Potential Conflict of Interest and Bias in the RACGP's Smoking Cessation Guidelines: Are GPs Provided with the Best Advice on Smoking Cessation for their Patients?

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Patient visits are an important opportunity for general practitioners (GPs) to discuss the risks of smoking and cessation strategies. In Australia, the guidelines on cessation published by the Royal Australian College of General Practitioners (the *Guidelines*) represent a key resource for GPs in this regard. The predominant message of the *Guidelines* is that pharmacotherapy should be recommended as first-line therapy for smokers expressing an interest in quitting. This, however, ignores established evidence about the success of unassisted quitting. Our analysis of the *Guidelines* identifies a number of potential conflicts of interest which may have affected the advice provided. These include extensive funding by the pharmaceutical industry of sources cited to support the recommendations, and relations between members of the *Guidelines* Content Advisory Group and the pharmaceutical industry. Recommendations issued by professional bodies have enormous potential impact upon public health and there is a need for the highest levels of scrutiny and transparency in their development. Information about research cited in guidelines should include funding sources, and developers should be free of obvious conflicts of interest. Smoking remains the leading preventable cause of global mortality. Concerns related to pharmaceutical industry funding of research, scientific integrity and recommendations on smoking cessation by medical advisory groups clearly have implications beyond Australia.

Introduction

Despite comprehensive tobacco control legislation that has led to an historically low daily smoking rate of 12.8 per cent Australians aged 14 years or older (Australian Institute of Health and Welfare, 2014), smoking remains a crucial public health challenge in Australia. Nearly 2.5 million continue to smoke daily and tobacco consumption is the country's leading preventable cause of mortality, accounting for an estimated 15,000 annual deaths (Australian Institute of Health and Welfare, 2014). Total related tangible and intangible costs to Australian society amounted to AUD 31.5 billion in 2004–2005 (Australian Institute of Health and Welfare, 2012). Given ongoing tobacco industry strategies to recruit new smokers (Hastings, 2014; Campaign for Tobacco-Free Kids, 2014), the importance of helping current smokers to quit is an urgent public health priority.

General practitioners' (GPs') advice to their patients provides an important opportunity to explain the health risks of smoking and discuss cessation strategies (Tracy *et al.*, 2014). Discussions are most effective with patients who present with a smoking-related illness. Simple advice appears to have a minimal effect on quitting success rates (Stead *et al.*, 2013) and many GPs are unenthusiastic about brief, unprompted interventions with smokers, citing time constraints and concerns that unsolicited interventions may alienate patients (Aveyard *et al.*, 2011). Such reservations notwithstanding, approximately 85 per cent of Australians attend a GP annually (Britt *et al.*, 2013) and these appointments represent important opportunities to discuss cessation.

In 2011, the Royal Australian College of General Practitioners (RACGP), the country's peak general practice body representing more than 21,000 GPs (Royal Australian College of General Physicians),

published *Supporting smoking cessation: a guide for health professionals* (the *Guidelines*) (Zwar *et al.*, 2011). Noting the important role that GPs can play in advising smokers on quitting, the *Guidelines* are designed to serve as a ‘practical, succinct and evidence based resource’ that ‘builds on momentum for cessation’ created by population-level interventions such as tax increases, restrictions on smoking, changes to tobacco display and packaging and the social marketing of smoking cessation (Zwar *et al.*, 2011).

In this article, we contrast cessation advice provided to GPs in Australia by the *Guidelines* with recent research into how smokers quit, and argue that the *Guidelines* do not accurately reflect current evidence about smoking cessation. In particular, the *Guidelines’* emphasis on pharmacologically assisted cessation is at odds with the high success rates of unassisted cessation (Smith and Chapman, 2014). Our analysis identifies a number of potential conflicts of interest and flaws in the evidence-based cited to support the *Guideline’s* recommendations. These include an over-reliance on pharmaceutical industry-funded research, and conflicts of interest amongst members of the Content Advisory Group (CAG) secondary to industry ties. The former is problematic both for potential bias in the research itself, and because pharmaceutical interventions are over-represented in the evidence base at the cost of other kinds of interventions.

These concerns about bias in the recommendations of the *Guidelines* are significant because of the weight that may be attached to advice issued by peak medical advisory bodies such as the RACGP. This kind of advice is endorsed by recognized authorities, may play a role in defining standards of care, provides recommendations to clinicians and can contribute to policy formulation (Stamatakis *et al.*, 2013; Baird and Lawrence, 2014). It is therefore imperative that such advice reflects the key issues, debates and evidence within their respective fields and to the greatest extent possible, is free of perceptions of conflict of interest (COI). We argue that the RACGP *Guidelines* fail to meet these important criteria. Finally, we make recommendations for strengthening future editions including a more comprehensive review of the relevant literature that is less dependent on industry-funded findings, and greater effort to reduce perceived COI among the guideline development group.

The *Guidelines’* Recommendations

The dominant message of the RACGP’s recommendations is that successful cessation requires pharmaceutical

intervention in the form of nicotine replacement therapy (NRT) patches, gum or spray, or medication such as Bupropion (Zyban) or Varenicline (Chantix, Champix). The *Guidelines* largely ignore or dismiss the value of unassisted cessation, despite this being historically the most successful means of quitting by which between two-thirds and three-quarters of former smokers have stopped smoking (Smith and Chapman, 2014). ‘Unassisted’ cessation is the use of ‘no aids, including NRT, how to quit or self-help materials, consulting a GP, advice from health professional, pharmacist or dentist, prescribed medication, using a quitline service, natural or alternative therapy, online quit smoking info, online quit smoking programme’ (Smith *et al.*, 2013).

The *Guidelines* state (p. 27) that:

Pharmacotherapy should be recommended to all dependent smokers who express an interest in quitting except where contraindicated. Some people prefer to try to quit without assistance and this choice should be respected, however, best results are achieved when medicines are used in combination with counselling and support although there is some evidence that nicotine replacement therapy (NRT) can increase quit rates with or without counselling. The choice of pharmacotherapy is based on clinical suitability and patient choice.

Unassisted quitting is acknowledged in this passage, but this is presented, at best, as a matter of patient choice rather than the ‘best results’ achieved through use of medication and support. Patient choice will be informed by, at least in part, discussion with their GP but if physicians are given the advice by their peak body that NRT increases success rates for quitting, with or without counselling or support, unassisted cessation is unlikely to be promoted. Similar reticence about unassisted quitting is found elsewhere within the *Guidelines*. While it is allowed that ‘the most common method used by most people who have successfully stopped smoking is unassisted cessation’, this point is moderated by the statement that ‘more than half of all smokers making quit attempts are using some form of help, mainly medications’ (p. 17). Similarly, it is acknowledged that many smokers are likely to try to quit without recourse to pharmacotherapy but that this approach has ‘a low likelihood of succeeding’ (p. 41). Thus despite these mentions of unassisted or ‘cold turkey’ quitting in the *Guidelines*, the overall tenor is to promote pharmacotherapy, with or without support, as first-line intervention for cessation.

Support for pharmacotherapy in the *Guidelines* reflects a reliance on impressive cessation rates reported by randomized controlled trials (RCTs). However, these

outcomes are not replicated in 'real world' settings. As described elsewhere (Chapman, 2011), RCTs are unrepresentative of the general population and notably exclude those with mental health problems who are heavily over-represented among smokers. Trial participants receive free pharmaceuticals, travel costs and expenses, and are far more likely to complete the recommended course of medication than is the case outside trial settings. Further, participants have frequent contact with researchers which can lead to Hawthorne effects, and NRT trials have been shown to have poor blindness integrity.

Despite positive findings from RCTs, valid questions remain regarding the effectiveness of pharmaceutically mediated cessation under real-world conditions, including how it compares with unassisted cessation. Studies published in 2013 found that NRT had no bearing on success of quit attempts (Alpert *et al.*, 2013), and that rather than helping smokers quit, extensive NRT marketing campaigns led to reduced expectations about how difficult it was to quit (Pierce *et al.*, 2012). More recent studies set in real world environments include Brown *et al.* (2014) who reported that NRT was both less effective outside of the RCT environment and had markedly worse outcomes than unassisted attempts. Two other studies (Kotz *et al.*, 2014a,b) meanwhile, found that smokers who used NRT purchased over the counter (OTC) were less likely to quit than those making unassisted attempts, but prescription medication with specialist or even minimal behavioural support resulted in improved quit outcomes compared to unaided attempts. Such concerns about the reliability of RCT evidence on the effectiveness of pharmaceutically assisted quitting raises the question of why the *Guidelines* are supportive of this intervention.

Potential Conflict of Interest in the *Guidelines*

We identified two potential sources of conflict of interest in the *Guidelines*, in the evidence cited to support recommendations and in the group responsible for drafting the *Guidelines*. We describe each of these in what follows, while in the discussion we canvas the possible effects of these conflicts of interest.

Evidence Cited in the *Guidelines*

We analysed the literature used to inform the *Guidelines*. Of the 202 peer-reviewed articles, systematic reviews,

reports and other publications cited in the *Guidelines*, 94 individual resources either recommended or dismissed various methods and treatments aimed at helping smokers to quit. The remaining 108 publications were related to issues such as smoking prevalence, associated health impacts, the role of health professionals in cessation and policy, and were not further considered.

Findings reported by the 94 studies were first categorized by whether their focus was on assisted or unassisted methods; studies of assisted cessation were then classified by type of assistance investigated in each study. Those recommending more than one approach, e.g. pharmacotherapy and counselling, were categorized by the main focus of the study. All studies were then assessed to determine the source of funding, and whether or not this was from pharmaceutical companies that manufacture cessation products. Systematic reviews cited in the *Guidelines* were analysed separately to determine funding for individual studies included in the reviews.

Of the relevant 94 peer-reviewed articles, systematic reviews, reports and other material cited as evidence, the vast majority (97 per cent) were studies of assisted cessation methods. These are categorized in Figure 1 using adapted RACGP headings. Nearly two-thirds (57, 63 per cent) of these studies reported positive quit rates in clinical trials of pharmacotherapy-assisted cessation including NRT delivery systems, Varenicline, Bupropion or Nortriptyline. Only four studies, which assessed cessation in the specific populations of pregnant and lactating women, and smokers with mental illness, urged caution in prescribing pharmaceutical-assisted cessation.

Studies of counselling via Quitlines or individual or group sessions accounted for 16 (17 per cent) of 91 studies on assisted cessation. In some cases, counselling was recommended to supplement pharmacotherapy. Of the remaining studies, 12 (13 per cent) focused on what the *Guidelines* describe as ineffective/unproven methods including hypnotherapy, acupuncture, Naltrexone, rapid smoking, biomedical feedback, physical activity, St John's wort and e-cigarettes. The remaining six studies (7 per cent) considered self-help material, primarily internet and phone texting support.

Three studies of unassisted cessation were cited. Two of these three studies (Baillie *et al.*, 1995; Hughes *et al.*, 2004) reported that quit strategies without some form of assistance were ineffective. Based on available evidence, neither study received pharmaceutical industry support; one published in 1995 included only partial information on funding, while the 2004 study was supported by the US National Institute on Drug Abuse. The third study is

Figure 1. Studies of cessation methods cited in RACGP guidelines.

a 2010 article that raised concerns about the fact that while unassisted cessation remains the most successful way to quit smoking, research into this method and its possible applications to current smokers has been largely neglected (Chapman and Mackenzie, 2010).

Funding

Statements on research funding and authors' competing interests from all publications cited in the *Guidelines* were analysed to determine whether studies and/or authors had received support from pharmaceutical companies that manufacture cessation products, or if researchers had other relevant industry connections such as consultancies or shareholdings. Other than studies that focused predominantly on pharmacotherapy, none of the publications or authors cited in the RACGP *Guidelines* reported receipt of funding or other support from industry. Of the 57 studies of pharmaceutical-assisted cessation identified in Figure 1, seven were excluded from the analysis of funding sources. Five of the excluded studies were systematic reviews, which are discussed below; one could not be sourced, thus the source of funding is unknown; and the last study reported receiving cessation products but not financial support from a pharmaceutical company. This left 50 studies that recommended the use of pharmacotherapy in quit smoking attempts; of these, 35 (70 per cent) reported receiving funding from and/or that researchers were otherwise supported by one or more pharmaceutical manufacturers of cessation medication (see Figure 2).

Figure 2. Pharmaceutical industry funding or other support.

Systematic Reviews

The *Guidelines* cite 22 systematic reviews across the four categories of assisted cessation shown in Figure 1. Of these, five focus on pharmaceutical assistance, eight on counselling, seven on unproven or ineffective methods and two review studies of self-help approaches. Of the five reviews of studies of pharmaceutical assistance, two were not further considered as one dealt with the specific sub-population of hospitalized smokers, and the other focused on counselling augmented by pharmacotherapy. The remaining three reviews (Hughes *et al.*, 2007; Stead *et al.*, 2008; Cahill *et al.*, 2011) assessed studies of pharmacotherapy assistance applicable to the general population of smokers and are included in our analysis. Only Cahill *et al.* (2011) included information on

funding sources, reflecting previous findings that roughly 30 per cent of Cochrane systematic reviews report on funding sources of cited research (Roseman *et al.*, 2012). We therefore searched original papers to determine the frequency of industry funding of the studies included in the remaining reviews by Hughes *et al.* (2007) and by Stead *et al.* (2008).

After identifying sources of funding, we then correlated funding source with the presence or absence of support for pharmaceutical assistance to quit in the 166 studies cited in the three reviews (see Table 1). The vast majority of studies cited in the reviews (154 of 166) supported pharmaceutical assistance. Of the 107 out of the 166 industry-funded studies, 102 reported positive results from NRT and other medication (61 per cent of the total studies). In contrast, five (3 per cent) industry-funded studies reported results that did not support pharmaceutical assistance.

The prevalence of industry-funded studies assessed by the systematic reviews cited in the *Guidelines* (as per Table 1) leads to an apparent evidence-base in support of the message that smokers need pharmaceutical assistance to quit.

Content Advisory Group

The CAG that oversaw development of the RACGP *Guidelines* consisted of eight members (excluding coordination and writing support personnel). Five were academics; three from universities, one from a Sydney hospital and one from Quit Victoria—a leading tobacco control organization based in Melbourne. The remaining three members were an employee of Quit Victoria, and one representative each from the National Practice Nurses Association and the Pharmaceutical Society of

Australia. Three of the five academic members of the CAG, including the Chair, disclosed financial links in the form of honoraria or support, and/or served on advisory boards for one or both of Pfizer Pty Ltd or GlaxoSmithKline Pty Ltd, both leading producers of cessation medications. A fourth academic member of the CAG listed no connections to the pharmaceutical industry, although a paper published more than 10 years earlier declared membership in, and receipt of educational untied grants from a Smoking Cessation Consortium supported by GlaxoSmithKline, as well as small consultancies for GlaxoSmithKline and Pharmacia related to promotion of smoking cessation (Borland, 2002). This last association occurred more than a decade ago, which exceeds the usual 3 years assumed by many journals to extinguish the effects of any association (Goozner *et al.*, 2008), but given current debates about pharmaceutical funding of clinical research, it may have been reasonable for this association to be declared.

Finally, one of two external reviewers identified in the *Guidelines* reported in a recently published article (Zwar *et al.*, 2014) that he had received honorariums for teaching, consulting and travel from Pfizer, GlaxoSmithKline and Johnson and Johnson Pacific. Thus of the eight CAG members, three including the chair had declared links with pharmaceutical companies who manufacture smoking cessation products, one had undeclared historical links and one of the two reviewers had likewise received relevant industry funding.

Discussion

This analysis of the RACGP *Guidelines* on smoking cessation raises a number of concerns. First, there is a lack

Table 1. Analysis of citations supporting pharmacotherapy cessation in selected Systematic Reviews

Systematic Review	Studies in review	Studies with results supporting pharmaceutical assistance			Studies with results NOT supporting pharmaceutical assistance		
		Industry funded	Other funding	Funding not listed	Industry funded	Other funding	Funding not listed
Cahill 2011	16	13 (81%)	2 (13%)	1 (6%)	—	—	—
Hughes 2007	53 ^a	31 (58%)	13 ^b (25%)	7 (13%)	—	2 (4%)	—
Stead 2008	97 ^c	58 (59%)	13 ^d (13%)	16 ^e (16%)	5 (5%)	4 (4%)	1 (1%)
Totals	166 (100%)	102 (61%)	28 (17%)	24 (14%)	5 (3%)	6 (4%)	1 (1%)

Figures rounded to 100%.

^aTotal of 65 studies included in systematic review: 12 not accessible for this analysis.

^bFive studies supplied with pharmaceutical product for research—but *no* pharmaceutical funding listed.

^cTotal of 131 studies included in systematic review: 34 not accessible for this analysis.

^dFour studies supplied with pharmaceutical product for research—but *no* pharmaceutical funding listed.

^eThirteen studies supplied with pharmaceutical product for research—but *no* pharmaceutical funding listed.

of attention to unassisted cessation, despite the considerable evidence that the large majority of existing former smokers quit without assistance (Chapman and Mackenzie, 2010; Edwards *et al.*, 2014). Second, the *Guidelines* recommend pharmacotherapy for ‘all dependent smokers who express an interest in quitting’ (*Guidelines*, p 20) despite the potential for bias in the industry-funded research cited as evidence about the efficacy of pharmaceutical assistance, which undermines the reliability of this recommendation. The recommendations seem to reflect the quantity rather than quality of the available studies. The *Guidelines* include no critical commentary regarding the imbalance between the numbers of studies that recommend pharmacotherapy (57 of 91) and those that recommend other forms of equally successful assisted cessation. Third, there is no discussion of the potential impact of the identified conflicts of interest of the members of the CAG.

Unassisted Cessation

The *Guidelines* largely ignore or dismiss the value of unassisted cessation, despite this being historically the most successful means of quitting. Between two-thirds and three-quarters of former smokers stopped smoking without assistance (Lee and Kahende, 2007; Shiffman *et al.*, 2008; Alpert *et al.*, 2013; Pierce *et al.*, 2012). Evidence of the efficacy of unassisted quitting is outlined in a 2014 systematic review of studies of population-level cessation published between 1986 and 2010, which demonstrates that the majority of quit attempts have been made unassisted (Edwards *et al.*, 2014). One particularly compelling indication of how smokers quit (not covered in the 2014 review) is contained in the American Cancer Society’s (2003) report which reported that 91.4 per cent of former smokers in the USA had quit unassisted.

More recent sources echo the Society’s findings. A 2008 analysis of cessation methods in the USA found that unassisted quitting produces 2.8 times more successful attempts than those relying on NRT (Shiffman *et al.*, 2008), while a Gallup poll taken in 2013 reported that 48 per cent of ex-smokers ‘just quit’ or stopped ‘cold turkey’, compared to 6 per cent that successfully quit using nicotine patches or gum, and 3 per cent that cited use of prescription drugs (Newport, 2013). A 2013 review of the situation in Australia (Smith *et al.*, 2013) reported that 54 per cent to 69 per cent of ex-smokers quit unassisted. We recognize that the evidence provided in the research cited here is considered to be less reliable than that derived from RCTs. However, the reliability of RCTs can be undermined not only by

methodological features, but also by industry funding. It thus seems odd to privilege potentially biased RCT evidence in developing the *Guidelines*, while omitting consideration of substantial non-RCT evidence.

In its lack of attention to unassisted cessation, the RAGCP *Guidelines* reflect much of the current thinking on cessation in Australia. Cancer Council Australia, the Heart Foundation, Australian Council on Smoking and Health and Quit Victoria all lobbied the Pharmaceutical Benefits Advisory Committee, the national body that oversees subsidization of prescription medicines, to provide subsidized NRT to all smokers in 2010 (Australia Department of Health, 2014) at a cost of roughly AUD \$9m annually (Australian Broadcasting Corporation, 2013). The return on this considerable investment is brought into question by the potential for bias in research demonstrating positive impacts on smoking cessation rates. A recent analysis of the impacts of a range of anti-smoking policies found, for example, that ‘availability of cessation medication was not statistically associated with smoking prevalence’ (Wakefield *et al.*, 2014).

The federal government’s National Tobacco Campaign website, meanwhile, states that smokers can double the chances of quitting by using medication, and questions the veracity of ex-smokers’ claims to have quit cold turkey (Government of Australia, 2012). Likewise Quit Victoria claims that ‘you will be more likely to succeed with a good coach like Quitline and with nicotine replacement products or quitting medication’ (Quit Victoria, 2014). The narrow perspective on cessation common both to these organizations and the *Guidelines* discounts the success of unassisted cessation, instead emphasizing pharmaceutical interventions in a manner that does not acknowledge the potential bias in evidence underpinning efficacy claims. The degree to which current cessation discourse is dominated by this pro-medication perspective has led to inadequate research into unassisted cessation (Chapman and Mackenzie, 2010) and to policy that either fails to acknowledge the historic effectiveness of unassisted quitting or actively discourages unaided cessation (Raupach *et al.*, 2013) despite its documented success rate (Smith and Chapman, 2014; Hung *et al.*, 2011). Thus while the *Guidelines* may well provide an accurate synthesis of the available evidence-base (narrowly construed), they fail to engage with an overview of the kinds of evidence which are relevant for an issue such as smoking cessation. In particular, they do not comment on the over-representation of RCTs of pharmaceutical cessation products; the difficulty of obtaining RCT evidence comparing assisted versus unassisted cessation; the

paucity of trials of unassisted quitting; and the need to take account of non-RCT evidence given that smoking cessation is a complex activity that occurs over time, making it very difficult to control for all variables.

Problems around Conflict of Interest and Bias

Given existing evidence on the success of unassisted cessation, the RACGP recommendation of pharmacotherapy for ‘all dependent smokers who express an interest in quitting’ (*Guidelines*, p 20) seems to be based upon a skewed and potentially biased evidence base. The evidence base is skewed in that it is dominated by studies of pharmaceutically assisted quitting, as our analysis shows. This is not a unique problem: a 2010 analysis found that just over 91 per cent of recent studies into smoking cessation methods focused on assisted cessation, and over half (52.9 per cent) made positive claims for the effects of pharmacotherapy. In a random sample of studies that supported use of pharmacotherapy, almost half (48 per cent) received funding or support from manufacturers of pharmaceutical cessation aids, compared to negligible levels of support for research on unassisted quit methods or studies that discussed prevalence of cessation methods (Chapman and Mackenzie, 2010). Our results support this finding: studies cited in the *Guidelines* of assisted cessation far outnumber those of unassisted cessation, and pharmacotherapy dominates the method of assistance that is studied.

The evidence for pharmaceutically assisted quitting is potentially biased as the majority of the studies are funded by industry. In 2007, Etter *et al.* reported that their review of selected controlled trials of NRT found that more than half (51 per cent) of industry-funded trials reported significant cessation effects compared to 22 per cent of trials not funded by the industry (Etter *et al.*, 2007). Findings from cessation research reflect broader concerns regarding the outcomes of industry-funded studies which can be several times more likely to return findings favourable to the sponsoring company than studies of the same product funded by government or not-for-profit organizations (Silverman *et al.*, 2010; Stamatakis *et al.*, 2013).

There are a number of possible reasons for these apparent discrepancies in outcomes depending upon sources of research funding. First, there may be publication bias resulting from publication of favourable, and withholding of unfavourable, results from commercially funded research (Lexchin *et al.*, 2003). Second, commercially funded research may use methods more likely to return positive results including use of

inappropriate comparators (such as non-equivalent doses, placebos instead of active agents); selection of outcomes which favour the trial drug; or statistical methods which mask or minimize adverse events (DeVries and Lemmens, 2006).

As well as intentional methodological manipulation, industry-funded research raises questions of COI, understood here as a situation in which professional judgement concerning a primary interest ‘is unduly influenced by a secondary interest’ that may be financial or non-financial (Norris *et al.*, 2011), among industry-funded researchers (Cosgrove *et al.*, 2013; Norris *et al.*, 2012). Financial conflicts of interest are relatively straightforward, and typically involve various fees or stipends paid to researchers. Non-financial conflicts such as career advancement, increased sense of self-worth, publications, future research funding and awards and advancement of scientific knowledge also have the potential to affect individual judgement (Norris *et al.*, 2011). In its 2009 assessment of conflicts in research, the Institute of Medicine (IOM) reported that while benefits to researchers working with industry exist, these relationships also risk the possibility that individual and institutional financial interests ‘may unduly influence professionals’ judgments about the primary interests or goals of medicine’, thereby threatening ‘the integrity of scientific investigations’ (Institute of Medicine, 2009). Such perceptions, the report added, raise concerns ‘about the openness of research and potential bias in the design, conduct, and reporting of research’ (Institute of Medicine, 2009).

Conflicts of interest can exert effects upon judgement, potentially rendering it unreliable. In clinical literature, such COI-related bias ‘almost always results in overestimation of benefit and underestimation of harm’ (Laupacis, 2006). It is important to note that such bias may be unintentional, and that clinicians and academic researchers are likely to believe that their scientific training and professionalism insulate them from external influences that could potentially affect their opinions and recommendations. However, studies in neuroscience, neuropsychology and other fields suggest that COIs create bias that can be unintended, or of which decision makers are unaware (Cosgrove *et al.*, 2013; Cain and Detksy, 2008).

In relying upon research dominated by industry funding, the *Guidelines* risk drawing their evidence from an unreliable source, yet they contain no discussion at all of the increasingly well-documented criticisms of industry-funded research. The ranking of evidence used in the *Guidelines* reflects standard evidence hierarchies which privilege systematic reviews of

randomized controlled trials, but take no account of the effects of the funding source on the results of the trials so reviewed. Thus the potential effects of industry funding upon the evidence is excluded from consideration.

Problems associated with industry funding of research are well beyond the control of the RACGP and its advisory panel on smoking cessation. However, the RACGP needs to be aware of the potential for conflicts of interest among members of guideline writing groups, and the appointment of such groups is well within its remit. The IOM (2011) attributes the significant influence of guidelines to having the ‘power to translate the complexity of scientific research findings into recommendations for clinical practice and potentially enhance healthcare quality and outcomes’, but also cautions that ‘the current state of CPG [clinical practice guidelines] development has yet to meet this potential’. Much of the failure of guidelines has been ascribed to COI amongst members of panels writing guidelines (Institute of Medicine, 2011; Neuman *et al.*, 2011; Williams *et al.*, 2011). Cosgrove *et al.* (2013) note that recommendations prepared by professional organizations and medical speciality groups are especially vulnerable to bias. The inherent danger in what one study has described as ‘a significant trend for some groups to emphasise poorly evidenced recommendations’ (Baird and Lawrence, 2014) is that clinicians and other medical personnel rely on GPCs for concise, accurate information.

However, disclosure of ties to industry, considered by many as a panacea to problems of conflict, does not eliminate bias from decision-making and may, counter-intuitively, exacerbate the situation (Cain *et al.*, 2005). Lowenstein *et al.* (2012) argue that disclosing financial or other links to industry enables physicians and medical researchers to provide biased advice due to two mechanisms: strategic exaggeration, the tendency ‘to provide more biased advice to counteract anticipated discounting’; and moral licensing, ‘the often unconscious feeling that biased advice is justifiable because the advisee has been warned’. Disclosure, in effect, runs the risk of making clinicians and researchers believe they are ‘impervious to bias’ (PLOS Medicine Editors, 2012).

While financial links between guideline authors and industry do not inevitably result in interpretations or decisions that benefit industry, they do raise questions around the guideline development process. Norris *et al.* contend that evidence of COI cannot prove that conflicts are causally related to specific recommendations, but ‘observational data can be used to explore relationships and to generate hypotheses on the extent and direction of the influences exerted by specific conflicts on

recommendations in CPGs’ (Norris *et al.*, 2011). Given the crucial role played by advisory panels that produce guidelines, indications of conflict among members will generate the sort of hypotheses that Norris *et al.* allude to, underlining the need for careful consideration of their composition.

In the case of the RACGP recommendations on cessation advice, the links between members of the CAG and industry do not categorically demonstrate industry influence on decisions taken by the members of the group in writing the recommendations. Such links can, however, create perceptions that *Guidelines*, which largely disregard the efficacy of unassisted cessation in favour of pharmacotherapy, and that also rely upon an evidence-base of predominantly industry-funded research, reflect a distinctly pro-industry position. The potential for such interpretation is exacerbated by the RACGP decision to include a link to GlaxoSmithKline, manufacturers of Nicabate NRT products, on its cessation guidance web page (Zwar *et al.*, 2011).

Recommendations

There are a number of ways in which future iterations of the *Guidelines* may be strengthened to avoid the criticisms we have raised here. First, guidelines should, at a minimum, include information on the funding of trials and studies cited. A 2011 Cochrane systematic review (Cahill *et al.*, 2011), that, unusually for publications in the series (Roseman *et al.*, 2012), includes funding sources for all cited research provides a useful model of how easily this can be achieved. Second, where much of the available research is industry funded, this should either be excluded, or be noted and commented upon in the *Guidelines*. As yet there is no agreed metric for discounting the findings of commercially funded research, but drawing guideline users’ attention to the potential bias in the evidence base is a minimal first step towards greater transparency.

Advisory panels that interpret studies and make recommendations should be assembled with greater emphasis on eliminating or at least mitigating COI amongst members. The IOM (2011) suggests that whenever possible, panel members should not have conflicts and when this is not possible, members with ties to industry should constitute a minority on the panel, and in all cases chairs and co-chairs should not have conflicts. It further recommends that advisory groups be multidisciplinary and include a range of methodological experts and clinicians. Others have suggested a

compromise in which members with disclosed conflicts be allowed to interpret data but not contribute to recommendations made by the guidelines or be present in the room when recommendations are developed (Guyatt *et al.*, 2010). It is particularly relevant to a discussion of Australian GP guidelines that the National Health and Medical Research Council, the country's leading body supporting research, makes similar recommendations (National Health and Medical Research Council, 2012) to those put forward by the IOM on conflicts of interest in guideline development groups.

Greater transparency of financial and non-financial conflicts among panel members is one obvious area that can be readily improved, and would allow for more informed assessment of quality and rationale for the inclusion of specific studies. All financial rewards, irrespective of the amount, should be disclosed given that the potential for even small gifts such as pens and other office stationery to influence professional behaviour by creating favourable implicit attitudes towards the products so advertised (Katz *et al.*, 2010; Grande *et al.*, 2009). This process should include reporting of potential conflicts that occurred beyond the arbitrary and generally short period, often 3 to 5 years, required by disclosure policy. Detailed and accurate reporting will facilitate exploring associations between potential conflicts and recommendations (Norris *et al.*, 2011).

At least three significant obstacles exist to adopting tighter controls on advisory panels. The seemingly extensive relationships that exist between the pharmaceutical industry and physicians, researchers and other health professionals (Yeh and Kesselheim, 2013) suggests that forming a panel of members without industry links may well be difficult, although it has been demonstrated recently that sufficient numbers of expert potential members without conflicts can be identified (Nissen, 2011). The second impediment is resistance from professional societies who argue that expertise frequently coexists with involvement in funded research and that the need to recruit members with the most applicable scientific training and knowledge is paramount and outweighs other concerns. Overcoming this obstacle may require a change in the culture of professional societies towards a greater understanding of the effects of conflicts of interest (Johnson and Rogers, 2014). The third obstacle relates to the second; many academic researchers and clinicians believe that the combination of professionalism and disclosure of any industry support provides sufficient assurance that any connections to the pharmaceutical industry will have no bearing on their decision-making. But as Cain and Detsky (2008) argue, the majority of conflicts result in unintentional

bias and are difficult to recognize, making disclosure an often inadequate response. Further research into methods for mitigating the effects of conflicts of interest is needed, given the limitations of disclosure as the standard response.

The RACGP recommendations have important implications for cessation strategies adopted by GPs, other health professionals and for the general public which increasingly turns to the internet for medical and health advice (Fox, 2008; Civljak *et al.*, 2010). It is an understatement to suggest that it is unfortunate that members of the CAG had conflicts of interest; that these conflicts were not explicitly addressed other than by disclosure; that the majority of the research underpinning the recommendations in the *Guidelines* was industry-funded and hence potentially unreliable; and that the CAG provided no commentary on these issues and their potential impact on the overall content of the *Guidelines'* recommendations.

The message that should be delivered by GPs to patients wishing to quit is that cessation is frequently a prolonged process of which unsuccessful attempts are a normal part; NRT and other pharmacotherapy may help many smokers but are certainly not necessary for quitting; and that unassisted cessation is the method followed by the majority of successful ex-smokers. Rather than a balanced discussion of available strategies for smoking cessation, the *Guidelines* disregard the historical reality that the large majority of existing former smokers quit unassisted (Chapman and Mackenzie, 2010; Edwards *et al.*, 2014) and instead, promote pharmacotherapy as the default for all smokers who wish to quit.

Finally, concerns related to industry funding of research, scientific integrity and recommendations on smoking cessation by medical advisory groups are clearly not restricted to Australia. Smoking remains the leading preventable cause of death globally (World Health Organization, 2015), and how to get smokers to quit is among the greatest challenges in public health. The message that NRT and other pharmacotherapy are crucial to successful population-level cessation has gained an unwarranted global prominence that is unsupported by research beyond RCTs. Perhaps the most striking evidence of this is the World Health Organization's MPOWER (2013) initiative which cites the need for broad '[a]ccess to free or low-cost cessation medicines'. We recommend that all research cited as evidence for smoking cessation be scrutinized for potential conflicts of interest and urge the funding of independent research into the full range of cessation strategies.

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