AlfredHealth

Public consultation on the post-market review of medicines for smoking cessation draft Terms of Reference

Alfred Health submission

Alfred Health welcomes the public consultation on the draft Terms of Reference of the post market review of medicines for smoking cessation subsidised through the Pharmaceutical Benefits Scheme (PBS). Alfred Health is widely recognised as a leader in the provision of treatment based healthcare, and more recently in preventative health. Smokefree environments and the clinical management of nicotine dependency are areas of key expertise and international leadership for Alfred Health.

Ensuring that medicines subsidised on the PBS are reflective of the latest clinical evidence has great potential to accelerate the decline in smoking prevalence in Australia by supporting more people who smoke to quit.

Alfred Health notes the draft Terms of Reference and this submission will provide comments on each:

1. **Collate the current clinical guidelines for medicines for smoking cessation and compare these to the Therapeutic Goods Administration (TGA) and PBS restrictions for these medicines**

Alfred Health would appreciate clarity around this term of reference regarding which clinical guidelines will be subject to review and whether international guidelines are within scope of this review. Unfortunately, there is an absence of National Health and Medical Research Council (NHMRC) Clinical Practice Guidelines for smoking cessation.

It would be prudent to consider reviewing the new edition of the Royal Australian College of General Practitioners (RACGP) *Supporting smoking cessation: A guide for health professionals* guidelines. A vast amount of work has recently been invested into a revised edition of these guidelines, due for release in 2020. This updated guideline was developed by a multidisciplinary Expert Advisory Group including representation from Alfred Health. In keeping with current international best practice of guideline development, the guideline was updated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to build upon the existing evidence base. (1) This involved the commissioning of the Joanna Briggs Institute (JBI) and the JBI Adelaide GRADE Centre to conduct an evidence review.

It is also our understanding that the Clinical Oncology Society of Australia has recently drafted a clinical document on smoking cessation in cancer patients.

Combination pharmacotherapy has been included in the United States Public Health Services Update of Clinical Practice Guidelines on the Clinical Treatment of Tobacco Use and Dependence since 2008. (2)

Many health services in Australia utilise evidence based nicotine replacement therapy (NRT) (combination therapy, higher dosages etc.) within their clinical guidelines and pathways including Alfred Health, New South Wales Health (Managing Nicotine Dependence: A Guide for NSW Health Staff) and Queensland Health (Smoking Cessation Clinical Pathway). It is also an approach adopted by Queensland Quitline.

The following clinical criteria is in place with respect to combination therapy:

- NRT- *The treatment must be the sole PBS-subsidised therapy for this condition*
- Varenicline- *The treatment must be the sole PBS- subsidised therapy for this condition*

Current PBS restrictions do not allow tailored prescribing of smoking cessation medicines, but rather limit prescribers to one single product (for the subsidy), which for many people who smoke will be suboptimal treatment. For high priority populations, such as those with a mental illness, cost can be a significant barrier to pharmacotherapy use. (3)

The following clinical criteria is in place with respect to duration of therapy:

- NRT- *Patient must not receive more than 12 weeks of PBS-subsidised nicotine replacement therapy per 12-month period. Patient who identify as an Aboriginal or Torres Strait Islander person, only two courses of PBS-subsidised NRT may be prescribed per 12-month period*
- Varenicline- *Patient must not receive more than 24 weeks of PBS-subsidised treatment with this drug per 12-month period*

It is important to consider whether current PBS restrictions may widen inequalities in terms of access to tailored and targeted strategies to support quitting such as combination therapy, higher doses and longer durations, noting that nicotine dependence is a chronic, relapsing condition and people who smoke will often require multiple attempts prior to successful quitting. (4)

A summary of the literature regarding safety and efficacy of combination therapy, higher dosages and longer durations is provided under the third Term of Reference.

Alfred Health would also welcome consideration for additional intermittent forms of NRT such as the oral mouth spray and the inhalator to be added to the PBS. While Alfred Health commended the addition of the nicotine gum and the nicotine lozenge to the PBS in 2017, these formulations will not be clinically appropriate for all people who smoke (or preferable).

2. Review the utilisation of PBS-listed medicines for smoking cessation including patient demographics, time on treatment, and the proportion using PBS subsidised combination treatment

Best practice smoking cessation treatment is to have a health professional deliver a brief intervention, which includes advice to quit and a combination of pharmacotherapy (as clinically appropriate) alongside multi-session behavioural intervention (such as telephone counselling provided by quitlines). (5)

The following treatment criteria is currently in place with respect to behavioural intervention (counselling):

- Varenicline- *Patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program or is about to enter such a program at the time PBS-subsidised treatment is initiated. Details of support and counselling program must be documented in the patient's medical records at the time treatment is initiated.*
- NRT- *Patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program or is about to enter such a program at the time PBS-subsidised treatment is initiated. Details of support and counselling program must be documented in the patient's medical records at the time treatment is initiated.*

However, for people who identify as Aboriginal or Torres Strait Islander, the above clinical criteria does not apply, however it is noted that *benefit is improved if used in conjunction with a comprehensive support and counselling program.*

Therefore, it would be ideal as part of the post-market review process to explore opportunities to ensure those accessing PBS-listed medicines for smoking cessation are engaged in behavioural intervention. Often health professionals suggest that a patient call a telephone quitline (reactive referral) rather than make the referral themselves (proactive referral). Evidence highlights that proactive referral is preferable; one study found linking people who smoke to a telephone quitline resulted in a 13-fold increase in the proportion engaging in evidence based behavioural intervention compared to providing details for the person to call themselves.(6)

3. Review the efficacy and safety of PBS-listed medicines and guideline-recommended medicines for smoking cessation, including those not currently PBS subsidised

Effectiveness in real world clinical practice as well as the controlled conditions of a clinical trial is critical in understanding the safety and efficacy of medicines for smoking cessation. It would be ideal for all forms of evidence to be included in the review alongside expert opinion.

NRT has a well-established safety and efficacy record which has allowed these products to be made widely available in pharmacies and supermarkets. In 2011, the Advisory Committee on Chemicals and Medicines Scheduling (ACMS) advised that the Schedule 4 exemption for nicotine in preparations for human therapeutic use as an aid for withdrawal from tobacco smoking be extended to include all preparations. Unlike cigarette smoke, NRT does not contain carbon monoxide and tar or any other chemical products produced when tobacco is smoked.

Blood nicotine levels achieved from recommended doses of a single form of NRT are about half those of regular smoking.(7) All NRT forms have minimal addiction potential as addictive potential is strongly influenced by speed and method of delivery of nicotine. (8)

No serious adverse effects of short or long term NRT use have been reported over many years that it has been available. (9) Adverse effects are usually relatively minor for most users and the rate of discontinuation due to adverse effects is relatively low.(10)

Nicotine is rapidly and extensively metabolised by the liver, primarily by the liver enzyme CYP2A6 (and to a lesser extent by CYP2B6 and CYP2E1) to cotinine. (7) Cotinine is subsequently metabolised to trans-3'-hydroxycotinine (3HC) exclusively or nearly exclusively by CYP2A6. The half life of nicotine averages around 2 hours, while the half-life of cotinine averages 16 hours. Nicotine and cotinine can also be metabolised by glucoronidation, primarily via UGT1A4, UGT1A9 and UGT2B10. Although

glucoronidation is usually minor pathway of nicotine metabolism, in people who have low CYP2A6 activity, glucoronidation can be a major determinant of nicotine clearance. It is important to note that there is considerable genetic polymorphism in CYP2A6 and UGT activity and is associated with a wide individual variability in the rate of nicotine metabolism. Sex hormones also substantially affect CYP2A6 activity. Therefore, people who metabolise nicotine more quickly, tend to be more dependent and find quitting more difficult. (11)

People who smoke are often under-dosed with smoking cessation medicines (e.g. one form only of NRT) and consequently, experience withdrawal symptoms leading them back to smoking (i.e. inadequate nicotine 'replacement'). (2) It is Alfred Health's view that people who smoke are likely to benefit from more targeted and tailored strategies to assist quitting. These may include using combination therapy, higher doses and longer durations to support a successful cessation attempt and prevent relapse. Approaches such as these ensure smoking cessation medicines are utilised in a way that meets the needs of the individual, as would be the case for medications to manage pain or opioid substitution therapy.

Combination NRT therapy

Combining the nicotine transdermal patch with an intermittent form of NRT has been shown to increase quit rates by 15-36% higher than monotherapy NRT.(12) Using two forms of NRT with differing pharmacokinetic properties provide improved symptom relief and enable people to quit more easily. This is because people who smoke and are attempting to quit experience a combination of moderate, steady background cravings for tobacco (which generally decrease in intensity over several weeks after quitting), and sudden bursts of an intense desire or urge to smoke, often triggered by a cue such as feeling stressed (these urges to smoke tend to get less frequent over time, however their intensity can remain strong even after many months of quitting). The transdermal patch provides slow but stable plasma nicotine concentrations assisting background cravings, while the intermittent forms deliver nicotine at a faster rate and is used to control breakthrough cravings in response to smoking cues. The intermittent forms allow for greater control over the amount and timing of dose. Some intermittent formulations also provide sensory stimulation that people who smoke find important in acutely relieving cravings. These cravings while usually brief can be quite intense and likely to be significant contributors to relapse. (13)

A recent systematic review included 63 studies (with 41,509 participants), the majority of which recruited people who smoked at least 15 cigarettes per day (although 19% (n=12) included those with lower dependence). Overall evidence favoured combination NRT over monotherapy NRT for smoking cessation (RR 1.25, 95% CI 1.1.5-1.36, 14 studies, 11,356 participants). When split into sub-groups, this was equally true for combination therapy compared to nicotine patch alone (RR 1.23, 95% CI 1.12-1.36, 12 studies, 8992 participants), or intermittent nicotine forms alone (RR 1.30, 95% CI 1.09-1.54, 6 studies, 2364 participants). (12)

A previous meta-analysis revealed that combination therapy for smoking cessation is significantly better than monotherapy NRT in all pooled comparisons. The combination NRT group had a significantly higher probability of abstinence at any time point. The aggregated relative risk of abstinence was 1.42 (95% CI 1.21-1.67), 1.54 (95% CI 1.19-2.00) and 1.58 (1.25-1.99) at 3, 6 and 12 months. (14)

In a recent review serious adverse events (SAEs) were reported rarely, with seven such events across the five studies that reported SAEs by treatment arm. There was no evidence of statistically

significant difference in SAEs between combination NRT and monotherapy NRT (RR 4.44, 95% CI 0.76-25.85, 5 studies).

The classic view in determining therapy for an individual is based on the number of cigarettes smoked per day, establishing a starting point in terms of initial dosing. However trials included in the review and analysis by Shah included people who smoked less than one pack per day, and these participants were able to tolerate combination therapy. (14)

Nicotine overdose associated with NRT use in people who smoke is uncommon. People who smoke are used to very large doses of nicotine from tobacco use. With combination NRT use, people who smoke are unlikely to receive doses of nicotine that are higher than that they received from their tobacco use. (15, 16)

Longer durations of NRT

Efficacy and safety of longer duration NRT has been supported by several randomised controlled trial (RCTs). In a RCT by Schnoll et al. 2015, participants in the extended and maintenance treatment arms (24 weeks and 52 weeks duration respectively) reported significantly greater abstinence at 24 weeks compared to standard treatment of 8 weeks (OR 1.70, p=0.04), had a longer duration of abstinence to relapse (mean 72 vs. 89 days, p<0.001), reported smoking fewer cigarettes per day if not abstinent (mean 5.8 vs. 6.4, p=0.02), and reported more abstinent days (mean 80.5 vs. 68.2 days, p=0.02). While this study didn't support efficacy of NRT use beyond 24 weeks, it is important to note that adherence to nicotine transdermal patches was lower in the maintenance (52 week) treatment arm.(17)

A meta-analysis highlighted that there are measurable benefits in studies of up to 18months of continued NRT usage for relapse prevention.(18)

Safety of longer durations of NRT is well documented in the literature. Moore and colleagues demonstrated that when NRT was used for 6-18months, there was no statistically significant difference to placebo in terms of mortality, serious adverse effects or discontinuation of therapy due to adverse effects. (19)

The best human data for considering longer duration use of NRT for both efficacy and safety is demonstrated by observational studies. The only such study is the Lung Health study which was a five year randomised trial to assess the effect of smoking cessation and reduction on chronic lung disease and pulmonary lung function. Among 5,887 subjects initially enrolled, a seven year period of additional surveillance was conducted in 3,220 subjects. (20) Although all subjects were offered NRT, and encouraged to use for only six months, many continued to use it for a longer duration. Despite the limitations, this study does not indicate a strong role for nicotine in promoting cancer risk in humans, and clearly if any, would be less than continued smoking. (21) Nicotine delivered through NRT has not received an International Agency for Research on Cancer (IARC) classification.

Approaches such as using longer durations of NRT which reduce relapse rates, could have a substantial impact on long term cessation.

Higher doses of NRT

Adding a second patch produces a modest increase in quit rates, of around 14 percent.(22) A review of the literature by Carpenter and colleagues, showed mixed evidence for support for higher doses of transdermal nicotine (22-44mg) being superior to standard doses. Interestingly though, higher

dose studies were generally restricted to people with higher dependence, likely diminishing positive cessation outcomes. (23)

Varenicline in combination with NRT

Chang and colleagues presented a meta-analysis that included two studies by Koegelenberg et al. and Ramon et al. which included 787 participants.(24, 25) The analysis indicated that combination of varenicline and nicotine transdermal patch was more effective for abstinence (at 24 weeks) than monotherapy with varenicline alone (OR 1.62, 95% CI 1.18-2.23). There were differences in levels of nicotine dependence between the studies. Greater nicotine dependency may reduce efficacy of the combination varenicline and nicotine transdermal patch on cessation. (26)

Chang and colleagues also aggregated adverse effects and generated pooled odds ratios. Participants receiving combination therapy (varenicline and NRT patch) reported more incidents of nausea (28.4% vs. 25.7%, OR 1.15, 95% CI 0.85-1.56) and insomnia (18.7% vs. 15.4%, OR 1.27, 95% CI 0.89-1.80).(26)

There is some evidence that using varenicline with NRT improves effectiveness and may be considered.

4. Review the cost-effectiveness of PBS-listed and guideline-recommended medicines for smoking cessation

Smoking remains the greatest cause of preventable morbidity and mortality in Australia (AIHW, 2019). In retrospect, smoking cessation is both cost and clinically effective, especially when compared with other preventive measures such as the treatment of hypertension or hypercholesterolemia. (27-29)

By the very nature of increased quit attempts, there will be an increase in the number of successful cessations. This is reliant on evidence based treatments and supports being used. Every person who quits smoking stands to benefit personally in health, social and financial contexts and likewise at a population level.

Thank you for your consideration of this submission.

If you have questions, please contact Ms Emma Dean, Population Health Lead, Alfred Health on (03) 90765076 or e.dean@alfred.org.au.

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