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# *LEARNING FROM WESTERN MEDICINE'S MISTAKES*

**October 2010**

**Presented by Baum, Hedlund, Artistei & Goldman**
**Attorneys at Law**

Synopsis:

Western Medicine has strayed from "evidence based medicine" as a result of being subjected to a massively funded corruption of the medical community so that we now have "spin based medicine" instead. Through documents and depositions obtained in American lawsuits not ordinarily publicly available, we have found dangerous differences between the coordinated marketing messages for pharmaceutical drugs and their actual clinical trial results and adverse event rates. A sampling of some of those documents such as pre and post marketing strategic business plans attached to this presentation shows the purposeful manipulation of academics, medical journals and mass media. Blockbuster drug sales flood extraordinary amounts of money into drug company coffers which enables them to influence clinical trial results, medical journal publications, regulators, politicians and the mass media. By restricting public access to the actual drug clinical trial results and adverse drug reaction data, drug companies have been able to "summarize," alter or mis-code their data to tell the stories their marketing teams use to create blockbuster sales. Thus, we have "spin based medicine" instead of "evidence based medicine." Russia has the opportunity to prevent what the West now has to cure.

The related Russian states are at a critical cross-roads where they could either be misled into "spin based medicine" or, instead, take simple steps to assure reliance on actual "evidence based medicine," i.e. , a choice between fake science and real science.

Recommendations

1. Once a drug is approved for sale, all clinical trial data, including raw data from case report forms, should be made publicly available to regulators, academics, the public, media and competitors;
2. Open access to adverse drug reaction reports should be required and accurate reporting of adverse drug reactions must be strictly enforced;
3. Direct to consumer advertising should be prohibited;

4. Advertising to physicians should be prohibited or, at a minimum, restricted;
5. Comparator drug trials should be required, not just placebo drug trials, with existing drugs at their recognized safe and effective treatment levels;
6. Drug company sponsoring of continuing medical education, physician sales meetings and academic chairs should be restricted.

Drug Company Strategies to Capture and Expand Markets

1. Development, purchase and cornering of "key opinion leaders";
2. Infiltration of regulatory bodies directly or through advisory bodies;
3. Buying off journalists through fully paid trips, academic chairs, scholarships, etc.;
4. Funding chairs of scientific academics;
5. Restriction on research results through confidential agreements and contracts;
6. Influencing physician prescriptions through "advisory boards," pre-paid conferences, payments made for prescriptions, free meals, free samples, etc.;
7. Misuse of medical journal articles to promote drugs through false science by:
    a. ghostwriting publications by manufacturers with their internal scientists' and marketing departments' spin or manipulation of actual clinical trial results, planned from inception to impart pre-new drug application, pre and post launch marketing messages to create a need, fend off comparator advantages and ultimately promote sales;
    b. publishing to regulators, academia and media "spin" and summaries of data contrary to what the clinical trials' raw data actually shows;
    c. preventing access to clinical trial raw data;
    d. placing names of multiple opinion leader academics on ghostwritten articles to give the impression that the articles are truthful and scientific;
    e. post clinical trial selection of "positive" end points and de-emphasis of failed primary endpoints.
8. Using research facilities that guarantee positive results;
9. Conducting clinical trials with misleading comparisons to placebos or under/overdosing of existing comparator drugs instead of properly dosed existing drugs on sale;
10. Using clinical trials not subjected to government review to support off label sales;
11. Failing to accurately report Adverse Drug Reactions to regulators—not reporting or miscoding events;
12. Taking over Continuing Medical Education programs by paying for, promoting and presenting their drugs during education programs;
13. Early influence on new physicians by visits designed to cultivate cooperative physicians and researchers at the college level;
14. Funding "patient advisory groups" that convey company marketing messages;
15. Influencing getting drugs placed on government and insurance company formularies;
16. Using clout of magazine, newspaper and TV advertising dollars to blunt criticism;
17. Taking over mass media to sell sickness in order to increase sales by:
    a. Creating disease states;
    b. Medicalization of normal life events and conditions.

Attachments

1. Publicly available strategic marketing plans and other documents related to a) Paxil, b) Seroquel, c) Avandia and d) Zoloft;
2. "CMAT" document regarding pediatric use of Paxil and "Study 329";
3. FDA email correspondence concerning "emotional lability";
4. Jureidini, McHenry and Mansfield, "Clinical trials and drug promotion: Selective reporting of study 329," *International Journal of Risk & Safety in Medicine*, 20 (2008) 73-81;
5. Pigott et al., "Efficacy and Effectiveness of Antidepressants: Current Status of Research," *Psychotherapy and Psychosomatics*, July 9, 2010, 79:267-2 (authors found antidepressant lack of efficacy "pretty jaw-dropping" and concluded that their "findings argue for a reappraisal of the current recommended standard of care of depression);
6. *Knipe v. SmithKline Beecham Corp.*, 583 F.Supp.2d 602, 640 (E.D.Pa. 2008), (when presented with internal documents regarding alleged concealment of Paxil's benefits versus risks, a United States federal court judge held that GSK's conduct evidenced a "wanton and willful disregard for the safety of its consumers").

# ATTACHMENT 1-a

# 1999 Tactical Plan

# *PAXIL*

**September 15, 1998**
**Prepared By:**

**Barry Brand**
**Tom Gibbs**
**Chris Hanson**
**Scott Sproull**

# You asked for it !!!

- Increased funds for 1999
- More flexible resource allocation
- New *Paxil* at the Movies
- Regional thoughtleader development
- New programs
- More clinical resources
- A heavier sales aid
- Enduring CME materials
- More "true" value added Managed Care pull through programs
- Enhanced training for SKF and SB Priority
- Anything else?

## ISAAC

*Initiative for Social Anxiety Assessment and Care*

ISAAC is designed to promote physician awareness about social anxiety and its occurrence within the population. An expert advisory panel of practitioners and academicians sponsored by Duke University Medical center in conjunction with SB have created the ISAAC program.

ISAAC provides real-time, patient-specific reporting to physicians. The 4-page color report enables physicians to see assessment data on the patient's emotional disability, quality of life, comorbid conditions and severity of social anxiety disorder. These data give the physician a starting point from which to initiate a discussion with the patient. Physicians receive an administrative fee payment of $100 per patient for each patient who enrolls in the program for up to 10 patients ($1000 maximum).

Screening with ISAAC has shown to increase new prescriptions of social anxiety disorder medications, including *Paxil*, by up to 20%. In addition, it enables you to build value-added relationships with your key physicians and secure future detailing visits.

**To enroll your physician into ISAAC:**

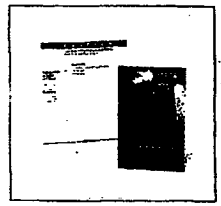
1. Call the ISAAC sales consultant support line at 1-800-492-0312 to obtain program materials. Enter your 5-digit employee number, followed by your 5-digit pin number, which is "PAXIL" (72945).
2. Read the color overview brochure and become familiar with the ISAAC kit components.
3. Identify and orient physicians in your territory to ISAAC using the color brochure.
4. Enroll a physician into ISAAC by faxing the completed ISAAC Physician Participation/Consent form and W-9 form to InfoMedics at 1-800-934-6760, while still in the physician's office. Remember to include your name on the form.
5. An ISAAC Program Kit will be mailed directly to the physician. InfoMedics will call you when the kit is mailed, so you can set up an ISAAC kit orientation meeting with your newly enrolled physician.
6. You can check the enrollment status of your invited physicians, or secure more ISAAC supplies by calling the ISAAC sales consultant support line at 1-800-492-0312.
7. Follow up with your physicians regularly to ensure that they are screening and enrolling patients.

**Target Audience:** psychiatrists

*See pages 25 and 26 of the appendix for sample forms.*



## CASPPER



*Case Study Publications for Peer Review*

CASPPER offers physicians assistance with the preparation and publication of case reports or papers relevant to the features and benefits of *Paxil*. Complete Healthcare Communications (CHC) has been contracted to assist physicians in developing a topic, coordinating the review process and preparing for the submission to the journal, as well as proofreading and production of tables or graphs.

**To initiate the program:**

1. Order ST4715 through Powerline.
2. Initiate a discussion with a physician you think may be interested in the program and introduce the idea behind the program (the CASPPER brochure offers tips for starting these conversations).
3. Work with the interested physician to identify patient cases.
4. Enroll your physician in the program by calling 1-888-721-5258 and leave a message for a plan coordinator on mailbox extension 7999088. Include your name, phone number, the name of your physician and topic information on the message. A plan coordinator will contact you to verify the details and the information will be forwarded to the editorial staff of CHC.

   OR

   Fax the "Publication Request" form in the back of the CASPPER brochure to CHC at 610-358-3636.
5. Participate as a liaison throughout the process, which allows you to establish and/or strengthen your relationships with key physicians and thought leaders in the psychiatric field.

**Target Audience:** psychiatrists, key physicians and thought leaders

*See page 27 of the appendix for sample form.*

**Market : United States**

# *Paxil* 2000 - 2002

## 1. PRODUCT

*Paxil* (paroxetine HCl) competes in the $7.5 billion SSRI (selective serotonin reuptake inhibitor)/SNRI (serotonin norepinephrine reuptake inhibitor) market. Current indications will include major depression, OCD, panic disorder and social anxiety disorder. Future indications include generalized anxiety disorder (GAD), post traumatic stress disorder (PTSD) and premenstrual dysphoric disorder (PMDD). PMDD approval will be for *Paxil CR* only and will be marketed under a separate trade name.

## 2. SITUATION ANALYSIS

**(a) Market Place – Structure and Dynamics**

Total prescriptions for the 1998 *Paxil* custom market were 81.0 MM, an increase of 21.8% vs. 1997. SSRIs (*Paxil*, *Prozac*, *Zoloft*, *Luvox* & *Celexa*) claimed 77% of TRX and 74% of NRX, but accounted for only 51% of TRX and 38% of NRX growth. SNRIs and atypicals (*Effexor*, *Serzone*, *Wellbutrin* & *Remeron*) claimed only 23% of TRX and 26% of NRX, but accounted for 49% of TRX and 62% of NRX growth. Major contributors were the expansion of anxiety disorder segments, driven primarily by *Paxil* and *Zoloft*, and the launch of *Wellbutrin* SR/Zyban for smoking cessation which nearly doubled *Wellbutrin*'s TRx share '98 vs. '97.

**(b) Product Performance (marketed products only)**

*Paxil*'s 1998 TRx custom market share was 21.9% (vs. 22.4% in 97). While *Prozac* and *Zoloft* lost 2.2 and 3.4 share points respectively in the depression market, *Paxil* minimized share loss to 0.5 share points in this market. Ongoing promotion of *Paxil* as the anxiolytic antidepressant effective in treating depressive comorbidity allowed *Paxil* to gain share in the anxiety market and minimize share loss to *Celexa* (launched 3Q98) in depression and *Zoloft* in Panic Disorder (launched 3Q97).

**(c) Customer Analysis**

*Paxil*'s share-point gap between psychiatry (which accounts for 40% of new prescriptions) and primary care grew to 7 points in '98 and has grown to 8 points in '99. Since 12/98, *Paxil* has lost 1.1 share points in psychiatry vs. 0.2 share points in primary care (12/98 thru 5/99). Psych share loss is a function of two factors: 1) psychiatry adopting/using new competitors at a greater rate than primary care; and 2) *Paxil*'s declining share of voice in psychiatry amid significant promotional noise from competition; '99 YTD audits place *Paxil* 6$^{th}$ in psych share of voice at 10.5% (vs. *Celexa* – 15.7%, *Zoloft* - 13.9% and *Prozac* – 13.8%).

Managed care continues to prefer *Paxil* vs. other competitors with *Paxil* availability topping out at 97% and formulary inclusion on 93% of formularies (68% list *Paxil* as preferred).

**(d) Competitor Situation**

In 1998, four significant competitive events affected market dynamics: 1) *Wellbutrin* SR fueled overall market growth but slowed SSRI momentum with a smoking cessation claim; 2) Wyeth jump-started *Effexor*'s sluggish share with its extended release formulation, increasing share 2 points in '98, also contributing to flattening *Paxil* share; 3) Pfizer's ongoing promotion of panic leveled *Zoloft*'s previously declining share; and 4) Forest launched *Celexa* leveraging positive labeling on drug interactions and sexual side effects to yield an exit NRx share of 3.8; 6.7 share points as of 5/99.

In 1999/2000, these competitive events are worth noting: 1) approval of *Effexor* for the treatment of generalized anxiety disorder (GAD) threatens *Paxil*'s anxiety franchise, 2) launch of UpJohn's *Vestra* (reboxetine), a novel mechanism, noradrenergic agent for the treatment of depression (will be helped by lack of sexual dysfunction, but hampered by BID dosing); 3) *Zoloft* and *Prozac* approvals for pre-menstrual dysphoric disorder (PMDD) – 70% of SSRIs are used by women (20% of women of child bearing age suffer from symptoms of PMS/PMDD); 4) launch of *Zoloft* for post traumatic stress disorder (PTSD) – becoming increasingly more prevalent with broader definition to include interurban violence and rape victims.

**(e) Key Assumptions**

Market

- 14.5% custom market TRx growth (vs. 17.0% in '99).
- Increased number of MCOs restricting the number of SSRIs on formulary.

Product

- *Paxil* unit growth of 13.3% (vs. 12.1% in '99)
- Price increase of 4.0% (CPI + 2%).
- Social anxiety disorder and DTC reverse negative share trend allowing *Paxil* to achieve '99 exit share of 22.4% (custom market).
- Depression accounts for 60% of business, anxiety for 25%, remainder from "all other" indications, e.g., pain, PMS.
- Psychiatry accounts for 40% of business, primary care for 45%, remainder from "all other", e.g., neurology, ob/gyn, cardiology.
- Retention on key managed care formularies.
- *Paxil* continues competitive level of DTC spend.
- Competitive level of detailing and promotion with psych reach/ frequency comparable to or better than primary care -- 1,820K total details (Psych- 425K, Primary care + Other- 1,395K).

Competition

- *Vestra* (reboxetine) launch 3Q99 (depression only).
- *Prozac* PMDD launch 1Q00; PTSD launch 1Q02; Panic Disorder launch 2Q01.
- *Zoloft* PTSD launch 4Q99; PMDD launch 3Q00.

## 3. PRODUCT POSITIONING STATEMENT

To primary care physicians and psychiatrists, *Paxil* is the drug of choice in depression with associated anxiety symptoms and in anxiety disorders (panic disorder, social anxiety disorder and obsessive compulsive disorder) because it delivers:

- Unsurpassed efficacy across a broad spectrum of highly comorbid disorders
- A unique tolerability profile benefiting patients with anxiety (i.e., low rates of treatment-emergent anxiety, nervousness and agitation), and
- Unlike its competitors, proven long-term safety in depression, panic disorder and OCD.

## 4. VISION AND THREE-YEAR STRATEGIC OBJECTIVES

**Vision:**

Surpass *Zoloft* to become the #2 antidepressant in NRX in 1999 and in TRX in 2000. By December 2000, match NRX share with *Prozac* and become #1 antidepressant in TRX in 2001.

**Strategic Objectives:**

- Exceed gross sales budget of $1.74 billion in '00, and $2.08 billion by 2002.
- Achieve annual TRx share of 20.8% in '00 (-0.4 vs. '99).
- Successfully reposition *Paxil* in Psychiatry via strong detail share of voice, efficacy positioning, and relationship marketing initiatives.
- Leverage broad spectrum of indications and social anxiety disorder exclusivity. Drive overall share growth via continued comorbid anxiety focus.
- Increase consumer driven demand / patients requests for *Paxil* by 50% in '00 through DTC.
- Minimize launch of competitive indications (*Prozac* – PMDD/PTSD, *Zoloft* – PTSD/PMDD, and new products (*Vestra* [reboxetine]).
- Maximize opportunities afforded by FDA Modernization Act and initiate pre-launch efforts for next key indications (GAD, PMDD, PTSD).
- Develop / grow adolescent market by leveraging recently completed studies in adolescent depression and OCD, and initiate clinical program for adolescent social anxiety disorder.
- Maintain access on key managed care accounts and grow share to or above national share level.
- Accelerate new indications (GAD, PMDD, PTSD).
- Evaluate new product line extension (5HT/5HT3) designed to reduce significant adverse events (i.e.- sexual dysfunction, nausea and vomiting) and extend patent life.

## 5. KEY ISSUES AND CRITICAL SUCCESS FACTORS

**Key Issue #1: Profile Differentiation**

**Rationale for differentiation as key issue:**

- Differentiation via new indications/formulations has repeatedly demonstrated significant share growth in the antidepressant category (*Paxil* / panic disorder; *Zoloft* / panic disorder; *Wellbutrin SR* / smoking cessation; *Effexor XR*).
- New competitive indications (*Effexor XR* / GAD; *Zoloft* / Panic) and encroachment of competitor claims mimicking *Paxil*'s anxiety-based positioning (*Serzone*, *Zoloft* & *Effexor XR*) have resulted in message dilution.
- Approvals for *Prozac* (PMDD/PTSD), *Zoloft* (PTSD/PMDD), *Effexor XR* (GAD), *Celexa* (depression) and *Vestra* (depression) serve to further increase the level of promotional noise.
- Managed care organizations are expanding the requirements for access on increasingly restricted antidepressant formularies. Products need to differentiate favorably on the basis of titration, switching, use of concomitant meds, compliance to treatment, potential for inappropriate use, price, related hospitalizations and physician visits.
- Negative competitive promotion (discontinuation syndrome, sexual dysfunction and weight gain) continues to weaken the profile of SSRIs to the benefit of SNRIs and atypical antidepressants. FDA's request for weight gain data and a potential labeling change could bolster competitor claims and negatively differentiate *Paxil*.

**Critical Success Factors:**

- Expansion of the social anxiety disorder market and its perception as a meaningful psychiatric disorder.
- Reposition of *Paxil* in Psychiatry as a more effective / better tolerated anxiolytic antidepressant.
- Successful return of growth in psychiatry.
- Continued ability to leverage anxiety position to grow overall market.
- Completion of clinical trials in GAD, PMDD and PTSD.
- Competitive levels of detailing and promotion to all specialities.
- Ability to differentiate in managed care (i.e.- attributes that advantage *Paxil* vs. competition).
- Access on key managed care formularies with market share equivalent to national average.

## KEY ISSUES AND CRITICAL SUCCESS FACTORS (cont.)

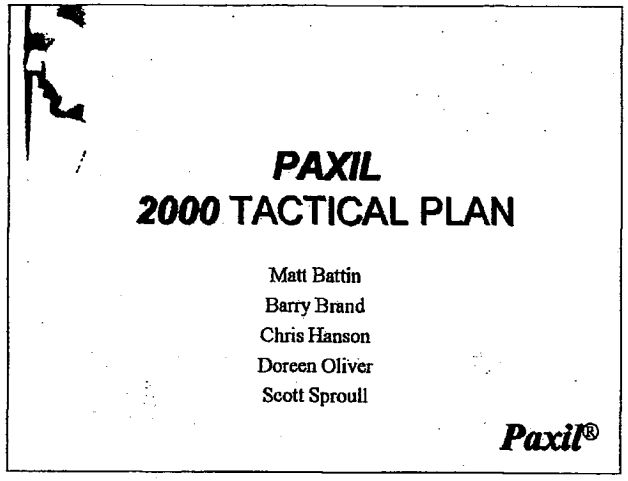
**Key Issue #2: Psychiatric Growth**

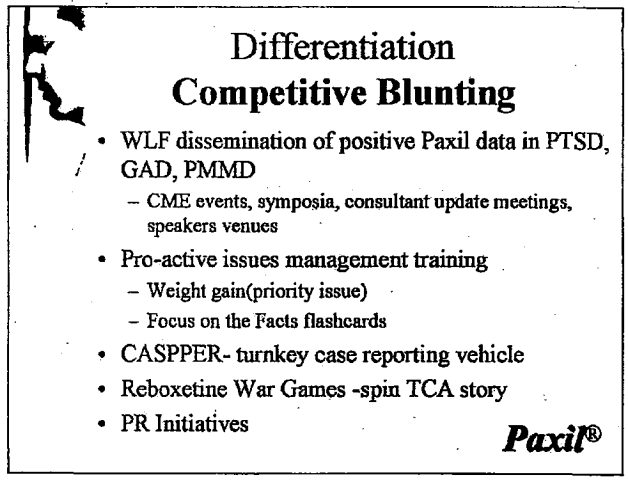
**Rationale for psychiatric growth as key issue:**

- Psychiatry accounts for 40% of annual NRx, are 4x more productive on a per capita basis than primary care, and are growing 16% annually.
- SSRI market detail volume to psychiatrists has increased significantly (+30% vs. '98) and will grow even faster with the launch of *Vestra* in 3Q99. Conversely, *Paxil* detail volume has declined (-13% vs. '98) ranking *Paxil* 6th in terms of share of voice.
- *Paxil* monthly market share (12/98 vs. 5/99) in psychiatry declined at 5.5 times the rate of primary care (Psych –1.1 vs. primary care –0.2); in contrast, share change for *Prozac* and *Zoloft* was comparable by specialty.
- *Paxil*'s broad spectrum positioning is favored by primary care, but is not as readily appreciated by Psychiatry who are dealing with referrals / treatment resistant patients. Psychiatrists are increasing use of 2nd line agents (*Effexor* XR, *Wellbutrin* SR, potentially *Vestra*) in search of efficacy from alternative mechanisms of action (Noradrenaline receptors vs. serotonin).
- Preliminary data suggest *Paxil* may have a norepinephrine effect at higher doses, thus allowing psychiatrists the promise of greater efficacy; benefits would include no time lost to medication washout and switch, *Paxil* tolerability already established, no medication waste, potential for greater efficacy in treatment resistant population.

**Critical Success Factors:**

- Achieve detail parity in psychiatry primarily through psychiatric sales force expansion and secondarily through bonus weighting and copromotion. Psychiatric growth through the next 24 months must exceed that of primary care.
- Psych reps must be thoroughly trained to differentiate in an increasingly crowded market and capable of resolving competitive issues (weight gain, sexual dysfunction, discontinuation syndrome, etc) and use superior *Paxil* efficacy data to differentiate the brand.
- Counter low share of psychiatric voice via third party programs and broad-based relationship marketing initiatives.
- Optimize customer targeting / segmentation.
- Develop and test efficacy-based positioning in psychiatry leveraging potential norepinephrine effect and strong clinical trial data in anxiety trials (i.e.- *Paxil* 32 point separation vs. *Zoloft* 12 point separtion from placebo in pivotal panic disorder trials).
- Implement clinical development plan to augment and support norepinephrine positioning.






# RVP Meeting

Inn at Penn

October 17, 2002

## Our deliverables

- Samples - specifically 12.5mg
- Promotion materials to help with "reason to believe"
- Slide kits for RMS
- CME programs supporting Paxil CR vs Lexapro

PAXIL CR

# Paxil CR 2003 Communications Plan

**Increased volume of publications, posters and communication of data**

**Provide continued support Paxil CR differentiation**

- Anxiety leverage
- Improved tolerability

**Leverage key publications**

- Allow for rep and speaker discussion
- Maximize impact through public relations
- Leverage findings through CME & symposia

PAXIL CR

PAXIL

# 2003 Tactical Plan

November 22, 2002

# Agenda

- 2002 Performance to date
- Current Situation
  - Market Dynamics
  - Key Objective
  - Strategic Review
- Professional
  - Message & Programs
  - Scientific Support & CME
- Consumer
- Managed Markets

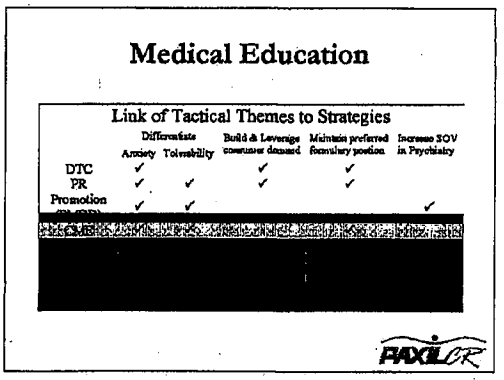
PAXIL CR

## 2003 Scientific Strategy

- Aggressive Datamining and Data Dissemination
  - Publications
  - CME
  - Congress Abstracts
- Short-term USP Trials to Support Paxil CR
  - Anxiety
  - Tolerability
- High Level KOL Interface
  - Product Management Tour
  - National Advisory Feedback
  - Local Advisory Feedback
  - Direct Mail Initiative to Physicians
- RMS / Neurohealth Alliance

PAXIL CR

## Medical Education



## CME Landscape

- Sales Representatives
  - Vendor complexity - Not user-friendly
  - Completely "hands-off" (set up & distribution)
- New GSK guidelines
- Evolving Data on depression & anxiety

## One core CME Company

Ease of use by reps / execution / roll out - rep focused
Content development - experts in psychiatry

CME Inc.

PAXIL CR

## CME Audioconference

- 5 On-demand & 1 Live audioconferences
- Desired Topics:
  - Remission and disability in anxiety - Pooled remission data in MDD
    - Quality of Life/Patient Satisfaction
  - Tolerability impact on early response/remission
  - Anxiety & Women - *anxiety symptoms/disorders in women*
    - Anxiety symptoms in PMDD (sleep, irritability, tension, anger)
  - Getting best treatment results in SAD
  - Identifying and treating depression & anxiety in hispanic population
  - Treating full spectrum of MDD - pain/physical symptoms and anxiety

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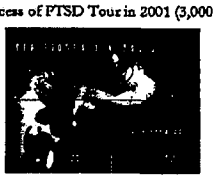
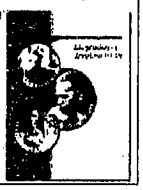
## CME Tour

- Saturday morning symposium - 4 CME credits + Hidden Diagnosis CD for 2 more credits = 6 Credits
- Avg 120 doctors per site (6,000 doctors desired)
- Interactive keypads / case studies
- World-class faculty (D. Sheehan, M. Pollack, J. Gorman, etc...)
- Success of PTSD Tour in 2001 (3,000 attendees)





## CME Tour

- **Spring Tour** - 15 psych mkts / 10 PCP mkts - Desired Topic: "Improving outcomes in dep / anx therapy"
  - Importance of Quality of Life/Patient Satisfaction in Anti-Depressant therapy
  - Tolerability and Adherence Review / Anti-Depressants Tolerability Analysis
  - SSRI Tolerability data - Duke & Other Databases
  - Review of disability data across Anti-Depressants anxiety trials
- **Fall Tour** - 15 psych / ob/gyn mkt / 10 PCP mkts - Desired Topic: "Identifying different faces of dep & anx"
  - Special needs in Elderly Depression
  - Importance of Quality of Life/Patient Satisfaction in PMDD
  - Review of anxiety symptoms/disorders in women & anxiety in women
  - Relieving Anxiety symptoms in PMDD (sleep, irritability, tension, anger)

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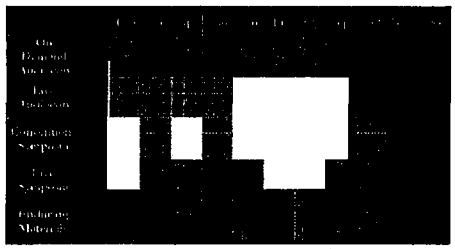
# CME Enduring Materials

- Psychiatric Times supplements (Print)
  - Desired Topics
    - "Treatment challenges in SAD" (January 2003)
    - "Depression and Anxiety: Achieving Successful Outcomes by Enhancing Compliance" (2002 Psych Congr)
    - "Dual action - norepi & serotonin - is it the end of the story?" How to achieve maximum outcome in anxiety & tolerability
- Journal Of Clinical Psychiatry supplement (Print)
  - Desired Topics
    - "SSRI residual choice - is there a benefit?"
    - Challenges in long term treatment of elderly depression - cognition, anxiety, sleep and medical comorbidity
- CME Pavillion (CD ROM)
  - Geriatric Congress (June 2003) - Treatment challenges in the elderly dep & anx population
  - Psych Congress (Oct 2003) - Unmet Needs in Anxiety (2003 ADAA)
    - Anxiety in women's health
    - Developmental implications of pediatric SAD
    - Tolerability and compliance in anxiety

PAXIL CR

## 2003 CME Storm



* Hypothetical 2003 CME programs & dates - only possible if CME company suggests our desired topics and dates

PAXIL CR

## Sales Representatives / CME

1. One phone call for sales representatives to set up CME programs
   - Audioconferences
   - Live symposia

2. Pre-marketing of CME programs through CME provider - follow up by sales representatives

3. CME provider to provide "Customer Service" to sales representatives

PAXIL CR

## Public Relations 2003

**All Stars Against Anxiety & Depression (March-May)**

- Impact anxiety/depression on men; branded message
- Ricky Williams (SAD) & Terry Bradshaw (depression)
- "Pep rally" launch with ADAA
- Six city tour (charitable tie-in)

**Proclamation Against Anxiety (M[illegible])**

- Mental Health Awareness Month + Anxiety Disorder Screening Day + National Proclamation: FFF Week
- Secure expanded media (national & local)
- Drive to Screening day sites

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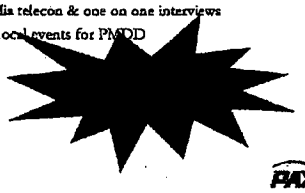
## Public Relations 2003

**The Doctor Is In (June - August)**

- Mental health & women; Paxil CR for women
- Dr. Donnica Moore & Society for Women's Health Research
- Media telecon & one on one interviews
- Six local events for PMDD



PAXIL CR

| 2003 Tactical Plan | |
|---|---|
| DTC | 29,987 |
| PR | 2,000 |
| Grants | 1,300 |
| Managed Markets | 5,103 |
| E. Business | 2,530 |
| CME | 4,262 |
| Professional Programs | 5,958 |
| Ad Boards | 1,510 |
| Conventions / Symposia | 3,340 |
| Publications / Scientific Support | 1,925 |
| T.L. | 1,900 |
| PMDD | 1,500 |
| HealthCare Education Fund | 7,600 |
| LR / Premiums | 4,727 |
| Journal Advertising | 1,839 |
| Samples | 17,430 |
| Total | 92,911 |

PR

***2003 Budget - Public Relations***

| Initiative | Agency | Out-of-Pocket | Project Total |
|---|---|---|---|
| **All-Stars Against Anxiety and Depression** | **$233,500** | **$177,500** | **$411,000** |
| *National Media Launch* | *$68,000* | *$92,750* | *$160,750* |
| *Paxil Local-motive (assumes six markets)** | *$157,500* | *$82,750* | *$240,250* |
| *Continuing The Momentum With Ricky in 2003* | *$8,000* | *$2,000* | *$10,000* |
| * Does not include GSK pledge incentive | | | |
| **Proclamation Against Anxiety - May** | **$63,000** | **$56,500** | ***$119,500*** |
| **The Doctor Is In** | **$151,000** | **$102,500** | **$253,500** |
| *Campaign Start-up* | *$10,000* | *$5,750* | *$15,750* |
| *Media Teleconference* | *$45,000* | *$40,250* | *$85,250* |
| *Dr. Donnica Media Extensions* | *$13,000* | *$12,000* | *$25,000* |
| *PMDD Local Media Tours (assumes six markets)* | *$83,000* | *$44,500* | *$127,500* |
| **Pump Up the Volume** | **$144,500** | **$119,500** | ***$264,000*** |
| *Delving Into Data (assumes two announcements)* | *$85,000* | *$81,500* | *$166,500* |
| *New Paxil CR Indications (assumes PMDD, social anxiety disorder)* | *$59,500* | *$38,000* | *$97,500* |
| **Paxil News Network/Opportunistic Media** | **$40,000** | **$10,000** | ***$50,000*** |
| **Issues Management/Competitive Blunting** | **$75,000** | **$25,000** | ***$100,000*** |
| **Media Monitoring** | **$12,000** | **$36,000** | ***$48,000*** |
| **Account Management** | **$180,000** | **$48,000** | ***$228,000*** |
| **2004 Planning** | **$21,000** | **$5,000** | ***$26,000*** |
| **Estimated Celebrity Fees** | **$0** | **$500,000** | ***$500,000*** |
| **Total** | **$920,000** | **$1,080,000** | **$2,000,000** |

## Attachment 1 - Program Descriptions

1. Social Anxiety Disorder Coalition:
This partnership between SmithKline Beecham, American Psychiatric Association (APA), American Academy of Family Practitioners (AAFP), Anxiety Disorder Association of America (ADAA) and Freedom From Fear (FFF) was created in 1998 to champion the development of professional and consumer education for social anxiety disorder. The membership of the coalition will be altered in 1999 and we will replace the consumer advocacy groups with more thoughtleaders in social anxiety disorder. The mission of the coalition will also evolve and focus on developing a consensus statement and treatment guidelines for social anxiety disorder. The outputs of the coalition will be published in a peer reviewed journal and distributed to our target audiences.

2. Partnership with ADAA and FFF:
Increasing public awareness of social anxiety disorder prior to launch will be generated through partnerships created between SmithKline Beecham, Anxiety Disorders Association of America (ADAA) and Freedom From Fear (FFF). Both of these organizations actively participate in many programs to increase awareness, education and diagnosis of anxiety disorders, including The National Anxiety Disorder Screening Day where tens of thousands of consumers are screened and treated for mood and anxiety disorders each year. ADAA and FFF are excited about the opportunity to partner with SB to educate consumers about social anxiety disorder and, more importantly, give patients hope because there are treatments available to overcome this debilitating disorder. Both ADAA and FFF are distributing patient education materials created by the Social Anxiety Disorder Coalition at their major conventions and events. Additionally, *Paxil* Product Management and FFF are working together to develop a Social Anxiety Disorder Community Outreach Program to be conducted at more than one thousand hospitals across the country.

3. Initiative for Social Anxiety Assessment and Care (ISAAC):
This national disease registry, conducted in conjunction with Duke University, will serve as a conduit to distribute background information regarding social anxiety disorder and diagnostic tools while capturing critical demographic and psychographic data about patients suffering from the disorder. During a two part audioconference (Part 1: diagnosis and treatment of social phobia / Part 2: information about the ISAAC program), 1,500 physician (ISAAC champions) will be enrolled in this program and established as regional experts. Participating physicians will receive an enrollment kit containing instructions, diagnostic and screening tools, patient education brochures and patient education videos. Physicians will use the provided tools and actively screen patients for social anxiety disorder. Patients who screen positive for the disorder will call a 1(800) number, answer a series of questions through an Interactive Voice Response system and be recorded as an entry in the registry. Results of the ISAAC program will be published and will provide important local prevalence data *Paxil* Product Management will be able to integrate into promotion when *Paxil* is approved for the treatment of social anxiety disorder.

4. Regional Advisory Boards:
In partnership with the sales organization, identify regional thought leaders and top speakers in psychiatry to serve on regional advisory boards (regions may want to have more than one advisory board depending on their geography). Each region will be allocated four fully funded advisory board meetings during 1999. Advisory boards will convene to provide clinical insight on competitive issues and *Paxil* promotional activities. The regional advisory boards will also serve as venues to present results of new clinical data such as the *Paxil* Social Anxiety Disorder Clinical Trials, GAD Clinical Trials, adolescent results, etc. RMAs will be trained to effectively facilitate this meeting and logistical support will be provided by an outside vendor. Each member of the advisory board will be provided with copies of the slide presentations for use during their speaking engagements.

5. Case Study Publication Plan:
Recognizing the importance of publishing new articles, the concept of this program is to develop and implement a mechanism to quickly publish case studies relevant to new clinical advantages of *Paxil* (i.e. social anxiety disorder, *Paxil* success in treating GAD, etc.) and to respond to issues initiated by our competition. This "win / win" program allows SB Sales Consultants to provide a valuable, turn key program to help physicians publish their case reports and, in turn, will expand the database of published articles supporting the benefits of *Paxil*.

6. CD Rounds - Consultants Update Meeting:
Convene key regional and local thought leaders and top speakers from around the country at a scientific exchange supported by SmithKline Beecham. The meeting will consist of a series of lectures by the preeminent thought leaders in psychiatry on the diagnosis and treatment of anxiety disorders (specifically social anxiety disorder). Attendees will receive copies of the slide presentations and also be trained on the latest version of the CD Rounds program. This information is intended to be integrated at their local speaking engagements.

7. CD Rounds - Local Programs:
CD Rounds is CME accredited for up to five hours and utilizes multimedia technology to deliver an engaging and interactive presentation focusing on a variety of psychiatric disorders including social anxiety disorder. SB Sales Consultants can contact Interactive Network for Continuing Education and request a specially trained physician on this program to present at a dinner program, grand rounds or other type of speaker program.

8. TeleConsult:
The TeleConsult Program will utilize new internet and videoconferencing technology to enable a community physician to have a "one on one" consultation with a national thought leader to discuss various patients and topics of interest. Possible discussion topics might include: social anxiety disorder, management of side effects such as discontinuation symptoms and weight gain, new clinical data (GAD, PTSD, adolescent depression, etc.) and cutting edge science of antidepressant therapy (antidepressant concentration in breast milk). This program is an intimate, convenient and cost effective vehicle to share thoughtleaders' knowledge to influence community physicians.

9. Distance Learning Network:
Approximately 375 hospitals will be linked via satellite to participate in a four program series on the recognition and treatment of social anxiety disorder. This program will reach over 10,000 physicians, psychologists, nurses and social workers.

10. National Symposia:
At the APA, U.S. Psych Congress, NCDEU and ADAA, present scientific data citing the prevalence, clinical characteristics and substantial disability associated with social anxiety disorder. In this scientific setting, the panel will also demonstrate the importance of diagnosing social anxiety disorder in terms of comorbid depression and other anxiety disorders. The symposia also include presentations on treatment options that feature the robust results of the *Paxil* Social Anxiety Disorder Clinical Trials and enduring materials (program booklet, slide kits, etc) for physicians to integrate into their own speaking engagements.

11. Other Third Party Support:
Other third party development includes the development of a treatment algorithm, dissemination of clinical data through investigator and consultant update meetings, audioconferences, CME series with *Primary Psychiatry*, creation of speaker slides / resources, etc.

12. Campaign Development:
The Social Anxiety Disorder Campaign development will employ standard primary research, concept testing and message development. The results of this research will shape the content used in the new sales materials (sales aid, scientific backgrounder, updated product monograph, patient education, diagnostic scales, etc).

13. Database Development / Consumer Profiling / Segmentation:
Additional consumer activities will focus on creating a social anxiety disorder patient database by integrating data accumulated through various sources including the ISAAC program, The National Anxiety Disorder Screening Day (sponsored by FFF), marketing research and direct to patient programs. This database of over 45,000 patients will enable *Paxil* Product Management to proactively apply segmentation techniques to better understand the demographic and psychographic profiles of social phobics. We will then forecast potential of various segments, and, target segments with the highest potential and profitability of responding to the direct to consumer effort. Based on the characteristics and profile of targeted segments, select the

# ATTACHMENT 1-b

**INTERNAL MEMORANDUM**

**Date:** 12-Feb-1997 03:40am EDT

Tel No: 01625 517679

**To:** See Below

**From:** Richard Lawrence

**Subject:** RE: US/Canada Investigator meeting and Study 15

---

I am not 100% comfortable with this data being made publically available at the present time....however I understand that we have little choice....Lisa has done a great 'smoke -and-mirrors' job!

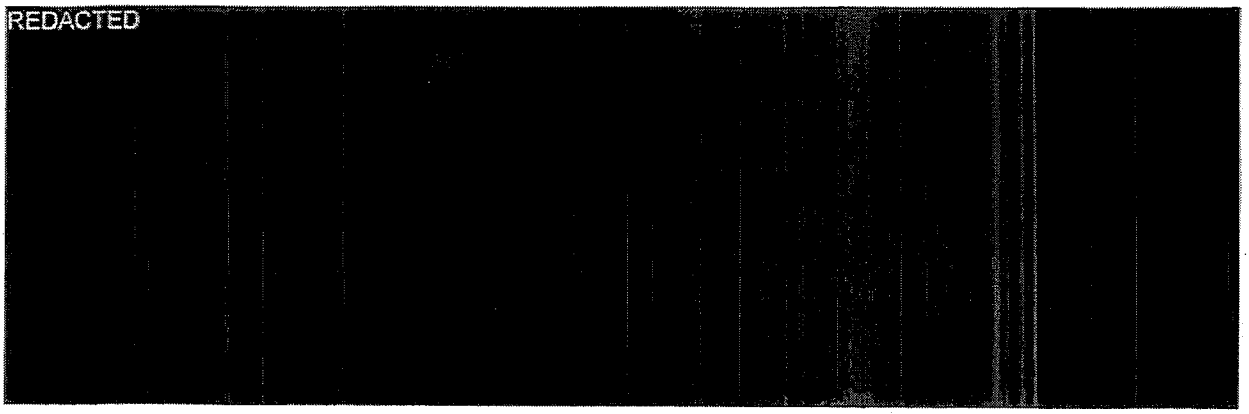
Adopting the approach Don has outlined should minimise (and dare I venture to suggest) could put a positive spin (in terms of safety) on this cursed study.

Athena, with Mark Sahl having left I am not certain who is replacing him. Whoever it is..... ought they speed a reserve press release through?

Richard

**Distribution:**

| | | |
|---|---|---|
| **To:** | Don Stribling | ( STRIBLING D@A1@APVXC1 ) |
| **CC:** | Lisa A. Arvanitis | ( ARVANITIS LA@A1@UWP00 ) |
| **CC:** | Don Stribling | ( STRIBLING D @ A1 @ APVXC1 ) |
| **CC:** | Richard Lawrence | ( LAWRENCE RA @ A1 @ APVXC1 ) |
| **CC:** | Athena M. Ruhl | ( RUHL AM@A1@UWP00 ) |
| **CC:** | Chris R. Griffett | ( GRIFFETT CR@A1@UWP00 ) |
| **CC:** | Ricky Bache | ( BACHE RA @ A1 @ APVXC1 ) |
| **CC:** | Joher Raniwalla | ( RANIWALLA J1 @ A1 @ APVXC1 ) |
| **CC:** | Georgia L. Tugend | ( TUGEND GL@A1@UWP00 ) |




Best regards,
*Kendra Baker*
Attorney
Legal Department
AstraZeneca
Tel. (302) 886-4233 Fax: (302) 886-8221
Kendra.Baker@astrazeneca.com

---

**From:** Scanlon Rose Ann RA
**Sent:** Tuesday, December 07, 1999 2:33 PM
**To:** Baker, Kendra
**Subject:** FW: 2 EPS Abstracts for APA

REDACTED

*Rose Ann Scanlon*
*Assistant General Counsel*
*AstraZeneca*
*Telephone: 302 886 4009*
*Fax: 302 886 8221*

---

**From:** Denerley Paul PM
**Sent:** December 07, 1999 10:24 AM
**To:** Scanlon Rose Ann RA
**Subject:** FW: 2 EPS Abstracts for APA

---

**From:** Tumas John JA
**Sent:** Monday, December 06, 1999 11:45 PM
**To:** Owens Judith J; Jones Martin AM - PHMS; Litherland Steve S; Gavin Jim JP
**Cc:** Holdsworth Debbie D; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert; Shadwell Pamela PG
**Subject:** RE: 2 EPS Abstracts for APA

Please allow me to join the fray.

There has been a precedent set regarding "cherry picking" of data. This would be the recent Velligan presentations of cognitive function data from Trial 15 (one of the buried trials). Thus far, I am not aware of any repercussions regarding interest in the unreported data.

That does not mean that we should continue to advocate this practice. There is growing pressure from outside the industry to provide access to all data resulting from clinical trials conducted by industry. Thus far, we have buried Trials 15, 31, 56, and are now considering COSTAR.

The larger issue is how do we face the outside world when they begin to criticize us for suppressing data. One

could say that our competitors indulge in this practice. However, until now, I believe we have been looked upon by the outside world favorably with regard to ethical behavior. We must decide if we wish to continue to enjoy this distinction.

The reporting of the COSTAR results will not be easy. We must find a way to diminish the negative findings. But, in my opinion, we cannot hide them.

Best regards,

John

---

**From:** Gavin Jim JP
**Sent:** Monday, December 06, 1999 1:59 PM
**To:** Owens Judith J; Jones Martin AM - PHMS; Litherland Steve S
**Cc:** Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert; Shadwell Pamela PG
**Subject:** RE: 2 EPS Abstracts for APA

Steve's comments are pertinent, as the EPS abstracts (for the APA) and the Scourge of EPS review both emanate from the ECNP symposium, and as such represent a potential transition of COSTAR data from a "closed" mtg to a public forum. Coming in late to the debate, the only directive I have on QUEST/COSTAR (contained in a document compiled by Ihor & Martin in August) suggested using them "as clinically appropriate", but independently.

I believe the newly-formed Commercial Support Team will be considering looking at potential ways of using COSTAR. With regards to the present outputs however, a short-term solution (given the impending APA deadline) is to avoid reference to COSTAR in the proposed APA abstract. Whether or not we discuss it in either the poster or the review subsequently will need to decided by the team, with reference to how we would then need to approach the efficacy story.

Regards
Jim

---

**From:** Litherland Steve S
**Sent:** 06 December 1999 11:51
**To:** Owens Judith J; Jones Martin AM - PHMS
**Cc:** Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Gavin Jim JP; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert
**Subject:** RE: 2 EPS Abstracts for APA

Martin has drawn our attention to an enduring problem which requires resolution as soon as possible.

- should we publish COSTAR? The disadvantages are obvious, not least that we provide the opposition with potentially damaging data when they calculate p values re the primary efficacy endpoint
- if not, can we extract some information and use this to support our messages? The following is scheduled to appear in Clear Vision (proceedings of the ECNP EPS meeting):

A second study comparing flexible dosing of risperidone (6-10 mg daily) and quetiapine (300-600 mg daily) reported that over 10 weeks significantly more risperidone patients (31.4%) than quetiapine patients (14.1%)In my draft 30.4 and 13.1% ; need to check experienced EPS or akathisia (30.4% and 16.6 15.4 in MR doc%, respectively) ($p<0.001$ for both comparisons) (Data on file).

This was sanctioned for the meeting but when it appears in Clear Vision it will be in the public domain. We can be accused of "cherry picking" and this may fuel demands to see the entire study (Cochrane would be most interested, for example).

- Are we using QUEST promotionally? If so, we could be accused of not telling the complete story

I am concerned that by doing nothing re COSTAR, except to allow details to emerge in dribs and drabs we are not taking control of the situation. An initial step may perhaps be to canvass expert opinion

outside the Company (I know that we have had some feedback but I understand this was conflicting and uncoordinated).

Steve

---

**From:** Jones Martin AM - PHMS
**Sent:** 06 December 1999 10:55
**To:** Owens Judith J
**Cc:** Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Gavin Jim JP; Litherland Steve S; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM
**Subject:** RE: 2 EPS Abstracts for APA

Judith

I have no real comments on the Juncos abstract, but am concerned about Tandon's.

In Tandon's results section, he refers to a randomised comparative study. This study is COSTAR. I think that we are still not comfortable about communicating the overall results of this study. Whilst this data may have been presented orally in London, I think this abstract would be the first time we have put anything 'down on paper'. Are we sure that this we can present the EPS data in isolation given the nature of the other results ? Will we not create a desire for further information about the study ? Can we not refer to published (non-comparative) data for risperidone, as we must be doing this for olanzapine ? Should we be looking at the ziprasidone data too ? They seem to have dose-response effect as well.

Martin

---

**From:** Owens Judith J
**Sent:** 02 December 1999 17:14
**To:** Wilkie Alison AM; Gavin Jim JP; Litherland Steve S; Murray Michael MF; Rak Ihor IW; Jones Martin AM - PHMS; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM
**Cc:** Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP
**Subject:** 2 EPS Abstracts for APA
**Importance:** High

Dear All
Please find attached, for your review, 2 EPS abstracts that are intended for submission to APA. The abstracts are based on presentations at the AstraZeneca symposium 'CLEAR VISION - A fresh look at EPS' held during this year's ECNP.
Please return any comments you may have by midday (UK time) **Monday 6 December.**
Kind regards
Judith
<<File: Juncos abstract.doc>><<File: Tandon abstract.doc>>
**Judith Owens**
**Ext: 24164**
**11F34 Mereside**

# ATTACHMENT 1-c

United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510-6200

July 12, 2010

**Via Electronic Transmission**

The Honorable Margaret A. Hamburg
Commissioner
U.S. Food and Drug Administration
White Oak Building 1
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Hamburg:

As Chairman and Ranking Member of the United States Senate Committee on Finance (Committee), we have a special responsibility to protect the health of the approximately 100 million Americans who receive health care through the Medicare and/or Medicaid programs, as well as to ensure that taxpayer and beneficiary dollars are appropriately spent on safe and effective drugs and devices. These responsibilities include overseeing the U.S. Food and Drug Administration (FDA) whose mission is, among other things, to protect the public health by assuring the safety, efficacy, and security of our nation's drug supply.

We would like to update you about our concerns regarding Avandia, a drug marketed by GlaxoSmithKline (GSK) to treat diabetes. As part of our oversight duties, we have requested documents from GSK that may shed light on safety and efficacy concerns with Avandia. Our staff reviewed those internal GSK documents and found the following:

- **GSK apparently failed to publish studies in a timely manner that found problems with Avandia**

- **Avandia was part of GSK's ghostwriting program**

In the following pages, we have provided further information on these topics for your review and consideration. We have also attached pertinent documents for FDA's review.

## GSK APPARENTLY FAILED TO PUBLISH STUDIES THAT FOUND PROBLEMS WITH AVANDIA

As far back as 2000, internal emails show that GSK executives sought to downplay scientific findings, which raised questions about the safety of Avandia. For example, in an internal email sent on October 23, 2000, a GSK executive sought to

downplay the fact that Avandia gave a worse lipid profile[1] than the competitor, ACTOS. At the time, GSK executives were concerned about a GSK study of ACTOS, called Study 175. In that email, a GSK executive wrote, "This was done for the US business, way under the radar and we lost in terms of LDL and Tgs....Per Sr. Mgmt request, these data should not see the light of day to anyone outside of GSK." [ATTACHMENT A]

In another email sent on July 6, 2001, GSK executives discussed not wanting to do a head to head trial between Avandia and ACTOS because of Study 175. In that email, a GSK executive wrote, "I agree that there is no benefit in doing a head to head study with [ACTOS] as the best result would be equivalence." [ATTACHMENT B] We have attached a copy of Study 175 for your review. [ATTACHMENT C]

We are concerned that Study 175 was not turned over to the FDA in a timely manner. A deputy director at the FDA Office of Drug Safety was asked whether it would "have been important...to know that in 2001 GlaxoSmithKline found that they lost against its competitor Actos" and responded:

> ...any information pertaining to a serious adverse event, such as myocardial infarction, and especially death, is a high alert for any safety officer at the FDA. So any information, including something like this, because the lipid profile go to some biological mechanism by which maybe one drug may have more safety –adverse event than another within the same drug class, it would be extreme important information for someone in my position to consider.[*sic*] [ATTACHMENT D]

On a separate occasion, GSK executives discussed, in email, whether to publish two GSK studies that also found problems with Avandia. In an email sent on July 20, 2001, a GSK executive responded, "Not a chance. These put Avnadia [sic] in quite a negative light when folks look at the response of the [Avandia] arm. It is a dificult [sic] story to tell and we would hope that these do not see the light of day. We have already published the better studies." [ATTACHMENT E]

Finally, GSK told Committee investigators that GSK examined Avandia for heart attack risk in 2001. GSK told Committee investigators that they never provided this document to FDA, but they did provide the underlying data to FDA. We have attached that 2001 report to this letter, in case the information may prove important to the FDA. [ATTACHMENT F]

[1] According to the Mayo Clinic: It's important to keep your cholesterol levels within healthy limits. And if

## AVANDIA WAS PART OF GSK'S GHOSTWRITING PROGRAM

As reported by the *Associated Press*, GSK created a "sophisticated ghostwriting program to promote its antidepressant Paxil." GSK called this program CASPPER.[2] Avandia was also part of GSK's CASPPER program and GSK created at least one ghostwritten article for an academic. While this behavior is not illegal, we would like to apprise you of what we found. In an internal GSK memo written on September 13, 2000, GSK explained the value of CASPPER. According to the document:

> CASPPER provides you the ability to offer assistance in the preparation and publication of case studies and other short communications relevant to the clinical use of Avandia....Your participation can help establish or enhance your relationships with your physicians or other healthcare professionals. [ATTACHMENT G]

Other documents show that GSK prepared at least one ghostwritten manuscript. For example, in an email sent on August 13, 2001, a GSK employee wrote, "[S]ee attached manuscript that has been ghost written for Haffner." Further down, the email continued, "Please find attached the Haffner manuscript....The manuscript is currently in a rough format that has not gone to the author yet." [ATTACHMENT H]

We have attached several drafts of the ghostwritten document for FDA to review, a draft of a letter with the study that is addressed to the journal Circulation, and copy of the study that was published in July 2002 in the journal *Circulation*. [ATTACHMENT I]

We appreciate your review of these documents. If you have any questions, please do not hesitate to contact Christopher Law of Senator Baucus's staff or Paul Thacker of Senator Grassley's staff at (202) 224-4515.

Sincerely,

Max Baucus
Chairman

Charles E. Grassley
Ranking Member

Attachments

[2] Perrone, Matthew, "Glaxo Used Ghostwriting Program to Promote Paxil," *Associated Press*, August 19, 2009.

# ATTACHMENT A

From: Martin I Freed/DEV/PHRD/SB_PLC

To: Stuart C Dollow/GB1/GlaxoWellcome@ExchangeUK @ SB

CC: Ameet Nathwani-1/DEV/PHRD/SB_PLC@SB_PHARM_RD@SB;
Christine L Blumhardt/SB-OTHER/PHRD/SB_PLC@SB_PHARM_RD@SB;
Colette M Bellin/HEP/WSO/SB_PLC@SB;
Hilary M Malone/TRAC/PHRD/SB_PLC@SB_PHARM_RD@SB;
JaiKrishna Patel/US1/GlaxoWellcome@ExchangeUS@SB;
Joanna M Balcarek/DEV/PHRD/SB_PLC@SB_PHARM_RD@SB

Subject: Re: [redacted]

Date: 03/29/2001 08:08:18 (GMT-05:00)

There was no Avandia v Actos study performed in exSB. Study 175 was an Actos only study performed to give us enough info using historical comparison to make a decision about large scale H-H. This was done for the US business, way under the radar and we lost both in terms of LDL and Tgs. Per Sr Mgmt request, these data should not see the light of day to anyone outside of GSK.

Marty

From: Stuart C Dollow/GB1/GlaxoWellcome@ExchangeUK on 29-Mar-2001 03:44

To: Joanna M Balcarek, Martin I Freed, Ameet Nathwani-1, Colette M Bellin, Hilary M Malone, Christine L Blumhardt
cc: JaiKrishna Patel
Subject: [redacted]

[redacted]

I have heard also that there was an Avandia vs Actos study performed in ex SB, but have not seen the data from this. can someone send me the data so that I can have as comprehensive a package as possible for Mike Ferris

Many thanks

Regards

Stuart

Dr Stuart Dollow
Global Clinical Head
Metabolic and Musculoskeletal Clinical Development
GlaxoSmithKline

Tel [redacted]
Fax [redacted]
email [redacted]

Attachments:
Revised Study 175 Headline Results Summary.doc

# ATTACHMENT E

From: Martin I Freed/DEV/PHRD/SB_PLC

To: Rhona A Berry/DEV/PHRD/SB_PLC@SB_PHARM_RD

CC: David 8 Harrison/GB1/GlaxoWellcome@ExchangeUK

BCC: Alexander R Cobitz/DEV/PHRD/SB_PLC

Subject: Re: Publications for 079 and 096

Date: 07/20/2001 13:37:11 (GMT-05:00)

Rhona - Not a chance. These put Avnadia in quite a negative light when folks look at the response of the RSG monotherapy arm. It is a dificult story to tell and we would hope that these do not see the light of day. We have already published the better studies...015 (?can't rmember ..maybe Gomis?) and 094 (Fonseca).

Marty

Rhona A Berry 20-Jul-2001 13:28

Metabolic CDPS UP 4310 tel [redacted] fax [redacted]
To: Martin I Freed
cc: David 8 Harrison
Subject: Publications for 079 and 096

Marty,

Are NAMA planning to publish manuscripts for studies 079 and 096?

Best regards,

Rhona
---------- Forwarded by Rhona A Berry/DEV/PHRD/SB_PLC on 07/20/2001 13:27 ----------
From: David 8 Harrison/GB1/GlaxoWellcome@ExchangeUK on 20-Jul-2001 07:52

To: Rhona A Berry
cc:
Subject: Publications

Hi Rhona,

I've been asked by EMA whether there are any plans to publish manuscripts based on studies 079 and 096. From CPMS it appears that both studies finished in 1998. Any ideas or ideas on who to contact?

Thanks - see you on Monday!

David

David Harrison
Avandia Publication Strategy Manager
GlaxoSmithKline
Greenford Building 6 Room G12
Phone [redacted] ([redacted] int)
Fax [redacted] ([redacted] int)

Attachments: embedded picture.tif

# ATTACHMENT G

**September 13, 2000**

**To:** All Avandia Consultants

**From:** Nejla Abbed
Avandia Product Management

**CC:** Avandia Product Team
D. Brand
D. Pernock
D. Tasse'
IHD Area Directors
Managed Care Segment Directors
RBAs
RSOAs
RVPs

**Subject:** ***Avandia*** **CASPPER**

## Highlights:

- In your field mail envelope, you will find a brochure to introduce you to the CASPPER program being sponsored by SmithKline Beecham and Avandia Product Management.

*Avandia* Product Management is launching CASPPER, Case Study Publications for Peer Review. This innovative program is a tool for you to bring value to your customers and gives you the opportunity to work closely on issues important to them. CASPPER provides you the ability to offer assistance in the preparation and publication of case studies and other short communications relevant to the clinical use of *Avandia*. SmithKline encourages publications to broaden the knowledge of Avandia and provide credible answers to competitive issues.

Your participation can help you establish or enhance your relationships with your physicians or other healthcare professionals. CASPPER supports your sales efforts by providing a valuable service to your customers and by increasing the literature for *Avandia*.

# ATTACHMENT H

From: Julia M Eastgate
Date Sent: 8/13/2001 2:44:57 PM
To: Murray W Stewart
CC: Arvind Agrawal-1
Subject: Haffner - CV review article

---

Murray - see attached manuscript that has been ghost written for Haffner. I think it is VERY poorly written....what are your thoughts? Also, I notice that the US refer to the '5 modifiable CV risk factors' but do not mention obesity. We have obesity down as one of our 5 modifiable risk factors and have combined the lipid factors under the umbrella 'dyslipidemia'. Am I correct in believing that the US have 'cherry picked' here because they do not want to address obesity?
Thanks
Julia

Dear All,

Please find attached the Haffner manuscript, 'Modifying cardiovascular risk in the Type 2 diabetes patient'. The manuscript is currently in a rough format that has not gone to the author yet. However, Michael DiMatteo would appreciate your comments at this time. The manuscript is to be targeted to the American Journal of Cardiology.

Please review the manuscript by close of business on Wednesday 15th August and return any comments to Michael with a copy to me.

Thanks, once more, for your review.

Regards

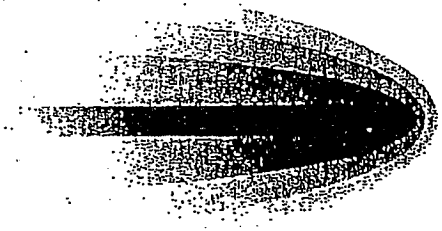
David

David Harrison
Avandia Publication Strategy Manager
GlaxoSmithKline
Greenford Building 6 Room G12
Phone [redacted] ([redacted] int)
Fax [redacted] ([redacted] int)

Murray )
Julia Eastgate
Head of Diabetes Communications, Europe
HW83, 3.316
Tel: + [redacted]
Fax: + [redacted]

# ATTACHMENT 1-d

# ZOLOFT: PSC UPDATE



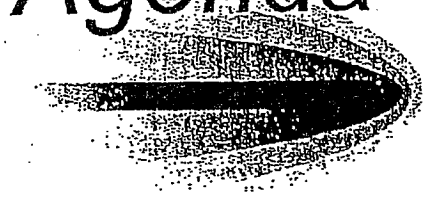
## STATUS REPORT AND PROCESS IMPROVEMENT CHANGES

Cathryn Clary

WWT Meeting

July 27,2000

# Agenda



- Purpose of publications
- Publication Process Update
- PSC and PSC subteams--Role
- Publications process
- PSC Update

# *Purpose of publications*

***What is the purpose of publications?***

- Medical communication of a new scientific finding
- Highlight efficacy, safety or tolerability feature of the drug
- Present results of a study or subanalysis
- Highlight drug's superiority to a competitor(s)
- Collaborate with opinion leaders

# *Purpose of Publications*

- Leverage good will with academic investigators
  - enhance relationships with potential speakers
- Inrease media and public perception of drug and of Pfizer
- Support regulatory requests worldwide
- Provide tools for sales force to drive prescriptions based on data

# *Purpose of publications: THE BOTTOM LINE*



***High quality*** and ***timely***

publications optimize our ability to

sell Zoloft most effectively

# *Areas needing process improvement*

- Under-resourcing of clinical and statistical groups
  - inadequate ability to "do it all"
- Conflicting priorities
  - With regulatory filings, closeouts etc
- Misalignment of goals
  - PGRD--Filings
  - PPG--Publications for marketing

# *PSC Process Re-engineering*

- Attempt to address problem areas
  - Under-resourcing=> Prioritization
  - Conflicting priorities==>Prioritization
  - Misalignment of goals==>ZSC working together to make sure that PGRD and PPG goals aligned around publication
- Process/Timeline Tracking Procedure instituted with new process to continue to identify/improve problems as we move forward

# PSC Composition and Function

- PSC Role
  - Strategic, not tactical body
  - Compromised of subteam heads as standing members
  - Takes inputs from subteams, prioritizes all manuscripts
  - Responsible for overall publication strategy
    - Reporting to ZSC
  - Sets strategy about review articles and others that do not fit into subteam structure
  - MAC-USA plays administrative/reporting function

# *PSC Composition*

- Subteam leaders from previous slide
- Sharon Hakes
- MAC-USA
- Other Zoloft manuscript champions welcome to attend *ad hoc*

# PSC Subteams/Subteam Leaders

| | |
|---|---|
| Depression | John Gillespie |
| OCD | Carol Austin |
| Panic Disorder | Cathryn Clary |
| PTSD | Cathryn Clary |
| Social Phobia | Roger Lane |
| Outcomes | Amy Grudzinski |
| Women | Vicki Gianakakos |
| Elderly | Tal Burt |
| QOL | Cathryn Clary |

# PSC Subteams--Strategic Role

- Each team plays strategic and tactical role
- As experts in a given area, review and prioritize all manuscripts in that area for alignment with marketing strategy, scientific merit, literature review, strength of discussion/ figures, etc
- Subteam leaders must agree with:
  - choice of journal
  - first author chosen for each manuscript
  - first author for each poster
  - content of posters/manuscripts
- Send articles for review to subteam leader, Cathryn or Sharon, for distribution

# PSC Subteams: Composition

- Membership: Commercial subteam leader, members from US and major market medical/marketing, CDO, CSA/CNS MSL as appropriate…ie
  - Gail Farfel on PTSD subteam
  - Donna Jermain(MSL) on Women's subteam

- Subteam leaders responsible for overall strategy in that area, prioritization and *timelines on key manuscripts*, minutes of meetings, process improvement reports, monthly report to PSC

# *Publication Process*

- MAC/PSC have instituted new publication process..with process improvement tracking
  - Subteams identify posters/pubs and prioritize them
  - Subteam leader starts tracking a manuscript at first draft..MAC reports variance from pre-determined ideal timelines

# *Publication Process*

- Process for manuscript review
  - First draft reviewed by subteam members
  - External author review
  - Incorporation of external author comments
  - Re-review by subteam/QC by CSA or CDO statistician
  - ZSC marketing signoff *prior to* submission
  - Timelines for all steps tracked

# *Publication Process*

- Over time will be able to identify which processes need improvement
- Subteams review and approve prior to author review
- ZSC team leaders see at first author review, then right before submission(subteam leader to send to them)
- Statistical review (CDO, CSA prior to submission)

# Data "Ownership" and Transfer

- Pfizer-sponsored studies belong to Pfizer, not to any individual
- Purpose of data is to support, directly or indirectly, marketing of our product
  - Through use in label enhancements, sNDA filings
  - Through publications for field force use
  - Through publications that can be utilized to support off-label data dissemination
- Therefore commercial marketing/medical need to be involved in all data dissemination efforts

# Data "Ownership" and Transfer

- Ideal: Peer-reviewed publication at launch of the new label
  - We currently fall far short of that benchmark
- Solution: PGRS databases are accessible to CDO for PPG use at time of database release
  - Primary manuscripts are authored by PGRD clinicians collaborating with appropriate subteam
  - Secondary analyses are led by PPG medical in conjunction with subteam strategy

# *Authorship of Posters/Manuscripts and Journal Selection*

- Academic/investigator authors
  - Strategic decision which needs to take into account *not only* contribution to study design, execution, and manuscript but also credibility, ability to serve as spokesperson for the data/study
- Journal Selection
  - Tactical decision involving timelines for review, ease of acceptance, ability to fast-track post-acceptance, overall flow of all sertraline articles
- Commercial subteam leader/PSC co-chair sign off on authorship of papers as well as journal selection

# *Authorship of Posters/Manuscripts*

- In line with JAMA guidelines
  - Routine statistical analysis or study report writing do not meet guidelines for authorship
- Pfizer authors
  - Generally academic investigators as first author optimal
  - Manuscripts should not have more Pfizer authors than external authors

# PSC Update

- On track for 36 peer-reviewed publications this year
- 10 + more than last year

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# Recent Publications

- **Elderly**
  - Bondareff et al. Comparison of sertraline and nortriptyline in the treatment of major depressive disorder in late life. *Am J Psychiatry May 00*
- **Anxiety**
  - AEP Symposium Proceedings in *J Psychopharma June 00*
  - Articles on OCD, Panic, PTSD, Social Phobia, Impulsivity
- **PTSD**
  - Brady et al. Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. *JAMA Apr 00*
  - Culpepper L. Recognizing and Treating Post-Traumatic Stress Disorder *Hippocrates June 00.*

# Recent Publications

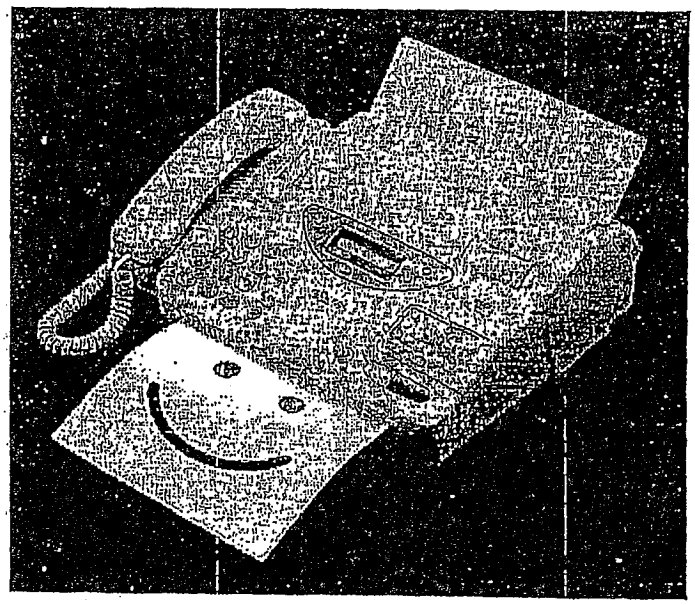
- **Panic Disorder**
  - Rapaport et al, Is placebo response the same as drug response in panic disorder? *Am J Psychiatry June 00.*
- **Outcomes Research**
  - Berndt et al, Lost human capital from early onset chronic depression. *Am J Psychiatry June 00.*
  - Berndt et al, Comparing SSRI treatment costs for depression using retrospective claims data: the role of nonrandom selection and skewed data. *Value Health May/June 00.*
  - Berndt, et al, Health care use and at-work productivity among employees with mental disorders. *Health Affairs Jul-Aug 00.*
  - Katzelnick, et al. Randomized trial of a depression management program in high utilizers of medical care. *Arch Fam Med Apr 00.*

# *Upcoming Publications*

| | |
|---|---|
| • Sert/fluox in late-life depression | August *J Clin Psych* |
| • Prime-MD Women validation | Sep *J Ob Gyn* |
| • SSRI weight gain | Sep *J Clin Psych* |
| • Sert/parox comparator | December *J Clin Psychopharm* |
| • Social Phobia relapse | Dec *J Clin Psychopharm* |
| • Sertraline in EtOH dependence | ?Sep *J Psychopharmacol* |
| • Gender in chronic depression | Aug/Sep *Am J Psych* |
| • Sertraline vs. amitriptyline | ?? *Pharmacopsychiatry* |
| • Sertraline vs clomipramine/severe dep | ?? *Int Clin Psychopharm* |

> *Additional articles on sertraline in head injury, platelet activation and diabetic neuropathy*

# LUSTRAL PRODUCT PLAN 1998



PREPARED BY VINCE HOLDER
NOVEMBER 1997

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5.2. Publication Strategy

There will be two arms to the 1998 publication strategy:

a) PPG/ZOLOFT publications and

b) UK LUSTRAL publications

Each strategy is coordinated into a plan with the following mutual objectives:

- to maintain awareness and usage of LUSTRAL/ZOLOFT
- to develop the product scientifically and practically
- to develop the already credible bibliography and for new indications and markets

The difference lies in the targeting of the UK plan to the UK market and the global orientations of the PPG plan.

The PPG plan includes clinical data to be published covering areas of pharmacokinetics, obsessive compulsive disorder, panic disorder, the elderly and a range of miscellaneous CNS indications.

The UK LUSTRAL plan will augment some of these international data and further concentrates on publication for LUSTRAL usage in special patient groups with depression.

These data will be published in respected UK journals with an added aim to include conference posters, abstracts, spin-off review and by-lined articles during 1998 to support the promotional strategy and messages.

# ATTACHMENT 2

Jackie
Westaway-1

14-Oct-1998
13:04

To: Barry Brand, Bonnie Rossello, Lionel D Houle, Jackie C Owens, Pascale Richelle, Beatrix Steffen, Luis DE LORENZO, Ken DiPangrazia, Roland Kaan, Eddy R Bete, Frank D Anton, S Srinivasan, Christophe Weber

cc: Julie Wilson-1, Sarah Daniels-1, Jill Andrews-1, Margaret M Black, Kelron T Sparrowhawk, Graham Griffiths-1, Susanne Borrett-1, Fiona Barnard-1, Paul Jenner-1, Jane M Nicholass, Anne J Ball

Subject: Seroxat/Paxil in Adolescent Depression

Please find attached to this memo a position piece, prepared by Julie Wilson of CMAT, summarising the results of the clinical studies in Adolescent Depression.

As you will know, the results of the studies were disappointing in that we did not reach statistical significance on the primary end points and thus the data do not support a label claim for the treatment of Adolescent Depression. The possibility of obtaining a safety statement from this data was considered but rejected. The best which could have been achieved was a statement that, although safety data was reassuring, efficacy had not been demonstrated. Consultation of the Marketing Teams via Regulatory confirmed that this would be unacceptable commercially and the decision to take no regulatory action was recently endorsed by the TAT.

As you will see from the position piece the positive trends in efficacy which were seen in Study 329 are being published as a poster at ECNP this year and a full manuscript is in development. Published references will therefore be available for the study. There are no plans to publish data from Study 377.

This report has been prepared for internal use only, Data on File summaries will be prepared and issued once the final reports from the studies have been approved. This position piece will also be available on The Seroxat/Paxil resource database

Best wishes

Jackie Westaway

October 1998

# SEROXAT/PAXIL
# ADOLESCENT DEPRESSION
## Position piece on the phase III clinical studies

## EXECUTIVE SUMMARY

Results from the 2 placebo-controlled, phase III clinical trials designed to assess the efficacy and safety of Seroxat/Paxil in adolescents with major depression are now available.

Study 329 (conducted in the US) showed trends in efficacy in favour of Seroxat/Paxil across all indices of depression. However, the study failed to demonstrate a statistically significant difference from placebo on the primary efficacy measures. The second study (study 377), which was conducted in Europe, South America, South Africa and the United Arab Emirates, showed a high placebo response rate and failed demonstrate any separation of Seroxat/Paxil from placebo.

Data from these 2 studies are insufficiently robust to support a label change and will therefore not be submitted to the regulatory authorities. Results from Study 329 will be presented in abstract form at the ECNP meeting (Paris, November 1999) and a full manuscript will be progressed. There are no plans to publish data from Study 377.

Prepared by CMAt-Neurosciences

 

October 1998

# SEROXAT/PAXIL
# ADOLESCENT DEPRESSION
## Position piece on the phase III clinical studies
## FOR INTERNAL USE ONLY

## SITUATION

2 SB sponsored, placebo-controlled, phase III clinical trials have been conducted, Study 329 (US) and Study 377 (Europe, South America, South Africa and Saudi Arabia), in order to assess the efficacy and safety of Seroxat/Paxil (up to 40mg/day) in the treatment of adolescents (aged between 13 and 18 years and 11 months) with unipolar major depressive disorder (diagnosed according to DSM IIIR, Study 329 or DSM IV criteria, Study 377).

**Study 329** was a placebo-controlled, imipramine comparator study with an 8 week acute treatment phase followed by a 6 month extension phase. The acute phase has completed and the extension phase is due to complete at the end of 1998. 275 patients were recruited to the study. Results from the acute phase of this study show that there were no statistically significant differences from placebo on either of the primary efficacy parameters (change from baseline in HAMD total scores and the proportion of responders-where response was defined as a $\geq$50% reduction from baseline in HAMD score or a HAMD score $\leq$8 at endpoint). However, trends in favour of paroxetine compared with placebo were seen across all the indices of depression (change from baseline in HAMD total [p=0.133], HAMD responders [p=0.112], CGI [p=0.094] and K-SADS [p=0.065] scores) and statistically significant differences from placebo were observed in the proportion of patients in remission (defined as a HAMD score of $\leq$8 at endpoint). In general, the response to imipramine was similar to that for placebo. The 6 month extension phase has now completed and is scheduled to report at the end of 1998.

**Study 377** was a 12 week placebo-controlled study, conducted in 276 adolescents with major depression. There was a high placebo response rate in this study and no statistically or clinically significant differences from placebo were observed on either of the primary efficacy variables (proportion of patients achieving a $\geq$50% reduction from baseline in total MADRS scores and change from baseline in the K-SADS-L

Prepared by CMAt -Neurosciences

 

depressive subscale score). The only differences from placebo (secondary efficacy variables) were seen in a subgroup of patients who were ≥16 years of age.

Possible explanations for the high placebo response include;

1) The large number of study visits
2) the duration of the assessments
3) The fact that concomitant psychotherapy was not excluded
4) Question marks about the adequacy of using currently available diagnostic criteria and rating scales in younger patients
5) Adolescents may be more susceptible to a placebo effect
6) Developmental issues. Children and adolescents may respond in a pharmacologically different manner due to quantitative and/or qualitative differences in neurotransmitter/receptor systems.

**Conclusions from these studies:**

- There were no differences in the safety profile of Seroxat/Paxil in adolescents when compared to that already established in the adult population

- The efficacy data from the above clinical trials are insufficiently robust to support a regulatory submission and label change for this patient population.

**OTHER DATA:**

**Ongoing studies**: SB France are conducting a locally funded double-blind, comparative study of Seroxat/Paxil with clomipramine in adolescents with major depression (Study 511). In addition, a study in adolescents with OCD (Study 453) is underway in the US. This study comprises a 16 week open label Seroxat/Paxil treatment phase, followed by double-blind, randomisation to paroxetine or placebo for a further 16 weeks of treatment. The regulatory acceptability of these 2 studies needs to be established.

**Published data**: A review of the literature shows that 2 studies assessing the use of paroxetine in the treatment of 34 adolescents and children with depression have been published (Rey-Sanchez and Gutierrez-Cesares, 1997; Findling et al; 1996).

The first study (Rey-Sanchez and Gutierrez-Cesares, 1997) was a retrospective survey of data from 25 adolescents (aged 13-17 years) treated with paroxetine. Patients were diagnosed according to ICD 10 criteria. In 13 of the patients unipolar major depression was not the primary diagnosis. 17 patients received paroxetine as a monotherapy, 8 also received concomitant psychotropic medications (n=7 benzodiazepines, n=1 haloperidol). Paroxetine was administered at doses of 10mg (14 patients) or 20mg/day (11 patients). No specific depression rating scales were used, response was based on clinical judgement. 76% patients had a satisfactory response (11 complete remission, 8 improved with residual symptoms). A lack of satisfactory response in was observed in 6 (24%) patients. Eight patients reported side effects (somnolence or sleep disorders n=6, asthenia n=4, nausea n=3, tachycardia n=2, diarrhea n=2, headache n=2, orthostatic hypotension n=1, restlessness n=1). Two patients were withdrawn due to one due to anxiety, one due to hypotension and dizziness)

The second study (Findling et al; 1996) was conducted in 9 patients aged between 7-15 years (children and adolescents) meeting DSM IV criteria for a major depressive disorder. Symptomatology was assessed using HAM-D for subjects aged 13 to 15 years, and the childhood depression rating scale (CDRS) subjects aged 12 or younger. Paroxetine was initially given at a dose of 10mg/day. This was escalated to 20mg/day if the patient had not responded after 4 weeks of treatment. 8/9 patients responded to treatment with paroxetine. Three patients had complete remission, 5 patients had a >50% reduction in total CDRS score from baseline. CGI improved in all patients. One patient withdrew from the study at week 2 due to an adverse experience. This patient was found to have elevated serum paroxetine levels and was a poor 2D6 metaboliser. Assessment of pharmacokinetic parameters in this study showed that paroxetine had a similar half life to that reported in the adult population (15.7h [sd 9.0h] vs 24h, respectively).

## COMPETITOR ACTIVITIES:

**Lilly** are believed to be in near to completing their phase III clinical trials in adolescent depression. One relatively large placebo-controlled 8 week study with an open 12 month follow-up period conducted in 96 patients (aged 8-18 years) has recently been published (Emslie et al; 1997 and 1998). These data show that 56% (27/48) patients on fluoxetine (20mg/day) compared with 33% (16/48) patients on placebo were rated as much or very much improved on the CGI at Week 6 (p=0.02. In the 12 month



 

follow-up period, 85% (n=74) patients recovered from the depressive episode (47 on fluoxetine, 22 on placebo and 5 on other antidepressants or lithium). Twenty nine (39%) of the patients (36% of those who had recovered on fluoxetine [17/47] and 41% of those who had recovered on placebo [9/22] had a recurrence of depression during the 12 month follow-up (a higher recurrence rate than seen in adults). Other published data on fluoxetine are from small open studies or individual case reports (Colle et al; 1994).

**Pfizer** already have positive data (including PK data) and are licenced in the US for the treatment of adolescent OCD. In addition, Pfizer are also believed to be conducting clinical trials in adolescent depression. Available published data are limited, derived from small open studies in adolescent depression (McConville et al; 1996; Tierney et al; 1995)

## TARGET

To effectively manage the dissemination of these data in order to minimise any potential negative commercial impact.

## PROPOSALS

- Based on the current data from Studies 377 and 329, and following consultation with SB country regulatory and marketing groups, no regulatory submissions will be made to obtain either efficacy or safety statements relating to adolescent depression at this time. However data (especially safety data) from these studies may be included in any future regulatory submissions, provided that we are able to go on and generate robust, approvable efficacy data. The rationale for not attempting to obtain a safety statement at this time is as follows;

  i) regulatory agencies would not approve a statement indicating that there are no safety issues in adolescents, as this could be seen as promoting off-label use

  ii) it would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine.

- Positive data from Study 329 will be published in abstract form at the ECNP (Paris, November 1998) and a full manuscript of the 329 data will be progressed.

Prepared by CMAt -Neurosciences

- The regulatory acceptability of Studies 511 and 453 and any other data in this patient population will continue to be investigated.

## REFERENCES

1. Rey-Sanchez F; Gutierrez-Cesares JR. Paroxetine in children with major depressive disorder: an open trial. J Am Acad Child Adolesc Psychiatry1997; 36 (10): 1443-1447.

2. Findling R Fiala S, Myers C et al. Putative determinants of paroxetine response in pediatric patients with major depression. Psychopharmacol Bull; 1996; 32 (3):446.

3. Emslie GJ, Rush AJ, Weinberg WA et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. Arch Gen Psychiatry; 1997; 54 (11): 1031-1037.

4. Emslie GJ, Rush AJ, Weinberg WA et al. Fluoxetine in child and adolescent depression: acute and maintenance treatment. Depression and Anxiety (US); 1998; 7 (1): 32-39.

5. Colle LM, Belair JF, DiFeo M et al. Extended open label fluoxetine treatment of adolescents with major depression. J Child Adolesc Psychopharmacol. 1994; 4 (4): 225-232.

6. McConville BJ, Minnery RL, Sorter MT et al. An open study of the effects of sertraline on adolescent major depression. J Child Adolesc Psychopharmacol. 1996; 6 (1):41-51

7. Tierney E, Joshi PT, Llinas JF et al. Sertraline for major depression in children and adolescents: Preliminary clinical experience. J Child Adolesc Psychopharmacol; 1995; 5 (1):13-27.



 

October 1998

Prepared by CMAt -Neurosciences

# ATTACHMENT 3

**Mosholder, Andrew D**

**From:** Katz, Russell G
**Sent:** Tuesday, June 03, 2003 9:24 AM
**To:** Mosholder, Andrew D
**Subject:** RE: Paxil and pediatric suicidality

**Tab 1**

Andy-

Thanks a lot. We'll send over a formal consult ASAP.

Rusty

-----Original Message-----
**From:** Mosholder, Andrew D
**Sent:** Tuesday, June 03, 2003 8:56 AM
**To:** Katz, Russell G
**Cc:** Willy, Mary E
**Subject:** RE: Paxil and pediatric suicidality

Hello, Rusty,
Yes, I would be interested in working on this consult. I've confirmed my availability to do so with my team leader, Mary Willy (I'm cc-ing her on this reply).
As I recall, a number of the other SSRI pediatric supplements showed signals for behavioral adverse events. But these were mainly events such as agitation and hypomania, not self-injury (unless, as you suggest, they were similarly obscured by inappropriate terminology).
Regards
Andy

> -----Original Message-----
> **From:** Katz, Russell G
> **Sent:** Monday, June 02, 2003 4:12 PM
> **To:** Mosholder, Andrew D
> **Subject:** Paxil and pediatric suicidality
>
> Andy-
>
> Hi, hope you are well.
>
> We have recently become aware of a presumed association
> between Paxil and suicidality in pediatric patients. We
> received a call from the EMEA a little over a week ago. A
> Dr. Raines told us that the company (GSK) had submitted data
> that demonstrated that use of Paxil in kids was associated
> with increased suicidality compared to placebo, and that the
> company proposed labeling changes; I believe she also said
> that it was in the news, and it was a big issue. Tom and I
> told her that the company had not informed us of any of this,
> and we agreed to look into it.
>
> It turns out that the sponsor was in the process of
> submitting to us a partial response to a question we asked in
> the Approval letter for the pediatric use (you, you may
> recall, were the reviewer). Specifically, we had asked them
> to further elaborate the events subsumed under the preferred
> term "Emotional Lability". We have received this partial
> response, and almost all of these events related to
> suicidality. The bottom line is that when data from the
> controlled trials in depression, OCD, and Social Anxiety are

> pooled, for "possible suicide related" events occurring
> during treatment or within 4 days after discontinuation, the
> rate is 0.14/patient-year on drug, and 0.05/patient-year on
> placebo, p=0.02. We have some problems with the methodology
> they used to capture cases, but this is the major finding,
> and it has us worried. The sponsor has not proposed labeling
> changes, and makes a feeble attempt to dismiss the finding.
> We are also awaiting the submission of what the sponsor
> submitted to the UK.
>
> We want to move quickly to evaluate this signal. We are
> planning to look at the NDAs for the other SSRIs to see
> whether or not similar events are being hidden by various
> inappropriate coding maneuvers, but we'd also like to compare
> the drugs in other meaningful ways if we can. We also want
> to call the sponsor very soon and ask some questions about
> their methodology.
>
> We want to send a consult over to you folks, and ask that you
> be assigned the project. Given your history with this
> application and this general issue, we think you would be the
> right person to help us think about the best way to approach
> the data in the other NDAs (and their sponsors), as well as
> to provide ideas for further sources of potentially relevant
> data and possible approaches to better evaluate this signal
> study (e.g., insurance claims databases, etc.). Anyway, I
> wanted to run this by you to see if you have any strong
> objections to being fingered as the guy to do this; if you're
> OK with it, we'll send a formal consult request. Also, we'd
> like you to be in on the phone call, if possible. Of course,
> we recognize that we'd need to get you the submission pronto.
>
> Hope you can do this; if you could let me know soon, either
> way, that'd be great.
>
> Thanks,
> Rusty

**Mosholder, Andrew D**

**Tab 2**

**From:** Laughren, Thomas P
**Sent:** Tuesday, June 03, 2003 12:53 PM
**To:** Nighswander, Robbin M
**Cc:** Katz, Russell G; Racoosin, Judith A; Dubitsky, Gregory M; Mosholder, Andrew D; David, Paul A
**Subject:** RE: reminder-weekly report

Robbin,

On 6-23-03, Rusty and I first became aware of concerns in the UK about an increased risk of suicidal ideation in pediatric patients taking paroxetine, based on results of new analyses of safety data from a pool of 6 pediatric studies (3 in MDD, 2 in OCD, and 1 in social anxiety disorder). These analyses were actually done in response to requests (included in our 10-10-02 approvable letter the Paxil pediatric supplement) for a more detailed breakdown of events subsumed under the broad heading, "emotional lability;" in particular, we were interested in analyses focusing on events considered to represent suicidality. These results had been sent to the MHRA (UK) before being sent to FDA, due to a difference in the timing of submissions. We have now received these data (in a submission dated 5-22-03, but not received until 5-28-03), as a partial response from GSK to our approvable letter for the Paxil pediatric supplement. These analyses suggest an excess risk of suicidality in patients taking Paxil compared to those taking placebo. The submission to the UK had also included draft labeling to describe this risk, however, I have been informed by David Wheadon, M.D., of GSK, that the MHRA has stated its intent to contraindicate paroxetine in pediatric major depressive disorder, on the basis of these data along with the negative results in the pediatric major depressive disorder studies. GSK does not agree, and they are currently negotiating with the UK and other European regulatory agencies. GSK intends to fully respond to the 10-10-02 approvable letter for the Paxil pediatric supplement by the third week of June, and this will include proposed labeling to address this risk, but also new language regarding the OCD claim in peds. Since the original review of the Paxil supplement, as well as the reviews of most other pediatric supplements for SSRIs, was done by Andrew Mosholder, M.D., and these requests were a direct result of Dr. Mosholder's review, we have submitted a consult to ODS and have asked that this consult be assigned to him in his new position in ODS. We seek his advice on further analysis and interpretation of the Paxil results, as well as more general advice on what might be done to reconsider the pediatric databases for other SSRIs. In addition, we would be interested in his thoughts on further studies that might be done to better understand this signal, e.g., a cohort study using claims based data, perhaps looking at hospitalization for suicidality as an endpoint.

Tom

-----Original Message-----
**From:** Nighswander, Robbin M
**Sent:** Tuesday, June 03, 2003 11:52 AM
**To:** Katz, Russell G; Laughren, Thomas P
**Subject:** FW: reminder-weekly report

Rusty and Tom:

Although I included a brief description in last weeks report, as you can see, John would like a longer summary. Last weeks report is attached.

Thanks

Robbin

<< File: OND1 Weekly Report May 28 2003.doc >>

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# Tab 3

## REQUEST FOR CONSULTATION

| TO (Division/Office): | | | FROM: | |
|---|---|---|---|---|
| Mail: ODS (Room 15B-08, PKLN Bldg.) | | | HFD-120/Division of Neuropharmacological Drug Products | |
| DATE: 6-5-03 | IND NO. | NDA NO.: 20-031/SES-037 | TYPE OF DOCUMENT: Minor Amendment | DATE OF DOCUMENT: 5-22-03 |
| NAME OF DRUG: Paxil (paroxetine HCl) Tablets | PRIORITY CONSIDERATION | | CLASSIFICATION OF DRUG: Selective Serotonin Reuptake Inhibitor (SSRI) | DESIRED COMPLETION DATE |

NAME OF FIRM: GSK

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER (SPECIFY BELOW):

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

COMMENTS/SPECIAL INSTRUCTIONS:

We have received a partial response (5-22-03) from GSK to our approvable letter for the Paxil pediatric supplement, including results of new analyses of safety data from a pool of 6 pediatric studies (3 in MDD, 2 in OCD, and 1 in social anxiety disorder). These analyses were in response to requests in our 10-10-02 approvable letter for a more detailed breakdown of events subsumed under the broad heading, "emotional lability;" in particular, we were interested in analyses focusing on events considered to represent suicidality. These analyses have been done, and they suggest an excess risk of suicidality in patients taking Paxil compared to those taking placebo. Since the original review of the Paxil supplement, as well as the reviews of most other pediatric supplements for SSRIs, was done by Andrew Mosholder, M.D., and these requests were a direct result of Dr. Mosholder's review, we ask that this consult be assigned to him. We seek his advice on further analysis and interpretation of the Paxil results, as well as more general advice on what might be done to re-evaluate the risk of suicidality in the pediatric databases for other SSRIs. In addition, we would be interested in his thoughts on epidemiological studies that might be done to better understand this signal, e.g., a cohort study using insurance claims based data, perhaps looking at hospitalization for suicidality as an endpoint.

If you have any questions, please feel free to contact the Safety Group Team Leader, Dr. Judith Racoosin (x4-5505), or the Project Manager, Mr. Paul David (x4-5530).

| SIGNATURE OF REQUESTER | METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND |
|---|---|
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
---
Russell Katz
6/6/03 12:39:48 PM

**Mosholder, Andrew D**

**From:** Mosholder, Andrew D
**Sent:** Thursday, June 19, 2003 4:30 PM
**To:** Katz, Russell G; Laughren, Thomas P; Andreason, Paul J; Stasko, Robert; Racoosin, Judith A; David, Paul A
**Subject:** Paroxetine suicidality data in 4-11-02 submission

**Tab 4**

Hello all,

During today's meeting there were some questions about exactly what data the sponsor provided on this topic, and why we asked for what we requested in the approvable letter. This prompted me to look back at the approvable letter, the original ISS for the supplement (which is still available via the EDR) and my clinical review from last October.

The sponsor did provide a line listing of all patients with serious adverse events (ISS Table 7.8) for both drug and placebo. This table showed suicide attempts such as overdoses coded as "emotional lability," which is how we knew that was being done. Using Table 7.8, I noted in my review that there was a higher rate of suicidality-related serious adverse events for paroxetine than for placebo in the acute trials, but that this was not statistically significant.

Additionally, the sponsor provided a line listing for *all* adverse events coded as "emotional lability," "hostility," or "agitation" (ISS Table 6.14). Although it included nonserious events as well as serious, it did not include placebo patients, only paroxetine patients. This table also showed suicide attempts coded as emotional lability.

As a result of this situation, we asked for the following in the approvable letter:

> Table 6.14 in the ISS listed paroxetine treated patients who experienced adverse events coded under the terms hostility, emotional lability or agitation. However, the table did not include placebo patients, nor did it include psychiatric adverse events that were coded under other terms. Please prepare an expanded version of this table, including all psychiatric and behavioral adverse events, and also those that occurred among placebo patients...

We also asked GSK to provide a rationale for their coding of suicide attempts as emotional lability.

Also, the data from the Social Anxiety Disorder trial was still blinded when the supplement was submitted.

I hope this historical information is helpful.

-Andy

**Mosholder, Andrew D**

**Tab 5**

**From:** Mosholder, Andrew D
**Sent:** Monday, June 23, 2003 10:24 AM
**To:** Racoosin, Judith A
**Subject:** RE: coding dictionary for paxil peds MDD supplemental NDA

Hi Judy,

Here's what is says in the Paxil pediatric supplement ISS, section 6.3.1.

> AEs were coded from the verbatim terms provided by the investigators by using the World Health Organization Adverse Reaction Terminology (WHO ART) codelist. These terms were then mapped to Adverse Drug Experiences Coding System (ADECS) classification to provide body system and preferred term. The ADECS is a COSTART based dictionary. Gender specific events were tabulated separately from gender non-specific events to allow percentages to be corrected for gender. As stated previously, the coding process differed between the acute clinical studies and acute clinical pharmacology Study 715 (i.e., for Study 715, terms were not mapped to ADECS). Therefore, body system and preferred terms will differ between these studies.

Of course, study 715 is not relevant here.

-Andy

> -----Original Message-----
> **From:** Racoosin, Judith A
> **Sent:** Monday, June 23, 2003 10:14 AM
> **To:** Mosholder, Andrew D
> **Subject:** coding dictionary for paxil peds MDD supplemental NDA
>
> Hi Andy,
> Do you know which coding dictionary was used for the paxil
> peds MDD supplemental NDA? You have probably already told me,
> but I just can't recall.
>
> thanks
> Judy

**Mosholder, Andrew D**

**From:** Pamer, Carol
**Sent:** Tuesday, June 24, 2003 9:13 AM
**To:** Racoosin, Judith A
**Cc:** Mosholder, Andrew D; Singer, Sarah J
**Subject:** FW: Suicide-related terms in WHO-ART?

**Tab 6**

Clear Day Bkgrd.JPG

From our coding guru, Sally Singer.

Carol

-----Original Message-----
**From:** Singer, Sarah J
**Sent:** Tuesday, June 24,2003 9:10 AM
**To:** Pamer, Carol; Goetsch, Roger A; Piazza Hepp, Toni D
**Cc:** Lu, Susan
**Subject:** RE: Suicide-related terms in WHO-ART?

Hi Carol,
I have an old COSTART manual; SUICIDE ATTEMPT did exist. The manual has a COSTART to WHOART translation table which states that SUICIDE ATTEMPT also existed in WHOART.
-Sally

-----Original Message-----
**From:** Pamer, Carol
**Sent:** Tuesday, June 24, 2003 9:07 AM
**To:** Goetsch, Roger A; Piazza Hepp, Toni D; Singer, Sarah J
**Cc:** Lu, Susan
**Subject:** Suicide-related terms in WHO-ART?

Good morning--

A question has come up about the way that suicides/suicide attempts were coded in a recent NDA supplement. Apparently the company chose a term like "emotional lability" when in actuality most were suicide attempts. They used WHOART and COSTART as their dictionaries (see below), and a dictionary I am not familiar with, ADECS. We are talking about CSK and Paxil pediatric supplement. FYI. How can we verify that WHOART has a specific term for suicide/attempts? I don't have a copy of a WHOART reference, if there is one around here. It would also be helpful to have someone verify for me that COSTART has Suicide Attempt and perhaps others for the same. Too many brain cells have come and gone for me since the era of COSTART!!

Thanks!

Carol

# ATTACHMENT 4

International Journal of Risk & Safety in Medicine 20 (2008) 73–81
DOI 10.3233/JRS-2008-0426
IOS Press



# Clinical trials and drug promotion: Selective reporting of study 329

Jon N. Jureidini [a,*], Leemon B. McHenry [b] and Peter R. Mansfield [c]

[a] *Discipline of Psychiatry, University of Adelaide, Adelaide, South Australia*
[b] *Department of Philosophy, California State University, Northridge, CA, USA*
[c] *Discipline of General Practice, University of Adelaide, Adelaide, South Australia*

**Abstract.** Selective reporting is prevalent in the medical literature, particularly in industry-sponsored research. In this paper, we expose selective reporting that is not evident without access to internal company documents. The published report of study 329 of paroxetine in adolescents sponsored by GlaxoSmithKline claims that "paroxetine is generally well tolerated and effective for major depression in adolescents". By contrast, documents obtained during litigation reveal that study 329 was negative for efficacy on all 8 protocol specified outcomes and positive for harm.

Keywords: Selective reporting, SSRI, litigation, industry sponsorship

## 1. Introduction

Selective reporting is a significant problem in drug trials [1]. One study found a discrepancy between the primary outcomes specified in the trial protocols, and those listed in the published paper in 62% of 112 trials. Only 50% of efficacy outcomes and 35% of harm outcomes were reported. Efficacy outcomes were more than twice as likely to be reported if they were statistically significant [2]. Selective reporting has been especially problematic in antidepressant research [3,4]. We use internal documents made available during a class action lawsuit (*Beverly Smith vs. SmithKline Beecham*) to illuminate selective reporting of study 329 of paroxetine (Paxil/Seroxat) in adolescent depression. This study was funded by SmithKline Beecham (SKB), now GlaxoSmithKline (GSK) after merging with Glaxo Wellcome in 2000. A report of study 329 was published by the *Journal of the American Academy of Child and Adolescent Psychiatry* (*JAACAP*) in July 2001 [5]. Its authors claimed that paroxetine was "generally well tolerated and effective for major depression in adolescents". The paper became one of the most cited in the medical literature in supporting the use of antidepressants in child and adolescent depression [6] and GSK claimed it demonstrated "REMARKABLE Efficacy and Safety" [7]. In 2007 systematic reviewers were still describing study 329 as a positive trial [8]. Yet this study was negative on all protocol-defined outcomes and demonstrated important safety problems [9].

The aim of this paper is to expose selective reporting that would not be apparent without access to documents that only emerged through litigation [10]. In June 2004 Californian law firm, Baum Hedlund, alleged that GSK misrepresented the safety and efficacy of paroxetine in the pediatric population. In the

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course of that (now largely settled) litigation, GSK were required to provide all relevant documents. Approximately 10,000 pages of documents were made available to J.N.J. by Baum Hedlund, who had contracted him to provide independent psychiatric review of the data. All documents were initially deemed confidential, but after Baum Hedlund made challenges that certain documents did not reveal trade secrets to competitors, some were released into the public domain. To ensure that this paper is based only on the publicly available documents P.R.M., who has not had access to the confidential documents, was given responsibility for quality control of a draft prepared by J.N.J. and L.B.M. All documents referred to in this paper are available to the reader (www.healthyskepticism.org/documents/PaxilStudy329.php), allowing verification of all claims. J.N.J. and L.B.M. assert that no document withheld from the public domain by confidentiality constraints imposed by GSK contradicts any of the documents cited here.

## 2. Changes in outcome measures

### 2.1. Initial study design

In 1992 Martin Keller, MD, Chairman of Psychiatry at Brown University, Rhode Island and colleagues successfully proposed to SKB a multi-site study of a selective serotonin reuptake inhibitor and a tricyclic antidepressant in adolescent major depression [11]. The 1993 protocol for the study (and its subsequent amendments) specified two primary outcome measures: change in total Hamilton Rating Scale (HAM-D) score; and proportion of responders (HAM-D $\leqslant 8$ or reduced by $\geqslant 50\%$) [12]. The protocol also specified six secondary outcome measures (see Table 1). Patients were enrolled between April 1994 and March 1997, with 275 patients completing the acute phase of the study by May 1997. The blind was broken in October, 1997 [13, p. 891]. *There was no significant difference between the paroxetine and placebo groups on any of the eight pre-specified outcome measures* [14].

### 2.2. Introduction of new outcome measures

However, by the time the data were analysed, many other new measures had been added to the list of secondary outcomes. There was a statistically significant difference between the paroxetine and placebo groups for only two of these additional secondary outcomes: remission (defined as HAM-D $\leqslant 8$); and the HAM-D depression item. Only these two of the extra measures introduced before analysing the data were reported when study 329 was first written up for submission to *JAMA* in 1999 [15]. By that

Table 1
Outcome measures (significant results in **bold**); ordering of outcome measures is from originals

| Protocol (1993, 1996) [12] | $p$ | Final paper (2001) [5] | $p$ |
|---|---|---|---|
| *Change in HAM-D total score | 0.13 | **HAM-D $\leqslant 8$** | **0.02** |
| *Responders (HAM-D $\leqslant 8$ or reduced by $\geqslant 50\%$) | 0.11 | *Responders (HAM-D $\leqslant 8$ or reduced by $\geqslant 50\%$) | 0.11 |
| Depression scale of K-SADS-L | 0.07 | **HAM-D depressed mood item** | **0.001** |
| Mean Clinical Global Improvement (CGI) score | 0.09 | **K-SADS-L depressed mood item** | **0.05** |
| Autonomous function checklist | 0.15 | **CGI 1 or 2** | **0.02** |
| Self-perception profile | 0.54 | Depression scale of K-SADS-L | 0.07 |
| Sickness impact scale | 0.46 | Mean CGI | 0.09 |
| Relapse during maintenance | 0.24** | *HAM-D total score | 0.13 |

*Protocol specified primary outcomes. **Not published, calculated by us, trend favours placebo.

Box 1
History of the four positive 'depression related variables' unspecified in the trial protocol

| | |
|---|---|
| HAM-D $\leqslant 8$ | |
| 1992 December | Part of the complex definition of 'responder' in Keller's proposal to SKB [11]. |
| 1996 October | Not specified as an outcome measure in the acute-phase protocol [14]. |
| 1997 April | First labelled as 'remission', a second "definition of 'response' during the acute phase" [16]. |
| 1999 February | Listed as an outcome variable in early drafts of the paper [15]. |
| 2001 July | By publication, 'remission' disappears altogether as a label, and 'HAM-D $\leqslant 8$' is conflated with 'HAM-D $\leqslant 8$ or reduced by $\geqslant 50\%$' – see Box 2 [5]. |
| HAM-D depression item | |
| 1997 August | Not mentioned before the official unblinding. |
| CGI 1 or 2 | |
| 1997 April | Mentioned as possible outcome [16]. |
| 1998 January | Not mentioned in 'Top Line Results' [17] three months after the blind was broken. Study 329 co-author Ryan noted at the time by hand on his copy of these 'Top Line Results' the percentage of subjects fitting into each of the CGI categories but there is no indication of any decision as to how to make use of this data [18, p. 450]. |
| K-SADS-L depressed mood item | |
| 1998 November | First documented as an outcome variable [14, p. 44]. |

time, four of the six negative protocol-specified secondary measures had also been removed from the list of secondary outcomes, and two further additional new positive outcome measures had been added (changes in K-SADS depression item and Clinical Global Improvement (CGI) scale of 1 or 2) (see Box 1). No document prior to eight months *after* breaking the blind mentions the K-SADS depression item as an outcome measure. The introduction of these additional outcome measures so long after initial data analysis is consistent with a statement by GSK's senior scientist James McCafferty, that analysis had revealed 'a strong statistical trend and we were looking for corroborative evidence' [13, p. 375].

Overall four of the eight negative outcome measures specified in the protocol were replaced with four positive ones, many other negative measures having been tested and rejected along the way (see Table 1). The rationale given for the extra measures was that they were added according to "an analytical plan developed prior to opening of the blind" [14, p. 15]. No written evidence of this plan has been produced, raising uncertainty about Keller et al.'s claim that their "depression-related variables were declared *a priori*" [5, p. 764].

### 2.3. *Conflation of primary and secondary outcomes*

Many drafts of a report of the study were written before submission, initially to *JAMA*. In the first draft, the distinction between primary and secondary outcome variables in the protocol was removed so that all 8 outcomes were described as 'primary' in the results section [15]. However, in later drafts the term 'primary' was replaced with 'depression-related' [19]. These 1999 drafts reported that paroxetine was effective on the grounds that four out of eight of these measures were positive, without disclosing that there was no significant difference on either pre-specified *primary* outcome measure (see Table 1). *JAMA* rejected the paper in October, 1999, and it was revised for submission to *JAACAP*. One of the *JAMA* reviewers had noted that "the definition of remission and response overlaps in this manuscript" [20]. From the first draft for *JAACAP* in April 2000 'remission' (HAM-D $\leqslant 8$) was eliminated from the "depression-related variables ... declared a priori" listed in the Methods section, thus reducing these

Box 2

Response (HAM-D $\leqslant$ 8)/remission (HAM-D $\leqslant$ 8 or reduced by $\geqslant$50%) conflation in the published paper [5]

**Abstract**

Under Method, the first main outcome measure is listed as "endpoint response" (defined as HAM-D $\leqslant$ 8 or reduced by $\geqslant$50%) but in the Results "HAM-D total score $\leqslant$ 8" appears for the first time and response is not mentioned (p. 762).

**Method**

Response is listed as an outcome and defined as "HAM-D $\leqslant$ 8 or reduced by $\geqslant$50%".

HAM-D $\leqslant$ 8 is not listed amongst the outcomes (p. 764).

**Results**

*Efficacy Results* (p. 765) begins with an explicit false claim:

> Of the depression-related variables, paroxetine separated statistically from placebo at end point among 4 of the parameters: [including] response (i.e. primary outcome measure).

In the following paragraph, where we would expect to find the response data, we instead see the data for "HAM-D total score $\leqslant$ 8 at end point".

All but the most careful readers would conclude that the HAM-D $\leqslant$ 8 figures being quoted show that response was a positive outcome.

**Figures**

The reader might easily assume that the two figures (p. 767) illustrate the two primary outcomes, but one of them is for HAM-D $\leqslant$ 8.

**Discussion**

Response is absent from the list of those items that did not separate statistically from placebo (p. 769). This change from earlier drafts [20] takes away a cue that might otherwise alert the reader to the repeated substitution of 'remission' for 'response'.

variables from eight to seven [21]. However the positive HAM-D $\leqslant$ 8 results were still reported in the Efficacy Results section, just where the reader would expect to find 'response' scores.

In July 2000, a *JAACAP* reviewer called for primary outcomes to be stated [22], forcing the authors to re-introduce them. But the lack of significant advantage for paroxetine on the two pre-specified primary outcomes was still not declared. Instead the authors continued to claim efficacy for paroxetine based on the conflation between response and HAM-D $\leqslant$ 8 that had begun in April 2000 with the elimination of 'remission' from the Method. This conflation now extended throughout the published paper, obscuring the negative primary outcome results by reporting positive HAM-D $\leqslant$ 8 results where negative 'response' (HAM-D $\leqslant$ 8 or reduced by $\geqslant$50%) results would be expected (see Box 2). Although HAM-D $\leqslant$ 8 is not listed as an outcome in the Method, its positive result is prominent in the text, appears at the head of the main results table and is the sole focus of Keller et al.'s Fig. 1. GSK subsequently sought to justify the conflation on the grounds that both 'response' and 'remission' were different ways of defining 'responders' [13, p. 287; 16]. But both the acute-phase protocol [14] and the published paper contained just one definition of responder: HAM-D $\leqslant$ 8 or reduced by $\geqslant$50%.

### 2.4. *Presentation of other outcomes*

The results of the other negative primary outcome measure, change from baseline HAM-D score, are also omitted from the text of the Results in the final paper. This outcome is graphically represented in a figure (Keller et al.'s Fig. 2), but without clear indication that the difference was non-significant. Only the main results table (Keller et al.'s Table 2) reports all eight outcomes accurately. The *JAACAP* paper

has been defended as follows: 'it clearly tells the reader in that table two all these variables are exactly described along with the exact key values so they could make their own decision on that' [13, p. 573].

## 3. Reporting of adverse effects

The abstract of the *JAACAP* paper states that: "Paroxetine was generally well tolerated in this adolescent population, and most adverse effects were not serious". Yet SKB's final report on the acute phase (completed in November 1998) documented many serious and severe adverse effects in the paroxetine group, several of them significantly more frequent than for placebo – see Table 2. Although suicidal thoughts and behaviour were grouped under the euphemism of 'emotional lability', Table 48 of SKB's internal final report [14, p. 109] clearly shows that five of the six occurrences of emotional lability were rated 'severe' and that all five had self-harmed or reported emergent suicidal ideas. Just a few minutes' reading of the serious adverse events narratives in this final report (pp. 276–307) would have revealed three more cases of suicidal ideas or self-harm that had not been classified as emotional lability. So the authors should have known that at least eight adolescents in the paroxetine group had self-harmed or reported emergent suicidal ideas compared to only one in the placebo group.

Relatively small numbers and brief follow up in RCTs lessen the likelihood of detecting serious adverse events (SAEs), so any signal should be highlighted. Yet early drafts of the paper prepared for *JAMA* did not discuss SAEs at all [15]. Subsequently SKB senior scientist McCafferty composed a paragraph on SAEs that appeared for the first time in the draft of July, 1999. It disclosed that 11 patients on paroxetine, compared to two on placebo, had SAEs, but did not mention the statistical significance of these figures. Subsequently McCafferty's disclosures of overdose and mania were edited out, and SAEs on paroxetine were attributed to other causes. Where McCafferty's draft reads:

> worsening depression, emotional lability, headache, and hostility were considered related or possibly related to treatment [20],

the published *JAACAP* paper states:

> only headache (1 patient) was considered by the treating investigator to be related to paroxetine treatment.

Table 2
Adverse events documented in SKB's final report of study 329 [14]

| Type of adverse event | Paroxetine ($N = 93$) | Placebo ($N = 87$) | $p^{\wedge}$ | Source table |
|---|---|---|---|---|
| Serious[#] | 11 (12%) | 2 (2.3%) | 0.01 | 48, p. 109 |
| Severe[##] | 27 (29%) | 15 (17%) | 0.06 | 14.3.1, pp. 231–238 |
| Hospitalisation | 6* (6.5%) | 0 | 0.004 | 48, p. 109 |
| Nervous system | | | | |
| Any | 56 (60%) | 29 (33%) | 0.001 | 14.2.1, p. 227 |
| Severe** | 17 (18%) | 4 (4.6%) | 0.003 | 14.3.1, pp. 231–238 |
| Requiring withdrawal | 8 (8.6%) | 2 (2.3%) | 0.056 | 49, p. 111 |
| Leading to dose reductions | 8 (8.6%) | 2 (2.3%) | 0.056 | 46, p. 105 |

$^{\wedge}$Calculated by us; [#]'resulted in hospitalisation, was associated with suicidal gestures, or was described by the treating physician as serious' [5]; [##]'incapacitating and prevents normal everyday activities' [14, p. 565]; *stated as 7 in published paper; **stated as 16 for paroxetine and 3 for placebo in Table 44, p. 101.

## 4. Reporting study 329 to health professionals

From the late 1990s paroxetine was promoted to SKB/GSK Neuroscience sales representatives [23]. In August, 2001, a memorandum from Paxil Product Management to "all sales representatives selling Paxil" stated: "This 'cutting edge,' landmark study is the first to compare efficacy of an SSRI and a TCA with placebo in the treatment of major depression in adolescents. *Paxil* demonstrates REMARKABLE Efficacy and Safety in the treatment of adolescent depression" [7]. The memorandum mentioned only positive outcomes. By contrast, the cardiac adverse effects of imipramine were emphasised.

SKB/GSK produced a series of *Med Query Letters* to doctors who requested information about paroxetine for childhood depression via sales representatives. There is no publicly available information about whether or not sales representatives actively prompted doctors to request this information. *Letters* characteristically started and ended with disclaimers like "*Paxil* is not FDA-approved for use in children or adolescents; therefore, we may not offer any recommendations regarding the use of *Paxil* in these patients" [24], but nonetheless provided selected information about study 329. For example, *Letters* omitted primary outcome results (1998 [25], 1999 [26], 2001 [24]) and serious adverse event results (1998, 1999, 2000 [27], 2001), or failed to mention other negative childhood depression studies when these results became available (2000, 2001). Other academic publications and presentations frequently did not disclose the results for the primary outcomes and serious adverse events [19,28–33].

## 5. Discussion

### *5.1. Were the results for study 329 positive or negative?*

There was no significant efficacy difference between paroxetine and placebo on the two primary outcomes or six secondary outcomes in the original protocol. At least 19 additional outcomes were tested. Study 329 was positive on 4 of 27 known outcomes (15%). There was a significantly higher rate of SAEs with paroxetine than with placebo. Consequently, study 329 was negative for efficacy and positive for harm.

### *5.2. Did selective reporting occur?*

Claims that paroxetine was "generally well tolerated and effective" [5] arose from selective reporting of the 15% of outcomes that were positive and selective under reporting of the other efficacy and SAE findings. The *JAACAP* paper has been defended on the grounds that readers could read in the results table that the two outcomes described as primary elsewhere (but not in that table) were negative [13]. However readers are more likely to be influenced by the abstract than the tables of a clinical trial report, as evidenced by the continued retransmitting of the false impression that study 329 found "significant efficacy on one of the two primary endpoints" [8]. A likely cause of this misunderstanding is the conflation of 'remission' and 'responder' and especially the false statement that "paroxetine separated statistically from placebo at end point among 4 of the parameters: [including] response (i.e. primary outcome measure)..." [5].

### 5.3. How did selective reporting happen?

In response to criticism in *JAACAP* in 2003, Keller et al. [34] indicated that they believed that paroxetine was effective and therefore viewed the efficacy results as a false negative arising from their mistake of using the HAM-D as their depression measure. They then searched for other outcomes that matched their beliefs about efficacy. Such searching has been described as "data torturing" [35], a form of confirmation bias in which information is sought to support pre-conceived beliefs. Confirmation bias could also lead authors who were unconcerned about adverse events to look less closely at that data and to attribute adverse events in the paroxetine group to non-drug causes such as "arguments with boyfriends" [36]. Confirmation bias could be well-intentioned, so that investigators might believe that what they had done was entirely appropriate. However it does not explain the conflation of 'remission' and 'responder', the changes to the descriptions of SAEs, or flaws that were detected by peer reviewers but were not corrected.

## 6. Conclusions

Since the publication of the results of study 329 in 2001, suspicions have emerged about its selective reporting [37,38]. Our detailed case study of proprietary documents from GSK regarding this study adds to the evidence that flaws in industry-funded research can be severe, and difficult to detect. The documents reveal that the published conclusions of study 329 and information provided by GSK to health professionals understated adverse effect rates and emphasised post-hoc measures that were not consistent with the unpublished, protocol-defined primary and secondary outcomes.

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# ATTACHMENT 5

Special Article

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# Efficacy and Effectiveness of Antidepressants: Current Status of Research

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**Key Words**
Antidepressant-resistant depression · Antidepressive agents · Depression relapse · Depressive disorder · Maintenance · Placebo treatment · Treatment continuation · Treatment-resistant depression

**Abstract**
***Background:*** This paper examines the current status of research on the efficacy and effectiveness of antidepressants. ***Methods:*** This paper reviews four meta-analyses of efficacy trials submitted to America's Food and Drug Administration (FDA) and analyzes STAR*D (Sequenced Treatment Alternatives to Relieve Depression), the largest antidepressant effectiveness trial ever conducted. ***Results:*** Meta-analyses of FDA trials suggest that antidepressants are only marginally efficacious compared to placebos and document profound publication bias that inflates their apparent efficacy. These meta-analyses also document a second form of bias in which researchers fail to report the negative results for the prespecified primary outcome measure submitted to the FDA, while highlighting in published studies positive results from a secondary or even a new measure as though it was their primary measure of interest. The STAR*D analysis found that the effectiveness of antidepressant therapies was probably even lower than the modest one reported by the study authors with an apparent progressively increasing dropout rate across each study phase. ***Conclusions:*** The reviewed findings argue for a reappraisal of the current recommended standard of care of depression. 

## Introduction

When medications are evaluated to determine their applicability to evidence-based clinical practice, it is important to assess their efficacy in randomized, double-blind, placebo-controlled trials (RCT) in addition to determining their effectiveness in treating real-world patients under conditions that simulate real-world practice.

## Efficacy

Due to long-held concerns about publication bias inflating perceived efficacy [1–4] and the resulting adverse impact on evidence-based care, public-minded researchers have long argued for a comprehensive registration data repository providing full access to drug trial protocols and results [1, 5, 6]. Though by no means complete, America's Food and Drug Administration (FDA)

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maintains a large repository of RCT trials as part of its new drug application process. Prior to conducting new drug application trials, drug companies must register them with the FDA, which includes pre-specifying the primary and secondary outcome measures and means of analysis. Pre-specification is essential to ensure the integrity of a trial and enables the discovery of when investigators selectively publish the measures that show the outcome the sponsors prefer following data collection and analysis, a form of researcher bias known as HARKing [7] or *'hypothesizing after the results are known'*.

Rising et al. [8] recently published a meta-analysis of all efficacy trials for new drugs approved by the FDA from 2001 to 2002 and the subsequent publication status of these trials 5 years later. Key findings were:

- New drug application studies with favorable outcomes were almost five times more likely to be published as those with unfavorable ones.
- 26.5% of pre-specified primary outcome measures were omitted from journal articles of new drug trials.
- Of the 43 primary measures not supporting efficacy, 20 (47%) were not included in the published results.
- 17 measures were only presented in the published studies and 15 of these showed positive effects for the new drug.

The analysis of Rising et al. [8] documents significant publication bias that inflates the apparent efficacy of new drugs. In addition to selective publication of positive trials, more disturbingly researchers at times fail to report the negative results of pre-specified primary outcome measures while highlighting in published studies positive results from a secondary or even a new measure as though it was their primary measure of interest. Besides casting doubt on the accurate reporting of individual drug trials in journal articles, their findings also directly challenge the validity of meta-analyses covering specific drugs and drug classes when limited to published studies.

Several antidepressant meta-analyses have been conducted using the FDA data repository to avoid the inflationary effects of publication bias. In 2008, Turner et al. [9] reviewed 74 trials of 12 antidepressants to assess subsequent publication bias and its influence on apparent efficacy.

In their meta-analysis, antidepressant studies with favorable outcomes were 16 times more likely to be published as those with unfavorable ones. According to the FDA scientific reviews though, only 38 trials (51%) found positive drug/placebo differences and 37 were subsequently published. The FDA judged the remaining 36 studies to be either negative (24 studies) or questionable (12 studies) – that is, no difference on the primary outcome but significant findings on a secondary measure. Only 3 (8%) were published reporting negative results, while the remaining 33 were either not published (22 studies) or published as though they were positive (11 studies) in contradiction to the FDA conclusions. Similar to Rising et al. [8], Turner et al. [9] report that in these 11 studies the authors did not report their negative results for the pre-specified primary outcome measure and instead highlighted positive results from a different measure as though it was their primary measure of interest.

Turner et al. [9] next compared the effect size derived from the FDA repository to that from the 51 published studies. This analysis found that the weighted mean effect size in the FDA data set was a modest 0.31 (95% confidence interval, 0.27–0.35) versus 0.41 (95% confidence interval, 0.36–0.45) in the published studies indicating a 32% inflation of the apparent efficacy of antidepressants. Their findings are similar to those of Kirsch et al. [10] in 2002 in a meta-analysis of 47 trials of 6 FDA-approved antidepressants. Though statistically significant due to the large combined number (n = 6,944), they found that the weighted mean difference between groups on the 17-item Hamilton Rating Scale for Depression (HRSD) was only 1.8 points and 57% of the trials found no significant drug/placebo differences [11].

Kirsch et al. [10] and Kirsch and Antonuccio [12] also examined patients' response as a function of dosing strength and time. These analyses found no advantage for higher antidepressant dosing. Regarding the common belief that drug effects are more enduring than placebo effects, they found that while patients' initial positive responses to both decrease over time, the correlation was higher for antidepressants ($r = -0.84$) than placebos ($r = -0.62$), suggesting that the effects of antidepressants diminish more rapidly than those of placebo.

In 2008, Kirsch et al. [13] examined the relationship between depression severity and efficacy in all 35 trials (n = 5,133) of four new-generation antidepressants. This analysis found no clinically significant difference (defined as a drug/placebo difference of $\geq 3$ on the HRSD) between antidepressants and placebos as a function of severity except for the most severely depressed patients (i.e. those with a $\geq 29$ HRSD score). However, even this difference was due to a decreased placebo response in more severely depressed patients, not an increased response to antidepressants.

Also in 2008, Barbui et al. [14] analyzed 40 paroxetine studies (29 published/11 unpublished; n = 6,391) using early trial termination for any reason (i.e. dropout) as the

primary outcome assessing it as the best available *'hard measure of treatment effectiveness and acceptability'* [14, p. 296]. Their analysis found no drug/placebo difference on this measure in contrast to a secondary one that paroxetine was clinically superior to placebo in patients' likelihood of achieving a ≥50% reduction in depressive symptoms. They also found that significantly more paroxetine patients dropped out due to side effects and increased suicidal tendencies. In a subsequent analysis though of these same studies, the apparent clinical superiority of paroxetine disappeared after statistically controlling for the differences in drug/placebo side effects [15, cited in 16, p. 19]. This finding is similar to that of Greenberg et al. [17] of an exceptionally high correlation between side effects and improvement in fluoxetine/placebo trials and suggests that when it does occur, the apparent superiority of antidepressants may be due to unblinding among study patients (and raters) given the greater frequency of side effects in active drug groups and patients' education about said effects as part of informed consent [18, 19]. Kirsch [16, pp 7–22] and Kirsch and Sapirstein [20], among others [18, 19, 21], argue that side effects enhance the placebo effects of antidepressants by confirming to patients that they are taking the active medication and thereby increasing their expectation of improvement. Given the often small drug/placebo differences in these studies, it would not take much such unblinding to account for positive results when they do occur. On the other hand, the fact that many RCTs fail despite significant drug/placebo side effect differences suggests that said effects alone are not sufficient to consistently result in greater improvement even if they do contribute to unblinding.

The analyses performed by Rising et al. [8] and Turner et al. [9] document that readers should be wary when researchers replace their pre-specified primary outcome measure with a new one. This concern is reinforced by recent analyses documenting widespread selective outcome reporting in industry-sponsored research and the inflationary effect that often occurs when the pre-specified primary outcome measure is not used to report findings [22, 23]. Perhaps the most troubling implications of the Rising-Turner-Kirsch-Barbui findings are that journal readers, seeking articles to guide evidence-based practice, may have been misled by meta-analyses and reviews based on biased published articles on antidepressant efficacy.

However, some explain only marginal superiority of antidepressants by the fact that subjects enrolled in RCTs do not necessarily present with adequate illness severity. Lieberman et al. [24] observed that early RCTs often enrolled hospitalized patients who were less responsive to placebo, whereas more recent trials typically enroll highly selected outpatients, contacted through mass media advertisements, who may be less severely depressed. In a meta-analysis of 75 RCTs published between 1981 and 2000, Walsh et al. [25] showed that the response to both antidepressants and placebos has increased over time with a significant positive correlation between year of publication and response. Parker [26] argues that this progressively increasing response to both compromises the ability to differentiate truly efficacious antidepressants from placebos, particularly among less severe patients.

Fava et al. [27] notes that the analysis of Walsh et al. [25] likely understates placebo response rates since most failed trials go unpublished; they estimate that the true rate is 35–45%. They then explore various potential causes for failed trial findings (e.g. measurement errors or diagnostic heterogeneity) and propose a new study design that might reduce placebo rates and thereby the number required to differentiate efficacious antidepressants from placebos. Both Fava et al. [27] and Otto and Nierenberg [28] observe that only two RCTs showing drug superiority are required for FDA approval regardless of how many were conducted, and both cite the example of paroxetine that took nine trials to get the two necessary to *'win'* approval [29]. The apparent lack of significant adverse consequences to drug companies from failed trials (other than added costs and delayed time to market) may have fostered a production-oriented mindset favoring trial quantity over quality (since it takes only two to win, and losses are not counted) too often resulting in flawed science and thereby the ensuing vigorous debate over methodology and interpretation while furthering the disconnect between trial findings and their application to clinical practice.

In an analysis of psychiatric outpatients with major depressive disorder (MDD), Zimmerman et al. [30] found that RCTs would have excluded 86% due to their having a comorbid anxiety or substance use disorder, insufficient depressive symptoms, and/or current suicidal ideation. Similarly, a post hoc analysis of STAR*D (Sequenced Treatment Alternatives to Relieve Depression) patients, the largest antidepressant effectiveness study ever conducted, found that 77.8% would have been excluded from RCTs due to having a baseline HRSD score ≤19, more than one concurrent medical condition, more than one comorbid psychiatric disorder, and/or a current depressive episode lasting >2 years [31]. This analysis

found that STAR*D patients who met RCT inclusion criteria had greater likelihood of remission than those more representative of the vast majority seeking care (34.4 vs. 24.7% remission rate). As Wisniewski et al. [31] note, by enrolling more representative patients RCT results would better estimate the benefit of an antidepressant in practice and may also reduce placebo response rates and the associated risk of failed trials. Likewise, Parker [26, p. 2] argues that the apparent limited efficacy of antidepressants may not be related to the modest effects of these compounds but rather to RCT design and methodological issues, *'whereby the "apples" assessed in such studies do not correspond to the "oranges" of clinical practice'.*

While the relative efficacy of antidepressants is not settled, progress will only come as RCTs enroll representative MDD samples for which the medication is intended under conditions that simulate real-world practice. Such trials should follow Gaudiano and Herbert's [19] recommendations for distinguishing between specific and nonspecific treatment effects, the first one being having an active placebo arm to reduce the likelihood of unblinding and thereby control the potential role of side effects in enhancing patients' expectation of improvement.

### Real-World Effectiveness of Antidepressants

In conformity with this goal of enrolling more representative MDD patients, the NIMH-funded STAR*D study [32–38]:

- enrolled 4,041 real patients seeking care versus persons responding to advertisements for depressed subjects;
- included patients with comorbid medical and psychiatric conditions as well as those whose current MDD episode was >2 years;
- included patients currently undergoing antidepressant treatment provided that there was not a history of nonresponse or intolerance to either step-1 or step-2 protocol antidepressants;
- used *'remission'* versus *'response'* as the primary criterion of successful treatment which is a higher clinical standard than used in prior effectiveness studies;
- provided 12 months of continuing care while monitoring the durability of treatment effects versus only reporting acute-care improvement.

STAR*D provided a very high quality of free acute and continuing care to maximize the likelihood that MDD patients would achieve remission and maintain it. Table 1 describes in detail the high quality of treatment and the extensive efforts of STAR*D to retain patients. The treatment protocol included state-of-the-art acute care to achieve remission followed by 1 year of continuing care for all patients who achieved a satisfactory clinical response. The goal of continuing care was to maintain remission and prevent relapse [39, p. 15].

The continuing-care phase of STAR*D also provided a real-world test of the practice guideline of the American Psychiatric Association (APA) that *'following remission, patients who have been treated with antidepressant medications in the acute phase should be maintained on these agents to prevent relapse'* [40, p. 15]. This guideline received the highest confidence rating of the expert panel.

STAR*D was designed to provide guidance in selecting the best *'next-step'* treatment for the many patients who fail to get adequate relief from their initial selective serotonin reuptake inhibitors (SSRI) trial by evaluating the relative efficacy of eleven pharmacologically distinct treatments [41]. Cognitive therapy (CT) was also an option in step 2, but too few patients included it as an acceptable treatment resulting in only 101 contributing data after randomization [33]. CT was therefore excluded from the primary step-2 switch and augmentation articles [33, 34]. Possible reasons so few patients found CT acceptable included: (1) biased self-selection since all patients started on citalopram in step 1; (2) the added costs of CT which STAR*D did not cover whereas it covered all medication and physician visit costs, and (3) CT patients had to go to another site to see a new non-physician professional [42, pp 748–749]. Despite these impediments, in a subsequent article STAR*D reported that the 101 step-2 patients who received CT *'(either alone or in combination with citalopram) had similar response and remission rates to those assigned to medication strategies'* [42, p. 739].

The conclusion section of the research design article of STAR*D states: *'STAR*D uses a randomized, controlled design to evaluate both the theoretical principles and clinical beliefs that currently guide the management of treatment-resistant depression in terms of symptoms, function, satisfaction, side-effect burden, and health care utilization and cost estimates. Given the dearth of controlled data, results should have substantial public health and scientific significance, since they are obtained in representative participant groups/settings, using clinical management tools that can easily be applied in daily practice'* [43, p. 136].

Given the *'substantial public health and scientific significance'* of STAR*D in evaluating the effectiveness of antidepressants when optimally delivered to real-world patients, it is critical that the methodology and findings of STAR*D are presented accurately.

**Table 1.** Highest quality of acute and continuing care to maximize remissions while minimizing relapse and dropouts

| Descriptor | Explanation |
|---|---|
| Optimized sustained study participation to minimize dropouts [41, pp 473–474] | – Promoted patients' study affiliation via STAR*D-branded brochures, bimonthly newsletters, and an informational video emphasizing the public health significance of STAR*D and the critical role played by patients;<br>– educated patients and families about depression and its treatment using a multistep educational package;<br>– used a letter reminder system to alert patients before appointments in those clinics without such systems who had a >15% rate of missed appointments;<br>– ensured timely follow-up and rescheduling of missed appointments by calling patients on the day of the missed appointment, and again within 24 h, if there was no response; the patient's physician sent a letter within 48 h if contact was not established;<br>– used a letter reminder system for all research outcome assessment calls during acute and continuing care;<br>– in every clinic visit, the clinical research coordinator discussed the research outcomes in phone calls with the patient to ensure that the calls were completed on schedule and worked to resolve any problematic issues regarding said calls [39, p. 75];<br>– paid patients USD 25.00 for participating in each telephonic research outcome assessment;<br>– permitted patients to re-enter acute and/or continuing care within 4 weeks after having dropped out [39, p. 80];<br>– recommended 1 year of continuing care for all patients who achieved a satisfactory clinical response with the essential goal of preventing relapse [39, p. 15];<br>– permitted continuing-care patients to remain in the study if they moved from the area [39, p. 81];<br>– provided all medical and pharmacological treatment care-free to patients. |
| Acute-care visits | Physicians met with patients on entry into each new step to initiate drug treatment with follow-up visits scheduled on weeks 2, 4, 6, 9, and 12, with an optional week 14 visit. |
| Measurement-based care | Conducted structured evaluations of symptoms and side effects at each visit and included a centralized treatment monitoring and physician feedback system to ensure consistent implementation of optimal care across research sites. |
| Aggressive medication dosing | Provided aggressive medication dosing with a fully adequate dose for a sufficient duration to *'ensure that the likelihood of achieving remission was maximized and that those who did not reach remission were truly resistant to the medication'* [32, p. 30]. |
| Liberal prescribing of non-study medications | Physicians had great leeway in prescribing non-study medications to treat comorbid symptoms resulting in:<br>– 17.2% taking trazodone for sleep;<br>– 11.9% taking an anti-anxiety medication;<br>– 16.7% taking either a sedative or hypnotic medication;<br>– an undisclosed percentage taking medications to address side effects [33, table 2]. |
| Continuing-care visits | Patients saw their physician every 2 months and continued taking their treatment medication(s) at the same doses, but their physicians were allowed to make any psychotherapy, medication, and/or medication dose changes to maximize the likelihood of maintaining patients' remission status [38, p. 1908]; additional continuing-care visits were scheduled when patients began to experience a return of depressive symptoms and/or intolerable side effects [39, p. 78]. |
| Clinical research coordinator (CRC) | Each site had a clinical research coordinator who [32, p. 30]:<br>– saw patients before each visit administering multiple measures to them including the QIDS-SR during each acute-care visit;<br>– assisted physicians in protocol implementation;<br>– provided patients with support and encouragement in protocol implementation. |
| Treatment designed to enhance subject retention | Treatment was designed to minimize dropouts and/or non-compliance including:<br>– open-label prescribing during acute and continuing care with no placebo control condition during any study phase;<br>– patients chose their acceptable treatment assignments for steps 2 and 3 to eliminate any concerns they might have about receiving an unacceptable assignment; this resulted in only 21 of 1439 (1.5%) step-2 patients making themselves available for random assignment to all treatment options [33, p. 1235] while only 29 of 377 (7.7%) did so in step 3 [36, p. 1521];<br>– during each step, patients could enroll immediately into the next step if they had intolerable side effects or had maximized the dosing of their current medication(s) without achieving a remission;<br>– during any step, patients could enter continuing care directly on their current medication(s) if they were treatment responders even if they had not achieved remission; this was done to minimize responders from dropping out in order to avoid having to discontinue their current medication(s) and start a new drug regimen. |

### Change in One of the Outcome Measures

As designed, the HRSD was the pre-specified primary measure of STAR*D and the Inventory of Depressive Symptomatology-Clinician-Rated (IDS-C30) the secondary one for identifying *'remitted'* (i.e. those with a score ≤7 HRSD) and *'responder'* (i.e. those with a ≥50% reduction in depressive symptoms) patients [41, p. 476, 43, p. 123]. These measures were obtained by research outcome assessors (ROAs) blind to treatment assignment at entry into and exit from each treatment level, and every 3 months during continuing care. Additional measures assessing symptoms, level of functioning, satisfaction, quality of life, side effect burden, and health care utilization were obtained by an interactive voice response (IVR) telephone system on the same schedule as the HRSD and IDS-C30 [43, p. 129] (table 2).

As mentioned earlier, STAR*D was designed to identify the best next-step treatment for the many patients who fail to get adequate relief from their initial SSRI trial. Due to

**Table 2.** Survival analysis by treatment step of patients who entered continuing care in remission

| Step | n[1] | 0–3 months[2] | 3–6 months[3] | 6–9 months[4] | 9–12 months[5] |
|---|---|---|---|---|---|
| 1 | 1,085 | 628 | 431 | 290 | 84 |
| 2 | 383 | 199 | 133 | 79 | 20 |
| 3 | 35 | 16 | 11 | 8 | 2 |
| 4 | 15 | 8 | 5 | 5 | 2 |
| Total | 1,518 | 851 | 580 | 382 | 108 |
| Relapse and/or dropout rate by quarter[6] | | 43.9% | 61.8% | 74.8% | 92.9% |

[1] Number of patients entering continuing care with a QIDS-SR-defined remission [38, table 5, column 2].
[2] Number of patients who called in at least once into the STAR*D IVR system during months 0–3 and did not relapse scoring in the moderate/severe depression range on the QIDS-SR [38, fig. 3, table, row 2].
[3] Number of patients who called in at least once during months 3–6 and did not relapse scoring in the moderate/severe depression range on the QIDS-SR during this or any prior assessment in months 0–3 [38, fig. 3, table, row 3].
[4] Number of patients who called in at least once during months 6–9 and did not relapse scoring in the moderate/severe depression range on the QIDS-SR during this or any prior assessment in months 0–6 [38, fig. 3, table, row 4].
[5] Number of patients who called in at least once during months 9–12 and did not relapse scoring in the moderate/severe depression range on the QIDS-SR during this or any prior assessment in months 0–9 [38, fig. 3, table, row 5].
[6] The percent of STAR*D remitted patients who relapsed and/or dropped out during continuing care.

the high study dropout rate in STAR*D which frequently resulted in missing exit IDS-C30 and HRSD assessments (and thereby the required imputation level made these assessments relatively uninformative), the statistical analytical plan was revised with input from the Data Safety and Monitoring Board prior to data lock and unblinding.

The revised statistical analytical plan of STAR*D dropped the IDS-C30 and replaced it with the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR), a tool developed by the principal investigators of STAR*D that is highly correlated with the HRSD (the primary measure) since it was administered at every visit [44–46]. In the step-1 to step-4 studies, the QIDS-SR was the secondary measure for identifying remissions and sole measure for identifying responders while the HRSD was the primary measure for identifying remitted patients [32–37].

As originally planned, STAR*D used the QIDS-SR in two ways. The research version was IVR administered on the same schedule as the other measures during steps 1–4 and as an *'interim'* monthly measure during continuing care [39, p. 120, table 3].

Patients also completed a paper-and-pencil QIDS-SR at the beginning of each clinic visit along with two self-rated side effect measures and a medication adherence questionnaire. These four self-assessments were overseen by non-blinded clinical research coordinators who reviewed the results to make certain that all items were completed and then saw the patient to administer the QIDS-C (the clinician-administered version with the identical 16 questions and response options as the QIDS-SR), the Clinical Global Impression Improvement Scale, and discuss with the patient any symptoms and side effects that he/she was experiencing as well as present patient education materials [39, p. 75].

The clinical research coordinators then recorded the six measures on the clinical record form for the treating physician's review before he/she saw the patient *'to provide consistent information to the clinicians who use this information in the protocol'* [43, p. 128]. In this way, the paper-and-pencil QIDS-SR was one of the *'clinical management tools that can easily be applied in daily practice'* [43, p. 136] of STAR*D and used as such in the *'measurement-based'* system of care of STAR*D as STAR*D states: *'To enhance the quality and consistency of care, physicians used the clinical decision support system that relied on the measurement of symptoms (QIDS-C and QIDS-SR), side-effects (ratings of frequency, intensity, and burden), medication adherence (self-report), and clinical judgment based on patient progress'* [32, p. 30]. This distinction between

**Table 3.** Remission and discontinuance rates in STAR*D by treatment step

| Treatment | Remission rate[1] | Discontinuance rate[2] |
|---|---|---|
| Step 1 | 25.4%<br>790 out of 3,110 | 26.6%[3]<br>826 out of 3,110 |
| Step 2 | 25.1%<br>324 out of 1,292 | 30.1%[4]<br>389 out of 1,292 |
| Step 3 | 17.8%<br>67 out of 377 | 44.8%[4]<br>169 out of 377 |
| Step 4 | 10.1%<br>11 out of 109 | 60.1%[4]<br>66 out of 109 |

[1] Calculated by combining all HRSD-defined remissions in each of steps 1–4 of the published study divided by each combined n of the study [32–37]. Step 1 includes the 234 patients who met the original ≥14 HRSD baseline admission criterion and were started on citalopram but then dropped out without a follow-up visit [32, fig. 1].

[2] The number of patients who dropped out for any reason including intolerance, lack of adequate response, declining to enter the next-step treatment phase, or declining to enter continuing care despite having a positive response during the current treatment phase.

[3] Calculated from figure 1 in the step 1 study.

[4] Calculated from figure 1 in the final report.

**Table 4.** HRSD and QIDS-SR remission rates

| Medication step study | HRSD | QIDS-SR | References |
|---|---|---|---|
| Step-1 citalopram | 790 | 943 | [32, table 4, row 1] |
| Step-2 switch | 155 | 186 | [33, table 3, rows 2 and 3] |
| Step-2 augmentation | 169 | 202 | [34, table 3, rows 2 and 3] |
| Step-3 switch | 38 | 24 | [35, table 4, rows 1 and 3] |
| Step-3 augmentation | 29 | 27 | [36, table 4, rows 13 and 14] |
| Step-4 | 11 | 16 | [37, table 3, rows 3 and 4] |
| Total | 1,192 | 1,398 | |

the originally intended use of the QIDS-SR as a clinical tool versus research measure is made explicit in both tables of the design article (tables 2, 3) [43, pp 128–129] and the Clinical Procedure Manual of STAR*D (tables 2, 4) [39, pp 119, 121].

The revised statistical analytical plan did not change any of the next-step comparison results of STAR*D, as both the QIDS-SR and HRSD found no significant group differences between treatments in all five comparisons. However, this decision appears to have inflated the reported remission and response rates of STAR*D. As stated in the step-1 article: *'Higher remission rates were found with the QIDS-SR than with the HRSD because our primary analyses classified patients with missing exit HRSD as nonremitters a priori. Of the 690 patients with missing exit HRSD scores, 152 (22.1%) achieved QIDS-SR remission at the last treatment visit'* [32, p. 34]. In the six step-1 to step-4 studies, there were 1,192 HRSD-identified remissions versus 1,398 QIDS-SR ones, an increase of 17.3% (table 4), and the major summary article of STAR*D only used the QIDS-SR to report its step-by-step acute and continuing-care findings [38].

### Change in Eligibility for Analysis Criteria

The step-1 article of STAR*D states that eligible patients *'had a non-psychotic major depressive disorder determined by a baseline HRSD score ≥14'* [32, p. 29]. This is a modest symptom severity threshold (see Davidson et al. [47] with a ≥20 HRSD inclusion threshold for example) though similar to many MDD patients seeking treatment [30].

Of the 4,790 patients administered the screening HRSD (completion time: 15 min [39, p. 118]), 4,041 were started on citalopram in their baseline visit [39, p. 17, 48]. Of these patients, 3,110 scored ≥14 on the more thorough and blinded ROA-administered HRSD (completion time: 20–25 min [39, p. 118]), 234 of whom failed to return for a follow-up visit. For the resulting 2,876 step-1 patients eligible for analysis [32, fig. 1], their baseline HRSD scores averaged 21.8 [32, table 1, row 2]. There were also 607 patients reportedly excluded (but later included – see discussion below) because their score <14 signified only mild depression and 324 patients were reportedly excluded (but later included) because they lacked a baseline ROA-administered HRSD [32, fig. 1].

The subsequent step-2 to step-4 articles of STAR*D continued to state that all patients had *'non-psychotic major depressive disorder'* and did not clarify a deviation from eligibility of step 1 for analysis criteria [32–37]. Specifically, the 607 patients who scored <14 in their baseline ROA assessment along with the 324 patients with no such assessment received citalopram in step 1, progressed to subsequent acute and continuing-care treatments, and were included in step-2 to step-4 articles and also in the summary article. Thus, 931 of the 4,041 STAR*D patients (23%) did not have a ROA-administered HRSD ≥14 when enrolled into the study.

The effect of including these patients' data was to lower the average step-1 HRSD from 21.8 to 19.9 [38, table 2, row 2]. STAR*D also included these 931 patients to recalculate the step-1 remission rate of citalopram in its summary article. In so doing, the step-1 remission rate was inflated to 36.8% from the original 32.8% of the step-1 article both based on the lenient QIDS-SR determination.

Perhaps a more serious problem is trying to determine the effect of these 931 patients in changing the relapse rate during continuing care. Initial symptom severity is a powerful predictor of relapse – with less depressed patients far less likely to relapse. For patients who entered the study with a HRSD <14, there is a special conundrum because STAR*D defined relapse as a HRSD ≥14. This means that 607 patients, in order to be counted as relapsed, had to score worse during continuing care than when they first entered the study.

In addition, a failure to consider dropout permitted STAR*D to assert a 67% *'cumulative'* remission rate after up to four medication steps [38, p. 1910]. STAR*D authors arrived at this figure simply by adding together its inflated QIDS-SR remissions in steps 1–4. STAR*D acknowledges that this assertion assumes no dropouts and the same remission rate for persisting patients as those who exited. These assumptions though are not true in the real world and were certainly not true in STAR*D since more patients dropped out from the study in each step than had a remission (table 3). Furthermore, comparing persisting patients' remission rates to dropouts is not possible since dropouts do not provide data.

Table 3 presents the HRSD-determined remission and dropout rates of STAR*D for steps 1–4. These data are quite important for a clinical understanding of the effectiveness of antidepressants in real-world patients receiving *'measurement-based'* state-of-the-art treatment:

- in step 1, 25.4% of patients had a remission while 26.6% dropped out [49];
- in step 2, 25.1% of patients had a remission while 30.1% dropped out;
- in step 3, 17.8% of patients had a remission while 44.8% dropped out;
- in step 4, 10.1% of patients had a remission while 60.1% dropped out.

### Continuing-Care Findings

One of the most important questions in evaluating antidepressants is how durable are the remissions. A major STAR*D contribution was to provide 12 months of follow-up data on remitted and improved patients' continued treatment. Patients who achieved remission during acute care were strongly encouraged to enter continuing care. In addition, responder patients who failed to attain remission and did not want to continue to the next acute-care step were encouraged to enter continuing care.

The protocol of continuing care *'strongly recommended that participants continue the previously effective acute treatment medication(s) at the doses used in acute treatment'* [38, p. 1908]. This recommendation is consistent with the APA continuation phase guideline that *'following remission, patients who have been treated with antidepressant medications in the acute phase should be maintained on these agents to prevent relapse'* [40, p. 15]. However, the STAR*D protocol was more naturalistic than the APA guideline in that physicians were allowed to make *'any psychotherapy, medication, or medication dose change'* [38, p. 1908] they deemed necessary to maximize patients' likelihood of sustaining remission. This included scheduling additional visits if depressive symptoms returned and/or intolerable side effects emerged [39, p. 78].

STAR*D made strong efforts to maximize retention and collect follow-up data. These efforts included continued use of all acute-care patient retention strategies during continuing care, prompting patients prior to all research outcome assessment phone calls, and paying patients USD 25.00 for taking said assessments as well as permitting patients to remain in the study if they moved from the area (table 1). Furthermore, informed consent was re-obtained for all patients entering continuing care to ensure their understanding of its treatment and outcome assessment procedures and expectations [39, p. 68].

For evaluating the outcome of continuing care, STAR*D authors decided to use the IVR-administered QIDS-SR that was originally intended as only an interim monthly measure during continuing care [39, p. 120, table 3], not the pre-specified HRSD and IDS-C30. If the patient called in and scored ≥11 on the QIDS-SR, relapse was declared; that score (said to correspond to a HRSD ≥14) indicated moderate-to-more-severe depression. Given this, it is important to note that STAR*D was not reporting the rate that remitted patients sustained remission, only the rate at which they relapsed while remaining in continuing care.

In calculating relapse, STAR*D authors decided not to use intent-to-treat procedures in which dropouts would count as continuing-care failures (despite the separate informed consent process) but instead use the data from patients who called into the IVR system once (or more)

during the 12 months. The calculated relapse rate was the proportion of patients relapsing of those who made at least one such call and reported a ≥11 QIDS-SR [38, table 5, column 6, footnote d).

By this relapse definition, the continuing-care patients who dropped out early and never called in, or the many patients who called in once or more without scoring ≥11 and then dropped out, could never meet the relapse criterion. Because the likelihood of relapse increases with time in follow-up, this definition is biased toward underestimating relapse rates. It is common for patients to lose hope when depressive symptoms return thereby increasing their likelihood of discontinuing a treatment that is no longer effective for them. This is particularly true for the 75% of STAR*D patients diagnosed with *'recurrent depression'* [38, table 2]. Given that most STAR*D patients had *'reoccurring'* depression and *'loss of hope'* is one of the most common symptoms of depression, it is reasonable to expect that many continuing-care dropouts relapsed.

The summary report of STAR*D identifies 1,854 remitted patients in steps 1–4 [38, table 3, row 8] yet only 1,518 consented to continuing care [38, table 5, column 2] while the other 336 dropped out. Many of these patients achieved their remission based on the paper-and-pencil QIDS-SR in their last clinic visit but then discontinued treatment without taking the HRSD despite the USD 25.00 payment for taking said measure (e.g. the step-1 article states, *'Of the 690 patients with missing exit HRSD scores, 152 (22.1%) achieved QIDS-SR remission at the last treatment visit'* [32, p. 34]. An additional 344 patients consented to continuing care but then dropped out during the 1st month without ever calling into the IVR system [38, table 5, column 5]. This indicates that 670 of 1,854 remitted patients (36.7%) of STAR*D dropped out within 1 month of their QIDS-SR remission. Due to its open-label prescribing though, the ultimate outcome for these patients (and all dropouts during any phase) is unclear since patients could continue their treatment without staying in STAR*D by paying for their medications and physician services that heretofore had been free. Given that such a decision required assuming this new cost which could be substantial, particularly for the one third who lacked insurance coverage [38, table 1], it is unlikely that many STAR*D dropouts continued their treatment on antidepressant medication(s).

The weighted mean relapse rate of STAR*D for remitted patients that called at least once into its IVR system was 37.4% (range: from 33.5% for step-1 to 50% for step-4 patients) and 64.4% for improved patients who entered continuing care not in remission (range: from 58.6% for step-1 to 83.3% for step-4 patients) [38, table 5, column 6]. Table 2 presents the survival analysis for the 1,518 patients who entered continuing care in remission. The numbers in table 2 represent the remitted patients who *'survived'*, i.e. did not relapse or dropout. Relapses of course represent unsuccessfully treated patients. Dropouts represent unsuccessfully treated patients as well, viewed from the intent-to-treat perspective. STAR*D authors highlighted their findings that *'relapse rates were higher for those who entered follow-up after more treatment steps ($p < 0.0001$)'* [38, p. 1911] and *'remission at entry into follow-up was associated with a better prognosis than was simple improvement without remission'* [38, p. 1912]. While both statements are statistically accurate, they do not address the fact that STAR*D patients' had extraordinarily high relapse and/or dropout rates during continuing care regardless of the treatment step their remission occurred nor their extent of acute-care improvement prior to entering continuing care.

These findings call into question continuation phase guideline of APA that *'following remission, patients who have been treated with antidepressant medications in the acute phase should be maintained on these agents to prevent relapse'* despite this recommendation having received the highest *'clinical confidence'* rating of the expert panel [40, p. 15].

## Discussion

Given its 35 million dollar cost and thoughtful design, STAR*D provides a rare opportunity to evaluate the effectiveness of antidepressants with real-world patients and therefore warrants analysis from multiple perspectives independent of those of its authors. While similar to the analysis of Fava et al. [50] documenting decreasing step-by-step remission rates with increasing rates of relapse and drug intolerance, our analysis found that the results of STAR*D appear even worse than previously realized. Even with the extraordinary care of STAR*D, only about one fourth of patients achieved remission in step 1. The study dropout rate was slightly larger than the success rate. The success rate of step 2 was slightly less than that of step 1 and the dropout rate was larger. The success rates in step 3 (17.8%) and step 4 (10.1%) were even more modest with still larger dropout rates (44.8 and 60.1%, respectively).

Of the 4,041 patients started on citalopram, 370 (9.2%) dropped out within 2 weeks. After up to four trials, each provided with vigorous medication dosing *'to ensure that*

*the likelihood of achieving remission was maximized and that those who did not reach remission were truly resistant to the medication'* [32, p. 30], only 1,854 patients (45.9%) obtained remission using the lenient QIDS-SR criteria. In each step, more patients dropped out than were remitted and this dropout rate steadily increased throughout the study. Of the 1,854 remitted patients, 670 (36.7%) dropped out within 1 month of their remission and only 108 (5.8%) survived continuing care and took the final assessment without relapsing and/or dropping out. Even for these 108 patients, it is unclear how many were one of the 607 whose baseline HRSD <14 signified only mild symptoms when first started on citalopram in step 1 and therefore had to score worse during continuing care than when they first entered the study to be counted as relapsed.

In STAR*D, failed trials had negative consequences for patients beyond not obtaining remission. Such failures decreased patients' likelihood for obtaining remission in subsequent trials while increasing their likelihood for drug intolerance, relapse, and/or dropping out. These negative effects lend support to the observation of Fava et al. [50, p. 262] that successive pharmacological manipulations *'may propel depressive illness into a refractory phase'* by fostering oppositional tolerance in which the antidepressant sensitizes some patients to depression. Chouinard and Chouinard [51, p. 75] document similar risks with atypical antipsychotics and estimate that 50% of treatment-resistant schizophrenia cases are related to supersensitivity psychosis. The following issue remains to be determined: the extent that diminishing outcomes of STAR*D are due to a subset developing such oppositional tolerance, patients' natural diminished expectations of improvement following each failure (i.e. a step-by-step diminishing placebo effect), other unknown factors, and/or some combination thereof.

Most importantly to clinicians, STAR*D results show that antidepressants were only minimally effective with real-world patients when provided consistent with *'the theoretical principles and clinical beliefs that currently guide the management of treatment-resistant depression'* [43, p. 136]. This admittedly harsh assessment is most evident when using study completion rates as the best *'hard measure of treatment effectiveness and acceptability'* [14, p. 296].

Turner et al. [9] demonstrates how publication bias inflates the perceived efficacy of antidepressants thereby promoting the widespread acceptance of this treatment. The separate analyses of Turner et al. [9] and Kirsch et al. [10] suggest that antidepressants are only marginally efficacious compared to inert placebos, though the findings in these trials may be due to the under-representation of less symptomatic patients with greater comorbidity (particularly anxiety disorders that have been found to lower antidepressant response rates [52]) and longstanding depressive illness who better characterize the majority seeking care. The analysis of Barbui et al. [15, cited in 16, p. 19] demonstrates how the apparent clinical superiority of paroxetine over placebo disappeared after statistically controlling for differences in drug/placebo side effects suggesting that side effects contribute to unblinding in RCTs and thereby enhance patients' expectation of improvement since they often guess correctly that they are getting the *'real'* drug and therefore anticipate improvement. Similar analyses are needed of antipsychotic/placebo antidepressant augmentation trials for *'treatment-resistant depression'* due to significant side effect profiles of antipsychotics and the role these might play in unblinding. Such analyses are crucial to evaluate properly Nelson and Papakostas' [53] recent meta-analysis finding that atypical antipsychotics were superior to placebo as augmentation agents since this analysis did not control for said differences in drug/placebo side effects and the fact that this apparent *'superiority'* was exceptionally modest, with 9 being the number needed to treat to have one additional remission in trials lasting only 6–8 weeks.

What more can we learn from STAR*D and the reviewed articles? First, even with exemplary pharmaceutical efforts it is difficult to achieve sustained recovery for patients reflecting the range of illness severity of STAR*D. Second, the results from efficacy trials (whether for medication, an evidence-based psychotherapy, or any other treatment) are limited in their ability to estimate a treatment benefit to the extent that the *'the "apples" assessed in such studies do not correspond to the "oranges" of clinical practice'* [26]. The analyses of Zimmerman et al. [30] and Wisniewski et al. [31] further highlight this fundamental disconnect between RCT patients and those most often presenting in real-world clinical practice. Third, the fact that the effectiveness rate in step-2 CTs was no better than antidepressants underscores that MDD – *with its common co-morbidities and recurrent nature* – is a serious, complex, and difficult-to-treat disorder whose treatment often results in fewer positive outcomes than would be expected from efficacy trials of its two most extensively researched interventions.

Fourth, it is worth considering whether or not the measurement-based system of STAR*D with its focus on measuring side effects and symptoms in every visit until *'remission'* was achieved hindered or helped patient care.

STAR*D authors clearly believed that it helped and even equated *'high quality care'* with their system stating: *'Finally, high quality of care was delivered (measurement-based care) with additional support from the clinical research coordinator. Consequently, the outcomes in this report may exceed those that are presently obtained in daily practice wherein neither symptoms nor side-effects are consistently measured and wherein practitioners vary greatly in the timing and level of dosing'* [38, p. 1914]. STAR*D encouraged all patients who did not achieve remission based on a number to enter the next trial despite the failure of QIDS/HRSD to differentially weight core depressive symptoms (e.g. mood, guilt, suicidal ideation, or anhedonia) and accessory ones (e.g. appetite, insomnia, or agitation) [54, 55] and patients' self-assessments of the relative importance of each. In the absence of a meaningful therapeutic alliance between the patient and doctor, relying instead on patients' recitation of side effects and symptomatic change to guide treatment, STAR*D may have failed to capitalize on a crucial ingredient necessary for patient improvement. In contrast, psychosomatic methods would likely have improved patient retention and outcomes given its use of more clinically-rich clinimetric assessment procedures, collaborative decision-making, and its focus on enhancing patients' self-efficacy by teaching them the self-management skills that are likely essential to sustain recovery from MDD [56]. Such psychosomatic methods are at their core *'psychotherapeutic'* and would likely enhance outcomes from any intervention, be it an antidepressant, a placebo, or some other strategy; particularly when applied to treating depressed – *often initially helpless and hopeless* – patients and their commonly occurring comorbid conditions.

Fifth, the continuation and maintenance phase guidelines of APA which essentially encourage open-ended use of antidepressants at *'the same full antidepressant medication doses'* as used in acute treatment appear misguided [40, p. 15]. While the guidelines of APA are consistent with the meta-analyses performed by Geddes et al. [57] and Papakostas et al. [58] reporting large effect sizes for antidepressants in preventing relapse, these analyses do not control for publication bias [59, 60] nor selective outcome reporting [22, 23], both of which may significantly inflate the findings from meta-analyses that fail to control for these common forms of researcher bias. For now, prospective naturalistic studies are likely a better guide to estimate real-world outcomes. In STAR*D, even for the 1,085 remitted patients in step 1 who consented to continuing-care and therefore had the highest likelihood of sustained recovery, only 84 (7.7%) did not relapse and/or dropout by the 12th month of continuing care. STAR*D results are similar to findings of Bockting et al. [61] that only 42% used antidepressants continuously during maintenance phase treatment, of whom 60.4% relapsed, whereas patients who stopped using antidepressants experienced less relapse, with only 8% of those who received preventive CT relapsing. These naturalistic continuation phase studies support Fava's [62, 63] hypothesis that long-term antidepressant use may worsen the course of depression. Besides these studies, failure to find any apparent benefit from continued antidepressant treatment, the recent finding that long-term use of SSRIs at moderate/high daily doses doubles the risk of diabetes [64], and the uncertain risk of oppositional tolerance, provides additional reasons for reexamining this all too common practice.

Finally, in light of the meager results of STAR*D, it is worth reconsidering the term *'treatment-resistant depression'* when referring to patients who do not respond favorably to drug treatment. Should we not direct our attention to what is wrong with our treatment rather than classifying some patients as having an exotic form of depression because they fail to respond? Our understanding is hampered by using language that wrongly implies that there is an exceptional subgroup of patients who are refractory to an otherwise effective treatment. The inescapable conclusion from STAR*D results is that we need to explore more seriously other forms of treatment (and combinations thereof) that may be more effective. This effort will require developing new service delivery models to ensure that as such treatments are identified, they are widely implemented [65, 66].

Despite the pervasive belief regarding the effectiveness of antidepressants and cognitive therapy (CT) among physicians and society at large, STAR*D shows that antidepressants and CT fail to result in sustained positive effects for the majority of people who receive them. STAR*D authors noted at the outset of the study that the *'results should have substantial public health and scientific significance'*. As healthcare professionals and in line with what STAR*D authors themselves recommend, we should take notice of what this largest antidepressant effectiveness trial ever conducted is telling us and reassess the role of antidepressant medications and CT in the evidence-based treatment for depression.

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## Conflicts of Interest

H. Edmund Pigott, PhD, and Gregory S. Alter, PhD, are founders of NeuroAdvantage, LLC, a for-profit neurotherapy company. During the past 3 years, Dr. Pigott has consulted for CNS Response, Midwest Center for Stress and Anxiety, and SmartBrain Technologies.

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# ATTACHMENT 6

EXCERPT



**H**

United States District Court,
E.D. Pennsylvania.
Marion L. KNIPE, Individually and as Administratrix and Administratrix Ad Prosequendum of the Estate of Harold Stanley Jake Garrison, Deceased, and Harold L. Garrison, Jr., Individually, Plaintiffs,
v.
SMITHKLINE BEECHAM d/b/a GlaxoSmithKline, Defendant.
**Civil Action No. 06-3024.**

Sept. 30, 2008.

**Background:** Plaintiffs brought products liability action against manufacturer of prescription antidepressant medication, alleging that teenager, who committed suicide, was injured by his ingestion of the medication. Manufacturer moved for summary judgment and plaintiffs moved to strike.

**Holdings:** The District Court, Buckwalter, Senior District Judge, held that:
(1) New Jersey rather than Pennsylvania law applied to substantive claims;
(2) fact issue existed regarding manufacturer's allegedly fraudulent or misleading promotion of medication as safe and effective for use in adolescents;
(3) fact issues existed regarding plaintiffs' off-label promotion claims;
(4) fact issues existed regarding plaintiffs' breach of express warranty claims;
(5) fact issue existed regarding plaintiffs' failure to warn claim;
(6) New Jersey rather than Pennsylvania law applied to punitive damages claim; and
(7) fact issue existed regarding manufacturer's actual malice, precluding summary judgment on punitive damages claim.

Motions granted in part and denied in part.

West Headnotes

**[1] Products Liability 313A 105**

313A Products Liability
313AI In General
313Ak105 k. What Law Governs. Most Cited Cases
(Formerly 313Ak3)

**Products Liability 313A 225**

313A Products Liability
313AIII Particular Products
313Ak223 Health Care and Medical Products
313Ak225 k. Drugs in General. Most Cited Cases
(Formerly 313Ak3)
Under Pennsylvania's choice of law principles, New Jersey rather than Pennsylvania law applied to substantive claims in plaintiffs' products liability action, which alleged that teenager, who committed suicide, was injured by his ingestion of manufacturer's prescription antidepressant medication, even though Pennsylvania was the situs of manufacturer's headquarters and principal place of business; plaintiffs and teenager resided in New Jersey at all relevant times, teenager went to a New Jersey physician for medical care, and that physician wrote the prescription, which was subsequently filled in New Jersey pharmacies, any purported representations or warnings to the

that with Accutane, the warnings were crystal clear, that she knew what signs of suicidality to look for while Jake was taking the medication and that she heeded those warnings. (Knipe Dep. 122:16-124:16.) As she was not given the same warnings with Paxil, she did not know to take the same precautions. (*Id.* 124:17-131:1.) Such testimony is more than sufficient to survive summary judgment on the issue of causation.

**d. *Direct-to-Consumer Exception***

Defendant's final challenge to the failure to warn claim contends that Plaintiff cannot rely on the direct-to-consumer ("DTC") advertising exception established by the New Jersey Supreme Court in *Perez*, 734 A.2d at 1256. In *Perez*, the court recognized that a pharmaceutical manufacturer generally had no duty to directly warn the consumer under the learned intermediary doctrine, which allows a drug manufacturer to discharge its duties by supplying warnings to the patient's physician. *Id.* It concluded, however, that the learned intermediary doctrine does not apply to "the direct marketing of drugs to consumers" where the consumers alleged that they were influenced by the advertising campaign for the drug. *Id.* at 1256-57. Defendants now argue that because Plaintiffs have testified that neither Jake nor his family saw the advertisements for Paxil, the exception cannot apply.

In the case at bar, Plaintiffs disclaim any intent to rely on the DTC exception since they have established causation through the learned intermediary doctrine. Therefore, the Court dismisses this argument by Defendant.[FN35]

FN35. In its reply brief, however, Defendant contends that Plaintiffs Complaint asserted that GSK owed a duty to warn the "consuming public." (Def.'s Reply Br. 17-18 n. 17 (quoting Compl. ¶ 34.).) The Court notes that this allegation is made as part of a general background statement in the Complaint and is not part of any of Plaintiffs' causes of action.

**5. *Punitive Damages***

The final point of contention between the parties concerns Plaintiffs' request for punitive damages. Defendant claims that punitive damages are not available for any *637 of the claims falling within the PLA, nor are they available for the breach of express warranty claim. Accordingly, it seeks dismissal of this count.

[35] The parties first dispute the law applicable to the punitive damages claim. Plaintiffs argue that, even if New Jersey law applies to the substantive claims, Pennsylvania law should apply to their claim for punitive damages under the principle of *depecage*. Under *depecage*, "different states' laws may apply to different issues in a single case." *Taylor v. Mooney Aircraft Corp.*, 265 Fed.Appx. 87, 91 (3d Cir.2008). Pennsylvania's choice of law analysis employs *depecage*. *Id.* (citing *Berg Chilling Sys., Inc. v. Hull Corp.*, 435 F.3d 455, 462 (3d Cir.2006)). Similarly, *depecage* is explicitly endorsed in comment (d) to Section 145 of the Restatement (Second) of Conflict of Laws, which states that "courts have long recognized that they are not bound to decide all issues under the local law of a single states, but instead each issue is to receive separate consideration if it is one which would be resolved differently under the local law rule of two or more of the potentially interested states." REST. (SECOND) OF CONFLICT OF LAWS § 145, cmt. d.

[36] Applying Pennsylvania's choice of law analysis, the Court finds that a real conflict exists between the laws of Pennsylvania and New Jersey. The Pennsylvania Supreme Court has not foreclosed the awarding of punitive damages in a strict liability action if the facts warrant such an award. *North Side Foods Corp. v. Bag-Pack, Inc.*, Civ. A. No. 06-1612, 2007 WL 954106, at *4 (W.D.Pa. Mar.28,

2007). An award of punitive damages is appropriate where the defendant's actions are so outrageous that they "demonstrate intentional, willful, wanton or reckless conduct." *SHV Coal, Inc. v. Cont'l Grain Co.*, 526 Pa. 489, 587 A.2d 702, 704 (1991). Where a defendant acts with an evil motive or a reckless indifference to the rights of others, punitive damages may be awarded. *Feld v. Merriam*, 506 Pa. 383, 485 A.2d 742, 747 (1984) (citing RESTATEMENT (SECOND) OF TORTS § 908(2)).

In New Jersey, section five of the New Jersey Products Liability Act provides:

> Punitive damages may be awarded to the claimant only if the claimant proves, by a preponderance of the evidence, that the harm suffered was the result of the product manufacturer's or seller's acts or omissions, and such acts or omissions were actuated by actual malice or accompanied by a wanton and willful disregard of the safety of product users, consumers, or others who foreseeably might be harmed by the product. For the purposes of the section "actual malice" means an intentional wrongdoing in the sense of an evil-minded act, and "wanton and willful disregard" means a deliberate act or omission with knowledge of a high degree of probability of harm to another and reckless indifference to the consequen ces or such action or omission. Punitive damages shall not be awarded in the absence of an award of compensatory damages.

N.J. STAT. ANN.. 2A:58C-5(a). In *McDarby v. Merck & Co.*, 401 N.J.Super. 10, 949 A.2d 223 (App.Div.2008), however, the New Jersey Superior Court expressly found that a claim for punitive damages in a products liability action under the New Jersey PLA, which relies upon an allegation of fraud on the FDA for proof of intentional wrongdoing or willful disregard, is preempted by *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 121 S.Ct. 1012, 148 L.Ed.2d 854 (2001). *Id.* at 276.

Given such a real conflict, and the fact that each state's interests would be impaired by application of the other state's law, the Court must then analyze the contacts***638** of each state. *Hammersmith v. TIG Ins. Co.*, 480 F.3d 220, 231 (3d Cir.2007). In *Kukoly v. World Factory, Inc.*, Civ. A. No. 07-1644, 2007 WL 1816476, at *2 (E.D.Pa. June 22, 2007), the Court considered the law applicable to a punitive damages claim in a products liability action where a true conflict existed between the states' laws. It noted that the defective product was distributed and sold in Pennsylvania, the injury occurred in Pennsylvania, the plaintiffs were domiciled in Pennsylvania, and the defendant placed its products into the stream of commerce where it was reasonably foreseeable the products would end up in Pennsylvania. *Id.* at *3. Plaintiffs did not travel to the defendant company's home state of Texas and, instead, purchased the allegedly defective product in a Wal-Mart store in Pennsylvania. The facts were unclear whether the injurious conduct occurred in China (from where the products were imported), at one of the five Wal-Mart distribution centers, or at the local Wal-Mart in Pennsylvania. Accordingly, the Court applied Pennsylvania law. *Id.*

This Court is similarly persuaded that New Jersey law must apply. Although Defendant is domiciled in Pennsylvania and likely made several of the decisions regarding the study and marketing of Paxil in Pennsylvania, the majority of crucial contacts occurred in New Jersey. Any marketing relevant to this case was directed to a New Jersey market. Jake Garrison was prescribed Paxil by a New Jersey physician, Plaintiffs purchased Paxil in a New Jersey pharmacy and Jake Garrison ultimately suffered all side effects in New Jersey.

Moreover, the Court is mindful that New Jersey has sought to comprehensively regulate products liability actions in its state through the PLA and that the PLA applies to all of the substantive claims in this action. Although this Court could technically apply one state's law with respect to liability and compensatory damages and

another state's law with respect to punitive damages, we recognize the inherent problem in doing so. "Indeed, mixing and matching the laws of different states in one case can readily lead to a result 'that neither state would allow ... [since when] a court combines elements of the laws of different states it may upset the delicate balance achieved by legislative compromise.' " *Petrokehagias v. Sky Climber*, Civ. A. Nos. 96-6965, 97-3889, 1998 WL 227236, at *8 (E.D.Pa.1998) (quoting *Schulhof v. Northeast Cellulose, Inc.*, 545 F.Supp. 1200, 1207-08 (D.Mass.1982)). As applying the same law to liability, compensatory damages and punitive damages in this case "serves the administrative interest of not creating undue confusion," the Court declines Plaintiffs' request for *depecage*. *Id.*[FN36]

FN36. Plaintiffs cite to *Kelly v. Ford Motor Co.*, 933 F.Supp. 465 (E.D.Pa.1996) in support of its argument that *depecage* should apply to allow a conflict of laws analysis with respect to a punitive damages claim. This case, however, is distinguishable in light of the fact that the court dealt with a motion for partial summary judgment solely on the claim for punitive damages. The court did not discuss *depecage*.

[37] Having concluded that New Jersey law applies to Plaintiffs' claim for punitive damages, this Court must examine whether such claim can survive summary judgment review under recent New Jersey jurisprudence. As noted above, in *McDarby*, defendant Merck submitted a new drug application to the FDA for its drug Vioxx. 949 A.2d at 231. The FDA approved the initial drug application, despite the existence of a possible linkage with cardiovascular risks. *Id.* at 259. Merck then completed a new study, which inadvertently ***639** confirmed those risks. *Id.* Although Merck submitted a supplemental new drug application with the results of the study, it attempted to disguise the severity of the cardiovascular adverse experiences associated with the drug. *Id.* At trial, the plaintiff received punitive damages on the grounds that if the complete study analysis had been furnished by Merck to the FDA, the FDA may have either not approved or responded in a different fashion to Merck's supplemental new drug application. *Id.* at 271-72. Although the court did not find the failure to warn claim itself preempted, it determined that the basis for the punitive damages claim was a fraud on the FDA allegation that fell within the precise contours of *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 121 S.Ct. 1012, 148 L.Ed.2d 854 (2001). *Id.* at 275-76. Ultimately, the New Jersey Superior Court held that "[b]ecause the punitive damages provisions of N.J.S.A. 2A:58C-5c impinge upon federal statute and regulation to the same extent that was recognized in *Buckman*, 531 U.S. at 349, 121 S.Ct. at 1017-18, we find the principles of implied preemption applied by the Court in *Buckman* to be applicable here." *McDarby*, 949 A.2d at 276.

[38] To the extent that Plaintiffs rest their claim for punitive damages on the allegation that GSK "manipulated the data" it submitted to the FDA in support of its supplemental NDA seeking approval of a pediatric indication for Paxil, this claim clearly falls within the bounds of *McDarby*. Any allegation that Defendant failed to submit or hid crucial data during an FDA approval process effectively invokes a fraud on the FDA claim. In turn, such a claim is impliedly preempted.[FN37]

FN37. Plaintiffs argue that *McDarby* was wrongly decided. They contend that this Court should instead follow the Second Circuit's reasoning in *Desiano, supra*, which interpreted a Michigan statute and found that *Buckman* was limited to a specific cause of action premised on fraud on the FDA and did not apply to a common law claim that required a finding of fraud on the FDA to overcome a statutory immunity. 467 F.3d at 92-93. As *Desiano* concerned a Michigan statute, however, and as this Court is concerned with New Jersey's interpretation of its own law, the Court rejects this argument.

Such a finding, however, does not automatically foreclose a punitive damage award, as Plaintiffs offer two other bases to support their claim. First, they assert that "motivated by monetary greed and the multi-million dollar annual profits, GSK marketed and sold a product without any warnings concerning the risk of suicidal behavior despite clear, statistically significant clinical trial results showing that Paxil-treated adolescent patients engaged in suicidal behavior four times the rate that placebo treated patients did" and hid the data from the medical community. (Pls.' Mem. Opp. Mot. Summ. J. 26.) Second, they allege that "[a]side from concealing the negative data, GSK actually promoted Paxil for treating pediatric/adolescent conditions, such as depression, by falsely claiming that Paxil was safe and effective." (*Id.* at 27.)

The Court declines to find that *McDarby's* prohibition on punitive damages extends to such assertions. As outlined in detail above, fraud on the FDA requires some type of fraud during the approval process for the intended use of the drug. Plaintiff's first two bases for punitive damages do not, in any way, suggest that GSK fraudulently induced the FDA to approve Paxil. As repeatedly emphasized by Plaintiffs, and as recognized by this Court, although Paxil had been approved for adult usage by the FDA, GSK had never sought approval for pediatric usage. In turn, the FDA's disclosure requirements never mandated the submission of any studies regarding effects on adolescents. Absent ***640** such FDA approval for pediatric usage and in the face of evidence showing risks inherent in known off-label Paxil use, GSK could have unilaterally changed its label to add a warning or simply sought to warn the medical community via "Dear Doctor" letters. *See Perry v. Novartis*, 456 F.Supp.2d 678, 682 (E.D.Pa.2006) ("The addition to labeling and advertising of additional warnings, as well as contraindications, adverse reactions, and precautions regarding the drug, or the issuance of letters directed to health care professionals (e.g., 'Dear Doctor' letters containing such information) is not prohibited by [FDA] regulations.") (quoting 44 Fed.Reg. 37434, 37447 (June 26, 1979)).[FN38] Yet, it allegedly chose not to do so. It is this claimed deliberate failure to disclose such adverse events to the medical community-not any "fraud on the FDA"-that supports Plaintiffs' claims for punitive damages.[FN39]

FN38. Indeed, contrary to its claims that it could not have acted outside FDA approval, GSK ultimately did send "Dear Doctor" letters regarding risks in pediatric use of Paxil, in May 2004, prior to the issuance of any FDA-approved labeling changes. (Pls.' Ex. 64.)

FN39. Defendant repeats arguments made in its preemption summary judgment motion that, as of September 2002, the FDA had found no reasonable evidence of an association between Paxil and increased suicidal thoughts by pediatric patients. This argument was fully addressed and rejected by this Court in *Knipe*, 2008 WL 4090995, at *22-24, 583 F.Supp.2d at 580-84.

In turn, such allegations find evidentiary support in the record. Beyond the evidence already discussed throughout this opinion showing that GSK knew of the risk of pediatric suicidality as of 1998, internal GSK documents suggest that Defendant acted with a wanton and willful disregard for the safety of its consumers. In the most telling of these documents, dated October of 1998, Defendant, discussing the problematic results of its Study 329, stated as follows:

**TARGET:** To effectively manage the dissemination of these data in order to minimise [sic] any potential negative commercial impact.

**PROPOSALS**

- Based on the current data from Studies 377 and 329, and following consultation with SB country regulatory and marketing groups, no regulatory submissions will be made to obtain either efficacy or safety statements relating to adolescent depression at this time. However data (especially safety data) from these studies may be included in any future regulatory submissions, provided that we are able to go on and generate robust approvable efficacy data. The rationale for not attempting to obtain a safety statement at this time is as follows;

i) regulatory agencies would not approve a statement indicating that there are no safety issues in adolescents, as this could be seen as promoting off-label use.

ii) it would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine.

- Positive data from St udy 329 will be published in abstract form at the ECNP (Paris, November 1998) and a full manuscript of the 329 data will be progressed.

(Pls.' Ex. 18.) [FN40] Given such evidence, Plaintiffs may be able to establish at trial ***641** that Defendant knew of the risks of pediatric use of its drug, yet failed to warn solely to increase the commercial profitability of Paxil. Such proof would constitute clear and convincing evidence of actual malice, which is not preempted by federal law. Accordingly, the Court denies Defendant's motion for summary judgment on this claim.

FN40. Again, Defendant cites evidence to dispute Plaintiff's assertions that GSK promoted Paxil for treating pediatric conditions. (Def.'s Reply Br. 21.) Such evidentiary disputes, however, highlight the existence of a genuine issue of material fact to be resolved by a jury.

## IV. CONCLUSION

In reaching the foregoing conclusions, the Court emphasizes that we make no definitive findings regarding liability. Rather, faced with literally hundreds of pages of both exhibits and legal briefing, the Court recognizes the presence of multiple genuine, indeed complicated, issues of material fact that must be resolved by a jury after a full trial on the merits. Accordingly, although the Court grants summary judgment on several minor claims, we decline to dismiss the bulk of the case at this juncture. An appropriate order follows.

### *ORDER*

**AND NOW,** this *30th* day of *September,* 2008, upon consideration of the Motion of Defendant GlaxoSmithKline ("GSK") for Summary Judgment on Plaintiffs' Causes of Action (Doc. No. 62); the Response of Plaintiffs Harold L. Garrison, Jr., individually, and Marion Knipe, individually and as administratrix and administratrix *ad prosequendum* of the Estate of Harold Stanley Jake Garrison (Doc. No. 99), and Defendant's Reply Brief (Doc. No. 119), together with Plaintiffs' Motion to Strike Evidence Submitted by GSK in Support of Its Motion for Summary Judgment (Causes of Action) (Doc. No. 106) and Defendant's Response thereto (Doc. No. 116), it is hereby **ORDERED** as follows:

1. Plaintiffs' Motion to Strike Evidence Submitted by GSK in Support of Its Motion for Summary Judgment is **DENIED;**

2. Defendant's Motion for Summary Judgment on Plaintiffs' Causes of Action is **GRANTED IN PART** and **DENIED IN PART** as follows:

a. With respect to Plaintiffs' claims for fraud and negligent misrepresentation, Defendant's motion for summary judgment is **GRANTED** to the extent that Plaintiffs base those claims on t he allegation that they were injured by Paxil's false or misleading warnings, but **DENIED** to the extent that Plaintiffs base those claims on the allegation that they were injured by Defendant's allegedly false and misleading advertising campaign for Paxil;

b. With respect to Plaintiffs' claims for off-label promotion of Paxil, Defendant's motion for summary judgment is **DENIED;**

c. With respect to Plaintiffs' claims for breach of express warranty, Defendant's motion for summary judgment is **DENIED;**

d. With respect to Plaintiffs' claim for negligent pharmaco-vigilance, Defendant's motion for summary judgment is **GRANTED;**

e. With respect to Plaintiffs' products liability claim for inadequate warnings under the New Jersey Products Liability Act, N.J. STAT. ANN.. 2A:58C-1, *et seq.*, Defendant's motion for summary judgment is **DENIED;** and

f. With respect to Plaintiffs' claim for punitive damages, Defendant's motion for summary judgment is **DENIED.**

It is so **ORDERED.**

E.D.Pa.,2008.
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