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Presentation to the  
Joint Meeting of the Peripheral and Central  
Nervous System Drugs Advisory Committee  
(PCNS) and the Psychopharmacologic Drugs  
Advisory Committee (PDAC)

*Neurontin / Lyrica and potentially suicide  
related adverse events (PSRAEs)*

**10 July 2008**

## **Pfizer representatives**

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## Pfizer position (1)

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- **Pregabalin and gabapentin represent a distinct class of compounds with a unique mechanism of action and should be evaluated separately from other AEDs**
  - **Large databases for pregabalin and gabapentin allow separate and robust analyses**
  - **Pregabalin and gabapentin contributed 35% of the total patients, but only 8.4% of the total events, in the FDA's meta-analysis**
- **Pfizer believes that the benefit/risk profile of pregabalin and gabapentin are properly represented in current product labeling.**
- **The available data do not support a boxed warning for suicidality for either product.**
  - **Such a warning would misrepresent the available evidence for pregabalin and gabapentin**
  - **Over-warning has the potential to negatively impact patient care**

## Pfizer position (2)

- Based on the totality of data, there is no evidence of an elevated risk for PSRAEs with either pregabalin or gabapentin
  - Updating the FDA's analysis (through 01 January 2008) demonstrates a reduction in the Agency's calculated risks for pregabalin and gabapentin
    - Approximately 2000 more pregabalin-treated patients
    - 50% reduction in odds ratio (0.94)
    - Reduction in risk difference from 0.52 to 0.13 for pregabalin
  - Inclusion of data from *all* available trials, including those without events of concern, demonstrates no elevated risk of PSRAEs



## Treatment class?

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- Common thread of effect in epilepsy does not imply equivalent risk profile across products
  - Product labeling shows differences in AE profiles across AEDs
- Products are used in a broad array of indications

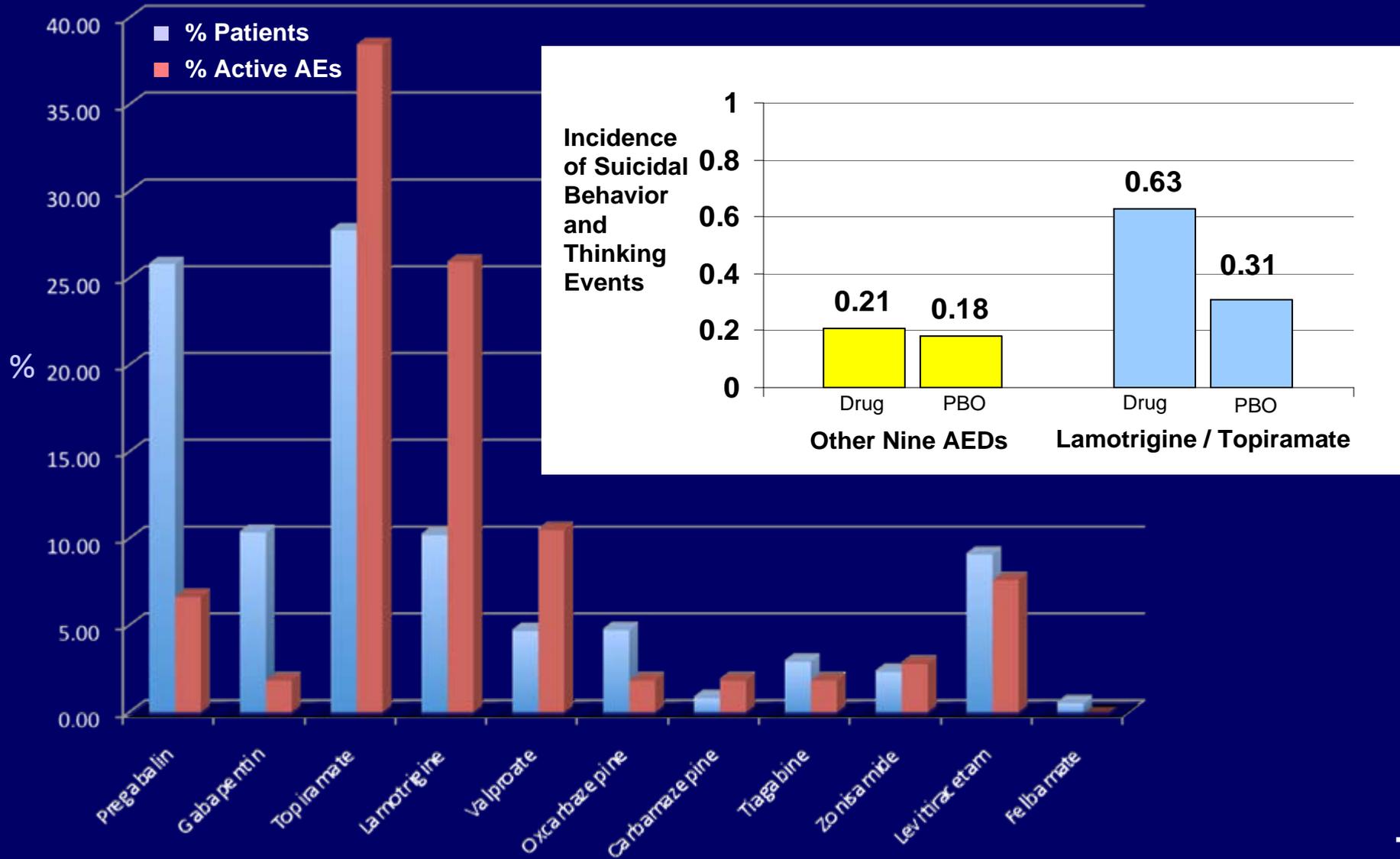
# Pharmacological class?

*Compounds have widely different mechanisms of action*

Compound	Mechanism of Action	Drug	Placebo	%N in FDA	%Events in FDA
Pregabalin	$\alpha_2 \delta$ ligand	7/7201	2/3125	23.5%	6.3%
Gabapentin	$\alpha_2 \delta$ ligand	2/2903	1/2029	11.2%	2.1%
Topiramate	Na <sup>+</sup> channel blocker; enhance GABA-A; inhibit AMPA/kainate	40/7742	8/3971	26.7%	33.8%
Lamotrigine	Na <sup>+</sup> channel blocker; N/P Ca <sup>2+</sup> channel blocker	27/2865	11/2070	11.2%	26.8%
Valproate	Na <sup>+</sup> channel blocker; T Ca <sup>2+</sup> channel blocker; GABA-T inhibitor	11/1327	9/992	5.3%	14.1%
Oxcarbazepine	Na <sup>+</sup> channel blocker	2/1342	1/827	4.9%	2.1%
Carbamazepine	Na <sup>+</sup> channel blocker	2/252	3/250	1.1%	3.5%
Tiagabine	GAT-1 blocker	2/835	0/608	3.3%	1.4%
Zonisamide	Na <sup>+</sup> channel blocker; T Ca <sup>2+</sup> channel blocker	3/672	1/438	2.5%	2.8%
Levetiracetam	SVA-2 ligand	8/2554	2/1549	9.3%	7.0%
Felbamate	Na <sup>+</sup> channel blocker; enhance GABA-A; inhibit NMDA receptors	0/170	0/170	0.8%	0.0%

# PSRAE incidence is not uniform across active groups

- Pregabalin and gabapentin contributed few events



# Identified products do not represent a class

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- Treatment class –
  - Common thread of effect in epilepsy does not imply equivalent risk profile across products
  - Variable indications
- Different mechanisms of action
- Unequal representation of events

## Incidence of potentially suicide-related events (c-casa 1-5) are virtually identical between pregabalin and placebo

Observed events based on 2006 submission to FDA

C-CASA Categories	Pregabalin N=7609; PY=1053.05			Placebo N=3279; PY=473.38		
	N	% <sup>a</sup>	n/PY	N	% <sup>a</sup>	n/PY
1: Completed Suicide	1	0.013	0.001	0		
2: Suicide Attempt	3	0.039	0.003	0		
3: Preparatory acts toward imminent suicidal behavior	0			0		
4: Self-injurious behavior, intent unknown	0			1	0.030	0.002
5: Suicidal ideation	3	0.039	0.003	2	0.061	0.004
6a: Not enough information; fatal	0			0		
6b: Not enough information; nonfatal	15	0.197	0.014	4	0.122	0.008
<b>Any event (1-5)</b>	<b>7</b>	<b>0.092</b>	<b>0.007</b>	<b>3</b>	<b>0.091</b>	<b>0.006</b>
<b>Any event (1-6b)</b>	<b>22</b>	<b>0.289</b>	<b>0.021</b>	<b>7</b>	<b>0.213</b>	<b>0.015</b>

AED = Antiepileptic drug; PY = Patient years

<sup>a</sup>n/N x 100

Data source: Pfizer Briefing Document, Appendix 2, Table 4.

# Only 3 events reported within gabapentin controlled clinical trials

## Event Types by Indication Using the 2006 FDA Response Gabapentin Studies

	Treatment	Event 1-4 n/patient- years	Event 1, 2, 3, 4 n/N	Completed Suicide	Suicide Attempt	Preparatory Acts	Suicidal Ideation
NeP	Gabapentin	0/161.651	0/1081	0	0	0	0
	Placebo	1/127.644 (0.0078)	1/785 (0.0013)	0	0	0	1
Epilepsy	Gabapentin	2/210.689 (0.0095)	2/778 (0.0026)	0	0	0	2
	Placebo	0/166.587	0/617	0	0	0	0
Other Psych	Gabapentin	0/21.487	0/144	0	0	0	0
	Placebo	0/22.256	0/145	0	0	0	0
Chronic Pain	Gabapentin	0/11.636	0/157	0	0	0	0
	Placebo	0/3.658	0/53	0	0	0	0
Other Studies	Gabapentin	0/59.973	0/478	0	0	0	0
	Placebo	0/32.520	0/236	0	0	0	0

Data source: Pfizer Briefing Document, Appendix 1, 10 July 2008, Page 2.

# Pfizer's updated analysis shows one new event

## Completed suicide reported in a placebo-treated patient

### Raw Event Counts: 2006 and 2008

<b>2006</b>	<b>Subjects Active/PBO</b>	<b>Completed Suicide</b>	<b>Suicide Attempt</b>	<b>Preparatory Acts</b>	<b>Suicidal Ideation</b>	<b>Total</b>
Gabapentin / Placebo	2623 / 1821	0 / 0	0 / 0	0 / 0	2 / 1	2 / 1
Pregabalin / Placebo	7276 / 3153	1 / 0	3 / 0	0 / 0	3 / 2	7 / 2
$\alpha_2 \delta$ / Placebo Total	9899 / 4974	1 / 0	3 / 0	0 / 0	5 / 3	<b>9 / 3</b>
<b>2008</b>	<b>Subjects Active/PBO</b>	<b>Completed Suicide</b>	<b>Suicide Attempt</b>	<b>Preparatory Acts</b>	<b>Suicidal Ideation</b>	<b>Total</b>
Gabapentin / Placebo	2623 / 1821	0 / 0	0 / 0	0 / 0	2 / 1	2 / 1
Pregabalin / Placebo	9215 / 4099	1 / 1	3 / 0	0 / 0	3 / 2	7 / 3
$\alpha_2 \delta$ / Placebo Total	11838 / 5920	1 / 1	3 / 0	0 / 0	5 / 3	<b>9 / 4</b>

Note: Exposure to  $\alpha_2 \delta$  ligands was approximately twice that of placebo.

2008 data provides approximately 40% more exposure to drug.

Data source: Pfizer Briefing Document, Tables 9 and 11.

## Descriptive statistics

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- Very few events
- Equally distributed between treatment groups
  - No difference in incidence of events between drug and placebo
- Updated analysis shows greater symmetry in events between treatment groups
  - Updated data can also be analyzed by FDA's methodology

## Analysis of rare events: issues (1)

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- Rarity of events will lead to unstable point estimates
  - Different ratio-based methods in the presence of rare events will give different point estimates
- Majority of studies do not have an event in either treatment group
  - Approx. 66% of FDA dataset
  - Approx. 80% of Pfizer dataset
- Ratio-based methods that don't account for the majority of data may inflate risk estimate
- Methods exist that allow use of all available data
  - Use of methods that can measure risk estimate with all data vs. only studies with events can provide an estimate of the effect of excluding those studies Non-ratio based risk estimates (risk difference) may provide the most accurate point estimate of risk
  - Allows inclusion of all data
- Mantel –Haenzsel estimates of a common odds ratio assume that the data estimates among the defined groups are consistent/poolable. As the Agency noted, there is insufficient statistical power to test for the “poolability” with rare events

# Ratio-based estimates of risk are unstable

*- derived values are method-dependent*

## Suicidality Rates from $\alpha 2 \delta$ Trials (Events 1, 2, 3, and 4) – Stratification by Trial All Placebo Controlled Trials Included<sup>a</sup>

Method	Odds Ratio	95% CI on Odds Ratio	Event Counts	
			A 2 $\delta$ N= 9899	Placebo N=4974
Mantel-Haenszel with '0.5' correction	0.891	0.342, 2.313	9/1771 <sup>b</sup>	3/946
Mantel-Haenszel	1.681	0.479, 5.902	9/1771 <sup>b</sup>	3/946
Logistic regression	1.792	0.473, 6.798	9/1771 <sup>b</sup>	3/946
Dersimonian-Laird random effects model <sup>c</sup>	0.882	0.319, 2.444	9/1771 <sup>b</sup>	3/946

Events included are completed suicide (1); suicide attempt (2); preparatory acts towards imminent suicidal behavior (3); suicidal ideation (5)

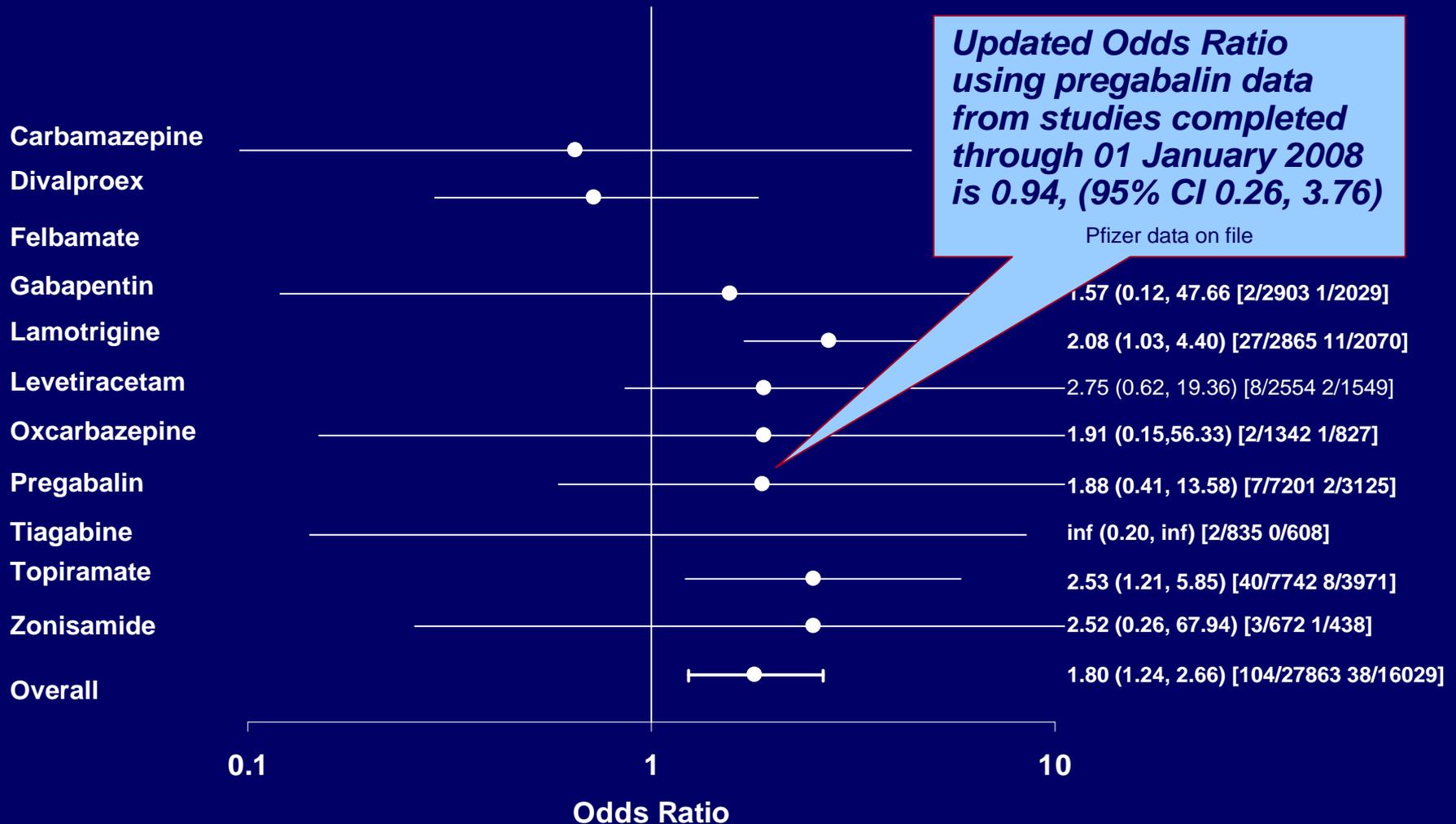
<sup>a</sup>See list of excluded trials in Table 4 and list of trails with single dose/single day treatment in Table 3

<sup>b</sup>These methods exclude subjects in trials with no suicidality events

<sup>c</sup>For Dersimonian-Laird, individual trial log odds ratio and their SEs were determined using Mantel-Haenszel with '0.5' correction

# FDA-calculated odds ratios

- Risk estimate for most products appears unstable

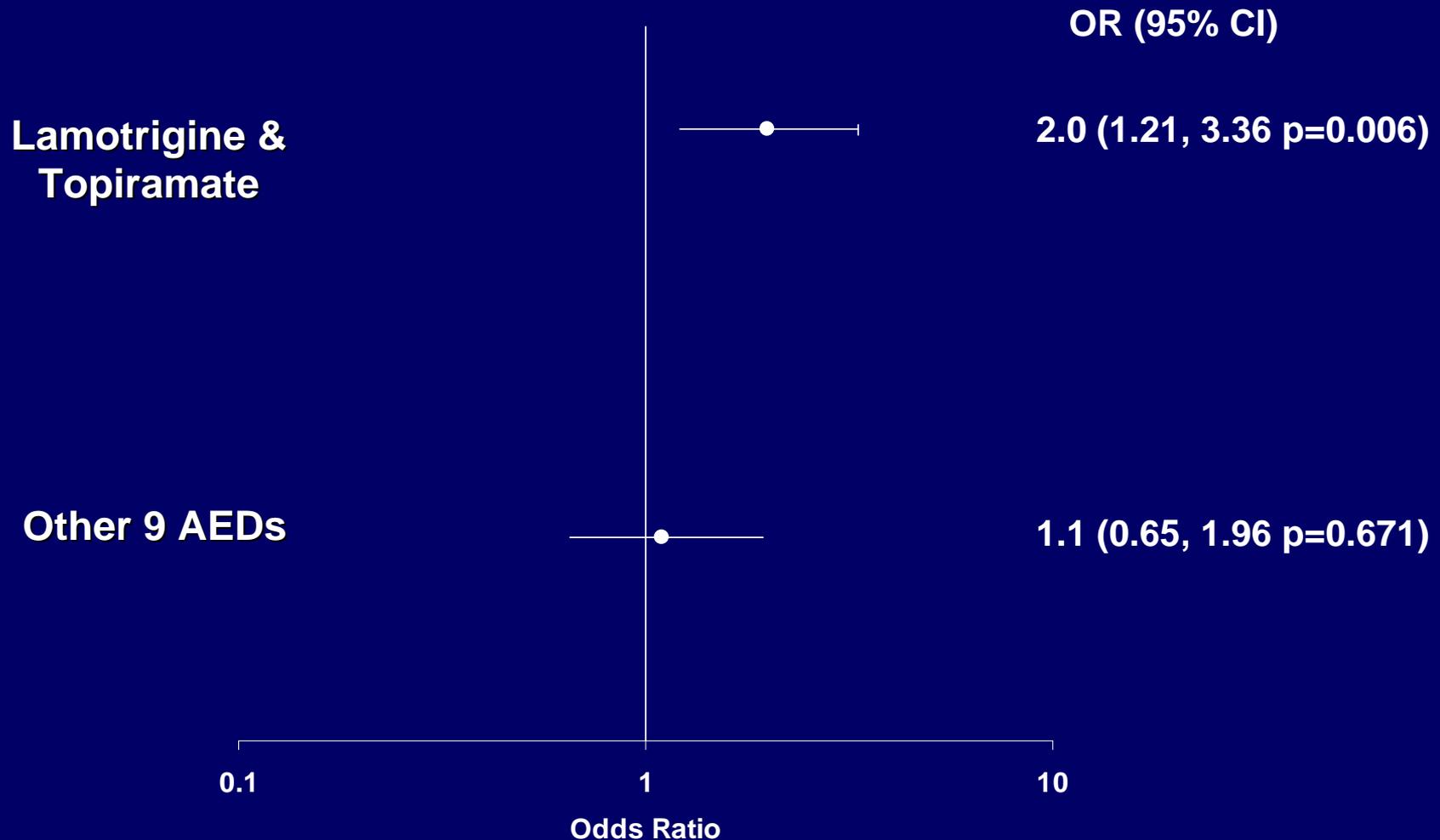


**Updated Odds Ratio using pregabalin data from studies completed through 01 January 2008 is 0.94, (95% CI 0.26, 3.76)**  
Pfizer data on file

\*Treat Events/Treat n Plac. Events/Placebo n)

# Comparison of unstratified odds ratios

## - Lamotrigine and Topiramate vs. 9 other AEDs



## Analysis of rare events: issues (2)

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- Rarity of events will lead to unstable point estimates
  - Different ratio-based methods in the presence of rare events will give different point estimates
- Majority of studies do not have an event in either treatment group
  - Approx. 66% of FDA dataset
  - Approx. 80% of Pfizer dataset
- Ratio-based methods that don't account for the majority of data may inflate risk estimate
- Methods exist that allow use of all available data
  - Use of methods that can measure risk estimate with all data vs. only studies with events can provide an estimate of the effect of excluding those studies
- Non-ratio based risk estimates (risk difference) may provide the most accurate point estimate of risk
  - Allows inclusion of all data
- Mantel –Haenzsel estimates of a common odds ratio assume that the data estimates among the defined groups are consistent/poolable. As the Agency noted, there is insufficient statistical power to test for the “poolability” with rare events

# Bayesian methods allow use of majority of data bias resulting from exclusion of data can be estimated

<i>Risk by exposure</i>	Median Ratio of Events	95% Credible Interval on Ratio	Event Counts (C-CASA 1-4)	
			Treatment (pt-days)	Placebo (pt-days)
All Pregabalin Studies	0.95	0.07, 7.56	7 / 511148	3 / 237122
Only Pregabalin Studies with Events	1.37	0.28, 12.8	7 / 103197	3 / 52267

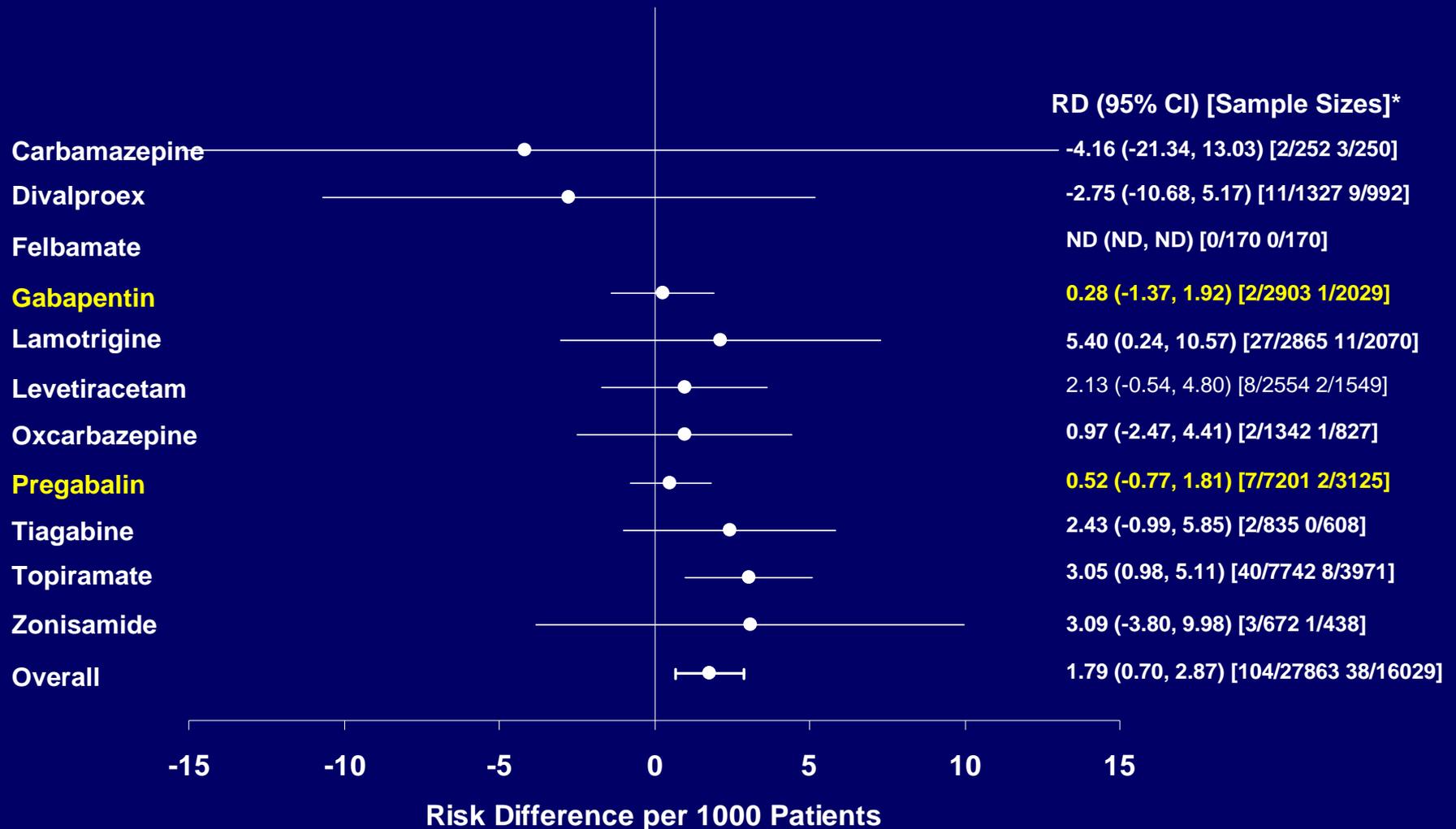
<i>Risk by event</i>	Median Odds Ratio	95% Credible Interval on Odds Ratio	Event Counts (C-CASA 1-4)	
			Treatment n/N	Placebo n/N
All Pregabalin Studies	1.07	0.13, 10.83	7 / 9215	3 / 4099
Only Pregabalin Studies with Events	1.52	0.24, 15.09	7 / 1643	3 / 761

*Bayesian model includes both event numbers as well as exposure duration in calculation of event ratios.*

Source: Pfizer briefing document, tables 19-21.

# FDA risk difference analysis utilizes all patient data

*- Results highlight lack of risk for pregabalin and gabapentin*



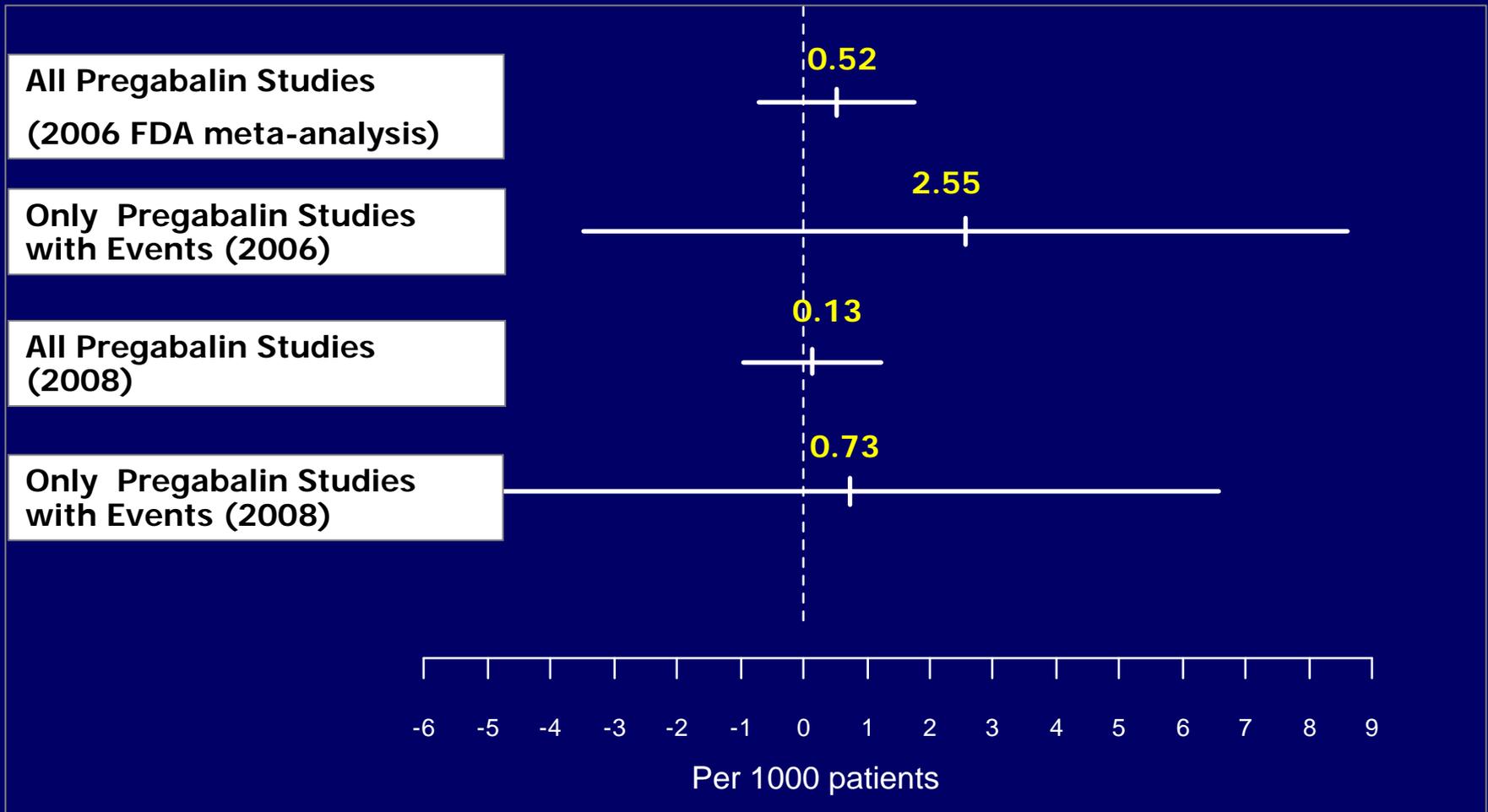
\*Treat Events/Treat n Plac. Events/Placebo n)

Note: RD and confidence intervals per 1000 patients

Data source: FDA Statistical Review and Evaluation, 23 May 2008, Table 4

# Estimate of risk difference is inflated by not accounting for studies with no events

Study adjusted Mantel-Haenszel risk differences (RD) and 95% confidence intervals; Categories 1-4



Source: Pfizer briefing document, table 22.

## Analysis of rare events: issues (3)

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- Rarity of events will lead to unstable point estimates
  - Different ratio-based methods in the presence of rare events will give different point estimates
- Majority of studies do not have an event in either treatment group
  - Approx. 66% of FDA dataset
  - Approx. 80% of Pfizer dataset
- Ratio-based methods that don't account for the majority of data may inflate risk estimate
- Methods exist that allow use of all available data
  - Use of methods that can measure risk estimate with all data vs. only studies with events can provide an estimate of the effect of excluding those studies
- Non-ratio based risk estimates (risk difference) may provide the most accurate point estimate of risk
  - Allows inclusion of all data
- Mantel –Haenzsel estimates of a common odds ratio assume that the data estimates among the defined groups are consistent/poolable. As the Agency noted, there is insufficient statistical power to test for the “poolability” with rare events

## Analysis of rare events - summary

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- Pooling across these drugs may not be appropriate, therefore Mantel-Haenszel based odds ratios may not be conclusive
- Difference-based risk estimates may provide more accurate and stable estimates
- When all available data is utilized, both the 2006 and 2008 analyses show no evidence of risk within pregabalin or gabapentin clinical trials

# Updated analysis of risk difference by indication

- risk difference differs numerically by indication

- estimate of risk can change sign with one additional event

## Pregabalin Studies

Indication	Active n/N	Placebo n/N	Risk Difference	95% CI for Risk difference
Fibromyalgia	0/1517	1/505	-0.002	-0.006, 0.002
Neuropathic Pain	0/3320	1/1586	-0.001	-0.002, 0.001
Psychiatry*	5/2324	1/1129	0.001	-0.001, 0.004
<i>Adjunctive</i> Epilepsy	2/1178	0/507	0.002	-0.001, 0.005
<b>All Studies</b>	<b>7/9215</b>	<b>3/4099</b>	<b>0.0001</b>	<b>-0.001, 0.001</b>

\*Psychiatry includes GAD and other psychiatry studies

## Gabapentin Studies

Indication	Active n/N	Placebo n/N	Risk Difference	95% CI for Risk difference
Neuropathic Pain	0/1081	1/785	-0.002	-0.004, 0.001
Epilepsy	2/778	0/617	0.003	-0.001, 0.007
<b>All Studies</b>	<b>2/2638</b>	<b>1/1836</b>	<b>0.0003</b>	<b>-0.001, 0.002</b>

## Is class labeling appropriate?

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- Do these drugs belong to a class?
  - Pregabalin and gabapentin, as  $\alpha 2 \delta$  ligands, are distinct pharmacologically
  - One common effect does not suggest common risk profiles
  - Inconsistency of event reporting suggests that product-specific labeling is more appropriate

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- Is the risk uniform for all drugs?
  - Signal driven primarily by two products
  - No evidence of risk, using all patient data, for pregabalin and gabapentin

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- Is a boxed warning appropriate for pregabalin and gabapentin?
  - No evidence of risk using all clinical trials data
  - Greatest usage in conditions for which risk difference is numerically lower than placebo
  - Updated analyses demonstrate diminished risk potential for pregabalin
  - Current data does not change risk-benefit profile for either pregabalin or gabapentin

# Conclusions

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- **Pregabalin and gabapentin represent a distinct class of compounds with a unique MOA and should be evaluated separately from other AEDs**
- **There is no evidence of an elevated risk for PSRAEs with either Pfizer compound**
  - **Updated data, using either ratio or difference-based methods, shows no evidence of risk**
- **Pfizer believes that the benefit/risk profile of pregabalin and gabapentin are properly represented in current product labeling.**
- **The available data do not support a boxed warning for suicidality for either product.**
  - **Such a warning would misrepresent the available evidence relevant to pregabalin and gabapentin**
  - **Over-warning has the potential to negatively impact patient care**