Modafinil has recently been approved by the South African Medicines Control Council (SAMCC) for the treatment of excessive daytime sleepiness (EDS) in patients with narcolepsy. It is registered as Provigil. The drug has also been used off-label for fatigue and sleepiness experienced by patients with multiple sclerosis (MS) and Parkinson’s disease.

Registered indication for modafinil: treatment of narcolepsy

Modafinil is a unique wake-promoting agent that is chemically distinct from traditional stimulants. The precise mechanism of action in narcolepsy is not known, but it is believed to work selectively to activate the cortex of the brain. The drug is effective and well tolerated in the treatment of EDS in narcolepsy patients.

Provigil is registered in South Africa to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy, as defined by either of the following two DSM-IV criteria in the absence of other clinically significant medical or psychotic conditions:

- recurrent daytime naps or lapses into sleep that occur almost daily for at least 3 months, as well as sudden bilateral loss of postural muscle tone in association with intense emotion (cataplexy), or
- excessive sleepiness or sudden muscle weakness with associated features: sleep paralysis, hypnagogic hallucinations, autonomic behaviours, disrupted sleep episodes; and polysomnography demonstrating one of the following: sleep latency less than 10 minutes or rapid eye movement (REM) sleep latency less than 20 minutes.

Modafinil is taken once daily. The registered dose in adults with narcolepsy is 200 mg given as a single dose in the morning. In elderly patients, elimination of modafinil may be reduced and lower doses should be used. The dose in patients with hepatic failure should be reduced by half (100 - 200 mg/day). The medication is expensive — the current cost (VAT inclusive) is R513.00 for 30 tablets (100 mg each) (single exit price as confirmed with the manufacturer).

Off-label uses of modafinil

Off-label uses include:
- MS
- Parkinson’s disease
- attention deficit/hyperactivity disorder (ADHD)
- affective disorders.

CONCERNS

- The studies in MS were small, of short duration and not double blinded. Patients were not randomised and subgroups of MS type were very small.
- It may be difficult to distinguish between certain common symptoms of MS and some side-effects of modafinil.
- The drug is currently not approved by the SAMCC or the FDA for use in MS and therefore additional investigations are needed.
- The studies in Parkinson’s disease were also very small (15 - 21 patients) and of short duration, and modafinil was found to be only modestly effective. The drug is not registered in South Africa for use in Parkinson’s disease.
- It must be stressed that the drug is also not registered in South Africa for ADHD, depression, bipolar mood disorder or Alzheimer’s disease and proper well-controlled clinical trials to assess the long-term safety and efficacy are needed.

CONCLUSION

At this stage it is not possible to establish the place of modafinil in the pharmacological treatment options available for the management of MS, ADHD, affective disorder, Parkinson’s or Alzheimer’s disease.

References available on request.

Elsabé van der Merwe
NEWER ANTI-EPILEPTIC DRUGS — NICE GUIDANCE

The National Institute for Clinical Excellence (NICE) has recently issued guidance on the use of the newer anti-epilepsy drugs in adults. This is due to the increasing number of prescriptions for newer drugs that are more expensive than the older medication.

The term ‘newer anti-epilepsy drugs’ refers to the following drugs:

- lamotrigine, e.g. Lamictin
- gabapentin, e.g. Neurontin
- oxcarbazepine, e.g. Trileptal
- vigabatrin, e.g. Sabril
- topiramate, e.g. Topamax
- levetiracetam, e.g. Keppra
- tiagabine (not registered in South Africa).

NICE recommends that the newer anti-epileptic drugs be used for the management of epilepsy in individuals who have not benefited from older therapies such as carbamazepine or sodium valproate. The newer therapies should also be used where older drugs are unsuitable owing to contraindications, drug interactions, poor tolerance and risk of pregnancy. Further guidance/recommendations include:

- Monotherapy as far as possible. Where initial therapy is unsuccessful, monotherapy with an alternative drug should be tried.
- Adjunctive/add-on therapy should only be considered where monotherapy attempts failed to result in seizure freedom.
- The risks and benefits of treatment with individual drugs should be assessed in view of possible drug interaction with oral contraceptives. The drug’s potential effect on an unborn child should be assessed in women of childbearing age.
- Precise and early diagnosis is crucial. Patients with a first seizure should be seen by a specialist as soon as possible.
- Treatment review at regular intervals.
- There are no differences in the choice of treatment or importance of monitoring of effectiveness and tolerability in different groups, e.g. older people compared with the general population.

Clinical guidelines on the diagnosis, management and drug treatment in epilepsy are due to be published by NICE later in 2004.

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INTENSIVE LIPID LOWERING IN ACUTE CORONARY SYNDROMES (ACSs)

The PROVE-IT (pravastatin or atorvastatin evaluation in infection therapy) study published in the New England Journal of Medicine in April 2004, shows that intensive LDL-cholesterol lowering reduces deaths and cardiovascular events in patients with ACS significantly more than moderate lipid-lowering therapy. A total of 4 162 patients with recent hospitalisation for an ACS were enrolled and randomised to moderate therapy (pravastatin 40 mg daily) and intensive therapy (atorvastatin 80 mg) and followed up for a mean of 24 months. The primary end-point was death and/or a major cardiovascular event. The rate of primary end-point was 26.3% for the pravastatin group and 22.4% for the atorvastatin group. This reflects a 16% reduction in the deaths and cardiovascular events for patients with intensive lipid lowering compared with moderate reduction. It is reported that the lead investigator from Harvard Medical School suggested that this effect is ascribed to the treatment’s effect on LDL. LDL-cholesterol levels for patients treated with standard dose pravastatin were 2.46 mmol/l compared with 1.6 mmol/l in those treated with intensive lipid-lowering therapy.

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HORMONE THERAPY-ASSOCIATED ASTHMA

A prospective cohort study published in the Archives of Internal Medicine has reported that the use of hormonal replacement therapy (HRT) by postmenopausal women is associated with an increased incidence of newly diagnosed asthma but not chronic obstructive pulmonary disease (COPD). The study, initiated in 1976, reported on 546 249 person-years of follow-up and the researchers found that current users of oestrogen therapy were twice as likely to be diagnosed with asthma as women who had never used HRT before. A similar incidence rate was found for existing users of combination HRT, i.e. oestrogen plus progestin. The researchers concluded that although female reproductive hormones may contribute to the asthma onset in adult women, it did not appear to hasten the development of COPD.