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Jay D. Amsterdam: The Paroxetine 352 Bipolar Study Ethical Conduct

Letter to the Office of Research Integrity – Lawyer's letter

Your letter to the Office of Research Integrity

There have been several letters from my attorney to the ORI that include (a) my original July 8, 2011, research misconduct complaint (containing all of the Penn email and other related documents). I already sent this to you as attachment #1. Although not sent to you, I would be happy to provide the actual attachment evidence documents contained in the July 8, 2011 complaint.

The letter to the Office of Research Integrity was written and sent by my lawyer It includes my Timeline for publication of Paxil Bipolar Study 352 without my knowledge.

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July 8, 2011

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Office of Research Integrity
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Re: Complaint of Scientific Misconduct against Dwight 1. Evans, Laszlo Gyulai; Charles Nemeroff, Gary S. Sachs and Charles 1. Bowden

Dear Dr. Wright:

On behalf of Dr. Jay D. Amsterdam, Professor of Psychiatry at the University of Pennsylvania, a charge of research misconduct is hereby submitted 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.

Dr. Amsterdam believes the individuals named above engaged in scientific misconduct by allowing their names to be appended to a manuscript that was drafted by a "medical communications company" (Scientific Therapeutics Information, "STI") hired by SmithKline Beecham (now known as GlaxoSmithKline, "GSK"), and which Dr. Amsterdam contends misrepresented information from a scientific research study (Paroxetine Study 352), which was funded by GSK and NIH. The manuscript (hereinafter "Study 352") was eventually published in the American Journal of Psychiatry (158:906-912; June 2001) suggesting that Paxil may be beneficial in the treatment of bipolar depression, without acknowledging the medical communication company's contribution or the extent of GSK's involvement. The published manuscript was biased in its conclusions, made unsubstantiated efficacy claims and downplayed the adverse event profile of Paxil. (Attachment A.) Since its publication, study 352 has been cited in hundreds of medical journal articles, textbooks and practice guidelines up to 2011. (See, e.g., Attachment B and C.) Although Dr. Amsterdam was a Co-Principal Investigator of the study and possibly enrolled the largest number of patients, he was excluded from the final data review, analysis and publication. (See Attachment D.)

Dr. Amsterdam only recently became aware that two of the lead authors of Study 352, including his direct supervisor, were linked to ghostwriting through a letter from the Project On Government Oversight (POGO) to NIH Director Francis Collins in November 2010, posted on POGO's website at http://www.pogo.org/pogofileslletters/ public-health/ph-iis-20101129.html. Like the examples contained in POGO's letter to NIH, Dr. Amsterdam believes the manuscript published in the American Journal of Psychiatry was ghostwritten by STI, which was hired by GSK and paid with GSK funds, and that the individuals above lent their names as "authors" to the manuscript.

Based upon evidence presented in this complaint and the documents attached hereto, it appears that most, if not all, of the" guest authors" were determined by GSK in conjunction with the "medical communications" firm, STI. STI has had a longstanding history of ghostwriting scientific and medical articles and textbooks which have been attributed to prominently known academics - a practice that has been the subject of mounting criticism. See, for example, an editorial in the Journal of the American Medical Association regarding ghostwriting in relation to Merck's promotion and sales of VIOXX. (Attachment E.)

The acknowledgement section of the published manuscript states that Study 352 was conducted and published with support from NIMH grant MH-51761. (Attachment A.) According to a recent search of the NIH Reporter database, NIMH grant MH-51761 was part of an "infrastructure support" and "core-patient recruitment and assessment" project for NIH-funded clinical research trials. (Attachment F.) In this case, it was used to support the recruitment and assessment of research subjects for participation in this GSK-sponsored and GSK-funded clinical trial of Paxil for the treatment of patients with bipolar type I major depression.

According to a letter written by Dr. Francis Collins, Director of the NIH, ghostwriting that involves a federal grant may be cause for an investigation of plagiarism. Dr. Collins stated in his letter, which was published on POGO's website:

> [A] case of ghostwriting involving NIH-funded researchers may be appropriate for consideration as a case of plagiarism; i.e., the appropriation of another person's ideas, processes, results, or words without giving appropriate credit; or fabrication, i.e., making up data or results and recording or reporting them. Such a case would be handled by the Office of Research Integrity (ORI) of the Department of Health and Human Services (HHS), which investigates research misconduct as defined in the PHS's 42 c.F.R. Parts 50 and 93, Policies on Research Misconduct and the Final Rule.
>
> (Attachment G.)

Moreover, according to a report on ghostwriting by Senator Charles Grassley (dated June 24, 2010), the University of Pennsylvania considers ghostwriting to be equivalent to plagiarism.[1]

While this incident took place some time ago (i.e., 2001), the manuscript has been cited hundreds of times up through 2011 according to an internet search on Google Scholar. (Attachment B.) In fact, Dr. Gyulai cited the paper again in a study he published in 2007 in the New England Journal of Medicine (Attachment H) and Dr. Sachs cited the paper in 2011 in the Journal of Clinical Psychiatry. (See Attachment C, Record 1.)

Moreover, the purported "findings" of Study 352 and the published results from other studies and articles that have cited this study have been used to support the design and implementation of at least two other NIMH-funded grants to study the efficacy and safety of antidepressant drugs (like Paxil) in bipolar depression. See, e.g., MH080097, Prevention of Relapse and Recurrence of Bipolar Depression and MH060353, Treatment of Bipolar Type II Major Depression.

Dr. Amsterdam submits this complaint in the hopes that ORI will conduct an investigation, impose appropriate penalties to correct the past publication of Study 352' s results, to prevent similar conduct from happening again, and hopefully prevent further use of this paper to support the dangerous prescription of Paxil to patients diagnosed with bipolar depression.

Pursuant to 42 C.F.R. Part 50.103(d)(13), Dr. Amsterdam should receive full and complete protection from retaliation and/ or defamation by either the University of Pennsylvania or any other parties involved in the production and publication of Study 352. Dr. Amsterdam requests the protections described in ORI's "Handling Misconduct - Whistleblowers." (Attachment I.)

To ensure that this complaint is taken seriously, and to alert interested parties, we are providing copies of this correspondence to Senator Charles Grassley, Senator Herb Kohl, and the Chairman and Ranking members of the House Energy and Commerce, and the House Committee on Oversight and Government Reform.

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[1] See: http://grassley.senate.gov / aboutjupload/Senator-Grassley-Report.pdf

In the following pages, we will layout Dr. Amsterdam's complaint in more detail.

Thank you for your time and interest in this important matter. Please apprise me of any further help I may offer to you.

Sincerely,

Bijan Esfandiari, Esq.

BE:gb

cc:

Dr. Jay Amsterdam
Senator Charles Grassley
Senator Herb Kohl
Sincerely, c::239
Bijan Esfandiari, Esq.
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. AMSTERDAM'S TIMELINE RE PUBLICATION OF PAXIL BIPOLAR STUDY 352 WITHOUT HIS KNOWLEDGE

In the mid-1990's, Dr. Amsterdam became a Co-Principal Investigator on a clinical trial, Paroxetine Study 352, comparing the antidepressant drugs imipramine (Tofranil®) and paroxetine (Paxil®) for the treatment of bipolar type I major depression (or manic depression). The trial was sponsored, in part, by GlaxoSmithKline which sells paroxetine under the brand names Paxil® in the US and Seroxat in other countries.

Dr. Amsterdam recruited one of the largest, if not the largest, patient samples into a study that comprised 18 other investigative-sites.

In early 2001, Dr. Amsterdam became aware that Dr. Dwight Evans and Dr. Laszlo Gyulai were attempting to publish data from the above referenced study. Although Dr. Amsterdam was a Co-Principal Investigator of Study 352 and enrolled one of the largest numbers of patients, he was excluded from the final data review, analysis and publication. (Attachment J, K, L and D.)

Dr. Amsterdam contacted his immediate supervisor and department chairman, Dr. Dwight L. Evans about the matter. In a March 22,2001 email to Dr. Amsterdam, Dr. Evans stated that he had discussed the issue with Dr. Karl Rickels who was also a professor in the Department of Psychiatry

at the University of Pennsylvania and Dr. Gyulai's direct supervisor. Dr. Evans assured Dr. Amsterdam that Dr. Rickels would be reviewing the matter and, once accomplished, he trusted there would be "an equitable outcome." (Attachment M.)

Dr. Amsterdam sent a follow-up email to Dr. Rickels on April 1, 2001 asking him what he had found during his investigation. Dr. Amsterdam explained to Dr. Rickels that, if he (Dr. Rickels) felt uncomfortable dealing with the matter, that he should let Dr. Amsterdam know so that he (Dr. Amsterdam) could "take up the issue with others at the University and/or the American Journal of Psychiatry." (Attachment J.) The American Journal of Psychiatry accepted the manuscript for publication in January 2001 (Attachment A at p. 911) and the study was eventually published in the June 2001 edition of the journal. Id.

On April 3, 2001, Dr. Rickels sent Dr. Amsterdam a letter discussing what he had learned during his investigation. (Attachment K.) In that letter, Dr. Rickels noted, among other things, the following information:

(1) Dr. Amsterdam was co-investigator of the trial;
(2) Dr. Amsterdam had enrolled more patients in the trial than Dr. Gyulai;
(3) The ghostwriting firm, STI, had chosen Dr. Gyulai as the paper's first author;
(4) GSK had decided to replace Dr. Gyulai as first author with Dr. Charles Nemeroff; and
(5) Academic investigators in the trial never reviewed or even saw the submitted manuscript.

On May 1, 2001, Dr. Amsterdam sent Drs. Evans and Rickels another email to explain that he was unsatisfied with the response and, since the last letter, there has been only "radio silence." As he wrote, "Am I to assume that it is okay in this department for a junior faculty member to abscond with data from a full professor and publish it without any ramifications?" (Attachment N.)

The following day, Dr. Rickels emailed Dr. Amsterdam and explained that Dr. Evans had tasked him (Dr. Rickels) with trying "to bring about a resolution." (Attachment O.)

On May 11, 2001, Dr. Amsterdam emailed Dr. Rickels and explained that he considered data that he (Dr. Amsterdam) accumulated in his research unit from the study "were misappropriated from me and used and published without my knowledge and without regard to the significant contribution that I made to this study." Dr. Amsterdam complained that the "theft and publication of [his] data should not go unnoticed and uncensured." He proposed that Dr. Gyulai write a letter of apology and be censured in order to ensure "this situation does not happen again." (Attachment P.)

Ten days later, Dr. Rickels emailed Dr. Amsterdam stating that he had shared Dr. Amsterdam's comments with Dr. Evans and, once he received a reply from Dr. Evans, he (Dr. Rickels) would like to meet with Dr. Amsterdam to discuss the topic. (Attachment Q.)

On Jun 13,2001, Dr. Amsterdam again emailed Dr. Rickels to complain that there had been no resolution of the matter. Dr. Amsterdam wrote: "Before I contact either University officials or the editorial board of [the American Journal of Psychiatry] regarding this egregious behavior, I await your last efforts at resolution of this problem./I (Attachment R)

That same day, Dr. Rickels responded that Dr. Gyulai had been ill and that Dr. Amsterdam would be contacted soon. (Attachment S.)

On June 29, 2001, Dr. Amsterdam received a formal letter from Dr. Rickels stating that Dr. Gyulai had returned part-time from sick leave and he intended to speak with Dr. Gyulai concerning "this unfortunate situation ... today." (Attachment T.)

On July 5, 2001, Dr. Gyulai sent a letter of apology to Dr. Amsterdam. In that letter, Dr. Gyulai explained that control of the paper had been taken away from him and that GSK published the paper without circulating the draft to all the participants and only allowed him (Dr. Gyulai) to see a near-final draft "when only minor changes could be done." (Attachment L.)

Four days later, Dr. Amsterdam sent an email to Dr. Rickels stating that the apology was not sufficient in light of the "deliberate misappropriation and publication of [his] data" without his knowledge. Dr. Amsterdam was insistent that some sort of reprimand was necessary to ensure "plagiarism" of a colleague's data never happens again. (Attachment U.)

The following day, July 20, 2001, Dr. Rickels sent Dr. Amsterdam a letter stating "it is unfortunate that [GSK] did not circulate the manuscript to you and I regret that Dr. Gyulai did not share it with you. Once again, as Dr. Gyulai's Program Director, I have expressed my belief that he should have done so." (Attachment V.)

TIMELINESS OF COMPLAINT

According to Office of Research Integrity (ORI) guidelines, rules governing research misconduct only apply if such conduct occurred within six years, unless "the respondent continues or renews any incident of alleged research misconduct that occurred outside the six-year limit through the citation, republication or other use for the potential benefit of the research record that is the subject of the allegation."

With respect to this condition, although the data were published in an NIH-supported study in 2001, Dr. Gyulai cited this study just four years ago, in a study published in 2007 in the New England Journal of Medicine. (Attachment H, at page 3.) This is well within the six-year window for filing a complaint of research misconduct. Moreover, the report that appeared under Dr. Evans', Dr. Gyulai's and the other authors' names has had an ongoing influence on the scientific field as evidenced by its citation in hundreds of medical journal articles, textbooks and practice guidelines, up through and
including 2011. (See Attachment B and C.)

EVIDENCE OF POTENTIAL GHOSTWRITING / ALLEGED PLAGIARISM

In defense of Dr. Gyulai, Dr. Rickels sent Dr. Amsterdam a letter on April 3, 2001, explaining that the "medical communications" firm, STI, had chosen Dr. Gyulai as the paper's first author. (Attachment K.)

At the time, Dr. Amsterdam was not aware of STI's involvement in ghostwriting scientific studies on behalf of prominent academics (including Dr. Evans and the other individuals named in this complaint) to promote sales of pharmaceutical agents. However, such behavior is now well understood. For instance, the Journal of the American Medical Association published an editorial in April 2008, excoriating Merck & Co. Inc. for using STI to publish a ghostwritten article in 2002 in JAMA to push sales of VIOXX. (Attachment E.) According to this editorial:

> Perhaps some editors, investigators, reviewers, and readers would see little or no harm in this failed disclosure because all other disclosures were made. However, if there was nothing to hide, why were the names (and affiliations) of the individuals who actually wrote at least the first draft of the manuscript omitted?

Indeed, although the spectral fingerprints of STI are readily apparent, STI's involvement was not disclosed in the manuscript draft or the final published article that appeared in the American Journal of Psychiatry. (Attachment A and D.)

As it turned out, Dr. Amsterdam discovered that his own supervisor, Dr. Dwight L. Evans, to whom Dr. Amsterdam had been complaining, published a scientific editorial in the prestigious journal Biological Psychiatry in 2003 that was ghostwritten by the very same "medical communications" firm that ghostwrote the 2001 American Journal of Psychiatry article (i.e., STI). Dr. Amsterdam discovered this while reviewing a letter that the Project On Government Oversight sent to NIH Director Frances Collins in November of 2010.[2]

According to documents, Sally Laden of STI ghostwrote the 2003 editorial for Biological Psychiatry for Dr. Dwight L. Evans and Dr. Dennis Charney. Dr. Charney was then an employee at the NIH Intramural Program and he is now Dean of Research at the Mt. Sinai School of Medicine in -New-YorK. (See e.g., Attachment Wand http://www.pogo.org/pogo-files/letters/public-health/ph-iis-20101129.html.)

In an email to a GSK employee, Ms. Laden wrote, "Is there a problem with my invoice for writing Dwight Evans' editorial for the [Depression and Bipolar Support Alliance], s comorbidity issue to Biological Psychiatry?" [See Attachment W] When the editorial was published, Drs. Evans and Charney "acknowledge[d] Sally K. Laden for editorial support." (Attachment X.)

In conclusion, it is ironic and troubling that Dr. Amsterdam brought his allegations of research misconduct to his direct supervisor and chairman, Dr. Evans, and his complaint was not only ignored by Dr. Evans (who simply handed it off to Dr. Rickels to resolve), but Dr. Evans himself was involved in the ghostwritten Study 352 article by STI and then, two years later, an editorial was also ghostwritten for him by STI.

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[2] See: http://www.pogo.org/pogo-files/letters/public-health/ph-iis-20101129.html

DR. AMSTERDAM'S CRITICISMS OF THE PUBLISHED PAXIL BIPOLAR STUDY 352

First, the study failed to recruit a sufficient patient sample size to adequately test the primary efficacy outcome measure. The primary efficacy outcome measure failed to show superiority of either antidepressant drug treatment compared to placebo. This important information was not reported in the manuscript. The authors then relied on post hoc analyses of subsets of the data to find a favorable result for the antidepressant Paxil. Specifically, this result was accomplished by sub-dividing patient cohorts for each treatment into sub-groups of "high" (Le., ~8.0 mEqjL) versus "low" (Le., <8.0 mEqjL) baseline serum lithium levels after the primary data analyses were found to be . negative. This post hoc data presentation was then presented as the primary study finding, and gave the false impression that one group of patients with low lithium levels (who may be unable to tolerate higher lithium levels) showed superior benefit with Paxil versus placebo (compared to imipramine versus placebo).

Moreover, patients with "low" lithium levels were presented as being a distinct patient group who were somehow different from patients in the "high" lithium level group. In fact, this was a disingenuous distinction because all of the patients in the study had what were considered to be adequate and clinically therapeutic lithium levels, or they would have been discontinued from the trial. Moreover, this sub-division of treatment cohorts into "high" versus "low" lithium level groups was not clinically meaningful and these data were added to the manuscript to produce a favorable outcome finding for promoting Paxil (in a study that was otherwise negative in its findings and that recruited an insufficient patient sample size to accurately test the null hypothesis for the primary efficacy measures).

Second, the published manuscript downplayed a well-known (and potentially dangerous) adverse event profile of Paxil. For example, the manuscript did not report any mania ratings (e.g., Young Mania Rating Scale), although the results section did hote that end-point mania analyses were performed. The manuscript portrayed Paxil as being safe and producing no manic symptoms or manic episodes (in either the entire Paxil-treated patient group or in the "high" or "low" lithium level sub-groups), a finding which was not supported by available clinical or research evidence in 2001 (or ubsequent to that date). As a result, the stated findings suggest that Paxil is a safe and well tolerated alternative to imipramine (the other antidepressant used in the study) which appeared to cause manic symptoms in both the "high" and "low" lithium level patient subgroups. Thus, these purported findings ran completely counter to almost all available clinical and research findings up to 2001 (and subsequent to that date), and suggested a treatment approach for bipolar depression (i.e., Paxil) which contradicted
much of the available clinical and research evidence, as well as most published practice guidelines for treating bipolar type I depression.

Third, the results in the published manuscript emphasized a substantial side effect profile for imipramine while minimizing and down-playing the side effect profile of Paxil. For example, the manuscript emphasized a substantial rate of sexual side effects for imipramine (an antidepressant drug not particularly known to produce this side effect), while down-playing the sexual side effect profile of Paxil, and suggested that there were no sexual side effects encountered with Paxil in the study. This was a grossly misleading fact which was further emphasized by the authors citing the

medical literature indicting only imipramine side effects while simultaneously omitting citations from the medical literature that accurately report the incidence of Paxil sexual side effects. In this regard, the published manuscript stated that "patients treated with imipramine reported a higher incidence of abnormal ejaculation (18.8%) and impotence (25.0%) than did patients receiving paroxetine (0.0% and 6.3%, respectively) or placebo (5.0% and 0.0%, respectively)". Moreover, in the discussion section of the published manuscript, this "finding" is further supported by literature citing the high sexual side effect rate with imipramine while providing no citations for Paxil-induced side effects – even though Paxil's sexual side effects were well known at the time of publication. In fact, the side effect bias favoring Paxil was so supportive and contrary to the available medical literature in 2001 that it would be reasonable for a reader to wonder whether SmithKline Beecham, Inc. actually provided the side effect citations to the" authors" for publication in the published manuscript.

Alarmingly, despite the foregoing enumerated deficiencies, Study 352 and its published results have been relied upon as justification for prescribing Paxil to patients diagnosed with bipolar depression, a practice with little benefit, per the above, and substantial risk of stimulating a manic reaction with an increased risk of suicide and other dangerous adverse reactions.

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Attachments A, B, C and D (Letter to the Office of Research Integrity – Lawyer's letter excerpt)

Dr. Amsterdam believes the individuals named above engaged in scientific misconduct by allowing their names to be appended to a manuscript that was drafted by a "medical communications company" (Scientific Therapeutics Information, "STI") hired by SmithKline Beecham (now known as GlaxoSmithKline, "GSK"), and which Dr. Amsterdam contends misrepresented information from a scientific research study (Paroxetine Study 352), which was funded by GSK and NIH. The manuscript (hereinafter "Study 352") was eventually published in the American Journal of Psychiatry (158:906-912; June 2001) suggesting that Paxil may be beneficial in the treatment of bipolar depression, without acknowledging the medical communication company's contribution or the extent of GSK's involvement. The published manuscript was biased in its conclusions, made unsubstantiated efficacy claims and downplayed the adverse event profile of Paxil. (Attachment A.) Since its publication, study 352 has been cited in hundreds of medical journal articles, textbooks and practice guidelines up to 2011. (See, e.g., Attachment B and C.) Although Dr. Amsterdam was a Co-Principal Investigator of the study and possibly enrolled the largest number of patients, he was excluded from the final data review, analysis and publication. (See Attachment D.)

Attachment A

Nemeroff CB, Evans DL, Gyulai L, Sachs GS, Bowden CL, Gergel IP, Oakes R, Pitts CD. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. American Journal of Psychiatry 2001;158(6):906-12.

Attachment B

Google scholar search of citations for Nemeroff CB, Evans DL, Gyulai L, Sachs GS, Bowden CL, Gergel IP, Oakes R, Pitts CD. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. American Journal of Psychiatry 2001;158(6):906-12.

Attachment C

ICI Website of knowledge. 2 pages, 183 references for Nemeroff CB, Evans DL, Gyulai L, Sachs GS, Bowden CL, Gergel IP, Oakes R, Pitts CD. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. American Journal of Psychiatry 2001;158(6):906-12.

Attachment D

Final ghostwritten draft of Nemeroff et al. manuscript for publication in the Am. J. Psychiatry. Nemeroff CB, Evans DL, Gyulai L, Sachs GS, Bowden CL, Gergel IP, Oakes R, Pitts CD. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. (Final draft of paper in Attachment A in Dr. Amsterdam's possession).

Attachments E and F (Letter to the Office of Research Integrity – Lawyer's letter excerpt)

Dr. Amsterdam only recently became aware that two of the lead authors of Study 352, including his direct supervisor, were linked to ghostwriting through a letter from the Project On Government Oversight (POGO) to NIH Director Francis Collins in November 2010, posted on POGO's website at http://www.pogo.org/pogofileslletters/public-health/ph-iis-20101129.html. Like the examples contained in POGO's letter to NIH, Dr. Amsterdam believes the manuscript published in the American Journal of Psychiatry was ghostwritten by STI, which was hired by GSK and paid with GSK funds, and that the individuals above lent their names as "authors" to the manuscript.

Based upon evidence presented in this complaint and the documents attached hereto, it appears that most, if not all, of the" guest authors" were determined by GSK in conjunction with the "medical communications" firm, STI. STI has had a longstanding history of ghostwriting scientific and medical articles and textbooks which have been attributed to prominently known academics - a practice that has been the subject of mounting criticism. See, for example, an editorial in the Journal of the American Medical Association regarding ghostwriting in relation to Merck's promotion and sales of VIOXX. (Attachment E.)

The acknowledgement section of the published manuscript states that Study 352 was conducted and published with support from NIMH grant MH-51761. (Attachment A.) According

to a recent search of the NIH Reporter database, NIMH grant MH-51761 was part of an "infrastructure support" and "core-patient recruitment and assessment" project for NIH-funded clinical research trials. (Attachment F.) In this case, it was used to support the recruitment and assessment of research subjects for participation in this GSK-sponsored and GSK-funded clinical trial of Paxil for the treatment of patients with bipolar type I major depression.

Attachment E

Catherine D. DeAngelis and Phil B. Fontanarosa: Impugning the integrity of medical science. The adverse effect of industry interest. Editorial. JAMA 2008;299:1833-5.

Attachment F

NIH RePORTER - NIH Portfolio Online Search Results. Nemeroff CB, Evans DL, Gyulai L, Sachs GS, Bowden CL, Gergel IP, Oakes R, Pitts CD. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. Am J Psychiatry 2001;158(6):906-12.
U.S. Department of Health and Human Services
Home > RePORTER > Search Results
Search Results - NIH RePORTER-NIH Research Portfolio Online ...
There were 22 results matching your search criteria.

Project Number	Sub #	Project Title	Principal Investigator	Organization	FY	Admin IC
5R24MH051761-05	9002	CORE-NEUROENDOCRINOLOGY, NEUROCHEMISTRY, AND BRAIN IMAGING	BONSALL, ROBERT W.	EMORY UNIVERSITY	1998	NIMH
5R24MHQ51761-04	9002	CORE-NEUROENDOCRINOLOGY, NEUROCHEMISTRY, AND BRAIN IMAGING	BONSALL, ROBERT W.	EMORY UNIVERSITY	1997	NIMH
5R24MH0517B1-03	9002	CORE-NEUROENDOCRINOLOGY, NEUROCHEMISTRY, AND BRAIN IMAGING	BONSALL, ROBERT W		1996	NIMH
5R24MH051761-05	9001	CORE-PATIENT RECRUITMENT AND ASSESSMENT	GOODMAN, SHERRYL	EMORY UNIVERSITY	1998	NIMH
5R24MH351761-04	9001	CORE-PATIENT RECRUITMENT AND ASSESSMENT	GOODMAN, SHERRYL	EMORY UNIVERSITY	1997	NIMH
5R24MH051761-03	9001	CORE-PATIENT RECRUITMENT AND ASSESSMENT	GOODMAN, SHERRYL		1996	NIMH
5R24MH051761-05	9004	CORE-EXPERIMENTAL DESIGN AND BIOSTATISTICS	MARSTELLER, FREDERICK A	EMORY UNIVERSITY	1998	NIMH
5R24MH051761-04	9004	CORE-EXPERIMENTAL DESIGN AND BIOSTATISTICS	MARSTELLER, FREDERICK A	EMORY UNIVERSITY	1997	NIMH
5R24MH051761-03	9004	CORE-EXPERIMENTAL DESIGN AND BIOSTATISTICS	MARSTELLER, FREDERICK A		1996	NIMH
5R24MH051761-05	9003	CORE-BIOLOGICAL TISSUES AND FLUIDS	NEMEROFF, CHARLES B	EMORY UNIVERSITY	1998	NIMH
5R24MH051761-05		INFRASTRUCTURE SUPPORT PROGRAM	NEMEROFF, CHARLES B	EMORY UNIVERSITY	1998	NIMH
5R24MH051761-04	9003	CORE-BIOLOGICAL TISSUES AND FLUIDS	NEMEROFF, CHARLES B	EMORY UNIVERSITY	1997	NIMH
5R24MH051761-04		INFRASTRUCTURE SUPPORT PROGRAM	NEMEROFF, CHARLES B	EMORY UNIVERSITY	1997	NIMH
3R24MH051761-04S1		INFRASTRUCTURE SUPPORT PROGRAM	NEMEROFF, CHARLES B	EMORY UNIVERSITY	1997	NIMH

5R24MH051761-03	9003	CORE-BIOLOGICAL TISSUES AND FLUIDS	NEMEROFF, CHARLES B		1996	NIMH
5R24MH051761-03		INFRASTRUCTURE SUPPORT PROGRAM	NEMEROFF, CHARLES B	EMORY UNIVERSITY	1996	NIMH
5R24MH051761-02		INFRASTRUCTURE SUPPORT PROGRAM	NEMEROFF, CHARLES B	EMORY UNIVERSITY	1995	NIMH
1R24MH051761-Q1A1		INFRASTRUCTURE SUPPORT PROGRAM	NEMEROFF, CHARLES B	EMORY UNIVERSITY	1994	NIMH
5R24MH051761-04S1	9001	CORE-PATIENT RECRUITMENT AND ASSESSMENT	Unavailable	EMORY UNIVERSITY	1997	NIMH
5R24MH051761-04S1	9002	CORE-NEUROENDOCRINOLOGY, NEUROCHEMISTRY, AND BRAIN IMAGING	Unavailable	EMORY UNIVERSITY	1997	NIMH
5R24MH051761-04S1	9003	CORE-BIOLOGICAL TISSUES AND FLUIDS	Unavailable	EMORY UNIVERSITY	1997	NIMH
5R24MH051761-04S1	9004	CORE-EXPERIMENTAL DESIGN AND BIOSTATISTICS	Unavailable	EMORY UNIVERSITY	1997	NIMH
Page Last Updated on March 8, 2011. This site is best viewed with internet Explorer (6.0 or higher) or Mozilla Firefox (2.0).						

Attachment G (Letter to the Office of Research Integrity – Lawyer's letter excerpt)

According to a letter written by Dr. Francis Collins, Director of the NIH, ghostwriting that involves a federal grant may be cause for an investigation of plagiarism. Dr. Collins stated in his letter, which was published on POGO's website: [A] case of ghostwriting involving NIH-funded researchers may be appropriate for consideration as a case of plagiarism; i.e., the appropriation of another person's ideas, processes, results, or words without giving appropriate credit; or fabrication, i.e., making up data or results and recording or reporting them. Such a case would be handled by the Office of Research Integrity (ORI) of the Department of Health and Human Services (HHS), which investigates research misconduct as defined in the PHS's 42 C.F.R. Parts 50 and 93, Policies on Research Misconduct and the Final Rule. (Attachment G.)

Attachment G

Letter from Francis S. Collins to Paull Thacker.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

FEB 17 2011

National Institutes of Health
Bethesda, Maryland 20892

Mr. Paul Thacker
Investigator
Project On Government Oversight
1100 G Street, NW, Suite 900
Washington, DC 20005-3806

Dear Mr. Thacker:
Thank you for your letter of November 29, 2010, in which you express your concern about financial conflicts of interest and ghostwriting in academia, particularly in medical schools.

I want to state clearly that the National Institutes of Health (NIH) does not condone the practice of ghostwriting, particularly situations in which investigators may have accepted
payment from private entities in return for allowing their names to be used as authors on publications in which they had very limited input. In fact, NIH's Intramural Research Program has authorship guidelines that are comparable to those described in the *Uniform Requirements/or Manuscripts Submitted to Biomedical Journals,* which were developed by the internal Committee of Medical Journal Editors.

While the NIH extramural policy governing NIH grantees does not use the term ghostwriting, Federal regulations and policies relating to Public Health Service (PHS)-supported research could be applicable to ghostwriting, depending on the specific circumstances of a particular case. For example, a case of ghostwriting involving NIH-funded researchers may be appropriate for consideration as a case of plagiarism; i.e., the appropriation of another person's ideas, processes, results, or words without giving appropriate credit; or fabrication, i.e., making up data or results and recording or reporting them. Such a case would be handled by the Office of Research Integrity (ORI) of the Department of Health and Human Services (HHS), which investigates research misconduct as defined in the PHS's 42 C.F.R. Parts 50 and 93, *Policies on Research Misconduct and the Final Rule.* If ORI makes a finding of research misconduct, the NIH may take appropriate enforcement action(s), which could include modification of the terms of the award, suspension, termination, withholding of support, temporary withholding of payment, conversion from an advance payment method to a reimbursement method, or debarment, among other options.

The NIH believes that ghostwriting should be addressed when scientific articles citing extramural Federal funding are submitted to journals for publication. Current policy requires all HHS grantees to acknowledge Federal funding when issuing statements, press releases, requests for proposals, bid invitations, and other documents describing projects or programs funded in whole or in part with Federal money. However, it does not require that all parties who contribute to a publication, including those that contribute financially, be acknowledged. The NIH is considering how best to address the issue of ghostwriting in the development and authorship of medical literature arising from Federal research funding.

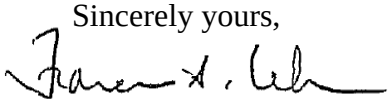
As you are aware, the NIH, on behalf of HHS and the PHS, is engaged in the rulemaking process to revise the regulations governing investigator financial conflict-of-interest (42 CFR Part 50 Subpart F, *Responsibility of Applicants for Promoting Objectivity in Research for which PHS Funding is Sought* and 45 CFR Part 94, *Responsible Prospective Contractors).* Because of its potential to create conflicts-of-interest that could bias or otherwise inappropriately influence NIH-supported research, "paid authorship" was specifically included in the proposed revisions to the regulations. By including "paid authorship" in *the* definition of "Significant Financial Interest" in the proposed rule, the NIH is sending a clear message to institutions and investigators alike that we support the principles of transparency and accountability in research and that institutions and

investigators engaging in such activity may be subject to more rigorous disclosure and reporting. The proposed rule may be accessed at http://wwvv.regulations.gov/search/Regs/home.html#documentDetail?R=0900006480af37ce.

The NIH is committed to preserving the public trust in the objectivity of NTH-supported research, and we strongly believe that all research should be conducted with the highest scientific and ethical standards. Thus, we have proposed substantial changes to the existing financial conflict-of-interest regulations to increase accountability and transparency, which are vital to managing the essential relationships between Government, NIH-funded research institutions, and the private sector.

Thank you again for your interest in the NIH and our programs. I am also sending this response to Ms. Brian.

Sincerely yours,



Francis S. Collins, M.D., Ph.D.
Director

Attachments H and I (Letter to the Office of Research Integrity – Lawyer's letter excerpt)

Moreover, according to a report on ghostwriting by Senator Charles Grassley (dated June 24, 2010), the University of Pennsylvania considers ghostwriting to be equivalent to plagiarism.

While this incident took place some time ago (i.e., 2001), the manuscript has been cited hundreds of times up through 2011 according to an internet search on Google Scholar. (Attachment B.) In fact, Dr. Gyulai cited the paper again in a study he published in 2007 in the New England Journal of Medicine (Attachment H) and Dr. Sachs cited the paper in 2011 in the Journal of Clinical Psychiatry. (See Attachment C, Record 1.)

Moreover, the purported "findings" of Study 352 and the published results from other studies and articles that have cited this study have been used to support the design and implementation of at least two other NIMH-funded grants to study the efficacy and safety of antidepressant drugs (like Paxil) in bipolar depression. See, e.g., MH080097, Prevention of Relapse and Recurrence of Bipolar Depression and MH060353, Treatment of Bipolar Type II Major Depression.

Dr. Amsterdam submits this complaint in the hopes that ORI will conduct an investigation, impose appropriate penalties to correct the past publication of Study 352' s results, to prevent similar conduct from happening again, and hopefully prevent further use of this paper to support the dangerous prescription of Paxil to patients diagnosed with bipolar depression.

Pursuant to 42 C.F.R. Part 50.103(d)(13), Dr. Amsterdam should receive full and complete protection from retaliation and/ or defamation by either the University of Pennsylvania or any other parties involved in the production and publication of Study 352. Dr. Amsterdam requests the protections described in ORr's "Handling Misconduct - Whistleblowers." (Attachment I.)

To ensure that this complaint is taken seriously, and to alert interested parties, we are providing copies of this correspondence to Senator Charles Grassley, Senator Herb Kohl, and the Chairman and Ranking members of the House Energy and Commerce, and the House Committee on Oversight and Government Reform.

Attachment H

Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, Friedman ES, Bowden CL, Fossey MD, Ostacher MJ, Ketter TA, Patel J, Hauser P, Rapport D, Martinez JM, Allen MH, Miklowitz DJ, Otto MW, Dennehy EB, Thase ME. Effectiveness of Adjunctive Antidepressant Treatment for Bipolar Depression. N Engl J Med 2007;356(17):1711-22.

Attachment I

Office of Research Integrity. Handling Misconduct – Whistleblowers. ORI Guidelines for Institutions and Whistleblowers: Responding to Possible Retaliation Against Whistleblowers in Extramural Research. November 20, 1995.
http://ori.hhs.gov/misconduct/Guidelines_Whistleblower.shtml.

Attachment J (Letter to the Office of Research Integrity – Lawyer's letter excerpt)

"DR. AMSTERDAM'S TIMELINE RE PUBLICATION OF PAXIL BIPOLAR STUDY 352 WITHOUT HIS KNOWLEDGE"

In the mid-1990s, Dr. Amsterdam became a Co-Principal Investigator on a clinical trial, Paroxetine Study 352, comparing the antidepressant drugs imipramine (Tofranil®) and paroxetine (Paxil®) for the treatment of bipolar type I major depression (or manic depression).

The trial was sponsored, in part, by GlaxoSmithKline which sells paroxetine under the brand names Paxil® in the US and Seroxat in other countries. Dr. Amsterdam recruited one of the largest, if not the largest, patient samples into a study that comprised 18 other investigative-sites.

In early 2001, Dr. Amsterdam became aware that Dr. Dwight Evans and Dr. Laszlo Gyulai were attempting to publish data from the above referenced study. Although Dr. Amsterdam was a Co-Principal Investigator of Study 352 and enrolled one of the largest numbers of patients, he was excluded from the final data review, analysis and publication. (Attachment J, K, L and D.)

Attachment J

Dr. Karl Rickels, 11:03 AM 4/2/01 -0400, SKB Bipolar study

To: Dr. Karl Rickels
From: "Dr. Jay D. Amsterdam" < jamsterd@mail.med.upenn.edu>
Subject: SKB Bipolar study
Cc: dlevans@mail.med.upenn.edu
Bcc:
Attached:

Karl,

It has been about 5 or 6 weeks since I brought to your attention the troubling issue of investigator contribution and authorship on manuscripts from the SKB BP I study. You will recall that at least one manuscript from this study is in press to the Am J Psych, and other manuscripts may also have been submitted to other journals. Again, it is my feeling that as a major investigator in this nineteen-site study, I should have been provided with data for review and consideration for authorship on these manuscripts. As we discussed, it was agreed upon in 1995 by you, me and Dr. Gyulai that if I would have a major input into this study at the Penn site and serve as a major contributor to the study, then I should have input into data analysis and authorship. In our discussion several weeks ago you indicated your recollection of this agreement, and your understanding of the situation and its potential ramifications and that you would look into the matter. As I have not heard from you regarding this potentially troubling situation I thought that I would take the liberty of reminding you of it. As one of the articles is no doubt close to publication, I felt it necessary to speak with Dr. Evans. I did this several weeks ago regarding the situation and he indicated to me that he would speak to you about it.

As I previously indicated to you it is not my intention to put you in a difficult situation, and that if you feel uncomfortable helping out in this matter, please let me know so that I can take up the issue with others at the University and/or the American Journal of Psychiatry.

I look forward to hearing from you at your earliest convenience, and I thank you for your assistance in this matter.

Regards,
Jay

Samuel Gershon's comment on collating document

This document is a careful and detailed report on gross improprieties in the marketing and advertising of this whole series of compounds.

This massive project illustrates the distortion of data at every level of its presentation for the purpose of marketing. Its use at scientific meetings to aid in the promotion of sales and biases the educational process to both students and practitioners. One should add at this point that the ultimate victim of these distortions is the patient. I wish to stress the importance of Amsterdam and his colleagues in collating all this careful evidence and preparing it for a broader audience.

Also, INHN is to be commended for undertaking the massive task of preparing this material and presenting it in a meticulous format for the readers to appreciate.

I would like this opportunity to inform readers that materials are gradually also being presented in INHN on a serious controversy, currently ongoing, dealing with the reporting and evaluation of a "new" potential "anti-Alzheimer's drug" and the current disputes appearing in the newspapers.

This, I guess, may become another example of the episode reported above.

Mark Kramer's comment on Samuel Gershon's comment

My truly good friend, Jay Amsterdam ("Prof. Jay" – my affectionate nickname for him) informed me that Dr. Gershon had commented on Jay's post. That was encouraging to Professor Jay. I get it! He's given all of us an embarrassment: incontrovertibly factual data which grandly documents the actual words and methods by which high level professionals from industry and academia – connected grandly to our ranks – have colluded to pollute the integrity of our field.

Of course, Jay is disappointed that responses to his disclosures have not been met with more interest and even activism from members of this devoted body. After all, I understand it's bulletins reach into organizations such as ACNP. I think P.J. must feel that the silence has been deafening in our ranks. Why isn't there an outcry from every quarter? Why aren't those who perpetrated these crimes against academia, industry and big publishing, outcast – made to pay in some way?

I felt Jay's email to me had a quality of shaming me. But I'm tired. I previously told him I was moving on from our field: that his fight was no longer my fight.

Besides, I said almost everything I wanted to about corruption (academic, corporate, anti-pharmacology cottage industries) in a long paper that I authored in response to honorable pioneer Dr. Barry Blackwell (Kramer 2016). I don't know that Barry liked it too much. The paper was really to set my mind as straight as possible on the issues. It's a shame that Don Klein expected more from me. I politely agreed with him that it could have been better. But then again that brilliant man was annoyed with a lot of things (may he rest in peace]. In the end, I really could not devise a strategy that would fix our fallen Humpty Dumpty – the one I once so loved dearly on the shaky wall.

And frankly, I told Jay as a friend that he would be so much better off, after he documented what he did, to try to advance the field further scientifically. I was concerned that his salutary efforts would be used against the field, such that really sick patients who might have benefited from a TCA for example, would be turned towards only those practicing in competing non-medical mental health industries.

To me, my friend Jay, despite the incredible efforts he's made (keep in mind with drastically failing, vision) coupled with the suffering he's endured in academia (despite being an impressively capable and productive clinical researcher), sounds at times like a looped jazz phrase: it's great the first time your hear it, it gets clarified second time, the third time it might be taken as a polyrhythmic variation, but the fourth time you just want to hear something else. I love David Healy for his ability to write clearly, his history telling, but I'm sick of his phrases too. f*** it!

Medicines trend to work better than placebo in clinical practice and in clinical trials. I learned this (a little more than anecdotally) from serial systematic placebo-controlled N of 1 experiments as a resident and I don't see why some guys don't understand that, if you don't. Withholding psychopharmaceutical drugs routinely for certain patients is immoral. Medicine is art as well as science; there likely will always be harms.

And it's true that jazz players, like some psychopharmacologists, do loop their phrases because they don't yet know what else to do. LOL – perhaps micro-dosed mushrooms will help.

I just can't, and don't want to, do anymore in this field. I've been with Jay from the very beginning of his current efforts. I respect him very much. I tried at times to help, but the wind is out of my sails for this kind of thing. It's actually out of my sails for psychopharmacology. I will die happily knowing that we documented what we know in the *Journal of Affective Disorders* about substance P (neurokinin type 1 receptor) antagonist antidepressants (multiple huge clinical

replications, means by which Merck and Co. likely dropped the ball/ why they were not commercialized) (Rupniak and Kramer 2017) and that's all I can do.

My disappointment is so heavy with our field, that it's painful to think of it, especially its lack of etiological science, not to mention it's now clear underlayment of corruption. Some etiological mechanisms eluding us might be in relationship to regional BBB endothelial dysfunction (involving gilia and inflammatory protein dynamics). I don't think much of psychopharmacology has much to do with neuronal circuitry at all (Auld and Robitaille 2003). But that's just what's left of my reeling analytical mind going a bit off axis

Playing advanced jazz piano is what brings me and others peace, discovery, and great enjoyment. This has always been my first love anyway. It is so now – especially in these last years of life.

So, when P.J. let me know about Sam's response I just dictated a sloppy response into my phone which revealed my cocky position. I inadvertently copied Tom Ban on it about where I stand so I was encouraged just to submit what I dictated. Okay here goes nothing. Maybe this will stir the pot a little for Jay's efforts, maybe it won't. By way of this, I allow my response requested to be bundled in with other responses to Jay. I think what I say is crude and freely associative ... but real.

---

professor j, thanks for copying me on this.
a few sayings

1] No good deed goes unpunished.

2] He who pays the piper calls the tune.

So, P.J. what's the plan?

Meanwhile my own crusade is getting rid of privatized water in my State. The suckers want to raise water rates 18%. The company's gross profit margin before taxes is 35% which equals

highly profitable. They only pay a million dollars in taxes in most years, and yet their net profits were ~$1.3 billion. So, out of every water bill a household pays in Pennsylvania now the company receives 1/3 of it in profit for shareholders and executives – who, by the way, make up to $24 million a year. The hourly rate of their average employee is $20 per hour. So, forget trickle down.

Wherever you turn Jay there's injustice and there's corruption. You can't tell me that AQUA water company did not get into Pennsylvania by greasing the wheels of Governors and the State Senates?

Problem: it's humanity Jay – that's the problem. It's really worse now because of huge income disparity. What drives people like Nemeroff, Evans, Keller, Montgomery et al. to do what they do (did) as KOLs shills? What happened to them? They undertook useful science early on, but why did they morph into something so unethical and so immoral? Is it fear? Need for control? It's not just money because they have enough, but apparently, they don't think so. So, then, it's power. But to what end?

You've done your work, Jay. I don't think that there's any more to be done unless you have a plan. Maybe I would join a plan, but I don't have one and will not invest the time to draw one up. It's not like we have a cohesive set of principles in our governing bodies in the US. We're a polarized mess.

Case in point: If people can't see that they ought to be vaccinated they're nuts (clinical diagnosis: "Mark Kramer's personal DSM version-1"). Also denying that there was an insurrection on Jan. 6th and that Trump and those Republican b****** who support his brand is a f****** freak show (code that for the DSM!).

The thing to be more worried about than old pharmacologists reading all these documents you've provided, is a knock on your door asking if you're Jewish. Smell the gas boychick!

There's nothing to be done, Jay – enjoy your life, love the lovable ones, drink wine, listen to good music... (www.mark-kramer.com).

I think most people realize there's nothing to be done, that's why you're hearing silence. Or maybe they don't want to hurt their relationships with KOLs, no matter the cost to their integrity.

Also, understand, as I'm sure you do, that most people, as they get older, have bandwidth limited to taking care of their own health and the health of their loved ones. My own Don Quixote seems to have left town – not entirely, but at least he'll try to get the water bills down.

References:

Auld DS, Robitaille R. Glial Cells and Neurotransmission: An inclusive view of synaptic function. Neuron 2003;40(2):389-400.

Kramer MS. Commentary. Innovation, propaganda, and jail time. Barry Blackwell: Corporate Corruption in the Psychopharmaceutical Industry. inhn.org.controversies. October 13, 2016.

Rupniak NMJ, Kramer MS. NK1 receptor antagonists for depression: Why a validated concept was abandoned. J Affect Disord 2017;223:121-5.

Barry Blackwell's comment on Mark Kramer's comment

I share Mark's kindly admiration for Jay's detailed documentation of overt, even blatant, corruption in the pharmaceutical industry abetted by well-known credentialled, once respected, academic psychopharmacologists, now also overlooked or ignored by professional organizations at the highest level of professional and national accountability.

I also share Mark's end of career frustration and tedium concerning issues deeply rooted in contemporary flaws within our social and political institutions. Income disparity bolstered by greed and addiction to unsightly wealth, absence of political compromise and balanced legislation, growing authoritarianism, threats of violence and false allegations of voter fraud, even doubts about the integrity and flexibility of the Constitution. Accompanied by a persistent, life-threatening viral pandemic, teetering on the brink of control.

Mark takes refuge in music, I turn to poetry, perhaps each of us clings to hope that "this too shall pass." Meanwhile INHN and our website still exist, Tom Ban remains at the helm so there is space and time to share our concerns and hopes.

Attachment K (Letter to the Office of Research Integrity – Lawyer's letter excerpt)

"DR. AMSTERDAM'S TIMELINE RE PUBLICATION OF PAXIL BIPOLAR STUDY 352 WITHOUT HIS KNOWLEDGE"

In the mid-1990s, Dr. Amsterdam became a Co-Principal Investigator on a clinical trial, Paroxetine Study 352, comparing the antidepressant drugs imipramine (Tofranil®) and paroxetine (Paxil®) for the treatment of bipolar type I major depression (or manic depression).

The trial was sponsored, in part, by GlaxoSmithKline which sells paroxetine under the brand names Paxil® in the US and Seroxat in other countries. Dr. Amsterdam recruited one of the largest, if not the largest, patient samples into a study that comprised 18 other investigative-sites.

In early 2001, Dr. Amsterdam became aware that Dr. Dwight Evans and Dr. Laszlo Gyulai were attempting to publish data from the above referenced study. Although Dr. Amsterdam was a Co-Principal Investigator of Study 352 and enrolled one of the largest numbers of patients, he was excluded from the final data review, analysis and publication. (Attachment J, K, L and D.)

ATTACHMENT K

April 3, 2001

Jay D. Amsterdam, M.D.
Department Psychiatry
University of Pennsylvania
3600 Market Street, 8th Floor
Philadelphia, PA 19104-2649

RE: Bipolar Paper Authorship

Dear Jay,

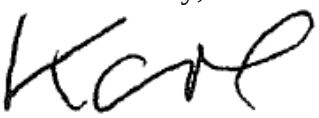
After you talked to Dwight Evans about the bipolar paper authorship problem, he called me to look into this matter. I did so and on March 29, 2001, I emailed Dwight what I could learn. I reported to him on the following points:

1. Dr. Gyulai was contacted to be the PI for the Penn Site in 1994.
2. In 1995, I suggested that Dr. Gyulai ask Dr. Amsterdam whether he could help him with the project as Dr. Gyulai had problems enrolling patients. Dr. Amsterdam at that time was short in research funds and thus his participation could benefit both Dr. Gyulai and Dr. Amsterdam. Dr. Gyulai would enroll more patients and Dr. Amsterdam would receive more income for his unit. At this time, Dr. Amsterdam became a co-investigator.
3. Penn enrolled 19 patients into the randomized part of the study, with Dr. Amsterdam enrolling 12 patients and Dr. Gyulai enrolling 7 patients.
4. On April 8, 1997, Dr. Gyulai was asked by Grace Johnson of STI to serve as first author of the paper and to review and comment on the enclosed draft #2. On May 14, 1997, Ms. Johnson forwarded a diskette containing draft #2. On December 3, 1997, Dr. Gyulai mailed to Dr. Gergel a revised draft of the paper.

5. As you know, at some later date, SKB decided to replace Dr. Gyulai with Charlie Nemeroff as first author.
6. All participants in the study, including Dr. Amsterdam, are acknowledged in the paper.
7. However, apparently these participants never had a chance to review or even just see the manuscript.
8. Probably one of the reasons Dr. Gyulai did not communicate with Dr. Amsterdam regarding the paper are the existing interpersonal conflicts between Dr. Gyulai and Dr. Amsterdam.
9. Dr. Gyulai recently communicated with SKB and requested permission to write a second paper as first author based on the same data. He proposed that this paper deal with an analysis of all HAM-D subscales and a 2 X 2 factorial analysis (2 treatment x high vs low Lithium levels). Dr. Gyulai expressed the hope that Dr. Amsterdam would be allowed by SKB to join him as one of several authors in this second publication.
10. Dr. Gyulai told me, but I have no independent confirmation, that he suggested to SKB that Dr. Amsterdam should be considered as an author for the first paper. This was turned down on the reasonable basis that only one author per site could be considered. In fact, several sites were not even considered for authorship.

I thought you might be interested in what I have learned.

Sincerely,



Karl Rickels, M.D.

KR:tch

Attachment L (Letter to the Office of Research Integrity – Lawyer's letter excerpt)

"DR. AMSTERDAM'S TIMELINE RE PUBLICATION OF PAXIL BIPOLAR STUDY 352 WITHOUT HIS KNOWLEDGE"

In the mid-1990s, Dr. Amsterdam became a Co-Principal Investigator on a clinical trial, Paroxetine Study 352, comparing the antidepressant drugs imipramine (Tofranil®) and paroxetine (Paxil®) for the treatment of bipolar type I major depression (or manic depression).

The trial was sponsored, in part, by GlaxoSmithKline which sells paroxetine under the brand names Paxil® in the US and Seroxat in other countries. Dr. Amsterdam recruited one of the largest, if not the largest, patient samples into a study that comprised 18 other investigative-sites.

In early 2001, Dr. Amsterdam became aware that Dr. Dwight Evans and Dr. Laszlo Gyulai were attempting to publish data from the above referenced study. Although Dr. Amsterdam was a Co-Principal Investigator of Study 352 and enrolled one of the largest numbers of patients, he was excluded from the final data review, analysis and publication. (Attachment J, K, L and D.)

ATTACHMENT L

UNIVERSITY OF
PENNSYLVANIA
MEDICAL CENTER

Jay D. Amsterdam, M.D.
Professor, Director,
Depression Research Unit,
Mood and Anxiety Disorders Section
Department of Psychiatry
University of Pennsylvania

7/5/01

Dear Jay,

I regret that there appears to be some misunderstanding about the publication of the data of the SKB PAR- 29060/352 study, which was conducted between 1994 and 1996 and I sincerely apologize for it. I understand that you feel that I took your data collected in this study and that I was unfairly one of the authors of the paper from the project, which appeared in the Am. J. Psychiatry.

I was the primary investigator of the Penn site and, as you know, I worked on early drafts of the paper. I did not determine authorship, and as you know, the paper was taken away from me as first author during the writing process. However, I regret that I did not discuss the issue of authorship with you. I agree with you that SKB should have circulated the paper to all participants. I only saw the final draft shortly before it was submitted when only minor changes could be done.

I hope that this clarifies some of the misunderstandings and makes it possible for us to work in a collaborative fashion. I am truly sorry about the whole matter and would be happy to personally meet with you and discuss these issues as colleague to colleague.

I remain sincerely yours,

Laszlo Gyulai, M.D.

cc: Dr. Dwight L. Evans
Dr. Karl Rickels

Attachment M (Letter to the Office of Research Integrity – Lawyer'sletter excerpt)

"DR. AMSTERDAM'S TIMELINE RE PUBLICATION OF PAXIL BIPOLAR STUDY 352 WITHOUT HIS KNOWLEDGE"

Dr. Amsterdam contacted his immediate supervisor and department chairman, Dr. Dwight L. Evans about the matter. In a March 22,2001 email to Dr. Amsterdam, Dr. Evans stated that he had discussed the issue with Dr. Karl Rickels who was also a professor in the Department of Psychiatry at the University of Pennsylvania and Dr. Gyulai's direct supervisor. Dr. Evans assured Dr. Amsterdam that Dr. Rickels would be reviewing the matter and, once accomplished, he trusted there would be "an equitable outcome." (Attachment M.)

Attachment M

Sender: psych@mail.med.upenn.edu
Mailer: QUALCOMM Windows Eudora Light Version 3.0.3 (32)
Date: Thu, 22 Mar 2001 04:31:18 -0500
To: jamsterd@mail.med.upenn.edu
From: "Dr. Dwight L. Evans, MD" <psych@mail.med.upenn.edu>
Subject: SKB Study
Cc: krickels@mail.med.upenn.edu

Dear Jay,

I have discussed the SKB study at length with Karl Rickels. He will review and look into the entire matter as it relates to the work that you did here at Penn. Once this is accomplished, I trust there will be an equitable outcome.

Dwight

Dwight L. Evans, MD
Ruth Meltzer Professor and Chairman
Department of Psychiatry
University of Pennsylvania Health System
3 Blockley Hall
Philadelphia, PA 19104
215-662-2818
215-662-6911 Fax
Email: psych@mail.med.upenn.edu

Attachment N (Letter to the Office of Research Integrity – Lawyer's letter excerpt)

On May 1, 2001, Dr. Amsterdam sent Drs. Evans and Rickels another email to explain that he was unsatisfied with the response and, since the last letter, there has been only "radio silence." As he wrote, "Am I to assume that it is okay in this department for a junior faculty member to abscond with data from a full professor and publish it without any ramifications?" (Attachment N.)

Attachment N

To: "Dr. Dwight L. Evans, MD" <psych@mail.med.upenn.edu>
From: "Dr. Jay D. Amsterdam" <jamsterd@mail.med.upenn.edu>
Subject: SKB study publication
Cc:
Bcc:
Attached:

Hi Dwight,

To date there has been only "radio silence" regarding the matter of the Am J Psychiatry publication. Am I to assume that it is okay in this department for a junior faculty member to abscond with data from a full professor and publish it without any ramifications? As you can see from Karl's review of this matter, my estimate of the situation was accurate and it appears as though the "high enroller in the entire 19 site SKB study" (me) was purposefully omitted from data review, analysis and publication. What do you suggest that I do at this point? I would appreciate your continued advice on this exceedingly troubling matter. I look forward to your suggestions at your convenience.

Best, as always,

Jay

Attachment O (Letter to the Office of Research Integrity – Lawyer's letter excerpt)

On May 1, 2001, Dr. Amsterdam sent Drs. Evans and Rickels another email to explain that he was unsatisfied with the response and, since the last letter, there has been only "radio silence." As he wrote, "Am I to assume that it is okay in this department for a junior faculty member to abscond with data from a full professor and publish it without any ramifications?" (Attachment N.)

The following day, Dr. Rickels emailed Dr. Amsterdam and explained that Dr. Evans had tasked him (Dr. Rickels) with trying "to bring about a resolution." (Attachment O.)

Attachment O

Sender: krickels@mail.med.upenn.edu
Mailer: QUALCOMM Windows Eudora Pro Version 4.2.2
Date: Wed, 02 May 2001 11 :23:55 -0400
To: jamsterd@mail.med.upenn.edu
From: "Dr. Karl Rickels" <krickels@mail.med.upenn.edu>
Subject: SKB study publication
Cc: "Dr. Dwight L. Evans, MD" <psych@mail.med.upenn.edu>

Dear Jay,

Dwight shared your email to him and asked me "to bring about a resolution". It would be helpful if you could let me know by email what steps you would like me or Dwight to take in this matter. After I receive your suggestions, I would be happy to come over to your office for any further clarification.

Best regards,
Karl
****
Karl Rickels, M.D.
Professor of Psychiatry
University of Pennsylvania
Department of Psychiatry
Mood and Anxiety Disorders Section
3535 Market Street
Suite 670
Philadelphia, PA 19104-3309

Telephone: 215-746-6417
Fax: 215-746-6551
email: krickels@mail.med.b1penn.edu

Attachment P (Letter to the Office of Research Integrity – Lawyer's letter excerpt)

On May 11, 2001, Dr. Amsterdam emailed Dr. Rickels and explained that he considered data that he (Dr. Amsterdam) accumulated in his research unit from the study "were misappropriated from me and used and published without my knowledge and without regard to the significant contribution that I made to this study." Dr. Amsterdam complained that the "theft and publication

of [his] data should not go unnoticed and uncensured." He proposed that Dr. Gyulai write a letter of apology and be censured in order to ensure "this situation does not happen again." (Attachment P.)

Attachment P

To: Dr. Karl Rickels
From: "Dr. Jay D. Amsterdam" <jamsterd@mail.med.upenn.edu>
Subject: SKB Paxil BP study publication
Cc:
Bee:
Attached:

Dear Karl,

Thank you for your nice email in response to my note to Dr. Evans. I have given a great deal of thought as to how to resolve this extremely troubling matter. As per your investigation there is little doubt that these data were misappropriated from me and used and published without my knowledge and without regard to the significant contribution that I made to this study.
It is certainly not my intention to embarrass any of the authors who will eventually receive all the accolades when this paper comes to print. However, I am sure you will agree that there is little doubt that I was systematically slighted by Dr. Gyulai. His statement to you that he contacted SKB about having my name included as an author does not, unfortunately, comport with what knowledgeable persons at SKB report.
I think that it is important to maintain the highest academic and collegial relationship at an institution such as Penn. Thus, the theft and publication of a professor's data by a junior faculty member should not go unnoticed and uncensured. Therefore, in an effort to assure that this situation does not happen again, I would propose the following:

1. Dr. Gyulai write a letter of apology to me acknowledging his wrong doing and that he will not do this again in the future.
2. That Dr. Gyulai receive a letter of censure from the chairman (copied to me) admonishing him not to engage in this sort of behavior in the future.
3. That Dr. Gyulai receive a letter of censure from you, his section chief (copied to me) admonishing him not to engage in this sort of behavior in the future.

I think that this would resolve the immediate problem in a private, but useful, fashion; and will not result in any embarrassment to people who were uninvolved with the Penn site and unaware of Dr. Gyulai's behavior. It will also serve as a warning that our academic freedom is paramount and should not be compromised by petty, personal vein glory.

I would be happy to discuss these suggestions with you at your convenience.

As ever,
Jay

Attachment Q (Letter to the Office of Research Integrity – Lawyer's letter excerpt)

On May 11, 2001, Dr. Amsterdam emailed Dr. Rickels and explained that he considered data that he (Dr. Amsterdam) accumulated in his research unit from the study "were misappropriated from me and used and published without my knowledge and without regard to the significant contribution that I made to this study." Dr. Amsterdam complained that the "theft and publication of [his] data should not go unnoticed and uncensured." He proposed that Dr. Gyulai write a letter of apology and be censured in order to ensure "this situation does not happen again." (Attachment P.)

Ten days later, Dr. Rickels emailed Dr. Amsterdam stating that he had shared Dr. Amsterdam's comments with Dr. Evans and, once he received a reply from Dr. Evans, he (Dr. Rickels) would like to meet with Dr. Amsterdam to discuss the topic. (Attachment Q.)

Attachment Q

X-Sender: krickels@mail.med.upenn.edu
X-Mailer: QUALCOMM Windows Eudora Pro Version 4.2.2
Date: Mon, 21 May 2001 10:37:12 -0400
To: jamsterd@mail.med.upenn.edu
From: "Dr. Karl Rickels" <krickels@mail.med.upenn.edu>
Subject: SKB Publication
Cc: dlevans@mail.med.upenn.edu

Dear Jay,

I have shared your comments RE: SKB Publication, with Dr. Evans. Once I hear a response from him, I would like to get together with you on this topic.

Sincerely,
Karl
****
Karl Rickels, M.D.
Professor of Psychiatry
University of Pennsylvania
Department of Psychiatry
Mood and Anxiety Disorders Section

3535 Market Street
Suite 670
Philadelphia, PA 19104-3309

Telephone: 215-746-6417
Fax: 215-746-6551
email: krickels@mail.med.upenn.edu

Attachment R (Letter to the Office of Research Integrity – Lawyer's letter excerpt)

On June 13, 2001, Dr. Amsterdam again emailed Dr. Rickels to complain that there had been no resolution of the matter. Dr. Amsterdam wrote: "Before I contact either University officials or the editorial board of [the American Journal of Psychiatry] regarding this egregious behavior, I await your last efforts at resolution of this problem." (Attachment R)

Attachment R

To: krickels@mail.med.upenn.edu
From: "Dr. Jay D. Amsterdam" <jamsterd@mail.med.upenn.edu>
Subject: Am. J Psych paper
Cc:
Bcc:
Attached:

Dear Karl:
Months of inactivity and languishing over the issue of the upcoming SKB bipolar study, from which I have been excluded as a principal author, have produced no resolution (satisfactory or otherwise).
The article containing the data stolen from me has now appeared in print in the Am. J Psych 158: 906-912, 2001.
I suppose that the inactivity that I have seen indicates that I must now proceed at other levels regarding the "unacademic" and "un-collegial" behavior of Dr. Gyulai. Before I contact either University officials or the editorial board of Am J. Psych regarding this egregious behavior, I await your last efforts at resolution of this problem.

Jay

Attachment S (Letter to the Office of Research Integrity – Lawyer's letter excerpt)

On Jun 13,2001, Dr. Amsterdam again emailed Dr. Rickels to complain that there had been no resolution of the matter. Dr. Amsterdam wrote: "Before I contact either University officials or the editorial board of [the American Journal of Psychiatry] regarding this egregious behavior, I await your last efforts at resolution of this problem. (Attachment R)

That same day, Dr. Rickels responded that Dr. Gyulai had been ill and that Dr. Amsterdam would be contacted soon. (Attachment S.)

Attachment S

X-Sender: krickels@maiLmed.upenn.edu
X-Mailer: QUALCOMM Windows Eudora Pro Version 4.2.2
Date: Wed, 13 Jun 200116:01:59 -0400
To: "Dr. Jay D. Amsterdam" <jamsterd@maiLmed.upenn.edu>
From: "Dr. Karl Rickels" <krickels@mail.med.upenn.edu>
Subject: Re: Am. J Psych paper
Cc: "Dr. Dwight L. Evans, MO" <psych@maiLmed.upenn.edu>

Dear Jay,
Sorry I have not responded earlier. Dr. Gyulai had a serious operation and is recuperating at home. I will definitely get back to you once Dr. Gyulai is returned to work.
Regards,
Karl

At 12:04 PM 6/13/01 -0400, you wrote:

Dear Karl:
Months of inactivity and languishing over the issue of the upcoming SKB bipolar study, from which I have been excluded as a principal author, have produced no resolution (satisfactory or otherwise).
The article containing the data stolen from me has now appeared in print in the Am. J Psych 158: 906-912, 2001.
I suppose that the inactivity that I have seen indicates that I must now proceed at other levels regarding the "unacademic" and "un-collegial" behavior of Dr. Gyulai. Before I contact either University officials or the editorial board of Am J. Psych regarding this egregious behavior, I await your last efforts at resolution of this problem.
Jay

Jay D. Amsterdam, M.D.
Depression Research Unit
3600 Market Street, 8th floor
Philadelphia, PA 19104-2649

ph 215.662.3462
fax 215.662.6443
email: jamsterd@mail.med.upenn.edu

****

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Philadelphia, PA 19104-3309

Telephone: 215-746-6417
Fax: 215-746-6551
email: krickels@mail.med.upenn.edu

Attachment T (Letter to the Office of Research Integrity – Lawyer's letter excerpt)

On June 29, 2001, Dr. Amsterdam received a formal letter from Dr. Rickels stating that Dr. Gyulai had returned part-time from sick leave and he intended to speak with Dr. Gyulai concerning "this unfortunate situation ... today." (Attachment T.)

Attachment T

UNIVERSITY OF PENNSYLVANIA

MEDICAL CENTER

Karl Rickels, M.D.
Stuart and Emily B. H. Mudd Professor

University of Pennsylvania School of Medicine Hospital of the University of Pennsylvania

Chief, Mood and Anxiety Disorders Section Department of Psychiatry

June 29, 2001

Jay D. Amsterdam, M.D.
Professor, Director,
Depression Research Unit,
Mood and Anxiety Disorders Section Department of Psychiatry University of Pennsylvania

RE:SKB PAR-29060/
352
Dear Jay,

Laszlo Gyulai has now returned part-time from his sick leave, and I want to assure you that I will discuss this unfortunate situation with him today. I am sorry that this situation has developed this far, and I can assure you that the problem is of concern to me. I hope, sincerely, that this matter can be resolved between you and Laszlo in a collegiate matter.

Best regards,

Karl Rickels, M.D.

cc: Dwight L. Evans, M.D.
Laszlo Gyulai, M.D.

KR:tch

3535 Market Street • Suite 670 • Philadelphia, PA 19104-3309 ¦ Tel: 215-746-6417 • Fax: 215-746-6551 • Email: krickels@mail.med.upenn.edu

Attachment U (Letter to the Office of Research Integrity – Lawyer's letter excerpt)

On July 5, 2001, Dr. Gyulai sent a letter of apology to Dr. Amsterdam. In that letter, Dr. Gyulai explained that control of the paper had been taken away from him and that GSK published the paper without circulating the draft to all the participants and only allowed him (Dr. Gyulai) to see a near-final draft "when only minor changes could be done." (Attachment L.)

Fourteen days later, Dr. Amsterdam sent an email to Dr. Rickels stating that the apology was not sufficient in light of the "deliberate misappropriation and publication of [his] data" without his knowledge. Dr. Amsterdam was insistent that some sort of reprimand was necessary to ensure "plagiarism" of a colleague's data never happens again. (Attachment U.)

Attachment U

e-mail sent 07/19/01

Dear Karl:

As you know, Dr. Gyulai sent me a letter on 7/05/01 regarding the SmithKline data and publication issue. I would like to inform you (as his Section Chief) that his letter is certainly NOT acceptable as an apology to me for his deliberate misappropriation and publication of my data.

This matter was certainly NOT a "misunderstanding" on my part; nor was Dr. Gyulai the "primary investigator of the Penn site..." In fact, if Dr. Gyulai would simply read the Penn IRB-approved consent form for this study, he would clearly see that Dr. Amsterdam was listed as the "Co-Principal Investigator" on this study (not to mention the highest patient enroller in the study).

Additionally, this study was NOT conducted at only one Penn site, but *was* conducted primarily from bipolar patients recruited from the *Depression Research Unit* under my direction!

Finally, I have no idea of whether Dr. Gyulai ever wrote (or did not write) several drafts of the manuscript, or whether "the paper was taken away ..." from him, because Dr. Gyulai sequestered ALL available data and drafts of ALL manuscripts and NEVER communicated any information to me (the Co-PI) regarding any of these issues.

Thus, if you (as Dr. Gyulai's Section Chief) feel that his "apology" is sufficient to assuage this degree of uncollegial and unethical culpability in this matter, and neither you nor the Chairman feel that a letter of reprimand admonishing Dr. Gyulai NEVER to plagiarize a colleague's data ever again, is appropriate, then I will certainly take this troubling matter further.

Please feel free to communicate your feelings to me regarding this issue in the *very near future* at your convenience.

Respectfully,

Jay

Attachment V (Letter to the Office of Research Integrity – Lawyer's letter excerpt)

On July 5, 2001, Dr. Gyulai sent a letter of apology to Dr. Amsterdam. In that letter, Dr. Gyulai explained that control of the paper had been taken away from him and that GSK published

the paper without circulating the draft to all the participants and only allowed him (Dr. Gyulai) to see a near-final draft "when only minor changes could be done." (Attachment L.)

Fourteen days later, Dr. Amsterdam sent an email to Dr. Rickels stating that the apology was not sufficient in light of the "deliberate misappropriation and publication of [his] data" without his knowledge. Dr. Amsterdam was insistent that some sort of reprimand was necessary to ensure "plagiarism" of a colleague's data never happens again. (Attachment U.)

The following day, July 20, 2001, Dr. Rickels sent Dr. Amsterdam a letter stating "it is unfortunate that [GSK] did not circulate the manuscript to you and I regret that Dr. Gyulai did not share it with you. Once again, as Dr. Gyulai's Program Director, I have expressed my belief that he should have done so." (Attachment V.)

Attachment V

UNIVERSITY OF PENNSYLVANIA MEDICAL CENTER

University of Pennsylvania School of Medicine Hospital of the University of Pennsylvania

Karl Rickels, M.D.
Stuart and Emily B. H. Mudd Professor
Chief, Mood and Anxiety Disorders Section Department of Psychiatry

July 20, 2001

Jay Amsterdam, M.D.
Director Depression Research Unit 3535 Market Street, Suite 3039 Philadelphia, PA 19104

Dear Jay:

I am responding to your recent e-mail regarding the SmithKline bipolar paper. I trust you know that I really want to resolve this situation. As I indicated to you before, I regret that Dr. Gyulai did not discuss the issue of authorship of the paper with you.

I do want to indicate my understanding of how the study was conducted here at Penn

. From my perspective, Dr. Gyulai was the principal investigator here at the Penn site. When it became clear that Dr. Gyulai was not recruiting at a rapid enough pace for the successful conduct of the study, I suggested that he discuss asking you to be involved with the study to increase the enrollment. From my memory, this occurred at a time when your program was in need of increased clinical trial activity and you were appropriately financially compensated for your work. I agree that you were very successful in recruiting subjects, but I do not believe Dr. Gyulai intended “deliberate misappropriation and publication’,’ of data.

Again, I regret that Dr. Gyulai did not discuss the authorship with you, and as Dr. Gyulai's Program Director, I made this very clear to him.

I also agree that it is unfortunate that Smith-Kline Beecham did not circulate the manuscript to you and I regret that Dr. Gyulai did not share it with you. Once again, as Dr. Gyulai's Program Director, I have expressed my belief that he should have done so.

I would be happy to sit and discuss this with you further, and I would be happy to involve Dr. Gyulai in this discussion with you if you'd like.

Sincerely,

Karl Rickels, M.D.
cc: Dwight L. Evans, M.D. Laszlo Gyulai, M.D.

Attachment W (Letter to the Office of Research Integrity – Lawyer's letter excerpt)

EVIDENCE OF POTENTIAL GHOSTWRITING / ALLEGED PLAGIARISM

According to documents, Sally Laden of STI ghostwrote the 2003 editorial for Biological Psychiatry for Dr. Dwight L. Evans and Dr. Dennis Charney. Dr. Charney was then an employee at the NIH Intramural Program and he is now Dean of Research at the Mt. Sinai School of Medicine in New York. (See e.g., Attachment W and http://www.pogo.org/pogo-files/letters/public-health/ph-iis-20101129.html.)

Attachment W

From:
Sally Laden < sally.laden@cox.net>
To:
eric.m.dube@gsk.com

Subject:

Proposal for 2 review articles

Date:

07/28/2003 09:40:30 (GMT-05:00)

Dear Eric:

Thank you for thinking of me for the Safety in Breast Feeding and the Tolerability of Paxil CR review articles. A proposal for both is attached. Please review and contact me with questions. As we discussed on Friday, X am not able to start work on these papers until September, but if we decide to move forward, I will reserve that month for these projects.

Two other questions:

1) Lydia Lewisfrom the DBSA asked me to be the writer for their upcoming dual diagnosis consensus meeting this November. She mentioned that Scott committed GSK to funding the writing costs for the consensus statement. Lydiais asking if GSK will be able to paying me directly rather than offering the DBSA a grant for the cost of the writing. I am having problems connecting with Scott. If you see him in the near future, would you inquire about this? I would submit the proposal directly to GSK and bill GSK directly.
(Thanks)

2) Is there a problem with my invoice for writing Dwight Evans, editorial for the DBSA, scomorbidity issue to Biological Psychiatry? I submitted it over a month ago and was wondering about the status. If the payment cycle >30 days, so be it. I was just wondering.

Thanks again Eric. I look forward to working with you again.

Sally Laden MSE Communications

898 Cahill Court Cheshire, CT06410

T 203 y271-1047 F 203 y271-1054 E sally.laden@cox.net - New business proposals.doc

Attachments: New business proposals.doc;embedded picture.bmp

Produced By GSK In In Re Paxil, C.P.Ct.PA (Pregnancy)

PAR07032165D
PAR070321650

Attachment X (Letter to the Office of Research Integrity – Lawyer's letter excerpt)

EVIDENCE OF POTENTIAL GHOSTWRITING / ALLEGED PLAGIARISM

In an email to a GSK employee, Ms. Laden wrote, "Is there a problem with my invoice for writing Dwight Evans' editorial for the [Depression and Bipolar Support Alliance], s comorbidity issue to Biological Psychiatry?" [See Attachment W] When the editorial was published, Drs. Evans and Charney "acknowledge[d] Sally K. Laden for editorial support." (Attachment X.)

Attachment X

Editorial

Mood Disorders and Medical Illness: A Major Public Health Problem

Despite efficacious and widely available antidepressants and psychotherapeutic interventions, the psychosocial and medical burden of depression is increasing. In fact, the World Health Organization projects that depression will continue to be prevalent, and by the year 2020, will remain a leading cause of disability, second only to cardiovascular disease (Michaud et al 2001). Although we do not know with certainty why rates and disability associated with depression are increasing, it is likely that this mood disorder continues to be remarkably under-recognized and under-treated. Depression frequently occurs in the context of chronic medical illness, and it is only relatively recently that the research community has turned its attention to the relationship between depression and chronic medical conditions. However, there is much work yet to be done. The recently released Institute of Medicine report (2003) acknowledged depression as one of a number of chronic conditions that requires priority action, but did not address the importance of comorbid depression and medical illness.

The relationship between depression and medical illnesses is complex. A chronically ill patient who also is clinically depressed may experience enhanced morbidity, a poorer prognosis, and even increased mortality from the medical diagnosis. Simply put, depression makes everything worse. But the association with depression goes beyond the effects of comorbidity on the course and outcome of a medical illness. A burgeoning body of evidence has now demonstrated that the relationship between depression and certain medical illnesses may indeed be bidirectional in nature. Depression may be both a cause and a consequence of some medical illnesses, such as cardiovascular disease, stroke, HIV/AIDS, cancer, and epilepsy.

In recognition of the need to increase awareness about this topic and improve the quality of life for persons with depression, the Depression and Bipolar Support Alliance, the world’s largest patient advocacy organization, convened a two-day, multidisciplinary consensus conference on November 12, 2002 in Washington, DC. Nearly 50 experts in the fields of psychiatry, cardiology, immunology, oncology, neurology, endocrinology, internal medicine, family medicine, federal health care agency policy and research, and patient advocacy participated in this process. Formal presentations centered around the perspectives and goals of the National Institutes of Health and the Food and Drug Administration, the personal and societal burden of depression and medical illness, and the epidemiology, mechanisms, diagnosis, treatment, and prognosis of depression in the context of cardiovascular disease, cancer, HIV/AIDS, stroke, neurologic diseases, diabetes, osteoporosis, obesity, and chronic pain. Workgroups met to discuss specific issues related to these topics and on the second day, workgroup leaders presented their findings and facilitated open discussions from the group.

Burden of Mood Disorders and Medical Illness

The functional impairment associated with depression contributes significantly to the economic burden of chronic medical illness. Depression also is becoming recognized as a cause of increased morbidity and mortality in chronic medical illness. As reviewed by Katon (2003), medical costs for patients with major depression are approximately 50% higher than the costs of chronic medical illness alone. In addition, Katon (2003) underscores the equally important, but often less appreciated, effects of depression on adverse health behaviors, such as smoking, unhealthy diet, sedentary lifestyle, and poor adherence to medical regimens (e.g., cardiac rehabilitation). The findings from a number of studies have established that major depression is associated with significant functional impairment, lost work productivity, occupational disability, and increased health care resource utilization, and that effective treatment restores functioning. Simon (2003) reviews these data in the context of evidence from recent cross-sectional, longitudinal, and treatment studies of depressed patients with and without arthritis, chronic obstructive pulmonary disease, diabetes, or heart disease. This emerging body of evidence demonstrates that depression significantly increases the burden of functional impairment in medical illness, and that treatment reduces disability and health service costs. The effect of other mood disorders, such as dysthymia or bipolar disorder, on the burden of chronic medical illness is remarkably understudied.

Cardiovascular Disease

It is now recognized that major depression and bipolar disorder are associated with increased rates of death from coronary heart disease (CHD), and that major depression or depressive symptoms increase the risk of incident CHD (Musselman et al 1998). As reviewed by Rudisch and Nemeroff (2003), as many as 27% of patients with CHD have major depression, but a substantially larger number of cardiac patients have subsyndromal depressive symptoms. Depression is a particularly lethal development for patients with acute myocardial infarction (MI). In the United States, there are approximately 150,000 deaths in the first year after an initial MI, and Carney and Freedland (2003) estimate that at least 90,000 of these deaths may be related to post-MI depression. The cumulative body of evidence in support of an association between depression and cardiovascular disease is large and impressive; Carney and Freedland (2003) evaluate this literature and outline future directions for research, including studies that will better elucidate the role of depression in the development and progression of atherosclerosis, ischemia, and arrhythmias.

One particularly diverse and robust field of research is dedicated to better understanding the mechanisms that underlie the relationship between depression and cardiovascular disease. In their paper, Joynt and colleagues (2003) overview seven probable mechanisms associated with depression that may be related to cardiovascular disease: noncompliance with cardiac rehabilitation and medical regimens; risk factor clustering (e.g., smoking, hypertension, diabetes, hypercholesterolemia, obesity); hypothalamic-pituitary-adrenal (HPA) axis hyperactivity and cortisol elevation; decreased heart rate variability; elevated plasma levels of pro-inflammatory cytokines leading to atherosclerosis; platelet activation and hypercoagulability; and psychological stress.

The demonstrated adverse effect of depression on the risk of new and progression of established CHD has spurred the next emergent area of clinical study in this field: the consequences of depression treatment on cardiovascular morbidity and survival. As noted in the

paper by Roose (2003), findings from the few open-label or randomized, controlled clinical trials suggest that the selective serotonin reuptake inhibitors (SSRIs), bupropion, and certain psychotherapeutic interventions are safe and effective treatment of depression in patients with CHD. The tricyclic antidepressants (TCAs) increase heart rate, cause orthostatic hypotension and conduction delays, have been shown to increase the risk of cardiac mortality, and should be avoided in this patient population. There is one published placebo-controlled trial, which suggests that SSRI treatment of depressed post-MI patients may improve outcome and increase survival, but this study was not adequately powered to find significant changes in these cardiac disease outcomes. Thus, it is still not known whether treatment of depression enhances the outcome of the cardiac disease. Further study is clearly needed.

Cancer

As with cardiovascular disease, there is a large and growing body of evidence in support of a relationship between depression and cancer. Research efforts have focused on depression as a risk factor for cancer, depression as a consequence of cancer, and the dynamics of comorbid depression and cancer. Large population studies suggest that depressed mood or stressful life events may increase the risk of cancer. Although it is acknowledged that these observations of increased risk may be due in part to earlier, undetected malignancies or factors other than depression (Lillberg et al 2003; Penninx et al 1998), these findings are compelling and further study is warranted.

Depression also is a common occurrence in patients with a wide range of different malignancies and often prevents patients from complying with treatment regimens and other health-promoting behaviors, thus worsening the prognosis. A diagnosis of cancer represents a significant life stressor, which in vulnerable persons can precipitate an episode of depression. In addition, patients with cancer may develop “sickness behavior” or depressive syndromes due to proinflammatory cytokine activation that is the result of tumor cell burden, tissue destruction, radiation treatments, and chemotherapy. The papers by Raison and Miller (2003) and Spiegel and Giese-Davis (2003) review the relationships between depression and cancer and offer insight into disease progression and treatment. Of immediate clinical utility are the findings of studies showing that pretreatment with serotonergic antidepressants can prevent neurotoxicity and clinical depression in patients treated with interferon-alpha.

HIV/AIDS

Mood disorders, including depression and mania, are prevalent in persons with human immunodeficiency virus (HIV) disease and may be associated with impaired quality of life, neurocognitive and functional impairment, and poor adherence to antiretroviral therapy. In addition, emerging data suggest that depression is associated with declining CD4 cell counts, accelerated disease progression, and increased mortality. In their paper, Cruess and colleagues (2003) discuss the negative impact of mood disorders on HIV/AIDS and review evidence for safety and efficacy of antidepressants, mood stabilizers, and novel pharmacotherapies in this population (Evans et al 2002a). Leserman (2003) also reviews this topic, but with a focus on the biological mechanisms underlying the relationship between mood disorders and HIV disease and the immune effects that result from this comorbidity (Leserman et al 1997; Evans et al 2002b). Patients with HIV/AIDS and comorbid depression are a significantly underserved and understudied population. Further epidemiologic, biological, and therapeutic studies are urgently needed to better understand the nature of this comorbidity, increase case-finding, and develop

effective treatment strategies.

Neurologic Disease

This special issue also includes papers devoted to the topics of depression and comorbid neurologic disorders, such as stroke, Parkinson's disease, Alzheimer's disease, and epilepsy. Of these neurologic disorders, the relationship between mood disorders and cerebrovascular accidents is particularly well-studied. As reviewed by Robinson (2003), depression is common in poststroke patients, with reported prevalence rates of approximately 20%; bipolar disorder is less common. There is no standardized diagnostic approach for poststroke depression, and the controversies surrounding various approaches are summarized by Robinson (2003). The findings of treatment studies showing efficacy of antidepressants, electroconvulsive therapy, psychostimulants, and cognitive behavioral therapy in patients with poststroke depression are of considerable clinical importance. Importantly, treatment of depression improves measures of function and cognition and may result in improved survival. Evidence that antidepressants may prevent poststroke depression offers hope. As with many other medical comorbidities, depression may increase the risk of stroke, and the findings of two large epidemiologic studies support the role of depression as a risk factor for stroke. These findings further underscore the importance of identifying the underlying biological mechanisms associated with depression comorbidity.

Depression occurs in roughly half of patients with Parkinson's disease and is associated with significant impairment, including reduction in fine motor skills and cognitive function. In their paper, McDonald and colleagues (2003) review the distinct presentation of depression in this population, discuss the challenges associated with diagnosis, and highlight the need for more sensitive screening and diagnostic tools.

Depression in this population may not be due simply to the disability and added life stressors associated with Parkinson's disease. Rather, emerging evidence suggests that depression in these patients may be a consequence of neurodegeneration. Treatment of depression in Parkinson's disease is complicated by variable responses, sensitivity to adverse effects, and drag interactions. Randomized, placebo-controlled trials, particularly of the SSRls and dopamine agents, are needed. The findings of functional neuroimaging studies are presented, which may eventually lead to the improved understanding of the neurocircuitry of depression in Parkinson's disease.

Even though depression occurs in as many as 50% of patients with Alzheimer's disease, contributing to accelerated functional and cognitive decline, impaired quality of life, care-giver depression, and earlier institutionalization, surprisingly little evidence-based data are available to inform diagnosis and treatment. The diagnosis of depression in this cohort is particularly challenging because symptoms, such as psychomotor retardation, insomnia, and emotional liability, which occur in nondepressed patients with Alzheimer's disease may be difficult to differentiate from a true depressive episode. Moreover, symptoms of dementia may mask an underlying depressive disorder. In an effort to guide research and better inform clinical care, the National Institute of Mental Health has undertaken the task of developing diagnostic criteria for depression in Alzheimer's disease. Lee and Lyketsos (2003) review these developments and describe an ongoing longitudinal study of depression and other neuropsychiatric comorbidities in new cases of Alzheimer's disease, which will provide valuable information on the epidemiology, natural course, and diagnosis of depression in this population.

Epilepsy is another neurologic disorder that often is complicated by comorbid depression. As many as 50% of epileptic patients seen in tertiary treatment centers may have depression, and

suicidality among depressed epileptics have been reported to be as high as 10 times the rate than in the general population. Kanner (2003) reviews the challenges related to diagnosing depression in epilepsy: patients often present with atypical depressive symptoms (e.g., anxiety, irritability, hypomania, pain); the peri-ictal period often is associated with a recurrent and short-lived dysphoria that is clinically significant but does not conform to standard diagnostic criteria; and antiepileptic drugs and surgical intervention can be iatrogenic causes of depression. Clearly, epilepsy is a risk factor for depression; however, recent evidence suggests that depression may increase the risk for epilepsy by 4- to 6-fold. Further studies are needed to better characterize this complex relationship.

Call for Action

The contributions made by this conference and the papers published in this special issue of *Biological Psychiatiy* should not simply be measured by the quality and quantity of the data, which are impressive. Rather, the strength of this publication also lies in the fact that the views of experts from widely divergent fields of clinical and scientific endeavor resonate along 4 basic themes: 1) Depression is very common in chronic medical illness; 2) Comorbidity with depression inevitably hinders recovery and worsens prognosis; 3) Medical illness is a risk factor for depression because of psychosocial stressors, functional impairment, and other biological mechanisms (e.g., Parkinson's disease); and 4) Depression may figure prominently as an etiologic factor in the onset and course of medical illness, particularly cardiovascular disease, stroke, HIV/AIDS, cancer, and epilepsy. The latter observation is truly remarkable. Much more research is needed to better understand this bidirectional relationship and identify possible common pathogenic, mechanistic pathways that link depression and serious medical illness.

These are powerful messages that must not be ignored. The weight of evidence is so persuasive that there should never again be a valid reason for not aggressively seeking out and treating depression in medically ill patients. Increasing awareness, reducing stigma, and maintaining a high level of vigilance for depression in medically ill patients must become a priority for clinicians. In addition, the efforts of the research communities must continue to better elucidate the prevalence, risk profile, diagnostic criteria, treatment, and biological underpinnings of the comorbid relationship between depression and medical illness. Only by furthering research efforts and aggressively diagnosing and treating depression, will we be able to achieve substantive gains in health care and in our patients' quality of life.

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