Publication Bias, with a Focus on Psychiatry: Causes and Solutions

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REVIEW ARTICLE

Publication Bias, with a Focus on Psychiatry: Causes and Solutions

Erick H. Turner

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Abstract Publication bias undermines the integrity of the evidence base by inflating apparent drug efficacy and minimizing drug harms, thus skewing the risk–benefit ratio. This paper reviews the topic of publication bias with a focus on drugs prescribed for psychiatric conditions, especially depression, schizophrenia, bipolar disorder, and autism. Publication bias is pervasive; although psychiatry/psychology may be the most seriously afflicted field, it occurs throughout medicine and science. Responsibility lies with various parties (authors as well as journals, academia as well as industry), so the motives appear to extend beyond the financial interests of drug companies. The desire for success, in combination with cognitive biases, can also influence academic authors and journals. Amid the flood of new medical information coming out each day, the attention of the news media and academic community is more likely to be captured by studies whose results are positive or newsworthy. In the peer review system, a fundamental flaw arises from the fact that authors usually write manuscripts after they know the results. This allows hindsight and other biases to come into play, so data can be "tortured until they confess" (a detailed example is given). If a "publishable" result cannot be achieved, non-publication remains an option. To address publication bias, various measures have been undertaken, including registries of clinical trials. Drug regulatory agencies can provide valuable unpublished data. It is suggested that journals borrow from the FDA review model. Because the significance of study results biases reviewers, results should be excluded from review until after a preliminary judgment of study scientific quality has been rendered, based on the original study protocol. Protocol publication can further enhance the credibility of the published literature.

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1 Introduction

1.1 Publication Bias Defined

Publication bias occurs when investigators, reviewers, and editors submit or accept manuscripts based on the strength and direction of study results [1]. It can occur because negative or inconclusive results are less likely to be submitted by authors, less likely to be accepted by journal editors and reviewers, or both. The term "publication bias" can refer to selective publication of entire trials, a.k.a. the file drawer problem [2], or to selective reporting of outcomes within those trials, a.k.a. outcome reporting bias [1, 3, 4] or spin [2, 5–8]. But the term can also encompass other phenomena, such as delayed publication [9–11], duplicate or multiple publication [12–15], place of publication bias [16], and citation bias [17–19].

1.2 Consequences of Publication Bias

Publication bias can inflate apparent drug efficacy, making it difficult to distinguish effective from ineffective drugs, reminiscent of the Dodo bird in Alice in Wonderland, who said, "Everybody has won, and all must have prizes" [20]. Equally important, publication bias can conceal drug harms. A prominent example came to light with the lawsuit brought by the State of New York against GlaxoSmith-Kline for suppressing data on suicidal thinking among children and adolescents treated with the antidepressant paroxetine [21]. With drug harms underreported [22] and efficacy inflated, both the numerator and the denominator of the risk–benefit ratio are affected, creating undue enthusiasm for treatment options and hindering clinicians' capacity to make informed distinctions between competing interventions.

1.3 Scope of This Article

Publication bias occurs throughout the scientific literature, but it may occur to the greatest extent in psychiatry and psychology [23]. This aim of this article is to review examples of publication bias with a focus on psychotropic drugs, and to discuss why it occurs, how it has been addressed, and what more needs to be done.

2 Pervasiveness of Publication Bias (Examples by Field)

2.1 Depression

A study by our group illustrates how publication bias can inflate apparent drug efficacy [24]. Using FDA Drug Approval Packages on 12 antidepressants, we identified a retrospective cohort of 74 FDA-registered premarketing trials. We tracked each trial into the published literature and asked whether it was published and, if so, whether the results agreed with those of the FDA. According to the published literature, nearly all trials were positive, i.e., the drug appeared superior to placebo on the primary outcome. By contrast, the FDA version of the same trials revealed that, in fact, only half of the trials were positive. This discrepancy was due to a combination of nonpublication and "spin." Of the 36 not-positive trials, only 3 (8 %) were published as not positive, 11 (31 %) were "spun" into apparently positive trials, and 22 (61 %) were left unpublished. We also examined the impact of publication bias on effect size (ES). We meta-analyzed twice, once with journal data and again with FDA data. With all drugs combined, publication bias inflated the (overall) ES from 0.31 to 0.41, an inflation factor of approximately one-third (32 %). For individual antidepressants, the inflation factor ranged from 11 to 69 %.

Regarding pediatric depression, a 2004 paper showed that, when unpublished antidepressant data were added to published data, the risk–benefit profile shifted from favorable to unfavorable [25]; a later paper provided evidence for delayed publication [9]. Paroxetine was the subject of the abovementioned lawsuit [21]. While the highly cited published version of Study 329 asserted the drug was both effective and safe [26], internal industry documents revealed that the trial was negative on all protocol-specified outcomes and that the occurrence of suicidal thinking had been downplayed [27, 28].

Returning to the use of antidepressants in adults, a study using data from the Swedish drug regulatory authority found that publications exaggerated the efficacy of five antidepressants through a combination of selective and multiple publication [15]. Elsewhere, multiple publication was detailed for duloxetine: six trials were "salami sliced" into 20 or more separately reported pooled analyses [12].

An analysis of data on reboxetine showed that data on 74 % of patients had not been published [29]. When the unpublished data were added to the analysis of efficacy, reboxetine's apparent statistical superiority to placebo vanished. Further, inclusion of these unpublished data revealed that reboxetine was not equivalent, but rather inferior, to competing antidepressants. (A decade earlier, the FDA had rejected reboxetine for marketing in the US due to lack of efficacy, but its evaluation was unfortunately not releasable to the public [30].)

The efficacy of agomelatine for depression was studied in ten premarketing trials: five were positive and published, while the five negative trials remained unpublished [31].

2.2 Other Psychiatric Indications

2.2.1 Schizophrenia

Publication bias also occurs with antipsychotics, as can be seen from the following article title: "Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine" [32] (the short answer is sponsorship). A separate report illustrated efforts to suppress and "spin" unflattering data on quetiapine and olanzapine, using excerpts from internal industry marketing department communications [7]. Also, a study by our group using FDA Drug Approval Packages found additional evidence of publication bias with eight antipsychotics [33]. Among 24 premarketing trials, four were unpublished. Of those four, three were nonsignificant on the primary outcome; in the fourth, the study drug beat placebo but was significantly inferior to an inexpensive competing drug (haloperidol). The issue of inferiority to an active comparator also arose

among the published trials. The fact that the antipsychotic iloperidone was inferior ($P < 0.05$) to two of three active comparators was apparent from the FDA reviews but not from the journal articles.

2.2.2 Bipolar Disorder

For bipolar disorder, publication bias has been reported for aripiprazole (maintenance treatment [34]), lamotrigine [35, 36], and gabapentin. Lamotrigine's efficacy for bipolar depression was initially reported in a highly cited 1999 article [37]. Five years later, online GSK trial reports, made available because of the abovementioned lawsuit, revealed that lamotrigine failed to demonstrate superiority to placebo not only in that published trial but in four unpublished trials. Also, publication bias in promoting the off-label use of gabapentin for bipolar disorder and other indications has been the subject of numerous articles [5, 38–43].

2.2.3 Autism

Returning to antidepressants, serotonin reuptake inhibitors have been reported to be effective for repetitive behaviors associated with autism spectrum disorders; however, an asymmetric funnel plot suggests that their efficacy may be exaggerated by publication bias [44].

2.3 Other Fields of Medicine

But publication bias is not restricted to drugs prescribed for psychiatric conditions. A narrative review documented publication bias in 40 indications throughout medicine [45]. Another research group has looked broadly across indications by comparing FDA Drug Approval Packages to the published literature, thus documenting evidence of outcome reporting bias [46] and inflation of drug effect size [47].

2.4 Beyond Medicine

Yet publication bias is not restricted to medicine. A recent review found that for "hard sciences" (including space sciences, physics, chemistry, and genetics), the proportion of positive studies was unrealistically high, ranging from 70 % to approximately 90 % [23, 48].

3 Who is Responsible for Publication Bias?

3.1 Authors vs. Journals

The responsibility for publication bias does not rest with a single party. For journal articles to be published, authors must be willing to submit, and journals must be willing to accept. When trials turn out negative, authors may self-censor, convinced the data are "not publishable." Authors are under no obligation to submit such data for journal publication, but if they do, they are free to emphasize results that present the drug in a positive light. Once manuscripts are submitted, journals may decline to consider them for publication, perhaps motivated by reasons discussed below.

3.2 Industry vs. Academia

The party submitting the manuscript might be associated with industry, academia, or both. In *The Truth About Drug Companies* [49], Marcia Angell argues that publication bias should be expected because it is simply consistent with industry's fiduciary duty to enhance profits for shareholders. Many academics collaborate with industry sponsors as "key opinion leaders" (KOLs) through consulting, promotional speaking, and/or authorship [50]. Such relationships offer financial rewards, name recognition, and prestige. In exchange, the academic typically signs confidentiality agreements, which can prohibit the disclosure of unflattering trial results [51–53].

Sponsorship by industry leads to more favorable conclusions than other forms of sponsorship [54]. However, publication bias is not restricted to industry—it has also been found with government-funded academic research in the US [55, 56], Canada [3], and the UK [57].

3.3 Motives

3.3.1 Authors

In academic environments, as competitiveness increases, so does publication bias [58]. Thus, there appear to be "ivory tower" incentives for publication bias that go beyond the financial incentives of corporations. First, researchers may be unlikely to publish articles acknowledging negative results for fear that they may adversely affect future grant prospects. Second, to avoid cognitive dissonance, researchers may be reluctant to admit they have "wasted" years researching hypotheses that were not borne out by the data. Third, hindsight ("I-knew-it-all-along") bias [59] may encourage HARKing, or hypothesizing after the results are known [60]. Fourth, readers appear to prefer a satisfying storyline [61], as opposed to reading about a trial whose hypothesis simply was not borne out by the data. In the words of Francis Bacon: "It is the peculiar and perpetual error of the human understanding to be more moved and excited by affirmatives than by negatives" [62]. Finally, through social proof [63], it seems appropriate to follow the lead of colleagues and role

models who devalue negative results through spin or nonpublication, even though this arguably constitutes scientific misconduct [64].

3.3.2 Journals

On the journal side, various factors can contribute to publication bias. Journals may prefer to publish manuscripts with findings that are "marketable," i.e., likely to attract the readers' attention. Because it is hard to manage the volume of new medical information [65], readers—whether they be health care providers, researchers, drug companies, or news reporters—must be selective. Articles in high-impact journals may be perceived as more important than those in lower-impact journals. Consistent with this, when identical content is published in two journals, roughly twice as many subsequent citations go to the journal with the higher impact factor [66].

Positive (statistically significant) results appear to receive preferential treatment during the peer review process. Manuscripts with positive results are more likely than those with negative results to be judged as methodologically sound and worthy of publication, even when their methods sections are identical [67]. Among clinical trials with small sample sizes, those published in high-impact journals tend to report larger effect sizes than those published in lower impact journals [68], suggesting that journals prefer "positive" over "negative" manuscripts.

One high-impact journal articulates this (understandable) preference in its instructions to authors: "*The Lancet* prioritises reports of original research that are likely to change clinical practice or thinking about a disease" [69]. Indeed, publication of meta-analyses in three high-impact journals (including *The Lancet*) was found to be associated with the degree to which they changed earlier perceptions, independently of study sample size and statistical significance [70]. Therefore, rather than stating that journals prefer manuscripts that are positive, it may be more accurate to state that they prefer manuscripts that are newsworthy.

3.3.3 News Media Reporters

One group of readers that needs to be selective is news media reporters. Reporters can play the role of information gatekeepers for "downstream" readers, because they screen articles during the embargo period before release to the public. If they find the storyline newsworthy, their news coverage can direct widespread attention to the article in question (without news coverage, the article may go unnoticed and uncited). Like other readers, reporters are inundated with new medical information, so they too must be selective. It seems possible that they preferentially scan the contents of high-impact journals, whose names their readers will readily recognize as authoritative.

3.3.4 Other Readers

"Downstream" readers include laypersons, clinicians, researchers, and drug companies. Readership among clinicians and researchers can translate into subscriptions and thus funds to sustain the journal [71]. Researchers may be stimulated to conduct and write up new research citing the index article, supporting the index journal's impact factor. When these researchers seek a "home" for their manuscript, they may prefer high-impact journals in order to better attract citations [66] and academic prestige.

4 How Does Publication Bias Occur?

4.1 Information Flow in the Peer-Reviewed System

How does the peer-reviewed system allow publication bias to occur? In our group's studies (above), how can the same trial be negative according to an FDA review but positive according to a journal article? If we contrast the flow of information in the peer-reviewed system with the FDA system, we can see that the former contains loopholes.

Each peer-reviewed journal article regarding a clinical trial begins as a general study idea. When this is elaborated into a protocol, one might articulate a plan to collect data on various related outcomes, but in order to control type I error [72] and avoid spurious associations [73], usually only one will be designated as the primary outcome. Once funding and regulatory approval have been secured, patient recruitment and data collection can begin. When the last patient's data have been collected, the investigator(s) can break the blind (assuming a double-blind design) and analyze the data. If the results pertaining to the primary outcome are statistically significant, the authors may enjoy a sense of success and vindication that their investments of time, energy, and funds have paid off.

But if the data are not statistically significant, the investigator may experience a sense of disappointment. As with other losses, initial reactions may include denial [74]. Convinced that the drug works, the investigator may believe that some error occurred during data collection or entry, but when no errors are found, he or she might wonder whether he or she designated the "wrong" outcome as primary. Here the investigator may enter a bargaining phase and explore whether post hoc reanalyses using non-primary methods yield more "publishable" *P* values.

For example, in trials comparing antidepressants to placebo, it is not uncommon to measure depressive symptoms using at least two observer-based rating scales,

the Hamilton Depression Rating Scale (HAMD) [75] and the Montgomery-Asberg Rating Scale (MADRS) [76]. If the HAMD has been designated as primary but it yields nonsignificant results, one might conduct a post hoc literature search and read that the HAMD, despite its long tradition as a gold standard for depression trials, is "psychometrically and conceptually flawed" [77]. One could thus rationalize, in hindsight, that the MADRS "tells the real story" and should be emphasized in the manuscript.

Alternatively, if the investigator has collected data using one of the extended versions of the HAMD, such as the 29-item version [78], he or she can opt to discard some of the items from the HAMD and reanalyze. This can be justified post hoc because there are several shorter versions of the HAMD, each with citable literature to support its use, including the 24-item [79], 21-item [75], 17-item [75], 7-item [80], and 6-item versions [81, 82].

The investigator's "degrees of freedom" [83] expand further when one realizes the data from any of these scales can be analyzed in various ways. For example, one might examine the data as a continuous variable using either ANOVA or, using the baseline score as a covariate, ANCOVA. Such a seemingly petty detail can be pivotal in determining whether the *P* value falls above or below 0.05, and thus whether the trial is deemed positive or negative.

At the investigator's option, the continuous data can be transformed to dichotomous by classifying each patient's score into one of two groups according to whether it falls above or below a cutoff score. A patient can be classified as remitted from depression in various ways: HAMD-17 score $\leq$7 [84], HAMD-7 $\leq$3 [80], MADRS $\leq$9 or $\leq$4 [85]; any of these, again, can be justified with supporting literature after the results are known. Another popular way to dichotomize is according to "response," which is commonly defined as occurring when a patient's score drops at least 50 % from its baseline [86, 87]. Exercising different methods of dichotomization, patients can be reclassified, potentially changing the significance of the results.

Next, there are various ways to handle the data from patients who drop out. In our study of antidepressant trials [24], 6 trials were FDA-negative (nonsignificant) using the prespecified primary method for handling dropouts (last-observation-carried-forward, a.k.a. LOCF, method) but were published as positive using non-primary methods. (Five additional trials were "spun" through other means, as detailed in that article's supplemental appendix).

Above are a few examples of a process that goes by various names, including outcome reporting bias, "statistical alchemy" [36], and HARKing [60]. As the saying goes, "If one tortures the data long enough, it will eventually confess to anything." Once "publishable" results have been obtained through HARKing, they can be submitted to a journal. But because few journals ask for the original trial protocol, manuscript reviewers have little choice but to take the submitted methods and results at face value. The average reader of the published product likely assumes that, having been vetted by peer review, the methods and results are what they appear to be.

Beyond choosing how to submit, authors can choose when to submit—hence the phenomenon of delayed publication [9–11]. For example, "The makers of a popular cholesterol lowering drug…posted results of a trial showing it was ineffective—but only after a Congressional inquiry was set up to look into why they had not published their results two years after the study was completed "[88]. Finally, the author can choose whether to submit—there is no legal requirement to publish trials, even when they have been registered (below).

4.2 Information Flow in the FDA System

How can these problems be addressed? Journals could close loopholes by borrowing from the FDA model for handling clinical trial data [89]. The FDA's evaluation of a trial occurs in two stages—before and after the trial. By contrast, journals become aware of the existence of trials only after the data have been collected, analyzed, and potentially subjected to HARKing.

4.2.1 Before the Trial

For premarketing trials conducted by drug companies, registration with the FDA has been required for several decades [90]. Upon registration, the FDA receives the sponsor's full protocol. In so doing, the FDA learns of the trial's existence as well as its methods, including the a priori statistical analytic plan. Using our hypothetical example of an antidepressant trial, the FDA might learn that the primary outcome will be based on the 21-item version of the HAMD, analyzed using ANCOVA, and that data from dropouts will be handled using mixed effects model repeated measures (MMRM, a method now favored by the FDA over LOCF [91]). The statistical significance of this primary outcome determines whether the trial will be declared positive, and supportive of marketing approval, or negative. Secondary outcomes are also declared in the protocol but are considered merely exploratory [72].

4.2.2 After the Trial

Assuming that the FDA has no objections to the protocol, data collection may begin. Later, after the sponsor has completed its clinical trials program and feels confident in the results, it submits a New Drug Application (NDA) to the FDA. Because the Agency learns of all planned trials through registration, and because its review

comprehensively lists all trials [92], it would immediately recognize any attempt by the sponsor to submit a "cherry-picked" subset of the trials. (To clarify, the review process differs from the approval process, whereby drug efficacy can be established based on positive results in a subset of trials [93]). Also, because the FDA reviewer has access to the original trial protocol, he or she can spot HARKing. In addition to summary data, the FDA receives raw data, with which the Agency statistician tries to replicate the sponsor's results. If the drug is approved, reviews by the statistician, Medical Officer, and others are compiled into the Drug Approval Package (DAP), which is made publicly available for download on the FDA website [90].

5 What Have Been the Solutions, and What Are Their Limitations?

5.1 Registration: Public Declaration of Intent to Conduct Trials

Steps taken to address publication bias have been reviewed in previous publications, and they will be summarized here. To date, the most significant step has been the development and evolution of clinical trial registries, the largest being ClinicalTrials.gov [94].

5.1.1 Timeline of Events Leading to Near-Comprehensive Registration

In November 1997, the Food and Drug Modernization Act (FDAMA) was passed [95]. While this law required trial registration, its scope was narrow and applied only to trials for "serious or life-threatening conditions." In February of 2000, ClinicalTrials.gov was established, but compliance with trial registration was poor, and few trials were registered [96]. The topic of registration took on greater urgency in 2004: following the abovementioned lawsuit regarding paroxetine for pediatric depression [21], Vioxx was withdrawn from the US market due to myocardial infarctions and strokes [97]. Also in 2004, the International Committee of Journal Editors (ICMJE) announced that its member journals would, starting July 2005, consider trials for publication only if they had been prospectively registered [98]. This policy was effective, increasing the number of registrations by 73 % between May and October of 2005 [96, 99], and their number has continued to increase.

Despite the success of ClinicalTrials.gov, registries have limitations. First, a requirement to register a trial does not translate into requirement to publish it—in a sample of trials registered with ClinicalTrials.gov, only about half (52 %) were published [94]. Second, HARKing remains possible—two studies found that over 60 % of primary outcomes registered in ClinicalTrials.gov were described vaguely [94, 100].

5.2 Making Trial Results Public

There have been efforts to make public not only trial plans but also trial results. As pointed out in 2004, the US Food and Drug Administration (FDA) has operated a semi-public registry and results database for several decades [90]. In early 2005, draft legislation called for the posting of trial results [101]; in 2007, this was modified and passed as the Food and Drug Administration Act of 2008 (FDAAA) [102].

This legislation requires that basic trial results be deposited in ClinicalTrials.gov, but its effect has been limited by its scope and by compliance issues. First, it has been found that approximately 80 % of the trials are not reported within the required time frame [103]. Second, the law does not apply to trials that lie outside the authority of the FDA, such as those trials conducted for off-label uses, drugs rejected by the FDA, phase 1 drug trials, behavior therapies, surgical procedures, and all trials conducted outside the US [104]. Third, FDAAA applies only prospectively, not retrospectively, so a "loophole" exists for drugs approved before 2008, which are prescribed in vast numbers [105]. Fourth, while results must be reported online at ClinicalTrials.gov, they need not be published in medical journals [94, 106], the medium more familiar to clinicians.

5.3 Self-Regulation by the Pharmaceutical Industry

Over the years, drug companies, in response to reports that they have hidden unflattering data, have often publicly declared their commitment to transparency. However, there might seem to be a tension between this and, as noted above, their fiduciary duty to generate profits [49]. In 2000, the year ClinicalTrials.gov was established, drug company executives expressed their intent to resist efforts to register trials [99]. In 2004, to settle a lawsuit, GSK established its clinical trials database. Within weeks, the Pharmaceutical Research Manufacturers of America (PhRMA, the lobbying organization representing major US drug companies) established the Clinical Study Results Database for its member drug companies (including GSK). However, reporting varied by drug company, some excluding trials completed before 2004. In 2011, this database was quietly decommissioned [107].

On the other hand, a consensus group of industry professionals has outlined ten recommendations for "closing the credibility gap" in their reporting [108], including: "make public all results, including negative or unfavourable ones, in a timely fashion, while avoiding

redundancy;" "report adverse event data more transparently;" "provide access to more complete protocol information;" and "transparently report statistical methods used in analysis." In October 2012, GSK announced that it would go beyond the summary data provided since 2004 and begin providing researchers, upon request, with (anonymized) patient-level data [109]. In February 2013, GSK went further by announcing plans to make patient-level data publicly available on its website [110]. Roche, by contrast, is currently unwilling to take such a step [111].

5.4 Role of Drug Regulatory Agencies in Addressing Publication Bias

For the hundreds of drugs in current use, drug regulatory agencies can provide access to clinical trial results that have been selectively unpublished.

5.4.1 FDA Transparency Policy—Current State and Limitations

For drugs approved by the FDA since 1997, the above-mentioned DAPs are available for download from the FDA website [for drugs approved earlier, DAPs can be obtained by making a Freedom of Information Act (FOIA) request]. However, limitations with this resource should be addressed. First, as with ClinicalTrials.gov [94], data are available only if they fall under FDA jurisdiction. If the FDA has reviewed but rejected a new drug application, it is deemed an unreleasable trade secret. Thus, no DAPs are available for off-label indications or for drugs rejected by the FDA, even though they may be prescribed widely overseas, such as reboxetine [30]. Second, formatting issues, which would seem easily addressed, render DAPs cumbersome [90]. Third, DAPs for drugs approved before 1997 could be made available for download, just as they are for more recently approved drugs. There was reason for optimism that these and related issues would be addressed after the FDA convened a Transparency Task Force in 2009 [112], but since then, there has been little sign of follow-through.

5.4.2 Other Drug Regulatory Authorities

Nevertheless, the FDA has historically been the only regulatory agency to provide substantial amounts of clinical trial data to the public. HealthCanada makes available Summary Basis of Decision documents on newly approved drugs, but these may be as brief as a single page. Data from the Swedish [15, 113] and the Swiss [114, 115] regulatory agencies have given rise to publications, the authors were agency employees; such data are not available to outside researchers.

The European Medicines Agency (EMA), after initial resistance [116], is becoming more transparent [117]. According to a recent EMA news release, "The proactive publication of clinical-trial data is expected to come into force on 1 January 2014" [118]. At the time of this writing, the details of this policy were yet to be finalized. One such detail is whether patient-level data will be made available [116, 119]; if implemented, this would go beyond the summary data in FDA DAPs.

5.5 The Role of Journals

5.5.1 Current Journal Practice

Journals have played a leading role in addressing publication bias. As noted above, the ICMJE requirement for registration was quickly followed by a manifold increase in registrations. But journals can do more. According to the ICMJE's website, member journals have an "obligation to publish negative studies" [120]. Unfortunately, perhaps from concern it might degrade impact factors, compliance among individual member journals appears to be rare, and, as noted above, negative studies seem to be explicitly discouraged [69]. However, there are a few exceptions: The *Journal of Cerebral Blood Flow and Metabolism* has a section set aside for negative results, and there is at least one medical journal that publishes only negative results: the *Journal of Negative Results in Biomedicine*. Among general medical journals, the editors of *Trials* and of the *PLOS* (Public Library of Science) journals state that they will consider trials for publication regardless of the strength and direction of the results; among psychiatry journals, the *Journal of Psychiatry and Neuroscience* has made a similar statement [121].

5.5.2 Proposals for Results-Blind Peer Review

5.5.2.1 Previous Proposals Even when journals state that their publication decisions will not be influenced by study results, in light of the study discussed above (Sect. 3.3.2) [67], one wonders whether editors and reviewers can help but be influenced by them. In my opinion, the only way to avoid this is to make the review process results-blind. Accordingly, one suggestion has been to review only the introduction and methods sections [122]. But in my opinion, this approach would not solve the problem because the writing of these sections would occur after the results are known and would thus be influenced by hindsight bias. A second suggestion has been for authors to submit a results section from which the numerical results, including *P* values, have been redacted [123]. Not only would this be subject to the limitations of the first approach, but the reviewer, upon reading the context surrounding the

redacted results, might well infer whether the results are positive or negative.

In order to preclude hindsight bias, the material reviewed should consist of hypotheses and methods generated before, not after, the results are known. Hence a third proposed approach is for authors to submit the introduction and methods sections before they know the results [124]. If the journal editors and reviewers are then sufficiently impressed by the scientific quality of those sections, they would render a (results-blind) pre-acceptance. "This contingent acceptance would be completed or not on the basis of final fulfilment of other core final elements of the trial such as quality of recruitment, statement of results, interpretation and discussion." Besides eliminating HARKing, this approach would encourage the publication of nonsignificant results. However, while this approach seems ideal, it may not be feasible in the near future, because it would require a sea change in the way journals and authors operate. Authors have been conditioned to write and submit only after the data have been analyzed, and they might have difficulty resisting the temptation to "peek" at the results until after they have submitted to and heard back from the journal. Enforcement could be problematic—how could the editors and reviewers be sure that the data had not been collected and analyzed before the manuscript was written?

5.5.2.2 Current Proposal A feasible solution, in my opinion, lies in the protocol. In the model proposed here, authors would submit the original trial protocol along with evidence that it was approved before the trial was undertaken, e.g., dated by the approving institutional review board or funding agency. (Protocol amendments would also be welcome, as long as they were verifiably approved before the blind was broken). In consideration of current review practices, the protocol would be submitted for journal review at the traditional time, after the data have been analyzed. With access only to materials written before the results were known, editors and reviewers would be obligated to render a preliminary judgment based on the quality of the science—the importance of the question and the methodological rigor deployed to answer it. Another criterion for protocol quality could be level of adherence to the recently published Standard Protocol Items for Randomized Trials (SPIRIT) guidelines [125]. So that journals are not burdened with low-quality submissions, a criterion for submission could be completion of the SPIRIT checklist, elements of which—such as basic design features—could be used to screen submissions.

After a preliminary acceptance is rendered, the final manuscript could be submitted and reviewed. At this stage, journal editors and reviewers would focus on how faithfully the manuscript adheres to the original protocol (perhaps using published methods for ascertaining outcome reporting bias [3, 4, 6, 41, 126]), how well any deviations from the protocol have been justified (see the section below), and the quality of the writing and data presentation.

An important limitation of this approach is that it does not address authors' tendency to submit selectively [127]. Over time, however, the current stigma associated with such data should disappear as they become recognized as not only "publishable" but expected [128], leading to a change in the prevailing culture. To be sure, all parties involved may not embrace this proposal, especially since some may be asked to do additional work. But paradoxically, protocol review can save significant time: a quick comparison with the manuscript should reveal whether undisclosed HARKing has occurred, in which case rejection or major revision can be recommended without further ado.

5.6 What Journal Reviewers Can Do

For those of us who contribute as journal reviewers, when we are asked to review a manuscript for a journal that does not require protocols, we can encourage the editor to require them in the future. Meanwhile, any clinical trial and its planned outcomes should be registered at trial inception; upon comparing these to the manuscript, one can verify that the outcomes have not been changed [129].

If the journal is one of the few that already require protocol submission, one should resist the temptation to skip reviewing the protocol, for the reasons noted above.

This is not to say categorically that all changes in methods constitute HARKing. A change in the methods could be explained by developments unforeseen by and beyond the control of the investigators, such as difficulty recruiting subjects. Assuming the reviewer finds the explanation plausible, he or she must then decide whether the preliminary acceptance should be rescinded due to a loss in study validity. Such changes could be reviewed more favorably if covered by a protocol amendment submitted with the original protocol.

5.7 What Authors and Investigators Can Do

What can authors and investigators do? Research funded by the United States National Institutes of Health must be freely and publicly disseminated in accordance with the NIH Public Access Policy (http://publicaccess.nih.gov/policy.htm). When writing protocols, investigators should clearly distinguish primary from secondary (exploratory) outcomes [72]. The outcomes should be specific and detailed enough that a statistically savvy colleague with

access to the raw data can replicate the analyses and *P* values. Some journals consider protocols for review (e.g., *The Lancet*) or publication (e.g., *Trials*, *Systematic Reviews*, F1000 journals). The time invested in doing so should pay off in terms of increased verifiability, credibility, and the impact of one's final publication.

5.8 What Clinicians Can Do

Clinicians not involved in research or the peer-review process can help combat publication bias by publicly calling upon their drug regulatory agencies to be more transparent. Only with full access to data regarding drugs can we, as prescribers, determine the true risk–benefit ratios of drugs and provide the level of care our patients deserve.

6 Conclusions

Publication bias compromises the integrity of evidence-based medicine because it leads to overestimation of drug benefits and underestimation of drug harms. It has been found throughout the peer-reviewed literature in medicine and science in general, so no drug should be considered exempt from its effects. However, psychiatrists need to be particularly aware of this problem, because the drugs they prescribe may be among the most affected. Here we have reviewed various examples from psychiatry, specifically drugs prescribed for depression, schizophrenia, bipolar disorder, and autism.

Publication bias is encouraged by a culture in which various parties—drug companies, academicians, journals, news media—favor positive over negative or null results. To address publication bias, various measures have been undertaken, including registries of clinical trials. Drug regulatory agencies can serve as a valuable source of unpublished data.

Despite these efforts, publication bias is likely to persist until a fundamental flaw in the peer-reviewed literature is addressed: knowledge of study results influences whether, how, and when manuscripts are written, and it influences how the study's scientific quality is judged by journal editors and reviewers. This paper proposed a possible solution to this problem, one in which the original study protocol plays a key role.

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