FDA Town Hall Update: SUDEP and Clinical Trials

Symposium Co-Chairs: Jacqueline French, M.D.

and

Billy Dunn, M.D.

Monday, December 8, 2014
Convention Center – Room 612, Level 6
3:00 – 5:00 p.m.
OVERVIEW
In 2011, a meta-analysis published in Lancet Neurology suggested that patients randomized into placebo-controlled add-on studies of antiepileptic drugs had a higher likelihood of having SUDEP if they were randomized to the placebo arm compared to addition of an active drug. This analysis was recently repeated by the FDA using data requested from the companies performing the trials. This symposium will discuss the following issues: 1) How do the findings impact the design of add-on studies of antiepileptic drugs? 2) What do these findings mean for clinical practice? The session will include a long interactive audience discussion session, as specifically requested by the FDA, to provide community input to the regulatory process.

Learning Objectives
- Define patient-specific risk/benefit ratios related to treatment interventions vs absence of intervention in treatment resistant patients
- Counsel patients regarding risks and benefits related to treatment interventions vs absence of intervention in treatment resistant patients
- Understand and counsel patients regarding risks and benefits related to treatment interventions vs absence of intervention in treatment resistant patients.

Target Audience
Intermediate: Epilepsy fellows, epileptologists, epilepsy neurosurgeons, and other providers with experience in epilepsy care (e.g., advanced practice nurses, nurses, physician assistants), neuropsychologists, psychiatrists, basic and translational researchers.

Advanced: Symposia will address highly technical or complex topics (e.g., neurophysiology, advanced imaging techniques or advanced treatment modalities, including surgery).

PROGRAM
Co-Chairs: Jacqueline A. French, M.D. and Billy Dunn, M.D.

3:00 p.m. Introduction
Billy Dunn, M.D.

3:05 p.m. Review of 2011 Analysis
Philippe Ryvlin, M.D., Ph.D.

3:20 p.m. Presentation of FDA Analysis
Mary Doi, M.D., M.S.

3:40 p.m. Potential Impact on Clinical Trial Design and Practice
Jacqueline A. French, M.D.

4:00 p.m. Interactive Panel/Audience Discussion
Eric Bastings, M.D.                       Norman Hershkowitz, M.D., Ph.D.
Mary Doi, M.D., M.S.                      Alice Hughes, M.D.
Billy Dunn, M.D.                          Sally Jo Yasuda, Pharm.D., M.S.

4:55 p.m. Conclusions
Jacqueline A. French, M.D.

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ABPN Core Competencies
The American Board of Psychiatry and Neurology has reviewed the Town Hall FDA Update and has approved this program as part of a comprehensive lifelong learning program, which is mandated by the ABMS as a necessary component of maintenance of certification.
Core Competency: Professionalism

FACULTY/PLANNER DISCLOSURES
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FACULTY / PLANNER BIO AND DISCLOSURES
Billy Dunn, M.D. (Co-Chair)
Dr. Billy Dunn is the Director of the Division of Neurology Products at the US Food and Drug Administration's Center for Drug Evaluation and Research.

Dr. Dunn has nothing to disclose

Jacqueline French, M.D. (Co-Chair)
Dr. Jacqueline French is a professor in the Department of Neurology NYU, in the Comprehensive Epilepsy Center, and Director of the Clinical Trials Consortium, an academic group that has performed a number of early phase clinical trails in epilepsy, and has developed new methodologies for epilepsy trials. She trained in Neurology at Mount Sinai Hospital in New York, and did her fellowship training in EEG and epilepsy at Mount Sinai hospital and Yale University. Dr French has focused her research efforts on development of new therapeutics for epilepsy, and new methodologies for clinical trials. She has been active in the Epilepsy Therapy Project, ILAE, and is past president of the American Epilepsy Society.

Dr. French discloses receiving support as Consulting/Advisory Board Activity from Consulting (on behalf of the Epilepsy Study Consortium) Acorda, Eisai Medical Research, Convergence, Electrocore, GlaxoSmithKline, GW Pharma, LCGH, Inc, Johnson & Johnson, Mapp Pharmaceuticals, Marinus,
Novartis, Lundbeck, Pfizer, Sepracor, Sunovion, SK Life Science, Supernus Pharmaceuticals, UCB Inc/Schwarz Pharma, Upsher Smith, Ultragenyx, Vertex Advisory board: UCB, Biotie, Electrocore, Eli Lilly, Acorda Therapeutics, Sunovion, Upsher-Smith; as Research Funding from For Profit Commercial Sources/Principal investigator from Principal investigator on multicenter trials for Eisai Medical Research, LCGH, Marinus, SK Life Science, Impax, Novartis, UCB Inc/Schwarz Pharma, Upsher Smith, Vertex. The HEP project receives research support from UCB, Pfizer and Lundbeck. The ASERT trial (completed) Received support from UCB, Supernus, Eisai, GSK, Lundbeck, J & J, Upsher-Smith, and Pfizer.

Eugenio Andraca-Carrera, Ph.D.
Dr. Andraca-Carrera has nothing to disclose.

Eric Bastings, M.D.
Dr. Bastins has nothing to disclose

Mary Doi, M.D., M.S.
Dr. Doi is a medical officer at the FDA in the Division of Neurology Products in the Office of New Drugs in the Center for Drug Evaluation and Research. She works on the Safety Team analyzing pre- and post-marketing data. She is a board-certified internist and has a Master of Science in Epidemiology.

Dr. Doi has nothing to disclose.

Norman Hershkowitz, M.D., Ph.D.
Norman Hershkowitz serves as a Team Leader for the Division of Neurology Products at the FDA, where he regulates all antiepileptic. He received his PhD in Pharmacology at Georgetown University in 1979 and MD the University of Texas Medical Branch in 1984. Norman's clinical residency was in Neurology at the University of Maryland, and he was a postdoctoral research fellow at Baylor College of Medicine and the NIH (as an NRC fellow), where he investigated the pathophysiology of epilepsy and the pharmacology of anticonvulsants. He was an Assistant and then Associate Professor of Neurology and Pharmacology at Georgetown University from 1988 to 1998 and subsequently joined the FDA. Norman has numerous research publications and book chapters.

Dr. Hershkowitz has nothing to disclose.

Alice Hughes, M.D.
Dr. Hughes has nothing to disclose.

Philippe Ryvlin, M.D., Ph.D.
Philippe Ryvlin is Professor of Neurology, Chair of the Department of Neurology and Epilepsy at Hospices Civils de Lyon, Director of the Translational and Integrative Group in Epilepsy Research at Lyon’s Neuroscience Research Centre (INSERM U1028, CNRS 5292) and co-Founder of the IDEE Institute, Lyon, France. He is also President of the European Epilepsy Monitoring Association (EEMA), co-Chair of the European Joint Task Force of the ILAE and IBE and coordinator of the European pilot network of reference centres in refractory epilepsy and epilepsy surgery (E-PILEPSY). He has published over 170 PubMed referenced papers on topics primarily related to epilepsy surgery, anti-epileptic treatments and Sudden Unexpected Death in Epilepsy (SUDEP).

Dr. Ryvlin discloses

Philip Sheridan, M.D.
Dr. Sheridan has nothing to disclose.
Mat Soukup, Ph.D.
Dr. Soukup has nothing to disclose.

Sally Yasuda, Pharm.D.
Dr. Yasuda has nothing to disclose.

Kevin Graber, M.D. (CME Reviewer)
Dr. Graber is an associate professor of neurology and neurological sciences at Stanford University, specializing in adult epileptology. He has research interests in mechanisms of posttraumatic epilepsy and vagus nerve stimulation.

Dr. Graber discloses receiving support as Research Funding from For Profit Commercial Sources/Principle Investigator from No 1099 reportable funding. 1. E37 investigator for Cyberonics sponsored trial, but did not enroll patients, and there is no salary support. 2. Small grant from LVIS Corporation for imaging research, but derive no salary.

Paul Levisohn (Medical Content Specialist, AES)
Dr. Levisohn is a member of the faculty of the section of Pediatric Neurology at The University of Colorado School of Medicine and Children's Hospital Colorado Neuroscience Institute, having joined the faculty over 15 years ago following a similar period of time in the private practice of pediatric neurology. His academic career has focused on clinical care for children with epilepsy with particular interest in clinical trials and on the psychosocial impact of epilepsy. Dr. Levisohn is currently a consultant on medical content for CME activities to staff of AES. He is a member of the national Advisory Board of EF and has been chair of the advisory committee for the National Center of Project Access through EF.

Paul Levisohn, M.D. has nothing to disclose.

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To help support this process, attendees who want CME will be asked to pay the following rates:

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<th>Category</th>
<th>Fees</th>
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<tr>
<td>Member Fees</td>
<td>$50 through January 16, 2015</td>
<td>$75 January 17 – February 27, 2015</td>
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<td>Non-member Fees</td>
<td>$75 through January 16, 2015</td>
<td>$100 January 17 – February 27, 2015</td>
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The online Evaluator will be left open through February 27, 2015. You must complete the evaluations and credit tracking by that date.

By completing this information online, attendees greatly assist the Council on Education and Annual Meeting Committee with important needs assessment data whereby the AES can further plan and address educational gaps to meet the needs of our learners.

A meeting attendance certificate will be available for international meeting attendees at the registration desk.
SUDEP in placebo-controlled randomized trials in patients with drug-resistant seizures

December 8, 2014

Philippe Ryvlin\textsuperscript{1,2} & Sylvain Rheims\textsuperscript{1}
Neurological Hospital (HCL), IDEE (Institut Des EpileptiEs)
and TIGER (INERIM U1028, UMR CNRS 5292), Lyon
Department of Clinical Neurosciences, CHUV, Lausanne

Learning Objectives

• To get insight into the risk of death and SUDEP in placebo-controlled randomized trials of add-on antiepileptic drugs
• To appreciate the potential of treatment revision for preventing SUDEP

Abbreviations used

- GTCS: Generalized Tonic-Clonic Seizure
- RCTs: Randomized Controlled Trials
- AED: Anti-Epileptic Drug
- OR: Odd Ratio

Methods: Systematic review

- double-blind, placebo-controlled randomized controlled trials (RCTs)
- add-on anti-epileptic drugs (AEDs)
- adult patients
- uncontrolled partial or PGTC seizures
- Jan 1, 1960, to Dec 31, 2010
- multiple databases
- Cochrane collaboration’s method

Disclosure

UCB pharma Speaker & consultant fees
Eisai Pharmaceutical Speaker & consultant fees
Cyberonics Speaker & consultant fees
Eisai drugs

Background

Pooled analysis of 4 case-control studies \textsuperscript{1}

- More than 3 GTCS/year: Odd Ratio (OR) = 15.5 (9.9-24.1)
- Polytherapy: Odd Ratio (OR) = 1.95 (1.1-3.5)

Reappraised analysis with OR adjusted on GTCS \textsuperscript{2}

<table>
<thead>
<tr>
<th>Number of concommitant AEDs</th>
<th>Odd ratio adjusted on the number of GTCS</th>
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<tbody>
<tr>
<td>0</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>1</td>
<td>0.5 (0.3-0.995)</td>
</tr>
<tr>
<td>2</td>
<td>0.9 (0.4-1.8)</td>
</tr>
<tr>
<td>3</td>
<td>2.0 (0.9-4.1)</td>
</tr>
<tr>
<td>&gt;4</td>
<td>1.6 (0.6-4.1)</td>
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</tbody>
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\textsuperscript{1} Hesdorffer et al. Epilepsia 2011, \textsuperscript{2} Hesdorffer et al. Epilepsia 2012
Results: Deaths and SUDEP

- 33 deaths in 21,224 patients and 5589 patient-years = 5.9 / 1000 PY
  - 20 SUDEP in 13% of trials:
    - 11 definite and 7 probable
    - 2 possible, with signs of aspiration at autopsy
    - 6 motor vehicle accident or traumatic shock
    - 2 suicide (remacemide 600 mg, vigabatrin 1000 mg)
    - 1 cerebral hemorrhage
    - 1 pulmonary embolism
    - 1 cerebral tumour
    - 1 diabetic ketoacidosis
    - 1 intracerebral hypertension

Main analyses

- Efficacious treatment vs Placebo - Definite and probable SUDEP
  - OR = 0.17 (0.05 – 0.57); p = 0.0046 [N=12 trials]
  - Risk difference = -0.0014 (-0.02 to 0); p = 0.0065 [N=109]
  - Similar values when considering possible SUDEP
  - No significant difference for the other causes of death (OR=0.89)
  - Results unchanged by adding non-eficacious to efficacious treatment (OR=0.14, p=0.0012) or to placebo (OR=0.2, p=0.0091)
  - Rate of definite & probable SUDEP per 1000 patient-year
    - Placebo: 6.8 (95% CI: 3.8 – 11.6)
    - Efficacious treatment: 0.8 (95% CI: 0.2 – 2.7)
    - Non-eficacious treatment: 3.7 (95% CI: 0.1 – 20.6)

- No impact of trial's duration on the level of risk

Methods: Statistics

- Primary analysis
  - Incidence of definite and probable SUDEP
  - Patients allocated to placebo vs efficacious active treatment
  - Mantel-Haenszel exact method without zero-cell corrections for a stratified odds ratio and associated 95% CI, with exclusion of trials with no event.

- Secondary and sensitivity analysis
  - Incidence of definite, probable and possible SUDEP
  - Non-eficacious and efficacious treatments pooled together
  - Non-eficacious treatment and placebo pooled together
  - Mantel-Haenszel risk difference with zero-event trials
  - SUDEP rate in trials with 3 versus >12 weeks duration
  - meta-regression on treatment duration

SUDEN in study arms

<table>
<thead>
<tr>
<th>STUDY</th>
<th>STUDY ARM</th>
<th>TYPE OF SUDEP</th>
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<tbody>
<tr>
<td>Buxton et al 1996</td>
<td>POS</td>
<td>Placebo</td>
</tr>
<tr>
<td>Sackellares et al 2004</td>
<td>POS</td>
<td>Placebo</td>
</tr>
<tr>
<td>Buxton et al 1996</td>
<td>GB</td>
<td>Placebo</td>
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</table>

Mean number of days [SD] between randomisation and SUDEN

- Placebo: 77 (65); Efficacious treatment: 70 (46); Inefficacious treatment: 73 (14)

Interpretation

- SUDEN rate per 1000 patient-years
  - Active treatment group = 0.9 (95% CI = 0.2 – 2.7)²
  - Placebo group = 6.9 (95% CI = 3.8 – 11.6)²
  - Open-label add-on studies = 3.8 (95% CI = 2.9 – 5.0)²
    - Lamotrigine = 3.4³ and 3.2³
    - Three other AEDs = 3.7 to 4.3³
    - Tiagabine = 3.8³

- Decreased risk of SUDEP during the first 3 months of add-on treatment?
- Increased risk in patients allocated to placebo?

Ref: Ryvlin et al. Lancet Neurol 2011
Increased risk in patients allocated to placebo?
- Patients often enter double-blind RCTs because of an aggravating and/or desperate clinical situation which would otherwise justify treatment revision. Allocating those patients to placebo withold such treatment revision and might place the patient at higher risk of SUDEP.
- In some patients, one of their baseline AEDs is withdrawn in order to fulfill RCTs inclusion criteria (number and type of baseline AEDs), with a risk of withdrawal-induced seizure aggravation which might promote SUDEP.

Transient decreased risk in patients allocated to add-on AED?
- On average, patients receiving an add-on AED suffer less seizures, including less GTCS, during the double-blind period of RCTs.

Interpretation

Limitations
- Retrospective study
- Meta-analysis
- Rare events
- Interpretation speculative
- No direct translation to clinical practice

Still a 7-fold difference in the risk of sudden death in young adults, which statistical significance is supported by p values < 0.005 that survives all sensitivity analyses.

A plea for industry support

Impact on Clinical Care and Practice
- Results from our meta-analysis support the view that treatment revision in patients with drug resistant seizures might reduce the risk of SUDEP.

Pooled analysis of open-label extension studies could confirm the protective impact of treatment « revision » against SUDEP, and suggest an optimal schedule for such revision.
FDA Meta-Analysis of Risk of SUDEP in Adjunctive Adult Epilepsy Trials

Mary Doi, M.D., M.S.
US Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Division of Neurology Products

Disclaimer

• The views expressed are those of the speaker and do not necessarily reflect the policies and practices of the FDA.

Outline

• Background
• Data Sources
• Methods
• Results
• Limitations
• Conclusion
• Discussion

Background

• Medically refractory epileptic population at higher risk for SUDEP than general epileptic population
• Ryvlin et al. meta-analysis published in 2011¹
  – Placebo subjects at higher risk for SUDEP
• FDA meta-analysis was initiated to assess whether the risk of SUDEP is higher in adults randomized to placebo versus those randomized to AEDs for adjunctive treatment.

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Data Sources

• Key to our analysis was our access to the raw data
• Requested the following data from AED Sponsors
  – deaths (along with full subject narratives)
  – study design
  – exposure (number of adult patients and patient-years)
  – efficacy results
  – demographic information

Data Processing/Verification

• Data submitted by the Sponsors were checked for completeness and accuracy
  – Multiple information requests were sent to clarify data (typos, missing info, etc)
  – Data cross-checked with original Clinical Study Reports
  – Data cross-checked with original references in Ryvlin’s meta-analysis
  – Data consolidated, verified, and submitted to Office of Biostatistics

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Trial Inclusion Criteria

• Double-blind, placebo controlled
• Adjunctive AED trials
• Performed in adults
• For indications: refractory partial onset or primary generalized tonic-clonic seizures
• Only trials for FDA approved AEDs
• Parallel or cross-over trials
  – For cross-over trials, only the first period (prior to cross-over) was included in the meta-analysis

Trials Excluded

• Open-label extension
• Monotherapy
• Single-blind
• Randomized withdrawal studies
• Studies that were terminated early
• Studies performed for specific syndromic epilepsies (e.g., Lennox Gastaut syndrome)

Exposure

• Definition of Efficacious Dose:
  – Doses of AEDs approved by the FDA
  – Higher than approved doses (or in-between doses)
• Length of Exposure:
  – Sponsor’s number of patients and patient-years in the safety population
  – Sponsors were requested to calculate time of exposure from the first to the last study dose
Endpoints

- **Primary endpoint:**
  - Definite and Probable SUDEP
- **Secondary endpoints:**
  - All cases of SUDEP (definite, probable, possible)
  - All deaths

Deaths

Only included deaths that occurred
- After at least 1 dose of the study drug
- Within 1 day of treatment discontinuation (or ≤1 day after last dose of the study drug)
- During the double-blind period
- In which the terminal event (e.g., pancreatitis) occurred while on drug (even though the death may have occurred off drug)
  - Deaths were excluded if terminal event was not treatment emergent (e.g., cancer with symptoms prior to starting the trial)

Event Adjudication - SUDEP

- Narratives of all deaths were independently evaluated by 3 FDA medical reviewers
- Blinded to the treatment arm
- Reviewers used an adjudication checklist (using latest definitions of SUDEP) to categorize the death as SUDEP (definite, probably, possible) or not SUDEP
- Consensus was reached for most cases (1 reviewer served as a tie-breaker for some cases)

Analysis Methods

- **Comparison of Interest:**
  - Subjects randomized to placebo to subjects randomized to an AED
- **Pre-specified primary analysis method**
  - Risk Ratio: Exact method stratified by trial
  - Patient years of exposure used as the denominator
- **Sensitivity analyses**
  - Risk Difference: Mantel-Haenszel stratified by trial
- All confidence intervals estimated and reported at a nominal α = 0.05 level (two-sided)

Pre-specified Analyses

- **Primary Analysis**
  - Comparison of the rate of definite and probable SUDEP in subjects receiving AEDs at efficacious doses versus placebo
- **Secondary analysis**
  - Comparison of the rate of definite and probable SUDEP in subjects receiving AEDs at any dose (efficacious and non-ef ficacious) versus placebo

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19 AEDs
- Partial-onset epilepsy:
  - divalproex sodium, eslicarbazepine acetate, febantum, gabapentin, lacosamide, levetiracetam, levetiracetam XR, lamotrigine, lamotrigine XR, oxcarbazepine, pregabalin, retigabine, tiagabine, topiramate, vigabatrin, valproic acid, zonisamide
  - 2 AEDs approved since Ryvlin’s metaanalysis: oxcarbazepine XR and perampanel
- Primary generalized tonic-clonic seizures:
  - levetiracetam, lamotrigine, topiramate

112 Trials in FDA Analysis*

Exposure

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<tr>
<th></th>
<th># Patients</th>
<th>Patient-years</th>
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<tbody>
<tr>
<td>Efficacious Doses</td>
<td>11447</td>
<td>3370</td>
</tr>
<tr>
<td>Non-ef ficacious Doses</td>
<td>628</td>
<td>193</td>
</tr>
<tr>
<td>Placebo</td>
<td>6502</td>
<td>1999</td>
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Primary Analysis*

<table>
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<tr>
<th></th>
<th>Efficacious Dose</th>
<th>Placebo</th>
<th>Exact Stratified Odds Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Patient-years</td>
<td>3370</td>
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<td>Definite, Probable SUDEP</td>
<td>5</td>
<td>10</td>
<td>0.28 (0.07, 0.94) p-value 0.026</td>
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With Secondary Endpoints*

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<tr>
<td>Definite, Possible SUDEP</td>
<td>6</td>
<td>11</td>
<td>0.91 (0.03, 0.95) p-value 0.021</td>
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<tr>
<td>All-Cause Death</td>
<td>13</td>
<td>16</td>
<td>0.11 (0.02, 1.14) p-value 0.079</td>
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Primary Analysis

<table>
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<tr>
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<td>Definite, Probable SUDEP</td>
<td>5</td>
<td>10</td>
<td>-3.65 (-7.03, -0.27) p-value 0.034</td>
</tr>
</tbody>
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*Trials with events included 21 trials in 11 AEDs

*Includes 1 study that contained only non-efficacious doses
With Secondary Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Efficacious Dose</th>
<th>Placebo</th>
<th>Mantel-Haenszel Risk Difference per 1000 patient-years (95% CI)</th>
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</tr>
<tr>
<td>Definite, Probable, Possible SUDEP</td>
<td>6</td>
<td>11</td>
<td>-3.31 (-7.48, -0.34) p-value 0.032</td>
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<tr>
<td>All-Cause Death</td>
<td>13</td>
<td>16</td>
<td>-3.98 (-8.42, 0.50) p-value 0.082</td>
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</table>

SUDEP Case Comparison: Primary Analysis

<table>
<thead>
<tr>
<th>SUDEP Cases (Definite &amp; Probable)</th>
<th>Efficacious Dose</th>
<th>Placebo</th>
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</thead>
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<tr>
<td>FDA</td>
<td>Ryvlin</td>
<td>FDA</td>
</tr>
<tr>
<td>Same Adjudication</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Different Adjudication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provided only by Sponsors</td>
<td>3(^*)</td>
<td>1</td>
</tr>
<tr>
<td>In AEDs not FDA-approved</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

\(^*\) Categorized as definite SUDEP by Ryvlin and possible SUDEP by the FDA
\(^\d\) Includes 2 deaths not reported in the published trials

Incidence of SUDEP in Medically Refractory Patients

- Efficacious dose subjects in adjunctive epilepsy trials: 3.5
- Placebo subjects in adjunctive epilepsy trials: 5.9

Outline

- Background
- Data Sources
- Methods
- Results
- Limitations
- Conclusion
- Discussion

Limitations

- Results are based on small number of SUDEP cases
  - Results sensitive to small changes in events counts
- Trial level data only
  - No subject level data
    - length of exposure before developing SUDEP
    - covariates that may be risk factors for SUDEP
    - treatment discontinuation or trial discontinuation
- May not be generalizable
  - Limited to studies in approved drugs
  - Did not expand to INDs

Outline

- Background
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Conclusion
• The results support a decreased risk of SUDEP in the active treatment groups compared to placebo in randomized, double-blind, placebo-controlled adjunctive trials of FDA-approved AEDs in adults.

Discussion
• Do the findings impact AED clinical trial design?
• Do the findings impact clinical practice for epilepsy patients?
Potential Impact on Clinical Trial Design and Practice  
12/8/2014  
Jacqueline A French MD  
NYU School of Medicine  
New York, NY

What does this data mean?

• There appears to be a difference in SUDEP rate between patients enrolled in the add-on placebo and add-on active drug
• There are two interpretations
  • Either
    – add-on AED reduces your risk of SUDEP from baseline
  • Or
    – Add-on placebo increases your risk of SUDEP from baseline

How can active drug reduce risk of SUDEP?

• If overall reduction of seizures is effective in reducing SUDEP risk
• If reduction of GTCC is effective in reducing SUDEP risk
• Data already exists that absolute number of GTCC predicts SUDEP risk

Number of GTCC/3 months and SUDEP risk

– 0–5 seizures OR set at 1
– 6–10 seizures OR 0.7  95% CI 0.2–2.5
– 11–20 seizures OR 19.4  95% CI 1.7–226
– 21–50 seizures OR 14.6  95% CI 1.3–165
– more than 50 seizures OR 11.7  95% CI 0.3–419

However, there was no evidence (before now) that this risk was alterable through active intervention!

Langan et al 2005

How can add-on placebo increase risk of SUDEP above baseline?

• Until now, we have acted based on our understanding that add-on placebo is “safe” because “we are not doing anything to them”
• In fact, Robert Temple of the FDA has been quoted to say
  – “This (Add-on) design is common in trials of therapy for cancer, heart failure, and epilepsy, in which omitting standard therapy would generally be unacceptable”

1 Temple Annals of Internal Medicine 2000

Disclosure

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I serve as the president of The Epilepsy Study Consortium, a non profit organization. NYU receives a fixed amount from the Epilepsy Study Consortium towards my salary. The money is for work performed by me on behalf of The Epilepsy Study Consortium, for consulting and clinical trial related activities. I receive no personal income for these activities.

Within the past year, The Epilepsy Study Consortium received payments for research services from: Acorda, Alexza, BioPharm Solutions, Biotie Therapies, Brabant Pharma, Eisai Medical Research, Georgia Regents University, GlaxoSmithKline, Gw Pharma Ltd., Marinus, Novartis, Pfizer, Pfizer-Neuroentis, Sage, Sk Life Science, Sunovion, Supernus Pharmaceuticals, Takeda, UCB Inc/Schwarz Pharma, Ultragenyx, Upsher Smith
Is this really true?

- Is add-on placebo the same as “standard therapy”?
- Perhaps not!
- Being randomized to placebo is like “active non-action”, meaning that under circumstances that would normally lead a clinician to adjust therapy (e.g. worsening, cluster or even failure to improve), the “treater” (in this case the investigator) sits on their hands.
- In 2014, there is almost always another “appropriate” drug that could be used, which will be withheld for 5-6 months until the study is complete.

Clinician take-home message

- Continued active attempts at seizure control are better than no active attempts to treat
- This is so far the ONLY (relatively) proven intervention that can decrease the risk of SUDEP

How about clinical trials?

- With this information, we could make one of several decisions
  - We could stop all add-on placebo-controlled trials
  - We could modify the design of add-on placebo-controlled trials
  - We could decide to continue our current practice
    - But we could ask for more info
- What would be the implications?

Implications of no placebo-controlled add-on trials

- What is left?
  - Active controlled trials
  - These usually end up with “no difference”
  - Are these interpretable?
  - What is the chance of a successful active superiority trial
- If we don’t come out with the right answer we have the potential to harm millions of people.

Change trial design?

- Is it sufficient to limit exposure to placebo?
- Time to event trial design?

Time to baseline seizure rate

- Event is individualized
- Patients exit the trial as soon as they experience a number of seizures equal to their average monthly baseline rate or a minimum time in the study
- If no effect: median time to event ~30 days
- If positive effect: median time to event >>30 days
- If negative effect: Median time to event < 30 days
Do we need more data?

- Is everyone at equal risk, or is there a sub-population at specific risk
  - Eg pts with higher GTCC frequency?
  - Pts on certain AEDs?
- Could we continue trials with placebo if we understand who was at risk?

Conclusion

- Next Steps:
  - Stop all add-on placebo-controlled trials?
    - This would likely be premature without more data
  - Modify the design of add-on placebo-controlled trials?
    - Very reasonable action as we gather more data
  - Continue our current practice?
    - Very hard to justify with the current knowledge at hand

Learning Objectives

- After reviewing this the attendee should be able to:
  - Provide explanations of why the SUDEP rate might increase as a result of being randomized to the placebo arm of randomized placebo-controlled add-on studies of antiepileptic drugs
  - Identify the reason placebo-controlled trials are important

Impact on Clinical Care and Practice

- Choices about whether to continue actively changing antiepileptic drugs in an attempt to improve seizure control can impact on the risk of SUDEP
- Patients who are at high risk for SUDEP (eg those with a high rate of GTCC seizures) should be cautioned that if they are randomized to the placebo arm of the study, their SUDEP rate might increase