NHS
Bassetlaw
Clinical Commissioning Group

NHS
Doncaster
Clinical Commissioning Group

Shared Care Protocol

For

Modafinil

This protocol developed by STHFT has been agreed by Doncaster & Bassetlaw Area prescribing committee.

The shared care of patients prescribed Modafinil must have a diagnosis for **Narcolepsy only.** No other indication is licensed for its use therefore any requests for shared care other than for narcolepsy should be returned to secondary care, with an explanation of why the request has been declined.

Doncaster and Bassetlaw Area Prescribing Committee

Approved April 24th 2014

THE SHEFFIELD AREA PRESCRIBING GROUP

Shared Care Protocol

For

Modafinil

Shared care protocol developed by:

Dr S Bianchi, Consultant Respiratory Physician, STHFT
Dr K Stewart, Consultant in Palliative Medicine, STHFT
Dr G Dennis, Consultant Neurologist, STHFT
Dr S Price, Consultant Neurologist, STHFT

Reviewed by: STHFT Medicine Safety Committee
NHS Sheffield CCG Formulary Sub Group

Approved by: Sheffield Area Prescribing Group

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Statement of Purpose

This shared care protocol (SCP) has been written to enable the continuation of care by primary care clinicians of **adult** patients initiated on modafinil for the licensed indication of narcolepsy at Sheffield Teaching Hospitals NHS Foundation Trust. The licensed indication for modafinil has been restricted across Europe to narcolepsy only.

Unlicensed therapeutic indications that been approved by the STH Medicine Safety Committee are also detailed in this SCP and are clearly indicated in the table under "Indication". These indications are classified as red on the Sheffield Traffic Light Drug (TLD) List, as defined below:

'RED TLD: Prescribing and ongoing supply is normally undertaken by a consultant or other physician within a secondary care service. In some exceptional circumstances and following discussion between primary and secondary care, GPs may consider it to be in the patient's best interest for drugs in the Red section of the traffic light scheme to be prescribed in primary care.'

Indication

	Indication	Clinical Speciality
1)	Hypersomnolence due to obstructive sleep apnoea despite CPAP (unlicensed indication)	Respiratory
2)	Fatigue or hypersomnolence associated with drug therapy prescribed for symptom management which is not responsive to methylphenidate or where methylphenidate is contra-indicated (unlicensed indication)	Palliative care
3)	Fatigue in multiple sclerosis (unlicensed indication)	Multiple sclerosis service
4)	a) Narcolepsy (with or without cataplexy) (licensed indication) b) Idiopathic hypersomnolence (unlicensed indication) c) Excessive daytime sleepiness (EDS) secondary to narcolepsy (with or without cataplexy) and other neurological disorders (unlicensed indication)	Neurology sleep clinic

Selection of patients

Clinical Speciality	Patient Selection Criteria
1) Respiratory	Robust exclusion of other sleep disorders (respiratory, neurological, psychological) and optimisation of sleep hygiene issues. Exclusion of patients with contra-indications (severe hypertension and cardiac arrhythmias). Careful consideration will also be given to any precautions to use detailed in the SPC.
2) Palliative care	Patient under the care of palliative care and meet the criteria of symptom management which is not responsive to methylphenidate or where methylphenidate is contra-indicated. Exclusion of patients with contra-indications (severe hypertension and cardiac arrhythmias). Careful consideration will also be given to any precautions to use detailed in the SPC.
3) Multiple sclerosis	Patients under the care of the Multiple Sclerosis Service who have not responded to fatigue management and lifestyle advice from a clinical nurse specialist in MS or an Occupational Therapist, and a trial of amantadine up to a maximum dose of 200mg morning and lunchtime. Exclusion of patients with contra-indications (severe hypertension and cardiac arrhythmias). Careful consideration will also be given to any precautions to use detailed in the SPC.

4) Neurology sleep clinic	Detailed clinical and polysomnographic evaluation will be undertaken for an accurate diagnosis. Exclusion of patients with contra-indications (severe hypertension and cardiac arrhythmias). Careful consideration will also be given to any precautions to use detailed in the SPC.

Dosage

Clinical Speciality	Dosing Regime
1) Respiratory	Initial dose: 50mg twice daily at 9am and 12pm. Increased to 100mg daily at 9am and 50mg daily at 12pm after 6 weeks. Increased to 100mg twice daily after a further 6 weeks. Incremental increases on a 6 week basis up to a maximum dose of 200mg twice daily or until side effects limit therapy.
2) Palliative care	Initial dose: 100mg each morning. Increased if necessary after one week to 200mg each morning. Maximum 400mg/24 hours.
3) Multiple sclerosis	Initial dose: 100mg each morning. Increased fortnightly as necessary by increments of 100mg to a maximum dose of 200mg twice daily. The second dose should be taken no later than lunchtime.
4) Neurology sleep clinic (for all indications)	Initial dose: 100mg each morning. Increased fortnightly as necessary by increments of 100mg to a maximum dose of 400mg daily in one or two divided doses. The second dose should be taken no later than mid afternoon.

Contra-indications

Hypersensitivity to the active substance or to any of the excipients.
Uncontrolled moderate to severe hypertension and in patients with cardiac arrhythmias.

Side –effects

Common side effects include:

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

Patients and relatives are to be made aware of the possibility of significant personality change.

The above details are not a complete list and the BNF and the SPC remain authoritative.

Monitoring

Once stabilised at least 3 monthly blood pressure and heart rate checks in primary care while on therapy.

Serious rash requiring hospitalisation and discontinuation of treatment has been reported with the use of modafinil occurring within 1 to 5 weeks after treatment initiation. Modafinil should be discontinued at the first sign of rash and not re-started.

Although there have been a limited number of reports, multi-organ hypersensitivity reactions (see SPC for further details) may result in hospitalization or be life-threatening. If suspected, modafinil should be discontinued.

If psychiatric symptoms develop in association with modafinil treatment, including psychotic, manic and suicide related symptoms, modafinil should be discontinued and not restarted.

Modafinil should be discontinued in patients who develop arrhythmia or moderate to severe hypertension (refer to NICE clinical guidance 127 [August 2011], Hypertension – Clinical management of primary hypertension in adults), and not restarted until the condition has been adequately evaluated and treated.

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.

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.

The above details are not a complete list and the BNF and the SPC remain authoritative.

Responsibilities of consultant clinician

- To discuss benefits and side effects of treatment with the patient/carer and obtained informed consent. Where the indication for modafinil is off-licence, in accordance with STH FT policy for the use of unlicensed and off-licence medicines, the prescriber will explain this to the patient with the potential benefits and risks of treatment
- To initiate modafinil in appropriate patients

- To check baseline BP (and document in patient held booklet) and ECG +/- 24 hour tape (if indicated – palpitations or cardiac risk factors)
- To ensure that arrangements are in place to undertake fortnightly BP and heart rate monitoring and checks for side effects, including rash and hallucinations. This may be undertaken by a community pharmacist, or by the patient themselves providing they have a BP meter which they have been trained to use and they know when to seek medical advice. BP and heart rate results should be documented in the patient held booklet.
- To prescribe the modafinil until the dose is stabilised
- To contact patient's GP to request prescribing under shared care and send a link to or copy of the shared care protocol.
- To advise the GP regarding continuation of treatment, including the length of treatment
- To discuss any concerns with the GP regarding the patient's therapy
- To undertake annual monitoring of BP and ECG +/- 24 hour tape (where indicated)

Responsibilities of the primary care clinician

- To refer appropriate patients to secondary care for assessment
- To agree to prescribe for patients in line with the shared care agreement
- To report any adverse reaction through the MHRA 'yellow card' reporting scheme and to the referring consultant
- To continue to prescribe for the patient as advised by the consultant
- To inform the consultant if the patient discontinues treatment for any reason
- To seek the advice of the consultant if any concerns with the patient's therapy, including waning of effect over time and problematic side effects
- To undertake blood pressure and heart rate monitoring as described in the monitoring protocol
- To conduct an annual medication review
- In the event that the GP is not able to prescribe, or where the SCP is agreed but the consultant is still prescribing certain items e.g. hospital only product; the GP will provide the consultant with full details of existing therapy promptly by fax on request.

Financial implications
BNF cost (BNF 65 March 13) for 200mg BD for 12 months: £2570

Ordering information
Modafinil is available through regular pharmaceutical wholesale chains

Support, education and information

Respiratory
Dr Stephen Bianchi & Dr Rodney Hughes, Consultants in Respiratory and Sleep medicine, STHFT
01142714279/01142714646

Palliative Care
Contact the initiating Palliative Care Consultant
Phone numbers available via Sheffield Palliative Care Formulary which is available on STHFT website & on NHS Sheffield website

Neurology
MS service: Patients under the care of the Sheffield MS service have access to the MS Clinical Nurse Specialist Service. Primary care staff also have access to the MS Clinical Nurse Specialist Service and relevant Consultant Neurologists (Drs Price, Lindert, Howell, Hickman, Nair and Prof Sharrack).
Sheffield sleep clinic: Dr Gary Dennis.

References

- Provigil SPC. Cephalon (UK) limited. Accessed via http://www.medicines.org.uk/EMC/medicine/11337/SPC/Provigil+100+mg+Tablets%2c+Provigil+200+mg+Tablets/
- Palliative Care Formulary Fourth Edition (www.palliativedrugs.com)
- Rammohan et al. Efficacy and safety of modafinil for the treatment of fatigue in multiple sclerosis: a two centre phase II study, JNNP 2002 72: 179-183
- Littleton et al. Modafinil for MS fatigue: does it work? Clin Neurol Neurosurg 2010 112; 29-31
- Brown et al Modafinil for the treatment of multiple sclerosis-related fatigue Ann pharmacother 2010 44; 1098-103
- Moller et al. HAGIL (Hamburg Vigil Study): a randomized placebo-controlled double-blind study with modafinil for treatment of fatigue in patients with multiple sclerosis. Multiple Sclerosis Journal 2011 17; 1002-1009
- Stankoff et al. Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study. Neurology 2005 64:1139-1143
- M. M. Ohayon, R. G. Priest, J. Zulley, S. Smirne, T. Paiva. Prevalence of narcolepsy symptomatology and diagnosis in the European general population . *Neurology 2002 58 :1826*
- Billiard M, Bassetti C, Dauvilliers Y, et al; EFNS Task Force. EFNS guidelines on management of narcolepsy. Eur J Neurol 2006; 13: 1035-48
- Shneerson JM. Sleep medicine: a guide to sleep and its disorders (2nd edition). Oxford: Blackwell, 2005
- Billiard M, Besset A, Montplaisir J, et al. Modafinil: a double-blind multicentric study. Sleep 1994; 17(8 Suppl): S107-12
- Broughton RJ, Fleming JA, George CF, et al. Randomized, double-blind, placebo-controlled crossover trial of Modafinil in the treatment of excessive daytime sleepiness in narcolepsy. Neurology 1997; 49: 444-51
- US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of Modafinil for the treatment of pathological somnolence in narcolepsy. Ann Neurol 1998; 43: 88-97
- US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of Modafinil as a treatment for the excessive daytime somnolence of narcolepsy. Neurology 2000; 54: 1166-75
- Britton T, Douglas N, Hansen A, et al. Guidelines on the diagnosis and management of narcolepsy in adults and children. Ashtead: Taylor Patten Communications, 2002
- Timothy I. Morgenthaler, Vishesh K. Kapur, Terry Brown, Todd J. Swick, Cathy Alessi, R. Nisha Aurora, Brian Boehlecke, Andrew L. Chesson, Jr., Leah Friedman, Rama Maganti, Judith Owens, Jeffrey Pancer, Rochelle Zak, Standards of Practice Committee of the AASM. Practice Parameters for the Treatment of Narcolepsy and other Hypersomnias of Central Origin An American Academy of Sleep Medicine Report: An American Academy of Sleep Medicine Report Sleep. 2007 December 1; 30(12): 1705–1711.
- British Sleep Society: www.sleeping.org.uk
- US Xyrem Multicenter Study Group. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. Sleep 2002; 25: 42-9
- Xyrem International Study Group. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. J Clin Sleep Med 2005; 1: 391-7
- MacDonald JR, Hill JD, Tanopolaky MA. Modafinil reduces excessive somnolence and enhances mood in patients with myotonic dystrophy. Neurology 2002; 59: 1876-80
- Högl B, Saletu M, Brandauer E, et al. Modafinil for the treatment of daytime sleepiness in Parkinson's disease: a double-blind, randomized, crossover, placebo-controlled polygraphic trial. Sleep 2002; 25: 905-9

Full prescribing information is given in the modafinil summary of product characteristics (SPC), available from www.emc.medicines.org.uk

For restriction of licence and safety warnings see MHRA Drug Safety Update March 2011 http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON111502