Australasian Sleep Association

PBAC minor submission July 2020

1. Introduction

Narcolepsy is estimated to affect approximately 1 in 2,000 people.[1] Characterised primarily by excessive daytime sleepiness (EDS), it can also be associated with other symptoms such as cataplexy, automatic behaviours (performing actions such as walking, eating, or driving, in a semiconscious way without awareness), hallucinations, difficulty sleeping at night and sleep paralysis. Most patients have difficulty functioning at school, work, and home, as well as in social situations. Narcolepsy is a debilitating disease that can severely affect a patient's day-to-day functioning and have a devastating impact on a patient's life including mental health issues and risks of conditions such as diabetes, obesity, and cardiovascular disease.

The current PBS listing for narcolepsy treatments is not aligned to Australia's National Strategy for Quality Use of Medicines (QUM), the goal of which is to make the best possible use of medicines to improve health outcomes for all Australians.[2]

The Pharmaceutical Benefits Scheme (PBS) Schedule lists dexamfetamine as first line for narcolepsy treatment with modafinil/armodafinil to only be prescribed as second line (either after failure or intolerance of dexamfetamine or where dexamfetamine poses an unacceptable medical risk). This has led to a distortion of prescribing practice that is contrary to National and International Guidelines, and consequently not reflective of best clinical practice.

The Australian Sleep Association (ASA) is seeking a change in the initial treatment phase and clinical criteria for the prescription of modafinil/armodafinil. The ASA specifically requests that the following two clinical criteria be reviewed and altered to reflect contemporary Guidelines on narcolepsy management:

- The treatment must be for use when therapy with dexamfetamine sulfate poses an unacceptable medical risk; OR

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1 https://www.aph.gov.au/Parliamentary_Business/Committees/House/Health_Aged_Care_and_Sport/SleepHealthAwareness/Report/section?id=committees%2Freportrep%2F024220%2F26954

2 https://www1.health.gov.au/internet/main/publishing.nsf/Content/nmp-quality.htm-copy2

- The treatment must be for use when intolerance to dexamfetamine sulfate is of a severity to necessitate treatment withdrawal.

Additionally, we request that the PBAC remove the requirement to resubmit the sleep study reports again before a switch from modafinil to armodafinil (or vice versa) can take place as this is an unnecessary step, which is burdensome to clinicians and delays treatment for patients.

2. The ASA Request

The ASA would like to outline the reasons for our request to change the PBS listing to allow for first line use of modafinil and armodafinil for narcolepsy. At the core of this request is that the current requirement of prior dexamfetamine use exposes patients to development of tolerance (necessitating higher doses), unnecessary risk of addiction and potential harm of cardiac arrhythmias and psychiatric disturbances. Further, despite its long history of use in clinical practice, dexamfetamine has limited high-level evidence for narcolepsy from published studies and a low benefit-to-risk ratio.

In contrast, both modafinil and armodafinil have been studied in large randomised, placebo-controlled studies and are recommended as first-line pharmacologic therapies in evidence-based practice guidelines for the past 13 years. Indeed, stimulants such as dexamfetamine are relegated as ancillary medicines and only when first-line treatments such as modafinil or armodafinil are not fully effective. US treatment guidelines for narcolepsy make first-level recommendations for modafinil/armodafinil and second-level recommendations include dexamfetamine. In European recommendations, modafinil and armodafinil are recommended first-line while dexamfetamine is considered second- or third-line [1].

2.1 Australian and International Guidelines

The Australian Therapeutic Guidelines recommend modafinil/armodafinil as a first line treatment, alongside dexamphetamine. However, it clarifies that modafinil/armodafinil be used given that it has fewer side-effects. Guidelines, practical guidance, and consensus publications recommending modafinil/armodafinil first line and dexamphetamine second/third line for narcolepsy include those written by authors representing the following organisations:

- American Academy of Sleep Medicine [2, 3]
- BMJ Best Practice [4]
- European Federation of Neurological Societies [5]
- European Sleep Foundation [6]

These recommendations form the foundation of many Institution Guidelines, all recommending modafinil/armodafinil as first line treatments [7-15]

2.2 Local consensus from ASA Members

A recent survey conducted among sleep physician members of the ASA garnered 56 responses out of 203 emails sent (responded survey attached). The results of the survey show that:

- About half of the respondents have more than 5 years' experience and about a third have more than 10 years' experience as sleep physicians
- An overwhelming majority (n = 55) believe that the PBS treatment algorithm does not reflect best practice and is not in line with international standards and hence:
    - Are dissatisfied to very dissatisfied with the current PBS reimbursement model that modafinil/armodafinil cannot be prescribed first line
    - Agree to strongly agree that the need to treat first line with dexamfetamine is an unnecessary step in the treatment of narcolepsy patients

Therefore, our members are supportive of the current submission and the request for a change to the current PBS listing requirements for modafinil/armodafinil.

3. CLINICAL EVIDENCE FOR DEXAMFETAMINE VS MODAFINIL/ARMODAFINIL IN NARCOLEPSY

3.1 Pharmacology

In adults with narcolepsy, modafinil and its r-enantiomer, armodafinil, are first-line therapies. Modafinil/armodafinil selectively activates wake-generating sites in the hypothalamus. They are highly selective dopamine transporter inhibitors and increase extracellular brain levels of dopamine. Relative to other stimulants that act through catecholaminergic mechanisms, they have low abuse potential and produce wakefulness with an attenuated compensatory sleep thereafter [16].

In contrast, dexamfetamine in the treatment of narcolepsy acts primarily through increasing the level of monoamines within the synaptic cleft by enhancing the release of noradrenaline, dopamine, and serotonin, and blocking their reuptake. Its pharmacology accounts for its addiction potential [17].

3.2 The role and use of dexamfetamine/dexamphetamine/dextroamphetamine

Dexamfetamine is indicated for the treatment of narcolepsy and hyperkinetic behaviour disorders in children (Australian Product Information). The usual daily dose ranges from 5 to 60 mg (given in divided doses) for optimal response. However, internationally this is not considered to be appropriate first-line treatment given the side effect profile.[3]

[3] https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Narcolepsy-Fact-Sheet

In June 2019 Drug Utilisation Sub-Committee (DUSC) analysis showed that while the number of patients on therapy for narcolepsy had increased from 2014 to 2018:[4]

- Dexamfetamine was the most used drug for narcolepsy by prescription volume and number of prevalent patients from 2015-2018, inclusive.
- There was a steep increase in the number of patients starting dexamfetamine for narcolepsy from 178 patients in the second quarter of 2018 to 465 patients in the fourth quarter of 2018 (this coincided with a 35.9% increase in patients new to narcolepsy therapy from 2017 to 2018).

A general concern of the ASA is that a Schedule 8 medicine, that is subject to abuse potential, is currently preferred over modafinil/armodafinil that have strong efficacy evidence and an established safety profile. Further, the above statistics worryingly demonstrate that a vast number of patients with narcolepsy are not being prescribed evidence-based therapies and as prescribers, we are failing to uphold the QUM principles and also failing in decreasing risk associated with exposing our patients to the detrimental short- and long-term effects of dexamfetamine.

Amphetamines were first introduced as a treatment for narcolepsy in the mid-1930s. Its derivatives (d-amphetamine, methamphetamine) became the mainstay of narcolepsy management. Their use as a class has become increasingly limited due to common sympathomimetic side effects (irritability, reduced appetite, and insomnia), potential for new-onset psychosis and increased risk of cardiovascular disease. These issues are exacerbated in the elderly and others with relevant comorbidities; additionally, tolerance can develop in up to a third of patients [1, 8, 11, 18]. Further, there is a high potential for diversion with dexamfetamine [19].

Important considerations in the pharmacologic management of patients with narcolepsy include efficacy, adverse effects, convenience of administration, abuse potential, and comorbidities. Therefore, international Guidelines consider modafinil and armodafinil to be first line, and dexamfetamine as second/third line [2].

3.3 Evidence for dexamfetamine

The need for more than one treatment for narcolepsy is not disputed. Treatments from more than one pharmacologic class are important in order to appropriately treat the narcolepsy spectrum. However, there is a disparity in the evidence available between the three currently listed PBS medications dexamfetamine, modafinil and armodafinil, with the latter two being supported by high quality randomised studies. It would

[4]http://www.pbs.gov.au/industry/listing/participants/public-release-docs/2019-06/armodafinil-24-month-review-dusc-prd-2019-06.PDF

be therefore more appropriate for the treatments with evidence to be first line, and this is reflected in the Guidelines that have been issued.

There is little evidence for amphetamine use in narcolepsy. There are three level 2 studies for dexamfetamine [20-22]. While many safe hypnotics are available, clinicians have very few options for wake promotion besides dopamine-acting compounds, such as modafinil and amphetamine-like stimulants. In the future hopefully newer agents (such as sodium oxybate, solriamfetol and pitolisant) will become available on the PBS. However, until this occurs it would be appropriate if what can be used first line is not restricted to dexamfetamine, the treatment with the most side effects.

The evidence for dexamfetamine is presented in Table 1 below, with the exclusion of the Mitler 1990 study of 5 patients. The evidence is not substantive and patient numbers are low.

Table 1: Evidence for dexamfetamine use in narcolepsy

	Narcolepsy	Multiple sleep latency test (MSLT) Minutes		Number of attacks of narcolepsy per day	
	N	Placebo	Methamphetamine/Amphetamine	No Treatment	Dexamphetamine
[21] 28 days 40–60 mg	16 (8 pairs)	4.29 ± 3.12	9.27 ± 4.65		
		No statistical analysis			
[22] Phase 1: 12 weeks; 10 mg	8			4.4 (0.6)	2-7 (0-7)
				p>0.05	
Phase 2: 8 weeks; 30 mg				4.4 (0.6)	2-2 (0-3
				P<0.01	

The adverse events are reported in Table 2. However, given that the side effects of concern have a long gestation period these are unlikely to be captured. It is also evident that side effects are dose-dependent, i.e. they increase with dose. As noted earlier, the use of amfetamines as a class has become increasingly limited due to common sympathomimetic side effects (irritability, reduced appetite, and insomnia), potential for new-onset psychosis and increased risk of cardiovascular disease. These issues are exacerbated in the elderly and others with relevant comorbidities; additionally, tolerance can develop in up to a third of patients [1, 8, 11, 18]. Further, there is a high potential for diversion with dexamfetamine [19].

Table 2: Adverse events for dexamfetamine

	Placebo	Methamphetamine/Amphetamine/ Dexamfetamine 10-20 mg/day	Methamphetamine/Amphetamine/ Dexamfetamine 30-60 mg/day	Study
Sweaty	6	5	3	[21]
Palpitations	2	1	2	[21]

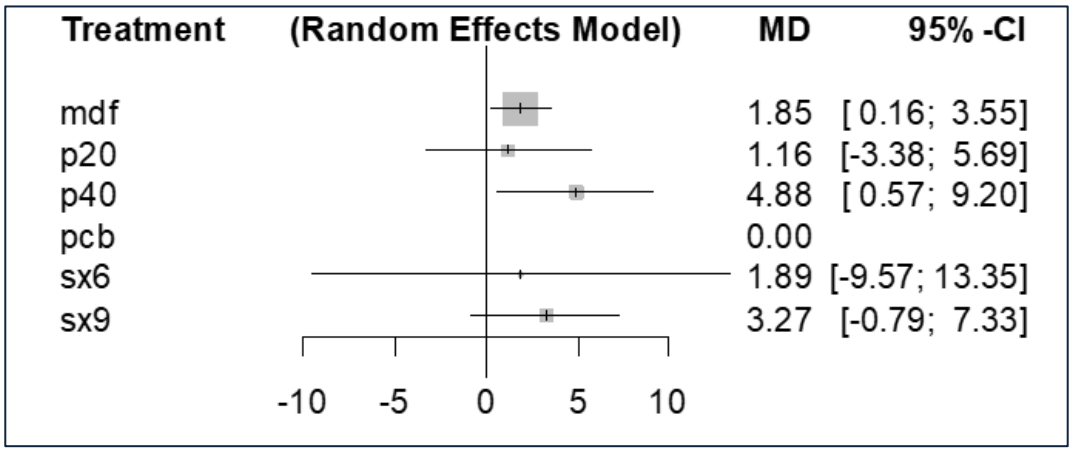
	Placebo	Methamphetamine/Amphetamine/ Dexamfetamine 10-20 mg/day	Methamphetamine/Amphetamine/ Dexamfetamine 30-60 mg/day	Study
On edge	7	6	4	[21]
Nervousness	0	2	2	[22]
Insomnia	0	1	5	[22]
Headache	1	3	4	[22]
Akathisia	0	2	3	[22]
Chest discomfort	0	1	1	[22]
Abdominal pain	0	1	1	[22]
Loss of appetite	0	4	3	[22]

3.4 The evidence for modafinil and armodafinil

The ASA is aware of the PBS listing of both modafinil and armodafinil based on clinical evidence. It is therefore accepted that the PBAC has reviewed the data and found it justifies the availability of these agents on the PBS. In our clinical experience we find that both treatments are efficacious and generally well tolerated. It is not our intent to represent the complete data here.

When comparing modafinil to placebo, Lehert and Falissard (2018) reported the results of a meta-analysis which compared trial outcomes for several narcolepsy treatments using a random effects network meta-analysis. As can be seen in Figure 1 (extracted from the Lehert and Falissard publication), the meta-analysis demonstrated that for the Maintenance of Wakefulness Test (MWT), modafinil was statistically significantly better than placebo [23].

Figure 1: Network Meta-analysis - Comparison other vs. placebo for Maintenance of Wakefulness Test (MWT)



Notes: mdf: modafinil, p20 and p40: pitolisant 20 and 40mg respectively: pcb: placebo; sx6 and sx9: sodium oxybate 6 and 9mg respectively. Source of image: [23]

Similarly a statistically significant improvement in MWT for modafinil versus placebo was reported in the meta-analysis published by Golicki et al.(2010), with a mean difference in the parallel studies of 2.81 (2.10,

3.53) [24]. The Golicki et al. meta-analysis also highlighted that modafinil appeared superior in terms of mean sleep latency when compared to placebo (as measured by the Multiple Sleep Latency Test: mean difference 1.11 (0.55,1.66)) [24].

Overall, there is substantive evidence of the effectiveness of modafinil (and by extension armodafinil) in patients with narcolepsy.

In terms of armodafinil the November 2015 PSD included a meta-analysis that indicated the non-inferiority of armodafinil vs. modafinil (see Table 3).

Table 3: Armodafinil MA from November 2015 PSD

Outcome	Analysis method	Trial 3020 (combined armodafinil 250mg and 150mg) vs. Placebo	Pooled Fry and Gross (combined modafinil 200mg and 400mg vs. Placebo)	Armodafinil vs Modafinil (indirect comparison)	
		Effect size (SE) [95% CI]	Pooled Effect size (SE) [95% CI]	Effect size (SE) [95% CI]	p-value
MWT	Primary Final visit LOCF	3.80 (1.07) [1.70, 5.90]	2.90 (0.41) [2.09, 3.71]	0.90 (1.15) [–1.35, 3.16]	0.4310

Note: Primary analysis for the submission. Final visit = week 12 (for trial 3020)/week 9 (Fry 1998 and Gross 2010) or last post-baseline visit. Both MWT and ESS were measured as the mean difference in change from baseline between treatment arms.

In terms of adverse events (AEs) too, the Lehert and Falissard (2018) network meta-analysis indicates that modafinil had a balanced profile for efficacy and safety compared to placebo [23]. The Golicki et al. meta-analysis reported risk differences between modafinil and placebo and these are highlighted in Table 4 below. Compared with the AEs reported in Table 2 for dexamfetamine, only nervousness and headache were common adverse events; where patients on dexamfetamine were respectively 2 and 3 times more likely to have these AEs than patients on placebo. The AEs with modafinil compared to placebo are not substantive, with only nausea and diarrhoea being statistically significantly more frequent with modafinil (bolded in Table 4).

Table 4: Adverse Events – Risk Difference Modafinil vs. Placebo

	Number of Studies	Risk Difference Effect Size (95% CI)
Nervousness	3	0.02 (–0.02, 0.06)
Headache	5	0.03 (–0.07, 0.13)
Pain	2	–0.03 (–0.09, 0.02)
Backpain	3	0.01 (–0.07, 0.08)
Flu syndrome	2	0.04 (–0.02, 0.09)

	Number of Studies	Risk Difference Effect Size (95% CI)
Nausea	**4**	**0.07 (0.03, 0.11)**
Diarrhoea	**3**	**0.04 (0.00, 0.07)**
Dyspepsia	3	–0.00 (–0.05, 0.04)
Dry mouth	3	0.01 (–0.08, 0.10)
Dizziness	2	–0.04 (–0.13, 0.05)
Rhinitis	2	0.03 (–0.05, 0.12)
Pharyngitis	2	–0.00 (–0.05, 0.04)
Dysmenorrhea	2	–0.01 (–0.07, 0.04)

Source: [24]

The safety profile of armodafinil is similar to that of modafinil (November 2015 PSD).

Overall, it may be concluded that both modafinil and armodafinil have been found to be effective and safe for treating narcolepsy.

4. Conclusions and recommendations

Therefore, it is concluded that the evidence for dexamfetamine is not sufficient to justify its differential first-line listing status, nor is the evidence for modafinil/armodafinil indicative of justifying a second line listing. We appreciate the price differential in favour of dexamfetamine but as clinicians we do not believe that this justifies leading to sub-optimal clinical practice for our patients.

The data presented above is not intended to promote one treatment over another. The ASA's mission is to lead and promote sleep health and sleep science across Australia and New Zealand and to advance the professional interests of its members. As the peak body it is therefore also charged with maintaining standards and clinical care for sleep patients, this submission is motivated by providing the best care for our patients, and therefore, we have no commercial interest in the medications impacted by our request. This is our first submission requesting a change to the PBS prescribing restrictions for narcolepsy.

In November 2008, a submission was considered by the PBAC, sponsored by CSL Limited on behalf of the then ASA and the Australian New Zealand Association of Neurologists (ANZAN) Joint Working Party. The November 2008 submission requested an amendment to the PBS listing of modafinil to allow use as first-line therapy for the treatment of narcolepsy. The Working Party had also requested changes to the diagnostic criteria for narcolepsy to be included. The PBAC did not accept the request.

Since then, armodafinil has also been made available for prescribing on the PBS. However, both modafinil and armodafinil continue to only be prescribed as second line (either after failure or intolerance of dexamfetamine or where dexamfetamine poses an unacceptable medical risk).

The ASA has worked within the current PBS restrictions for many years. However, as a clinical association we are concerned that the current PBS criteria are potentially harmful to patients, in that they are exposed to unnecessary risk with the perceived requirement of prior dexamfetamine use. Further in the interest of eliminating unnecessary paperwork, the removal of the requirement to resubmit all the sleep study reports before a switch from modafinil to armodafinil or vice versa, would be appreciated.

We await the PBAC's recommendation, on what we believe is an important clinical decision.

Yours truly

Alan Young
President

Sutapa Mukherjee
Clinical Chair

5. References

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