

Jay D. Amsterdam: The paroxetine 352 bipolar study Ethical conduct

Email from Jay Amsterdam to Tom Ban, November 7, 2021

Second Office of Research Integrity Complaint

Dear Tom:

Thank you for your nice follow up email, and for your suggestions regarding the posting of the second tranche of the primary source documents pertaining to the study 352 paroxetine misconduct case.

As you may recall, there have been several letters from my lawyers to the Office of Research Integrity (ORI) of the Department of Health and Human Services that include the original July 8, 2011, study 352 paroxetine research misconduct complaint letter (containing primary source email and other documentation). These documents have already been posted on the INHN historical website from August 5, 2021, to January 13, 2022.

Regrettably, however, the letter from the University of Pennsylvania ORI Inquiry Committee, who was designated by Penn to investigate the allegations of research misconduct of July 8, 2011, was also designated by the Penn administration as being confidential. Therefore, the Penn Inquiry Committee report of allegations of misconduct is not directly available for posting on the INHN website.

However, despite this designation by Penn, a point-by-point rebuttal of the Penn Inquiry Committee's conclusions are now provided to the INHN historical record as part of a second, follow up complaint of research misconduct to the ORI by my lawyer. This second misconduct complaint provides the INHN reader with additional primary and secondary source documentation rebutting the original Penn Inquiry Committee's conclusion that no research misconduct had occurred when the Penn (and other) professors had appended their names to a ghost written, plagiarized article published in the American Journal of Psychiatry. This second complaint was made to the ORI on June 25, 2012.

As previously indicated, this second ORI complaint describes in exquisite detail, a point-by-point rebuttal of Penn's assertion that their professors did not engage in any form of academic or scientific misconduct.

In contrast, this second ORI misconduct complaint now includes additional evidence that ghost writing, plagiarism, editorial corruption, data manipulation and university obfuscation had indeed occurred, and that the university and its professors would assert plausible deniability of

wrongdoing by denying the existence of these vital inculpatory documents showing evidence to the contrary.

I believe that this second tranche of historical documents is vital to the understanding of how the clinical and scientific record can become corrupted by the Academy itself; and why a knowledge of this evidence is so important to the health and well-being of our field *writ large*.

With kind regards,

Jay

Second Office of Research Integrity Complaint

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The challenge of pursuing science in a morally justified way
is one that every generation must take up.

— Amy Gutmann and James Wagner

Re: Complaint of Scientific Misconduct against Dwight L. Evans, Laszlo Gyulai,
Charles Nemeroff, Gary S. Sachs and Charles L. Bowden

Dear Dr. Wright:

On behalf of Dr. Jay D. Amsterdam, Professor of Psychiatry at the University of Pennsylvania, a charge of research misconduct was submitted to your office against Dr. Dwight L. Evans, Professor of Psychiatry and Chairman of the Department of Psychiatry at the University of Pennsylvania, Dr. Laszlo Gyulai, Associate Professor of Psychiatry at the University of

Pennsylvania, Dr. Charles B. Nemeroff, Professor of Psychiatry and Chairman of the Department of Psychiatry at the University of Miami, Dr. Gary S. Sachs, Professor of Psychiatry at Harvard University, and Dr. Charles L. Bowden, Professor of Psychiatry and Chairman of the Department of Psychiatry at the University of Texas at San Antonio. See Exhibit 1, July 8, 2011 Complaint.

In the Complaint, Dr. Amsterdam alleged that the individuals named above engaged in scientific misconduct by allowing their names to be appended to a manuscript that was drafted and revised by the medical communications company, Scientific Therapeutics Information, Inc. (hereinafter "STI"), which was hired by SmithKline Beecham, now known as GlaxoSmithKline ("GSK"), and which Dr. Amsterdam contended misrepresented information from a scientific research study (Paroxetine Study 352) funded by GSK and the NIH. The manuscript (herein-after "Study 352") was eventually published in the American Journal of Psychiatry (158:906-912, June 2001) and suggested that Paxil may be beneficial in the treatment of bipolar depression, without data to support this conclusion and without acknowledging contributions of STI and GSK in drafting and publishing the study report. The published manuscript was biased in its conclusions, made unsubstantiated efficacy claims and downplayed the adverse event profile of Paxil.¹

Dr. Amsterdam's Complaint was filed with the Office of Research Integrity ("ORI") on July 8, 2011. The University Of Pennsylvania School Of Medicine commenced an internal inquiry into the allegations shortly thereafter, and completed its inquiry in December 2011, concluding that a formal investigation was not warranted. To date, none of the other academic institutions have initiated an internal inquiry of the research misconduct allegations. On December 5, 2011, Dr. Amsterdam received a letter from J. Larry Jameson, M.D., Ph.D., Dean of the University of Pennsylvania School of Medicine stating:

The University considers allegations of this type to be very serious. I am confident that the Committee reviewed your allegations thoroughly and fairly, in accordance with University policy. Having reviewed the Committee's report, I accept their findings and conclusion that further investigation is not warranted.

See Exhibit 2. We respectfully submit that the University of Pennsylvania Committee's inquiry lacked depth and completeness, and was selective in its examination of the available evidence.²

Contrary to the University's claim of a "thorough review," the University intentionally chose not to obtain and examine important documentary evidence it was aware existed from the files of the ghostwriting firm, STI, which would have provided the Committee highly relevant information not otherwise available to them. The Inquiry Committee relied on the word of the two University

¹ A copy of the manuscript was attached as Exhibit A to Dr. Amsterdam's July 8, 2011 Complaint.

² For the reference of On we are including a complete copy of the Committee's Report and accompanying Exhibits (two volumes).

of Pennsylvania Respondents as factual, while the unexamined STI documents appear to contradict the Respondents' testimony. More disappointing was that, despite essentially acknowledging that the article in question was ghostwritten, the University held that Drs. Evans and Gyulai were not guilty of any violations because, according to the University, ghostwriting was an acceptable practice during the relevant time period (1998-2001). The University's conclusions not only contradict common sense, but further contradict the University's own previous statements on this issue. In 2009, for instance, the University of Pennsylvania told the U.S. Senate Investigating Committee that it considered ghostwriting to be plagiarism and a violation of the University's policies. The University's representation to the U.S. Senate appears to have been forgotten and ignored when it came to judging the acts of its own faculty. It is disappointing that an Ivy League school which claims to be driven by a credo of ethics has given sanctuary to such conduct.

We also submit that Dr. Evans may not have provided the Inquiry Committee with all available evidence in his possession (e.g., email correspondence that may still exist on the University of Pennsylvania server). This important information may have been withheld from the Committee or may have been overlooked by the Committee.

Finally, we believe the Inquiry Committee, in choosing not to examine important evidence in this case, arrived at incorrect conclusions regarding the scope and degree of scientific misconduct and conflict-of-interest that was inherent in the preparation of the study 352 manuscript, the degree of efficacy data misrepresentation, safety data omission, publication bias, and misrepresentation of study 352 results (see Exhibits described herein).

Thus, we believe Dr. Jameson's conclusion, that "further investigation is not warranted," is erroneous and we encourage further investigation of Dr. Amsterdam's allegations by ORI. Our basis for this opinion is set forth herein. In conducting its inquiry, we would encourage ORI to do what the University of Pennsylvania failed to do, which is to obtain the STI documents which confirm the veracity of Dr. Amsterdam's allegations and contradict the testimony and statements given by the Respondents.³ We would be more than willing to assist ORI (or any other Governmental investigative agency) in guiding them to the key STI documents that are probative to this issue, supportive of Dr. Amsterdam's allegations, confirm the flaws of the Committee's conclusions and shed further light on the erroneous testimony provided by the Respondents.

INQUIRY COMMITTEE'S ANALYSIS

³ It is our understanding that STI was willing to forward its documents to the University of Pennsylvania for review, however, the University intentionally chose not to review these highly probative documents. The University's struthious approach to the probative and available STI documents is disturbing and creates the impression that its inquiry was anything but intended to discover the truth.

A. Allegations Relating to Authorship and "Ghostwriting"

The Committee determined the allegations relating to authorship and ghostwriting essentially posed two questions:

- The first allegation - that Dr. Evans and Dr. Gyulai allowed their names to be appended to a manuscript drafted by a medical communications company and, thereby, Dr. Evans and Dr. Gyulai were not legitimate authors of the manuscript.
- The second allegation - that the manuscript was "ghostwritten" by STI and that the authors of the published manuscript failed to appropriately acknowledge STI's contribution.

I. Are Dr. Evans and Dr. Gyulai Legitimate Authors of the Publication?

(a) Contrary to the Committee's Conclusions, Dr. Evans Was Not a Legitimate Author of the Publication

Relying solely upon the testimony of Dr. Evans, the Committee concluded that Dr. Evans satisfied the criteria for authorship as established by the International Committee of Medical Journal Editors (ICMJE). We believe there is reason to doubt whether Dr. Evans participated sufficiently in the design and conduct of study 352, or in the preparation and review of the manuscript, to be considered a legitimate author. As Dr. Amsterdam explained to the Inquiry Committee, Dr. Evans told Dr. Amsterdam (during Dr. Amsterdam's initial telephone conversation with Dr. Evans in March of 2001, about possible plagiarism associated with the 352 study), that Dr. Evans' research site at the University of Florida had recruited only one or two study subjects and that these subjects who were recruited were treated by Dr. Evans' associate, Dr. Jeffrey Staab. This information was provided by Dr. Amsterdam to the Inquiry Committee on August 8, 2011. However, it does not appear the Committee made any attempt to verify the extent of Dr. Evans' involvement in the study while he was at the University of Florida by either retrieving the research records from Dr. Evans' investigative site in Florida or by contacting Dr. Staab (currently at the Mayo Clinic in Rochester, Minnesota). Certainly, the recruitment of only two study subjects into a project that sought to recruit a total of 186 subjects would not constitute a significant contribution to the conduct of the study. Moreover, there were a total of 19 investigative sites in the study, with the majority having a low subject enrollment. In this regard, draft one of the manuscript (and all subsequent extant drafts of the manuscript) indicates that 14 of the 19 investigative sites had recruited fewer than eight subjects. The modest contribution of these investigators was only mentioned in the "acknowledgements" section of the published article. It appears the Inquiry

Committee relied solely upon the word of Dr. Evans to verify that he made a significant contribution to the conduct of the study.

Despite the above facts, it does not appear the Committee inquired into who selected or determined that a particular investigator should (or should not) be assigned as an author on the manuscript, or which author or non-author investigator (if any) should receive a draft of the manuscript for review and revision. It also appears that the Committee did not investigate the extent of the contribution made to the study by the GSK-named authors, or by what criteria authorship on the manuscript was determined. This information would have been important for the Committee in making a determination of whether (or not) Dr. Evans (or any of the GSK-designated authors) satisfied the Committee's criteria for legitimate authorship.

As to the issue of significant contribution to drafting and revising the article, again, the Committee relied solely upon Dr. Evans' word that he made editorial contributions to the writing of several drafts of the manuscript. It does not appear that Dr. Evans provided any documentary evidence to the Inquiry Committee to support the conclusion that he met the requirements for authorship on the manuscript. In this regard, Dr. Evans failed to provide any handwritten or typed drafts of the manuscript to the Committee that would demonstrate a substantial contribution. Notably, the Committee acknowledged that "**Neither Dr. Evans nor the Committee could locate any written record of Dr. Evans's revisions.**" See Committee Report at 8.

Moreover, the Committee deliberately chose not to examine important documents which could have been provided to them by Scientific Therapeutics Information, Inc. (STI). The documents likely would have provided a clearer picture of Dr. Evans' involvement (or lack thereof) in the manuscript preparation. These documents would also likely have provided the Committee with additional information about Dr. Evans' involvement with the 'ghostwriting' firm (STI) and GSK in the preparation of the manuscript, and that Dr. Evans had little or no editorial or scientific input into the drafting of the manuscript. The fact that the Inquiry Committee chose to ignore these important documents raises serious questions about the veracity of the inquiry and doubts about the Committee's conclusions.

Indeed, the evidence produced by GSK demonstrates that the preliminary drafts of the study 352 article were conceptualized and drafted by STI and not by any of the named authors. For example, Exhibit 9 of the Committee Report indicates that draft one of the manuscript was written by STI expressly for GSK. Similarly, Exhibit 10 of the Committee report indicates that draft two of the manuscript was also written by STI (after receiving approval and revisions of draft one by GSK). Thus, at this stage of the manuscript development, there was no indication of authorship, either academic or non-academic.

Thus, despite the Inquiry Committee's conclusion that Dr. Evans fulfilled the three main requirements for authorship on draft three of the manuscript (prepared by STI and GSK), the

available evidence does not support the Committee's conclusion that Dr. Evans made a substantive contribution to the preparation of the manuscript.

Additional doubt as to Dr. Evans' substantial input into the preparation of the manuscript comes from a statement written by Dr. Gyulai in a letter to Dr. Amsterdam dated July 5, 2001. See ORI Complaint Attachment L. Dr. Gyulai stated that he had not seen any drafts of the manuscript after draft two before he briefly saw the final pre-submission draft of the STI and GSK-produced manuscript one week prior to submission to the American Journal of Psychiatry.

In sum, it appears that Dr. Evans' contribution to the preparation of the manuscript was limited to his commenting on, and approving, STI and GSK ghostwritten drafts of a manuscript on which he was designated as second author, and of which he had no direct knowledge of the accuracy of the data analyses, data interpretation (i.e., the inclusion or exclusion of particular data analyses related to safety and efficacy), or the accuracy, or the information that was written in the manuscript (by the ghostwriters). In consequence, Dr. Evans allowed his name to be appended as an author to a ghostwritten manuscript as part of a study for which he made only a minimal contribution.

Moreover, in contrast to the Committee's conclusion that the lack of evidence supporting Dr. Evans' statements did not "undercut his representations to the Committee," we would suggest that there were, in fact, some compelling reasons for doubting the veracity of Dr. Evans' statements to the Inquiry Committee.

In this regard, on November 29, 2010, only six months prior to the filing of the current ORI Complaint of research misconduct against Dr. Evans et al., the Project on Government Oversight sent an open letter to Dr. Francis Collins, Director of the National Institute of Health, alleging that Dr. Evans had appended his name as an author to a ghostwritten article that was prepared by Sally Laden at STI and published in the scientific journal Biological Psychiatry in 2003 (see <http://www.pogo.org/pogo-files/letters/public-health/ph-iis-20101129.html>).

Evidence of the ghostwritten article with Dr. Evans as author was provided in the letter to Dr. Collins in the form of an e-mail letter from Sally Laden to a GSK administrator asking for compensation for writing the article on behalf of Dr. Evans in Biological Psychiatry (see <http://pogoarchives.org/m/ph/gw/gw-attachment-b.pdf>). Coincidentally, STI writer, Sally Laden, the person who ghostwrote Dr. Evans' 2003 Biological Psychiatry article, is the same individual who drafted and ghostwrote the Study 352 manuscript that is at issue in this complaint.

Thus, it appears Dr. Evans has been engaged in lending his name to ghostwritten articles with the same "ghosts" (i.e., Sally Laden) at STI beginning in 1997 to at least 2003, and that he had little or no involvement in the drafting and revision of the study 352 manuscript prior to its submission for publication.

In fact, the very same Sally Laden has been identified in at least three other ghostwriting scandals, including the Nemeroff/Schatzberg Psychopharmacology Handbook for Primary Care Physicians (also published by the American Psychiatric Association), the Cyberonics VNS article which resulted in Dr. Nemeroff's resignation as editor of the journal in which it was published, and the now infamous GSK study 329 on Paxil for pediatric depression.⁴

(b) Contrary to the Committee's Conclusions, Dr. Gyulai was Not a Legitimate Author of the Publication

Dr. Gyulai has likewise engaged in scientific misconduct by allowing his name to be appended to a ghostwritten industry-drafted manuscript.

As outlined in Dr. Amsterdam's initial complaint, Dr. Amsterdam was a co-principal investigator on the Study 352 clinical trial. Specifically, when Dr. Gyulai faced difficulties recruiting research subjects, Dr. Amsterdam's highly productive research unit was brought into the study by Dr. Gyulai's supervisor (Dr. Karl Rickels). Dr. Amsterdam was designated as Co-Principal Investigator by the University of Pennsylvania Office of Regulatory Affairs (or the Institutional Review Board) at his Penn investigative site. Dr. Amsterdam's involvement proved to be a success as he ultimately recruited at least 19 study subjects, or more subjects than most, if not the most, of all of the investigative sites. When Dr. Amsterdam agreed to participate in Study 352, it was his understanding that his role was not just limited to patient recruitment, but that he would be involved in all aspects of the study, including data review, data analysis, and manuscript preparation. Dr. Amsterdam was, however, left out of the post-clinical trial data analysis and manuscript preparation. It is Dr. Amsterdam's contention that he was intentionally left off from the review of the data and the drafting of the manuscript because the study sponsor, GSK, and the other "authors" knew Dr. Amsterdam's professional ethics would not allow him to lend his name to a ghostwritten work, and most importantly, his morals would not allow the alteration and manipulation of data and would not allow the other "authors" to turn a failed study into an undisclosed promotional marketing manuscript for the sponsor.

Moreover, in contrast to the Inquiry Committee's conclusion that "Dr. Gyulai was actively involved in drafting and revising the manuscript," Exhibits 9, 10, and 11 of the Committee Report demonstrate that Dr. Gyulai did not assume the responsibility for preparing the first, second, or third drafts of the manuscript (which was ghostwritten by STI and GSK).

⁴ See Wilson, D. "Drug Maker Wrote Book Under 2 Doctors' Names, Documents Say," The New York Times, November 30, 2010, B3; Holden, C. "The Undisclosed Background of a Paper on a Depression Treatment," Science, 2006, 313/5787: 598-599; Shashok, K., Jacobs, A. "Who's watching whose ethics? Slanted reporting of the medical writer's role in the Neuropsychopharmacology-Cyberonics case," The Write Stuff, 2007, 16/1: 1-3; McHenry, L., Jureidini, J. "Industry-sponsored ghostwriting in clinical trial reporting: a case study," Accountability in Research, 2008, 15:152-167.

Moreover, even if Dr. Gyulai did make revisions to draft two of the manuscript, he must have been aware that he was appending his name as first author to a manuscript that was ghostwritten by STI and GSK and that was provided to him at the draft-two level by GSK (see Committee Report Exhibits 9, 10, and 11).

Further, in a July 5, 2001 letter (see ORI Complaint Attachment L), Dr. Gyulai admitted that he had not seen a draft of the study 352 manuscript after he made his revisions to draft two, until he was provided with a pre-submission draft of the manuscript (probably draft seven) until one week prior to its submission to the American Journal of Psychiatry. Thus, Dr. Gyulai was approving a scientific manuscript for publication for which he had insufficient knowledge of the accuracy of the data provided by GSK. This comports with the evidence Dr. Gyulai provided to the Inquiry Committee in Appendix A of the Committee Report which indicates that Dr. Gyulai had very little input into the preparation, review, or revision of the manuscript after early 1997 until just prior to its submission to the American Journal of Psychiatry in 1999.

In sum, Dr. Gyulai knowingly signed the copyright agreement for a manuscript that was ghostwritten by STI and GSK, he knowingly lent his name to a manuscript for which he had not seen the data and for which he had little or no knowledge of the accuracy of the data analyses and made conclusions that he could not substantiate.

By knowingly appending their names as authors to a ghostwritten manuscript, Drs Evans and Gyulai were in violation of the "Responsible Conduct of Biomedical Research: A Handbook for Biomedical Graduate Studies Students" on plagiarism that was in use at the time of publication (see <http://www.med.upenn.edu/bgs/docs/BIOETHICSHANDBOOK4-04.pdf>).

II. Should Another Contributor to the Publication Have Been Named as an Author or Listed in the Acknowledgment Section?

After reviewing the evidence presented by Dr. Amsterdam, the Inquiry Committee was forced to concede that STI and GSK played a significant role in preparing and drafting the manuscript. Notably, the evidence revealed STI and GSK wrote the initial manuscript drafts one and two without any input from the researchers who participated in study 352 (see Committee Report Exhibits 9 and 10). The authors listed on the title page of the manuscript draft three were solely determined by GSK after manuscript draft two was produced by STI and GSK (see Committee Report Exhibit 11). Subsequent drafts of the manuscript were primarily revised and prepared by STI and GSK with little or no input from the GSK-designated authors. As the Committee noted, despite STI's significant role in the preparation and drafting of the manuscript, the final published article makes no mention of STI's role in the article and does not mention that three of its authors, Ivan P. Gergel, M.D., M.B.A., Rosemary Oakes, M.S. and Cornelius Pitts, R.Ph. are GSK employees.

Instead of admonishing Drs. Evans and Gyulai for their involvement in a ghostwritten and plagiarized work, the Committee, unfortunately, went out of its way to find a path to whitewash the conduct of its employees. Significantly, the Committee acknowledged that, according to the University's current policies as well as assurances the University recently gave Senator Grassley's Office,⁵ the practice of ghostwriting and failing to identify as author an individual who made substantial contributions to the writing constitutes plagiarism and is a violation of the University's rules and regulations. See Committee Report at 12. Specifically, the University Guidelines Provide:

[University of Pennsylvania] Professionals are prohibited from allowing their professional presentation of any kind, oral or written, to be ghostwritten by any party, including Industry. Ghost-writing (also referred to as ghost authorship) is the failure to identify as an author, someone who has made substantial contributions to research or writing of a manuscript or professional presentation that merited authorship, or an unnamed individual who participated in writing the manuscript or professional presentation. Ghost authorship may range from authors for hire with the understanding that they will not be credited, to major contributors not named as an author, to commercial entities or contractors writing an article, manuscript or other professional presentation and listing a non-participating physician as an author.

See Exhibit 17 to the Inquiry Committee's Report. Thus, the University's current guidelines clearly acknowledge that ghostwriting is prohibited, and the Inquiry Committee essentially concluded that Drs. Evans and Gyulai violated the current University guidelines and engaged in plagiarism by appending their names to a ghostwritten manuscript. Nonetheless, because the guidelines did not go into effect until 2006, five years after the publication of the manuscript, the Committee concluded that Dr. Evans' and Gyulai's conduct was not prohibited or unethical at the time the manuscript was published, in 2001.

Essentially, and contrary to the University's representations to Senator Grassley's Office, the Committee effectively concluded that, at all times prior to 2006, plagiarism was an acceptable practice at the University of Pennsylvania. The Committee's conclusions defy logic and are an offense to common sense. To support its proposition that plagiarism was an accepted practice in 2001, the Committee cites a study showing "evidence of ghost authors" in 11% of articles published in 1996 (see Committee Report at 10) and states that certain journals, including the American Journal of Psychiatry, which published the offending manuscript, had not yet placed any restrictions on ghostwritten articles. Thus, the Committee effectively concludes that, because a small minority of academics with questionable ethics (11%) were involved in ghostwritten work,

⁵ United States Senator Charles Grassley has been at that forefront of investigating the unethical practice of ghostwriting in medical journal articles.

this justifies the practice. Allowing the unethical conduct of a few to set the ethical standard of the majority is unacceptable.

Moreover, contrary to the Committee's conclusions, ghostwriting was never an acceptable practice. Indeed, as the Committee concedes, in 1995, long before the Study 352 manuscript was published, prestigious journals such as the Journal of the American Medical Association (JAMA) had recognized that ghostwriting was unacceptable and clarified its policies mandating that all individuals who provide writing and editing assistance be acknowledged in the manuscript. See Committee Report at 10.

More importantly, the Committee did not need to resort to adopting the standards of other journals and unethical practitioners. Rather, in 1999, the University of Pennsylvania's own Bioethics professor, Arthur Caplan, Ph.D., publicly admonished the practice of ghostwriting as an unacceptable practice. Specifically, in a July 10, 1999 article published in the medical journal, *The Lancet*, Dr. Caplan is quoted as stating:

[T]he reader has a right to expect that the person whose name is on an article in a scientific journal is the person who wrote it...I don't think we should have to be looking for ghosts, goblins, or any other spirits that might have been involved, but aren't credited or acknowledged... [the offer of the help of a ghost author] is a lure to some people because it's an easy way to get a publication and covers the fact that they aren't good writers, or are too busy to do it themselves. But none of these seem to me to be effective reasons or justifications.

Larkin, "Whose Article is it Anyway," *The Lancet* Vol. 354 (July 10, 1999) (attached as Exhibit 4). Thus, three years prior to the publication of the study 352 article, it was common knowledge at the University of Pennsylvania that ghostwriting was a form of plagiarism and was ethically reprehensible.⁶

Indeed, in addition to JAMA and *The Lancet* article referenced above, even prior to the publication of the study 352 manuscript, a number of physicians and medical journal editors had already gone on the record in the late 1990s lamenting that the pharmaceutical industry had created a "crisis of credibility" by infiltration and pollution of the medical literature. See e.g., Cullen, D., "Ghostwriting in Scientific Anesthesia Journals," *Journal of Clinical Anesthesia*, 1997, 9: 349-350; Rennie, D., Yank, V. Emanuel, L. "When Authorship Fails," *JAMA*, Aug. 20, 1997, 278/7: 579-585; Flanagan, A., Cary, L., Fontanarosa, P., et al., "Prevalence of Articles with Honorary Authors and Ghost Authors in Peer-Reviewed Medical Journals," *JAMA*, July 15, 1998, 280/3:222-224; Rennie, D., Flanagan, A., Yank, V., "The Contribution of Authors," *JAMA*, July 5, 2000, 285/1: 89-91. In sum, contrary to the Committee's conclusion, in 2001 ghost-writing was

⁶ It appears the Inquiry Committee did not even bother to question its own Bioethics professor regarding this issue. Had it bothered to do so, it likely would have learned that, even at the time of the publication of the Study 352 manuscript, the practice of ghostwriting was an unacceptable and unethical practice.

not an acceptable practice, but rather was viewed by the majority of academics, including the University's own Bioethicist, as an unacceptable and unethical practice.

Finally, one might reasonably question whether the Committee's stated criteria of "only those with key responsibility for the material in the article should be listed as authors" actually occurred in the case of the study 352 manuscript. While the Inquiry Committee seemed preoccupied with understanding the policy of whether (or not) the listed authors should (or should not) acknowledge the writing contribution of ghostwriters and a pharmaceutical company in the production of scientific manuscripts in 2001, concerns over policy in 2001 appears to sidestep the more important issue of scientific accuracy and potential bias in scientific journal articles ghostwritten and/or ghost-managed, i.e., those articles that originate from a pharmaceutical company's publication strategy, are produced by a for-profit medical communication or public relations company, are funded by the pharmaceutical company and remain the property of that company until the legal transfer of ownership when the article is submitted for publication.

This is certainly the circumstance of the study 352 manuscript and hundreds, if not thousands, of other ghostwritten articles produced in like manner. In spite of the efforts of ICMJE to formulate policies to curb ghostwriting, many former and current ghostwriters have gone on record to reveal how they continue to ghostwrite comfortably within the policies. See especially, Matheson, A., "How Industry Uses the ICMJE Guidelines to Manipulate Authorship —And How They Should Be Revised," *PloS Medicine*, 2011, 8:e1001072; Logdberg, L., "Being a Ghost in the Machine: A Medical Ghostwriter's Personal View," *PloS Medicine*, 2011, 8:e1001071.

In the case of the study 352 manuscript, it appears that most of the GSK-designated authors did not have hands-on knowledge in the conduct of the study, nor did they have "key responsibility for the material in the article." In this regard, Dr. Nemeroff and Dr. Evans had very little, if any, direct input into the daily conduct of the 352 study, and certainly not enough to warrant being listed as the first and second authors on a manuscript published in one of the world's leading medical journals. Rather, their positions as authors on the manuscript were solely determined by GSK for the purpose of appending the names of "key opinion leaders" to the manuscript for marketing and commercial promotion of paroxetine.

Should there be any question about this strategy of using key opinion leaders as named 'authors' in publications for increasing market share for paroxetine or differentiating GSK's product from its competitors, numerous GSK business and publication plans for paroxetine in the late 1990s make it clear that this is precisely the intention of the marketing department. GSK's Case Study Publications for Peer Review (CASPPER) program is one such instance of how this worked for paroxetine. See e.g., Exh. 5 (De-classified Paxil document, PAR000570546).

B. Allegations Relating to Misrepresentation of Data and Bias

In his complaint, Dr. Amsterdam also alleged that the Respondents engaged in research misconduct by (a) misrepresenting post hoc analyses as a priori; (b) made unsubstantiated efficacy claims; (c) failed to adequately report adverse events and safety information; and (d) that the involvement of GSK and STI caused the published manuscript to be "biased in its conclusions."

I. Did the Manuscript Misrepresent Post Hoc Analyses as A Priori.

The Committee erroneously concluded that the published version of the manuscript accurately reflected the primary efficacy analysis as specified in the study protocol and thus was a priori.

In contrast to the Committee's conclusion, the analysis comparing the change from baseline in Hamilton Rating Scale for Depression (HAMD) scores in the high versus low lithium level subgroups did appear to be a post hoc analysis. In this regard, the amended protocol clearly defined the a priori primary and secondary analyses for the study, and a comparison of high versus low lithium level subgroups does not appear (see Exhibit 18 of the Committee Report):

- 1) The statistical methodology in section 4.3.3; has been revised to include analyses related to lithium stratification. Section 4.3.5 now specifies that "the comparison of primary interest is paroxetine versus placebo across (regardless of) lithium strata; this test will be performed at a two-tailed significance level of $\alpha = 0.05$ " (Exh. 18, p. 6, Amendment #1, ¶ 5);
- 2) Primary efficacy parameters Change from baseline in Hamilton Rating Scale for Depression (HAMD) total score (1st 17 items). Change from baseline in Clinical Global Impressions (CGI) severity of illness item" (Exh. 18, p. 11, Synopsis, ¶ 5);
- 3) Secondary efficacy parameters:
 - Proportion of patients responding (HAMD score < 7 at endpoint).
 - Proportion of patients with CGI global improvement score < 2 (Exh. 18, p.12.)
- 4) "The time point of primary interest for all efficacy assessments will be each patient's last observation. Of secondary interest will be data from earlier time points (weekly visits)" (Exh. 18, p. 12);
- 5) "Safety evaluations will consist of adverse event monitoring, laboratory evaluations, vital signs and the DSM-III-R Mania/ Hypomania Assessment to determine the following:
 - Proportion of patients experiencing adverse events.
 - Proportion of patients withdrawn due to adverse events.
 - Proportion of patients experiencing manic or hypomanic reactions.(Exh. 18, p. 12.)

Moreover, the primary analysis of paroxetine versus placebo was "negative" in the 352 study and there was no statistically significant group interaction effect observed between stratified high and low lithium level groups. Therefore, there was no a priori statistical need to examine this group interaction effect as either a primary or secondary study outcome measure. In addition, the purpose of the high/low lithium level stratification was methodological in nature and made as an a priori statistical correction. Thus, the purpose of the lithium level stratification was to assure that the three main treatment groups in the study (i.e., paroxetine, imipramine, and placebo) would be evenly balanced with subjects having high and low baseline lithium levels. Notably, even the Inquiry Committee questioned the reason for performing separate statistical analyses on subgroups of patients with high or low baseline serum lithium levels (despite the Committee's conclusion that it was an a priori, rather than post hoc, analysis).

Finally, STI documents (which the Inquiry Committee chose not to examine) contain evidence that contradict the conclusions of the Committee on these issues.

The Committee also concluded that the safety analyses in the publication accurately describe the analyses specified in the protocol and, thus, were a priori. Again, we respectfully disagree with the Committee's conclusion that "the reporting of the safety data was not a deviation from accepted practices in the reporting of research results." For example, at the time study 352 was designed and conducted, there was much concern and debate in the psychiatric community about the nature and rate of antidepressant-induced manic reactions. The publications listed below represent only a small sample of the many articles published on this subject and provide a glimpse of the extent of the controversy and concern over antidepressant-induced mania in patients with bipolar depression:

Peet M: Induction of mania with serotonin re-uptake inhibitors and tricyclic antidepressants. *Br J Psychiatry*, 164:549-550, 1994.

Sachs GS et al.: A double-blind trial of bupropion versus desipramine for bipolar depression. *J Clin Psychiatry* 55:391-393, 1994.

Altshuler LL, et al.: Antidepressant-induced mania and cycle acceleration: a controversy revisited. *Am J Psychiatry* 152:1130-1138, 1995.

Prien RF, Klett CJ & Caffey EM Jr: Lithium carbonate and imipramine in prevention of affective episodes: a comparison in recurrent affective illness. *Arch Gen Psychiatry* 29:420-425, 1973.

Walu. TA & Goodwin FK: Rapid cycling in manic-depressives induced by tricyclic antidepressants. *Arch Gen Psychiatry* 36:555-559, 1979.

Altshuler L, et al.: The impact of antidepressant discontinuation versus antidepressant continuation on 1-year risk for relapse of bipolar depression: A retrospective chart review. *T Clin Psychiatry* 62:612-616, 2001.

Grunze H, et al.: New perspectives in the acute treatment of bipolar depression. *World J Biol Psychiatry* 1:129-136, 2000.

Cohn JB, et al.: A comparison of fluoxetine, imipramine and placebo in patients with bipolar depressive disorder. *Int Clin Psychopharmacology* 4:313-322, 1989.

Kupfer DJ, et al.: Citalopram as adjunctive therapy in bipolar depression. *I Clin Psychiatry* 62:985-990, 2001.

Diler RS & Avci A: SSEI-induced mania in obsessive-compulsive disorder. *Am Acad Child Adolesc Psychiatry* 38(1): 6-7, 1999.

Christensen RB: Paroxetine-induced psychotic manias, *Am J Psychiatry* 152(8): 399-400, 1995.

In contrast, the study 352 published manuscript makes no mention of the fact that specific mania rating measures, like the DSM-III-R Mania/ Hypomania Assessment and Young Mania Rating Scale (YMRS), were obtained during the conduct of the study, nor does it present these critical data in the published manuscript. In this regard, Exhibit 18 of the Committee Report displays the study 352 protocol that was amended on November 23, 1993. The protocol mentions the inclusion of the YMRS and other mania symptom rating measurements:

The Young Mania Scale (YMS) will be used to assess severity of hypo-manic/manic symptoms. The relationship between changes from baseline for the YMS and HAMD total scores will be evaluated.

See Committee Report Exhibit 18 at page 25.

Also assessed as a safety endpoint will be the proportion of patients who develop manic or hypomanic reactions. Patients will be assessed using the Mania/ Hypomania Assessment derived from the DSM-III-R criteria (see appendix D). Mania or hypomania, if experienced during the course of the trial, will be recorded as an adverse event and these patients will be withdrawn from the study.. The Young Mania Scale will be administered to patients developing such symptoms.

See Committee Report Exhibit 18 at page 4.

4.4.3 Mania and Hypomania

Mania and hypomania defined by criteria listed in the DSM-III-R, will be analyzed using Logistic Regression methodology. Effects in the model will include treatment, investigator and treatment by investigator interaction; if the interaction is not

significant then it will be dropped from the model. These analyses will be performed using the LOGISTIC procedure of the SAS system.

See Committee Report Exhibit 18 at page 26.

On the other hand, Exhibit 9 of the Inquiry Committee Report displays draft one of the study 352 manuscript, which was prepared on March 1, 1997, for Muriel L. Young, M.D. at GSK by Grace Johnson and Sally Laden at STI. This draft mentions only DSM-III-R measures of mania and hypomania, but makes no mention of the YMRS measure.

Exhibit 10 of the Inquiry Committee Report displays draft two of the study 352 manuscript dated April 7, 1997, prepared for Muriel Young, M.D. at GSK by Grace Johnson and Sally Laden at STI. Similarly, this draft mentions only DSM-III-R measures of mania and hypomania, but makes no mention of the YMRS measure.

In contrast, Exhibit 11 of the Committee Report displays draft three of the study 352 manuscript dated September 24, 1997, prepared for Muriel Young, M.D. at GSK and now displaying GSK-designated authors (Laszlo Gyulai, M.D., Gary Sachs, M.D., Dwight Evans, M.D., Charles Nemeroff, M.D. PhD, Muriel L. Young, M.D., Cornelius D. Pitts, RPh, William D. Bushnell, MS, Ivan P Gergel, MD), does mention that the YMRS measure was completed at each study visit but presents no data analysis of this measure.

However, in Exhibit 13 of the Committee Report, draft three (actually draft four) dated June 24, 1998, makes no mention of the YMRS measure. This draft was prepared for Cornelius Pitts, R.Ph. at GSK by Grace Johnson and Sally Laden at STI, and was assigned the following GSK-designated authors: Charles B. Nemeroff, MD, PhD, Dwight L. Evans, MD, Gary Sachs, MD, Laszlo Gyulai, MD, Charles L. Bowden, MD, Muriel L. Young, MD, Cornelius D. Pitts, RPh, William D. Bushnell, MS, Ivan P. Gergel, MD.

Finally, in the 2001 published article (see ORI Complaint Attachment A) "authored" by Charles B. Nemeroff, MD, PhD, Dwight L. Evans, MD, Laszlo Gyulai, MD, Gary S. Sachs, MD, Charles L. Bowden, MD, Ivan P. Gergel, MD, MBA, Rosemary Oakes, MS, Cornelius D. Pitts, RPh, no mention is made of the YMRS measure having been obtained during the study. Rather, the published article merely provides a numerical listing of clinician-identified manic episodes.

A similar pattern of under-reporting important safety data is also apparent with respect to the DSM-III-R Mania/ Hypomania Assessment rating scale. Although this measure is mentioned in drafts one, two, three, and four of the manuscript (see Exhibits noted above), no mention of this safety measure being obtained in the study was included in the published article (see ORI Complaint Attachment A). Thus, the ratings of drug-induced manic symptoms were not reported in the published manuscript.

In sum, contrary to the Committee's conclusion, the discrepancy in the reporting of protocol safety data throughout the manuscript draft preparation and final published article clearly represents a deviation from accepted practices in the reporting of research results.

The Committee correctly determined that the published manuscript did not accurately reflect the a priori sample size estimates as described in the protocol. Specifically, the Committee found:

that this discrepancy in reporting of the sample size represents a deviation from accepted scientific practice in reporting research methods. In particular, the statement that "[t]he study was designed to enroll 35 patients per arm" is not an accurate representation of the a priori study design as described in the protocol.

See Committee Report at 14. Notwithstanding this finding, the Committee went on to conclude that this deviation was not a serious deviation and further concluded that "the reporting of the statistical power in the manuscript (estimated at 70%) provides the reader with a clear indication that the statistical power of the study did not achieve conventional levels." It is surprisingly forgiving of the Inquiry Committee to state that the reporting of the statistical power in the manuscript provides the reader with a clear indication that the statistical power of the study did not achieve conventional levels.

It is also surprising the Committee did not express more concern over the reasons for the gradual, unexplained reduction in stated power estimates from those originally described in the study protocol, and that this gradual reduction in power estimate between manuscript drafts and the published article may have hidden the fact that the 352 study was a failed (i.e., non-informative) trial as a result of under-recruiting its original sample size goal.

The inability to achieve the needed statistical power for the study was, in fact, the primary reason for GSK adding the additional Penn investigative site (i.e., Dr. Amsterdam's research clinic) to the study. It appears likely that the gradual reduction in stated sample size power estimates between manuscript drafts was an attempt on the part of GSK to artfully hide the fact that the 352 study was actually a failed (i.e., non-informative) trial.

The power estimate statement in the published article is disingenuous at best, and deceptive to the average reader of the American Journal of Psychiatry (who is not necessarily statistically sophisticated). In this regard, the published article failed to inform journal readers of the original or "true" power estimate necessary for demonstrating a statistically significant difference in the primary outcome measure (i.e., paroxetine versus placebo) of the study. Not only was the single primary outcome measure of paroxetine versus placebo underpowered in the 352 study, it follows that all of the other primary, secondary, and additional post hoc analyses were also under-powered. Thus, any statistically significant findings presented in the published article should have been taken with a grain of salt, and were most likely statistical artifact rather than clinically meaningful findings. It is troubling that this important fact seems to have been overlooked by the Inquiry Committee. It is even more troubling that no mention of this fact is made in the published

manuscript (which clearly emphasized the positive findings of paroxetine as statistically significant and clinically meaningful).

Moreover, the change in stated sample size estimates occurred prior to publication, over several drafts of the manuscript. This downward manipulation of power estimates appears to have been contrived, with the final change in power estimate likely occurring after the study was completed. If so, this change would likely represent a substantial departure from Good Clinical Practice Guidelines policies for the conduct of clinical trials in humans. The authors of the manuscript (which included the GSK statistician) should have been aware of this important deviation from normal scientific method and reporting of results.

In this regard, the study protocol states (see Exhibit 18 of Inquiry Committee Report):

4.2.2 Sample Size

The number of patients required for the comparison of interest using the HAMD total score is based on the following assumptions: Significance level (2 tailed), $\alpha = 0.05$; Power (1 - Beta) = 0.9; Detectable difference between paroxetine and placebo at 5 HAMD points; Standard deviation, based on previous studies of 8.5; This results in an estimate of 62 patients per treatment group.

In contrast, manuscript draft one (see Exhibit 9 of Inquiry Committee Report) contains no mention of a power analysis, but does contain the following statement in the discussion portion of the manuscript:

The small sample size was another limitation of our study. However, our analysis suggests that the power of the study was adequate to determine statistical differences between groups. If at least 35 patients were recruited per treatment group, there would be a 70% chance of detecting a 5-point difference on the HAMD score (SD=8.5) between treatment groups.

Similarly, manuscript draft two (see Exhibit 10 of Inquiry Committee Report) contains no mention of a power analysis, but does contain the same disclaimer noted above in draft one.

However, manuscript draft three dated September 24, 1997 (see Exhibit 11 of the Inquiry Committee Report) contains a power estimate:

The study was designed to enroll 46 patients per arm, which would allow 80% power to detect a 5-point difference on the HAMD score (SD=8.5) between treatment groups.

This draft also contains the following limitation / disclaimer statement in the discussion section of the paper:

Because the study under enrolled by 20 patients, small sample size was another limitation of our study. However, our analysis suggests that the power of the study was

adequate to determine statistical differences between groups. If at least 35 patients were recruited per treatment group, there would be a 70% chance of detecting a 5-point difference on the HAMD score ($SD=8.5$) between treatment groups.

Manuscript draft four (marked draft III) dated June 24, 1998 (see Exhibit 13 of Inquiry Committee Report) also contains a power estimate:

The study was designed to enroll 46 patients per arm, which would allow 80% power to detect a 5-point difference on the HAMD score ($SD=8.5$) between treatment groups.

This draft also contains the following limitation / disclaimer statement in the discussion section of the paper:

Because only a small number of patients experienced manic and hypomanic episodes, these episodes were not analyzed.

Finally, the published article (see ORI Complaint Attachment A) has been purged completely of all reference to the original, or subsequent, sample size estimates. It now provides only a disingenuous power statement that happens to comport with the number of subjects enrolled in the paroxetine group (i.e., $n=35$) and hides the fact that the 352 study was a failed trial that recruited an insufficient number of study subjects:

The study was designed to enroll 35 patients per arm, which would allow 70% power to detect a 5-point difference on the Hamilton depression scale score ($SD=8.5$) between treatment groups.

As a result, no information about the original, true power estimate, the original sample size requirements, or the inability to recruit a sufficient subject sample is ever provided to the reader of the published article.

The Committee further downplays the relevance of the sample size sleight-of-hand by stating that "It is noteworthy that the AJP statistical reviewer did not raise concerns about the sample size." See Committee Report at 14. The Committee's conclusion is directly contradicted by the STI documents which the committee intentionally chose not to inspect.

Moreover, it appears that, while Dr. Jack Gorman was serving as Editor of the American Journal of Psychiatry and closely involved in the editorial review process of the 352 study manuscript, he was also receiving substantial financial compensation from GSK for the purpose of promoting Paxil for a variety of FDA approved and unapproved indications. For example, while serving as Editor of the American Journal of Psychiatry, Dr. Gorman was also on GSK's speaker's bureau and served as a consultant to GSK in the promotion of Paxil (including participation in

GSK-funded symposia, advertising videos, GSK-funded lectures, co-authoring GSK-funded articles in medical journals and book chapters).⁷

The Committee also whitewashed the data manipulation by contending that any flaws with the reporting of sample size was the sole responsibility of Rosemary Oakes, a GSK bio-statistician involved in the 352 study and a named author on the published article. In this regard, however, we would remind the Committee that the GSK bio-statistician (and all of the named authors) are responsible for manipulating the sample size estimates for the published manuscript. In addition, Ms Oakes is also named as a Respondent in the ORI Complaint.

Although the Committee concludes that Ms. Oakes' statistical and sample size analyses are solely her own responsibility and not a deviation from accepted practices in the reporting of research results, the evidence noted above would suggest otherwise. We would contend that Ms. Oakes was not solely responsible for the manipulation of the study power estimates, rather, it was the responsibility of every author on the manuscript to be aware of, and responsible for, the manipulation of sample size estimates. We would also suspect that Ms. Oakes, who was not questioned by the Inquiry Committee, might have a different opinion from that expressed by the Committee.

Moreover, based upon the evidence provided above, that Ms. Oakes (and all of the named authors) misrepresented sample size calculations in order to hide the fact that the 352 study was a failed (i.e., non-informative) trial with insufficient statistical power to test adequately the primary or secondary study outcomes that were reported in the published article. For the Inquiry Committee to conclude that Ms. Oakes is solely responsible for changing the sample size calculations in order to make them comport with the sample size that was enrolled in the study, is to ignore the responsibility of the other authors (in particular, the academic authors) who should have been aware of this issue - had they actually been involved in the data analysis and manuscript preparation.

However, the evidence appears to indicate that the academic authors were almost completely uninvolved in the data analysis and manuscript preparation, and were merely serving as key opinion leaders on the manuscript for commercial and marketing purposes.

Even the Committee would agree that, not just Ms. Oakes, but all of the authors should be responsible for the misrepresentations made in the manuscript.

⁷ Specifically, it appears that Dr. Gorman had his name appended to at least one ghostwritten article (written by Sally Laden from STI). This article, entitled National Depressive and Manic-Depressive Association Consensus Statement on the Use of Placebo in Clinical Trials of Mood Disorders, was published in the Archives of General Psychiatry 2002;59:262-270, and was 'co-authored' by Charles B. Nemeroff, Dwight L. Evans, Charles Bowden, Gary Sachs, and Sally K. Laden of STI (among other) (see <http://archpsyc.ama-assn.org/cgi/content/abstract/59/3/262>).

II. Did the manuscript make unsubstantiated efficacy claims?

We disagree with the Committee's conclusion that "the publication [made] clear statement of negative findings..." In our opinion, the published article did not make a clear and honest statement about the statistical power aspects of the study and the negative findings of the primary and secondary outcome measures. Rather, the published article misrepresented the sample size issue and minimized the negative findings of the primary and secondary outcome measure of efficacy. The published article emphasized the positive finding of a tertiary post hoc analysis (that may well have been a statistical artifact) that had clear-cut commercial bias favoring paroxetine. The published manuscript hid the original and amended sample size estimates that showed the study was a failed trial and under-reported the safety outcome measures.

While the published article's conclusion does note that paroxetine (and imipramine) may be beneficial in patients with bipolar depression who have low serum lithium levels, neither the abstract nor the published article itself clearly indicates that the study had insufficient power to test this hypothesis or to make this claim. The published article also does not inform the reader that the positive "finding" was the result of a post hoc exploratory analysis. Indeed, the STI documents that the Committee chose to ignore, would provide a more accurate picture of the true state of affairs.

Finally, the peer reviewers of the manuscript submitted to the American Journal of Psychiatry were not provided with sub rosa information indicating that the manuscript was not drafted or revised by the named authors (see Exhibits above), nor were the peer reviewers informed that the named authors of the manuscript were designated as such by GSK and not based on the degree of their involvement in the study. The peer reviewers were also not informed that the manuscript was almost completely revised by STI and GSK (with little, if any, author input).

III. Did the Manuscript Inadequately Report Adverse Effects or Safety Concerns?

The Committee concluded that the published article's failure to include the YMRS safety data did not represent a deviation in the reporting of research data. However, the study protocol clearly states that formal YMRS scale and DSM-III-R Mania/Hypomania Assessment were obtained at each study visit and analyzed using logistic regression models (see Exhibit 18 of the Committee Report). As noted above, mention of formal mania safety measures varied between manuscript drafts and ultimately did not appear in either the GSK website Clinical Trial Summary report⁸ or in the published article (see ORI Complaint Attachment A).

Exhibit 18 of the Committee Report contains the Protocol of Study 352 that was amended on November 23, 1993. The protocol mentions the inclusion of the YMR measurement:

⁸ http://www.gsk-clinicalstudyregister.com/result_comp_list.jsp?compound=Paroxetine) and http://www.gsk-clinicalstudyregister.com/result_detail.jsp;jsessionid=2051B69F607DD9B3E9CD39AD914F7316?protocol=29060%2F352&studyid=F1D83A94-2628-4C9C-83A5-11D00A2D30AC&compound=Paroxetine

The Young Mania Scale (YMS) will be used to assess severity of hypomanic/manic symptoms. The relationship between changes from baseline for the YMS and HAMD total scores will be evaluated"

See Committee Report Exhibit 18 at page 25.

Also assessed as a safety endpoint will be the proportion of patients who develop manic or hypomanic reactions. Patients will be assessed using the Mania/ Hypomania Assessment derived from the DSM-III-R criteria (see appendix D). Mania or hypomania, if experienced during the course of the trial, will be recorded as an adverse event and these patients will be withdrawn from the study. The Young Mania Scale will be administered to patients developing such symptoms.

See Committee Report Exhibit 18 at page 4.

4.4.3 Mania and Hypomania

Mania and hypomania defined by criteria listed in the DSM-III-R, will be analyzed using Logistic Regression methodology. Effects in the model will include treatment, investigator and treatment by investigator interaction; if the interaction is not significant then it will be dropped from the model. These analyses will be performed using the LOGISTIC procedure of the SAS system.

See Committee Report Exhibit 18 at page 26.

On the other hand, Exhibit 9 of the Committee Report contains draft one of the manuscript, which mentions only DSM-III-R Mania/Hypomania measure, but makes no mention of the YMRS measure.

Exhibit 10 of the Inquiry Committee Report contains draft two of the manuscript dated 04/07/1997, which mentions only DSM-III-R Mania/Hypomania measure of mania and hypomania, but makes no mention of the YMRS measure.

Exhibit 11 of the Committee Report contains draft three of the manuscript dated 09/24/1997, which mentions that the YMRS measure was completed at each study visit.

However, in Exhibit 13 of the Committee Report, draft three (actually draft four) dated June 24, 1998, the YMRS measure again disappears. Finally, in the 2001 published article (see ORI Complaint Attachment A), no mention is made of the YMRS measure. The manuscript states only: "Because only a small number of patients experienced manic and hypomanic episodes, these episodes were not analyzed."

C. In Addition to Failing to Obtain the Relevant STI Documents, the Committee Also Failed to Question the Other Respondents Named In Dr. Amsterdam's Complaint.

In addition to choosing not to examine the STI documents, the Inquiry Committee also chose not to obtain the testimony of the other Respondents named in the ORI Complaint.⁹ We believe this additional information would have provided the Committee with a broader and more comprehensive understanding of the true nature of Dr. Amsterdam's allegations of research misconduct. By choosing not to obtain the testimony of the other respondents named in the case, we believe the Inquiry Committee lost the opportunity of obtaining important information that may have corroborated (or called into question) the testimony provided to the Committee by Dr. Evans and Dr. Gyulai.

D. Conclusion

The Committee's failure to examine critical evidence, and its finding that further investigation is not necessary, has left a false impression that nothing improper occurred with respect to the publication of Study 352. That simply is not the case. The public's false perception has only been compounded by statements made in the press by the University of Pennsylvania and the Respondents that are simply not true. For instance, the University's spokesperson, Susan Phillips, wrote in an email to a reporter that "the review clearly concluded that this was not a case of ghostwriting or plagiarism." Contrary to Ms. Phillips' statement, the Inquiry Committee did not find that this was not a case of ghostwriting. With respect to the charge of plagiarism, the publication of study 352 escaped only because, according to the Committee's contorted interpretation, standards back in 2001 were not what they are today.

Likewise, in a written statement, Dr. Evans wrote: "After a thorough review, the inquiry concluded that each and every allegation lacked substance and credibility." Charles Nemeroff (first author on the published manuscript) on the other hand reportedly told Nature Magazine that, while he was aware of STI's involvement in the preparation of the manuscript, "All [STI] did was help collate all the different authors' comments and help with references. **We wrote the paper.**"¹⁰ Dr. Nemeroff's statement is demonstrably false as illustrated by the Committee report itself, yet the public statement lives on in perpetuity.¹¹ Respondent Dr. Gary S. Sachs (fourth author on the manuscript) reportedly told the Boston Globe that he was "perplexed" by the allegations of ghostwriting and wrote in an email: "These allegations are simply inconsistent with my experience

⁹ These other respondents included: Drs. Charles Nemeroff, Gary S. Sachs and Charles Bowden, all of whom are listed as guest authors on the Study 352 published manuscript.

¹⁰ <http://www.nature.com/news/2011/110712/full/475153a.html>. See Exh. 6.

¹¹ Nemeroff's misrepresentations have been repeated in other publications as well, e.g., in Science Insider. <http://news.sciencemag.org/scienceinsider/2011/07/penn-psychiatist-accuses-five.html?ref=hp>. See Exh. 7.

and the finding of the study. When the data became available, I went to Philadelphia to help Dr. Gyulai draft the manuscript. **We started with a blank page.**"¹² Sachs similarly told Science Insider that he was "kind of mystified" by the allegations and that he did not know that STI was involved with the manuscript. Again, Dr. Sachs' statement does not comport with either the evidence provided to the Inquiry Committee (see Committee Report Exhibit 9 and Exhibit 10) or with the statements provided to the Committee by Dr. Evans and Dr. Gyulai (see Committee Report at 7-8). See also comments reportedly made to Nature by Dr. Charles L. Bowden (fifth author on the published manuscript) stating: "I never had any sense that the manuscript was ighostwritten."¹³ The conclusion drawn from these statements is that the inquiry found the "authors" of study 352 "innocent" of all allegations.¹⁴

In contrast, the University of Pennsylvania's conclusions have been criticized by numerous outside academics. For instance, as recently as May 31, 2012, an article published in the journal Society by Jonathan Leo and Jeffrey Lacasse talks specifically about the University's decision in "Medical Ghostwriting: A University-Sanctioned Sleight of Hand?" The authors state that, "instead of indicating a vigilant response to ghostwriting, [the University of Pennsylvania] (perhaps inadvertently) sanctions ghostwriting." They point out that the primary conclusions of the University "did not result from scrutinizing the paper for a ghostwriter, but were instead explanations for why the listed authors deserved to be on the byline of the paper."¹⁵

Georgetown University professor of pharmacology, Dr. Adriane Fugh-Berman complained that the University's conclusion "was wrong" and called the University's refusal to conduct further investigation a "cop-out." Eric Campbell, professor of medicine at Harvard stated that the committee's conclusion "seems very disingenuous" and that the University's failure to reprimand Evans and Gyulai sends a message that "if you're very senior member of a faculty, the rules don't apply to you."¹⁶ The University's findings have been called "the George Costanza Excuse for Medical Ghostwriting"¹⁷ and has been characterized in such ways as "UPenn looks the other way,"¹⁸ and the University of Pennsylvania "just blew it off."¹⁹

¹² <http://www.boston.com/Boston/whitecoatnotes/2011/07/psychiatrist-files-ghostwriting-complaint-against-harvard-doctor-and-four-others/6aFZbOoy4uH2Mf9CF6cCKL/index.html>. See Exh. 8.

¹³ <http://www.nature.com/news/2011/110712/full/475153a.html>. See Exh. 6.

¹⁴ Leo and Lacasse, "Medical Ghostwriting: A University-Sanctioned Sleight of Hand? Soc, May 31, 2012. See Exh. 9.

¹⁵ Leo and Lacasse, Exh. 9.

¹⁶ Kumar, "Critics Respond to dismissal of ghostwriting accusations," The Daily Pennsylvanian, March 11, 2012. See Exh. 10.

¹⁷ <http://www.madinamerica.com/2012/03/the-george-constanza-excuse-for-medical-ghostwriting/> See Exh. 11.

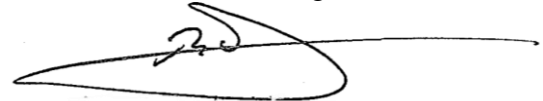
¹⁸ <http://www.pharmalot.com/2012/03/upenn-looks-the-other-way-at-ghostwriting/>. See Exh. 12.

¹⁹ <http://pogoblog.typepad.com/pogo/2011/07/amy-gutmann-do-the-right-thing-by-president-obama-be-a-leaderand-resign.html>. See Exh. 13.

The issues raised in Dr. Amsterdam's complaint of industry-influenced research, corruption of science and the medical literature and respected academics lending their names to ghostwritten work with little or no access to the data are issues of vital public health importance. As Leo and Lacasse explain, "The medical community is currently trying to come to grips with the idea that much of the clinical trial literature has not been written by named authors, and, instead, has been written by medical writers employed by pharmaceutical companies who are not listed on the author byline. The success of virtually all of the blockbuster drugs has been tainted by charges of ghostwriting."²⁰ This is not a time to whitewash an investigation involving important issues of public health and scientific ethics.

We respectfully urge the ORI to undertake a more thorough and complete investigation of the allegations of research misconduct that considers all available evidence.

With kindest regards,

A handwritten signature in black ink, appearing to read 'Bijan Esfandiari', written over a horizontal line.

Bijan Esfandiari, Esq.

BE:gb

Enclosures

cc: Dr. Jay Amsterdam w/ enclosures

Sean V. Burke, Esq., Associate General Counsel, Univ. of Pennsylvania w/ enclosures Senator

Charles Grassley w/ enclosures

Senator Herb Kohl

Chairman, House Energy and Commerce, Fred Upton

Ranking Member, House Energy and Commerce, Henry Waxman

Chairman, House Committee on Oversight and Govt. Reform, Darrell E. Issa

Ranking Member, House Committee on Oversight and Govt. Reform, Elijah Cummings Dr.

Donna Shalala, President, Univ. of Miami

Dr. Thomas J. LeBlanc, Office of the Provost, Univ. of Miami

Dr. Pascal J. Oldschmidt, Sr. V.P. for Medical Affairs & Dean of Miller School of Medicine

Dr. Drew Faust, Office of the President, Harvard University

Jeffrey S. Flier, M.D., Dean, Harvard Medical School

Dr. Ricardo Romo, President, Univ. of Texas San Antonio

William L. Henrich, M.D., President, Univ. of Texas Health Science Center at San Antonio

²⁰ <http://www.phannalot.com/2012/06/ghost-sts-in-the-pharma-attic-jonJeff-explain/>. Exh. 14.