Shared Care Guideline

Modafinil – Excessive sleepiness associated with narcolepsy and cataplexy

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. (BNF66)
- 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 Papworth Hospital Pharmacy Department.
- Patients will be reviewed at Papworth Hospital Out-Patient Clinic for treatment response prior to a decision 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, GP and patient for this Shared Care Guideline can be found within this document.

Sharing of care depends on communication between the specialist, GP 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. Further information about the general responsibilities of the hospital specialist and GP can be found here

1. Scope

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

2. Aim

To provide clear and concise information to general practitioners 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, ~~for both narcolepsy~~ 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. The dose needs to be halved in the presence of severe liver or renal impairment (ie 100 to 200 mg daily).

Availability:

- Modafinil is available generically as 100 mg tablets.

Further information can be found in the Summary of Product Characteristics
http://www.medicines.org.uk/emc/medicine/28661.

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)

- Include 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, dyspepsia, agitation, aggression and abnormal liver function tests.

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

- Hypertension, hypotension, bradycardia, arrhythmia.
- Dyskinesia, hypertonia, hyperkinesia, amnesia, migraine, tremor, vertigo, CNS stimulation, hypoaesthesia, incoordination, movement disorder, speech disorder, taste perversion
- Dyspnoea, increased cough, asthma, epistaxis, rhinitis
- Pharyngitis, sinusitis
- Eosinophilia, leucopenia
- Hypercholesterolaemia, hyperglycaemia, diabetes mellitus, increased appetite

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. It should be noted that no serious skin rashes have been reported in adult clinical trials (0 per 4,264) of modafinil. However, **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 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**.

Further information can be found in the Summary of Product Characteristics http://www.medicines.org.uk/emc/medicine/28661.

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 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.

- 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.

Further information can be found in the Summary of Product Characteristics http://www.medicines.org.uk/emc/medicine/28661.

8. Contraindications

- Modafinil is contraindicated for use during pregnancy and lactation, in children and in patients with uncontrolled moderate to severe hypertension or arrhythmia. It is contraindicated in patients with a known hypersensitivity to modafinil or any constituents of the tablets (including lactose, talc, maize, starch amongst others).

- As modafinil tablets contain lactose they should not be used in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption.

Further information can be found in the Summary of Product Characteristics http://www.medicines.org.uk/emc/medicine/28661.

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 recommended for patients treated with modafinil. Adequate contraception will require continuation of these methods for two months after stopping modafinil.

- **Ciclosporin:**
  Modafinil induces metabolism of ciclosporin resulting in a reduced plasma concentration of ciclosporin (possibly by up 50%).

Further information can be found in the Summary of Product Characteristics http://www.medicines.org.uk/emc/medicine/28661.

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 – 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 GP requesting shared care for the patient.
- Inform the GP after each clinic attendance if there is any change to treatment or monitoring.
- Inform GP of patients who do not attend clinic appointments.
- To provide any advice to the patient/carer when requested.

b. General Practitioner:

- Agreement to shared care guideline by the GP.
- Report any adverse events to the hospital specialist, where appropriate.
- Request advice from the hospital specialist when necessary.

c. Patient or parent/carer:

- Report to the hospital specialist or GP 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 GP.

12. Contact numbers for advice and support

Papworth Hospital NHS Foundation Trust		
Specialist	**Post**	**Telephone** (direct line)
Dr Ian E Smith	Director of RSSC and Consultant Sleep Physician	01480 364164
Dr Tim Quinnell	Consultant Sleep Physician	01480 364174
Dr Mike Davies	Consultant Sleep Physician	01480 364542
Dr Nick Oscroft	Consultant Sleep Physician	01480 364551
Mrs Netta Tyler	RSSC Directorate Pharmacist	01480 364762
Pharmacy Medicines Information Service		01480 364179
Pharmacy Medicines Helpline		01480 364739 (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 Management

Document ratification and history	
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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
http://www.medicines.org.uk/emc/medicine/28661.