interest and commitments to professional integrity. (Miller Deposition, pp. 90-94, 368, 480-481.)

Dr. Miller advised J&J about locating its new drug, Consta, in the TMAP algorithm, again in disregard of conflict of interest standards with regard to his other responsibilities to TMAP and to his professional obligations. (Miller Exhibit, 656) He attended a J&J advisory board meeting at a luxury hotel (Turtle Creek), and then asked J&J employees "where in the algorithm we [J&J] thought that Consta should be positioned." (Stanislav Exhibit, 599) The record is filled with evidence demonstrating how often Miller discussed the placement of Consta in the TMAP algorithm. (Miller Exhibit, 658) Apparently, he wanted it placed high; one J&J employee told another that Miller wanted it to be an "early choice," not just "another first choice." (Leech Exhibit, 832) In this way, J&J inserted itself into the TMAP algorithm development process, aided and abetted by Miller, as well as by Crismon. The company viewed both Miller and Crismon as "primary drivers." (Miller Exhibit, 656)

Miller, along with Shon and Crismon, gave J&J advice frequently not only on Consta but also on other issues as well. "During the last few months," wrote one J&J employee, "Steve Shon, Miller and Crismon have spent a considerable amount of field time with most of the PHS&R Managers. These 'state visits' have been in the form of influencing, implementing, monitoring, and managing TMAP or TMAP-like initiatives. Shon and Miller are also on the CME Public Sector series faculty (2000, 2001, and 2002 series)- specific to TMAP initiatives." (Roman Exhibit, 145) For a member of TMAP to be so involved with the major drug company affected by TMAP presents glaring violations of conflict of interest principles and professional medical standards.

7) Is the ghostwriting of scientific research articles appropriate, and if not, why not?

Scientific integrity requires that research papers present the most objective, accurate, and thorough report of all the evidence. Research design and findings must fully reflect the data gathered and the results analyzed. In the first instance, this standard requires that authors be responsible for the veracity of the material presented. If they have not participated in gathering and analyzing the material, if they allow their

names to be added to a paper in which they have had no or only minor involvement, they cannot fulfill this professional obligation. Indeed, they are committing deceit, giving journal editors, reviewers, and readers the erroneous impression that they vouch for the presentation of the data. At the same time, articles that omit the names and affiliations of those who have performed research, analysis, and writing are also misrepresentations. Editors, reviewers, and readers must be informed about who actually carried out the activities. In order to evaluate findings, they must know whether the authors were independent researchers or employees of a pharmaceutical company or consulting firm. If either of these two scientific and professional standards are violated, if there are sins of commission (adding names), or omission (not including names), then gross misconduct, what is labeled ghostwriting, has occurred. (See "Uniform Requirements of the ICJMA," NEJM January 23, 1997)

8) Did defendants engage in ghostwriting of scientific research articles?

Yes. These principles notwithstanding, J&J frequently assigned authors to articles that they had not researched or written or used authors whose participation was not acknowledged. J&J frequently hired medical communication companies to carry out research and writing; J&J employees (some of whom might eventually be listed as authors) reviewed the work. J&J or the communications company would "invite" one or more "external authors" or "guest authors" to lend their names to the publication. None of this process would be reported in the submitted or published article. Journal editors, reviewers, and readers had no way of knowing what role the company played in its production. The result of all these practices was to make ghostwriting systemic, subverting the scientific integrity of data.

It should also be noted that in J&J-supported research that involved ghost writing, the message of the article was consistently favorable to the J&J product. Ghostwriting helped market J&J products at the cost of violating scientific and professional standards.

J&J adopted a series of specific practices that violated scientific and professional standards. As I will document below, J&J stipulated that J&J employees should not be listed as first authors in an article. Second, J&J

wanted its marketing divisions to be extensively involved in setting out the research agenda and defining desired outcomes. J&J employees articulated this position. As an internal reviewer of a draft manuscript (Ris-USA-121 Inpatient) on Risperdal wrote his J&J key contact: "I think it [the manuscript] misses the mark a little bit. Although we like to think we develop these manuscripts for scientific purposes, the real value is when a sales rep can reference them, show them, present them, etc." He continued: "The data is something you cannot change, but I do think the commentary can be framed to help a rep argue that R/C should be started on the inpatient unit prior to discharge. I know this is not a review paper, but it is a subanalysis that allows us a little more flexibility to shape it as we like." (J-TX2247482-3)

Third, regardless of the actual work performed by the authors, it was J&J or a contracted medical communications firm, like Excerpta Medica (EM), who determined whether or not to "invite" "external authors." Decisions were often made after the manuscript had been drafted, reviewed internally, and revised. External authors were usually the first authors listed for the study. To enhance the reputation of the study and strengthen its marketing impact, J&J often made those it considered KOLs the first authors.

J&J organized and funded two types of research on efficacy and side effects of Risperdal. The first was an investigator-initiated research program. Researchers would propose a study which J&J would then fund or not fund. (As we have seen, researchers would suggest research outcomes that would please J&J.) The second was a J&J-initiated research program, conducted in-house by J&J employees, or in some cases, outsourced to a commercial research organization. To assist in writing and arranging for the publication of the results of its sponsored research, J&J hired medical communications companies. These organizations were given the task of managing a large number of the in-houses research projects. They reported to J&J on a regular basis so that the company's employees could track the writing and placement of the publications. These reports are very valuable in analyzing the record of J&J in ghostwriting, particularly the reports of EM, a Reed Elsevier Company that was frequently hired by J&J.

Two EM reports, "Risperidone Publication Program Status Reports," July 2003 and December 2003, demonstrate the pervasiveness of ghost writing. (J-TXCID127174 July 2003) Of the 80 articles listed in the July 2003 schedule, 16, or 20 percent, note "author TBD," or "author to be

confirmed." Of the 65 articles that EM was developing in December 2003, 14 or 22 percent had "Author TBD" or author "to be confirmed." These two EM reports, distributed to over 50 J&J employees in the United States, Europe, and Canada, reveal just how carefully EM and J&J managed the writing and presentation of articles, posters, and abstracts. J&J had to sign off before EM could begin writing or revising an article; before EM could invite external authors; or before EM could make submissions to medical journals. (J-TXCID rev 2127275 July 03 and Mahmoud Exhibit, 683).

Reports of meetings between EM and J&J reveal that employees of the two companies discussed how and when to use external authors in sponsored research. In a Minutes Update: August 11, 1999, EM noted: "Janssen authors cannot be 1st or 2nd. Immediate needs [for authors]: RIS 112, RIS 79, RIS 102." Precisely why this decision was made is not clear, but it appears to be a marketing decision to give the papers greater currency by obscuring the precise role of J&J. An article with a J&J employee as first author would have less marketing power than one in which the author was a KOL. In another section of the minutes labeled "Immediate needs: RIS-112, RIS-79, and RIS-102." EM queried J&J: "There appears to be a question whether J&J needs to also have external authors for its outcome studies: "Same policy for outcomes?" (J-TXCID1222079)

The frequent use of KOLs as assigned first authors of sponsored studies can be found in documents produced by J&J. For example, in September 2002, J&J staff listed as a priority for developing its Child and Adolescent segment, "to visit with select KOLs." Four of the ten KOLs on that list Lawrence Scahill, Robert Findling, Michael Aman, and Peter Jensen are first authors of studies that will be discussed below. (Lin Exhibit, 1074)

EM's July and December 2003 reports provide further documentation on the marginality of the external author. Even when the external author is selected early in the drafting of the article, he/she has only a limited role. The external author is kept informed, but it is EM that writes the article and the J&J team that reviews it. In the July 2003 report page 35, the proposed article and the possibility of Scahill becoming the external author is mentioned: "Use of atypical antipsychotics in managing severe behavioral problems in autistic children," (L. Scahill, to be confirmed)" EM notes that it had completed the outline for the article on February 12, 2003. EM then sent the outline to J&J on May 5, 2003. On June 13, 2003, EM followed up on the inquiries made by the J&J reviewers. Scahill had no part in these crucial

activities. (TXCIDrev2127213) The EM December 2003 report noted that in July 7, 2002, J&J employees Joseph Lin and Gahan Pandina approved the suggested author—Scahill. On August 11, 2003, EM sent the outline to Scahill, who had agreed to be the author a week before. EM reported that he responded positively to the outline. EM then began to draft the article. When EM completed the first draft, it updated Scahill on the status of the article. On September 23, 2003, EM sent the draft to J&J for review. EM then revised the article and on November 24, 2003, it again sent the article to J&J to review again. The author was not part of the process, although his name was to be attached to the article. (J-TXCIDrev1511827) The selection of Scahill may reflect his ongoing relationship with J&J. He was a J&J KOL, a member of its CNS Child and Adolescent Advisory Board during the years 2002-2003. For his participation J&J paid him honorarium and expenses in excess of $31,171. 46. (Hunt Exhibit, 1628)

EM also developed manuscripts for Supplements to medical journals. EM paid for the Supplement and then passed the cost along to J&J. In the case of the American College of Clinical Pharmacy, it turned transcripts into articles, writing the introduction and discussion sections of the Supplement, and "trafficking the supplement." This process is enumerated in EM's invoice to J&J of January 13, 1998. EM billed J&J $26,000 for preparing a supplement for the American College of Clinical Pharmacy—"The Changing Applications of Newer Antipsychotic Drugs"/O'Connor. The supplement contained three articles. EM charged $8000 for preparing each article and $2000 for Intro/Discussion. The invoice included pass-through costs of $1,700— $500 honoraria for each of the three authors (Litrell, O'Connor, Tugrul) and $200 for permissions. In the case of Supplements, authors not only received academic credit but honoraria that EM paid on behalf of J&J. (J-TX2214886)

The posters that J&J presented at medical conferences also undermined scientific integrity. After J&J decided that a poster at a conference would be useful, it selected a presenter. If the data might have a negative impact on marketing, for example, a study showing evidence of high EPS side effects, then the poster was omitted. As a company employee noted to J&J staff after reviewing abstracts for an APA meeting: I "singled out the ones that appeared to me to be 1) potentially interesting to targeted media types; 2) important to the brand; and 3) doable from a regulatory point of view." Of one proposed abstract on the Impact of Weight Gain, she remarked: "Down side: Only J&J authors." On another: "My bias now is

not to publicize it, due to the study country [India] and the high EPS rate." On still another: "No recognized external author." (J-TXCID 1049756-7)

The posters demonstrate in yet other ways how J&J exercised undue influence over scientific research. External authors had to ask J&J's permission to present a poster based on J&J-sponsored research. When J&J was pleased with the presentation, it was prepared to fund the cost of travel. Thus, Steven Saklad (University of Texas, pharmacology faculty) wanted to present a poster at the APA meeting (October 1999) based on work funded by J&J; accordingly, he informed a J&J employee (Mahmoud), of his intention. Mahmoud reported to J&J: "We would be happiest, when possible (and I think Steve agreed) if we have the opportunity to see drafts before they are final and provide our comments to Steve." Another J&J employee (Leech) told Mahmoud: "Steve has agreed to let Excerpta submit the abstracts and format the poster. This gives us better control over the content of the poster.....I am sure Steve would be willing to change the slant of the presentation to meet the needs of his audiences. He is ready to share the data—have poster-will travel. Where do you want the data presented? ACCP ASHP? ACNP? He is willing and wants to do them all." (Mahmoud Ex. 685)

In this same spirit, Leech informed colleagues: "I have attached an abstract that was presented at NCDEU on work funded by Janssen. The data shows that Risperdal patients have a shorter length of stay in the State Hospital, long remission and lower cost. Steve Saklad is interested in presenting at ASHP (Dec 99) ACNP (Dec 99) and is being submitted for the psych Services Meeting in Oct 99 by Excerpta. What help can we give him?" (Mahmoud Exhibit, 685)

The section that follows provides many examples of J&J's ghostwriting practices. In all these examples, J&J worked closely with a medical communication firm, most often EM. J&J routinely hired EM and other such firms to provide assistance with writing and drafting articles for publication in medical journals. As J&J's Gahan Pandina declared in his deposition: "An author was "a scientific contributor, someone that participated in the generation, summarization and interpretation of the data." (Pandina Deposition, 198) By contrast, a medical writer was "a technical person who puts together the information and results per the guidelines and per the instructions of the authors." However, as we shall see, medical writers hired by J&J composed the first and additional drafts of a paper even

before authors were identified. Moreover, although the writers were performing as authors, J&J did not have their contributions acknowledged in published articles. Neither editors nor readers could know of their role in the preparation of the publication.

J&J also exerted very close oversight of forthcoming publications. Teams of J&J employees were assigned to review each manuscript during its drafting, before it was submitted for publication, and during the revise and resubmit process prior to final acceptance for publication. Having a team of reviewers read the manuscript and make substantive changes was company practice. (Pandina Deposition, 522) "Manuscripts that are based on company data would be reviewed by the compound development team. We have clinical reports that we write that are consistent and it is important for us to have the clinical conclusions from those clinical research reports correspond to our company interpretation of the data and the overall expert interpretation of that the data....be consistent with the primary data." Nevertheless, J&J did not disclose its employees' roles in the preparation of the manuscript either to the editors or to the readers of the journal. By not acknowledging that its employees' revisions and having it appear that the principal author had made the changes, J&J violated the principle that requires full disclosure about the funders' role in writing or editing of a manuscript.

1. RIS-USA-64

Madhusoodanan S, Brecher M, Brenner M, Kasckow J, Kunik M, Negron AE, Pomara N, "Risperidone in the Treatment of Elderly Patients with Psychotic Disorders," American Journal of Geriatric Psychiatry 1999; 7: 132-138.

Message: "Risperidone was well tolerated and efficacious in elderly patients with schizophrenia or schizoaffective disorders." (Abstract: 132)

"In conclusion, risperidone was a safe, well-tolerated, and effective antipsychotic in elderly patients with schizophrenia and schizoaffective disorders." (Conclusion, 137)

The EM billing to J&J for its work on this article reveals just how extensive the involvement of the medical communications company was in developing articles and how marginal the external author was. EM typically

billed J&J separately for each manuscript that it developed and the invoice set out in detail the various tasks that EM had performed to prepare the manuscripts for publication. On January 13, 1998, EM sent J&J an invoice for $15,000 for Manuscript Development on RIS-USA-64—"Risperidone in Elderly Patients with Psychotic Disorders/Madhusoodanan." [Madhusoodanan was a physician at St. John's Episcopal Hospital in New York.] EM enumerated its services: preparing 5 drafts and a final manuscript; coordinating all Janssen/Author reviews; securing all relevant information from a target journal; preparing the submission package (including redrawn figures); obtaining permissions for author(s); and managing the project through submission to the target journal. EM also billed for its consultation with the "designated author," Madhusoodanan. (J-TX2214881)

In a related document entitled "Primary Reports," EM discussed more about RIS-USA-64. It listed the authors as Madhusoodanan et al. It listed EM as the writer and set as the primary audience for the article, psychiatrists. EM noted (4/29/98) when the article was accepted for publication. It also noted that it had arranged for poster presentations of the findings of RIS-USA-64 at six professional meetings, including the American Psychiatric Association (APA), and the International Psychogeriatric Association (IPA). (J-TX2524103)

RIS-USA-64 appeared in the American Journal of Geriatric Psychiatry (Spring 1999, 7, 2: 132-138). Madhusoodanan was the first author. The second author was a J&J employee, Martin Brecher. **There is no disclosure in the article of the role of EM. No mention is made of the fact that it prepared five drafts as well as the final manuscript. Beyond noting that Brecher was a J&J employee, the article gave no indication of J&J's role as funder or organizer. There is no indication that Madhusoodanan was a "designated author," not actual author. Journal editors, reviewers, and readers would have incorrectly believed that the work was done by Madhusoodanan.** So too, there is no indication that the third author, Ronald Brenner, was a member of J&J's Certified Speakers Bureau Program. (Hunt Exhibit, 1628) Thus, it is not surprising that the article's conclusion reiterates a message J&J was eager to promulgate: Risperidone was "a safe, well-tolerated, and effective antipsychotic in elderly patients with schizophrenia and schizoaffective disorders." By using medical communications companies to draft articles based on J&J-sponsored research, and having J&J employees help develop the messages that were

presented to the public sector, J&J was undermining scientific integrity to promote marketing.

A second EM invoice was sent to J&J on February 13, 1998. It made clear that not only were there academic rewards for guest authors (publishing enhanced their reputations), but they also received such tangible benefits as expense-paid trips and honoraria to academic meetings and international conferences; these expenses and honoraria were paid for by EM on behalf of J&J. Noted on the EM invoice were "Pass-Through Costs" of $4,331.92 for Madhusoodanan for presenting a poster related to RIS-USA-64 at the IPA meeting in Jerusalem. Madhusoodanan also received a $1000 honorarium for the presentation. In addition, J&J, through EM, reimbursed Madhusoodanan $784.77 for his hotel, $1751.15 for his airfare, $590.00 for conference registration, and $200 for food, tips, and ground transportation. (J-TX2214878)

2. RIS-USA-251

Mittal D, Jimerson NA, Neely EP, Johnson WD, Kennedy RE, Torres RA, Nasrallah HA, "Risperidone in the Treatment of Delirium: Results from a Prospective Open-Label Trial," Journal of Clinical Psychiatry 2004; 65: 662-667.

Message:

"Low-dose risperidone can improve cognitive and behavioral symptoms of delirium in medically ill patients." (Abstract, 662)

"In conclusion, results of this open-label study indicate that risperidone is an effective and safe alternative to conventional antipsychotics and in the treatment of delirium." (Conclusion, 666)

The EM Report of July 2003, referring to RIS-USA-251, "Treatment of delirium with Risperidone," noted on October 23, 2002: "need Janssen approval to begin." It added: "Received approval from Janssen reviewers (4/18/03), and only then "completed and sent revisions to...[authors]" (J-TXCIDrev2127179) It was EM and J&J who were primarily responsible for drafting the findings and analysis, with the ostensible authors coming in at the end of the process.

The last author on RIS-USA-251 is Henry Nasrallah, a J&J KOL. Nasrallah participated in regional meetings, CNS Summits, and was a member of J&J's Speaker Bureau Program. From 2000 to 2004, Nasrallah received $73,000 from J&J for participating in these activities. (Hunt Exhibit, 1628)

3. RIS-USA-209

Muslant BH, Gharabawi GM, Bossie CA, Mao L, Martinez RA, Tune LE, Greenspan AJ, Bastean JN, Pollock BG, "Correlates of Anticholinergic Activity in Patients with Dementia and Psychosis Treated with Risperidone or Olanzapine," Journal of Clinical Psychiatry 2004; 65: 1708-1714.

Message: "Efficacious doses of olanzapine increased Anticholinergic activity in older patients with dementia, while similarly efficacious doses of risperidone did not." (Abstract, 1708)

"Thus, these data indicate that one possible reason for the lack of efficacy of olanzapine at higher doses in dementia may be its potential for increased Anticholinergic activity. This possibility should be considered in other populations such as older patients with schizophrenia, as higher doses of olanzapine are being investigated as possible treatments for schizophrenia." (Conclusion, 1713)

On page 3, July 2003 the EM report discusses RIS-USA-209 "Impact of the Anticholinergic effect of atypical antipsychotics on safety in elderly patients." It notes a possible author (Tune), and then adds, TBD. Although EM notes that they are planning to publish RIS-USA-209 in the next 6 months, it is still waiting for J&J to assign external authors. (J-TXCIDrev2127279) The article was published in December 2004.

4. RIS-INT-57

Lasser RA, Bossie CA, Zhu Y, Gharabawi G, Eerdekens M, Davidson M, "Efficacy and Safety of Long-Acting Risperidone in Elderly Patients with Schizophrenia and Schizoaffective Disorder," International Journal of Geriatric Psychiatry 2004; 19: 898-905

Message:

"Long-acting risperidone was associated with significant symptom improvements in stable elderly patients with schizophrenia or schizoaffective disorder. Treatment was well tolerated." (Abstract, 898)

"Our data suggest that the long-acting formulation of risperidone will offer a new treatment option for elderly patients, eliminating the need for daily dosing and potentially improving outcomes." (Conclusion, 904)

EM notes of RIS-INT-57: "Risperidone microspheres for treatment of psychotic disorders in elderly patients (Davidson, Lasser, Bossie, Eerdekens, Zhu, Gharabawi; external authors to be confirmed)." The roster of names is composed in advance of confirmed participation. (p.13, July 2003) As of 7/22/03, EM reports on extensive comments from J&J employees, and notes that more internal reviews are needed. Its next step is "to incorporate comments" and send to "Janssen reviewers." It also plans to "ask C. Bossie [a J&J employee] when to send to aus [authors]." (J-TXCIDrev2127189)

5. RIS-IND-2

Khanna S, Vieta E, Lyons B, Grossman F, Eerdekens M, Kramer M, "Risperidone in the Treatment of Acute Mania: Double-blind, Placebo-Controlled Study," British Journal of Psychiatry 2005; 162: 229-234.

Message:

"In patients with severe manic symptoms, risperidone produced significant improvements in YMRS scores as early as week 1 and substantial changes at end-point. Treatment was well tolerated." (Abstract, 229)

"Results confirm those of other trials involving diverse patient populations in which risperidone was found to be effective and safe in patients with acute mania." (Conclusion, 234)

External authors played a minimal role in the design and development of the RIS-IND-2 manuscript, its revision, and the choice of journal for publication, and post-publication, a letter to the editor. IND-2 was a 3 week randomized, double-blind trial conducted at eight sites in India.

("Risperidone in the Treatment of Mania or mixed Episodes of Bipolar Disorder")

The "Publication kickoff meeting" for RIS-IND-2 was held July 23, 2002, with J&J team members and two representatives from EM present. (J-TX4311837) In the first instance the report notes: "Lengthy discussion ensued around the importance of authorship from internal and external perspectives, and from clinical vs. commercial perspectives." The group recommended "potential authors" and the order of authors, and then made assignments among themselves as to who would be contacting suggested authors. Authorship determination came from the team, not from work submitted or performed by authors— indicating that ghostwriting was a key element in IND-2. (J-TX4311838)

Further substantiation of this conclusion came be found in the report note that follows the discussion of authors. "M. Kramer [of J&J] reviewed IND-002 data with the team and a list of key messages were tentatively developed." The formulation of these messages by the J&J team in advance of the selection of authors makes clear is another indication of the role of ghostwriting in this protocol.(J-TX4311838)

EM started writing IND-2 in September 2002. It sent the first draft of the article to J&J's Mood Publication Review Team for comments. Also, in September, two physicians, one Indian and one Spanish, were named as first and second author. (J-TX3086311) Shortly thereafter, a J&J product director noted that investigator meetings for IND-2 would be taking place. He commented: "I am not concerned regarding the IND-002 investigator meetings because they are all Indian physicians and will have no impact in shaping perceptions of US prescribers." (J-TX3086308)

On January 14, 2003, EM sent a second draft, responding to comments by several J&J employees. There is no mention by EM of external authors or of the two men who will become the first and second authors. Between 5-28/03 and 6/11/03, EM "formatted & edited revised ms." "7-1-03: Completing edits & formatting." The first mention of authors in this draft review is 10/7/03, "authors reviewing mss. for approval." By then, J&J had already selected the The British Journal of Psychiatry for submission. (J-TXCIDrev2127198) In the December 2003 report, IND 2 has five authors: Khanna, Vieta, Grossman, Lyons, Kramer. The two first authors are external authors. Sumant Khanna is from New Delhi and Eduard Vieta, from

Barcelona. (J-TXCIDrev1511810) The article is published in 2005 in The British Journal of Psychiatry under a different title: "Risperidone in the Treatment of Acute Mania: Double-blind, Placebo-Controlled Study." It appeared with 6 authors: Khanna, Vieta, Lyons, Grossman, Eerdekens and Kramer. The last four were J&J employees, the company that supported the study. Despite the history, Khanna is the corresponding author. There is no statement on his precise role in the study. The same is true for Vieta. Once again, the active engagement of EM in the writing process is not acknowledged. And once again, J&J published data that was favorable to Risperdal. The findings included statements that patients given Risperdal "demonstrated significantly greater improvements than those given placebo on each of the efficacy measures." (at p. 233) More, Risperdal "was generally well tolerated, as evidenced by the low incidence of other adverse events and the high completion rate." (at p. 233)

Finally, the role of the authors was so minimal that on March 24, 2006, EM billed J&J $5100 for composing a "Reply letter to the editor for RIS-IND-2." (EXCERPTA0005369) The EM tasks, as it reported it, included: "Development of a letter to the editor- includes research, phone calls, literature search, first draft (average 3 pages, sent to client and author for review). Reference articles, second draft (includes comments from client review and from each author sent to client and author for final review). final (sic) draft (includes finalizing from client review and from each author), copy editing, styling for journal, proofreading, and submission package. (EXCERPTA0005370)

6. RIS-USA-250

Ganguli R, Brar JS, Mahmoud R, Berry SA, Pandina GJ, "Assessment of Strategies for Switching Patients from Olanzapine to Risperidone: A Randomized, Open-Label, Rater-Blinded Study," BMC Medicine 2008: 6: 17.

Message:

"Switching via any strategy was associated with significant improvements in positive and anxiety symptoms and was generally well tolerated."

"Our study confirms that stable outpatients with schizophrenia or schizoaffective disorder who require an alternative treatment can be safely switched from olanzapine to risperidone and experience improvements in symptom control. Our results also suggest that the rapid initiation of the new medication and the very gradual withdrawal of the old medication may be more successful than more rapid withdrawal strategies."

Another example of how marginal a designated author was to a published article comes from RIS-USA-250. (J-TXCID1216826) To increase its sales, J&J decided to design a clinical trial whose outcome would persuade its "strategic customers" to switch patients from Olanzapine to Risperdal. The trial designed to implement this strategy was known as the Risperidone Rescue Study. Sally Berry was the Medical Director and Gahan Pandina the clinical Director, and Courtney Lonchena the project manager; all were J&J employees. The protocol was agreed upon in 2000. In November 2001, while the trial was underway, J&J's Updated Monthly Report stated that the goal of the trial was "Product Differentiation:" So as to "Maximize cost and reimbursement opportunities, the trial should demonstrate correction of olanzapine-induced glucose dysregulation by Risperdal and will provide data to advise our strategic customers on how to switch patients from Zyprexa to Risperdal." As J&J was aware, "Competitors have published switching data." J&J's "Outcome Statement" stipulated: "Submission of one or more abstracts to one or more major psychiatry meetings on effective strategies by which patients with schizophrenia can be converted from olanzapine to risperidone treatments by January 2002 for a study cost of no more than $2.8 M."

Rohan Ganguli, a J&J KOL, was the designated "external author," and he was sent materials for review. In 2002, he was asked by J&J to become first author on an abstract to be presented to a professional medical meeting and he agreed. (EXCERPTA 0031719 and....725) Ganguli only saw the manuscript after it was vetted, reviewed, and commented upon by the J&J team. (JTXCIDrev2127221, for details on manuscript review) In this case, the eventual publication did disclose some of the process. Acknowledgments included the fact that J&J "had a role in writing and decision to submit." Still, readers would not know just how extensive the J&J role actually was and the market-based reasons why the project was undertaken in the first place. (Ganguli et al., "Assessment of Strategies for switching patients...." BMC Medicine, 2008.) Again, it should come as no

surprise that the article's conclusion in 2008 faithfully mirrored the original aim: "Patients…who require an alternative treatment can be safely switched from olanzapine to risperidone and experience improvements in symptom control."

7. RIS-CAN-23

Shea S, Turgay A, Carroll A, Schulz M, Orlik H, Smith I, Dunbar F, "Risperidone in the Treatment of Disruptive Behavioral Symptoms in Children with Autistic and other Pervasive Developmental Disorders," Pediatrics 2004; 114: e634-e641.

Message:

"Risperidone was well tolerated and efficacious in treating behavioral symptoms associated with PDD in children." (e634)

"The encouraging efficacy outcomes achieved with this agent offer new hope for the management of behavioral symptoms exhibited by children with PDD." (e640)

The politics of author assignment is illuminated by the report of a Risperdal Data Rollout meeting held on April 21, 2004 by Johnson & Johnson. One item agenda was a discussion of RIS-Can-23-Subanalysis April 21, 2004 (J-TXCID1174074-5). The meeting notes declare: "Responsibilities were discussed and it was agreed that Gahan Pandina [of the company] would take primary responsibility for all the sub-analyses and publication." Although Pandina was in the US office and was responsible for data management and publication, authorship was to rest elsewhere. "JOI requested that whenever possible we include at least one of the Canadian investigators on subsequent publications. It was also noted that a European KOL…be included on a targeted publications (sic)." In keeping with this decision: "The list of Canadian investigators was reviewed." The RIS-CAN-23 Subanalysis was published in Pediatrics 2004 under the title: "Risperidone in the Treatment of Disruptive Behavioral Symptoms in Children with Autistic and Other Pervasive Developmental Disorders." The authors were those suggested at the April 24, 2004 meeting and a J&J Canada employee was the last author. In this case, there was no conflict of interest statement or a description of authors' contributions. The article

acknowledges J&J support but gives no information about J&J's role in the process and author selection, a failure which constitutes improper conduct.

8. RIS-USA-79

Csernansky JG, Mahmoud R, Brenner R, "A Comparison of Risperidone and Haloperidol for the Prevention of Relapse in Patients with Schizophrenia," New England Journal of Medicine 2002; 346: 16-22

Message:

"Adult outpatients with clinically stable schizophrenia and schizoaffective disorder have a lower risk of relapse if they are treated with risperidone than if they are treated with haloperidol" (Abstract, 16)

"Our results demonstrate that substantial reductions in the risk of relapse can be achieved in such patients with the use of risperidone, even in comparison with the use of an effective conventional antipsychotic." (Conclusion, 21)

J&J wanted an article that endorsed Risperdal published in the most prestigious medical journal, The New England Journal of Medicine (NEJM), believing it would benefit its sales. (J-TX2168744) On January 3, 2002 an article appeared in the NEJM authored by John G. Csernansky, Ramy Mahmoud, a J&J employee and Ronald Brenner: "A Comparison of Risperidone and Haloperidol…." The message was consistent with J&J's marketing message. "Adult outpatients with clinically stable schizophrenia or schizoaffective disorder have a lower risk of relapse if they are treated with risperidone than if they are treated with haloperidol." The article contains no information on authors' responsibilities and manuscript development; there is a conflict of interest statement that acknowledges J&J financial support and sources of industry support for Csernansky and Brenner. When an NEJM editor asked prior to publication about methods, it was J&J who supplied the content for the reply to the queries. More, the NEJM was told: "Drs. Csernansky and Brenner were never members of the clinical research team in charge of the study." (J-TX2260221) Publication proceeded, but it does not speak well for J&J or the NEJM that the lead author was not even a member of the clinical research team.

Indeed, as late as March 26, 2001, J&J was still discussing who would be the final authors of the manuscript. On June 26, 2001, while the manuscript was still undergoing revision at J&J, Mahmoud wrote colleagues at J&J: "One BIG question- I was under the impression (perhaps mistaken) that Brenner would NOT be an author… did we submit with him as an author?" In the manuscript, Brenner did become the third author. Clearly, then, authorship was a J&J negotiation, not a reflection of who actually conducted and wrote the manuscript.

Csernansky was not a member of the research team but he was member of a J&J Speaker Bureau program—he received $1500 honorarium each time he spoke-- and beginning in 2000, an attendee at its yearly CNS summits. He received between $2500 and $5000 for each meeting he attended. Between 2000 and 2003, J&J paid Csernansky at least $61,731 for his activities promoting Risperdal. (Hunt, 1628)

An email string on the NEJM article also contains a message from a J&J employee and NEJM author Mahmoud to the J&J CNS team. (October 23, 2001) Mahmoud's language makes clear that this is J&J's publication. They own it despite the fact that the first and last authors are external authors. Mahmoud did not include the external authors on this email:

> Great news! We have final acceptance on our NEJM paper!
>
> This must have been a new world record for number of reviews and editorial exchanges…but we always had the answers. A great big thanks to all who contributed to this process (please pass along my thanks to anyone I may have missed!) This will help our business tremendously—none of our competitors have, or are likely to have, any long term relapse comparisons showing unequivocal superiority over an active treatment.
>
> I will advise as soon as know the exact publication date, but we can immediately mark all materials related to this paper with "in press" and we can prepare plans on how to use this so we can act quickly when it hits. (J-TX2168744)

This same message was repeated by other J&J employees. One wrote: "The most important point here, however, is that CSERNANSKY CAN HELP US DRIVE BUSINESS!!!... If a doc says anyone can manipulate

numbers, ask them why Lilly hasn't done it." The memo ends with the phrase: "CRUSH THEM." (J-TX2614229) Another declared: "This is a great opportunity to 'Change the way our key customers Rx atypicals' and drive RISPERDAL market share. Let's take advantage of it." (J-TX2614230)

J&J did take advantage of it. Csernansky was funded to present the findings to consumers, including patient advocacy groups. (J-TXCID1131384) And J&J told staff in its 2003 Franchise Plan that the NEJM article "Supports Risperdal's long term efficacy advantage vs other antipsychotics with a unique study design and published in a premier medical journal for both primary care and specialists." As a result of the publication J&J was able to revise its sales aid and sales training workshop, as well as add new CME materials, and slide sets. (J-TX2165928)

Records that J&J sales representatives submitted to the company also indicate that they discussed the NEJM article when visiting physicians in Texas. For example, one rep reported during a visit to a physician in Texas City, Texas: "Focused on long term efficacy via Csernansky (sic) well tolerated and low side effect profile." (J-TX711191) Another, after visiting a physician in Big Spring Texas, notes: "Discussed Csernansky data for Relapse prevention. Doctor said he has always thought Ris was great for efficacy." (J-TX2720333) So too, a sales rep who visited a physician in Rosenberg, Texas commented: "Focus on Csernansky data reporting long-term efficacy and safety at correct doses."(J-TX2841053) These reports indicate that J&J sales reps used the NEJM article to persuade Texas physicians about the safety and efficacy of Risperdal. The Texas physicians who were encouraged by the sales representatives to use Risperdal based on the findings presented in the NEJM study were not informed about the role of the J&J employees in the study.

Even without being privy to all these details, an editorial accompanying the article raised the crucial question of whether research conducted by the pharmaceutical companies and the goals of the research were problematic: "In view of the fierce competition…these trials would benefit from being designed and conducted by researchers who are independent of the pharmaceutical manufacturers. Rather than being targeted primarily at meeting the demands of the regulatory authorities, the studies should aim to produce reliable, clinically useful estimates of the effects of treatment." (NEJM 2002; 346: 58)

9. [No Ris Number]

Jensen PS, Buitelaar J, Pandina GJ, Binder C, Haas M, "Management of Psychiatric Disorders in Children and Adolescents with Atypical Antipsychotics: A Systematic Review of Published Clinical Trials," European Journal of Child and Adolescent Psychiatry 2007; 16: 104-120.

Message:

"The review of published scientific data suggests that most of the atypical antipsychotics, excluding clozapine, have a favourable risk/benefit profile and effectively reduce disabling behaviours in paediatric psychiatric patients."(Abstract, 104)

"There is growing evidence of favourable risk/benefit profile of risperidone, olanzapine, and quetiapine in both short-and long-term studies." (Conclusion, 117)

The secondary role that J&J assigned external authors, to the clear detriment of scientific integrity, appears in the origins and publication of Risperdal in pediatric use. The J&J team wanted to produce a "pediatric positioning briefing document," which would position "Risperdal in all pediatric indications, pharmacological and non-pharmacological." (February 10, 2004)(J-TXCID1261508) EM carried out the assignment, with a proposed title: "Antipsychotics for the management of psychiatric disorders in children and adolescents: The current state of the art." Its "Strategic Objectives" were carefully defined and included:

> Promote the concept that psychiatric disorders in children require treatment, non-pharmacological and pharmacological. Notes on quality of life and consequences of not treating this population.
>
> Position Risperdal as the pharmacological treatment for severe behavioral symptoms that occur across disorders, i.e. autism and bipolar disorder…in children and adolescents.

To leverage data from clinical trials and open-label studies in DBDs, autism and bipolar, to underpin Risperdal key efficacy and safety messages.

Focus on positive outcomes (risk/benefit; costs; successful early treatment)

(J-TXCID1261509)

EM proposed that conclusions of the article include "the need for treatment and Risperdal being the most established treatment choice in children and adolescents." (J-TXCID1261512) The EM Publication Briefing Document also suggested several KOLs as possible authors: "KOL Pub team: Please advise: Stan Kutcher in Canada or Sandra Fisman? If European journal- Jorg Fegert in germany (sic), Peter Jenssen (sic)in US?" (J-TXCID1261509)

The marginality of the external authors was increasingly relevant as EM continued to develop this manuscript. Developing the manuscript was a joint effort by EM and J&J. On April 21, 2004 EM sent J&J a first draft of the "so-called pediatric positioning paper. "Could you please let us know your ideas and comments on this paper? As we currently do not have an author for this paper could you also give some suggestions for an opinion leader to author this paper." (J-TXCID1204312) On May 6, EM wrote again noting it had only a few comments: "We however prefer to have your thoughts on the scope of the paper including some suggestions for external authors and preferred journal." (As above....311) On May 13, EM wrote: "It would be very helpful to receive some guidance in relation to the flow, format and subject discussed in this paper and whether you think this is too marketing oriented or not, in order to prepare a next draft. Besides that we would like have some suggestions for external authors on this paper. Maybe an (sic) US and a European KOL? Your input will be much appreciated." (...311) J&J's concern was with the market impact of the article, not its substance. As one of them noted: "If we try to describe efficacy in multiple diagnoses, this will support the argument of pseudospecificity of the effects on symptoms, and be perceived negatively by clinicians even if it what they believe.... I think the message is too broad and the intent a bit transparent." (As above....310-311)

The article eventually appeared in the European Journal of Child and Adolescent Psychiatry in 2007. The authors were a US KOL, Peter S. Jensen, a European KOL, Jan Buitelaar, and 3 J&J authors, Pandina, Binder, and Haas. Jensen was the only proposed author from EM to be included. The published article did note funding from J&J and identified the three J&J authors. However, there is no conflict of interest statement, and no information on the contribution of the authors or mention of the fact that medical writers were involved. There is sufficient overlap of language and data from early EM draft to the published article to justify the conclusion that the authors had improperly put their names on and failed to credit EM's work.

It should be noted that the title on the first draft of the EM article and the title on the published article are the same. The published article included citations that EM used in the first draft. More, EM designed three tables for the first draft and they reappear in slightly revised form in the published article.

Examples of similar language:

First draft: "Common, disabling psychiatric disorders in children and adolescents, include disruptive behavioral disorders (DBD), pervasive developmental disorders (PDD), schizophrenia, and bipolar disorder. These disorders include disturbing and disruptive behavioral symptoms that significantly impact quality of life for both the patient and their caregivers." (J-TXCID1204317)

Page 104 Published article: "Common disabling psychiatric disorders in children and adolescents that have been targeted for treatment with atypical antipsychotics include disruptive behavioural disorders (DBDs), pervasive developmental disorders (PDDs), tic disorders, schizophrenia, and bipolar disorder. These disorders include disturbing and disruptive behavioural symptoms that have a significant and often long-lasting negative effect on the quality of life for both the patients and their caregivers."

First Draft: "DBD of childhood include conduct disorder (severe destructiveness and violence), oppositional defiant disorder (e.g. tantrums), and DBD not otherwise specified. DBD is the most common reason for psychiatric referral in children." (J-TXCID1204317)

Page 105 Published article:

Disruptive behavioral disorders (Table 1)
DBDs of childhood include conduct disorder (destructiveness and violence), oppositional defiant disorder (e.g. defiance of authority and rule-breaking behaviour), and DBD-not otherwise specified. These are among the most common reasons for psychiatric referral in children."

First Draft: "Short-term reduction of DBD symptoms has been demonstrated with both olanzapine and risperidone (Table 1). With both medications, significant behavioral improvement occurred within the first 1-2 weeks of treatment. Long-term maintenance of DBD has been demonstrated with risperidone in both open-label and double-blind studies, with children followed up to three years. (Croonenberghs (RIS-INT-41), Buitelaar (INT-79), Croonenberghs (INT-70), Olah HUN 4). (J-TXCID1204322)

Page 105 Published Article: "Short–term reductions in DBD symptoms have been demonstrated with both olanzapine and risperidone (Table 1)….In the double-blind and open-label risperidone (0.002-0.006,g/kg/day) trials and the one open-label trial with olanzapine (0.25-0.30 mg/kg day), significant behavioural improvement was seen within the first 1-2 weeks of treatment….Long-term maintenance of efficacy in treating DBD has been demonstrated with risperidone in open-label studies (Croonenberghs 2005, Findling 2004, Reyes 2006, Turgay 2002)

First Draft: "Schizophrenia is typically recognized in young adults rather than children. Childhood-onset schizophrenia occurs for about 0.01% of children <12 years old, with incidence increasing during the teenage years." (Remschmidt, 2002) (J-TXCIDD1204318)

Page 110 Published Article: "Schizophrenia and bipolar disorder are typically recognized in adolescents or young adults rather than children. Childhood-onset schizophrenia is reported in about 0.01% of children aged <12 years, with the incidence increasing during the teenage years "Remschmidt, 2002).

First Draft: Safety and tolerability of atypical antipsychotics in pediatrics "In general, atypical antipsychotics are better tolerated with improved compliance compared with conventional neuroleptics (Chakos, 2001)….The most frequent significant AEs reported with atypical antipsychotics are sedation and weight gain. (J-TXCID1204324-5)

Page 114 Published Article:
Safety and tolerability of atypical antipsychotics in paediatrics
"In general, atypical antipsychotics are better tolerated and show improved medication compliance than typical antipsychotics." (Chakos 2001)....The most significant adverse events reported with these atypical antipsychotics in a paediatric population were sedation and weight gain."

First Draft: "Somnolence occurs frequently with atypical antipsychotics, although it is usually transient and mild to moderate in severity. The impact of somnolence can be reduced by switching from morning to evening dosing, using divided dosing, or reducing dosage (Soderstrom, 2002; Shea CAN 23 submitted). (J-TXCID1204325)

Page 114 Published Article: "Somnolence was frequently reported with atypical antipsychotics, although it was usually mild to moderate in severity and infrequently resulted in treatment discontinuation. The impact of somnolence was effectively reduced in studies with olanzapine and risperidone by switching from morning to evening dosing, using divided dosing, or reducing dosage." (Shea 2004, Soderstrom 2002)

First Draft: "Physical and sexual development must also be carefully studied in pediatric patients, especially when exposed to long-term therapy. Growth was assessed in 350 children and sexual maturation in 222 children who participated in long-term treatment with risperdone for DBD (Dunbar, 2004). After 12 months, mean height increase was 1.2 cm greater in children treated with risperidone compared with placebo. In addition, there was no delay in progression through Tanner staging with risperidone." (J-TXCID1204326)

Page 115 Published Article: "Physical and sexual development should also be carefully studied in paediatric patients, particularly when exposed to long-term therapy. A recent meta-analysis assessed growth in 350 children and sexual maturation in 222 children who participated in long-term treatment of DBD with risperidone. (Dunbar, 2004) After 12 months, there was no inhibition of the expected growth (National Health and Nutrition Examination Survey data and growth velocity charts), nor was there any delay in sexual maturation as assessed by Tanner staging, with risperidone."