Scottish Muscle Network

Network Guideline for Prescribing of Modafinil in Patients with Myotonic Dystrophy Type 1

Myotonic Dystrophy Subgroup of the Scottish Muscle Network

NOTE

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined based on all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

Quick Glance Summary Protocol

Non- compliance with safety monitoring should prompt hospital doctor to recommend that GP discontinue modafinil prescription

Eligibility

Consider modafinil if:

- Excessive daytime sleepiness significantly impacting on everyday function (typically, Epworth score ≥ 12, though high Epworth without social impact is not itself an indication)
- Patient has been assessed for sleep disordered breathing, and treatment has been initiated if present.

Modafinil is not recommended if:

- Patient has recent myocardial infarction, angina or left ventricular hypertrophy.
- Primary complaint is of fatigue or apathy, as opposed to excessive sleepiness specifically.

Patient Counselling

- Give patient information sheet and outline known concerns regarding potential toxicities.
- Explain that ongoing prescription is conditional, depending on their compliance with safety monitoring as outlined below.
- Advise patient to stop immediately and seek advice if significant side effects. Mention specifically:
  - syncope, palpitations, chest pain, change in mood, personality, or behaviour.
  - skin rashes

Baseline Assessment & Initiation

- Perform baseline ECG and echocardiogram. Record resting heart rate and blood pressure. ·
- Ask GP to prescribe modafinil 200mg mane.

Assessment at 2 weeks post-initiation

- Repeat ECG, resting heart rate and blood pressure – discontinue modafinil and seek advice if significant changes.
- Review efficacy:
- If no obvious benefit, as GP to add 200mg at lunchtime.

Assessment at 6 weeks post-initiation

- Repeat ECG, resting heart rate and blood pressure – discontinue modafinil and seek advice if significant changes.
- Review efficacy:
  - If still no obvious benefit at this stage, discontinue modafinil.
  - If clinical benefit seen and patient wishes to continue, ensure ongoing screening is in place as below.

Ongoing monitoring

All patients receiving modafinil should be:

- Seen annually in a myotonic dystrophy management clinic (co-ordinated by the local regional clinical genetics service)
- Under the care of a cardiologist, ideally with experience of myotonic dystrophy (a list of recommended physicians is avilable as an appendix to the Scottish Myotonic Dystropy Management Guidelines
- Undergo at least two-yearly review by a respiratory physician to exclude emergent or worsening sleep disordered breathing.

Statement of Purpose

This guideline has been produced to facilitate the supported prescribing by primary care physicians of modafinil, for treatment of excessive daytime somnolence due to myotonic dystrophy type 1. The document will outline the patient selection process, protocol for initiation and monitoring, and define the responsibilities of the Primary Care Doctor and Hospital Doctor (usually the patient's Consultant Clinical Geneticist or Neurologist).

Background

Myotonic dystrophy (DM1) is a dominantly inherited, multisystem disorder resulting from the expansion in size of a repeated sequence of DNA within the DMPK gene. Symptoms are highly variable, although clinical features may include muscle weakness and wasting, fatigue, cataracts, cardiac conduction abnormalities and susceptibility to type 2 diabetes mellitus.

Excessive daytime sleepiness (EDS) is common, affecting up to 88% of patients [1] and may severely impact on employment and social functioning. The causes of EDS are complex, although respiratory muscle weakness leading to sleep disordered breathing and apnoeas can be a contributory factor. However, it is also recognised that severe EDS may be present in the absence of sleep disordered breathing, confirming that a primary effect of DM1 on the brain results in a central component to sleepiness symptoms (reviewed in [2]).

For DM1 patients in which sleep disordered breathing is a predominant feature, treatment with nocturnal ventilation may effect an improvement in EDS symptoms. For the majority however, in whom EDS is primarily caused by central factors, treatment options are extremely limited.

The wakefulness-promoting drug modafinil has been utilised for many years in DM1. In the UK, prescribing of modafinil is only formally licenced for treatment of narcolepsy with or without cataplexy, thus use in DM1 is considered "off-label". Several studies have examined its use in relatively small cohorts of DM1 patients [3-8], generally finding the drug to safe but with variable evidence of efficacy. Cochrane review acknowledged some evidence for efficacy, but concluded that further large-scale studies are required [9]. Nonetheless, audit data from a large cohort of 145 patients [10] as well as the consensus experience of clinicians from the SMN Myotonic Dystrophy Subgroup (2017), support modafinil as an effective treatment with low side-effect profile in selected patients with DM1.

Patient selection/eligibility

Indications to consider modafinil

- Excessive daytime sleepiness that is significantly impacting on daily functioning; eg ability to care for family or meet demands of employment
- Epworth Sleepiness Score will typically be high (≥12). However, high Epworth without social impact is not in itself an indication for modafinil. Likewise, patients with DM1 may underreport symptoms therefore collateral history is useful [11].
- Patient with EDS has been assessed by respiratory service, and judged not to have significant sleep disordered breathing. Note modafinil should not routinely be viewed as an alternative for patients with sleep disordered breathing who are unable to comply with ventilation.

Cautions and contra-indications

The following is not a complete list, and the BNF and electronic medicines compendium (eMC) remain authoritative.

- Modafinil should not be considered where primary complaint is of fatigue or apathy without significant EDS.
- Modafinil is not recommended for patients with recent myocardial infarction, angina or left ventricular hypertrophy
- Modafinil is not recommended for use during pregnancy or in women of childbearing potential unless they are using effective contraception. As modafinil may reduce the effectiveness of hormonal contraception, alternative additional methods of contraception are required (see Selected Interactions).
- Modafinil should not be used during breast feeding

Undesirable effects

The following is not a complete list, and the BNF and electronic medicines compendium (eMC) remain authoritative.

The most commonly reported adverse drug reaction is headache, affecting approximately 21% of patients. This is usually mild or moderate, dose-dependent and disappears within a few days.

Other common (≥1/100 to ≤1/10) reported side effects include:
Decreased appetite, nervousness, insomnia, anxiety, depression, abnormal thinking, confusion, irritability, dizziness, somnolence, paraesthesia, blurred vision, tachycardia, palpitation, vasodilatation, abdominal pain, nausea, dry mouth, diarrhoea, dyspepsia, constipation, asthenia, chest pain.

Selected Interactions

Modafinil may increase its own metabolism via induction of CYP3A4/5 activity but the effect is modest and unlikely to have significant clinical consequences.

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.

Hormonal 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.

Other medicinal products: Substances that are largely eliminated via CYP2C19 metabolism, such as diazepam, propranolol and omeprazole may have reduced clearance upon co-administration of modafinil and may thus require dosage reduction. In addition, *in vitro* induction of CYP1A2, CYP2B6 and CYP3A4/5 activities 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 presystemic elimination, particularly via CYP3A enzymes in the gastrointestinal tract. Examples include ciclosporin, HIVprotease 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 [12].

Patient Counselling

Patients should be supplied with the Patient Information Sheet for Modafinil in Myotonic Dystrophy. Before prescription is initiated, a discussion with the Hospital Doctor should be undertaken, emphasising:

- Off-label status of prescription and known concerns regarding potential toxicities
- Ongoing prescription of the drug is conditional on the patient's compliance with safety monitoring as outlined below
- Patient should specifically be advised to stop modafinil immediately and seek advice if significant side effects develop. Mention specifically:
  - syncope, palpitations, chest pain
  - skin rashes

Monitoring

Each of the following monitoring visits should be completed by the responsible Hospital Doctor, with outcome communicated to the Primary Care Doctor (GP) by letter.

MONITORING VISIT	KEY COMPONENTS
Baseline	• Give patient information sheet and carry out patient counselling if not already done • Perform baseline ECG, and echocardiogram if none in past year, and record resting heart rate (seek cardiology advice if significant abnormality)* • Record blood pressure. • If no concerns, ask GP to prescribe modafinil 200mg mane
2 weeks post-initiation	• Repeat ECG, resting heart rate and blood pressure. • Discontinue modafinil if significant changes • Review efficacy – if no obvious benefit, ask GP to add 200mg at lunchtime
6 weeks post-initiation	• Repeat ECG, resting heart rate and blood pressure • Discontinue modafinil and seek advice if significant changes.* • Review efficacy – if still no obvious benefit at this stage, discontinue modafinil – if clinical benefit seen and patient wishes to continue, ensure ongoing screening is in place as below
Ongoing monitoring	All patients receiving modafinil should be seen annually in a myotonic dystrophy management clinic. In Scotland, these are co-ordinated by the local regional clinical genetics service. The clinician who reviews the patient at this clinic will ensure the following is also in place: • At least annual review by a cardiologist, ideally with experience of myotonic dystrophy. A list of recommended physicians is available as an appendix to the Scottish Myotonic Dystrophy Management Guidelines (www.smn.scot.nhs.uk) • At least two-yearly review by a respiratory physician to exclude emergent or worsening sleep disordered breathing • Repeated failure to comply with safety monitoring as outlined above should prompt the hospital doctor to contact the patient's GP, recommending discontinuation of modafinil prescription.

*If patient has evidence of uncontrolled hypertension, defined as systolic BP > 140 mmHg or diastolic BP > 90 mmHg, do not prescribe modafinil and refer back to GP for investigation and management.

Do not prescribe modafinil and consider cardiology referral if the following ECG features are present:

- PR > 220 ms
- QRS > 120 ms
- evidence of left ventricular hypertrophy
- pathological Q waves or T-wave inversion
- rhythm other than sinus (atrial fibrillation or flutter, sinus bradycardia, 2nd or 3rd degree heart block

Responsibilities

Hospital Doctor

All patients receiving modafinil will have a named responsible hospital consultant (the Hospital Doctor). This will typically be the Consultant Clinical Geneticist or Consultant Neurologist with responsibility for the patient's annual myotonic dystrophy review. Completion of these responsibilities may be delegated to an appropriate clinician, such as speciality nurse, staff grade doctor or specialty registrar. The Hospital Doctor will:

- Identify patients suitable for consideration of modafinil, and ensure other relevant morbidities have been excluded (principally sleep disordered breathing)
- Screen patient's past medical history for contra-indications to modafinil
- Complete patient counselling and supply patient information sheet
- Carry out ecg and bp screening at initiation, 2 weeks and 6 weeks, and seek appropriate advice or referral in event of an abnormal result
- Ensure long-term monitoring by cardiology and respiratory teams is in place, and that patient attends these
- Communicate effectively with gp throughout the initiation process, and be available to discuss any concerns within a reasonable timescale
- In the event of non-compliance with safety monitoring, to communicate with gp to advise of this and recommend cessation of prescription

Primary Care Doctor (GP)

Under the SCP, the primary care doctor is asked to:

- Review patients current medications for potential interations with modafinil
- Issue prescriptions for modafinil
- Report any adverse reaction through the MHRA 'yellow card' reporting scheme and to the referring Hospital Doctor
- Seek advice of the Hospital Doctor in the event of any concerns about the patient's therapy
- Discontinue modafinil prescription if advised of patient's non-compliance with safety monitoring by the Hospital Doctor
- Follow up and manage patients found incidentally to have significant hypertension during the assessment process

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