FDA Introductory Remarks / Regulatory History

Judith A. Racoosin, MD, MPH
Deputy Director for Safety
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II, CDER, FDA
Agenda

• Regulatory History
• Drug Utilization
• Criteria for Product Labeling Sections
• Plan for the day
Smoking Cessation Product Approval Dates

• Nicotine Replacement Therapy (NRT)
  – First available by prescription in the mid-80’s
  – Many more products approved in the 90’s with the over-the-counter (OTC) switches occurring in the mid 90’s

• Zyban (bupropion)- May 1997
  – Drug moiety (bupropion) was previously approved as Wellbutrin in 1985 for major depressive disorder

• Chantix (varenicline)- May 2006
Safety Issue Emerges

• European Medicines Agency (EMA) first alerted FDA to the concern about suicidality with varenicline in May 2007, about a year after FDA approval

• Sample varenicline cases
Chantix - Example Case #1

• F/36/varenicline
• A consumer reported experiencing a complete personality change, a violent temper going into unnecessary rage and stated that her brain felt like it had completely been scrambled, from about day 14 of treatment.
• The consumer believed this was not due to smoking cessation, as she has quit smoking before and never ever felt like this.
Chantix- Example Case #2

- M/61/varenicline
- Patient reported experiencing “suicidal thoughts where he was contemplating the best method to kill himself –slicing an artery” after approximately 1 weeks’ treatment with varenicline.
- Varenicline treatment was discontinued for one week, during which the event resolved.
- Then treatment resumed. When he increased the dose to 1 mg BID, he became “very depressed, was in bed for 16 hours...felt like a zombie.” His wife told him his behavior was very aggressive.
- The patient discontinued varenicline a second time due to the events. The suicidal thoughts, depression, feeling like a zombie resolved; aggression persisted.
- Smoking status was not documented.
Support for Drug-Relatedness in Cases Submitted to FDA’s Adverse Event Reporting System (FAERS)

- Temporal association: onset often occurred shortly after dose initiation or scheduled up-titration
- Positive de-challenge/re-challenge cases
- In some cases, patient had not quit smoking
- Events were often specifically identified as different from previous quit attempts, never-before-experienced, etc.
- Possibility of precipitated withdrawal
FDA’s Evaluation of Neuropsychiatric Adverse Events with Smoking Cessation Drugs

- Through the remainder of 2007 and in 2008, FDA reviewed adverse event reports submitted to FAERS for varenicline, with bupropion and NRT as comparators, as well as sponsor submissions describing case reports they had received.

- As FDA’s evaluation of the cases progressed, and the level of concern regarding the safety signal increased, the placement of labeling language about the association became more prominent in varenicline labeling, moving from Adverse Reactions to Warnings and Precautions.

- Through the review process, we became aware that similar cases had been reported with bupropion, and ultimately a boxed warning was added to both varenicline and bupropion labeling in July 2009.

- FDA posted public communications to describe the evaluation of the safety issue and regulatory actions being taken.
Zyban – Example Case #1

• F/28/bupropion
• Two weeks after starting bupropion, patient reported feeling ‘emotional’ and having regular crying fits. Patient reported having threatened to kill herself and stated, ‘I didn’t care if I lived.’
• No previous history of depression documented.
Zyban – Example Case #2

• M/50/bupropion
• After about one month of bupropion treatment for smoking cessation, patient with history of military service and no prior history of PTSD experienced severe panic attacks, flushing, flashbacks, sleep loss, and “full blown PTSD symptoms” causing loss of work/functioning and self-confidence.
• Reporting physician noted “no life triggering events or stressors”
• Negative dechallenge; required medical treatment
Additional FDA Safety Authorities were Invoked

• In addition to labeling changes, FDA required the following:
  – Risk Evaluation and Mitigation Strategy (REMS)
  – Postmarketing Requirement (PMR)
  – May 2008 for varenicline; Feb 2009 for bupropion

• Rationale for PMR
  – Spontaneous reports generated a safety signal; however, FDA needed a trial to systematically evaluate the risk of neuropsychiatric adverse events in a defined population of smoking cessation patients
FDA Issues Further Guidance for the Postmarketing Requirement

- June 2009 Information Request Letter described trial design requirements for draft protocol submission
  - A large randomized, double-blind, active- and placebo-controlled trial
  - Treatment arms include varenicline, bupropion, NRT, and placebo
  - Compare the risk of clinically significant neuropsychiatric adverse events, including, but not limited to, suicidality
    - determine whether individuals with prior history of psychiatric disorders are at greater risk for development of clinically significant neuropsychiatric adverse events compared to individuals without prior history of psychiatric disorders
    - The trial should be sufficiently powered to adequately assess clinically significant neuropsychiatric events with each treatment and in both of the two subgroups (i.e., with and without psychiatric disorders).
- March 2010 letter formalized randomized controlled trial (RCT) requirements and milestone dates
Other FDA Activities to Investigate Signal of Neuropsychiatric AEs with Smoking Cessation Drugs

• Observational studies
  – VA’s Center for Medication Safety
  – DoD’s U.S. Army Medical Command’s Pharmacovigilance Center

• October 2011 Drug Safety Communication described findings
Prior Consideration of Changes to Boxed Warning

• In April 2014, Pfizer submitted a labeling supplement seeking to remove the boxed warning from Chantix labeling
  — “...since 2009, more reliable data on the NPS [neuropsychiatric] safety of Chantix have become available, including meta-analyses of placebo-controlled clinical trials and data from observational studies comparing varenicline to other smoking cessation pharmacotherapies. As presented in this submission, these data do not support an association between treatment with Chantix and serious NPS [neuropsychiatric] events.”

• FDA sought the input of the PDAC and DSaRM ACs in considering this data

• Shortly before the October 2014 Chantix advisory committee meeting, a group of five consumer organizations submitted a Citizen’s Petition asking that FDA strengthen the Chantix boxed warning about neuropsychiatric adverse events.
2014 Advisory Committee Meeting Outcomes

• The majority of the committee agreed that more data were needed and recommended to retain the current boxed warning statements and reassess once the ongoing post-marketing safety outcome trial designed to capture serious neuropsychiatric adverse events was completed.

• Similarly, FDA decided to wait to respond to the Citizen Petition until we were able to review the results of the safety outcome trial.
Agenda

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U.S. Sales Distribution Data

Sales of smoking cessation products* in packages/bottles sold by prescription status (OTC vs Rx) to all U.S. channels of distribution, 2011-2015


*Only includes products labeled for smoking cessation. Does not include products that may be used off-label, such as Wellbutrin (bupropion) SR and XL generic equivalents.

**IMS NSP estimates a capture of approximately 50% of the total OTC market, the OTC sales data shown are likely an underestimation of total OTC sales.
Patient Data

Nationally estimated number of patients who received dispensed prescriptions for smoking cessation products* through U.S. outpatient retail pharmacies, 2006-2015

Source: IMS Health, Total Patient Tracker (TPT), Data extracted June and July 2016
*Includes products labeled for smoking cessation. Does not include other products that may be used for smoking cessation, such as Wellbutrin (bupropion) SR and XL and generic equivalents.
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• Regulatory History
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Warnings and Precautions Section

• Should describe serious or clinically significant adverse reactions that occurred with the drug or risks that are expected to occur

• Each Warnings and Precautions section should include a succinct description of a topic and should include (if known):
  – Known risk factors for adverse reaction
  – Outcome
  – Numerical estimate of risk or adverse reaction rate
  – Steps to take to prevent, monitor, or manage an adverse reaction

See 21 CFR 201.57(c)(6) and Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling guidance
Boxed Warning

• Ordinarily used in the following situations:
  – Adverse reactions that are so serious in proportion to potential benefit that it is essential it be considered in assessing risks and benefits of using a drug,
    OR
  – There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of drug,
    OR
  – Drug approved with restrictions to assure safe use because drug can be safely used only if distribution or use is restricted

• Can also be used in other situations:
  – To highlight a warning that is especially important to prescriber
  – For a drug that poses risk-benefit considerations that are unique among drugs in a drug class

See Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling guidance
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Based on the Results of the PMR Safety Outcome Trial, What has been Requested by the Sponsors?

• Pfizer has proposed the boxed warning about neuropsychiatric adverse events be removed from Chantix labeling

• Pfizer’s labeling proposal for Chantix retains the Warning in Section 5.1 with some changes to reflect the PMR safety outcome trial results

• GSK has proposed that Zyban be released from the REMS requirement, but they will still maintain the Medication Guide
Today’s Presentations

• Pfizer will make the industry presentation; GSK, though a recipient of the PMR and a co-sponsor of the trial, declined to participate in this AC meeting

• FDA evaluation of the PMR safety outcome trial
  – Clinical review
  – Statistical review

• FDA review of the published observational studies relating to smoking cessation products and neuropsychiatric adverse events
Topics for Discussion

• Trial design and conduct
• Psychiatric history as a risk modifier for neuropsychiatric adverse events
• Impact of trial results and sensitivity analyses on labeling
Clinical Review of the PMR Safety Outcome Trial

Celia Winchell, M.D.
Clinical Team Leader, Addiction Products
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II, CDER, FDA
Outline

• History
• Review Observations About Trial Results
• Efficacy Findings
Why Did FDA Require This Study?

• Post-marketing reports of a specific nature
• Events unlikely to have been well-captured in completed trials
• Frequency of events impossible to estimate from spontaneous reports
• Populations studied didn’t include patients with psychiatric diagnoses
  – Neither safety nor efficacy known in this population
  – Relative balance of benefit/risk - difficult to gauge
FDA’s Objectives for PMR Trial

• Quantify risk of NPS events with Chantix and Zyban
  – Place alternative (NRT) into context
• Facilitate benefit/risk comparison by incorporation of efficacy assessment
• Determine benefit and risk in population with psychiatric history
Choice of Endpoint

• Suicide, psychiatric hospitalization
  – Too narrow
  – Infeasible

• “Standardized MedDRA Query (SMQ)” not available to cover all events of interest

• Need for a novel endpoint/collection approach
NPS Composite Outcome

• Components
  – Mood disturbances (depression /suicidality [suicidal ideation, suicidal behavior, suicide], mania)
  – Events involving hostility/aggression (homicidal ideation, “agitation” [emotional upset])
  – Perceptual abnormalities/psychotic experiences (delusions, hallucination, paranoia, psychosis)
  – Anxiety/panic
  – Events defying other descriptions characterized just as “feeling abnormal”

• Focus on symptoms interfering with the subject’s usual functioning
  – Operationalized as mild, moderate, or severe
    • Mild – does not interfere with subject’s usual function.
    • Moderate – interferes to some extent with subject’s usual function.
    • Severe – interferes significantly with subject’s usual function.
Primary pre-specified safety endpoint

• At least one treatment emergent “severe” adverse event
  – anxiety, depression, feeling abnormal, or hostility
  and/or

• The occurrence of at least one treatment emergent “moderate” or “severe” adverse event
  – agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide.
Neuropsychiatric Adverse Event Inventory (NAEI)

• Semi-structured interview
• To be administered by trained interviewers
• Follow-up questions were to be used for clarification, frequency/duration, severity, and degree of functional impairment related to the symptom.
Collection of Events

- Assessments were to be done in the following order:
  1. Volunteered AE report – opening question on how the subject has been feeling in general
  2. Follow up on previously reported AEs that are still ongoing
  3. Clinical rating scales as specified in the protocol
  4. NAEI
  5. Columbia Suicide Severity Rating Scale.
Anticipated Challenges

• Inter-rater reliability
  – Large role of PI/site staff to interpret patient reports
    • Neuropsychiatric AE reports to contain verbatim narratives
    • Centralized MedDRA coding

• Cross-cultural/language differences

• Site differences (smoking cessation clinics vs. psychiatric clinics vs. general clinical research sites)

• Lack of validation of primary safety outcome
Phase 4 Study A3051123

• Study design
  – Randomized, double-blind, 24-week, NRT and placebo-controlled, triple-dummy designed, multi-center (150), parallel group study
  – Treatments 1:1:1:1
Study Results

• Patient Disposition
• Efficacy findings
• Review findings that raised questions about interpretation of results
• Sensitivity analyses to address concerns
Enrollment

• 150 centers in 16 countries
  – 140 centers actually enrolled patients
  – 139 centers treated patients

• 8144 subjects randomized; 8058 treated
  – 2016 varenicline
  – 2006 bupropion
  – 2022 NRT
  – 2014 placebo
PHx Cohort-Primary Diagnoses

• ~70% affective disorders
  – Major Depression
  – Bipolar-I, Bipolar-II

• ~19% anxiety disorders
  – Panic Disorder with or without Agoraphobia
  – Post-Traumatic Stress Disorder
  – Obsessive-Compulsive Disorder
  – Social Phobia
  – Generalized Anxiety Disorder

• ~9% psychotic disorders
  – Schizophrenia
  – Schizoaffective Disorder

• <1% borderline PD
# Trial Disposition

## Non-PHx Cohort

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<tr>
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<th>NRT</th>
<th>Placebo</th>
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<td>Treated</td>
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<td>990</td>
<td>989</td>
<td>1006</td>
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<td>Completed Study (24 wks)</td>
<td>787 (79.5%)</td>
<td>783 (79.2%)</td>
<td>767 (76.2%)</td>
<td>787 (78.8%)</td>
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<td>Completed Treatment (12 wks)</td>
<td>793 (80.1%)</td>
<td>772 (78.1%)</td>
<td>777 (77.2%)</td>
<td>803 (80.4%)</td>
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<tr>
<td>Discontinued Treatment:</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>No longer willing</td>
<td>61 (6.2%)</td>
<td>63 (6.4%)</td>
<td>79 (7.9%)</td>
<td>89 (8.9%)</td>
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<tr>
<td>Adverse Events</td>
<td>57 (5.8%)</td>
<td>74 (7.5%)</td>
<td>73 (7.3%)</td>
<td>26 (2.6%)</td>
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## PHx Cohort

<table>
<thead>
<tr>
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<th>Varenicline</th>
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<th>Placebo</th>
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<tr>
<td>Treated</td>
<td>1026</td>
<td>1017</td>
<td>1016</td>
<td>1015</td>
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<tr>
<td>Completed Study (24 wks)</td>
<td>811 (79.0%)</td>
<td>803 (79.0%)</td>
<td>790 (77.8%)</td>
<td>765 (75.4%)</td>
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<tr>
<td>Completed Treatment (12 wks)</td>
<td>772 (75.2%)</td>
<td>765 (75.2%)</td>
<td>761 (74.9%)</td>
<td>725 (71.4%)</td>
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<tr>
<td>Discontinued Treatment:</td>
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<tr>
<td>No longer willing</td>
<td>62 (6.0%)</td>
<td>70 (6.9%)</td>
<td>66 (6.5%)</td>
<td>83 (8.2%)</td>
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<tr>
<td>Adverse Events</td>
<td>108 (10.5%)</td>
<td>101 (9.9%)</td>
<td>85 (8.4%)</td>
<td>94 (9.3%)</td>
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## Efficacy Results

Continuous Abstinence Rate (%), CO-confirmed, Overall and by Cohort – Full Analysis Set (FAS) Population

<table>
<thead>
<tr>
<th>CA (%)</th>
<th>Varenicline (N=2037)</th>
<th>Bupropion (N=2034)</th>
<th>NRT (N=2038)</th>
<th>Placebo (N=2035)</th>
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<td><strong>Weeks 9-12</strong></td>
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<tr>
<td>Overall</td>
<td>33.5</td>
<td>22.6</td>
<td>23.4</td>
<td>12.5</td>
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<td>Non-PHx</td>
<td>38.0</td>
<td>26.1</td>
<td>26.4</td>
<td>13.7</td>
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<tr>
<td>PHx</td>
<td>29.2</td>
<td>19.3</td>
<td>20.4</td>
<td>11.4</td>
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<tr>
<td><strong>Weeks 9-24</strong></td>
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<tr>
<td>Overall</td>
<td>21.9</td>
<td>16.2</td>
<td>15.7</td>
<td>9.4</td>
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<td>Non-PHx</td>
<td>25.5</td>
<td>18.8</td>
<td>18.5</td>
<td>10.5</td>
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<tr>
<td>PHx</td>
<td>18.3</td>
<td>13.8</td>
<td>13.0</td>
<td>8.3</td>
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</table>

p<0.05 in all model-based comparisons except for bupropion vs. NRT
NPS findings

• Serious and severe NPS events did occur
• Events are more common in patients with psychiatric history/diagnosis than without
• Events occur in patients on placebo as well as in patients on treatment
• Issues with data collection, coding, and reporting require sensitivity analyses to evaluate frequency of events
Review Observations

• Incomplete/inadequate data collection
• Data coding issues
• Data reporting issues
• Issues raising concerns of data reliability
• Errors in choice of terms for the primary endpoint
Data Collection Issues

• NAEI was used as a checklist, not a tool to guide a semi-structured interview

• Full report of patient’s experience was not reliably captured
  – Sites were not familiar with doing this
  – The unique nature of the safety signal made this very important

• It is not possible to know, in most cases, what the patient actually said. All we have is that the patient endorsed a symptom on the checklist
Data Collection Issues

• Key information about circumstances was often not collected
  – A patient died in a “head-on collision” and the report does not say whether the patient was the driver of the car
Data Coding Issues

• Investigator assessment of severity very inconsistent
  – Narratives describing events of similar impact (e.g. missed days of work) were sometimes assessed as mild, sometimes severe
  – In many cases, information was either not collected or not reported to explain the assessment of severity
  – A patient had a psychiatric hospitalization for depression that the investigator assessed as “mild”
Data Coding Issues

• Cases with identical verbatims coded differently
  – “anger” (verbatim) coded to “irritability” (not in the NPS endpoint) instead of anger (in the NPS endpoint)
  – “restlessness” sometimes coded to agitation (in the NPS endpoint), sometimes not

• Cases with multiple symptoms coded to only one term, losing the “flavor” of a syndromic phenomenon

• NPS cases involving multiple symptoms assigned to a particular subcomponent, ignoring other symptoms
  – Subcomponents ultimately not informative
Data Coding Issues

• AE terms that are psychiatric *diagnoses*, not symptoms, in patients without prior diagnosis
  – If correct, a new diagnosis of major depression would be very significant—not coded as NPS event

• Errors always occur, but these errors were notable and suggested a lack of familiarity with psychiatric terminology, language barriers, or some other problem with accurately capturing and coding patient experiences
  – Insomnia → lack of rest → restlessness → agitation
  – “down and lonely” → depressed affect → ”flat affect” → psychosis
  – Social withdrawal → ”detachment” → flat affect → psychosis
Data Reporting Issues

- Full narrative story is very important in appreciating a complex phenomenon with many symptoms
- Narratives appeared to be automatically generated, filling in the start and stop dates of the MedDRA-coded event without any context, background, or coherence
  - Patient verbatims were not included
- Narratives were uninformative, omitting crucial information for interpreting events
- Lack of integration of safety data streams
Issues Raising Concern of Data Reliability

• A number of sites had unqualified people performing procedures that were supposed to be done by mental health professionals, or people who (even if qualified) needed to be “retrained” on how to do the structured diagnostic interview for psychiatric diagnosis.

• Investigators at several sites either met criteria for disclosure of financial interests, arrangements and payments under 21CFR54.4, or were involved in ongoing arrangements such as speakers’ bureaus related to the Sponsors.

• Two sites among 26 audited by the Sponsor found to be unreliable by Sponsor

• Sensitivity analyses were done with/without sites
Error in Choice of Terms for the Primary Endpoint

– The preferred term “dysphoria” was included among the list of terms that would be included as “aggression”
  • A “corrected” analysis placed dysphoria into depressed mood category

– No separate cognitive impairment component
  • Terms suggesting problems with thinking are subsumed under “feeling abnormal”
Sensitivity Analyses

• Effect of heterogeneity
• Effect of sites identified as unreliable during Sponsor’s audit
• Effect of sites where investigators had disclosable interests or ongoing speakers’ bureau arrangements
• Effect of adding in certain events not included in protocol-specified NPS endpoint
  – Depression/depressed mood coded as moderate
  – Moderate/severe irritability (to capture miscoded anger/aggression events)
  – Moderate dysphoria
Conclusions

• Across sensitivity analyses, the conclusions about the findings of the study are consistent.
  – In the non-PHx cohort, serious or significant neuropsychiatric AEs occurred in all treatment groups, but the incidence was similar across treatment arms.
  – In the PHx cohort, serious or significant neuropsychiatric AEs occurred in all treatment groups, and were consistently somewhat more frequent in the varenicline and bupropion treatment arms.
  – The vast majority of events, although having an impact on patient functioning, were not of a serious nature and were usually transient.
  – Serious AEs in the PHx cohort primarily involved psychiatric decompensation
• All three treatment drugs were effective aids to smoking cessation; the prospect of health benefit from abstinence from smoking is substantial.
• The balance of benefit and risk of smoking cessation products appears to differ based on history of psychiatric illness, but is favorable for both populations.
Statistical Review of the PMR Safety Outcome Trial

Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
September 14, 2016

Eugenio Andraca-Carrera, Ph.D.
Division of Biometrics VII
Office of Biostatistics / Office of Translational Sciences
Center for Drug Evaluation and Research
US Food and Drug Administration
Outline

- Statistical methods
- Primary results
- Sensitivity analyses of primary endpoint
- Additional safety endpoints and analyses
- Statistical comments and summary
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• Statistical methods
• Primary results
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• Additional safety endpoints and analyses
• Statistical comments and summary
Trial Objective

• The **primary objective** of the PMR trial was to **estimate** the risk of NPS events by treatment and cohort

• No pre-specified statistical hypotheses

• No pre-specified risk margin to rule out

• No multiplicity corrections – all confidence intervals are shown at the nominal 95% confidence level
Primary Analysis Methods

• **Analysis population**
  - ‘Safety Analysis Population’: all treated subjects

• **Event ascertainment**
  - All events occurring from first dose to last dose + 30 days

• **Primary endpoint**
  - NPS composite event

• **Statistical model**
  - Estimate risk difference of NPS events (and nominal 95% CI) for every pair-wise comparison of treatments by cohort (Non-PHx and PHx) through a generalized linear model for binary data with an identity link function.
Outline

• Statistical methods
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Primary Results: Non-PHx Cohort

Cumulative NPS Event %

End of Treatment + 30 days

Varenicline | Bupropion | NRT | Placebo
---|---|---|---
13 / 990 (1.3%) | 22 / 989 (2.2%) | 25 / 1006 (2.5%) | 24 / 999 (2.4%)
Primary Results: PHx Cohort

Cumulative NPS Event %

Days from Randomization

End of Treatment + 30 days

Varenicline | Bupropion | NRT | Placebo
---|---|---|---
67 / 1026 (6.5%) | 68 / 1017 (6.7%) | 53 / 1016 (5.2%) | 50 / 1015 (4.9%)
Risk Difference of NPS Events

### Non-PHx

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<tr>
<td>V - P</td>
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<td>B - P</td>
<td>-0.08 (-1.38, 1.21)</td>
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<td>N - P</td>
<td>-0.21 (-1.54, 1.12)</td>
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<tr>
<td>V - N</td>
<td>-1.07 (-2.21, 0.08)</td>
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<td>B - N</td>
<td>0.13 (-1.19, 1.45)</td>
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<tr>
<td>V - B</td>
<td>-1.19 (-2.30, -0.09)</td>
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### PHx

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<th>RD (95% CI)</th>
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<td>B - P</td>
<td>1.78 (-0.24, 3.81)</td>
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<td>N - P</td>
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<td>B - N</td>
<td>1.42 (-0.63, 3.46)</td>
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<tr>
<td>V - B</td>
<td>-0.20 (-2.34, 1.95)</td>
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Outline

• Statistical methods
• Primary results
• Sensitivity analyses of primary endpoint
• Additional safety endpoints and analyses
• Statistical comments and summary
Motivation

• Dr. Winchell identified issues associated with:
  - Data collection
  - Coding errors
  - Data reporting and reliability

• Additional statistical assessments
  • Conduct sensitivity analyses of primary endpoint
  • Conduct analyses of secondary and exploratory safety endpoints
Heterogeneity of NPS Rates by Site

• Descriptive analyses were conducted to evaluate NPS event rates by site

• Plots of NPS events across sites by cohort:
  – Subjects per site (horizontal axis) vs. subjects with NPS event (vertical axis)
  – 95% and 99% prediction bands assuming a common event rate within the cohort and a binomial distribution for the number of subjects with an NPS event within each site
  – 1 dot = 1 site, red dots = outlier sites (outside 99% band)
NPS Event Rates by Site: Non-PHx Cohort

Pooled event rate: 2.1%

4 outlier sites (1.2 expected)
NPS Event Rates by Site: PHx Cohort

Pooled event rate: 5.8%

11 outlier sites (1.3 expected)

60 sites with no NPS events (45 expected)
Heterogeneity of NPS Rates by Site

• Heterogeneity **not** explained by:
  – Country
  – Sub-cohort of PHx cohort
  – Randomized treatment
  – Sites with financial disclosures

• Heterogeneity observed in other known adverse events, such as ‘Irritability’ and ‘Abnormal Dreams’

• **Sensitivity analysis to account for heterogeneity**: Negative Binomial model to estimate the rate ratio of NPS events with same covariates as primary model (treatment, cohort, treatment x cohort, USA)
Outline

- Statistical methods
- Primary results
- Sensitivity analyses of primary endpoint
- Additional safety endpoints and analyses
- Statistical comments and summary
# Deaths

<table>
<thead>
<tr>
<th></th>
<th>Varenicline deaths / N</th>
<th>Bupropion deaths / N</th>
<th>NRT deaths / N</th>
<th>Placebo deaths / N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-PHx</strong></td>
<td>0 / 990</td>
<td>1 / 989</td>
<td>1 / 1006</td>
<td>3* / 999</td>
</tr>
<tr>
<td><strong>PHx</strong></td>
<td>0 / 1026</td>
<td>2 / 1017</td>
<td>1 / 1016</td>
<td>1 / 1015</td>
</tr>
</tbody>
</table>

*Includes 1 suicide*
Planned Neuropsychiatric Instruments

- HADS (Hospital Anxiety and Depression Scale)
- CGI-I (Global Clinical Impression of Improvement)
- C-SSRS (Columbia-Suicide Severity Rating Scale)
# C-SSRS

## Non-PHx

<table>
<thead>
<tr>
<th></th>
<th>Varenicline N = 990</th>
<th>Bupropion N = 989</th>
<th>NRT N = 1006</th>
<th>Placebo N = 999</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suicidal Behavior</strong></td>
<td>0</td>
<td>0</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td><strong>Suicidal Ideation</strong></td>
<td>7 (0.7%)</td>
<td>4 (0.4%)</td>
<td>3 (0.3%)</td>
<td>6 (0.6%)</td>
</tr>
<tr>
<td><strong>Self-Injurious Behavior</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

## PHx

<table>
<thead>
<tr>
<th></th>
<th>Varenicline N = 1026</th>
<th>Bupropion N = 1017</th>
<th>NRT N = 1016</th>
<th>Placebo N = 1015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suicidal Behavior</strong></td>
<td>0</td>
<td>1 (0.1%)</td>
<td>0</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td><strong>Suicidal Ideation</strong></td>
<td>27 (2.6%)</td>
<td>15 (1.5%)</td>
<td>20 (2.0%)</td>
<td>25 (2.5%)</td>
</tr>
<tr>
<td><strong>Self-Injurious Behavior</strong></td>
<td>2 (0.2%)</td>
<td>1 (0.1%)</td>
<td>0</td>
<td>1 (0.1%)</td>
</tr>
</tbody>
</table>
Exploratory Neuropsych Endpoints

• Severe only NPS events
• NPS+ composite endpoint = NPS endpoint plus moderate or severe “Irritability” plus moderate or severe “Depressed mood disorders”
• ‘Corrected’ NPS event
  - Original NPS endpoint incorrectly categorized “dysphoria” as aggression instead of depression
## Severe Only NPS Events

<table>
<thead>
<tr>
<th></th>
<th>Varenicline events / N (%)</th>
<th>Bupropion events / N (%)</th>
<th>NRT events / N (%)</th>
<th>Placebo events / N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-PHx Cohort</strong></td>
<td>1 / 990 (0.1%)</td>
<td>4 / 989 (0.4%)</td>
<td>3 / 1006 (0.3%)</td>
<td>5 / 999 (0.5%)</td>
</tr>
<tr>
<td><strong>PHx Cohort</strong></td>
<td>14 / 1026 (1.4%)</td>
<td>14 / 1017 (1.4%)</td>
<td>14 / 1016 (1.4%)</td>
<td>13 / 1015 (1.3%)</td>
</tr>
</tbody>
</table>
NPS+ Composite Endpoint

% Subjects with Event

Non-PHx
- Varenicline
- Bupropion
- NRT
- Placebo

PHx
- Varenicline
- Bupropion
- NRT
- Placebo

NPS
NPS+
### Risk Difference of NPS+ Events

#### Non-PHx

<table>
<thead>
<tr>
<th></th>
<th>RD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V - P</td>
<td>-1.25 (-2.93, 0.43)</td>
</tr>
<tr>
<td>B - P</td>
<td>-0.74 (-2.46, 0.97)</td>
</tr>
<tr>
<td>N - P</td>
<td>-0.75 (-2.49, 0.99)</td>
</tr>
<tr>
<td>V - N</td>
<td>-0.50 (-2.11, 1.11)</td>
</tr>
<tr>
<td>B - N</td>
<td>0.01 (-1.67, 1.69)</td>
</tr>
<tr>
<td>V - B</td>
<td>-0.51 (-2.12, 1.10)</td>
</tr>
</tbody>
</table>

#### PHx

<table>
<thead>
<tr>
<th></th>
<th>RD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V - P</td>
<td>1.65 (-1.03, 4.33)</td>
</tr>
<tr>
<td>B - P</td>
<td>0.85 (-1.79, 3.49)</td>
</tr>
<tr>
<td>N - P</td>
<td>-1.10 (-3.63, 1.42)</td>
</tr>
<tr>
<td>V - N</td>
<td>2.75 (0.14, 5.37)</td>
</tr>
<tr>
<td>B - N</td>
<td>1.96 (-0.62, 4.53)</td>
</tr>
<tr>
<td>V - B</td>
<td>0.80 (-1.92, 3.52)</td>
</tr>
</tbody>
</table>
Corrected NPS Event

- Corrected NPS events
  - Primary NPS endpoint incorrectly categorized “dysphoria” as aggression instead of depression
- A small number of “dysphoria” events were observed in the trial
  - Incident rates were similar to the primary NPS incidence rates
  - Risk difference findings were consistent with the primary NPS endpoint
Outline

• Statistical methods
• Primary results
• Sensitivity analyses of primary endpoint
• Additional safety endpoints and analyses
• Statistical comments and summary
Statistical Comments

Issues identified in the review of the PMR safety trial

• Clinical review team identified issues associated with:
  - Data collection
  - Coding errors
  - Data reporting and reliability

• High heterogeneity of NPS event rates across sites
Statistical Comments

• High heterogeneity of NPS event rates across sites
  - Not explained by various covariates
  - Sensitivity analyses that better account for site heterogeneity are consistent with the primary analysis

• Sensitivity analyses were conducted to address endpoint definition and coding errors
  - Findings were consistent with the analysis of the primary NPS endpoint
Summary of Findings

• Non-PHx Cohort:
  - Lower incidence of NPS events observed on varenicline
  - Incidence of severe NPS events and C-SSRS events was low and balanced across treatment arms

• PHx Cohort:
  - Higher incidence of NPS events observed on varenicline and bupropion than on placebo
  - Incidence of severe NPS events and C-SSRS events was similar in all treatment arms
REVIEW OF OBSERVATIONAL STUDIES OF NEUROPSYCHIATRIC EVENTS ASSOCIATED WITH SMOKING CESSATION PRODUCTS

Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

September 14, 2016

Chih-Ying (Natasha) Pratt, Ph. D.

Division of Epidemiology-II
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Conclusions (of the 2014 DEPI assessment on observational data)

- The limitations of the observational studies preclude a conclusion of “no association” of varenicline with neuropsychiatric risk.
- It is challenging to evaluate varenicline-associated neuropsychiatric risk using observational data due to:
  - The difficulty in capturing all relevant outcomes and correctly classifying varenicline-related NPS adverse events.
  - The difficulty in avoiding the selection of “healthier” varenicline users.
- The ongoing safety trial is likely to offer better insights into varenicline’s neuropsychiatric risks.
Outline

• Scope of the DEPI literature review
• Summary of the epidemiologic studies and their findings
• Major limitations of the available epidemiologic data
• Assessment of the epidemiologic data
The 2016 DEPI PubMed literature search

412 English language articles

Study selection criteria for in-depth review
• Reported relative risk of neuropsychiatric events
• Used an adequate design to differentiate temporal relationship between drug exposure and outcomes
• Attempted to account for baseline group differences

8 articles eligible for in-depth review
• Excluded two studies
  • Gibbons et al.
  • Gunnel et al.

6 articles for in-depth review
Disclosure

- Two articles describe studies that were collaborative research projects between the FDA and other federal agencies:
  - Meyer et al. 2013
    - FDA and the U.S. Army Office of the Surgeon General, U.S. ARMY MEDICAL COMMAND’s Pharmacovigilance Center (PVC) (referred to hereafter as the “DoD study”)
    - Two members of the DEPI review team are listed as authors on the Meyer et al. publication
  - Cunningham et al. 2016
    - FDA and Department of Veterans Affairs (VA) Center for Medication Safety (VAMedSAFE) (referred to hereafter as the “VA study”)


Studies included in the in-depth review

1. DoD study/Meyer et al., *Addiction* 2013
2. VA study/ Cunningham et al., *Addiction* 2016
3. Pasternak et al., *Addiction* 2013
4. Thomas et al., *BMJ* 2013
6. Molero et al., *BMJ* 2015
Outline

• Scope of the DEPI literature review
• Summary of the epidemiologic studies and their findings
• Major limitations of the available epidemiologic data
• Assessment of the epidemiologic data
## Overview of the reviewed studies

<table>
<thead>
<tr>
<th></th>
<th>DoD study/ Meyer</th>
<th>VA Study/ Cunningham</th>
<th>Pasternak</th>
<th>Thomas</th>
<th>Kotz</th>
<th>Molero</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td></td>
<td></td>
<td>Retrospective cohort study</td>
<td></td>
<td></td>
<td>Self-controlled study</td>
</tr>
<tr>
<td><strong>Data sources</strong></td>
<td>Military health system data</td>
<td>VA health care databases</td>
<td>Danish nation-wide health care data</td>
<td>UK CPRD linked to mortality data and inpatient data</td>
<td>UK QResearch database</td>
<td>Swedish nation-wide health care data</td>
</tr>
<tr>
<td><strong>% with psychiatric history</strong></td>
<td>12%</td>
<td>14% prior psychiatric hospitalization; 38% depression</td>
<td>22%</td>
<td>46%</td>
<td>36% depression; 10% suicide attempts</td>
<td>13.5%</td>
</tr>
</tbody>
</table>

V: Varenicline; N: Nicotine replacement therapy, B: Bupropion; CPRD: Clinical Practice Research Datalink
Main outcomes studied

• Neuropsychiatric (NPS) medical encounters
  – Hospitalizations
  – Emergency department (ED) visits
  – Outpatient visits

• Suicide-related outcomes
  – Fatal self-harm identified by mortality data
  – Medical encounters for non-fatal self-harm
Main findings

Favors varenicline or bupropion

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR = 0.5</th>
<th>1.0</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPS hospitalization (primary diagnosis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPS hospitalization (all diagnoses)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPS outpatient visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPS hospitalization (primary diagnosis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization for depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization for bipolar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization for schizophrenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPS Emergency department visit or hospitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient visit for depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient visit for depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPS in- or outpatient visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In- or outpatient visit for anxiety condition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In- or outpatient visit for mood condition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In- or outpatient visit for psychosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicide or non-fatal self-harm (from hospitalization or mortality data)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicide or non-fatal self-harm (from hospitalization or mortality data)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicide or non-fatal self-harm (from outpatient data)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicide or non-fatal self-harm (from outpatient data)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicide or non-fatal self-harm (from hospitalization or mortality data)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NPS: Neuropsychiatric; HR: Hazard ratio;
a Meyer et al.
b Final report of the VA study: Varenicline and Mental Health Disorders, June 2011
c Pasternak et al. d Kotz et al. e Molero et al. f Thomas et al.
Outline

• Scope of the DEPI literature review
• Summary of the epidemiologic studies and their findings
• Major limitations of the available epidemiologic data
• Assessment of the epidemiologic data
Limitation #1 - Outcome misclassification & under-ascertainment

<table>
<thead>
<tr>
<th>Main Outcomes</th>
<th>DoD study / Meyer</th>
<th>VA Study / Cunningham</th>
<th>Pasternak</th>
<th>Thomas</th>
<th>Kotz</th>
<th>Molero</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropsychiatric (NPS) hospitalizations identified by ICD-9 codes</td>
<td>NPS emergency department (ED) visits or hospitalizations identified by ICD-10 codes</td>
<td>Inpatient visit for non-fatal self-harm identified using READ codes</td>
<td>Suicide death</td>
<td>Outpatient visits for depression or non-fatal self-harm identified using READ codes</td>
<td>In- or outpatient visits for psychiatric conditions or ED, in- or outpatient visits for suicide attempt identified by ICD-10 codes</td>
<td>Suicide death</td>
</tr>
</tbody>
</table>
Concerns on outcome measures (1)

• No chart review was done to confirm that the identified events indeed happened
  – The sensitivity and specificity of the outcome measures were not reported in all the reviewed studies
Concerns on outcome measures (2)

• Diagnostic codes might not have well-captured the NPS adverse events that patients experience while taking varenicline or bupropion
  – “couldn’t make myself get out of bed”
  – “not myself”
  – “felt like a zombie”
  – “wanted to die”
  – “thought about killing myself”
Concerns on outcome measures (3)

• Some patients experiencing varenicline-associated or bupropion-associated NPS adverse events might contact (or be referred to...) the legal system, rather than the medical system
Summary of the concerns on outcome measures

• Under-ascertainment of outcomes
  – ICD codes are inadequate to capture all the relevant outcomes

• Misclassification of outcomes
  – the NPS events that were captured might not all be related to varenicline or bupropion
Limitation #2 - Differential prescribing or use of smoking cessation products

- Some studies included data from the timeframe after the publicity of varenicline’s NPS risk
- Bupropion has also been associated with NPS adverse events

**differential prescribing or use:** Patients with a higher (perceived) NPS risk being less likely to receive varenicline or bupropion
Limitation #2-
Differential prescribing or use of smoking cessation products

<table>
<thead>
<tr>
<th></th>
<th>Thomas</th>
<th>Kotz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time frame</strong></td>
<td>Sep 2006 to Oct 2011</td>
<td>Jan 2007 to Jun 2012</td>
</tr>
</tbody>
</table>

**Drug Safety Update**

**Volume 1, Issue 7**

**February 2008 from MHRA and CHM**

**Varenicline: safety update**

**Keywords:** varenicline, Champix, smoking cessation, depression, suicidal thoughts, suicidal behaviour

Depression has been reported in patients using varenicline who are trying to stop smoking, and symptoms of depression may include suicidal thoughts and behaviour. Patients who are taking varenicline who develop suicidal thoughts should stop their treatment and contact their doctor immediately.
### Measured Psychiatric history or past psychotropic use by treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Thomas (N=81,545)</th>
<th>Varenicline (N=31,260)</th>
<th>Bupropion (N=6,741)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous psychiatric illness</td>
<td>48.5%</td>
<td>41.1%</td>
<td>42.8%</td>
</tr>
<tr>
<td>Alcohol misuse</td>
<td>7.1%</td>
<td>4.9%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Previous drug misuse</td>
<td>3%</td>
<td>1.8%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Previous self-harm</td>
<td>10.5%</td>
<td>8.9%</td>
<td>8.1%</td>
</tr>
<tr>
<td>Previous hypnotics use</td>
<td>23%</td>
<td>19.3%</td>
<td>19.1%</td>
</tr>
<tr>
<td>Previous antipsychotic use</td>
<td>21%</td>
<td>15.8%</td>
<td>15.6%</td>
</tr>
<tr>
<td>Previous antidepressant use</td>
<td>47.7%</td>
<td>41.1%</td>
<td>41.9%</td>
</tr>
<tr>
<td>Kotz (N=106,759)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous depression</td>
<td>38%</td>
<td>32%</td>
<td>34%</td>
</tr>
<tr>
<td>Previous self-harm</td>
<td>11%</td>
<td>9%</td>
<td>9%</td>
</tr>
</tbody>
</table>
Measured Psychiatric history or past psychotropic use by treatment groups

<table>
<thead>
<tr>
<th>Treatment</th>
<th>NRT (N=81,545)</th>
<th>Varenicline (N=31,260)</th>
<th>Bupropion (N=6,741)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Previous self-harm</td>
<td>11%</td>
<td>9%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Varenicline and bupropion users appeared to be at lower neuropsychiatric risk than NRT users → potential for bias
Findings of Thomas & Kotz studies

Suicide/non-fatal self-harm
*Thomas et al.*

- Hazard ratio (vs. NRT)
  - 0.88 (0.52-1.49)

General practitioner (GP) visit for depression
*Kotz et al.*

- Hazard ratio
  - 0.66 (0.63-0.69)

GP visit for suicide or non-fatal self-harm
*Kotz et al.*

- Hazard ratio
  - 0.56 (0.46-0.68)

The observed decreased risk was likely due to bias from differential prescribing/use of smoking cessation products.
Limitation #3 - Confounding by nicotine withdrawal symptom

<table>
<thead>
<tr>
<th></th>
<th>Molero</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Self-controlled study</td>
</tr>
<tr>
<td>Time frame</td>
<td>Nov 2006 to Dec 2009</td>
</tr>
<tr>
<td>Data sources</td>
<td>Swedish Nationwide health care data</td>
</tr>
<tr>
<td>Exposure</td>
<td>Varenicline-exposed period</td>
</tr>
<tr>
<td>Reference group</td>
<td>Unexposed period</td>
</tr>
</tbody>
</table>

→ introduced confounding that makes varenicline exposed time appear to increase NPS risk, even if varenicline is in fact risk neutral
Findings of Molero study

Neuropsychiatric event

- Anxiety condition
  - Mood condition
  - Psychosis
  - Suicide

Hazard ratio (vs. Unexposed period)

- Favors varenicline: 1.18 (1.05-1.31)
- Favors non-use of varenicline: 1.27 (1.06-1.51) 1.28 (1.07-1.52) 0.94 (0.73-1.20) 1.00 (0.72-1.37)

Unclear whether the observed increased risk was due to varenicline use or to the choice of the reference period.
## Limitation #4 - Bupropion as reference group

<table>
<thead>
<tr>
<th></th>
<th>Pasternak</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Retrospective cohort study</td>
</tr>
<tr>
<td><strong>Time frame</strong></td>
<td>Jan 2007 to Dec 2010</td>
</tr>
<tr>
<td><strong>Data sources</strong></td>
<td>Danish Nationwide health care data</td>
</tr>
<tr>
<td><strong>Exposure</strong></td>
<td>Varenicline or bupropion</td>
</tr>
<tr>
<td><strong>Reference group</strong></td>
<td>Bupropion</td>
</tr>
</tbody>
</table>

**WARNING: NEUROPSYCHIATRIC REACTIONS; AND SUICIDAL THOUGHTS AND BEHAVIORS**

**NEUROPSYCHIATRIC REACTIONS IN PATIENTS TAKING BUPROPION FOR SMOKING CESSION**

Serious neuropsychiatric reactions have occurred in patients taking ZYBAN® for smoking cessation [see Warnings and Precautions (5.1)]. The majority of these reactions occurred during bupropion treatment, but some occurred in the context of discontinuing treatment. In many cases, a causal relationship to bupropion treatment is not certain, because depressed mood may be a symptom of nicotine withdrawal. However, some of the cases occurred in patients taking ZYBAN who continued to smoke.

The risks of ZYBAN should be weighed against the benefits of its use. ZYBAN has been demonstrated to increase the likelihood of abstinence from smoking for as long as 6 months compared with treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

**SUICIDALITY AND ANTIDEPRESSANT DRUGS**

Although ZYBAN is not indicated for treatment of depression, it contains the same active ingredient as the antidepressant medications WELLBUTRIN®, WELLBUTRIN® SR, and WELLBUTRIN XL®. Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term trials. These trials did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in subjects over age 24; there was a reduction in risk with antidepressant use in subjects aged 65 and older [see Warnings and Precautions (5.2)].

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber [see Warnings and Precautions (5.2)].
Finding does not provide reassurance of varenicline’s neuropsychiatric safety because bupropion also has been associated with neuropsychiatric adverse events.
# Limitation #5 - Assess the impact of psychiatric history

<table>
<thead>
<tr>
<th></th>
<th>DoD study/Meyer</th>
<th>VA Study/Cunningham</th>
<th>Pasternak</th>
<th>Thomas</th>
<th>Kotz</th>
<th>Molero</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with PHx</td>
<td>12%</td>
<td>14% prior psychiatric hospitalization; 38% depression</td>
<td>22%</td>
<td>46%</td>
<td>36% depression; 10% suicide attempts</td>
<td>13.5%</td>
</tr>
<tr>
<td>Assesses the impact of PHx</td>
<td>Yes, with limitations</td>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
<td>Yes, with limitations</td>
</tr>
</tbody>
</table>

PHx: psychiatric history
Subgroup findings of the Molero study

<table>
<thead>
<tr>
<th>Condition</th>
<th>Overall population</th>
<th>Non-PHx</th>
<th>PHx</th>
<th>Hazard ratio (vs. Unexposed period)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anxiety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall population</td>
<td></td>
<td></td>
<td>1.27 (1.06-1.51)</td>
</tr>
<tr>
<td></td>
<td>Non-PHx</td>
<td></td>
<td></td>
<td>1.41 (0.99-2.00)</td>
</tr>
<tr>
<td></td>
<td>PHx</td>
<td></td>
<td></td>
<td>1.23 (1.01-1.51)</td>
</tr>
<tr>
<td><strong>Mood</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall population</td>
<td></td>
<td></td>
<td>1.28 (1.07-1.52)</td>
</tr>
<tr>
<td></td>
<td>Non-PHx</td>
<td></td>
<td></td>
<td>1.17 (0.86-1.60)</td>
</tr>
<tr>
<td></td>
<td>PHx</td>
<td></td>
<td></td>
<td>1.31 (1.06-1.63)</td>
</tr>
<tr>
<td><strong>Psychoses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall population</td>
<td></td>
<td></td>
<td>0.94 (0.73-1.20)</td>
</tr>
<tr>
<td></td>
<td>Non-PHx</td>
<td></td>
<td></td>
<td>3.52 (0.81-15.27)</td>
</tr>
<tr>
<td></td>
<td>PHx</td>
<td></td>
<td></td>
<td>0.90 (0.70-1.16)</td>
</tr>
</tbody>
</table>

PHx: psychiatric history

Unclear whether the observed increased risk was due to varenicline use or to the choice of the reference period.
Subgroup findings of the DoD/Meyer, VA and Pasternak studies

<table>
<thead>
<tr>
<th></th>
<th>Overall cohort</th>
<th>No PHx</th>
<th>PHx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DoD study /Meyer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>19,933</td>
<td>15,867</td>
<td></td>
</tr>
<tr>
<td>NPS outcome</td>
<td>23</td>
<td>32</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>17,338</td>
<td>14,105</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14,105</td>
<td>2,595</td>
<td>1,762</td>
</tr>
<tr>
<td></td>
<td>2,595</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td><strong>VA study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>14,131</td>
<td>14,131</td>
<td>14,131</td>
</tr>
<tr>
<td>NPS outcome</td>
<td>16</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>13,811</td>
<td>13,811</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13,811</td>
<td>2,034</td>
<td>2,034</td>
</tr>
<tr>
<td></td>
<td>2,034</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td><strong>Pasternak</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>17,935</td>
<td>17,935</td>
<td>14,089</td>
</tr>
<tr>
<td>NPS outcome</td>
<td>39</td>
<td>46</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>14,089</td>
<td>13,962</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13,962</td>
<td>3,846</td>
<td>3,973</td>
</tr>
<tr>
<td></td>
<td>3,846</td>
<td>36</td>
<td>37</td>
</tr>
</tbody>
</table>

V: Varenicline; N: Nicotine replacement therapy; B: bupropion; NPS: neuropsychiatric; PHx: psychiatric history

Most of the observed outcomes were from patients WITH psychiatric history
Subgroup findings of the DoD/Meyer, VA and Pasternak studies

**DoD/Meyer**
- **V vs. N**
  - Overall population
  - Non-PHx: 0.80 (0.21-2.98)
  - PHx: 1.07 (0.46-2.46)

**VA study**
- **V vs. N**
  - Overall population: 0.76 (0.40-1.46)

**Pasternak**
- **V vs. B**
  - Overall population: 0.85 (0.55-1.30)
  - Non-PHx: 0.33 (0.09-1.22)
  - PHx: 1.01 (0.64-1.59)

Hazard ratio

V: Varenicline; N: Nicotine replacement therapy; B: Bupropion; PHx: Psychiatric history
Outline

• Scope of the DEPI literature review
• Summary of the epidemiologic studies and their findings
• Major limitations of the available epidemiologic data
• Assessment of the epidemiologic data
## Summary of major study limitations

<table>
<thead>
<tr>
<th>Limitations</th>
<th>DoD study/ Meyer</th>
<th>VA study/ Cunningham</th>
<th>Pasternak</th>
<th>Thomas</th>
<th>Kotz</th>
<th>Molero</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome misclassification &amp; under-ascertainment</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Differential prescribing/use</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Highly likely</td>
<td>Highly likely</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Confounding by nicotine withdrawal symptoms</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Highly likely</td>
</tr>
</tbody>
</table>
Conclusions

• Existing observational data alone are insufficient to either confirm or refute an increased neuropsychiatric risk associated with either varenicline or bupropion use among patients with or without psychiatric history.

• Neuropsychiatric safety of smoking cessation products should be assessed based on the totality of the available data, including case reports, observational and clinical trial data.
FDA Backup Slide Shown
NPS event rate by country and cohort

<table>
<thead>
<tr>
<th>Country</th>
<th>Non-PHx</th>
<th>PHx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>events / n</td>
<td>%</td>
</tr>
<tr>
<td>UNITED STATES</td>
<td>50 / 1875</td>
<td>2.7%</td>
</tr>
<tr>
<td>GERMANY</td>
<td>15 / 400</td>
<td>3.8%</td>
</tr>
<tr>
<td>FINLAND</td>
<td>3 / 178</td>
<td>1.7%</td>
</tr>
<tr>
<td>BULGARIA</td>
<td>0 / 260</td>
<td>0.0%</td>
</tr>
<tr>
<td>CANADA</td>
<td>3 / 136</td>
<td>2.2%</td>
</tr>
<tr>
<td>ARGENTINA</td>
<td>2 / 218</td>
<td>0.9%</td>
</tr>
<tr>
<td>SPAIN</td>
<td>2 / 147</td>
<td>1.4%</td>
</tr>
<tr>
<td>SLOVAKIA</td>
<td>0 / 118</td>
<td>0.0%</td>
</tr>
<tr>
<td>SOUTH AFRICA</td>
<td>4 / 224</td>
<td>1.8%</td>
</tr>
<tr>
<td>NEW ZEALAND</td>
<td>2 / 67</td>
<td>3.0%</td>
</tr>
<tr>
<td>RUSSIAN F.</td>
<td>0 / 68</td>
<td>0.0%</td>
</tr>
<tr>
<td>MEXICO</td>
<td>3 / 133</td>
<td>2.3%</td>
</tr>
<tr>
<td>AUSTRALIA</td>
<td>0 / 31</td>
<td>0.0%</td>
</tr>
<tr>
<td>BRAZIL</td>
<td>0 / 9</td>
<td>0.0%</td>
</tr>
<tr>
<td>DENMARK</td>
<td>0 / 107</td>
<td>0.0%</td>
</tr>
<tr>
<td>CHILE</td>
<td>0 / 13</td>
<td>0.0%</td>
</tr>
</tbody>
</table>