THE CHALLENGES OF PROVIDING ACCESS TO FIRST-LINE MEDICINES FOR PATIENTS WITH NARCOLEPSY IN AUSTRALIA

Applicable terms of reference

"Without compromising the assessment of safety, quality, efficacy or cost-effectiveness, whether the approval process for new drugs, could be made more efficient, including through greater use of international approval processes, greater alignment of registration and reimbursement processes or post market assessment"

Contributors

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General Summary

- Access to many first-line medicines for management of narcolepsy is not available in Australia (pitolisant, solriamfetol) or too difficult and costly for our patients (sodium oxybate)

- Orphan drug status for narcolepsy medicines would encourage pharmaceutical companies to introduce new first-line medicines for this rare disease in Australia

- Better alignment with rigorous international treatment guidelines and approval processes for first-line medicines used for rare diseases, is needed.

INTRODUCTION

Narcolepsy types I and 2 (NT 1 and 2) are rare neurological disorders characterized by an irrepressible need to sleep, or daytime lapses into sleep. Both disorders are associated with abnormal nocturnal sleep, such as fragmented sleep, hypnagogic hallucinations and sleep paralysis episodes. Investigation findings for both disorders include a Multiple Sleep Latency Test demonstrating a daytime mean sleep latency of less than 8 minutes, with two sleep-onset rapid eye movement sleep periods. NT 1 is accompanied by cataplexy, a sudden onset loss of muscle tone with retained consciousness precipitated by strong emotions. The underlying pathology of NT 1 is loss of the neurotransmitter hypocretin (also known as orexin) from the hypothalamus, either due to dysfunction or damage of neurons[1]. Deficient levels of hypocretin in the cerebrospinal fluid have long been recognized as a key marker of NT 1[2] and form part of its diagnostic criteria[1]. **The most debilitating symptom in these disorders (NT 1 and NT 2) is daytime somnolence. Patients with narcolepsy experience reduced health-related quality of life** in domains of physical and social function, as well as mental health disturbances[3,4]. The prevalence of NT 1 lies between 25 and 50 per 100,000 people[5]. However, the prevalence of narcolepsy in Australia is not known. There is no Australian data registry, nor is cerebrospinal fluid testing to confirm a diagnosis of NT 1 readily available in Australia.

The management of narcolepsy focuses on reducing excessive daytime sleepiness (EDS), aiming for maximal return to normal function, treating cataplexy, minimising overnight sleep disruption, sleep-related hallucinations and sleep paralysis. In Australia, there are two classes of drugs available to reduce EDS on the Pharmaceutical Benefits Scheme (PBS): wakefulness promoters (modafinil and armodafinil) and stimulants (dexamfetamine). The PBS only allows access to wakefulness promoters, via the Complex Drugs Program, if dexamfetamine poses an unacceptable medical risk to the patient or has resulted in intolerance. **This PBS restriction places, in effect, dexamfetamine as the first available option for treatment of narcolepsy related EDS in Australia, unlike in other first-class health systems, where stimulants such as dexamfetamine are used as second- or even third-line agents[6].** In regards to cataplexy, clomipramine is listed on the PBS as an anti-cataplectic agent. Several other anti-depressants are also often used for management of cataplexy and other rapid eye movement (REM) related symptoms including sleep related hallucinations and paralysis. Australian clinicians and narcolepsy patient groups have repeatedly voiced concerns about the inability to access many recommended first-line agents available to patients in other first-class health systems**.** One of these drugs is sodium oxybate, which is not listed on the Australian Register of Therapeutic Goods but can be supplied under Category B of the Special Access Scheme at a cost of up to $20,000/ year. The novel histaminergic agent pitolisant also has anti-cataplectic effects, in addition to wakefulness-promoting effects, but is also unavailable in Australia.

As regards global clinical leadership for Australian clinicians, the American Academy of Sleep Medicines (AASM) practice parameters and the European Federation of Neurological Sciences (EFNS) guidelines are widely used to drive best practice in narcolepsy management[7-8]. Although updated guidelines are currently in

development, the AASM practice parameters published in 2007[7] listed only modafinil and sodium oxybate as 'Standard' level recommendations for the treatment of narcolepsy. Dexamphetamine and methylphenidate were listed as 'Guideline' recommendations, reflecting lower levels of evidence for their usage. The EFNS guidelines for the management of narcolepsy are scheduled to be updated in late 2020. The current version published in 2006[8] recommended modafinil and sodium oxybate as first-line treatments for hypersomnolence and cataplexy, respectively whilst methylphenidate and anti-depressants were relegated to second-line therapy.

On the basis of randomized, double-blind, placebo-controlled, multicentre, parallel-group trials demonstrating treatment efficacy for both hypersomnolence and cataplexy, sodium oxybate was approved for use in narcolepsy by the United States Food and Drug Administration (FDA) in 2002 and by the European Medicines Agency (EMA) in 2005. Modafinil was approved by the FDA in 1998, and armodafinil in 2007, both for the management of EDS in sleep disorders such as narcolepsy. Between 2016 and 2020, two other drugs have been approved for use in narcolepsy by both the FDA and the EMA: pitolisant and solriamfetol (dopamine and noradrenaline reuptake inhibitor). Of these novel and efficacious medications, only sodium oxybate is available (via SAS category B exemptions) in Australia, although it is too costly for patients (not available on the PBS) and difficult to access (very few clinicians are experienced in its prescription).

LIMITATIONS OF CURRENT MODEL AND PROPOSED CHANGES

Australia needs to re-examine the issue of access to drugs in diseases that are clinically recognised but rare, such that access is at par with other developed countries that may follow different models of health care.

The orphan drugs program is one avenue to provide such access. Instituted in 1997, Australia's orphan drugs program is seen at par with other such programs across the globe, especially since its revision in 2017[9,10]. However, some criteria required for orphan drug listing make it difficult for drugs such as those for EDS treatment in narcolepsy patients to make it to this register, i.e. the 5 in 10,000 patients level of disease rarity as a cut off, given there are no studies of narcolepsy prevalence in Australia[9]. Similarly, EDS is a symptom of other sleep disorders such as obstructive sleep apnoea which falsely inflates EDS prevalence, becoming conflated with a key criterion in the orphan drug designation applications, i.e. that the drug should treat the condition in only one patient set (medical plausibility)[9]– of course this could be offset by a restrictive PBAC recommendation limiting a new drug for use only in narcolepsy patients or by several applications each specifying a sleep disorder with EDS as a symptom for the drug under application[9].

It has been reported that disadvantaged by a smaller market size, Australia's lead time for authorising drugs within the orphan drugs scheme is longer than in countries such as the US[11]. Amongst comparable nations, Australia is also usually never the first in authorising drugs with an orphan drug status[11]. Recently in comparing Canada (which does not have an orphan drugs program) with Australia's program, researchers concluded that having the program did not necessarily advantage

Australia in terms of number of orphan drug listings or the timeliness of these listings[12].

Despite an overall robust orphan drugs scheme, the problems highlighted above have placed Australia well behind other countries with respect to narcolepsy treatment. As an example, in 2007, the EMA's Committee for Medicinal Products for Human Use (CHMP) granted an orphan drug designation to pitolisant, one of the novel agents used to address EDS in narcolepsy[13]. This listing was based on the recognition that narcolepsy is a rare condition and the fact the pitolisant had been shown to be effective in reducing EDS in narcolepsy to a significantly greater extent than placebo [13]. The designation as an orphan drug by the EMA, allowed pitolisant to qualify for ten years' market exclusivity in the EU market[13].

Pitolisant is relatively novel, but, as yet, even modafinil or armodafinil, older drugs for EDS treatment in narcolepsy do not have primacy in Australia and are effectively second line. Modafinil and armodafinil also would not classify within the orphan drugs scheme to treat EDS in narcolepsy, as they are already listed for use in other indications[9]. For these two drugs, one may then consider the general listing and approval by the PBAC for PBS listing as first line options for EDS treatment in narcolepsy patients. Modafinil and armodafinil in this scenario are required by the PBAC to demonstrate cost effectiveness against older drugs used for the same purpose. Whilst demonstrable for effectiveness in comparison with placebo, given the small numbers of patients involved, it would probably be unviable for manufacturers to run head to head trials of modafinil/armodafinil versus dexamfetamine specifically in narcolepsy patients; indeed currently there is a paucity of such trials, leaving patients with narcolepsy who have EDS without access to safe and effective medications.

Orphan drugs registry:

- It is recommended that the Guidelines for Orphan Drug Register listing consider the case of rare disease where prevalence has not yet been studied in Australia (prevalence threshold criteria) and in such cases allow reasonable extrapolation of prevalence from comparable countries[9].

- Streamline processes so that separate applications are not required if a drug treats symptom types that occur across several diseases, rather listing of orphan drug status for varied diseases can be made within one application[9].

- Clarify the statement within the orphan drugs eligibility criteria that the drug applying for orphan drug listing target a condition considered ‘debilitating’[9].

- Clarify the statement within the Orphan Drugs Application eligibility criteria that the “medicine provides a significant benefit in relation to the efficacy or safety of the treatment, prevention or diagnosis of the condition, or a major contribution to patient care, compared to existing therapeutic goods”[9].

- Work with patients and clinical stakeholders (e.g. not for profit clinical or patient support organisations) to co-design managed access programs for drugs treating rarer conditions[14].

- Engage in developing strategies to lower drug costs charged by manufacturers for drugs that could be listed on the Orphan Drugs Registers through a suite of incentives[12, 15].

General registry e.g. on ARTG:

- Consider ways to provide best quality treatment access to Australians at par with global practice guidelines for any given rare diseases.

- Use a case based rather than formulaic approach to making decisions for ARTG/PBS listing in drugs where comparative effectiveness trials for new drug versus placebo are available even though comparability for the new drugs with existing, less targeted or less safe/effective drugs is not yet established.

General:

- Link recommendations from Parliamentary Inquiries with Regulatory bodies such as the TGA/PBAC to create opportunities for improving access to best quality care. For example, the recent Parliamentary Inquiry into Sleep Health Awareness recommended that "*the Australian Government work with patient advocacy groups such as Narcolepsy Australia or the Sleep Health Foundation to make a submission for the listing or registration of Sodium Oxybate under the Orphan Drug Program*."[16] However, despite these recommendations being made over a year ago, no such moves have been initiated and patients continue to pay heavily for use of sodium oxybate leading to disparities in access for narcolepsy patients who cannot afford this medicine.

CONCLUSION

Narcolepsy is a rare, clinically debilitating, lifelong medical disorder, where international treatment guidelines and regulatory frameworks are in stark contrast with the Australian therapeutic and regulatory environment. Improved processes for allowing Australian patients timely access to contemporary treatments are vital, to ensure equity in obtaining care, for these often challenging disorders. Improved alignment with international registration and reimbursement processes will be the key to modernising narcolepsy care in Australia. Robust post-marketing assessments will ensure that timely access to treatment is balanced with longitudinal safety assessments.

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