

Tamiflu Update

FDA Pediatric Advisory Committee

Hoffmann-La Roche
November 27, 2007

Tamiflu

Clinical Safety Update

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Director, Drug Safety Risk Management

Pediatric Advisory Committee's Charge from November 2005

- FDA is to return after 1 influenza season with a brief update to the PAC on any new developments in either adverse events or new information that may have developed within the next year
- In 2 years, the PAC would expect a complete review of 2 influenza seasons and to have additional information from the sponsor from their US United Healthcare Claims Database and any other studies or databases to which they have access
 - Roche undertook additional pre-clinical and clinical work to evaluate CNS penetration and pharmacologic mechanism

Tamiflu Indication and Neuropsychiatric Precaution in the US PI

Indications:

- Treatment of uncomplicated influenza in patients ≥ 1 year symptomatic for no more than 2 days
- Prophylaxis of influenza in patients 1 year and older

Current Neuropsychiatric Precaution:

There have been post-marketing reports (mostly from Japan) of self-injury and delirium with the use of TAMIFLU in patients with influenza. The reports were primarily among pediatric patients. The relative contribution of the drug to these events is not known. Patients with influenza should be closely monitored for signs of abnormal behavior throughout the treatment period

Roche's Assessment of Neuropsychiatric Adverse Events (NPAEs) in Pediatric Population

Update

- Seasonal Tamiflu usage by region
- Post-marketing safety reports

Potential role of Tamiflu

- Integrated Clinical Trial Database
- An update of Health Claims Databases

Potential role of influenza

- Reports of NPAEs on other/no anti-viral treatment
 - GPRD medical database
 - Literature case reports
 - MHLW public website of influenza cases

Exploration of possible pharmacological mechanisms for NPAEs

- Systemic pharmacokinetics
- CNS penetration
- PD (neuraminidases and other molecular targets)
- Possible pharmacogenetic or drug-drug interaction

Overall assessment and conclusion

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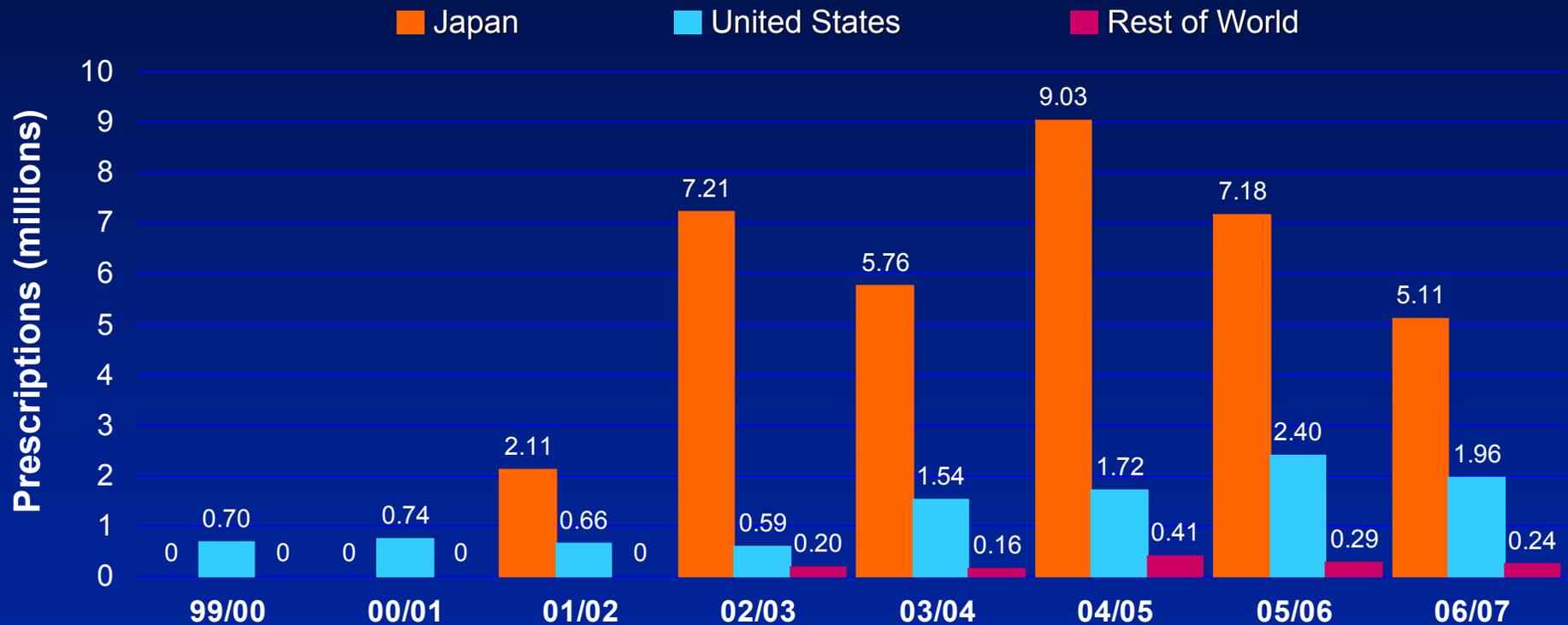
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Tamiflu Prescriptions by Season and Region: All Ages

48.0 Million Total Rx



Data courtesy of Hoffmann-La Roche, Inc.

Japan: IMS Quarterly Rx Data until June 2007, Biannual data until June 2007

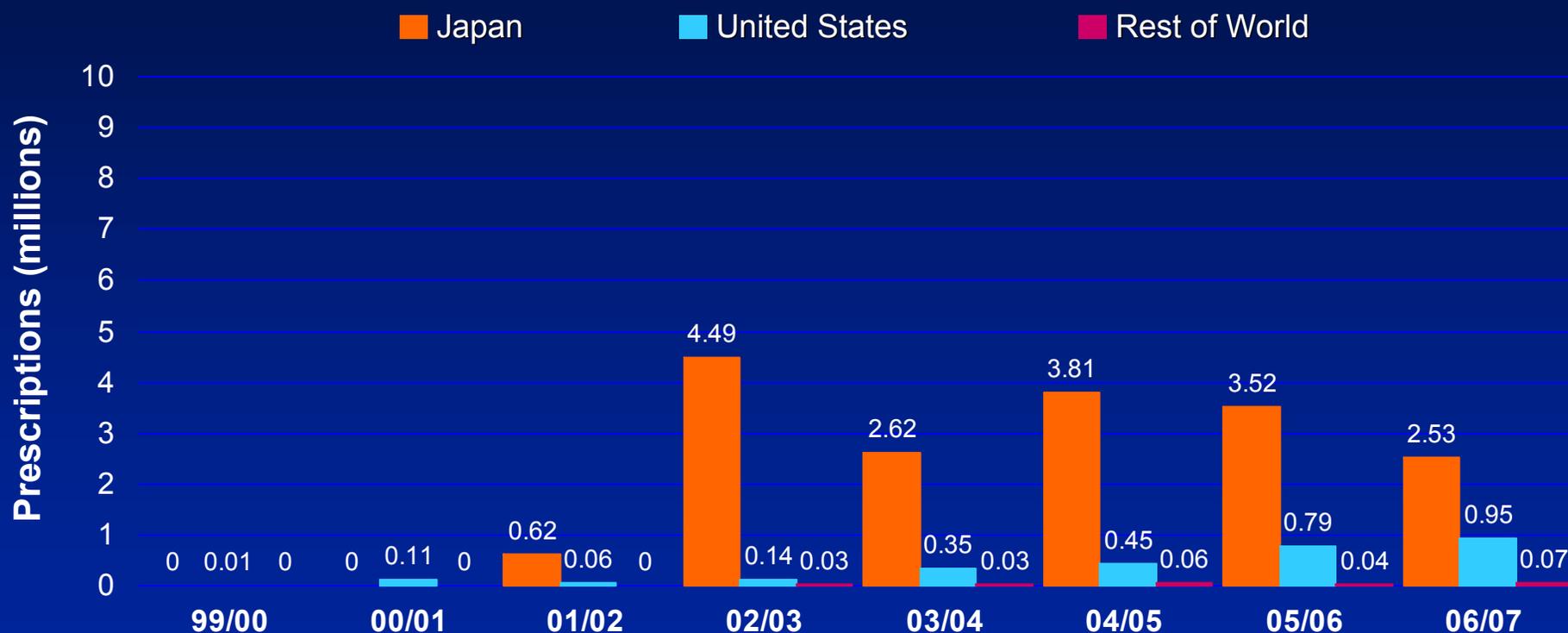
United States: IMS Weekly prescriptions until June 2007

Rest of World: IMS MIDAS Quarterly Retail data (Germany, France, Brazil, Canada) until June 2007

Season refers to October-June data only

Tamiflu Prescriptions by Season and Region: Pediatric vs. Adult Usage

20.7 Million Total Pediatric Rx



Data courtesy of Hoffmann-La Roche, Inc.

Japan: IMS Quarterly Rx Data until June 2007, Biannual data until June 2007

United States: IMS Weekly prescriptions until June 2007

Rest of World: IMS MIDAS Quarterly Retail data (Germany, France, Brazil, Canada) until June 2007

Season refers to October-June data only

Why Is Tamiflu Usage so Much Greater in Japan?

Clinical Management of Influenza in Japan

Universal health coverage in Japan

- 28% of Japanese population received flu vaccination in 2006¹
- Early consultation: 91% within first 48 hours¹
- Almost all patients receive a rapid diagnostic test (reimbursed)²
- 2004/2005 season: 60% of influenza patients received anti-virals
 - Anti-virals are reimbursed; 83% receive Tamiflu²
- Guidelines for management of influenza pts with encephalitis/encephalopathy recommend Tamiflu³

1. SSRI Physician Market Research, 2000.

2. Decision Resources. Influenza; 2006

3. Morishima T. Influenza associated encephalopathy - Guidelines. *Japanese Journal of Neurosurgery* 2006; 58 (7): 561-569.

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Methodology to Identify Post-marketing Cases of Interest in Roche Drug Safety Database

Case definition of neuropsychiatric AEs

- 51 MedDRA HLTs (= 98 PTs) in psychiatric and neurologic SOC
 - Accident/injury SOC was also reviewed as a possible sequela to delirium

Population: Pediatrics (≤ 16 years old)

- Cumulative all serious*/non-serious NPAE review
 - Subset of all prophylaxis cases
- Characterization of serious* NPAEs in last 2 flu seasons
 - Review period: August 16, 2005 to September 15, 2007
 - Categorization into 13 groups using ICD-9 schema
 - Database analysis and single case medical review

* Regulatory definition of serious: AE resulting in death, life-threatening, hospitalization or prolongation of hospitalization, persistent or significant disability, congenital anomaly or birth defect or considered clinically significant by medical reporter

Methodology: 98 Preferred Terms Collapsed into 13 Categories

- Abnormal Behavior
- Accident/Injury
- Cognition Disturbance
- Convulsions
- Delirium
- Delusions/Perceptual Disturbance
- Depressed Level of Consciousness
- Encephalitis
- Loss of Consciousness
- Miscellaneous – Psych
- Panic Attack
- Parasomnia
- Suicidal Events

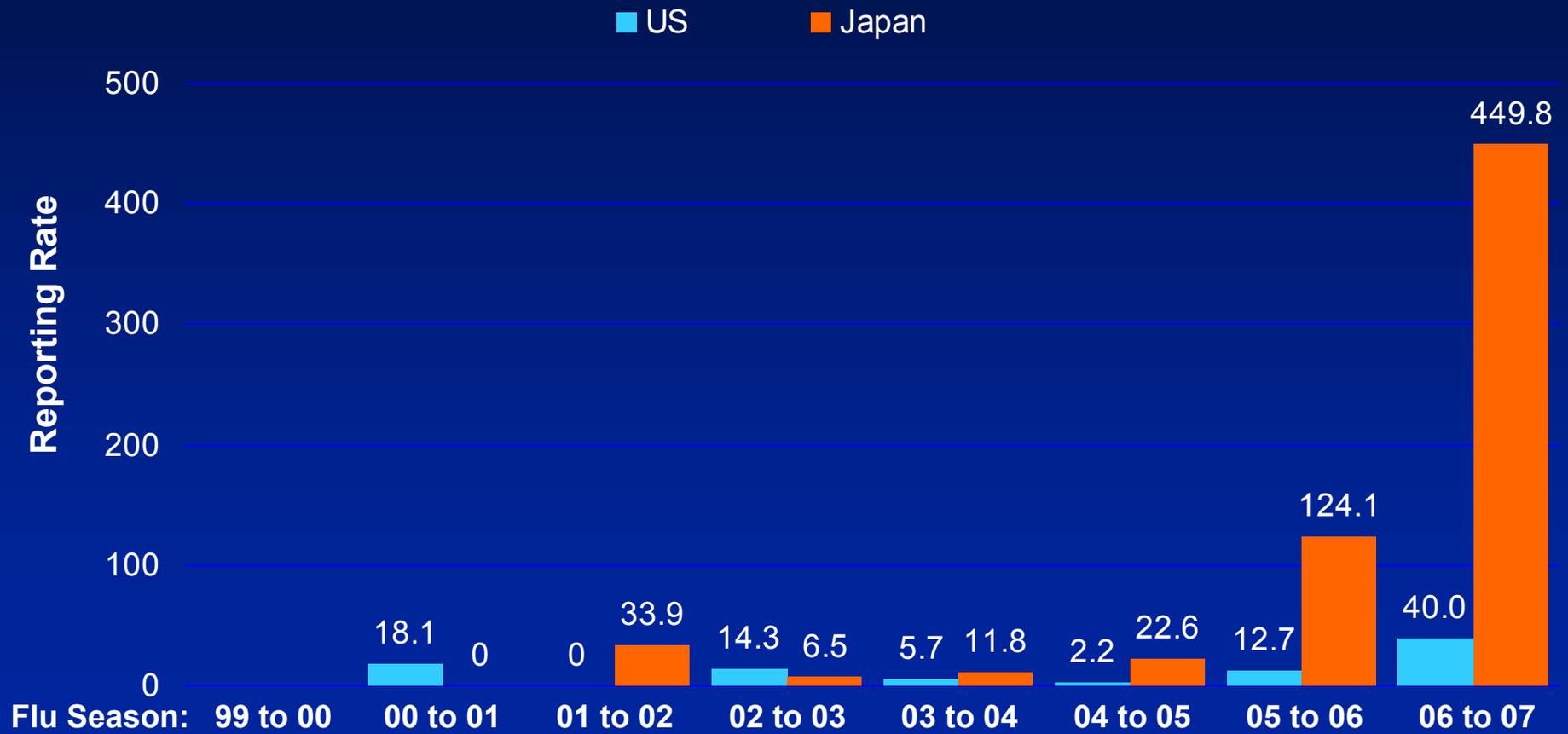
All NPAEs – Cumulative Reporting Rate in Pediatric Patients per Million Rx Written

US, Japan, Rest of World

Region	Patients (with one or more NPAEs)	Total Rx (Millions)	Overall Reporting Rate (Pts with NPAEs/ 1,000,000 Rx Written)
US	55	2.85	19
Japan	1745	17.59	99
Rest of World	8	0.23	35

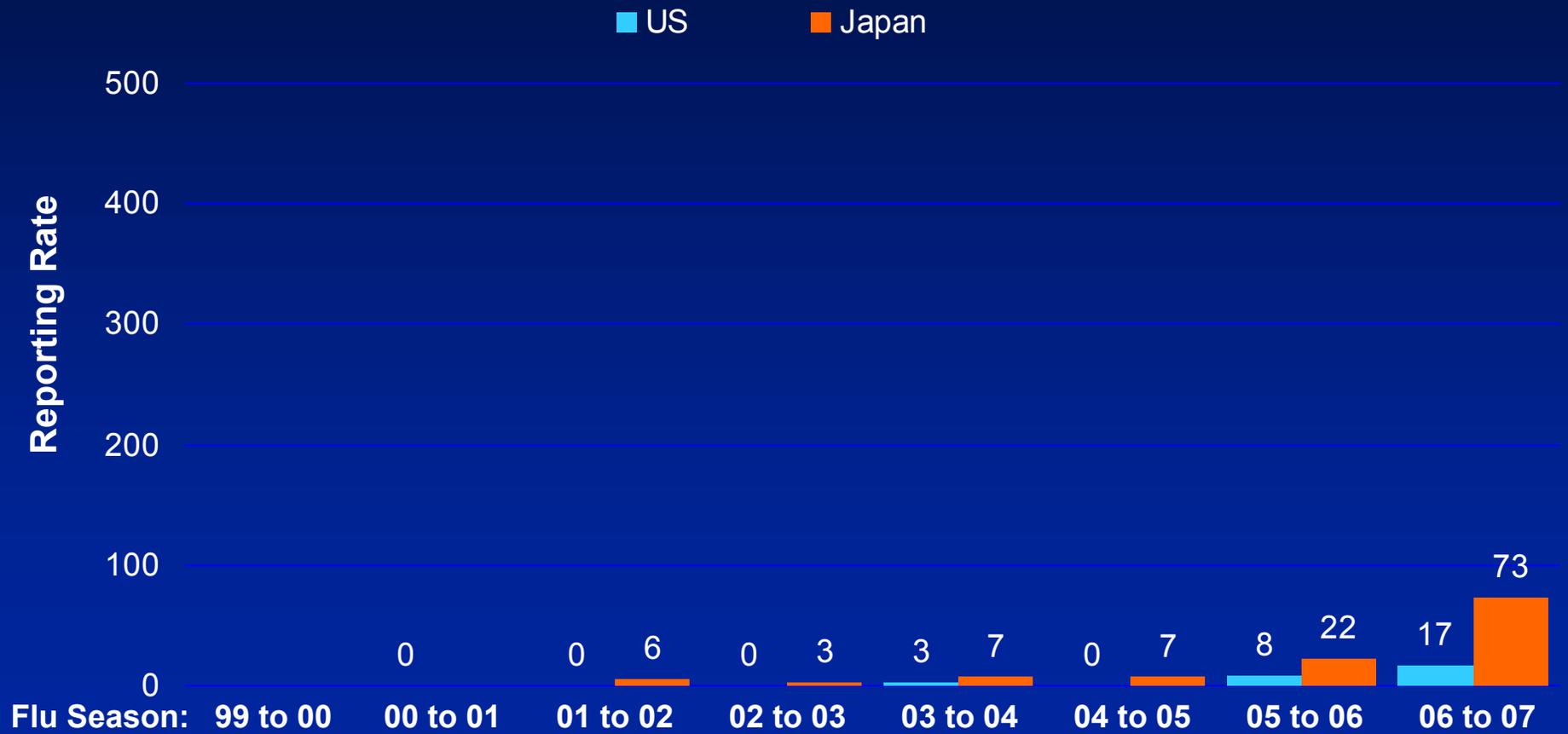
All NPAEs – Seasonal Reporting Rate in Pediatric Patients per Million Rx Written

US, Japan



Serious NPAEs – Seasonal Reporting Rate in Pediatric Patients per Million Rx Written

US, Japan

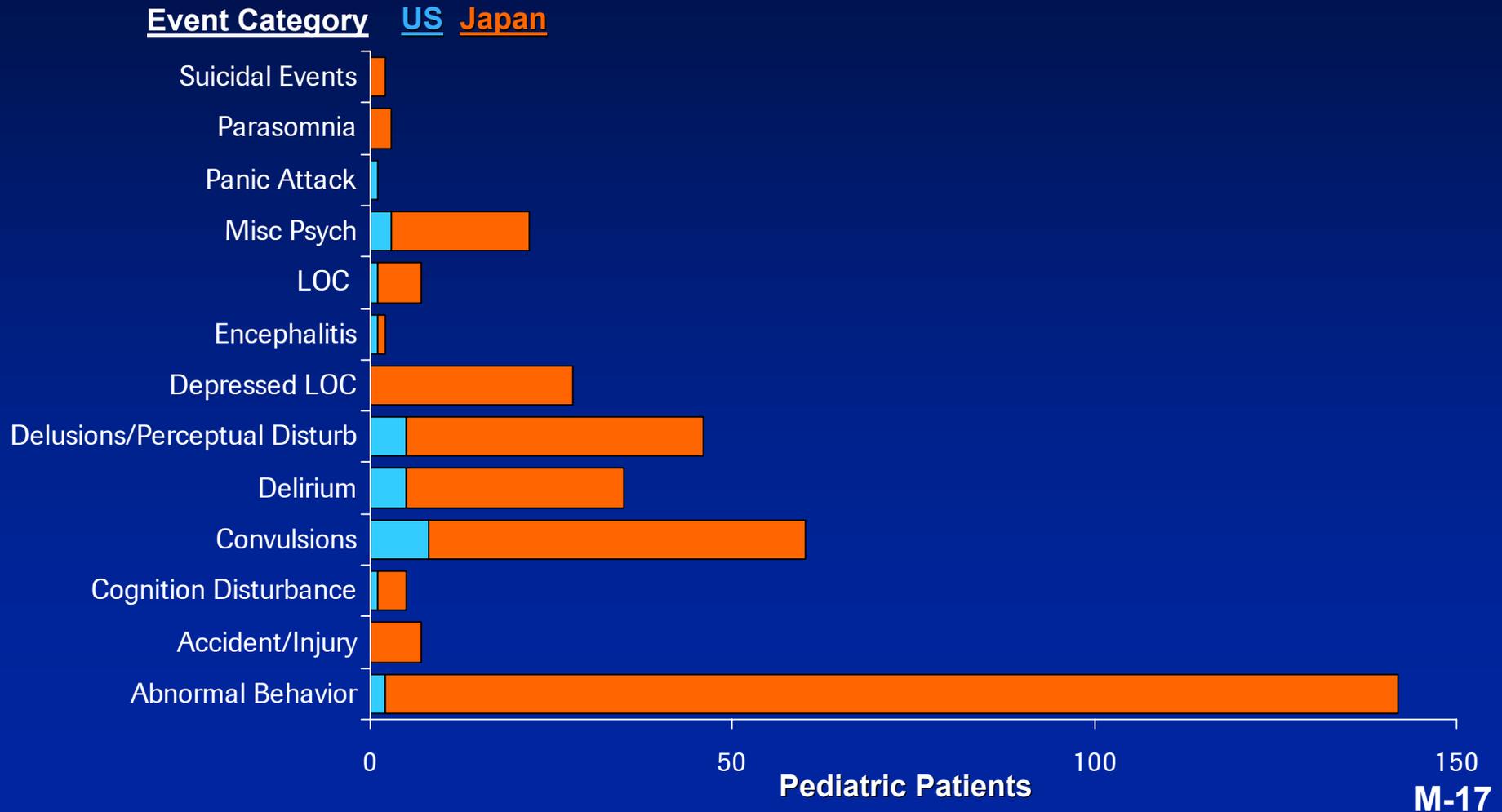


Possible Factors Related to Increased Reporting of NPAEs During 2005-2007

- No increase in the incidence of influenza vs. previous seasons
- No changes in drug manufacturing, formulation, or dosage and administration
- Increase in physician and consumer awareness
 - Reports of fatal accidents with abnormal behavior resulted in MHLW's decision to restrict usage in 10-19 yr olds in Japanese PI, March '07
 - “Dear Healthcare Professional” letters in Japan, February & March '07
 - MHLW website request for NPAE reports in influenza patients, treated and untreated
 - Increased Japanese media reports 05/06 and 06/07 influenza seasons

Serious NPAEs – Category Distribution in Pediatric Patients Over the Last 2 Flu Seasons

Total US: 22 Pts with 27 NPAEs; Japan: 264 Pts with 333 NPAEs



Serious NPAEs – Event Categorization of Pediatric Patients by Flu Season

Total US: 22 Pts with 27 NPAEs; Japan: 264 Pts with 333 NPAEs

Serious Event Category	US		Japan	
	Season 1 (05/06)	Season 2 (06/07)	Season 1 (05/06)	Season 2 (06/07)
Abnormal Behavior	0	2	35	105
Accident/Injury	0	0	2	5
Cognition Disturbance	0	1	2	2
Convulsions	4	4	13	39
Delirium	0	5	15	15
Delusions/Perceptual Disturbance	1	4	17	24
Depressed Level of Consciousness	0	0	11	17
Encephalitis	0	1	0	1
Loss of Consciousness	0	1	0	6
Miscellaneous – Psych	1	2	8	11
Panic Attack	0	1	0	0
Parasomnia	0	0	0	3
Suicidal Events	0	0	0	2

Demographic Characteristics of Pediatric Patients with Serious NPAEs Over Last 2 Flu Seasons in US and Japan

US: 22 Cases; Japan: 264 Cases

Age distribution of reports:

	$\geq 1-2$ y	3-5 yr	6-12 yr	13-16 yr	Unknown
US	4 (18.2%)	3 (13.6%)	10 (45.5%)	5 (22.7%)	0 (0%)
Japan	14 (5.3%)	36 (13.6%)	140 (53.0%)	72 (27.3%)	2 (0.8%)

Gender ratio of reports:

- US 1.4:1 male:female
- Japan 1.8:1 male:female

Onset of Pediatric Serious NPAEs Relative to Diagnosis of Influenza and Start of Tamiflu

Onset of serious NPAE as reported:

- 67% of serious NPAEs occur within 2 days after diagnosis of influenza
- 80% of serious NPAEs occur within 2 days after start of Tamiflu
- Association with reported fever: 44% of all NPAEs

Unable to differentiate role of drug and disease

Outcome of Pediatric Serious NPAEs in Last 2 Flu Seasons

- Majority of reported NPAEs had a duration < 1 day
 - 87% resolved/improved
 - 11% not reported, 2% persisting
- 22 accident/injuries, identified from database and single case review
 - All reported from Japan
(15 M; 7 F; (2) 6 yo; (20) 11-16 yo)
 - 2 events not associated with NPAEs
- 4 fatal cases
 - All reported from Japan
 - 3 fatal accidents (2M; 1F; 12-14 yo) & 1 encephalitis

Reported Prophylaxis Cases in Pediatrics

- 6 case reports in peds \leq 16 yrs**
- Confounders were present in all 6 cases
 - 3 cases (delirium; convulsions; agitation) had documented pyrexia
 - Delirium case diagnosed with influenza and treated with Tamiflu
 - 1: not suggestive of NPAE (LOC due to orthostatic hypotension)
 - 1: bacterial encephalitis
 - 1: agitation started prior to Tamiflu

**Additional 1 case report in patient $>$ 16 to \leq 21 yrs: 17 yo US male; several psych events, limited information, follow up information pending due to unavailability of the HCP

Summary:

Post-marketing Reports of NPAEs

Similarities and Differences in US and Japanese Cases

Similarities:

- Early onset of NPAE as reported
 - 80% NPAEs occur at day 0-2 after start of Tamiflu
 - Onset during acute phase of influenza disease
 - Fever at onset of NPAE
- Gender and age distribution similar
- Majority of events are self-limited with no sequela

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Differences:

- Reporting rate is greater in Japan
 - 0.4 pts with NPAEs per 10,000 Rx written in US
 - 4.5 pts with NPAEs per 10,000 Rx written in Japan
- Serious accidents and fatalities have been reported from Japan

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NPAE Reports in Tamiflu Treated Children in Clinical Studies

- Roche conducted clinical treatment studies (ex-Japan)

NPAE Categories	Tamiflu N=1080 n (%)	Placebo N=738 n (%)	Difference 95% CI
Misc – psych*	3 (< 1)	2 (< 1)	-0.6, 0.6

*Anxiety, irritability

- Japanese pediatric registration study
 - Open-label study in 70 children aged 1-12 (median age 4 yrs)
 - Adverse events profile similar to registration studies outside of Japan
 - No deaths and no neuropsychiatric events reported

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i3 Drug Safety Study of Neuropsychiatric AEs United Healthcare – US Insurance Claims Database

*Study Included Outpatients with a Clinical Diagnosis
of Influenza Aged One Year or Older*

Inclusion/exclusion criteria

- Received either Tamiflu or no anti-viral medication on the diagnosis day
- Not hospitalized on diagnosis day
- Covered all flu seasons between 1999-2005
- Continuous enrollment in health plan for 6 months prior to diagnosis
- Excluded patients with anti-viral Rx or influenza Dx within 3 months of Dx day or vaccination on Dx day

i3 Drug Safety Analysis

United Healthcare Database

- Propensity Scores used to adjust for confounding and ensure comparable cohorts
- Three categories of neuropsychiatric events were identified for study outcomes
 - Any neuropsychiatric event
 - Neuropsychiatric event but excluding chronic disorders, conditions with stated etiology, congenital or hereditary disorders, spinal cord disorders
 - Neuropsychiatric outcomes specific to CNS stimulation (psychotic reactions, delusion, delirium, confusion, euphoria, hallucination, insomnia, nightmares, night terrors, anxiety, agitation, nervousness, restlessness, irritability, headache, panic states, aggressive behavior or seizures)

i3 Drug Safety Analysis United Healthcare Database

*Outcomes and Adjusted Odds Ratios
Ages 17 and Younger; 1999-2005*

Outcome	Oseltamivir N = 20,501		No Anti-virals N = 84,871		Adjusted Odds Ratio
	N	%	N	%	
Any neuropsychiatric event	251	1.22%	1,032	1.22%	0.96 (0.83, 1.12)
Major neuropsychiatric events	224	1.09%	878	1.03%	1.00 (0.85, 1.18)
Specific to CNS stimulation	157	0.77%	605	0.71%	1.03 (0.85, 1.25)

MedStat Study of Neuropsychiatric AEs

MarketScan – US Employer-based and Medicare Claims Database

*Study Included Outpatients with a Clinical Diagnosis
of Influenza Greater than 0 Years of Age*

Inclusion/exclusion criteria

- Received either Tamiflu or no anti-viral medication
- Required availability of medical and pharmacy data
- Required continuous enrollment in health plan for 3 or more months prior to diagnosis
- Covered all flu seasons between October 2000 and March 2006
- Excluded any with claims for vaccination procedures or anti-virals other than Tamiflu

MedStat Analysis – MarketScan Database

- Treatment Group – Influenza diagnosis and Tamiflu Rx
- Control Group – Influenza diagnosis and no anti-viral Rx
- Propensity score matching on patient characteristics
 - Included age, gender, region, population density and co-morbidity
- Psychiatric outcome included events such as: delirium, delusion, anxiety, psychosis, suicide and self-inflicted injury

MedStat Analysis – MarketScan Database

*Adjusted Odds Ratios for Psychiatric Outcomes
per Age Category; 2000-2006*

	Tamiflu Users N = 14,214		No Anti-viral N = 14,220		Adjusted Odds Ratio
	N	%	N	%	
All Pediatric	72	0.5%	113	0.8%	0.67 (0.5, 0.93)
<1	0	0.0%	0	0.0%	n/a
1-2	0	0.0%	0	0.0%	n/a
3-5	2/2386	0.1%	6/2376	0.3%	0.34 (0.07, 1.70)
6-12	29/5632	0.5%	45/5651	0.8%	0.67 (0.4, 1.12)
13-17	41/4615	0.9%	62/4621	1.3%	0.66 (0.43, 1.02)

Roche Analysis of US Claims Databases

United Healthcare & MarketScan

- Objective: update previous analyses of neuropsychiatric events
- Utilized identical selection criteria, age groupings, ICD-9 codes and categories in both databases
 - Pediatric > 0 year of age to ≤ 16 years of age
- Same methodologic approach as done for post-marketing reports
 - NPAEs categorized into 13 groups
- Covered influenza seasons: October 2001–September 2006
- Included NPAEs occurring within 14 days of index date
- Propensity score matching performed to ensure comparable cohorts

Neuropsychiatric Events: UHC Database

Tamiflu (n=30916) / No Anti-viral (n=30728)

All Season Comparison; Age 0-16; Oct 1, 2001-Sept 30, 2006

All NPAEs

Abnormal Behavior



N/A

Cognition Disturbance

N/A

Convulsion



N/A

Delirium

Delusions/Perceptual Disturbance



Depressed Level of Consciousness



Encephalitis



Loss of Consciousness



Misc - Psych



Panic Attack

N/A

Parasomnia



Suicidal Events

N/A

Odds Ratio

0.5

1

2

3

← Increased Risk: No Rx

Increased Risk: Tamiflu →

N/A = 0 event, unable to calculate

Neuropsychiatric Events: MarketScan

Tamiflu (n=26287) / No Anti-viral (n=26153)

All Season Comparison; Age 0-16; Oct 1, 2001-Sept 30, 2006

All NPAEs

Abnormal Behavior

Cognition Disturbance

Convulsion

Delirium

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Depressed Level of Consciousness

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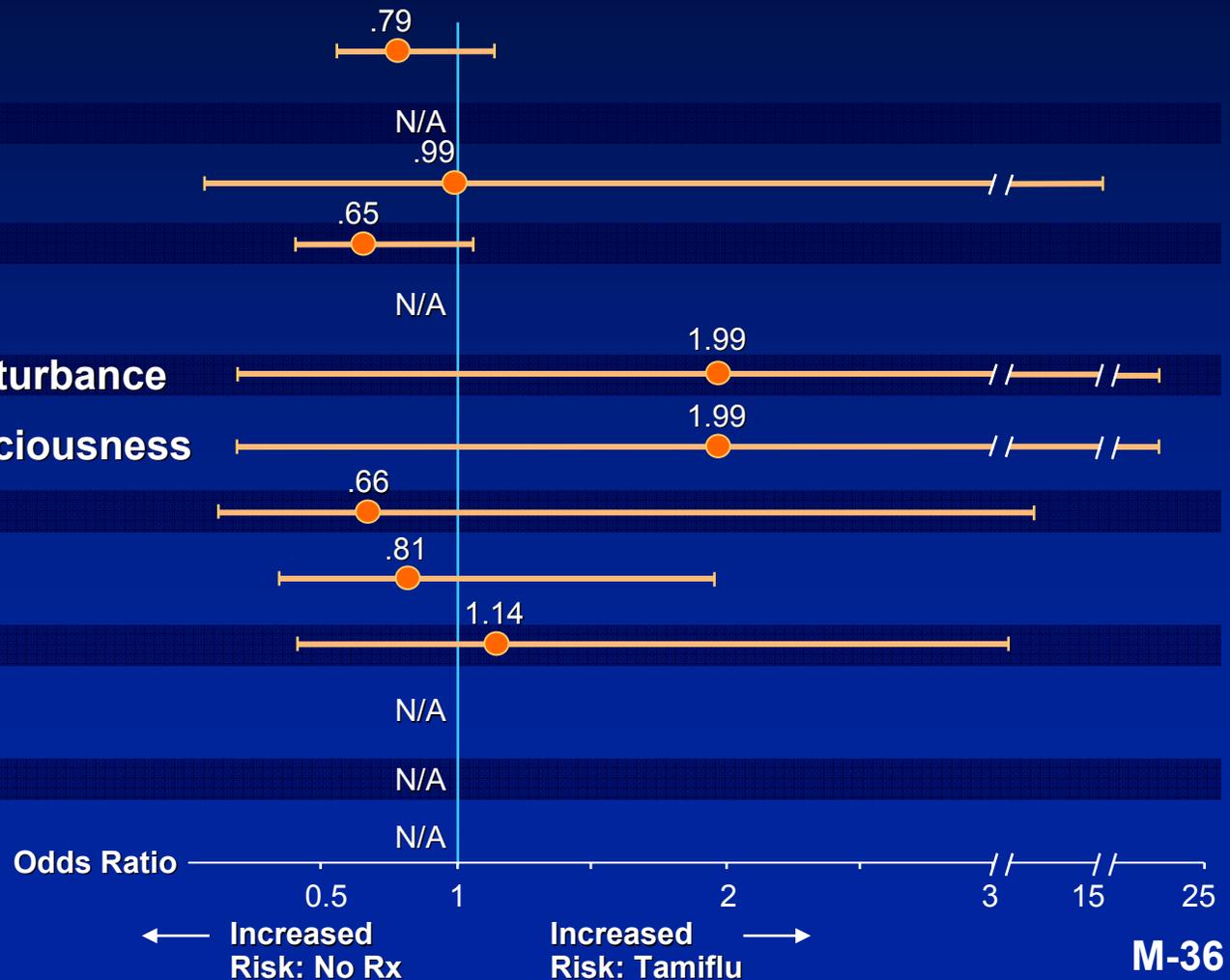
Loss of Consciousness

Misc - Psych

Panic Attack

Parasomnia

Suicidal Events



N/A = 0 event, unable to calculate

Summary: Potential Role of Tamiflu

Clinical trials of influenza treatment:

- No difference in incidence of NPAEs
Tamiflu vs. Placebo

UHC and MarketScan databases:

- Odds ratio results indicate no statistically significant increased risk in any NPAE category in Tamiflu treated patients vs. patients on no anti-viral Rx

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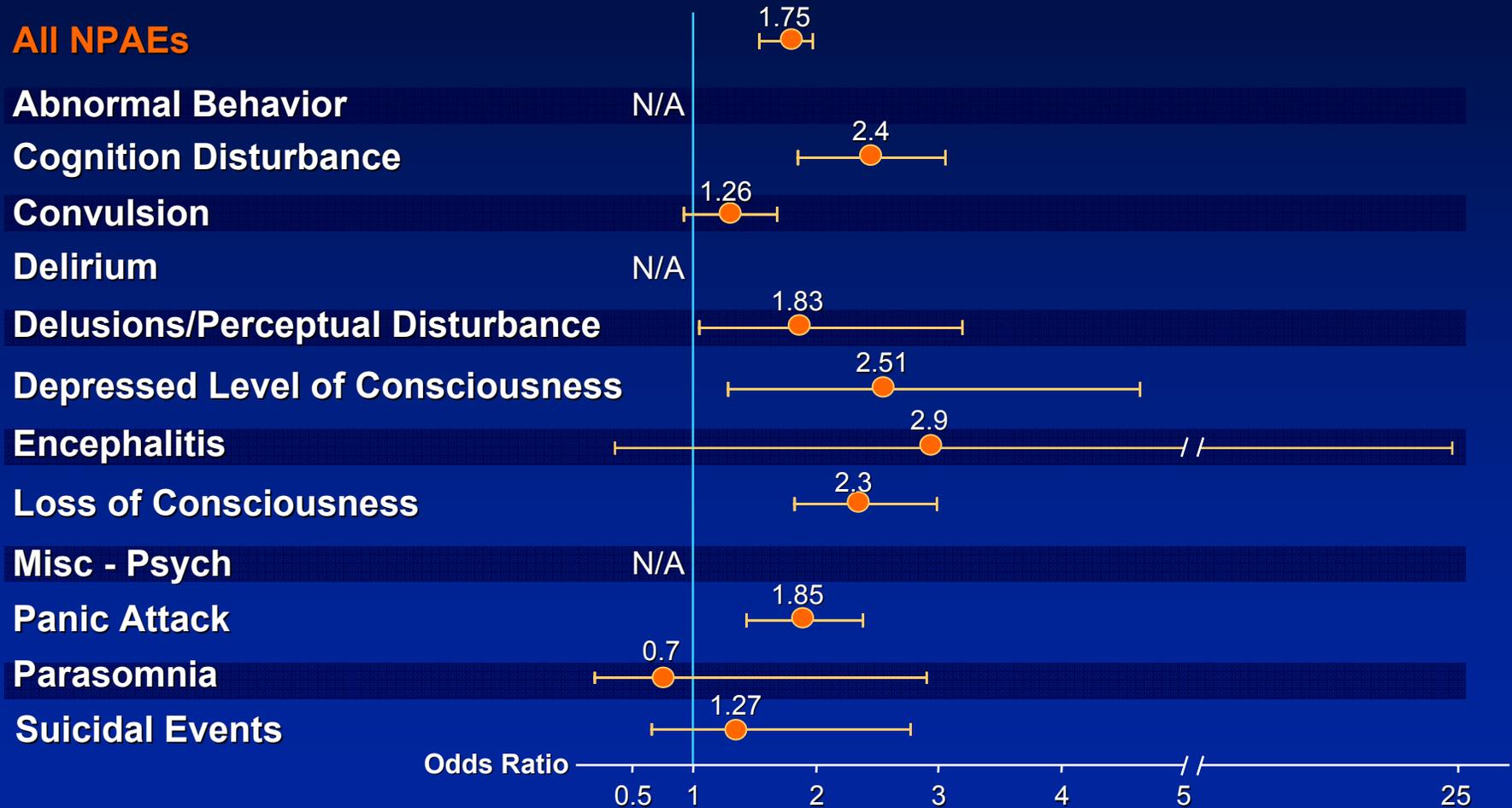
General Practice Research Database (GPRD)

Epidemiologic NPAE Analysis in Influenza

- UK database
- Longitudinal medical database of over 3 million active patients' medical records
- Patients diagnosed with influenza or influenza like illness
 - Identified between October 1, 2001 to March 31, 2006
 - Comparator: General GPRD population
- Same methodologic approach as done for post-marketing reports
 - NPAEs categorized into 13 groups
- Patient followed for 30 days after diagnosis for NPAEs
- Analysis for all ages and separately for those ≤ 16

Adjusted* Odds Ratios of NPAEs in Influenza and in General GPRD Population: All Ages

Influenza Pts (n=68,771) ; General GPRD Population (n=3,012,203)



N/A = 0 event, unable to calculate
 *Adjusted for age, gender and hx of NPAEs

← Increased Risk – Gen'l Pop. Increased Risk – Influenza Pts →

Literature: Search for Case Series of NPAEs Reported in *Untreated* Influenza Patients

Japan

- Retrospective survey of 6,121 pediatric influenza patients¹
 - 9 patients with delirious behavior of which 5 were on no anti-influenza treatment
 - Onset of NPAE within first 24 hours of illness
- Review of 14 hospitalized patients for abnormal behavior²
 - 6 had NPAEs before start of anti-viral therapy
 - Onset of NPAE shortly after onset of pyrexia

¹ Okumara A, et al. Delirious behavior in children with influenza: its clinical features and EEG findings. *Brain Dev* 2005; 27: 271-274.

² Goshima N, et al. Clinical study of abnormal behaviour during influenza. *Infection and Immunity in Childhood* 2006; 18: 376.

Literature: Search for Case Series of NPAEs Reported in *Untreated* Influenza Patients

Taiwan

- Retrospective review of 84 children (< 18 yo) with influenza A¹
 - 18 pts with confusion; 9 visual hallucinations; 4 seizures
- Review of 154 hospitalized influenza patients²
 - 6 visual or olfactory hallucinations or personality changes
- Case series of 5 pediatric patients with influenza A presenting with visual hallucinations and abnormal behavior³
 - Onset within 3 days of febrile illness

1 Wang YH, et al. Clinical characteristics of children with influenza A virus infection requiring hospitalization. *J Microbiol Immunol Infect* 2003; 36: 11-116.

2 Lin CH, et al. Neurologic manifestations in children with influenza B virus infection. *Pediatr Infect Dis J* 2006; 25: 1081-1083.

3 Huang Y-C, et al. Influenza A associated central nervous system dysfunction in children presenting as transient visual hallucination. *Ped Infect Dis J* 2003; 22: 366-368.

NPAE Reports in Patients Not Taking Tamiflu

Posted on MHLW Website

	No Anti-viral	Amantadine	Zanamivir
Patients (n)	25	5	12
Male/Female	18/7	3/2	8/4
< 20 yr/ ≥ 20 yr	24/1	3/2	11/1
Abnormal Behavior	20	2	10
Accident/Injury	2	0	0
Cognition Disturbance	0	4	1
Delirium	4	0	1
Delusion/Perceptual Disturbance	2	1	2
Depressed LOC	1	1	0
Misc - Psych	1	2	2
Parasomnia	1	0	0
Suicidal Events	0	0	1
Deaths	1	1	0

Similar NPAE Reports in Patients Not Taking Tamiflu

Posted on MHLW Website

- Male teenager with influenza A, not receiving anti-viral treatment (OTC only). Died due to fall from 9th story building
- On second day of receiving zanamivir (Relenza[®]) suddenly started shouting and tried to go out a 2nd floor window; her parents restrained her; the drug was continued with no further episodes
- Four hours after receiving amantadine for influenza, a male teenager attempted to jump off a balcony when stopped by family. Upon becoming afebrile, he returned to normal

Summary: Potential Role of Influenza

- 1.75 to 2.5-fold statistically significant increase in risk for NPAEs in influenza patients (all ages) compared with general population (GPRD)
- NPAEs in influenza patients not receiving Tamiflu treatment appear similar to those reported with Tamiflu
 - Mainly in children and adolescent patients
 - Reporting imbalance in males
 - Early in course of influenza illness; temporal association with fever
 - Delirium and behavioral abnormalities which infrequently lead to injury

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Evaluation of Possible Pharmacological Mechanisms for NPAEs

Dr. Craig Rayner
Clinical Pharmacology Team Leader

Evaluation of Possible Pharmacological Mechanisms for NPAEs

1. Systemic Pharmacokinetics
2. CNS penetration
3. PD (neuraminidases and other molecular targets)
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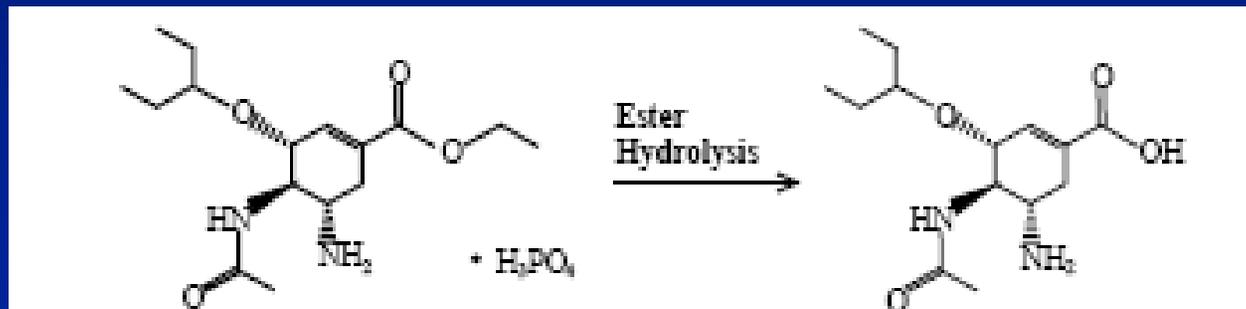
Tamiflu Pharmacology

Oseltamivir (OP)

- Ester prodrug is absorbed orally

Oseltamivir carboxylate (OC)

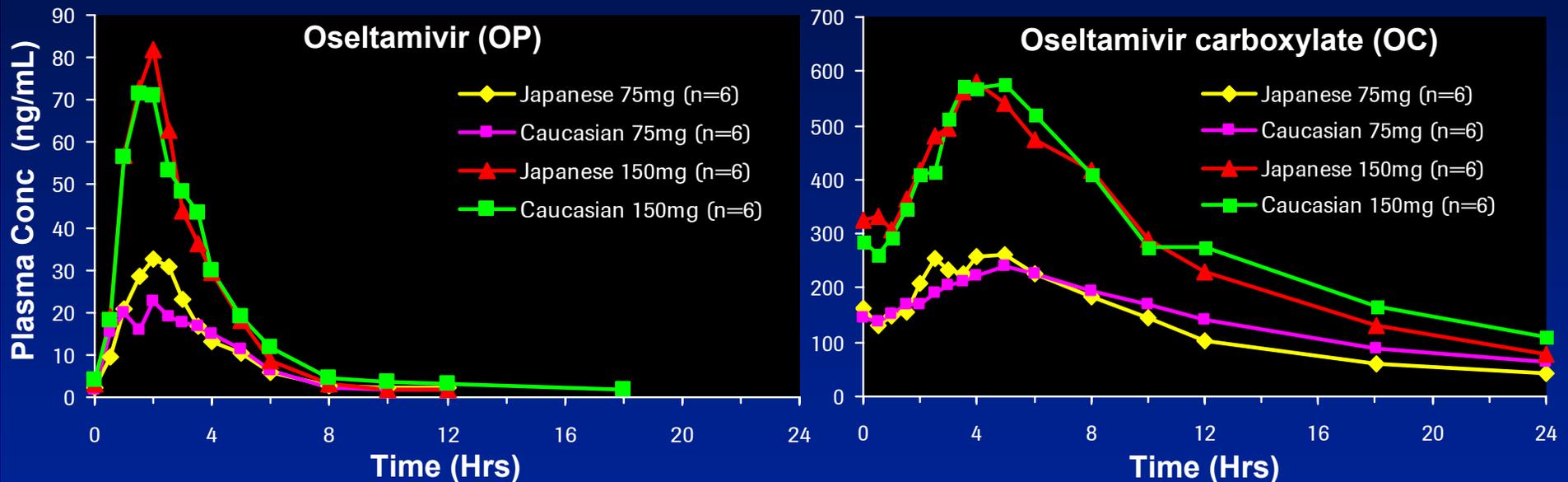
- Active metabolite formed following rapid and extensive conversion in liver



- Neuraminidase inhibition prevents viral replication and limits the severity and duration of illness

No Systemic PK Difference Observed Between Japanese and Caucasian Adults and Children

Mean PK profiles in Japanese and Caucasian Adult Volunteers following oseltamivir PO bid for 7 days (Schentag et al. *J Clin Pharm* 2007)



- Similar concentrations with limited data in Japanese and Caucasian Children
 - OP → 3.63 to 26.75 ng/mL (Caucasian) and 3.95 to 22.05 ng/mL (Japanese)
 - OC → 139 to 274 ng/mL (Caucasian) and 167 to 298 ng/mL (Japanese)

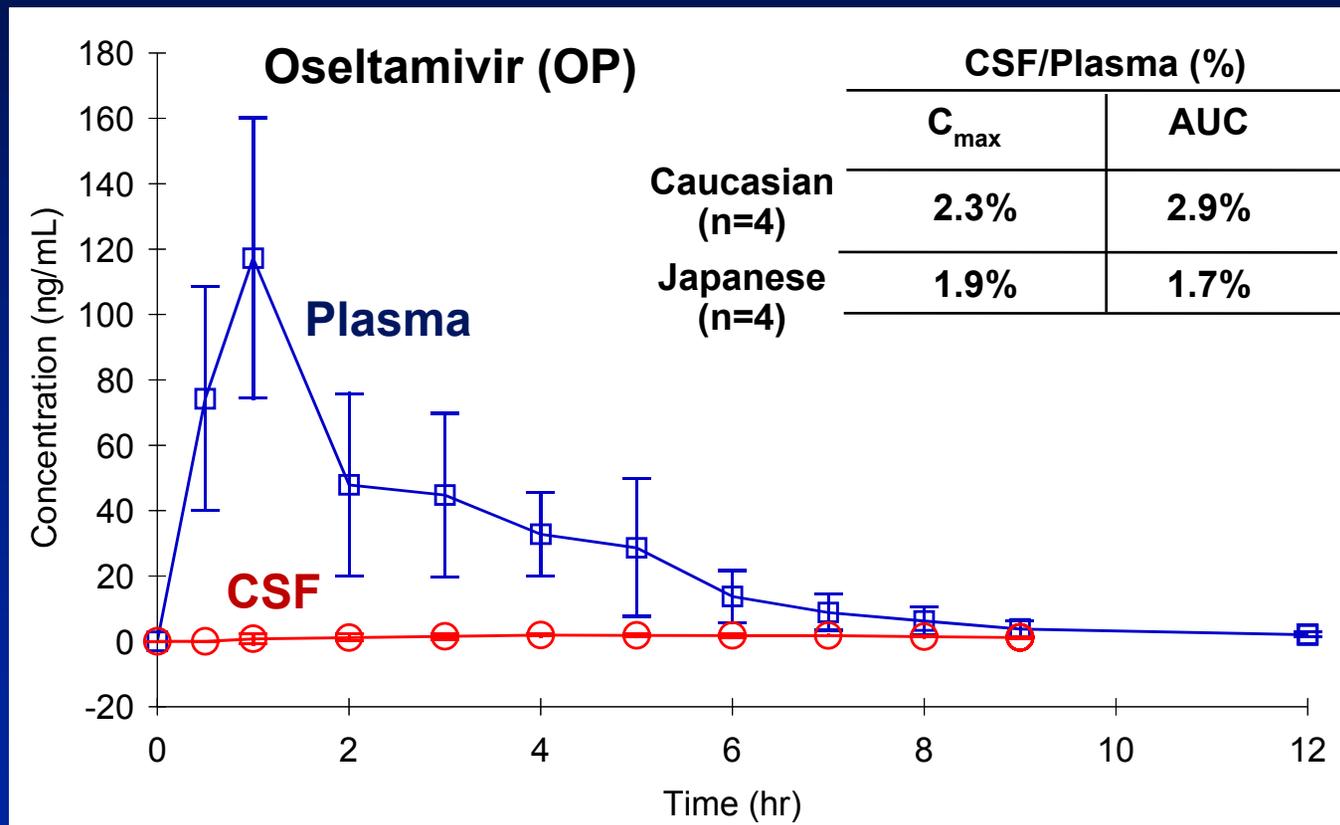
(Gieschke et al. *Options* 2007)

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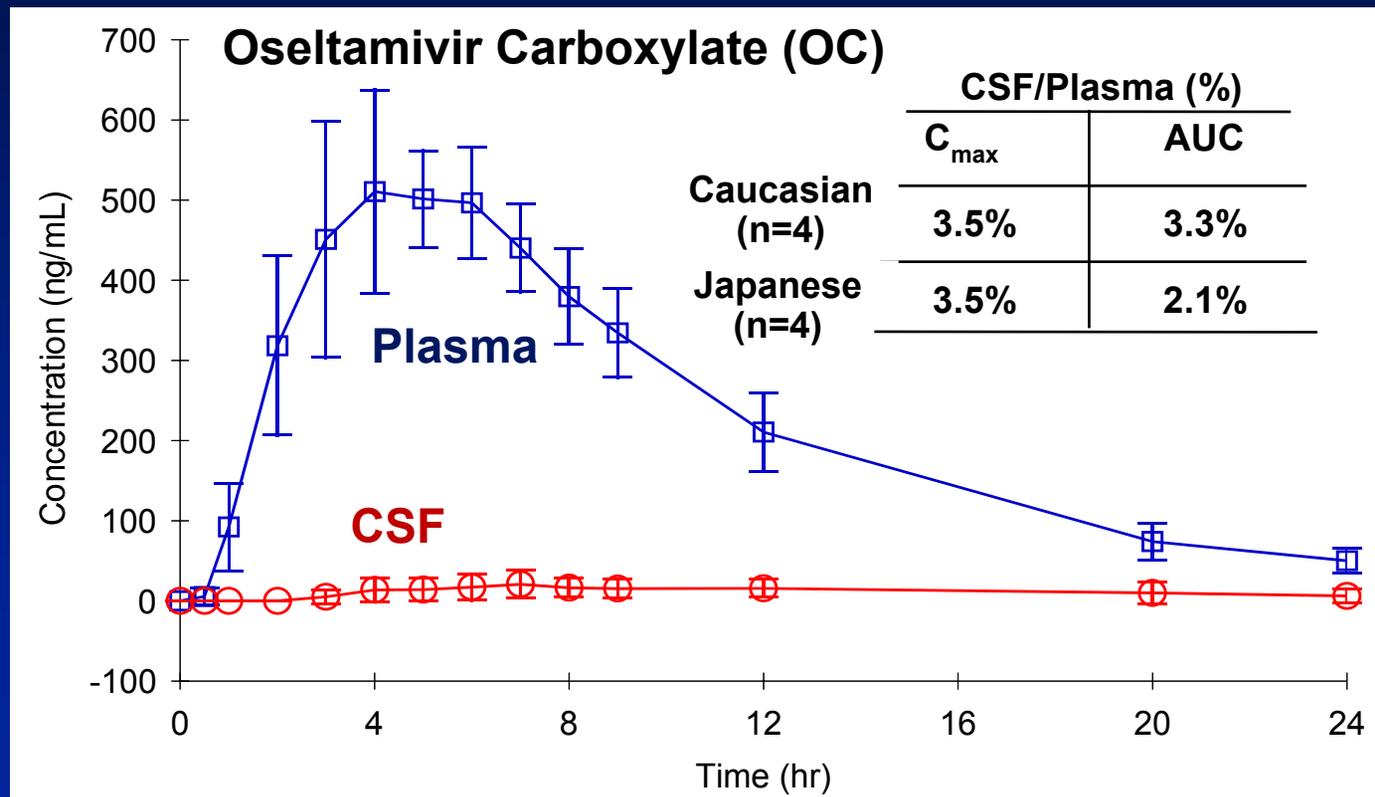
Clinical Study Shows Limited CNS Penetration in Healthy Volunteers

Mean (\pm SD) Plasma and CSF PK profiles in Adult Volunteers following a single PO dose of oseltamivir 150 mg (Study BP21288)



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Mean (\pm SD) Plasma and CSF PK profiles in Adult Volunteers following a single PO dose of oseltamivir 150 mg (Study BP21288)



Recent non-clinical studies suggest CSF is a marker for brain concentrations

Two Literature Reports in Influenza Infected Patients

10 y old male (Caucasian) with influenza B encephalitis

- Plasma and CSF samples 3 hrs after last dose of oseltamivir 75 mg bid (5.5 days)
- OP and OC quantified in plasma (OP: 6.9 ng/mL; OC 401 ng/mL; consistent with expectations) but not detected in CSF

13 y old male (Japanese) fell to his death from a building

- Subject fell ~6 hrs after single 75 mg dose of Tamiflu
- Autopsy samples for OC showed blood concentration of 400 ng/mL (consistent with expectations)
- OC concentrations were not higher than LLOQ (0.1 µg/g) in several brain regions
- OP was not detected in any tissue tested (LLOQ: 0.1 µg/g)
- LLOQs >85x less than the concentration where no relevant activity was detected on > 150 targets

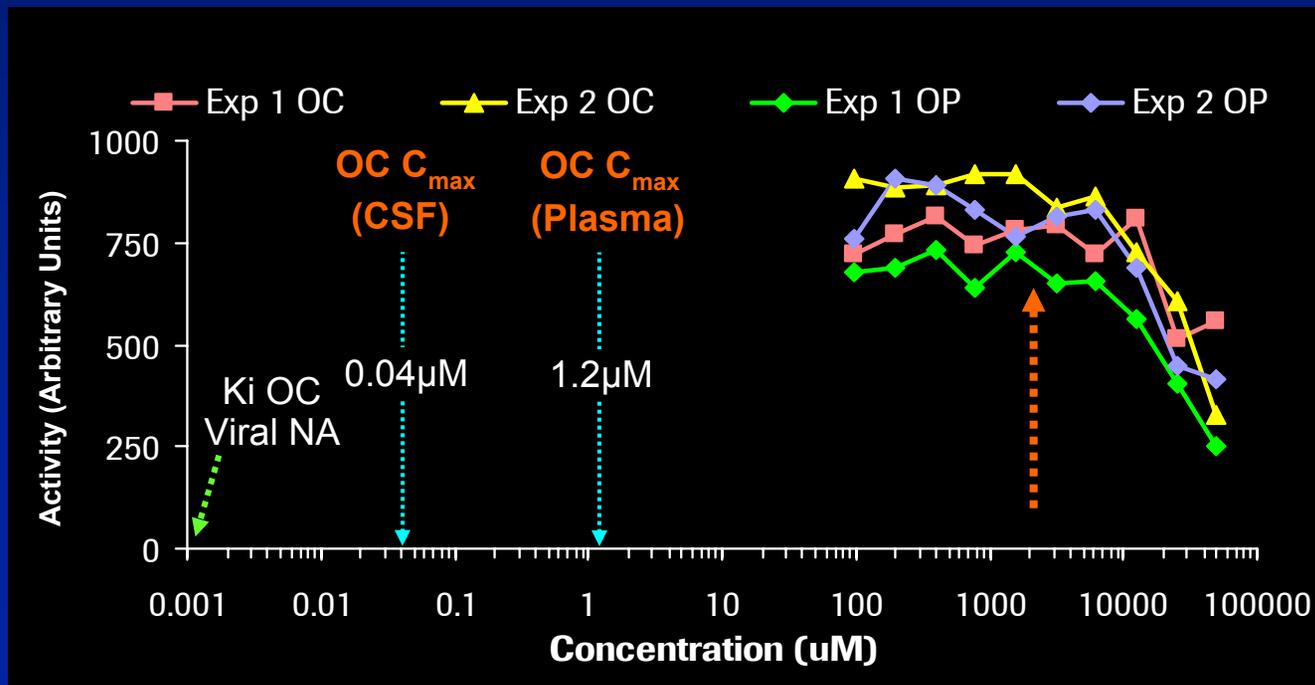
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- 3. PD (neuraminidases and other molecular targets)**
4. Potential pharmacogenetic or DDI (drug interaction) mechanism

OP and OC Have No Effect on Human and Other Mammalian PD Targets

- No relevant activity (3 and 30 μM) at 155 different mostly human targets including those relevant for emotion/behavior (e.g., DA and NMDA receptors)
- Inhibition of mammalian neuraminidase requires $> 1000\times$ therapeutic plasma concentrations

Monkey brain neuraminidase: inhibition by OC and OP



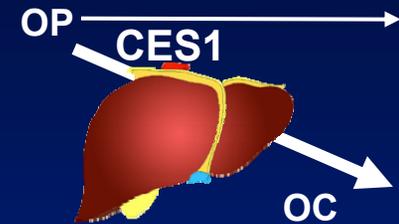
Evaluation of Possible Pharmacological Mechanisms for NPAEs

1. Systemic Pharmacokinetics
2. CNS penetration
3. PD (neuraminidases and other molecular targets)
4. Potential pharmacogenetic or DDI (drug interaction) mechanism

Available Data Suggest Pharmacogenetic Basis for NPAEs are Unlikely

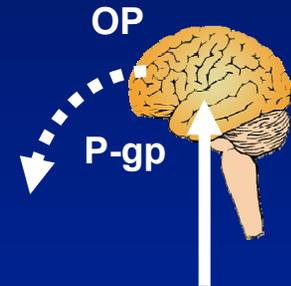
Carboxylesterase 1 (CES1)

- Liver conversion of OP to OC
- In absence of CES metabolism, predicted levels of OP would be within the range of exposures observed in clinical studies without NPAEs



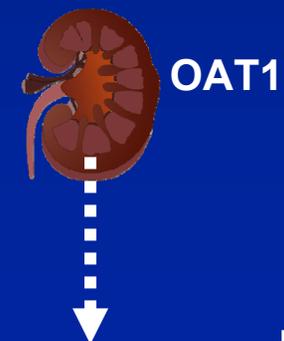
P-glycoprotein (P-gp)

- As well as passive transport, OP is exported from brain by P-gp
- In absence of P-gp export, predicted brain levels of OP are expected to be well within established safety margins



Organic Anion Transporter 1 (OAT1)

- OC is a weak substrate for renal tubular secretion by OAT1
- Magnitude of systemic change 2.5x with probenecid (OAT inhibitor) which is well within exposures in clinical studies



DDI Assessment of NPAE Cases

- Oseltamivir has low DDI potential
 - No role of CYP450 or Phase II pathways
 - Clinical studies show no DDI with influenza con meds including acetaminophen, aspirin, amoxicillin
- Directed DDI assessment of NPAE cases ≤ 16 y in Roche Safety Database
 - No con meds reported: 54% (overall) vs. 30% (serious)
 - No signal for DDI identified in serious cases following systematic literature review of con meds (n=161) examining potential for CES-1, P-gp, OAT-1 interference
- Overall, no signal for DDI identified

Evaluation of Possible Pharmacological Mechanisms for NPAEs: Conclusions

1. Systemic Pharmacokinetics

- Similarity in systemic PK in Japanese and Caucasians adults and children

2. CNS Penetration

- Limited extent of CNS exposure of OP and OC based on clinical and non-clinical data

3. PD (neuraminidases and other molecular targets)

- At well above therapeutic doses no relevant effects of OP and OC on human and primate PD targets including neuraminidases

4. Potential Pharmacogenetic or DDI Mechanism

- No plausible pharmacogenetic mechanism related to PK that could explain higher frequency of NPAEs in Japanese
- DDI assessment of NPAE cases showed no signal for OAT-1, P-gp, CES interference

Evaluation of Possible Pharmacological Mechanisms for NPAEs: Future Activities

- **Disposition and potential activity within the CNS of OP and OC**
 - *In vitro* functional activity using human neuraminidases (Neu1 to 4) expressed in cell based systems
 - Direct brain administration of OP and OC in rats to assess distribution, behavior and histopathology
 - Juvenile rat toxicology study assessing behavior, histopathology and brain disposition after oral administration of OP
 - Further *in vitro* and *in vivo* studies on CNS penetration and local conversion of OP to OC, including in human tissue
- **Directed clinical assessments for potential for CNS activity**
 - Japanese healthy volunteer polysomnography study
 - NIH PK/PD safety study of 3 mg/kg OP in influenza patients < 24 months

Roche's Assessment of Neuropsychiatric Adverse Events (NPAEs) in Pediatric Population

Update

- Seasonal Tamiflu usage by region
 - Post-marketing safety reports
-

Potential role of Tamiflu

- Integrated Clinical Trial Database
 - An update of Health Claims Databases
-

Potential role of influenza

- Reports of NPAEs on other/no anti-viral treatment
 - GPRD medical database
 - Literature case reports
 - MHLW public website of influenza cases
-

Exploration of possible pharmacological mechanisms for NPAEs

- Systemic pharmacokinetics
 - CNS penetration
 - PD (neuraminidases and other molecular targets)
 - Possible pharmacogenetic or drug-drug interaction
-

Overall assessment and conclusion

Summary

Neuropsychiatric AEs

Potential Role of Tamiflu

- Clinical trial data, claims databases: No increase risk of NPAEs in influenza patients taking Tamiflu versus not taking drug
- No pharmacologic mechanism identified to account for NPAEs

Potential Role of Influenza

- Emerging evidence further supports the role of influenza
 - GPRD database, literature, MHLW website

Post-marketing Reports

- Majority of reports from Japan, predominantly in children
- Majority of delirium-like events occur early in the course of influenza and early after starting Tamiflu
 - Difficulty in differentiating drug from disease
- Cannot definitively exclude a contribution by drug

The Current Tamiflu Neuropsych US PI Labeling Continues to be an Accurate Assessment of All Available Updated and Expanded Data

Current Neuropsychiatric Precaution:

There have been post-marketing reports (mostly from Japan) of self-injury and delirium with the use of TAMIFLU in patients with influenza. The reports were primarily among pediatric patients. The relative contribution of the drug to these events is not known. Patients with influenza should be closely monitored for signs of abnormal behavior throughout the treatment period

Future Activities

- Continued post-marketing pharmacovigilance
- Ongoing non-clinical and clinical studies to assess CNS involvement
- Kaiser-Permanente observational cohort study to estimate background rates of NPAEs in patients with:
 - Clinical diagnosis of influenza
 - Lab-confirmed influenza
 - Tamiflu treatment vs. untreated