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PHARMAC and tobacco control in New Zealand: two licensed funded options are already available (with responses by Holt et al and the Editor)

Context

Shaun Holt and colleagues have recently written about PHARMAC and bupropion, citing this as an example of the "adverse effect PHARMAC has on the health of New Zealanders through restricting the availability of medications."[1]

However, it is difficult to reconcile this argument with the fact that there are already two licensed fully-funded and effective treatment options for smoking cessation—nortriptyline and nicotine replacement therapy (patches and gum).

Nortriptyline is an effective treatment that is available already

The benefits of nortriptyline were alerted to the *Journal* as far back as July 2002,[2] noting the results of a recent Cochrane review[3] on the effectiveness of both bupropion and nortriptyline. The Cochrane review concluded that nortriptyline and bupropion both had a small effect on cessation. The National Health Committee's (NHC) revised smoking cessation guidelines of May 2002[4] supported nortriptyline as a viable alternative. Nortriptyline has been licensed for smoking cessation treatment since April 2003, fully-funded on the NZ Pharmaceutical Schedule.

The backgrounder to the NHC guidelines[5] (http://www.nzgg.org.nz/guidelines/0025/smoking_cessation_background.pdf) summarised that there was evidence for the effectiveness of nortriptyline either alone or in combination with NRT, assigning a grade of "I" for the quality of that evidence.

We don't think that the perceived absence of "A" recommendations for nortriptyline in smoking cessation in some now-dated international guidelines is a problem, for the following reasons:

- The key reason that nortriptyline was not assigned an "A" evidence grading in the US guidelines (June 2000)[6] was because it had not been registered by the FDA for smoking cessation at the time the guidelines were published. That is no longer the case. The US guidelines were restricted to evidence up to 1 January 1999, and any concerns over potential side effects may have been superseded by the publication in 2001 of the Cochrane review. The US guidelines stated that "nortriptyline is an efficacious smoking cessation treatment."
- Again, the 2000 HEA guidelines for the UK[7] (cited by Holt et al as confining "A" grade recommendations to bupropion) predated the 2001 Cochrane review. Given the HEA guideline's predisposition to Cochrane reviews as the key evidence source, we are sure they would now be advocating nortriptyline as well; as such they are out-of-date.
- The other relevant guidelines for the UK were those of the Royal College of Physicians (2000).[8] These noted that nortriptyline was the other antidepressant

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that appeared to increase cessation (alongside bupropion), noting that bupropion was the only non-nicotine smoking cessation therapy marketed in the US at the time (http://www.rcplondon.ac.uk/pubs/books/nicotine/7-management.htm).

The Cochrane review was substantially updated in July 2004, detailing now six RCTs for nortriptyline smoking cessation. Four more RCTs for nortriptyline smoking cessation[9–12] have been published since the two trials.[13,14] used by the original Cochrane review of 2001. The updated Cochrane review states that overall nortriptyline doubles the odds of smoking cessation, as does bupropion.[3]

Nortriptyline is licensed for smoking cessation

Regarding any past "off-label" prescribing of nortriptyline for non-approved indications (Section 25 of the Medicines Act), the background information to the NHC guidelines specifically addressed this issue, stating that "In the case of nortriptyline, there is good evidence to support its use in smoking cessation and considerable evidence from its use as an antidepressant about its safety." The letter in the *Journal*[2] claimed that Medsafe had advised that if there was a Cochrane review supporting nortriptyline's use then there was little risk in practitioners prescribing it.

Nortriptyline was registered in New Zealand for smoking cessation within 11 months of the updated guidelines' publication.

No mention of the Cochrane review, nor the material in the New Zealand guidelines about nortriptyline

Having advised the authors of many of these points by email, we were surprised that Holt and colleagues made no direct mention of the Cochrane review, nor the material in the New Zealand guidelines about nortriptyline.

Cost effectiveness

We are not aware of the evidence behind the statement that bupropion is "more cost-effective than the majority of treatments currently funded by PHARMAC." The only head-to-head clinical trial that we are aware of (cited in recent updates to the Cochrane review) did not show a significant difference between the two drugs for this indication. It is difficult to see how spending some $316 extra per course for arguably no extra benefit becomes "more cost-effective".

Bupropion costs 25 times that of a 12-week course of nortriptyline. Funding bupropion would have meant not funding other almost certainly more cost-effective options. This would have lost the health gains that have happened from spending that money on those medicines, when there would likely be no health gains from bupropion over nortriptyline.

Comment

We are very aware of the burden of tobacco-related illness, and that bupropion is a useful adjunct to nicotine replacement therapy. As is nortriptyline. We appreciate the authors' efforts to improve smoking cessation in Maori through using bupropion,[15] although expense to patients may needlessly be a problem. Since the NHC guidelines were published in May 2002, prescriptions for nortriptyline have risen by 60%, hence suggesting perhaps 27,800 courses of nortriptyline for smoking cessation.

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PHARMAC is still waiting for the supplier of bupropion to respond to our request for further evidence, so there has never been a formal decision not to fund the drug. Not actively funding bupropion is consistent with Government's legislative requirement that PHARMAC get the best health outcomes from within the funding provided—where bupropion is overpriced when compared to the alternative. The evidence for nortriptyline is good. Having nortriptyline available is entirely consistent with a Ministry of Health that is committed to smoking cessation and the health of disadvantaged groups in New Zealand.

Conclusion

When there are two similarly efficacious treatments available, responsible clinical practice suggests we use the less expensive. Perversely, by siphoning funds from other better potential investments, funding bupropion would have adversely affected the health of New Zealanders by restricting the availability of those medicines.

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Conflict of interest: Scott Metcalfe is externally contracted to work with PHARMAC for public health advice.

References:

1. Holt S, Harwood M, Aldington S, Beasley R. PHARMAC and tobacco control in New Zealand: Government policy 'up in smoke'. N Z Med J 2002;118(1216). URL: http://www.nzma.org.nz/journal/118-1216/1502/
2. Arroll B. A cheap medication for smoking cessation. N Z Med J. 2002;115(1156). URL: http://www.nzma.org.nz/journal/115-1156/86/
3. Hughes JR, Stead LF, Lancaster TR. Antidepressants for smoking cessation (Cochrane Review). In: The Cochrane Library, Issue 1. Oxford: Update Software; 2002.
4. Guidelines for smoking cessation. Wellington: National Health Committee on Health and Disability; 2002. Available online. URL: http://www.nzgg.org.nz/guidelines/dsp_guideline_popup.cfm?&guidelineID=25 Accessed June 2005.
5. Guidelines for smoking cessation: revised literature review and background information. Wellington: National Health Committee on Health and Disability; 2002. Available online. URL: http://www.nzgg.org.nz/guidelines/0025/smoking_cessation_background.pdf Accessed June 2005.
6. Fiore MC, Bailey WC, Cohen SJ, et al. Treating tobacco use and dependence. Clinical Practice Guideline. Rockville, MD: US Department of Health & Human Services. Public Health Service; 2000. Available online. URL: http://www.guideline.gov/summary/summary.aspx?ss=15&doc_id=2360&nbr=1586&string= Accessed June 2005.
7. West R, McNeill A, Raw M. Smoking cessation guidelines for health professionals: an update. Thorax. 2000;55:987–99. Available online. URL: http://thorax.bmjjournals.com/cgi/content/full/55/12/987 Accessed June 2005.

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8. Nicotine Addiction in Britain. A report of the Tobacco Advisory Group of the Royal College of Physicians. Royal College of Physicians; 2000. Available online. URL: http://www.rcplondon.ac.uk/pubs/books/nicotine/ Accessed June 2005.
9. Hall SM, Humfleet GL, Reus VI, et al. Psychological intervention and antidepressant treatment in smoking cessation. Arch Gen Psychiatry. 2002;59:930–6.
10. Hall SM, Humfleet GL, Reus VI, et al. Extended nortriptyline and psychological treatment for cigarette smoking. Am J Psychiatry. 2004;161:2100–7.
11. da Costa CL, Younes RN, Lourenco MT. Stopping smoking: a prospective, randomized, double-blind study comparing nortriptyline to placebo. Chest. 2002;122:403–8.
12. Prochazka AV, Kick S, Steinbrunn C, et al. A randomized trial of nortriptyline combined with transdermal nicotine for smoking cessation. Arch Intern Med. 2004;164:2229–33.
13. Prochazka AV, Weaver MJ, Keller RT, et al. A randomized trial of nortriptyline for smoking cessation. Arch Intern Med. 1998;158:2035–9.
14. Hall SM, Reus VI, Munoz RF, et al. Nortriptyline and cognitive-behavioral therapy in the treatment of cigarette smoking. Arch Gen Psychiatry. 1998;55:683–90.
15. Holt S, Timu-Parata C, Ryder-Lewis S, et al. Efficacy of bupropion in the indigenous Maori population in New Zealand. Thorax. 2005;60:120–3.

Bupropion and PHARMAC revisited: response by Holt et al

The letter from PHARMAC (above) responding to our manuscript entitled *PHARMAC and tobacco control in New Zealand: Government policy up in smoke*[1] provides a concerning insight into its modus operandi. These concerns include:

- PHARMAC appears to be either unaware of Government policy or does not feel obliged to follow Government policy. In particular, PHARMAC has not provided any substantive justification as to why it has ignored the Ministry of Health's five-year plan for tobacco control,[2] in particular to give substantial weight to interventions for which there is strong scientific evidence of effectiveness, and to those which give benefit to large proportions of the community, and to maximise the benefits of targeted interventions (people with the greatest health needs such as Maori and low income New Zealanders) and minimise potential adverse effects.
- PHARMAC appears to be prepared to make statements that are simply incorrect. For example, PHARMAC states that it is not aware of the evidence behind the statement that bupropion is more cost-effective than the majority of treatments currently funded by PHARMAC, yet the National Health Committee Guidelines for Smoking Cessation[3] (referenced in the PHARMAC letter) states that smoking cessation interventions cost less than US$1,000 per life year saved, whereas a comparison cost estimate for the treatment of moderate hypertension and drug therapy for hyperlipidaemia are approximately US$10,000 and US$60,000 per life year saved respectively. In addition, we understand that in 2001 PHARMAC was provided with a comprehensive cost-effectiveness analysis of bupropion by the manufacturer which showed that for bupropion the cost per life year saved ($1,540) was similar to that of nicotine replacement therapy ($1,570) but considerably less than that for the use of other common treatments such as hypertension treated with ACE inhibitor or calcium antagonist ($1,815 to

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$213,893), statins ($11,667), and oestrogen for postmenopausal women ($13,611 to $162,040).

- PHARMAC appears to consider medications which have different pharmacological effects and different side-effect profiles as equivalent for the purpose of funding. This flawed approach appears to have become a key feature of PHARMAC's practice. This consideration is relevant to the comparison between bupropion (an 'atypical' antidepressant with both dopaminergic and adrenergic actions) and nortriptyline (a tricyclic antidepressant). As mentioned in the National Health Committee Guidelines, there are more concerns about the potential side effects of nortriptyline than with the first-line medications NRT and bupropion.[2] There will be some patients in whom bupropion is the preferred agent compared with nortriptyline just as there will be other patients in whom nortriptyline will be the preferred agent due to the differing side effect profiles.
- PHARMAC appears to be 'selective' in its review of the scientific evidence base on which its decisions are made. For example, PHARMAC does not mention that the Cochrane review[4] states that there have been 24 trials of bupropion, yet only 6 trials of nortriptyline for smoking cessation. Indeed, the efficacy and safety of bupropion has been demonstrated in a comprehensive Phase 3 programme, with studies in populations such as Maori and African-Americans, and in patients with COPD and ischaemic heart disease.[5–8] In contrast, the 6 studies involving nortriptyline have been limited by their small size, inadequate outcome measures, inappropriate data collection and confounding factors.[9–15] In the only published study which has compared bupropion with nortriptyline, the smoking cessation rate at 6 months was 16% with bupropion and 9.6% with nortriptyline, representing a non-statistically significant relative benefit reduction with bupropion of 71% compared with nortriptyline.[9] As this study was inadequately powered to determine equivalence between the two agents, it does not provide scientific evidence on which to claim that nortriptyline is equivalent to bupropion. Given the importance of smoking cessation in New Zealand (and in Maori in particular), we contend that people should be entitled to treatments which have been proven to be effective and safe in the different populations in which it would be prescribed.
- PHARMAC appears to use delay in the approval of funding as a method to restrict the availability of medications. In this case, bupropion was registered and approved for use in May 2000, and endorsed by the National Health Committee in 2002, despite nortriptyline only becoming available for registered use in 2003.
- PHARMAC appears to have an unfortunate tendency to personally criticise those who advocate the availability of proven medications which are recommended internationally but not available or restricted for use in New Zealand. We refer to its statement "Having advised the authors of many of these points by email we were surprised that Holt and colleagues made no direct mention of the Cochrane review, nor the material in the New Zealand guidelines about nortriptyline". The information contained in the Cochrane Review[4] and the New Zealand Guidelines[3] was reviewed in our report and the PHARMAC emails were cursory at best.

We stand by our conclusion that the decision by PHARMAC not to fund bupropion is directly contrary to Government policy and is inconsistent with evidence-based

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medicine and with United States and United Kingdom guidelines. The PHARMAC decision seriously questions the Ministry of Health's commitment to smoking cessation and the health of disadvantaged groups in New Zealand, particularly Maori. We concur with the view of Dr Pippa McKay that a review of PHARMAC and its operations is well overdue.[16]

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Competing interests: S Holt and R Beasley coauthored the study of the efficacy of bupropion in Maori.[9] P3 Research and the Medical Research Institute of New Zealand have received research funding from AstraZeneca, Aventis-Pharma, GlaxoSmithKline, Novartis, and Roche. S Holt and R Beasley have received honoraria for speaking at symposia from AstraZeneca, GlaxoSmithKline, and Novartis. S Holt is a Specialist Advisor to the Asthma & Respiratory Foundation of New Zealand. R Beasley is a member of WHO/NHLBI GINA Assembly, the International Association of Asthmology, and the Research Council of the World Allergy Organization. M Harwood is a member of National Maori Ethical Review Working Group (Ministry of Health), the Executive Committee Te ORA (Maori Medical Practitioners Association), and is a coauthor of *Hauora IV; Maori Health Statistics 1991 to 2001* (Eru Pomare Maori Health Research Centre).

References:

1. Holt S, Harwood M, Aldington S, Beasley R. PHARMAC and tobacco control in New Zealand: Government policy 'up in smoke'. N Z Med J 2002;118(1216). URL: http://www.nzma.org.nz/journal/118-1216/1502/
2. Ministry of Health 2004. Clearing the Smoke: A five-year plan for tobacco control in New Zealand (2004–2009). Wellington: Ministry of Health. Available online. URL: http://www.moh.govt.nz/moh.nsf/0/aafc588b348744b9cc256f39006eb29e?OpenDocument Accessed June 2005.
3. Guidelines for Smoking Cessation. Wellington: National Health Committee on Health and Disability, 2002. Available online. URL: http://www.nzgg.org.nz/guidelines/dsp_guideline_popup.cfm?&guidelineID=25 Accessed June 2005.
4. Hughes JR, Stead LF, Lancaster TR. Antidepressants for smoking cessation [Cochrane Review]. In: The Cochrane Library, Issue 1, 2002 Oxford: Update Software.
5. Ahluwalia JS, Harris KJ, Catley D et al. Sustained-release bupropion for smoking cessation in African Americans. JAMA. 2002;288:468–74.
6. Tonstad S, Farsang C, Klaene G, et al. Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study. Eur Heart J. 2003;24:946–55.
7. Tashkin D, Kanner R, Bailey W, et al. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. Lancet. 2001;357:1571–5.
8. Holt S, Timu-Parata C, Ryder-Lewis S, Weatherall M, Beasley R. Efficacy of bupropion in the indigenous Maori population in New Zealand. Thorax. 2005;60:120–3.

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9. Hall SM, Humfleet GL, Reus VI, et al. Psychological intervention and antidepressant treatment in smoking cessation. Arch Gen Psych 2002;59:930–6.

10. da Costa CL, Younes RN, Lourenco MT-C. Stopping smoking: a prospective, randomized, double-blind study comparing nortriptyline to placebo. Chest, 2002;122:403–8.

11. Hall SM, Reus VI, Munoz RF, et al. Nortriptyline and cognitive-behavioral therapy in the treatment of cigarette smoking. Archives of General Psychiatry 1998;55:683–90.

12. Hall SM, Humfleet G, Maude-Griffin R, et al. Nortriptyline versus bupropion and medical management versus psychological intervention in smoking treatment (PA 5A). Society for Research on Nicotine and Tobacco, 7th Annual Meeting, March 23-25, Seattle, Washington; 2001;31.

13. Hall SM, Humfleet GL, Reus VI, et al. Extended nortriptyline and psychological treatment for cigarette smoking. American Journal of Psychiatry. 2004;161:2100–7.

14. Prochazka AV, Weaver MJ, Keller RT, et al. A randomized trial of nortriptyline for smoking cessation. Archives of Internal Medicine. 1998;158:2035–9.

15. Prochazka AV, Reyes R, Steinbrunn C, et al. Randomized trial of nortriptyline combined with transdermal nicotine for smoking cessation (PO3 26). Abstract Book. Society for Research on Nicotine and Tobacco, 7th Annual Meeting, March 23-25, Seattle, Washington; 2001;73.

16. MacKay P. Is PHARMAC's sole-supply tendering policy harming the health of New Zealanders? N Z Med J. 2005;118(1214). URL: http://www.nzma.org.nz/journal/118-1214/1433

NZMJ Editor's response

The recent article on bupropion is the first in a series of peer-reviewed articles on the influence of PHARMAC on drug prescribing in New Zealand. PHARMAC is very important for healthcare in New Zealand. It has a key role in helping New Zealand get the most from its very limited healthcare dollar. It is, however, important that quality of the spending is looked at as well as the quantity of drug acquired.

PHARMAC has a very large budget. Unlike the Drug Industry, it is accountable to the New Zealand public. The series that we are running explores the value we are getting for the money spent.

PHARMAC does not like criticism, if the intimidating phone calls and numerous emails I have been receiving from them are anything to go by. No doubt in the next few months they will try and undermine what we are doing. I expect a lot of correspondence from them (e.g. two letters to the editor in this edition) however it also helps to create a lively and interesting debate.

Frank A Frizelle
Editor, NZMJ

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