Modafinil for the treatment of fatigue in lung cancer

PROTOCOL SUMMARY

Full title of study
Modafinil for the treatment of fatigue in lung cancer: a multicentre, randomised, double-blinded, placebo-controlled trial

Primary objective
To assess the efficacy of modafinil in the management of fatigue in lung cancer

Secondary objectives
To evaluate the safety and tolerability of modafinil in this patient group, to help determine the dose-response relationship and to evaluate the effect of modafinil on the secondary outcomes of daytime sleepiness and depression

Background
Fatigue is one of the commonest and most debilitating symptoms experienced by patients with cancer. It affects over 70% of patients, and is perceived to be the symptom with the greatest negative impact on quality of life. Despite the magnitude of the problem, there has been inadequate research into the management of cancer-related fatigue, particularly in relation to pharmacological intervention.

Other than drugs that treat the underlying cause of fatigue, such as erythropoetin, central nervous system (CNS) stimulants are the only class of drug with established efficacy against fatigue. Traditional CNS stimulants, such as methylphenidate, tend to cause adverse effects such as insomnia and agitation. Modafinil is a novel and well-tolerated CNS stimulant, widely used to promote wakefulness in shift-workers and pilots. It is chemically unrelated to the older drugs, with a more selective site of action and fewer side-effects. There is evidence that modafinil can reduce fatigue in healthy individuals and patients with chronic non-malignant disease. No controlled studies have been published evaluating modafinil in those with cancer, despite multiple calls in the literature for such research to be undertaken.

Feasibility study
We conducted an open-label pilot study to determine the feasibility of undertaking a randomised controlled trial. Twenty patients with lung cancer received modafinil 100mg daily for one week, followed by 200mg in the second week. There was a statistically and clinically significant reduction in fatigue. Out of fifteen patients that completed the study, ten chose to continue modafinil after the study. The secondary outcomes of excessive daytime sleepiness and anxiety/depression also improved significantly and the drug was well-tolerated. We concluded that it would be both feasible and worthwhile to undertake the proposed controlled trial.

Proposed study design
This will be a multicentre, phase IV, randomised, double-blinded, placebo-controlled trial. Patients will be randomised between two parallel groups, those in the treatment group taking modafinil and those in the control group taking an inactive, matched placebo. A total of 206 patients will be recruited over a period of eighteen months, with 103 patients in each arm.

Study population

Outpatients attending a selected oncology clinic in each of fifteen centres in London, Cambridgeshire, Thames Valley, Manchester, Wales, Wiltshire, Kent, Essex, Uxbridge, Hampshire ,West Yorkshire, County Durham and North Yorkshire, Cheshire, Norfolk, North Yorkshire and Surry who fulfil the eligibility criteria.

Inclusion criteria include:

- Diagnosed with Non-small cell lung cancer (NSCLC)
- Stage 3 or 4 disease, or recurrent disease after surgery or radiotherapy
- WHO performance status 0-2
- Screening score of 5 or more in a 10-point numerical rating scale of fatigue

Exclusion criteria include:

- Received radiotherapy or chemotherapy in the last 4 weeks
- Commenced on an EGFR tyrosine kinase inhibitors e.g. Gefitinib (Iressa®) and Erlotinib (Tarceva®) within the last 6 weeks.
- Commenced on antidepressants or steroids in the last 2 weeks
- Received blood transfusion in the last 2 weeks
- Currently taking warfarin
- Potentially fertile women of childbearing age
- Major psychiatric illnesses requiring intervention in secondary care, arrhythmia, cor pulmonale or left ventricular hypertrophy
- Uncontrolled hypertension with blood pressure of more than160/100mmHg

Study schedule

The study treatment period will be 28 days. Patients in the treatment arm will take a fixed dose-titration schedule of modafinil, starting at 100mg on day 1 and increasing to 200mg on day 15. Those in the control arm will take one matched placebo capsule from day 1, increasing to two capsules on day 15. Patients will be assessed on three occasions.

	Day 0	**Day 14 ± 2 days**	**Day 28 ± 2 days**
Time	Baseline assessment	Midpoint assessment	Endpoint assessment
Location	In clinic	By telephone or in clinic	By telephone or in clinic
Method	Completion of baseline data form Baseline blood test Completion of case record form	Completion of case record form	Completion of case record form

Outcome measures

Change in score between baseline and 28 days of the following:

- Fatigue subscale of the Functional Assessment of Chronic Illness Therapy, FACIT-fatigue (primary outcome)
- Epworth Sleepiness Scale, ESS
- Hospital Anxiety and Depression Scale, HADS
- Quality of life linear analogue scale, QOL-LAS

Trial management

- Chief Investigator: Dr Bee Wee
- Principal Investigators: Dr Nick Bates, Dr Fiona Blackhall, Dr Kate Fife, Dr Mary O'Brien, Ms Gillian Stent, Dr Paddy Stone, Dr Yvonne Summers, Prof Michael Bennett, Dr Declan Cawley, Dr Melanie Piggott, Dr Anthony Byrne, Dr Sarah Lowndes, Dr Yolande Saunders, Dr Tony Dhillon, Dr Crosse, Dr Haq, Dr Azribi, Dr Shakespeare, Dr Sheikh, Dr Waite, Dr Smith, Dr Chan and Dr Davis.

- Trial Co-ordinator: Dr Ronja Bahadori
- Trial Data Manager: Ms Lois Sims
- Study Statistician: Ms Susan Dutton
- Project Steering Group: Dr Bee Wee, Dr Nick Bates, Dr Kate Fife, Dr Anna Spathis

This study is part of the NCRN portfolio and is funded by the NCRI and its partners and Sobell House Hospice Charity. It is registered on the ClinicalTrials.gov website. The study is sponsored by the University of Oxford and is managed from the trials office based in the Study Centre, Sir Michael Sobell House, Churchill Hospital in Oxford. Enquiries about the trial should be addressed to the Trial Co-ordinator on ronja.bahadori@ndm.ox.ac.uk