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PERSONAL VIEW

From *caveat emptor* to *caveat venditor*: time to stop the influence of money on practice guideline development

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Introduction

Many proponents of evidence-based medicine (EBM) call for the universal implementation of clinical practice guidelines (CPGs). The assumption is that CPGs are trustworthy and valid, and because they are based on empirical data, they are not vulnerable to the idiosyncrasies of expert opinion. Although advocates of EBM certainly recognize that recommendations in CPGs are always a synthesis of evidence, interpretation and opinion, they argue that the use of guidelines will lead to better patient outcomes because the recommendations are based primarily on scientific evidence. Thus, it is not surprising that the number of physicians reporting that CPGs have had a 'substantial effect on their practice' has increased in recent years [1]. However, concerns have been raised that CPGs are too often based on disease-oriented rather than patient-oriented outcomes and that their standardized use will undermine collaborative decision making. More recently, questions have been raised about the potential for bias when treatment recommendations are developed by industry-funded researchers [2–5]. In response to concerns that the trustworthiness and clinical utility of CPGs were being compromised because of financial conflicts of interest (FCOI) on the part of guideline authors, the Institute of Medicine (IOM) recently recommended that, 'whenever possible', authors should avoid FCOI, and, at minimum, those with a conflict should comprise a minority of the guideline development group (GDG) [6].[1] The IOM explicitly states that the guideline chair should not have FCOI. Although previous research has examined the extent and type of FCOI of CPG authors [2,7] and assessed the quality of CPGs [8], there are currently no empirical data on the possible effect of FCOI on treatment recommendations [9]. This gap in the literature is due in part to the fact that current assessment tools are not robust enough to assess the more indirect effects of FCOI. This essay identifies some of the limitations of current quality assessment tools, argues that current methods of addressing FCOI will not provide enough of a safeguard to protect against potential bias and offers solutions for reform.

The main instrument currently available for assessing guideline quality is the second version of the Appraisal of Guidelines and Research and Evaluation (AGREE II) instrument. Additionally, the Canadian Hypertension Evaluation Program (CHEP) provides a grading scheme for recommendations. Although these instruments have merit, all grading systems have shortcomings [10,11]. Also, despite their promise, these instruments require time and training, and were not designed to have clinical utility for routine medical practice. Perhaps most importantly, none of these tools include all of the criteria necessary to address the three components identified by the IOM as prone to errors in guideline development: the validity of the guideline development process, the validity of the supporting research and the possibility that commercial interests may exert an influence on treatment recommendations [6]. Thus, the hierarchy system that is typically used when assessing guideline quality may obscure or misrepresent the actual quality of evidence [12].

Even if primary care physicians had time to consistently use the AGREE or CHEP, the negative effects of FCOI (i.e. decreased quality/trustworthiness) may be indirect and more difficult to detect with traditional rating systems. The busy clinician needs to be able to quickly evaluate the process used for validating the evidence, both for its internal validity and for its focus on patient-oriented outcomes. Such a tool would help clinicians assess the credibility and trustworthiness of the CPG, especially if the GDG has a financial stake in the recommendations. Although disclosure of commercial ties on the part of the guideline sponsor or GDG was initially hailed as a solution to the problem of potential bias resulting from FCOI, transparency has had its own iatrogenic effects.

Disclosure is not the answer

In order to enhance accountability and in response to practices such as overstating efficacy and underreporting adverse effects of medications, the International Committee of Medical Journal

[1] Although professional and intellectual conflicts of interest are also worthy of investigation and discussion as part of the wider conflict of interest debate, the effect of guild interests on CPGs is beyond the scope of this paper.

Editors (ICMJE) developed recommendations for disclosure of authors' commercial ties. Disclosure policies have since grown increasingly common, including among organizations that develop CPGs, with the intention of increased accountability among their users. The current ICMJE recommendations take steps towards increasing transparency and accountability in publishing, but industry has been shown to elude them [13]. Further, policies that require disclosure of potential conflicts of interest do not address the bias that may result from such conflicts. Transparency may simply '[shift] the problem from one of "secrecy of bias" to "openness of bias" ' [14]. The inadequacy of transparency as a solution to potential bias was recently evidenced by the controversial American College of Cardiology/American Heart Association cholesterol guidelines regarding cardiovascular risk [15]. The new guidelines would increase the number of Americans for whom statins are recommended by 7.5 million [16]. Over half of the members of the GDG had ties to the companies that manufacture medications used to treat hyperlipidaemia, including the chair (just prior to accepting the position as panel chair) and one of the co-chairs of the committee. These disclosures led one expert to say that the new guidelines are a 'big kiss to big pharma. . . . According to the new risk calculator all African American men aged 65 and up with normal blood pressure and normal cholesterol levels should be on statins. That's an outrage and is unsupported by clinical evidence' [16]. Clearly, disclosure alone does not eliminate the potential for perceived or actual bias.

Disclosure may also have its own unintended consequences, and reporting of FCOI is not a reliable measure of research credibility [17]. Studies have shown that individuals may give even more biased advice after they have disclosed a conflict of interest [18] and that physician disclosure of FCOI may *increase* patient trust [19]. On the other hand, researchers have found that physicians tended to discount study results and rigor when they believed the study was industry funded, even when the study was of high methodological quality [20]. It is indeed difficult for anyone who is not an expert to identify a biased opinion, and even when this may be possible, disclosure requires individuals to assess motives and guess whether actions, decision making or interpretation of data may have been affected by conflicts of interest [21]. Thus, transparency alone is insufficient for assessing the trustworthiness of a study or CPG.

A case example: CPGs for depression

There are documented concerns about the quality of the evidence base for the recommendation of antidepressant treatment for mild-to-moderate depression [22]. For example, an increasing number of meta-analyses have found that the efficacy of antidepressants varies with the severity level of the disorder, with clinically significant improvement typically found only in more severely depressed patients [23–25]. The authors of 2009 Cochrane review also concluded that there is not enough quality evidence to support the efficacy of antidepressants for mild depression [26].

Elsewhere we reported that two meta-analyses independently concluded that, because of a lack of demonstrated efficacy, antidepressant medication should not be the first-line intervention for mild-to-moderate depression [27]. In 2008, Kirsch *et al*. concluded that 'drug–placebo differences increased as a function of initial severity, reaching conventional criteria for clinical significance only for patients at the upper end of the very severely depressed category' [25]. In a 2010 patient-level meta-analysis, Fournier *et al*. found that 'true drug effects [an advantage of (antidepressant medications) over placebo] were nonexistent to negligible among depressed patients with mild, moderate, and even severe baseline symptoms' [23]. The authors of both studies made the explicit recommendation that antidepressants should not be the first-line recommendation for mild-to-moderate depression.

Ensuring that CPGs for depression accurately address the efficacy data and risks and benefits of pharmacological treatment – and thus are trustworthy – is an important public health issue; in the United States 80% of prescriptions for antidepressants are written by non-psychiatrist physicians [28] who turn to CPGs as a trusted resource. Unipolar major depression was calculated to be the second leading cause of years lived with disability worldwide [29]. It is also a significant source of expenditure, estimated to be $83.1 billion in the United States alone in 2000, of which $26.1 billion was direct medical costs [30]. Clearly, the social, economic and public health burden of depression is great.

Recent CPGs developed outside of the United States have explicitly addressed the risk/benefit issue of pharmacological treatment as a front-line intervention. The National Institute for Health and Care Excellence (NICE) in the United Kingdom and recent Dutch guidelines for depression incorporate these recent meta-analyses into their review of relevant literature to support the explicit recommendation that antidepressants should *not* be the first-line treatment for mild-to-moderate depression (see table for summary of recommendations) [31,32]. None of the panel members of the Dutch guideline reported FCOI and the majority of the NICE panel members were free of industry ties. However, the authors of a widely used guideline for depression in the United States interpreted these meta-analyses quite differently and actually cited these studies in order to *support* the use of antidepressants as a first-line treatment for mild-to-moderate depression. They state that 'response rates in clinical trials typically range from 50 to 75% of patients, with some evidence suggesting greater efficacy relative to placebo in individuals with severe depressive symptoms as compared to those with mild to moderate symptoms' [33]. All of the authors of this guideline had significant financial ties to drug firms, and the majority served on speakers bureaus for the manufacturers of antidepressants [27]. Although these examples do not preclude the possibility of a high-quality guideline being produced by a GDG with extensive FCOI, they do indicate the risks of bias and the need to better understand the relationship between FCOI of GDG and quality of recommendations.

Recommendations

As the above example shows, it is time to explore IOM's concern that FCOI of GDGs result in clinical guidelines that are not as valid or trustworthy as guidelines produced by individuals who do not have FCOI. However, as we note above, current quality assessment tools provide only a cursory measure of FCOI. Thus, we make the following recommendations:

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Table 1 Initial treatment recommendations for mild depression

Intervention type	US guideline [35]	UK guideline [33]	The Netherlands guideline [34]
Lifestyle	*	X	X
Low-intensity psychological†		X	X
Psychotherapy	X	X	X
Antidepressant medication	X		
Psychotherapy plus medication	X		
Other somatic therapies	X		

*Clinical practice guideline recommends that 'If a patient with mild depression wishes to try exercise alone for several weeks as a first intervention, there is little to argue against it' (p. 30). Exercise is not included in American Psychiatric Association's table of recommended treatment modalities.
†For example, guided self-help or computerized cognitive-behavioural therapy.

• Initial attempts have been made to develop quality assessment tools [34] that have robust measures of FCOI and clinical utility for the busy clinician, and further efforts of this kind should be strongly encouraged. Because of the broad clinical impact that such measures might have regarding improved cost-effective patient care, agencies within the Department of Health and Human Services such as the Agency for Healthcare Research and Quality should consider the creation and implementation of these types of measures a high priority.
• GDGs and medical specialty groups that develop CPGs should provide detailed disclosure about any FCOI with the makers of products featured in the CPG, including the value of any cash or in kind donations.
• As a baseline measure of trustworthiness, if the GDG or the medical specialty group that produces the CPG has a financial stake in the recommendations, clinicians should look closely at what oversight mechanisms were in place (e.g. independent review panels) to ensure objectivity and minimize bias [17].
• More data are needed on the quality and trustworthiness of different guidelines across a single disease category such as Major Depressive Disorder. Researchers could then test the hypothesis that guidelines produced by independent multidisciplinary groups are of higher quality than those produced by specialty or professional groups with FCOI. If researchers find that guidelines produced by individuals without FCOI are of higher quality and that there is an association between GDGs with FCOI and recommendations that are favourable to industry, these data could provide further empirical support for the importance of prohibiting, rather than disclosing or managing, FCOI in GDGs.
• More research is needed to assess the effectiveness of IOM's recent standards for increasing trustworthiness of guidelines (e.g. the negative impact of FCOI on the trustworthiness of guidelines may be attenuated when GDGs are multidisciplinary and/or when there are independent review panels).
• A precautionary principle approach is recommended whereby the default position should be to avoid FCOI in the production of CPGs.

Conclusion

The dichotomy of subjective expert opinion versus objective scientific fact is an untenable one. Clinical interpretations of medical evidence will inevitably differ [35] and having reliable evidence will not guarantee sound, collaborative decision making (see e.g. [36]). However, the goals of person-centred medicine are undermined if physicians do not have valid guidelines to which they can turn. When CPGs are produced by medical specialty groups, especially those with strong and pervasive industry ties, there is a tendency for GDGs to recommend market-driven treatment options (e.g. pharmacotherapy) when less expensive and safer (e.g. lifestyle change) approaches are available (see Table 1). And when commercial interests trump clinical science, the informed consent process is compromised; the ethical principle of autonomy requires that practitioners receive accurate and complete information on the (possible) benefits and harms of all treatment options. Certainly, GDGs strive to produce high-quality guidelines and more research is needed to determine the extent to which FCOI of GDGs may affect guideline quality [37]. But in the meantime, in order to facilitate informed choice by patients, we advocate a precautionary principle approach whereby the default position should be to avoid FCOI in the production of CPGs.

Conflict of interest

The authors declare no conflict of interest.

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References

1. O'Malley, A. S., Hoangmai, H. P. & Reschovsky, J. D. (2007) Predictors of the growing influence of clinical practice guidelines. *Journal of General Internal Medicine*, 22, 742–748.
2. Als-Nielsen, B., Chen, W., Gluud, C. & Kjaergard, L. L. (2003) Association of funding and conclusions in randomized drug trials. *JAMA: The Journal of the American Medical Association*, 290, 921–928.
3. Choudhry, N. K., Stelfox, H. T. & Detsky, A. S. (2002) Relationships between authors of clinical practice guidelines and the pharmaceutical industry. *JAMA: The Journal of the American Medical Association*, 287, 612–617.
4. Genuis, S. (2005) The proliferation of clinical practice guidelines: professional development or medicine-by-numbers? *American Board of Family Practice*, 18, 419–425.

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5. Grilli, R., Magrini, N., Penna, A., Giorgio, M. & Liberati, A. (2002) Practice guidelines developed by specialty societies: the need for critical appraisal. *Lancet*, 355, 103–106.
6. Institute of Medicine (IOM) (2011) Clinical Practice Guidelines We Can Trust. Washington, DC: National Academies Press.
7. Mendelson, T. B., Meltzer, M., Campbell, E. G., Caplan, A. L. & Kirkpatrick, J. N. (2011) Conflicts of interest in cardiovascular clinical practice guidelines. *Archives of Internal Medicine*, 171 (6), 577–584.
8. Burgers, J. S., Fervers, B., Haugh, M., Brouwers, M., Browman, G., Philip, T. & Cluzeau, F. A. (2004) International assessment of the quality of clinical practice guidelines in oncology using the Appraisal of Guidelines and Research and Evaluation instrument. *Journal of Clinical Oncology*, 22, 2000–2007.
9. Norris, S. L., Holmer, H. K., Ogden, L. A. & Burda, B. U. (2011) Conflict of interest in clinical practice guideline development: a systematic review. *PLoS ONE*, 6, e25153.
10. Djulbegovic, B. (2006) Evidence and decision making. *Journal of Evaluation in Clinical Practice*, 12, 257–259.
11. Atkins, D., Eccles, M., Flottorp, S., *et al*. (2004) Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches. *BMC Health Services Research*, 4, 38.
12. Glasziou, P., Vandenbroucke, J. & Chalmers, I. (2004) Assessing the quality of research. *British Medical Journal*, 328, 39–41.
13. Matheson, A. (2011) How industry uses the ICMJE guidelines to manipulate authorship – and how they should be revised. *PLoS Medicine*, 8, e1001072.
14. Krimsky, S. (2010) Combating the funding effect in science: what's beyond transparency? *Stanford Law Policy Review*, 21, 101–123.
15. Silverman, E. (2013) The new cholesterol guidelines and conflicts of interest. Available at: http://www.forbes.com/sites/edsilverman/2013/11/20/the-new-cholesterol-guidelines-and-conflicts-of-interest/ (last accessed 1 April 2014).
16. Lenzer, J. (2013) Majority of panelists on controversial new cholesterol guideline have current or recent ties to drug manufacturers. *British Medical Journal*, 347, f6989.
17. Resnik, D. B. & Elliott, K. C. (2013) Taking financial relationships into account when assessing research. *Accountability in Research*, 20, 184–205.
18. Cain, D. M., Loewenstein, G. & Moore, D. A. (2005) The dirt on coming clean: perverse effects of disclosing conflicts of interest. *Journal of Legal Studies*, 34, 1–25.
19. Sah, S. (2012) Conflicts of interest and your physician: psychological processes that cause unexpected changes in behavior. *Journal of Law, Medicine, & Ethics*, 40, 482–487.
20. Kesselheim, A. S., Robertson, C. T., Myers, J. A., Rose, S. L., Gillet, V., Ross, K. M., Glynn, R. J., Joffe, S. & Avorn, J. (2012) A randomized study of how physicians interpret research funding disclosures. *New England Journal of Medicine*, 367, 1119–1127.
21. Kassirer, J. P. (2008) Medicine's obsession with disclosure of financial conflicts: fixing the wrong problem. In Science and the Media: Delgado's Brave Bulls and the Ethics of Scientific Disclosure (eds P. J. Snyder, L. C. Mayes & D. D. Spencer), pp. 79–89. Waltham, MA: Academic Press.
22. Moncrieff, J. & Kirsch, I. (2005) Efficacy of antidepressants in adults. *British Medical Journal*, 331, 155–157.
23. Fournier, J. C., DeRubeis, R. J., Hollon, S. D., Dimidjian, S., Amsterdam, J. D., Shelton, R. C. & Fawcett, J. (2010) Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA: The Journal of the American Medical Association*, 303, 47–53.
24. Khan, A., Leventhal, R. M., Khan, S. R. & Brown, W. A. (2002) Severity of depression and response to antidepressants and placebo: an analysis of the Food and Drug Administration database. *Journal of Clinical Psychopharmacology*, 22, 40–45.
25. Kirsch, I., Deacon, B. J., Huedo-Medina, T. B., Scoboria, A., Moore, T. J. & Johnson, B. T. (2008) Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Medicine*, 5, e45.
26. Arroll, B., Elley, C. R., Fishman, T., Goodyear-Smith, F. A., Kenealy, T., Blashki, G., Kerse, N. & Macgillivray, S. (2009) Antidepressants versus placebo for depression in primary care. *Cochrane Database of Systematic Reviews*, (3), CD007954.
27. Cosgrove, L., Bursztajn, H. J., Erlich, D. R., Wheeler, E. E. & Shaughnessy, A. F. (2012) Conflicts of interest and the quality of recommendations in clinical guidelines. *Journal of Evaluation in Clinical Practice*, 19, 674–681.
28. Cascade, E., Kalali, A. H. & Halbreich, U. (2008) Antidepressant prescribing by specialty and treatment of premenstrual dysphoric disorder. *Psychiatry*, 5, 14–15.
29. Ferrari, A. J., Charlson, F. J., Norman, R. E., Patten, S. B., Freedman, G., Murray, C. J., Vos, T. & Whiteford, H. A. (2013) Burden of depressive disorders by country, sex, age, and year: findings from the Global Burden of Disease Study 2010. *PLoS Medicine*, 10, e1001547.
30. Greenberg, P. E., Kessler, R. C., Birnbaum, H. G., Leong, S. A., Lowe, S. W., Berglund, P. A. & Corey-Lisle, P. K. (2003) The economic burden of depression in the United States: how did it change between 1990 and 2000? *Journal of Clinical Psychiatry*, 62, 1465–1475.
31. National Institute for Health and Clinical Excellence (NICE) (2009) Depression: The Treatment and Management of Depression in Adults, NICE Clinical Guideline No. 90. London, UK: Author.
32. Van Weel-Baumgarten, E. M., Van Gelderen, M. G., Grundmeijer, H. G. L. M., *et al*. (2012) NHG standaard eepressie (tweede herziening). *Huisarts en Wetenschap*, 55, 252–259.
33. American Psychiatric Association (2010) Practice Guideline for the Treatment of Patients with Major Depressive Disorder, 3rd ed. Available at: http://psychiatryonline.org/content.aspx?bookid=28&sectionid=1667485 (last accessed 1 February 2012).
34. Lenzer, J., Hoffman, J. R., Furberg, C. D. & Ioannidis, J. P. A. (2013) Ensuring the integrity of clinical practice guidelines: a tool for protecting patients. *British Medical Journal*, 347, f5535.
35. Miles, A., Loughlin, M. & Polychronia, A. (2008) Evidence-based healthcare, clinical knowledge and the rise of personalized medicine. *Journal of Evaluation in Clinical Practice*, 14, 621–649.
36. Djulbegovic, B., Soares, H. P. & Kumar, A. (2006) What kind of evidence do patients and practitioners need: evidence profiles based on 5 key evidence-based principles to summarize data on benefits and harms. *Cancer Treatment Reviews*, 32, 572–576.
37. Moynihan, R. N., Cooke, G. P., Doust, J. A., Bero, L., Hill, S. & Glasziou, P. P. (2013) Expanding disease definitions in guidelines and expert panel ties to industry: a cross-sectional study of common conditions in the United States. *PLoS Medicine*, 10, e1001500.

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