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ARTICLE

Conflicts of Interest in Clinical Practice Guidelines

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Abstract
Clinical practice guidelines are used increasingly across medical specialties and settings, making evaluation of their utility and validity a critical public health issue. In this paper, we describe some of the challenges that specialty organizations face as they try to ensure that their guidelines are trustworthy and useful. We examine the practice guidelines for Major Depressive Disorder recently published by the American Psychiatric Association (APA), identify five sources of potential bias that may affect the guideline development process and offer suggestions based on our review. For example, even for mild depression, this guideline privileges pharmacotherapy over other interventions, despite questions about the risk/benefit ratio and the increasing concern over the iatrogenic harms of SSRIs and SNRIs. We compare recommendations from international scientific groups (e.g. NICE) with those produced by specialty societies in an effort to demonstrate some of the ways in which conflicts of interest, both intellectual and financial, may unduly influence guidelines.

Keywords
Clinical practice guidelines, conflicts of interest, depression, person-centered medicine

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Introduction
Clinical practice guidelines (CPGs), designed to improve healthcare outcomes, have been criticized for not producing their intended result because of overly formulaic care [1], wide variations in guideline quality [2] and because they discourage concordance [3] and patient insight [4]. Moreover, when ‘mono-disciplinary specialists’ [5] develop CPGs, there is the risk that the recommended courses of action may unduly reflect the vested interests of the specialty groups that produce the guidelines. Added to this bias are the financial conflicts of interests, either of individual guideline authors or the specialty society itself. Concerns about CPGs becoming “marketing and opinion-based pieces” [6] have escalated and in March of this year, the U.S. Institute of Medicine (IoM) issued a report, “Standards for Developing Trustworthy CPGs” [7]. There are numerous examples of specialty groups producing guidelines that do not support, or even contradict, recommendations made by disinterested parties (see Table 1).

In this article, we describe some of the challenges specialty organizations face as they try to assure their final product is balanced and accurate, citing some examples (see Table 1). For further illustration, we also explore, in depth, the practice guideline for Major Depressive Disorder (MDD) recently published by the American Psychiatric Association (APA) [17]. We have selected this guideline for review because it is a prominent and trusted resource in the U.S. and because its focus on the primacy of pharmacotherapy differs from guidelines in other countries (e.g. Canada and the UK). We make five observations and offer suggestions based on our review.

Intellectual Conflict of Interest - Challenge 1: Content Over Process
Guideline development groups (GDG) without methodologists involved may be more likely to accept research results at face value, especially if the results confirm current beliefs [18]. Being a researcher does not necessarily mean that one is trained in clinical epidemiology and has expertise in interpreting evidence from randomized controlled trials (RCTs) [19]. For example, developers of the APA guideline consider all
double-blind RCTs to be Level A evidence \[17, \text{p.103}\] and do not address methodological issues such as duration, study conduct or end-points (e.g. remission versus reduction in symptoms) that can affect the quality of the study.

Methodological experts are essential to a GDG because they are better equipped than content experts or researchers to address critical methodological issues and questions that arise \[20\]. Given that the internal and external validity of clinical research is quite variable and dependent on a number of factors, uncritically accepting meta-analyses and double-blind randomized controlled trials is not a method for assuring an adequate evidence base \[21-23\]. Approximately 75% of clinical trials published in major journals are industry funded \[24\]. Given that the odds are 5.3 times greater than commercially funded studies will support their sponsors’ products than non-commercially funded investigations, study results should not be accepted at face value \[21, \text{p.921}\].

For example, one of the most commonly applied intent-to-treat models - last observation carried forward (LOCF) - can artificially bias results in favor of the study drug \[25,26\]. This model assumes a randomization of drop-outs that is not supported by any theory or data \[27,28\] and it is also a model that fails to assess differences in outcomes in patients who keep taking the drug \[29\]. The high drop-out rates for participants enrolled in psychotropic drug trials is a pernicious problem; average drop-out rates of 50-64% have been reported in antipsychotic studies and 37% in antidepressant (AD) studies \[28\]. Thus, the appropriateness of using LOCF and other analytic techniques to control for attrition is an important methodological issue that deserves attention by guideline developers when making recommendations about efficacy of ADs. For example, Dubovsky and Dubovsky \[29\] make a critical point that is not addressed in this guideline: in many comparator trials, Selective Serotonin Re-uptake Inhibitors (SSRIs) appeared to be at least as effective as tricyclic ADs (TCAs). However, “because
some TCAs such as imipramine are not as well tolerated and more likely to be discontinued early, . . . for more severely depressed patients who are more motivated to continue it until it works, imipramine may be more helpful. (Use of LOCF) misses the impact of adherence to treatment” (italicization ours) [29, p.51].

All guideline development groups should include content experts, but when specialty societies produce CPGs, the majority of the panel should be composed of individuals independent of the specialty group who have expertise in methodology and epidemiology [30-32]. For example, Germany’s approach to depression guideline development began with the critical appraisal of international guidelines for depression conducted by multidisciplinary focus groups of experts in evidence-based medicine (EBM).

**Intellectual Conflict of Interest - Challenge 2: Confirmation Bias**

A particular challenge in the guideline development process is how to include, in the most accurate and balanced way, the results of one’s own research. That is, when a researcher designed, analyzed, or interpreted the results of an RCT or meta-analysis he may have an implicit bias toward the study and may not be as open to considering questions about the study’s quality [33].

All members of the APA guideline committee are also active researchers in major depressive disorder. The IoM recommends that researchers and writers of systematic reviews should not formulate guidelines [34-36]. The UK National Institute for Health and Clinical Excellence (NICE) allows researchers to participate in guideline development, but further stipulates that, “understanding of evidence-based medicine is essential” [16]. In keeping with the IoM and NICE’s suggestions, in those instances where a conflict is unavoidable and the expertise is essential, individuals should recuse themselves when assessing the studies for which they have served as PIs or authors.

**Intellectual Conflict of Interest - Challenge 3: Acknowledging and Addressing Controversies**

Controversies or limitations to the available evidence should be clearly outlined or reflected in guidelines. For example, in the APA guideline, the iatrogenic harms of pharmacologic treatment and the documented lack of efficacy for patients with mild to moderate depression [37-39] are not reflected fully in the weighing and interpretation of evidence. There exists controversy about the risk/benefit ratio of prescribing ADs as a first-line intervention for mild to moderate depression [16,37,38,40], especially when it is a first episode. The controversy is due to the increasing documentation of and concern about adverse side effects [c.f. 41] and because most RCTs were not adequately powered to address questions of efficacy of AD use for mild depression [37, p.48]. Two well-publicized meta-analyses independently concluded that because of a lack of efficacy, AD medication should not be the first line intervention for mild to moderate depression [37,38]. In light of these results, “efforts should be made to clarify to prospective clinicians and prospective patients that . . . there is little evidence to suggest that . . . (antidepressants) produce specific pharmacological benefit for the majority of patients with less severe depression” [37, p.32].

Although these meta-analyses are cited in the guideline, the context in which they are referenced does not provide the reader with a fully accurate understanding of their conclusions. Instead, the following statement is made in the guideline’s executive summary: “response rates in clinical trials typically range from 50-75% 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” [17, p.31]. Thus, the reader is left with the erroneous impression that there is a clear evidence base for the use of ADs for mild to moderate depression and that ADs work even more effectively for severe depression.

This is not to suggest that ADs should never be prescribed for mild or chronic sub-threshold depression; certainly ADs have helped many people. However, for a guideline on depression to be useful to clinicians it needs to spell out more clearly under what conditions ADs should be prescribed for mild episodes of depression and for chronic sub-threshold depressive symptoms. Most importantly, the risk/benefit issue of prescribing ADs merits more detailed attention. For example, the citation of a 50-75% response rate gives the impression that half to three fourths of patients can expect a clinically meaningful benefit of medication, a benefit that would likely be perceived as substantial enough to outweigh concerns about adverse side effects. What does not get addressed in this guideline is the fact that the response rates are often based on disease-oriented, not patient-oriented, outcome measures and should not be conflated with remission. That is, the effect size set by the UK National Institute for Clinical Excellence (NICE) and used in depression trials is 0.5 or a drug/placebo difference of 3 points on the Hamilton Depression Rating Scale [38]. Thus, the statistically significant benefit reported in large RCTs is best characterized as a disease-oriented outcome measure and may not be clinically meaningful or relevant to patients. Guideline readers may not be aware of the way in which citing a response rate from large clinical trials can inflate the absolute treatment effect [c.f. 3]. Patients have a right to be fully informed about the likelihood and type of benefit derived from taking a medication. Quoting response rates without the appropriate context can obscure.
and the evidence of selective reporting of favorable results. Guidelines from specialty groups run the risk of favoring new treatments and approaches, especially if their use is limited primarily to that specialty or if the group’s members played a large role in their development. The APA guideline group limited their search of the literature to articles published after the year 2000 and the authors acknowledge a bias toward newer treatments based on their methods. The bias toward “newer is better” is not unique to psychiatry, but it is problematic in light of the increasing concerns over the iatrogenic harms of SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) and the evidence of selective reporting of favorable results.

To address the practice of selectively reporting favorable results, guideline developers should review unpublished studies. Additionally, they should consider the role that publication bias may play (e.g. using funnel plots to assess for publication bias) when assessing and rating the strength of the evidence. This recommendation is congruent with and extends the IoM requirement that guideline developers establish “evidence foundations for and rating strength of recommendations”.

Financial Conflict of Interest - Challenge 1: Duty to the Group’s Membership

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Financial Conflict of Interest - Challenge 2: When to Prohibit and When to Manage Conflicts

Growing financial relationships between all medical subspecialties and industry have prompted congressional inquiry, spurred new federal regulations on conflict of interest (COI) and provided the rationale behind the recently enacted Physicians Payment Sunshine Act [H.R. 3590, Section 6002]. During the time period of APA’s CPG development, 100% of work group members reported commercial ties to the companies that manufacture the medications recommended in the guideline and all of the members had multiple financial conflicts of interest. Other guidelines have this issue [36,39], with groups such as NICE and the Canadian Network for Mood and Anxiety Treatments allowing guideline developers to have financial conflicts of interest as long as they were disclosed. The APA attempted to mitigate the potential for bias by adding a review panel that evaluated the guidelines for possible industry influence (they concluded there was none). Yet at least 2 of the 5 members of the independent panel had industry ties they did not report. These financial associations, most notably the fact that the chair and the majority of the GDG members participated on speaker bureaus, raise questions about the objectivity and integrity of the guideline. Speakers Bureau participation is usually prohibited (e.g. for faculty in medical schools), as it is widely recognized to constitute a significant FCOI. The pharmaceutical companies refer to individuals who serve on Speakers Bureaus as “key opinion leaders” (KOLs), because they are seen as essential to the marketing of both diseases and drugs.

Moreover, there is no evidence to support the assumption that only current financial associations with industry affect behavior and some evidence suggests past and/or the promise of future industry relationships may exert a “pro-industry habit of thought” [45] or a “partisan perspective in the medical literature” [46]. Therefore, we recommend a rebuttable presumption of prohibiting financial conflicts of interest among authors of practice guidelines. In those circumstances where no independent individuals with the requisite expertise are available, individuals with associations to industry could serve as consultants to the GDG, but they would not have decision-making authority about treatment recommendations. Certainly, an independent review panel should have no industry ties. In addition, there should be transparency of the decision-making process by which an independent review panel allows individuals with FCOI to serve on the GDG.

Conclusion: producing useful and trustworthy guidelines

“American medicine is seriously threatened by conflicts of interest whose symptoms signal the corruption of the medical mission and the profession’s ideals.”[48].

Numerous studies in behavioral ethics and social psychology [49-51] have demonstrated that it is part of the human condition to have implicit biases - and remain blissfully ignorant of them. Hence, it is unrealistic to expect the guild of any service industry, on its own, “to harness its self-interest and to act according to beneficence alone” [52]. Medicine is no different. These suggestions to avoid conflicts of interest are not difficult to implement [53]. They are feasible and necessary and in light of the fact that “various medical interventions are directly contributing to the burden of illness” [54], the stakes are
high. Therefore, in order to restore public trust and integrity in medicine and ensure unbiased, evidence-based practice, it is critical to prohibit certain conflicts and better manage others. If these safeguards are not put in place, perhaps it is time to call a moratorium on medical specialty groups producing guidelines.

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