Free academic discourse and the law: the case of liposomal bupivacaine

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ABSTRACT

Liposomal bupivacaine has been the topic of intense academic debate over the past years culminating in an industry-initiated libel lawsuit against the American Society of Anesthesiologists and various other defendants. In this Daring Discourse, we first aim to provide a general overview of main themes in the ongoing controversy: (1) between-study heterogeneity, (2) the high number of negative high-quality reviews and meta-analyses, (3) publication bias in the context of an active role of industry and (4) difference between statistical and clinical significance. We then discuss the contents of the lawsuit, its potential implications and what the recent resolution of this lawsuit means for the future of research and the academic discourse on liposomal bupivacaine.

INTRODUCTION

Liposomal bupivacaine has been the topic of intense academic debate over the past years with the majority of reviews and meta-analyses failing to demonstrate a clinically relevant benefit over more traditional options such as plain bupivacaine.[1–4] In 2021, the ongoing controversy culminated in an industry-initiated libel lawsuit against the American Society of Anesthesiologists (ASA) and various other defendants.[5] In this *Daring Discourse*, we aim to provide a general overview of main themes in the ongoing controversy, the lawsuit and its interpretation as well as what it means for the future of research.

CURRENT CONTROVERSY

Two influential meta-analyses[4 6] and one narrative review[1]—published in the past 2 years—concluded that the current body of literature fails to support routine use of liposomal bupivacaine, suggesting that it has no advantages over regular bupivacaine. Furthermore, given the number of studies involved, questions have been raised regarding the value of additional trials.

The first meta-analysis combined 23 randomized-controlled trials (RCTs) comparing liposomal to plain bupivacaine in adult patients undergoing peripheral nerve block or local infiltration analgesia; a total of 1867 patients were included.[6] Here, Dinges *et al* report clinically irrelevant, although statistically significant, differences between liposomal and plain bupivacaine in terms of mean pain scores at 24 hours and morphine equivalent consumption at 24 and 72 hours after surgery.[6]

This meta-analysis was strengthened by a 'trial sequential analysis,[7]' which determines a 'required information size' reflecting the number of included participants needed to reach conclusive results with a meta-analysis, concluding that future studies are unlikely to change the effect estimators for pain scores and morphine equivalent consumption at 24 hours after surgery.[6] The second meta-analysis, by Hussain *et al*, synthesized data from nine RCTs (619 patients) and focused on effectiveness of liposomal versus non-liposomal bupivacaine used perineurally. The authors describe a statistically significant—but clinically unimportant—improvement in the 24-hour to 72-hour weighted mean area under the curve rest pain scores when comparing perineural liposomal bupivacaine with plain local anesthetic.[4] Interestingly, statistical significance did not persist after excluding an industry-sponsored trial. No benefits were observed for a variety of secondary outcomes including opioid consumption, rest pain severity at various time points up to 72 hours postoperatively, time to first analgesic request, opioid-related adverse effects, patient satisfaction, length of hospital stay, and functional recovery. Concerns regarding industry-sponsored trials are further echoed in a narrative review by Ilfeld *et al*.[1] Here, the authors described 76 RCTs—concerning use of liposomal bupivacaine for both surgical infiltration or as part of a peripheral nerve block—and found that for almost half of included studies, authors reported potential conflicts of interest, either direct funding from the manufacturer of liposomal bupivacaine or being concurrently paid consultants and/or employees. Importantly, industry funding appeared to be associated with a higher likelihood of results favoring liposomal bupivacaine. Moreover, 35 to 40% of included studies had evidence of high risk or some concern for bias. Heterogeneity was another noted concern. Similar to Dinges *et al* and Hussain *et al*, they concluded that the current extensive evidence base does not support the routine use of liposomal bupivacaine over standard local anesthetics in the treatment of postoperative pain.[1]

Heterogeneity

Heterogeneity in general is a commonly mentioned critique affecting meta-analyses on the use of liposomal bupivacaine, particularly regarding the nature of control groups, surgical context and modes of administration. Both Dinges *et al*[6] and Hussain *et al*[4] compellingly address heterogeneity. Specifically, the former authors note that it is of limited value to compare absolute effects of liposomal bupivacaine in regional and local infiltration analgesia with varying controls; however, a difference in the effectiveness of liposomal compared with plain bupivacaine would suggest a true pharmacological effect as the relative difference between the two should be stable among all of its uses.[6] Hussain *et al* go further and assess heterogeneity in various sensitivity analyses. They report that statistical significance of their primary outcome's effect estimate hinged on the inclusion of an industry-sponsored trial.[4]

Equipoise

An important implication of these publications is that they represent an extensive body of literature that is not in support of routine use of liposomal bupivacaine in the treatment of postoperative pain. Given the number of studies involved, this conclusion carries a level of definitiveness, which is further supported by a trial sequential analysis performed by Dinges *et al*.[6] Logically, this leads to the question if and under what circumstances trials should continue to enroll patients in studies of liposomal bupivacaine's effectiveness. Central to this discussion is the concept of equipoise,[8] a key ethical principle in RCTs stating that a patient may be enrolled into an RCT only when substantial uncertainty exists, which of the treatment arms would most likely benefit them. While there is no clear definition of

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'substantial uncertainty',[9] one could take the position that this principle may be violated if future liposomal bupivacaine trials were to be performed, especially when considering its comparatively high price point.[10] Ideally, research costs and risks for trial participants should be offset by the scientific knowledge generated. Here too, the net balance may not appear to favor continuing RCTs evaluating liposomal bupivacaine without explicitly considering its value proposition. This is further exacerbated by the existence of only a few formal cost-effectiveness analyses, which may have partly driven liposomal bupivacaine's exclusion from formularies at institutions nationwide.[11] Indeed, it is important to consider the larger, societal context (eg, public trust in the value of medical research) and societal cost of research (eg, decisions about health coverage that cannot be viewed separately) when thinking about ethical guidelines for physician and patient decision-making regarding the use of liposomal bupivacaine and circumstances under which to continue RCTs.

Publication bias

Concerns regarding publication bias represent another challenge in interpreting research on liposomal bupivacaine. Both Dinges *et al*[6] and Hussain *et al*[4] report generally low risks of publication bias. While publication bias can have various sources, it is mainly investigated to refute that the probability of publication is dependent on the statistical significance of a study's results. It is in this context that experiences described in another meta-analysis on liposomal bupivacaine may contribute to the erosion of trust as the authors describe the painstaking efforts to gather unpublished data.[12] Indeed, concerns about not publishing negative results, especially with an active role of industry, are not new.[13] While industry-funded studies should not be inherently suspect—indeed, some evidence points towards a higher quality of industry—versus publicly funded RCTs[14]—this finding deserves additional scrutiny. What is particularly concerning is the active role of the manufacturer in shaping the academic discourse on this drug with recent claims of payments for …*bogus research grants* (as stated in the press release by the US Attorney's Office, District of New Jersey).[15] Other examples include an overly optimistic interpretation of study results regarding its length of action, leading the FDA to publish a warning letter based on misleading advertising.[16] Although, this warning has been rescinded since, any pattern of potentially problematic industry involvement—or at least the appearance thereof—erodes trust between academia and industry, which is especially worrying in a time where there is a dire need for collaboration in the search for novel non-opioid analgesics.

Clinical relevance

Finally, differentiation between statistical significance and clinical relevance is generally addressed in the liposomal bupivacaine literature.[1 4 6] Assessments of clinical relevance are dependent on various parameters such as the nature of the outcome, the patient population of interest or 'anchors' utilized. Moreover, minimal clinically important effects can be determined in a variety of ways.[17] For example, Dinges *et al* cite other studies to determine a clinically relevant pain score difference of >1.5 on a 0–10 scale: Cepeda *et al*[18]—a study focused on acute pain—and Farrar *et al*[19]—a study focused on chronic pain. In terms of assessing an opioid-sparing effect, clinical relevance was determined based on their own clinical experience and set at >30%. One strategy is for journals to advocate for a priori registration in PROSPERO and include key information that will inform the interpretation of results, including definitions of predetermined minimal clinically important effects and their rationale. Such information will be particularly important in studies where statistical significance does not reflect clinical significance, as has been described in various liposomal bupivacaine studies.[1 4 6]

LIBEL LAWSUIT

In the context of the aforementioned ongoing controversies, the manufacturer of liposomal bupivacaine filed a libel lawsuit on April 14, 2021 against various parties including the ASA, the editor-in-chief of Anesthesiology, and (explicitly named) all authors involved in three papers published in the February 2021 edition of Anesthesiology.[1 4 5 20] Here, the plaintiff asked for retraction of the three papers and pecuniary damages.[5] The request for retraction was based on alleged *false and misleading statements and conclusions that disparage (liposomal bupivacaine)*. The lawsuit goes even further and alleges (separately for each author) that they *knew or recklessly disregarded the fact that (their) statements (about liposomal bupivacaine) were false or misleading* suggestive of mal intent on part of the authors. The suit, for example, mentions some methodological shortcomings in the meta-analysis while also noting that two authors practice in Canada—where liposomal bupivacaine is not available—and thus *these authors are likely commenting on a product they have never actually used*. Singling out several individuals, the suit additionally alleged that they failed to disclose payments from some of the plaintiff's competitors while anesthesiology's editor-in-chief was singled out and alleged to have *a significant bias against (liposomal bupivacaine), in favor of opioids for treatment of pain* and is *using his position to advance a pro-opioid agenda and disparage competitive alternatives like (liposomal bupivacaine*). These allegations are not trivial, at points very specific and personal, and could silence lines of research in fields even outside of anesthesiology. Further emphasizing this negative impact on academics are the plaintiff's alleged suffered financial damages for which they appeared to seek compensation.[5]

RESOLUTION AND IMPLICATIONS FOR ACADEMIC DISCOURSE

On February 4, 2022, the District Court dismissed plaintiff's case.[21] Plaintiff appealed, and on March 24, 2023, the Third Circuit Court of Appeals affirmed the District Court's dismissal.[22] Given the potential grave consequences of the lawsuit, we provide context for and analysis of the dismissal below.

The lawsuit against the ASA and aforementioned individuals (ie, defendants) consisted of a single claim of trade libel under New Jersey law. Defendants moved the Court to dismiss the case under Federal Rule of Civil Procedure 12(b)(6), which asked the Court to dismiss plaintiff's claim on the ground that the complaint did not adequately allege facts that stated an actionable claim for trade libel. In general, policy when reviewing a 12(b)(6) motion is for the court to be plaintiff-friendly, so as not to deprive a plaintiff of due process: the court formally takes as true all of a plaintiff's allegations of fact and makes all reasonable inferences in favor of the plaintiff. Furthermore, when allegations are not adequately pled, courts will typically give plaintiffs leave to amend, i.e., to address the pleading problems and correct their complaint. Here, the Court granted defendants' 12(b)(6) motion, and further, the Court dismissed *with prejudice*, which indicates that in the Court's view, there was no way in which Plaintiff could amend their allegations to amount to a case.

In arriving at their conclusion, the District Court did not make new law; it

applied established precedent, primarily ONY vs Cornerstone Therapeutics[23] which held that a statement of scientific conclusion about unsettled matters of scientific debate could not give rise to a defamation action. Quoting *ONY*, the Court wrote that contested scientific hypotheses *are more closely akin to matters of opinion, and are so understood by the relevant scientific communities*. Therefore, as a scientific conclusion cannot be either true or false, and since falsity is one of the required elements in a trade libel claim under New Jersey law (the other three being publication, malice, and special damages), it followed that a scientific conclusion could not give rise to a trade libel claim. In sum, the Court wrote that *a scientific conclusion based on non-fraudulent data in an academic publication is not a 'fact' that can be proven false through litigation*.

In addition, the Court opined that defendants' methodologies were not required to be indisputable to benefit from this legal protection; only falsification of data would have caused the respective publications to fall outside the scope of protected scientific opinion. While acknowledging that plaintiff had identified grounds for possibly legitimate scientific debate in raising issues about the methodologies used by defendants, the Court held that *even a methodologically flawed conclusion in an academic publication on an area of scientific uncertainty is incapable of defamatory meaning*.

Exercising its right to appeal, plaintiff then brought its case before the Third Circuit Court of Appeals, pursuant to which it enjoyed a full round of fresh legal briefing, oral argument, and de novo review of the District Court's dismissal. Under a de novo review, the appeals court gives no deference to the lower court's decision. On its own analysis, the Court of Appeals came to the same conclusion as the District Court, holding that *the statements that form the basis of (plaintiff's) trade libel claim are nonactionable opinions* that cannot support a trade libel claim. To determine whether defendants' statements were nonactionable opinions, the Court of Appeals, applying existing law, considered the content, verifiability, and context of defendants' statements. By each of these three factors, and echoing the District Court's conclusion, the Court of Appeals wrote that the scientific conclusions at question constituted nonactionable *opinions as a matter of law, and no new factual allegations, including criticisms about the bases for these opinions, would disturb that conclusion*. Thus, roundly rejecting plaintiff's complaint and finding no way for plaintiff to state a claim, the Court of Appeals affirmed the District Court's dismissal with no leave to amend.

Taken together, the ongoing controversy on liposomal bupivacaine and its potential place in daily clinical practice merits a broad discussion among perioperative researchers and clinicians alike on the potential need for parameters that may justify continuing trials that enroll patients to study liposomal bupivacaine's effectiveness. In a perfect world, industry would play a productive role in these discussions as we strive to improve on available pharmaceuticals and applications of analgesic drugs. While the lawsuit has resulted in some erosion of trust between academia and industry, we emphasize continued collaboration, reflective of a collective desire to prolong nerve blocks beyond the simple duration of bupivacaine. The Courts' decisions here should be taken as some reassurance for the larger scientific community. As the District Court wrote, *the peer-review process—not a courtroom—… provides the best mechanism for resolving scientific uncertainties*. We agree.

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