely

[insert consultant name]