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Psychiatric adverse events in oseltamivir prophylaxis trials: novel comparative analysis using data obtained from clinical study reports

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Abstract

Purpose: Estimating the rate of adverse events (AEs) caused by a treatment in clinical trials typically involves comparing the proportions of patients experiencing AEs in intervention and control groups. However potentially important information, including duration, recurrence, and intensity of events, is lost. In this study we illustrate how the additional information can be obtained and incorporated into analyses of AEs.

Methods: Data on psychiatric AEs were extracted from clinical study reports (CSRs) provided by the manufacturer of oseltamivir in four prophylaxis randomised trials in adults and adolescents. We analysed the incidence, recurrence, duration and intensity of events, using logistic regression models where the outcome compared was proportion of days suffering from an event, and developed novel presentation techniques.

Results: Psychiatric adverse events were generally more frequent, longer and more intense in the treatment than placebo arms. Logistic regression models confirm the apparent association overall (odds ratio [OR] 3.46, 95% confidence interval [CI] 1.28 to 9.32), particularly for events classified as severe (OR 34.5, 95% CI 3.66 to 325). However, the absolute difference in proportion of days suffering from severe psychiatric adverse events between groups was small.

Conclusions: This example analysis shows evidence of a causal effect of oseltamivir on psychiatric AEs, not apparent in the published versions of the same trials and a Cochrane review which showed a non-significant 81% increased odds of experiencing a psychiatric event. This unique and important finding was dependent on obtaining previously unavailable data from clinical study reports and using novel analyses and presentation methods.

Key words: adverse events, clinical trials, oseltamivir, prophylaxis

Key points:

There has been much scientific debate on whether oseltamivir plays a causal role in the development of psychiatric adverse events.

Using detailed previously unavailable data obtained from clinical study reports of prophylaxis trials and novel statistical and graphical methods we show evidence of a causal effect of oseltamivir on psychiatric adverse events.

The increase in absolute risk of experiencing a psychiatric adverse event is small

We believe our methods can be used more generally to provide new insights into the unintended effects of pharmaceutical interventions.

Introduction

Oseltamivir [Tamiflu^{R}] is a neuraminidase inhibitor approved by the US Food and Drug Administration (FDA) in 1999 for treating and preventing influenza. Many governments across the world stockpiled oseltamivir after 2005 in response to a potential influenza pandemic so that hundreds of thousands of doses of oseltamivir could have been administered quickly if necessary(1).

In 2007 Japan banned oseltamivir use in teenagers because of observed abnormal behaviour causing accidental deaths in those administered the drug(2). In 2008, the manufacturer reviewed oseltamivir's safety, reporting significantly *fewer* patients randomised to the drug (12/1662; 0.7%) had neuropsychiatric AEs compared to placebo (20/1128; 1.8%; $p < 0.05$) in prophylaxis trials, citing "data on file"(3). A 2009 Cochrane systematic review of published trials, found no evidence of neuropsychiatric AEs in the trials (4) however a 2014 Cochrane update review, now including previously unpublished clinical study reports (CSRs), reported a statistically non-significant increase in psychiatric on-treatment AEs in four prophylaxis trials (relative risk [RR] 1.81, 95% confidence interval [CI]: 0.97 to 3.37), and a statistically significant increase in neurological on-treatment AEs (RR 1.21 , 95% CI: 1.03, 1.42)(5).

CSRs are produced by pharmaceutical companies for regulators as part of the drug approval process and have been available since 2010 to independent researchers through the European Medicines Agency (EMA) as well as directly by some pharmaceutical companies. They contain more detailed information than publications, including duration and severity of AEs, otherwise not available(6), and should be analysed where possible to report the additional details(7). Use of this additional important source of information has been limited to date (5).

There are other reasons to exploit CSRs more: simple comparison of proportions of patients with AEs can be misleading because of recurrent AEs, and unequal follow up periods(8). Intensity of AEs is also not assessed in a simple comparison of proportions of patients reporting AEs. Accordingly, we capitalise on the additional information in CSRs to better explore the full extent of psychiatric AEs associated with prophylactic use of oseltamivir, addressing many of the several weaknesses of a naive analysis. This required us to develop new methods because of the paucity of prior experience of analysing information in CSRs.

Methods

Selection of studies: We included all prophylaxis randomised studies of oseltamivir compared to placebo where a CSR was available, using prophylactic trials because of their increased patient surveillance time and because the psychiatric AEs reported were less likely to be attributed to influenza-like-illness when patients were influenza free at baseline, Table 1.

Data sources: CSRs were supplied by the manufacturer of oseltamivir in 2013 after an open data campaign initiated by the British Medical Journal (www.bmj.com/tamiflu). Prior to 2013 some incomplete CSRs had been received from the EMA. Information available from the reports in relation to oseltamivir use included duration, intensity, the relationship of adverse events (AEs) to medication as judged by study investigators, day of initiation, Medical

Dictionary for Regulatory Activities (MedDRA) preferred term (e.g. 'nausea') for each AE, and the patients: gender, treatment group assignment, dates of starting and ending treatment, and age (Box). Data was extracted by MJ and independently checked by CDM. We only included on-treatment events classified in the CSRs under the "psychiatric" system organ class and did not recode or reclassify events, apart from two in trial WV15825 that were originally misclassified but subsequently corrected (9). The CSRs used for this analysis are available at http://datadryad.org/resource/doi:10.5061/dryad.77471, (accessed 17 May 2017).

Adverse events were defined in the clinical trials as any change from the patient's baseline condition which occurred during the trial after treatment began irrespective of whether it was thought to be related to the study treatment. Symptoms of influenza were not counted as adverse events unless they fulfilled the criteria for serious adverse events. Exact timing on when information was obtained from patients on adverse events throughout the follow up period differed between studies, Table 1. Information on AEs was obtained via patient interview and recorded onto standardised AE case report forms. Any unresolved adverse events at the end of the study were followed up until they were either resolved or until an explanation was obtained as to why no end date was available. Further detail on the information collected on adverse events for each clinical trial is available in the blank case report forms contained in Module 2 of the CSRs (see complete data, referenced above, for access).

Statistical methods: We compared the proportion of days patients suffered from psychiatric AEs between trial groups. For example, a patient with depression for 10 days and subsequently anxiety for 5 days over the 8 week follow up would have 15/56 days suffering from psychiatric adverse events. This accounts for multiple AEs, as well as their duration, which is not possible if a simple dichotomy between proportions of patients affected is used.

We analysed the data using single stage individual patient meta-analysis via logistic regression models(10). Differences in AE rates between trials (possibly due to differences in baseline demographics such as age or differences in follow up duration) were accounted for by including a categorical variable in the models indicating each trial data; and a variable in the model tested the interaction between trial and treatment group on the outcome. Intensity of the AE was incorporated into a second analysis by using weighted nominal logistic regression, with weights and outcome based on the number of days the patient suffered from each of severe, moderate, mild and no psychiatric adverse event. As the unit of analysis was days within patients, we estimated cluster robust standard errors to account for repeated measures where each patient was a cluster.

Percentages of days affected by psychiatric AEs by intensity were estimated from predicted probabilities obtained from the weighted nominal logistic regression model. We also estimated number of patient days of treatment that would lead to one additional day of suffering from a psychiatric AE of any intensity. We did this by subtracting the estimated proportion of days affected by psychiatric AEs in the placebo group from that of the treatment group and then taking the reciprocal of this value. We also made an adjustment to account for most patients being treated for 6 weeks but followed up for a further 2 weeks.

One of the trials (WV15673/97) included three treatment groups: placebo, oseltamivir 75 mg o.d., or oseltamivir 75 mg b.i.d. for 6 weeks. For the main analysis we combined the two oseltamivir groups however in an additional analysis we investigated the dose response effect of oseltamivir in trial WV15673/97 using logistic regression with the explanatory variable treatment group coded as -1 (placebo), 0 (oseltamivir 75 mg o.d.), or 1 (oseltamivir 75 mg b.i.d.).

In addition to the statistical analysis we present plots of the psychiatric adverse events over the follow up of the studies for individual patients. For each patient with an event, a horizontal line segment shows day of initiation as well as duration of the event. Intensity is illustrated using different line styles and events unresolved at the end of the follow up are indicated using hollow circles. Multiple events within patients can be shown using multiple line segments and numbers of patients with events are shown on the y-axis. Plots are stratified by treatment group with numbers of patients contributing to safety assessment provided next to the treatment group labels.

Results

AEs in the treatment group were more frequent and severe, of longer duration, and possibly of earlier occurrence, than in the placebo group in the three prophylaxis trials of 6 weeks of treatment with oseltamivir for individuals exposed to influenza, Figures 1 & 2. A post-exposure prophylaxis trial, WV15799, where exposure to medication was for only 7 days, had few events, Figure 3. There were 13 types of AEs reported in the four clinical trials (classified by MedDRA preferred terms), Table 2.

The proportion of days patients suffered from a psychiatric adverse event was greater in oseltamivir groups, odds ratio (OR) 3.46 (95% confidence interval [95% CI] 1.28 to 9.32). A test for interaction between trial and outcome showed evidence (P=0.01) that WV15799 had a different treatment effect on AEs than the other three trials, with an OR at <1. If WV15799 is excluded from the analysis, the OR increases from 3.46 to 4.12 (95% CI 1.40 to 12.1). Analysing the intensity of the AEs showed little difference between groups (OR 1.23, 95% CI 0.30 to 5.04) for mild AEs, but a statistically non-significant increase for moderate AEs (OR 4.34, 95% CI 0.79 to 24.0), and a large, significant increase for severe AEs (OR 34.5, 95% CI 3.66 to 325). However, the predicted proportions of days affected by psychiatric adverse events from the weighted nominal logistic model, illustrating the absolute differences between groups, are small, Table 3.

In the additional analysis of trial WV15673/97 there was insufficient evidence of a dose-response effect of oseltamivir on proportion of days patients suffered from a psychiatric adverse event, odds ratio (OR) 1.30 (95% confidence interval [95% CI] 0.74 to 2.27).

Discussion

We found patients using oseltamivir had a greater than 3-fold increased odds of suffering from a psychiatric AE compared to those using placebo, most notably for events with severe intensity, suggesting a causal effect. Although the relative effect is very high for severe

events, the absolute increase is small when considered in the context of all patients included in the study over the 3-8 week follow up periods. The effect was consistent over the three trials where exposure to treatment was 6 weeks long, but not for the one study, where exposure was for only 1 week, perhaps because of the reduced exposure, reduced follow up, or insufficient power to discern enough AEs. There was insufficient evidence of a dose-response effect of treatment on odds of suffering from a psychiatric AE however this analysis was only able to be performed using one trial hence power is low.

One important limitation of this research is that children were not included in any of the trials (despite oseltamivir being approved by the FDA for treatment prophylaxis for patients aged ≥1 year). Clearly, the definition of 'neuropsychiatric adverse event' is critical. The different conclusions between the manufacturer sponsored report and the Cochrane review is attributable to the manufacturer (in consultation with the FDA) creating a post-hoc definition for neuropsychiatric adverse events while the original classifications reported in the CSRs for psychiatric and neurological adverse events were maintained for the current study and the Cochrane review(11).

Perhaps even more important than these findings specific to oseltamivir is our use of novel methods based on using CSRs. Obtaining access to these documents has allowed us to conduct very detailed analyses far beyond what is possible with conventional published trials, allowing us to incorporate important information only available in the CSRs, including multiple events suffered by individual patients, duration of events, and the intensity of events. Some of the data used for this study had been previously extracted from CSRs for a systematic review of neuraminidase inhibitors (5). Data extraction was somewhat labour intensive however CSRs are required to conform to a reporting standard(12) and the oseltamivir CSRs were relatively easy to navigate around once familiarity of the format had been attained. In future work we plan to investigate whether AE data from CSRs can be converted from pdf format to electronic spreadsheet format to facilitate full analysis of all AE data contained in CSRs.

This study illustrates the importance of transparency of clinical trial data. Transparency can be improved with public access to clinical study reports. This has already occurred to some degree with the EMA releasing CSRs to independent researchers on request since November 2010(13). Furthermore the EMA began proactively publishing CSRs submitted as part of marketing-authorisation applications for human medicines in 2016 and, in a second phase, plan to release de-identified individual patient data (IPD)(14). Recently the FDA has implemented a pilot study to trial the release of CSRs (15) and some pharmaceutical companies allow researchers to potentially access CSRs and individual patient data from their clinical trials (https://restoringtrials.org/insitutions-offering-data-access/).

Conclusions

Oseltamivir appears to play a causal role in the development of psychiatric adverse events however the absolute risk is small. CSRs provide a much richer database of information on adverse events compared to other sources, including publications. Our methods can be used

to fully utilize this information and provide additional insights into the unintended effects of pharmaceutical interventions. This has great relevance to future new drugs and their evaluation, especially for important early warnings of AEs.

Ethics statement: This study involves secondary analysis of published data hence it did not require ethical approval

Funding: No specific funding was obtained to conduct this study

Competing interests:

The manufacturer of oseltamivir (Roche Products Pty Limited) unconditionally provided the full clinical study reports used for the Cochrane review of neuraminidase inhibitors referenced in the manuscript. However the partial clinical study reports used for the current study were provided unconditionally by the European Medicines Agency (EMA). Neither the EMA nor the manufacturer had any additional role in the production of the manuscript or design/conduct of the current study.

MJ and CDM were co-recipients of a UK National Institute for Health Research grant for the systematic review discussed in this article (HTA – 10/80/01 Update and amalgamation of two Cochrane Reviews: neuraminidase inhibitors for preventing and treating influenza in healthy adults and children—http://www.nets.nihr.ac.uk/projects/hta/108001). This review focused on oseltamivir, manufactured by Roche, and zanamivir, manufactured by GlaxoSmithKline. MJ is also a co-recipient of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews and reports personal fees from Laura and John Arnold Foundation, outside the submitted work. CDM receives grant funding for the Acute Respiratory Infections Cochrane Group, and for other research funding from the Australian NHMRC. He receives book royalties from Elsevier and Wiley, and has been paid consultancy funding together with colleagues for work on shared decision making from BUPA (UK) and the Australian Commission for Safety and Quality in Healthcare. SET declares no competing interests.

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Box: Excerpt of Clinical Study Report on adverse events reported in oseltamivir trial WV15825 to illustrate the information available on each adverse event reported

Appendix 16 Listing of Adverse Events On Treatment in the Oseltamivir Group (Cont.)

Treatment : Ro 64-0796 75mg od
(N = 276)

(...continuing)

CRIN /Pat.	Sex	Age (yr)	Weight (kg)	-- Treatment -- Start	End	From	Study Day	To	Dur. (days)	Intensity	Relation to TT	Outcome
23638/3207	M	83	43.1	07JAN99	17FEB99							
DEPRESSION ENDOGENOUS						15JAN99	9	22JAN99	8	SEVERE	UNRELATED	RESO - NO SEQUEL
CHRONIC OBSTRUCTIVE AIRWAYS DISEASE ...EXACERBATED						11FEB99	36	12FEB99	2	MODERATE	REMOTE	RESO - NO SEQUEL
23638/3211	M	83	83.9	07JAN99	16FEB99							
SYNCOPE						16FEB99	41	23FEB99	8	MODERATE	UNRELATED	RESO - NO SEQUEL
23639/3119	F	87		08JAN99	18FEB99							
INFLUENZA						08FEB99	32	17FEB99	10	MODERATE	UNRELATED	RESO - NO SEQUEL
23639/3120	F	92	57.2	08JAN99	15JAN99							
KIDNEY INFECTION NOS						15JAN99	8	16JAN99	2	MODERATE	REMOTE	RESO - NO SEQUEL
23639/3122	F	69	47.6	08JAN99	15JAN99							
PARANOID SCHIZOPHRENIA						15JAN99	8	23MAR99	68	SEVERE	UNRELATED	RESO - NO SEQUEL
23640/3301	F	87	59.0	08JAN99	18FEB99							
CONSTIPATION						21JAN99	14			MILD	UNRELATED	UNRESOLVED
HAEMORRHOIDS						21JAN99	14	21JAN99	1	MODERATE	UNRELATED	RESO - NO SEQUEL
23642/2901	F	81	58.1	09JAN99	21FEB99							
RHINITIS ALLERGIC NOS						14JAN99	6	15JAN99	2	MILD	UNRELATED	RESO - NO SEQUEL
RIGORS						20JAN99	12	21JAN99	2	MILD	REMOTE	RESO - NO SEQUEL
FATIGUE						20JAN99	12	21JAN99	2	MILD	REMOTE	RESO - NO SEQUEL
23642/2906	F	92	54.4	09JAN99	22FEB99							
URINARY TRACT INFECTION NOS						13FEB99	36	22FEB99	10	MODERATE	UNRELATED	RESO - W. SEQUEL
23642/2908	F	76	61.2	10JAN99	04MAR99							
DIZZINESS (EXC VERTIGO)						14JAN99	5	14JAN99	1	MILD	UNRELATED	RESO - NO SEQUEL
23642/2909	M	91	63.5	10JAN99	18JAN99							
CONFUSION						14JAN99	5	18JAN99	5	SEVERE	POSSIBLE	RESO - NO SEQUEL
DEPRESSION NOS						14JAN99	5	18JAN99	5	SEVERE	POSSIBLE	RESO - NO SEQUEL
HALLUCINATIONS						14JAN99	5	18JAN99	5	SEVERE	POSSIBLE	RESO - NO SEQUEL
23642/2910	F	75	49.9	09JAN99	04MAR99							
SWEATING INCREASED						14JAN99	6	14JAN99	1	MILD	UNRELATED	RESO - NO SEQUEL
23642/2912	F	77	68.0	09JAN99	19JAN99							
NAUSEA						17JAN99	9	29JAN99	13	MILD	PROBABLE	RESO - NO SEQUEL

(continuing...)

Table 1: Study details on the four prophylaxis trials of oseltamivir for influenza

Trial	**WV15825(16)**	**WV15673/97(17)**	**WV15708**	**WV15799(18)**
Unit of randomisation	Individuals (in nursing homes)	Individuals	Individuals (in nursing homes)	Households
Treatment	Oseltamivir 75 mg o.d. for 6 weeks	Oseltamivir 75 mg o.d. or 75 mg b.i.d. for 6 weeks	Oseltamivir 75 mg o.d. for 6 weeks	Oseltamivir 75 mg o.d. for 7 days
Sample size (safety population)	272 placebo 276 treatment	519 placebo 1040 treatment	182 placebo 190 treatment	461 placebo 494 treatment
Age group	Elderly	Adults	Elderly	Adults and adolescents
Study duration	8 weeks	8 weeks	8 weeks	3 weeks
Adverse events information collected	Weeks 3, 6, 8 and any illness visit	Weekly	Weeks 3, 6, 8 and any illness visit	Daily for 8 days then at 21 days
Psychiatric adverse events published	No*	No	Entire study unpublished	No

*Not reported in the original publication, although they were reported in an erratum(9)

Table 2: Psychiatric adverse event (AEs) types in oseltamivir prophylaxis trials, classified by MedDRA

	Number of AEs	
Psychiatric AE type	**Oseltamivir**	**Placebo**
Confusion	4	2
Depression	10	4
Anxiety	4	6
Psychosis	2	0
Schizophrenia	1	0
Bipolar disorder	0	1
Sleeping disorder	2	0
Stress symptoms	2	0
Restlessness	1	0
Nervousness	1	0
Suicide ideation	1	0
Alcohol related	6	2
Hallucinations	*1	0
Total	35	15

*One patient classified as having severe hallucinations in the Oseltamivir group of study WV15825 was also classified as having severe depression and severe confusion simultaneously. For the purposes of our analysis this was considered to be one psychiatric event.

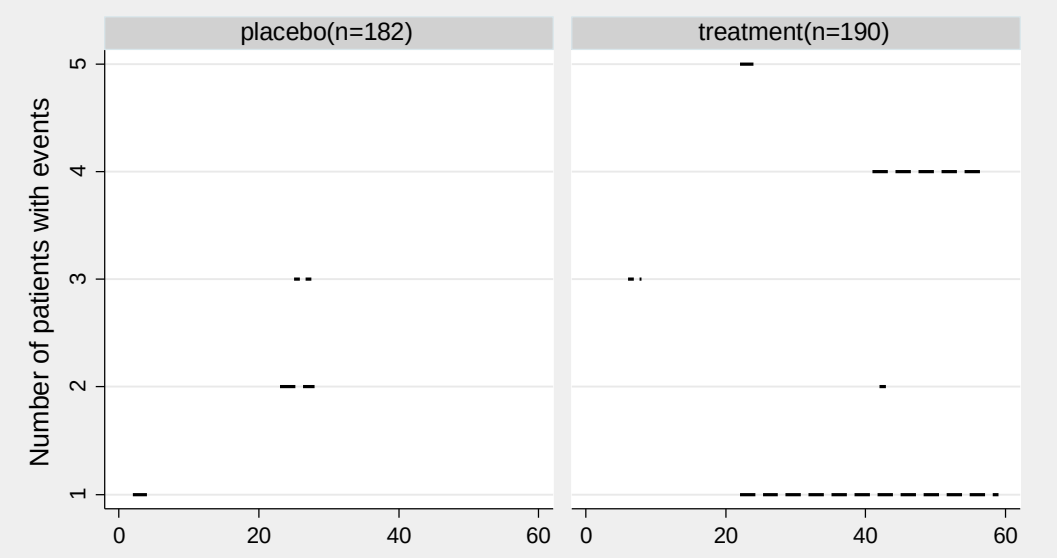
Table 3: Predicted percentage of days affected by psychiatric adverse events (AEs) in oseltamivir prophylaxis trials from a nominal logistic regression

Treatment group	Placebo				Oseltamivir			
Intensity of AE	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
Percentage of days affected*	99.83	0.11	0.05	0.005	99.51	0.13	0.21	0.15

*Using these percentages, approximately 290 patient days of treatment with oseltamivir would lead to 1 additional day of suffering from a psychiatric AE of any intensity

Figure 1: Psychiatric AEs in two prophylaxis trials of the elderly with oseltamivir taken once daily for 6 weeks

Trial WV15708



Trial WV15825

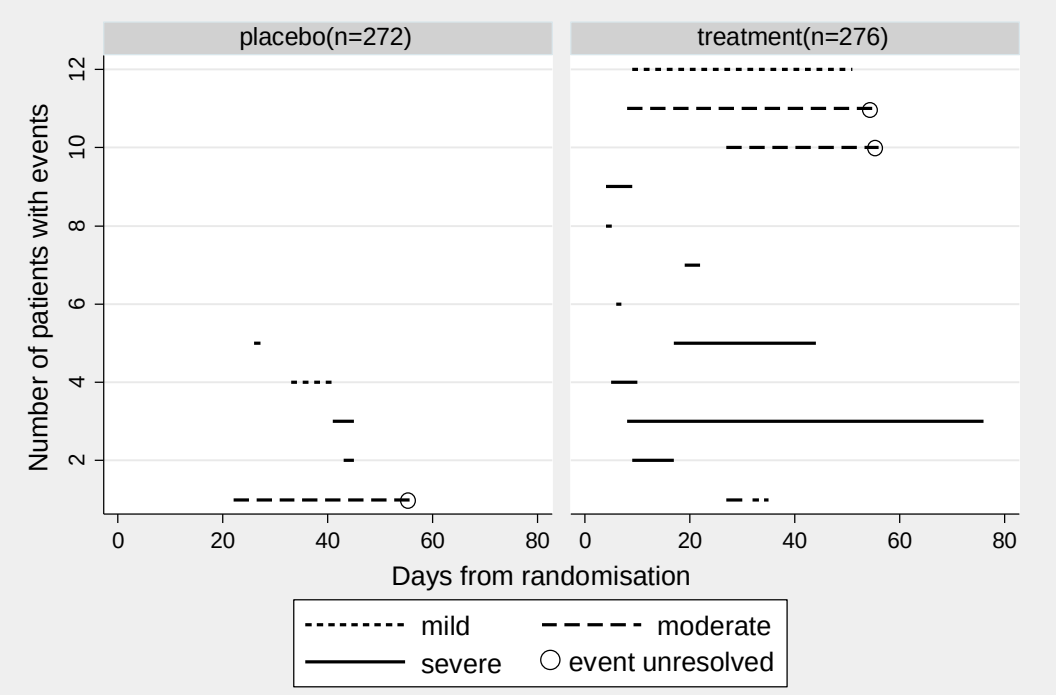


Figure 2: Psychiatric AEs in trial WV15673/97 of oseltamivir taken once daily or twice daily for 6 weeks

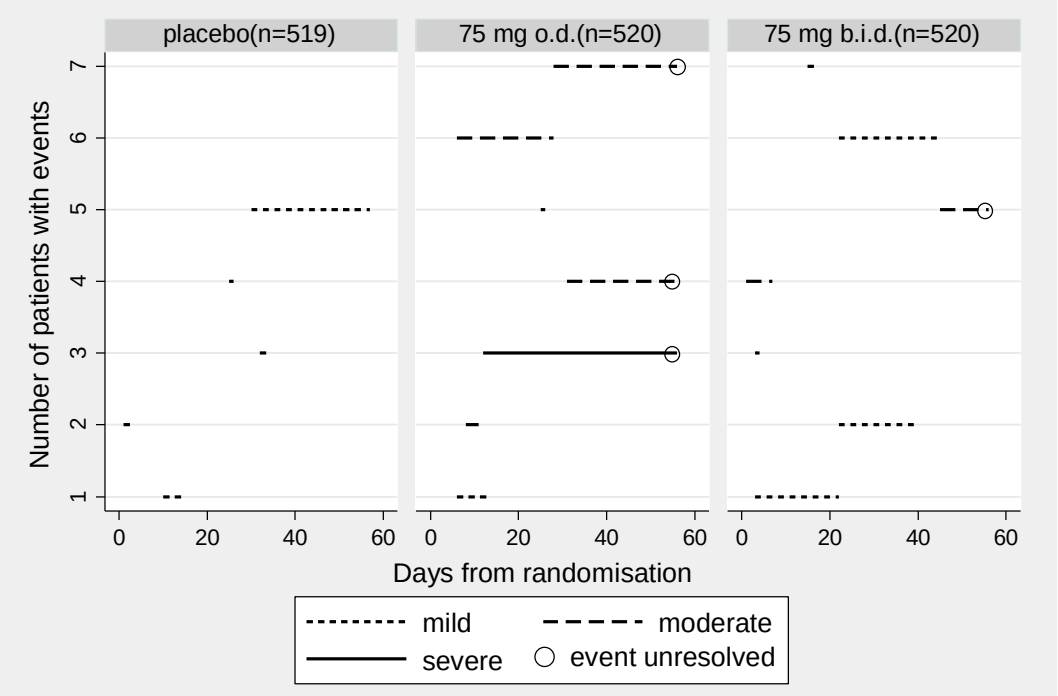


Figure 3: Psychiatric AEs in trial WV15799 of oseltamivir taken once daily for 7 days