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Conflicts of interest and the quality of recommendations in clinical guidelines†

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Abstract

Background There is increasing concern that conflicts of interest affect the development process of clinical practice guidelines. We evaluated The American Psychiatric Association's Practice Guideline for the Treatment of Patients with Major Depressive Disorder to determine the existence of financial and intellectual conflicts of interest and examine their possible effects. We selected this guideline because of its influence on clinical practice and because this guideline recommends pharmacotherapy for all levels of depression, despite controversies over the evidence base.

Methods and Findings We determined the number and type of financial conflicts of interest for members of the guideline development group as well as for the independent panel charged with mitigating any effect of these conflicts. We also quantified the potential for intellectual conflicts of interest. We examined the quality of references used to support recommendations, as well as the degree of congruence between the research results and the recommendations. Fewer than half (44.4%) of the studies supporting the recommendations met criteria for high quality. Over one-third (34.2%) of the cited research did not study outpatients with major depressive disorder, and 17.2% did not measure clinically relevant results. One-fifth (19.7%) of the references were not congruent with the recommendations. Financial ties to industry were disclosed by all members (100%) of the guideline development committee with members reporting a mean 20.5 relationships (range 9–33). The majority of the committee participated on pharmaceutical companies' speakers' bureaus. Members of the independent panel that reviewed the guidelines for bias had undeclared financial relationships. As a marker of intellectual conflict of interest, 9.1% of all cited research and 13% of references supporting the recommendations were co-authored by the six guideline developers.

Conclusions The prevalence of conflicts of interest among panel members was high. The quality of the evidence cited raises questions about the validity of the recommendations. Attention to the quality of cited studies and to the risk of bias resulting from conflicts of interest should be a priority for guideline development groups.

Introduction

Clinical practice guidelines (CPGs) are intended to enhance the practice of evidence-based medicine by streamlining health care delivery and improving the process and outcomes of patient care. However, there is increasing concern about the quality of guidelines, particularly those produced by professional organizations and medical specialty groups [1–16]. The most obvious quality issue is that limitations of current methodology affect guideline development; the science of developing recommendations for clinical practice based on the best available evidence continues to evolve [1,17–19].

However, financial conflicts of interest (COIs) and intellectual bias can also influence recommendations, especially those from professional advocacy groups (Table 1) [5,6,8,20–25]. Financial COIs occur when individuals or the profession they represent have

Table 1 Steps in guideline development susceptible to methodology flaws or conflicts of interest. [Correction made here after initial online publication.]

1. Framing: Viewpoint and underlying assumptions*†
2. The questions that are asked*†‡
3. Data gathering and selection†‡
4. Data evaluation*‡
5. Data interpretation
   a. Internal validity*‡
   b. External validity*†
6. Judgments of data (results of research vs. conclusions)*†
7. Lack of explicit evidence-linking with resulting evidence 'slippage'†‡
8. Lack of testing or external validation of guidelines (verification)‡

*Financial conflict of interest.
†Intellectual conflict of interest.
‡Methodology flaw.

the potential to receive financial gain from a recommendation. An intellectual COI exists when adherence to a specific point of view 'could unduly affect an individual's judgment about a specific recommendation' ([4], p. 739). Frequently, intellectual COIs arise from academic activities or interests on the part of guideline developers that create the potential for confirmatory bias [26]. Although it is difficult to quantify or qualify intellectual COIs, guidelines produced by specialty societies are particularly vulnerable to bias resulting from these conflicts [26]. Biases from financial and/or intellectual COIs may result from the ability of such conflicts to affect decision making in a way that is completely hidden from the person making the decision [27]. Recent neuroscience investigations demonstrate that effective decision making involves not just cognitive centres, but also emotional areas such as the hippocampus and amygdala [28]. This interplay of cognitive-emotional processing allows COIs to affect decision making in a complex and unintended way.

Although increased attention has been given to improving the guideline development process [29–31], these tools have not resulted in marked improvement in the development of guidelines by specialty societies [5,6,11,12,29,32,33]. Improvement is needed because guidelines produced by specialty groups run the risk of overestimating benefit and underestimating harm [34]. In previous papers, we expressed our concern about the guideline development process used by the American Psychiatric Association (APA) and the recommendation of pharmacotherapy as a first-line intervention for all levels of depression despite controversies over the evidence base [11,12,33]. Specifically, antidepressant medication and psychotherapy are identified in APA's most recent CPG as appropriate 'monotherapies' for mild to moderate depression. However, the prominence of pharmacotherapy in the Executive Summary, the 'Recommended Modalities for Treatment' Table and in the clarification section of the guideline, clearly gives pharmacotherapy precedence over other therapies [12].

We have developed an approach to guideline evaluation that incorporates checks for COIs as well as evidentiary threats to the validity of the recommendations. The objectives of this study were to assess the quality of the cited evidence in APA's Practice Guideline for the Treatment of Patients with Major Depressive Disorder, third edition [35] to document the prevalence of COIs, and to examine the effect of COIs on the recommendations in this CPG.

Methods

We examined guidelines developed by a work group of experts drawn from the APA's membership. The guideline development process employed by the work group included a literature review, but the method of literature search, evaluation and interpretation was not described in the guidelines. Guideline developers were not prohibited from industry relationships, but were required to disclose all COIs. In response to a recommendation from the Institute of Medicine [20] that guideline work groups should have no significant relationships with industry, the Association added an independent review committee consisting of clinicians and researchers without declared COIs to assure the recommendations were not affected by industry influence. The final draft of the guideline was reviewed by this independent panel, whose members declared that they had 'no current relationships with industry'. The Independent Review Panel 'found no evidence of bias' ([35] p.11). No information was provided regarding the assessment and decision-making process for the Independent Review Panel's conclusion.

The guideline begins with an executive summary followed by a section, 'Formulation and Implementation of a Treatment Plan' (Part A.II), which provides explication and includes supporting references. The method of searching and selecting articles for inclusion is not described. In the reference list, each reference is ranked from [A], 'randomized double-blind clinical trial,' to [G], 'other, including textbooks, expert opinion, and case reports.' Systematic reviews are given a rank of [E] in this rubric. The third section of the document, 'Review and Synthesis of Available Evidence' (Part B.V), provides clarification and support for the recommendations and summarizes the literature review used by the guideline developers.

Recommendations for treatment are stated in general terms and vary across the different sections in wording, tone and emphasis. To link recommendation statements to the supporting evidence, we coalesced treatment guidelines from the three sections into 12 single statements. We have described our method of synthesis in a previous publication [12].

To determine the number and type of financial COIs for members of the guideline development group, we tallied the reported pecuniary ties of all guideline developers. Undisclosed financial relationships of the independent review panels were tallied for the 3 years prior to publication of the guideline, a process congruent with other research [11,36] and consistent with APA's definition of a financial COI (see e.g. DSM5.org). We searched Medline and Lexis-Nexis Academic for publications in which financial ties with industry were disclosed by the oversight committee members. We also searched the US Patent and Trademark Office website for patents pending or awarded to determine whether members had any intellectual property in a drug or medical device whose sales could be affected by practice guideline recommendations. Internet search engines were used to access other reliable disclosures (e.g. author disclosures provided at peer-reviewed conferences). Consistent with previous research [12,37], only unambiguous information previously and directly reported by the independent review panel within the 3-year time period was included.

Following Norris *et al.* [21], intellectual bias was determined by documenting the number of publications that were authored by the guideline development committee and cited as evidence for a

Table 2 Criteria for high-quality research*

Study design: Studies of effectiveness: Randomized controlled trial of any quality, *a priori* subgroup analysis of a randomized controlled trial, systematic review or meta-analysis. Systematic reviews and meta-analyses had to include a comprehensive search (and not, for example, including only company-sponsored research). Study results had to be statistically significant or, if a negative study, of adequate power. Studies of tolerability or overdose: Randomized controlled trials or observational studies of withdrawal rates or withdrawals because of side effects.
Study populations representative of a clinical population: Outpatients with diagnostic criteria for major depressive disorder. Studies were excluded if they studied patients with dysthymia or bipolar disorder, used unspecified criteria for diagnosing major depressive disorder or if the majority of patients were not treated as outpatients.
Clinically important outcomes: At least one: Hamilton Depression Rating Scale, Montgomery–Åsberg Depression Rating Scale, maintenance of depression. For tolerability studies, withdrawals or withdrawals because of side effects. For studies of overdose: significant clinical effects or completed suicide rate.
Results: Statistically significant results or, if a negative study, adequate study power; for meta-analysis, no heterogeneity mentioned.

*Adapted from reference [40].

Table 3 Financial relationships disclosed by guideline developers

Guideline developer	Pharmaceutical company relationships	Medical device company relationships	Other*	Speakers' bureaus†	Total
1 (Chair)	13	2	2	3	17
2	7	0	8	0	15
3	2	0	7	0	9
4	20	1	3	6	24
5	18	1	6	6	25
6	28	2	3	‡	33

*Publishers or investment consulting groups.
†These relationships also included as pharmaceutical company relationships.
‡Not listed separately from other relationships with pharmaceutical companies.

specific recommendation, and by determining whether only content experts (i.e. psychiatrists) were represented on the guideline development committee.

To evaluate the potential impact of COIs on the use of evidence, references linked to the recommendations in part A.II and in the evidence report (Part B.V) were retrieved and assessed for major threats to internal and external validity (Table 2) [13,16,38]. These criteria correspond to Grade A evidence using the Canadian Hypertension Evaluation Program rubric [39] and Strength of Recommendation Taxonomy grade A [40,41], and are similar to internal and external validity assessment of the US Preventive Services Task Force (USPSTF) [42]. Each cited reference was independently evaluated using these criteria by two researchers (DRE and AFS). Differences were resolved through discussion.

Results

All members of the guideline development committee and the oversight committee were US-based psychiatrists and were members of the APA. Financial ties to industry were disclosed by all members (100%) of the guideline development committee (Table 3), with members reporting a mean 20.5 relationships (range 9–33).

One member of the independent review panel had undeclared financial relationships to pharmaceutical manufacturers of antidepressants in the three years before the publication of the guidelines, including receiving honoraria and consulting fees. Two other members had financial relationships with pharmaceutical companies, but we were unable to ascertain if these were in existence between 2007 and 2010 (i.e. within the designated 3-year time period). These ties included speakers' bureau participation, research funding and consulting fees. We obtained this information from public disclosures previously made by these members. All of the financial ties of the guideline committee and review panel were with pharmaceutical companies that manufacture antidepressants. Current disclosure policies do not require disclosure of the amount of money given to an individual by industry; thus, consistent with previous research [36], it was not possible to determine the amount of industry money received by any individual. However, it has been well documented that even small gifts can influence doctoral behaviour and prescribing practices [43,44].

The 12 synthesized recommendations were supported by 130 references. We included 128 (98.5%) of these references in our analysis; two Cochrane Reviews had been withdrawn by the time of this study and were not available for analysis. It is the policy of the Cochrane Library to withdraw reviews if a more recent revision is available or emerging evidence that contradicts the review's conclusions demands a retraction. Agreement for quality determination was high (kappa = 0.8381, 95% confidence interval 0.7481–0.9344).

Fewer than half of the studies ($n = 44$, 34.4%) used to support the guidelines met all five criteria for high quality (Table 4). Thirty-two per cent of the references investigating treatment were not randomized controlled trials (RCTs), *a priori* subgroup analyses, or

Table 4 Percent of citations supporting the recommendations meeting quality criteria

Criteria	Percent high quality
Studies meeting all four quality criteria	34.4
Randomized controlled trial or systematic review	68.0
Representative study population	65.6
Clinically important outcome measured	82.8
Statistically significant results	57.8

systematic reviews with a thorough search. Clinically relevant results were not measured in 17.2% of the citations. Approximately one-third (34.2%) of cited research did not study outpatients with major depressive disorder, but instead enrolled patients with dysthymia, inpatients or mixed inpatient/outpatients. Seventeen (13%) of the 130 papers supporting the recommendations were published by one of the guideline developers. Most of these papers were research, reviews or editorials involving a pharmaceutical. Of these 17 studies, 82% (14/17) were cited as evidence in the guideline for efficacy, safety or favourable risk/benefit ratio of antidepressants. Citations used to support the recommendations did so 80.3% of the time; for the rest, the reference did not apply or the data from the study disagreed with the recommendation.

For example, two well-publicized meta-analyses independently concluded that because of a lack of efficacy, antidepressant medication should not be the first-line intervention for mild to moderate depression [12,45]. Noting a benefit only for the most severely depressed patients, Fournier *et al*. concluded 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. . . . [E]fforts should be made to clarify to clinicians and prospective patients that whereas [antidepressant medications] can have a substantial effect with more severe depressions, there is little evidence to suggest that they produce specific pharmacological benefit for the majority of patients with less severe acute depressions' ([46] pp. 51–52).

Kirsch *et al*. reported similar findings: 'Drug–placebo differences increased as a function of initial severity, rising from virtually no difference at moderate levels of initial depression to a relatively small difference for patients with very severe depression, reaching conventional criteria for clinical significance only for patients at the upper end of the very severely depressed category' ([45] p. 260).

However, the results from these meta-analyses are interpreted in this way in the guideline: '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 with those with mild to moderate symptoms' ([35] p.31). This statement, and the identification of antidepressants as a first-line intervention for mild to moderate depression, is not congruent with the research because it suggests that medication is effective for all levels of depression. The language used in the guideline and the recommendation of medication for all severity levels obscures the main finding of both meta-analyses: Antidepressants were found to be effective only for the most severely depressed patients and thus should not be a first-line intervention for patients who are mildly or even moderately depressed.

Discussion

In this analysis of the APA's Practice Guideline for the Treatment of Patients with Major Depressive Disorder, we identified the presence of possible bias introduced by financial and intellectual COIs. The evidence base cited for the recommendations often did not meet basic criteria for quality and sometimes did not support the recommendations.

Financial relationships with pharmaceutical companies were common among all guideline developers and were present in some members of the oversight committee who were supposed to be free from financial conflicts. The majority of the guideline authors served on speakers' bureaus as did at least one member of the independent review panel. Speakers' bureau participation is usually prohibited elsewhere (e.g. for faculty in medical schools), as it is widely recognized to constitute a significant financial COI. Pharmaceutical companies refer to individuals who serve on speakers' bureaus as 'key opinion leaders' because they are seen as essential to the marketing of diseases as well as drugs. The Institute of Medicine recommendations suggest that, 'whenever possible,' guideline developers avoid a financial COI and, at minimum, those with a conflict represent a minority of the development group. They explicitly ban the guideline chair from having financial ties [29]. Although it has been argued that it is not feasible to find experts without industry ties, it has been shown that content experts without financial COIs are available to serve on guideline development committees [47].

The impact of financial relationships recommendations has been well documented [22,23,48–50]. Recent guidelines from the National Heart Lung and Blood Institute recommending lipid screening of approximately 40% of the children in the United States has been called, 'evidence of a broken process,' because of extensive ties between the expert panel and the pharmaceutical industry [50]. A US professional society was the subject of a legal investigation; in the settlement, a state Attorney General noted important financial COIs and suppression of scientific evidence that had tainted the guideline development process [22,23]. A similar court ruling occurred in France, resulting in the withdrawal of two guidelines from the French Health Authority following charges that chairpersons of both working groups had 'major' financial COIs [49]. In contrast, other guideline developers face stricter precautions against bias arising from COIs. The United Kingdom's National Institute for Health and Clinical Evidence have instituted more rigorous safeguards and procedures, and personnel at the National Collaborating Centres must have no personal financial COIs [51,52].

Groups that have greater safeguards in place to prevent conflicts tend to produce guidelines that differ substantially from this depression guideline. For example, the National Institute on Health and Clinical Excellence (NICE) addresses the risk/benefit issue regarding the primacy of pharmacotherapy and explicitly states that antidepressant medication *should not* be the first-line choice for individuals with mild depression [53]. Recent Dutch guidelines recommend antidepressants as first-line treatment only in cases of severe depression [54].

There is a well-documented evidence base for the efficacy of non-pharmacological interventions in the treatment of mild to moderate depression, particularly for exercise [55,56] and psychotherapy [57,58]. Both NICE and the recent Dutch guidelines use this evidence to support their recommendations for non-pharmacologic therapies as first-line alternatives to pharmacological treatments [53,59]. It is possible that the guideline development group for this CPG was concerned about certain populations not having access to non-drug interventions (e.g. fewer psychotherapists in rural areas). However, the recommendation for antidepressant use for all levels of depression is made for all populations (see e.g., fig. 1, in [35], p. 31) regardless of access.

These guidelines also are at risk of an intellectual COI, in that all guideline work group members were from the same profession, were active researchers in the pharmacological treatment of depression, and were members of the professional society developing and promoting the guidelines. Although content expertise is needed, it is increasingly recognized that for CPGs to be valid and trustworthy, a mix of content experts and methodologists is warranted [29]. For example, while it is important that the panel members considered all types of evidence, from case reports that are categorized as 'low-quality' to 'high-quality' RCTs, the finding that 34% of the cited RCT research did not study outpatients with major depressive disorder and over 17% did not measure clinically relevant outcomes provides further support that methodologists without intellectual or financial COIs need to be part of all guideline development groups.

It has been suggested that professional societies may not be able to provide unbiased guidance. As mentioned in a recent editorial, '. . . Although it is true that individual medical providers care deeply about their patients, the guild of health care professionals – including their specialty societies – has a primary responsibility to promote its members' interests. . . . But it is a fool's dream to expect the guild of any service industry to harness its self-interest and to act according to beneficence alone – to compete on true value when the opportunity to inflate perceived value is readily available' ([60], p. 1078). This is a critical point, especially in light of the fact that this guideline has enormous influence – approximately 80% of all prescriptions for antidepressants are written by non-psychiatrists [61] – and this guideline is the trusted resource to which many doctors and nurse practitioners turn.

Other researchers have noted the effect of intellectual COIs on guideline results [4–6,8,21,23,49]. In an evaluation of guidelines for screening mammography, Norris and colleagues found that the substance of guideline recommendations was related to the number of recent publications of guideline developers [21]. A consensus statement from three US endocrinology societies rejected recommendations from the scientific review they commissioned [62] because, 'In the opinion of our panel members, the consensus conference recommendations in the areas delineated above are contrary to the practice of many, although not all, experts . . .' ([63], p. 582). Similarly, subsequent guidelines from the American Academy of Pediatrics [64] and the American College of Radiology contradict guidelines of the USPSTF regarding the management of kernicterus [65] and screening for breast cancer [66].

It should be emphasized that a CPG author's mere association with industry is not meant to imply that inevitably he/she will make interpretations that favour industry. Financial ties between industry and academic researchers bring attention to the generic risk that the guideline development process may be compromised. Moreover, most people with COIs – from doctors [67] to US Supreme Court Justices [68] – do not recognize the effect of these conflicts on their judgments [27]. Declaring or acknowledging conflicts does not mitigate their effects. As previously noted, both social science and neuroscience literature demonstrate that transparency alone is an insufficient solution because bias is often implicit and unintentional.

In fact, disclosure may not only normalize COIs, but may also worsen bias. For example, 'moral licensing' occurs when disclosure of a COI reduces feelings of guilt of the advisor, resulting in more biased advice because advisees 'have been warned' [69–71]. In practice, moral licensing occurs as experts in a field acquire numerous financial or intellectual relationships with the pharmaceutical industry, allowing them and frequently their audience to rationalize that the relationships somehow 'cancel out' one another. Such findings have critical implications for clinical experts charged with developing diagnostic and practice guidelines; disclosure of their industry relationships may make them more favourable to pharmacological products [72].

There are several limitations to our study. We had to synthesize recommendations from the guideline by comparing statements presented in several sections of the guideline. Other researchers may have synthesized the recommendations in a slightly different way since subtle differences in wording can affect the interpretation of recommendations [73,74]. Also, because the general statements in the executive summary (Part A) are not linked to the evidence, we may not have identified all of the citations used in the process that shaped the guidelines. Our criteria for determining quality should be considered *de minimus* and we may have failed to identify low-quality research used to support recommendations. Additionally, our measures of intellectual COIs (previously cited studies and membership in specialty societies) have limitations. However, these measures have been identified as important areas to explore in order to understand the effect of intellectual COI on guideline development [26]. Although these results do not point to a direct causal relationship between financial or intellectual COIs and guideline quality, our findings contribute to the growing body of data on the effects of these conflicts on CPGs.

It was beyond the scope of this study to replicate the literature search conducted by the GDG, conduct a systematic review of all of the literature on pharmacological and non-pharmacological interventions, and identify high-quality studies that were omitted from the guideline. However, future research should try to determine if there are a significant number of omitted studies in guidelines produced by specialty groups.

Despite these limitations, our method of evaluation of these guidelines can be used to provide a more thorough assessment of practice guidelines. It builds on the criteria developed by McAlister [16] by adding checks for financial and intellectual COIs as well as criteria recommended by the Institute of Medicine [29]. Our approach offers advantages over another instrument developed to evaluate practice guidelines. The AGREE II instrument aims to identify higher-quality guidelines through the use of a 23-item tool evaluating six quality related domains. Each item has a 7-point Likert-like response scale [75]. However, its focus is on the evaluation of the guideline development process and reporting.

It does not evaluate COIs except to address the composition of the guideline development group and to determine whether COIs have been 'recorded and addressed'. Its scoring system does not provide a cut-off to distinguish low-quality from high-quality guidelines. Also, it does not weigh the relative effect of the quality indicators on guideline quality, for example the criterion, 'the views of the funding body have not influenced the content of the guideline', is given no more weight than, 'a procedure for updating the guideline is provided'. As a result, the AGREE II criteria are better suited as a blueprint for guideline developers rather than an evaluation tool for potential users of a guideline. Because clinical interpretations of medical evidence will differ [76] it is critical that users of CPGs and patients be aware that COIs may exert undue influence on these interpretations [77,78].

Guideline development has matured to the point where all guidelines are typically labelled as being 'evidence-based'. However, what should be a straight line from the current best evidence to guidelines for clinical practice is more akin to a tortuous path, and that is why individual authors and groups have worried that guideline quality has declined rather than improved over time [20,29,79,80]. Therefore, we suggest that when specialty groups with strong industry ties produce CPGs, users should read closely the disclosure statements of the authors and consider 'how [COI] may have influenced recommendations' ([21], p.e25153).

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