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# Exposure to acetaminophen and potential risk of abnormal behaviors reported in influenza and non-influenza patients. Case-control study with the Japan Adverse Drug Event Reporting

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***Corresponding Author:***
Dr. Yasuo Oshima,
MD, PhD, FACP, The Institute of Medical Science, The University of Tokyo - Japan

***Submitting Author:***
Dr. Yasuo Oshima,
MD, PhD, FACP, The Institute of Medical Science, The University of Tokyo - Japan

***Other Authors:***
Dr. Hideyuki Ikematsu,
Professor, Department of Clinical Trials, Center for Advanced Medical Innovation, Kyushu University - Japan

Dr. Koichiro Yuji,
Instructor, The Institute of Medical Science, the University of Tokyo - Japan

Dr. Tetsuya Tanimoto,
Visiting Scientist, Cancer Institute, Japanese Foundation for Cancer Research - Japan

Dr. Arinobu Tojo,
Professor, The Institute of Medical Science, the University of Tokyo - Japan

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# Exposure to acetaminophen and potential risk of abnormal behaviors reported in influenza and non-influenza patients. Case-control study with the Japan Adverse Drug Event Reporting

***Author(s):*** Oshima Y, Ikematsu H, Yuji K, Tanimoto T, Tojo A

## Abstract

**Background:** Our preliminary analyses of an adverse event database found a “signal” on actaminophen-associated abnormal behavior. Abnormal behavior by Japanese children taking oseltamivir has been repeatedly reported and described. However there is no literature dealing with acetaminophen-associated abnormal behaviors, which is analyzed and further described in this paper.

**Methods:** 216,945 records registered to JADER between 2004 and 2011 were analyzed. Age, sex, reporting year, and underlying illness were compared between cases of abnormal behavior and controls without abnormal behavior. Multivariate logistic regression modeling was used to investigate confounding and interaction with age group, gender, reporting year, and an underlying disease.

**Results:** Of 4,544 acetaminophen-treated cases, 260 (5.7% [95%CI; 5.2-6.4]) exhibited abnormal behaviors. Of the 260 cases, factors associated with abnormal behavior were male (196 case; 75.4% [69.7 – 80.5]), under 20 years old (242; 93.1% [89.3 – 95.8]), reported in 2007 or 2008 (169; 65.0% [58.9 – 70.8]), and with influenza (253; 97.3% [94.5 – 98.9]) as an underlying disease. Multivariate logistic regression analysis indicated a relationship between influenza and acetaminophen and an interaction between acetaminophen and oseltamivir. According to subgroup analysis with influenza (n=2,164), patients taking oseltamivir had fewer abnormal behaviors, because teenagers had been reported to be at high risk for abnormal behaviors and doctors were advised to avoid prescribing oseltamivir to them.

**Conclusion:** Acetaminophen-associated abnormal behavior occurred mostly in persons with influenza. Given the relationship to influenza and the interaction of oseltamivir, the reported acetaminophen-associated abnormal behaviors were most likely induced by the underlying disease, not by the drug itself.

## Introduction

After reports of neuropsychiatric adverse events and abnormal behaviors by Japanese children taking oseltamivir since the 2004-2005 influenza season, this type of adverse event has become the focus of much attention. Exhaustive efforts have been made to clarify a causative relationship between the suspected drug, oseltamivir, and abnormal behavior. These included comparison of post-marketing spontaneous adverse event reports, preclinical and clinical studies, analysis of medical records in the UK General Practice Research Database, and the abnormal behaviors of Japanese and Taiwanese children with influenza. Reviews of the accumulated data did not suggest causality (1, 2). In contrast, acetaminophen has escaped scrutiny. Because physicians commonly use acetaminophen in treatment, they believe that it is generally safe as long as it is used properly.

Because the number of clinical trial participants is much fewer than the number of patients who will be treated with the investigational drug in clinical practice, premarketing clinical trials may fail to detect rare ADRs or ADRs specific to particular population subgroups. Thus, many ADRs are unknown at the time of the launch or even long after the launch of a drug. In order to track ADRs, the World Health Organization (WHO) and health authorities such as the U.S. Food and Drug Administration (FDA) run safety databases. The WHO safety database, termed VigiBase, contained more than 6.0 million individual case safety reports (ICSRs) as of Jan 2013 (http://www.bridgetodata.org/ , last accessed on Mar 2013) and the Adverse Event Reporting System (FAERS) of the U.S. FDA had over 4.0 million ICSRs as of Sep 2012 (http://www.fda.gov/ , last accessed on Mar 2013). In order to assist pharmacovigilance activity through these large databases, several statistical methods have been promulgated that automatically extract a manageable number of “signals” for further evaluation. The commonly used methods are the proportional reporting ratio (PRR) (3), the

reporting odds ratio (ROR) (4), the Baysian Confidence Propagation Neural Network (BCPNN) (5), and the (multi) Gamma Poisson Shrinker (mGPS) (6). The BCPNN and the mGPS of the above mentioned methods are used for the WHO and FDA safety databases, respectively (7, 8).

The Japanese Pharmaceutical and Medical Devices Agency (PMDA) has run its own safety database since 2004. The safety database is termed JADER (Japanese Adverse Drug Event Report database) and has been open to the public since May 2012. The publicly available JADER allows researchers to study adverse events and to assess the potential risk of pharmaceutical drugs.In our preliminary screening, we used the BCPNN method with the JADER database to search for ”signals”. The objective of this study is to describe and to investigate one of the detected signals, acetaminophen-associated abnormal behavior.

# Methods

**Study design:** This study is composed of mainly two parts. The first part is an explorative signal detection study in which we describe “signals” or potential drug risks. The second part of the study is a case-control study where we compare demographical and underlying disease regarding the potential risk.

**Setting:** We used a public version of the JADER database, from the PMDA that was released in May 2012. This version of the database includes adverse drug reactions reported to the PMDA between Apr 2004 and Dec 2011.

**Subjects:** We prepared four datasets for specific purposes (Table 1). The first dataset was the whole JADER database (Dataset 1; n=216,945), which was used for “signal” detection. The second dataset included only acetaminophen-treated patients (Dataset 2; n=4,544). This dataset was used to describe and compare the demographic data of patients exhibiting abnormal behaviors and other acetaminophen-treated patients who did not. It was extracted by a search for their drug (generic name) in the “Drug201204_teiseiban” table that included “Acetaminophen.” The third dataset contains influenza patients (Dataset3; n=2,164), and was used for a stratified analysis. Dataset 3 was extracted by searching the Hist201204_teiseiban table that included “influenza” as the underlying diseases. The fourth dataset was of influenza patients treated with acetaminophen (Dataset 4; n=671). Dataset 4 includes the patients of Datasets 2 and 3. Dataset 4 was used to compare the ADRs of oseltamivir and acetaminophen-treated influenza patients. The raw data handling and basic tabulations were performed as previously reported (9-12).

**Analysis:** The potential risk or “signal” for the combination of a specific drug and an adverse event was calculated based on the Information Component (IC) value as reported before (5, 7). The detected 65,952 signals were sorted by “McLachlan’s sensitivity”, one of the Bayesian estimators (13-15). The rates of the abnormal behaviors were shown for the indicated drugs. The 95% confidence interval (95%CI) for the rate was calculated as previously reported (16). The indicated numbers are the number of cases or non-cases of the conditions indexed for calculation of the rate. The number of identified abnormal behavior cases and comparisons was tabulated by reporting year, sex, age group, and underlying illness. Demographic data are shown with the number of cases, the crude odds ratio with 95%CI, and *P*-value calculated with two-sided Fisher’s exact test or Chi-squared test. Because of the nature of spontaneous reports, the calculated *P*-values are shown to highlight the differences in characteristics between patients with abnormal behaviors and the comparison group, but were not intended to test for statistical differences. Variables showing an association with an abnormal behavior by univariate analysis were further analyzed by multivariate unconditional logistic regression analysis using the R-statistical package (R Foundation for Statistical Computing, Vienna Austria 2012). Records with missing data were removed from the multiple logistic regression analysis.

# Results

There were 216,945 adverse event cases recorded in the JADER database between 2004 and 2011 (Dataset 1). Of these 4,544 were treated with acetaminophen (Dataset 2). 2,164 cases (Dataset 3) were extracted from Dataset 1 whose underlying diseases included influenza. Of these 2,164, 671 were treated with acetaminophen (Dataset 4). (Table 1)

The BCPNN yielded more than 50 thousands combinations with a potential risk of a drug-adverse event (Table 2). We listed drugs frequently reported as being associated with abnormal behaviors in Table 3. Of 216,945 records, 838 (0.4% [95%CI; 0.4-0.4]) were cases of abnormal behaviors. Of these 260 (5.7% [95%CI; 5.1-6.4]) cases of abnormal behavior were associated with 4,544 actaminophen-treated cases (Table 3). The characteristics associated with a high number of reports were male (196 cases), ages

under10 (97 cases), age 10-19 (145 cases), and report year of 2007 (108 cases) or 2008 (61 cases) (Table 4). Because there was an increase in the number of abnormal behavior reports in 2007 and 2008, we handled these two years as a single categorical variable, in the logistic regression analysis. Similarly, we handled age under 20 as a single categorized variable. Besides the above, the most characteristic factor was influenza as an underlying disease (253 cases). According to logistic regression analysis of dataset1, concordance was found between acetaminophen and influenza (supplemental table, Full Model; Model A vs. Model B, Minimum Model; Model D vs Model E), but there was no interaction between acetaminophen and influenza (Full Model; Model B vs. Model C, Minimum Model; Model E vs. Model F). Based on these results, we did a more detailed analysis with the 2,164 cases (Dataset3) who had influenza as an underlying disease. The use of oseltamivir was associated with reduced acetaminophen-associated abnormal behavior (Model H vs. Model I). The interaction of oseltamivir and acetaminophen is shown in Fig 1. The rates of abnormal behaviors among the cases without oseltamivir treatment without and with acetaminophen were 29.2% [95%CI; 25.4-33.7] and 52.3% [45.8-58.8] respectively. Thecorresponding rates for cases treated with oseltamivir were 24.4% [21.7-7.1] and 29.6% [25.4-34.2] respectively. Thus, the use of oseltamivir appeares to be related to fewer acetaminophen associated abnormal behaviors. Comparison was done of the age distribution of abnormal behavior between patients with and without oseltamivir for the influenza cases (Fig 2). Most of the cases without oseltamivir were in the 10-19 years age group. Thus, use of oseltamivir might avoid high risk age group. The prescription of oseltamivir appeared to be a confounding factor related to the abnormal behaviors associated with acetaminophen. This appeares to be a well-known epidemiological effect, so-called “confounding by indication”.

# Discussion

The BCPNN that used all of the cases in JADER (Dataset1) yielded more than 50,000 combinations of potential adverse events and drugs (Table 2) Most of the combinations are well known, such as myelosuppression associated anti-neoplastic cytotoxic agents, hemorrhage associated with anti-coagulation agents, hypersensitivity associated with iodinated contrast agents, hypoglycemia associated anti-diabetic agents, or infection associated with immunosuppressants. Among these, abnormal behaviors associated with acetaminophen drew our attention. Although acetaminophen is widely used as an analgesic antipyretic drug and is easily purchased over the counter, abnormal behaviors associated with it have rarely been reported. We have never experienced abnormal behaviors associated with acetaminophen in our own clinical practice. Thus, the result was unexpected and we decided to do further examination using data mining methodology. First, we listed the top 10 most frequently reported drugs associated with abnormal behaviors (Table 3). The rate of abnormal behaviors appeared high for acetaminophen (5.7% [95%CI; 5.1-6.4]) compared with that for all drugs (0.4% [95%CI; 0.4-0.4]). Oseltamivir and zanamivir also have high report rates, which should be interpreted with caution because both drugs have undergone active surveillance for abnormal behaviors and have been widely covered in the media. The images of both have been affected by non-scientific reporting (7).

We compared the demographic data of 4,544 cases with and without abnormal behaviors treated with acetaminophen (Dataset 2) with and without abnormal behavior. The characteristics of ICSR with abnormal behaviors included male, age under 20 years, and reported in 2007 or 2008.

Newly marketed pharmaceuticals, by virtue of their novelty alone, sometimes elicit adverse-event reports at high rates, and the report rate tends to decrease over time. This tendency is known as the Weber effect (17). It is also well known that media coverage accelerates reports of specific adverse events. However, acetaminophen is a medicine that was first synthesized in 1878 and that was introduced for clinical use in 1887 (18). As far as the authors know, acetaminophen was not a topic of wider public attention until recently. Thus, the increased reports from 2007 and 2008 suggest that the increased number of reports was affected by other factor(s) that may have nothing to do with the medicine itself. Moreover, most of the cases with abnormal behavior had influenza, thus the reports of abnormal behavior appears to be related to the underlying disease. We did multivariate logistic regression analysis to clarify how influenza affected the reporting of abnormal behavior from the point of view of an epidemiological effect. The multivariate logistic regression analysis using dataset 1 showed a confounding effect for influenza and acetaminophen. (supplemental table, Full Model; Model A vs. Model B, Minimum Model; Model D vs. Model E, the difference between the full model and the minimum model was the number of

concomitantly used medicines. ) Thus, the effect appeared to be a result of the underlying disease. A limitation of the study is the possibility of multiple co-linearity problems when we put the related variables together in one model, such as for influenza as an underlying disease and anti-influenza drugs that are prescribed exclusively for influenza. However, both models indicated the same results regarding the influence of the influenza, the minimum model without anti-influenza drugs and the full model with all potential and available variables, including anti-influenza drugs. Thus, regardless of the model, the confounding of influenza was robust.

This result lead us address to test the possibility that a concomitantly administered acetaminophen happened to be reported when the oseltamivir-associated adverse event was reported. If the acetaminophen were just a concomitant medication, acetaminophen associated abnormal behavior cases would be associated with oseltamivir. On the contrary, oseltamivir was associated with decreased acetaminophen associated abnormal behavior reporting (n = 2,164; Model H vs. Model I in Dataset 3). In dataset 3, because all cases had influenza as an underlying illness, there would not be multiple co-linearity between the use of oseltamivir and influenza, thus an interaction based on abnormal behavior was shown between influenza and acetaminophen (Figure 1). Among the acetaminophen-treated patients, the rates of abnormal behavior with and without oseltamivir were 29.6 % [95%CI; 25.4 - 33.7] and 52.3 % [95%CI; 45.8 - 58.8], respectively. The rate of acetaminophen-associated abnormal behavior appeared to be decreased in patients with oseltamivir. On the other hand, among the patients without acetaminophen with and without oseltamivir the rates were 24.4 % [95%CI; 21.7 – 27.1] and 29.4 % [95%CI; 25.4 – 33.7], respectively. The rate of abnormal behavior was not affected by oseltamivir use. Thus, the interaction indicated by the logistic regression models was confirmed. In order to further explore these effects, we calculated the age distribution of patients treated with acetaminophen (Dataset 4, Figure 2). Few teenagers were treated with oseltamivir. This is because of the health ministry recommendation that doctors not prescribe oseltamivir to teenagers, who had been reported in the media to be at high risk for abnormal behaviors associated with oseltamivir treatment. Physicians would have thus avoided the prescription of oseltamivir for teenagers because of the high risk for abnormal behavior. Patients were often treated with symptomatic therapy based on antipyretics such as acetaminophen. Based on these conditions, the reported acetaminophen-associated abnormal behavior events were most likely influenza-induced events.

# Strength and limitations of this study

Screening of existing databases, such as JADER can be done quickly and at an affordable cost. This exploratory approach will provide useful data for interested scientists. Regarding the potential confounding by indication, for example fever, since we have no access to the raw data, we cannot do further evaluation. Moreover, due to the incompleteness and inconsistencies of witnessed adverse event reporting, analyses of databases can supplement, but not replace controlled epidemiologic studies.

# Conclusion(s)

Association with abnormal behaviors as an adverse event by patients treated with acetaminophen was found by a data mining method, BCPNN. Given that, the large majority of the cases reported had influenza as the underlying disease, the reported acetaminophen-associated abnormal behaviors were most likely associated with adverse events induced by the influenza itself.

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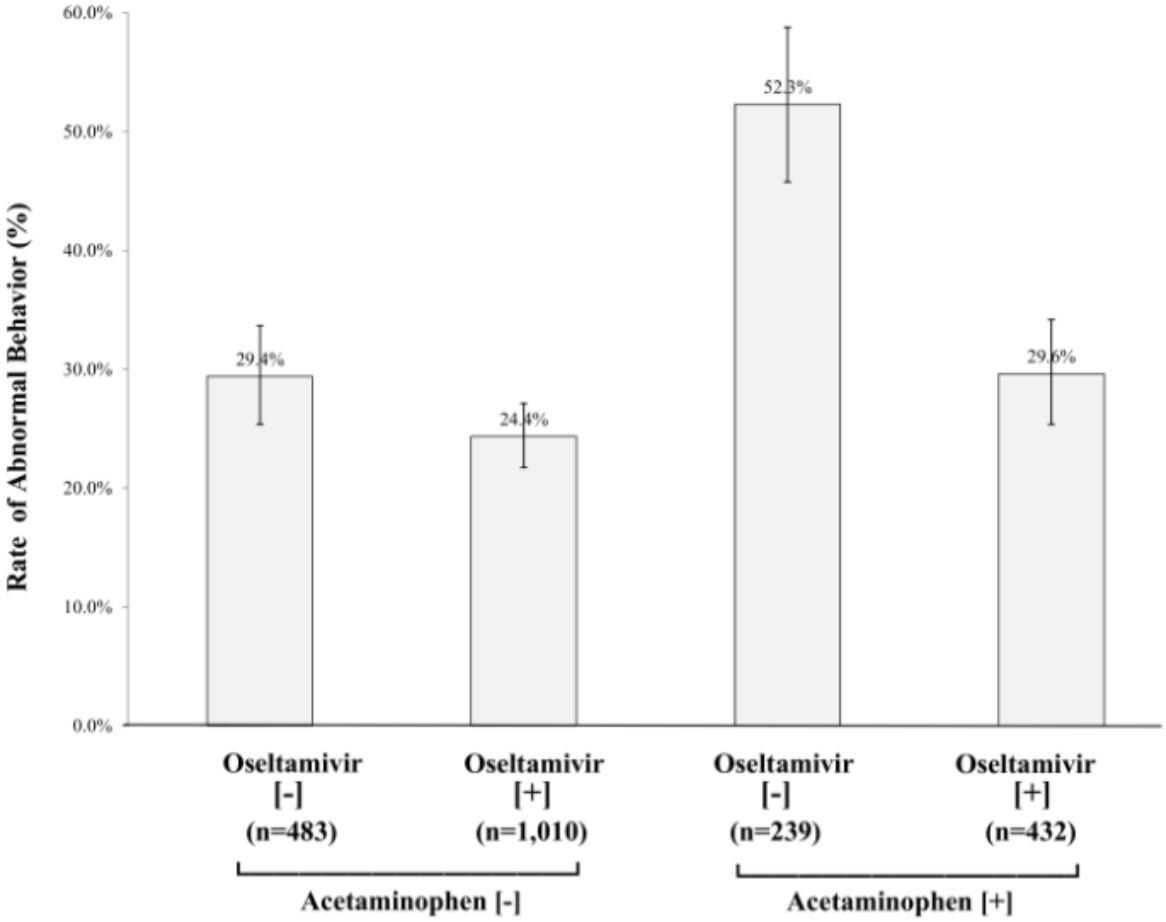
# Illustrations

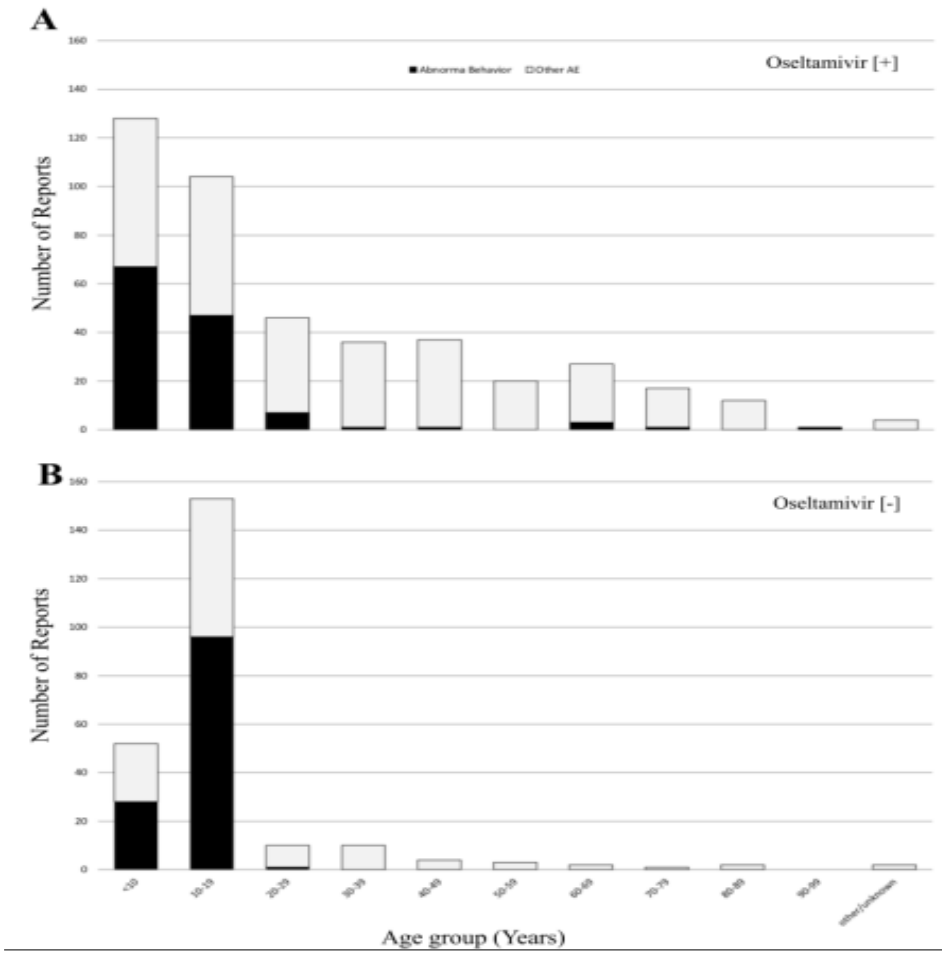
## Illustration 1

Figure 1. Rates of abnormal behaviors Rates of abnormal behavior associated with use of acetaminophen and oseltamivir patients with influenza (Dataset 3; n=2,166) are shown. Confidence intervals were obtained by the procedure first given in Clopper and Pearson (16).



# Illustration 2

Figure 2. Age distribution of abnormal behaviors and other AE reporting Distribution of abnormal behaviors (closed bar) and other adverse events (AE; open bar) of influenza patients treated with acetaminophen (Dataset 4; n=671) are shown in 10 year cohorts. Panels A and B indicate the age distribution of patients treated with (n=432) and without oseltamivir (n=239), respectively



# Illustration 3

Summary of Dataset

**Table1. Summary of Dataset**

| Dataset | Short Description | Number | Data Extraction |
|---|---|---|---|
| Dataset 1 | Whole the JADER database | 216,945 | All cases registered into the JADER database |
| Dataset 2 | Subjects treated with acetaminophen | 4,544 | Subjects whose item [drug(generic name)] in the table [Drug201204_teiseiban] includes "Acetaminophen" |
| Dataset 3 | Subjects with influenza | 2,164 | Subjects whose item [underlying disease and so on] of the table [Hist201204_teiseiban] includes "influenza" |
| Dataset 4 | Subjects with influenza treated with acetaminophen | 671 | Subjects exist in both Dataset 2 and Dataset 3 |

# Illustration 4

Signal detection in the JADER database (Dataset 1, n=216,945)

**Table 2. Signal detected in the JADER database (Dataset 1, n=216,945)**

| Drug Code | Event Effect | Count | Expected Count | Count per Expected Count | Drug Margin | Event Margin | McLachlan's Sensitivity |
|---|---|---|---|---|---|---|---|
| Acetaminophen | Abnormal bhaviour | 259 | 12 | 21.0 | 7,709 | 2,953 | 4.24E-06 |
| Amrubicin hydrochloride | Neutrophil count decreased | 461 | 33 | 13.9 | 1,819 | 33,728 | 8.49E-06 |
| Alteplase | Haemorrhagic cerebral infarction | 483 | 2 | 229.1 | 1,258 | 3,099 | 1.27E-05 |
| Alteplase | Cerebral haemorrhage | 166 | 5 | 32.3 | 1,258 | 7,549 | 1.70E-05 |
| Alendronate sodium | Osteonecrosis of jaw | 279 | 13 | 21.5 | 6,346 | 3,785 | 2.12E-05 |
| Iopamidol | Anaphylactic shock | 510 | 38 | 13.6 | 2,295 | 30,242 | 2.55E-05 |
| Iopamidol | Shock | 265 | 15 | 17.9 | 2,295 | 11,898 | 2.97E-05 |
| Iohexol | Anaphylactic shock | 372 | 20 | 18.4 | 1,236 | 30,242 | 3.39E-05 |
| Iomeprol | Shock | 173 | 7 | 25.9 | 1,037 | 11,898 | 3.82E-05 |
| Irinotecan hydrochloride | Diarrhea | 568 | 87 | 6.5 | 7,330 | 21,959 | 4.24E-05 |
| Irinotecan hydrochloride | Neutropenia | 735 | 91 | 8.1 | 7,330 | 22,843 | 4.67E-05 |
| Irinotecan hydrochloride | Leukopenia | 480 | 59 | 8.2 | 7,330 | 14,834 | 5.09E-05 |
| Insulin aspart | Anti-insulin antibody positive | 110 | 1 | 97.4 | 2,729 | 765 | 5.52E-05 |
| Insulin aspart | Hypoglycaemia | 331 | 21 | 15.9 | 2,729 | 14,143 | 5.94E-05 |
| Insulin glargine | Hypoglycaemia | 327 | 12 | 26.5 | 1,615 | 14,143 | 6.36E-05 |
| Infliximab | Pneumocystis jiroveci pneumonia | 274 | 16 | 16.7 | 3,838 | 7,917 | 6.79E-05 |
| Edaravone | Haemorrhagic cerebral infarction | 385 | 4 | 104.7 | 2,193 | 3,099 | 7.21E-05 |
| Erlotinib hydrochloride | Interstitial lung disease | 565 | 76 | 7.4 | 2,179 | 64,724 | 7.64E-05 |
| Oxaliplatin | Neutropenia | 1,523 | 120 | 12.7 | 9,714 | 22,843 | 8.06E-05 |
| Oxaliplatin | Leukopenia | 1,023 | 78 | 13.1 | 9,714 | 14,834 | 8.49E-05 |
| Oseltamivir phosphate | Abnormal bhaviour | 387 | 4 | 97.1 | 2,496 | 2,953 | 8.91E-05 |
| Capecitabine | Palmar-plantar erythrodysaesthesia syndrome | 262 | 8 | 34.9 | 3,466 | 4,004 | 9.33E-05 |
| Carbamazepine | Drug rash with eosinophilia and systemic sympt | 632 | 32 | 19.6 | 7,788 | 7,652 | 9.76E-05 |
| Glibenclamide | Hypoglycaemia | 286 | 22 | 12.8 | 2,925 | 14,143 | 1.02E-04 |
| Glimepiride | Hypoglycaemic coma | 191 | 9 | 21.7 | 7,014 | 2,322 | 1.06E-04 |

Most sensitive 25 out of 65,952 signals are shown

# Illustration 5

Number of Reports with Anbormal Behavior (Dataset 1, n=216,945)

**Table 3. Number of Reports with Abnormal Behavior (Dataset 1, n=216,945)**

| Drug | Number of Subjects with Indexed Drug | | Proportion of Abnormal Behavior | |
|---|---|---|---|---|
| | Abnormal Behavior (n=838) | Total (n=216,945) | [95% Confidence Interval] | |
| Oseltamivir | 387 | 1,824 | 21.2 % | [19.4 - 23.2] |
| Zanamivir | 272 | 630 | 43.2 % | [39.3 - 47.1] |
| Acetaminophen | 260 | 4,544 | 5.7 % | [5.1 - 6.4] |
| Carbocisteine | 138 | 5,025 | 2.7 % | [2.3 - 3.2] |
| Tipepidine | 100 | 997 | 10.0 % | [8.2 - 12.1] |
| Ambroxol | 62 | 3,418 | 1.8 % | [1.4 - 2.3] |
| Cyproheptadine | 47 | 538 | 8.7 % | [6.5 - 11.4] |
| Clarithromycin | 46 | 4,567 | 1.0 % | [0.7 - 1.3] |
| Dextromethorphan | 33 | 1,532 | 2.2 % | [1.5 - 3.0] |
| Chlorophenyramine | 38 | 3,910 | 1.0 % | [0.7 - 1.3] |
| All Drug | 838 | 216,945 | 0.4 % | [0.4 - 0.4] |

# Illustration 6

## Characteristics for Acetaminophen-treated Subjects (Dataset 2, n=4,544)

**Table 4. Characteristics for Acetaminophen-treated Sbujects (Dataset 2, n=4,544)**

| | Abnormal Behavior* (n=260) | | Other Adverse Event* (n=4,284) | | Crude Odds Ratio¶ | Fisher's Exact Test Chi-square Test |
|---|---|---|---|---|---|---|
| Variable | number of case | (%) | number of case | (%) | [95% Cnfidence Interval] | *P*-value§ |
| Gender | | | | | | |
| Male | 196 | 75.4% | 2,106 | 49.2% | 3.17 [2.36 - 4.29] | <0.001 |
| Female | 63 | 24.2% | 2,166 | 50.6% | 0.31 [0.23 - 0.42] | (Fisher) |
| Gender Missing | 1 | 0.4% | 12 | 0.3% | | --- |
| Report Year | | | | | | |
| 2004 | 0 | 0.0% | 378 | 8.8% | 0.00 [0.00 - 0.15] | |
| 2005 | 14 | 5.4% | 399 | 9.3% | 0.55 [0.30 - 0.96] | |
| 2006 | 17 | 6.5% | 432 | 10.1% | 0.62 [0.35 - 1.03] | |
| 2007 | 108 | 41.5% | 490 | 11.4% | 5.50 [4.18 - 7.22] | <0.001 |
| 2008 | 61 | 23.5% | 495 | 11.6% | 2.35 [1.70 - 3.19] | (Chi-square) |
| 2009 | 43 | 16.5% | 631 | 14.7% | 1.15 [0.80 - 1.62] | |
| 2010 | 14 | 5.4% | 777 | 18.1% | 0.26 [0.14 - 0.44] | |
| 2011 | 3 | 1.2% | 682 | 15.9% | 0.06 [0.01 - 0.18] | |
| Age (Year) | | | | | | |
| <10 | 97 | 37.3% | 453 | 10.6% | 5.03 [3.80 - 6.64] | |
| 10-19 | 145 | 55.8% | 377 | 8.8% | 13.05 [9.92 - 17.21] | |
| 20-29 | 8 | 3.1% | 305 | 7.1% | 0.41 [0.18 - 0.84] | |
| 30-39 | 1 | 0.4% | 420 | 9.8% | 0.04 [0.00 - 0.20] | |
| 40-49 | 2 | 0.8% | 369 | 8.6% | 0.08 [0.01 - 0.30] | <0.001 |
| 50-59 | | 0.0% | 600 | 14.0% | 0.00 [0.00 - 0.09] | (Chi-square) |
| 60-69 | 3 | 1.2% | 758 | 17.7% | 0.05 [0.01 - 0.16] | |
| 70-79 | 2 | 0.8% | 677 | 15.8% | 0.04 [0.00 - 0.15] | |
| 80-89 | 1 | 0.4% | 257 | 6.0% | 0.06 [0.00 - 0.34] | |
| 90- | 1 | 0.4% | 30 | 0.7% | 0.55 [0.01 - 3.32] | |
| Other or Missing | 9 | 3.5% | 38 | 0.9% | | --- |
| Underlying Illness | | | | | | |
| Influenza | 253 | 97.3% | 418 | 9.8% | 334.80 [158.59 - 827.03] | <0.001 |
| Other Disease | 7 | 2.7% | 3,866 | 90.2% | 0.00 [0.00 - 0.01] | (Fisher) |

* All data are shown as number (%) ¶In case there are more than two categories, the odds ratio for an indexed category is calculated in comparison with all other categories. § The *P*-values are calculated intended to highlight difference worth further attention, but not to test the differences. † Abbreviations; PMDA, Pharmaceuticals and Medical Devices Agency in Japan

# Illustration 7

## Logistic regression results (shown as Estimate and P value) in whole JADER (DATASET 1. n=216,945)

**Logistic regression results (shown as Estimate and *P* value) in whole JADER (DATASET 1. n=216,945)**

| | Model A‡ | | | Model B | | | Model C | | | Model D | | | Model E | | | Model F | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Variables | Estimate | Pr(>\|z\|) | | Estimate | Pr(>\|z\|) | | Estimate | Pr(>\|z\|) | | Estimate | Pr(>\|z\|) | | Estimate | Pr(>\|z\|) | | Estimate | Pr(>\|z\|) | |
| (Intercept) | -7.85948 | < 2e-16 | *** § | -7.46399 | < 2e-16 | *** | -7.46177 | <2e-16 | *** | -7.93815 | <2e-16 | *** | -7.43382 | < 2e-16 | *** | -7.43271 | <2e-16 | *** |
| Acetaminophen | 0.52671 | 1.44E-06 | *** | 0.37055 | 0.000885 | *** | 0.19009 | 0.6293 | | 2.21677 | <2e-16 | *** | 0.40534 | 0.000188 | *** | 0.36256 | 0.3488 | |
| Oseltamivir | 4.59481 | < 2e-16 | *** | 2.74356 | < 2e-16 | *** | 2.75634 | <2e-16 | *** | | | | | | | | | |
| Zanamivir | 4.92929 | < 2e-16 | *** | 3.07791 | < 2e-16 | *** | 3.08913 | <2e-16 | *** | | | | | | | | | |
| Tipepidine | 0.3018 | 0.10889 | | 0.22913 | 0.229189 | | 0.22926 | 0.2296 | | | | | | | | | | |
| Carbocisteine | 0.0358 | 0.80931 | | -0.01944 | 0.897455 | | -0.01844 | 0.9028 | | | | | | | | | | |
| Cyproheptadine | -0.2622 | 0.27374 | | -0.33472 | 0.165081 | | -0.33501 | 0.1652 | | | | | | | | | | |
| Chlorophenylramine | 0.08276 | 0.71998 | | 0.0543 | 0.818328 | | 0.05836 | 0.8054 | | | | | | | | | | |
| Ambroxol | 0.12776 | 0.49522 | | 0.07677 | 0.686126 | | 0.07782 | 0.6824 | | | | | | | | | | |
| Dimemorfan | 0.90774 | 0.00844 | ** | 0.78106 | 0.023464 | * | 0.77828 | 0.0242 | * | | | | | | | | | |
| Clarithromycin | -0.52971 | 0.01115 | * | -0.50611 | 0.016486 | * | -0.50435 | 0.0171 | * | | | | | | | | | |
| Dextromethorphan | -0.0877 | 0.72108 | | -0.1595 | 0.518406 | | -0.16171 | 0.5132 | | | | | | | | | | |
| LT20 ¶ | 2.02159 | < 2e-16 | *** | 1.95385 | < 2e-16 | *** | 1.95631 | <2e-16 | *** | 3.50446 | <2e-16 | *** | 2.07416 | < 2e-16 | *** | 2.07488 | <2e-16 | *** |
| GenderF | -0.29482 | 0.27468 | | -0.67196 | 0.012138 | * | -0.66902 | 0.0125 | * | -0.15851 | 0.4899 | | -0.67419 | 0.010774 | * | -0.67392 | 0.0108 | * |
| GenderM | 0.19455 | 0.46172 | | -0.17899 | 0.494852 | | -0.17601 | 0.5019 | | 0.51758 | 0.0212 | * | -0.1969 | 0.447547 | | -0.19673 | 0.4479 | |
| HighReportYear † | 1.13226 | < 2e-16 | *** | 1.08311 | < 2e-16 | *** | 1.08261 | <2e-16 | *** | 1.45151 | <2e-16 | *** | 1.11147 | < 2e-16 | *** | 1.1114 | <2e-16 | *** |
| Flu | | | | 2.19163 | < 2e-16 | *** | 2.16633 | <2e-16 | *** | | | | 4.80929 | < 2e-16 | *** | 4.80614 | <2e-16 | *** |
| Acetaminophen:Flu | | | | | | | 0.19727 | 0.6304 | | | | | | | | 0.04648 | 0.9082 | |

¶ LT20 includes teenagers, less than 10, newborn, child and adolescence. †HighReportingYear includes reporting year 2007 and 2008. § Signif. codes are as follwos; <0.001 '***', <0.01 '**', <0.05 '*' <0.1 '.'
‡ Formulas for indexed models are as follows; Model A: formula = Abnormal.Behaviour ~ Acetaminophen + Oseltamivir + Zanamivir + Tipepidine + Carbocisteine + Cyproheptadine + Chlorophenylramine + Ambroxol + Dimemorfan + Clarithromycin + Dextromethorphan + LT20 + Gender + HighReportYear, Model B:formula = Abnormal.Behaviour ~ Acetaminophen + Oseltamivir + Zanamivir + Tipepidine + Carbocisteine + Cyproheptadine + Chlorophenylramine + Ambroxol + Dimemorfan + Clarithromycin + Dextromethorphan + LT20 + Gender + HighReportYear + Flu, Model C:formula = Abnormal.Behaviour ~ Acetaminophen + Oseltamivir + Zanamivir + Tipepidine + Carbocisteine + Cyproheptadine + Chlorophenylramine + Ambroxol + Dimemorfan + Clarithromycin + Dextromethorphan + LT20 + Gender + HighReportYear + Flu + Acetaminophen * Flu, Model D:formula = Abnormal.Behaviour ~ Acetaminophen + LT20 + Gender + HighReportYear, Model E:formula = Abnormal.Behaviour ~ Acetaminophen + LT20 + Gender + HighReportYear + Flu, Model F:formula = Abnormal.Behaviour ~ Acetaminophen + LT20 + Gender + HighReportYear + Flu + Acetaminophen * Flu

# Illustration 8

## Logistic regression results (shown as Estimate and P value) in cases with influenza (DATASET 3. n=2,164)

**Logistic regression results (shown as Estimate and *P* value) in cases with influenza (DATASET 3. n=2,164)**

| | Model G ‡ | | | Model H | | | Model I | | | Model J | | | Model K | | | Model L | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Variables | Estimate | Pr(>\|z\|) | | Estimate | Pr(>\|z\|) | | Estimate | Pr(>\|z\|) | | Estimate | Pr(>\|z\|) | | Estimate | Pr(>\|z\|) | | Estimate | Pr(>\|z\|) | |
| (Intercept) | -4.25413 | < 2e-16 | *** § | -4.5581 | < 2e-16 | *** | -4.6581 | < 2e-16 | *** | -4.5267 | < 2e-16 | *** | -4.4684 | < 2e-16 | *** | -4.55115 | < 2e-16 | *** |
| Acetaminophen | 0.39303 | 1.05E-03 | ** | 0.3852 | 0.000929 | *** | 0.6893 | 0.000231 | *** | 0.27 | 0.0639 | . | 0.07496 | 0.817 | | 0.35885 | 0.0312 | * |
| Oseltamivir | 1.244816 | 2.79E-05 | *** | 1.1599 | 5.92E-05 | *** | 1.3268 | 1.18E-05 | *** | 1.1665 | 5.26E-05 | *** | 1.17154 | 4.91E-05 | *** | 1.16196 | 5.80E-05 | *** |
| Zanamivir | 1.446226 | 1.68E-06 | *** | 1.3659 | 3.52E-06 | *** | 1.3518 | 5.40E-06 | *** | 1.2552 | 4.07E-05 | *** | 1.37414 | 3.00E-06 | *** | 1.36816 | 3.44E-06 | *** |
| Tipepidine | 0.149816 | 0.46032 | | | | | | | | | | | | | | | | |
| Carbocisteine | -0.09399 | 0.56773 | | | | | | | | | | | | | | | | |
| Cyproheptadine | -0.29989 | 0.23782 | | | | | | | | | | | | | | | | |
| Chlorophenylramine | 0.022211 | 0.93406 | | | | | | | | | | | | | | | | |
| Ambroxol | 0.007712 | 0.97043 | | | | | | | | | | | | | | | | |
| Dimemorfan | 0.417776 | 0.25936 | | | | | | | | | | | | | | | | |
| Clarithromycin | -0.52246 | 0.02261 | * | | | | | | | | | | | | | | | |
| Dextromethorphan | -0.10414 | 0.69447 | | | | | | | | | | | | | | | | |
| LT20 ¶ | 2.376185 | < 2e-16 | *** | 2.471 | < 2e-16 | *** | 2.4651 | < 2e-16 | *** | 2.4694 | < 2e-16 | *** | 2.35367 | < 2e-16 | *** | 2.47117 | < 2e-16 | *** |
| GenderF | -0.69597 | 0.09585 | . | | | | | | | | | | | | | | | |
| GenderM | -0.05562 | 0.89232 | | | | | | | | | | | | | | | | |
| HighReportYear † | 1.280046 | < 2e-16 | *** | 1.2489 | < 2e-16 | *** | 1.2527 | < 2e-16 | *** | 1.2525 | < 2e-16 | *** | 1.24989 | < 2e-16 | *** | 1.23091 | < 2e-16 | *** |
| Acetaminophen:Oseltamivir | | | | | | | -0.4998 | 0.037205 | * | | | | | | | | | |
| Acetaminophen:Zanamivir | | | | | | | | | | 0.3216 | 0.1871 | | | | | | | |
| Acetaminophen:LT20 | | | | | | | | | | | | | 0.35952 | 0.3 | | | | |
| Acetaminophen:HighReportYear | | | | | | | | | | | | | | | | 0.05165 | 0.8244 | |

¶ LT20 includes teenagers, less than 10, newborn, child and adolescence. †HighReportingYear includes reporting year 2007 and 2008. § Signif. codes are as follwos; <0.001 '***', <0.01 '**', <0.05 '*' <0.1 '.'
‡ Formulas for indexed models are as follows; Model G:formula = Abnormal.Behaviour ~ Acetaminophen + Oseltamivir + Zanamivir + Tipepidine + Carbocisteine + Cyproheptadine + Chlorophenylramine + Ambroxol + Dimemorfan + Clarithromycin + Dextromethorphan + LT20 + Gender + HighReportYear, Model H:formula = Abnormal.Behaviour ~ Acetaminophen + Oseltamivir + Zanamivir + LT20 + Gender + HighReportYear, Model I:formula = Abnormal.Behaviour ~ Acetaminophen + Oseltamivir + Zanamivir + LT20 + HighReportYear + Acetaminophen * Oseltamivir, Model J:formula = Abnormal.Behaviour ~ Acetaminophen + Oseltamivir + Zanamivir + LT20 + HighReportYear + Acetaminophen * Zanamivir, Model K:formula = Abnormal.Behaviour ~ Acetaminophen + Oseltamivir + Zanamivir + LT20 + HighReportYear + Acetaminophen * LT20, Model L:formula = Abnormal.Behaviour ~ Acetaminophen + Oseltamivir + Zanamivir + LT20 + HighReportYear + Acetaminophen * HighReportYear

## Illustration 9

Logistic regression results (shown as Estimate and P value) in cases with Acetaminophen use (DATASET 2. n=4,544)

**Logistic regression results (shown as Estimate and *P* value) in cases with Acetaminophen use (DATASET 2. n=4,544)**

| | Model M‡ | | | Model N | | | Model O | | | Model P | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Variables | Estimate | Pr(>\|z\|) | | Estimate | Pr(>\|z\|) | | Estimate | Pr(>\|z\|) | | Estimate | Pr(>\|z\|) | |
| (Intercept) | -7.63496 | 6.12E-08 | *** § | -8.02827 | 1.34E-07 | *** | -7.2539 | < 2e-16 | *** | -7.8348 | < 2e-16 | *** |
| Oseltamivir | 3.7718 | < 2e-16 | *** | 0.6961 | 0.164 | | 3.7791 | < 2e-16 | *** | 0.4525 | 0.328 | |
| Zanamivir | 4.19647 | < 2e-16 | *** | 1.11599 | 0.028 | * | 4.2333 | < 2e-16 | *** | 0.8949 | 0.0571 | . |
| Tipepidine | 0.26286 | 0.37705 | | 0.29667 | 0.333 | | | | | | | |
| Carbocisteine | -0.21906 | 0.3828 | | -0.20042 | 0.432 | | | | | | | |
| Cyproheptadine | -0.41989 | 0.28666 | | -0.43177 | 0.283 | | | | | | | |
| Chlorophenylramine | 0.39247 | 0.33526 | | 0.05744 | 0.894 | | | | | | | |
| Ambroxol | -0.10344 | 0.74565 | | -0.1382 | 0.668 | | | | | | | |
| Dimemorfan | 1.34308 | 0.00568 | ** | 0.78892 | 0.099 | . | | | | | | |
| Clarithromycin | -0.48654 | 0.12248 | | -0.37133 | 0.243 | | | | | | | |
| Dextromethorphan | 0.43078 | 0.21791 | | 0.48874 | 0.178 | | | | | | | |
| LT20 ¶ | 2.62875 | < 2e-16 | *** | 2.37355 | < 2e-16 | *** | 2.7449 | < 2e-16 | *** | 2.5367 | < 2e-16 | *** |
| GenderF | -0.04737 | 0.97259 | | -0.14008 | 0.924 | | | | | | | |
| GenderM | 0.70953 | 0.60567 | | 0.62221 | 0.671 | | | | | | | |
| HighReportYear † | 1.33974 | 6.93E-13 | *** | 1.2253 | 1.09E-10 | *** | 1.271 | 1.14E-12 | *** | 1.1832 | 9.13E-11 | *** |
| Flu | | | | 3.95039 | 3.19E-11 | *** | | | | 4.2299 | 1.89E-13 | *** |

¶ LT20 includes teenagers, less than 10, newborn, child and adolescence. †HighReportingYear includes reporting year 2007 and 2008. § Signif. codes are as follwos; <0.001 '***', <0.01 '**', <0.05 '*' <0.1 '.'

‡ Formulas for indexed models are as follows; Model M:formula = Abnormal.Behaviour ~ Oseltamivir + Zanamivir + Tipepidine + Carbocisteine + Cyproheptadine + Chlorophenylramine + Ambroxol + Dimemorfan + Clarithromycin + Dextromethorphan + LT20 + Gender + HighReportYear, Model N:formula = Abnormal.Behaviour ~ Oseltamivir + Zanamivir + Tipepidine + Carbocisteine + Cyproheptadine + Chlorophenylramine + Ambroxol + Dimemorfan + Clarithromycin + Dextromethorphan + LT20 + Gender + HighReportYear + Flu, Model O:formula = Abnormal.Behaviour ~ Oseltamivir + Zanamivir + LT20 + HighReportYear, Model P:formula = Abnormal.Behaviour ~ Oseltamivir + Zanamivir + LT20 + HighReportYear +Flu