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Neuropsychiatric Adverse Events and Oseltamivir for Prophylaxis

We would like to query the numbers of neuropsychiatric adverse events (NPAE) reported by Toovey et al.,[1] who state "in randomized controlled studies, significantly fewer oseltamivir patients (12/1662; 0.7%) reported NPAEs than placebo recipients (20/1128; 1.8%; $p < 0.05$)" referenced to "Data on file, Roche, 2008".

The text is vague, but the data appear to be from five prophylaxis randomized controlled trials conducted more than 10 years ago as the total number of patients match those reported by Toovey et al.[1] Three trials were conducted in adults: two in the US (WV15673 and WV15697)[2] and one in Japan (JV15824).[3] Two trials were conducted in the elderly: WV15708, in the Southern Hemisphere; and WV15825, in the US and Europe.[4]

Prophylaxis trials can be particularly useful for determining causality because, unlike treatment trials, adverse events cannot be attributed to the disease (influenza). In Roche oseltamivir treatment trials, events attributed to the disease were not collected as adverse events unless they met the definition of a serious adverse event.

A small proportion of the data from the above prophylaxis studies can be accessed via journal publications[2-4] and one study appears to be unpublished (WV15708). However, the publications are all brief (7–15 pages) and report little information on adverse events and no information on psychiatric adverse events. This should be compared with the company clinical study reports (CSRs) for the same studies, which are hundreds to thousands of pages in length and were submitted to regulators as part of Roche's marketing application.[5] Thus, the majority of clinical data from oseltamivir trials remain unpublished and invisible to researchers. allowing bias and distortion to creep into any research synthesis based on journal publications.

Although Roche failed to honour its promise of providing independent investigators with 'full study reports', we requested and received, through a freedom of information request to the European Medicines Agency undertaken in relation to our Cochrane review,[6] 2359 pages of Roche's 'data on file', including the first two modules of the CSRs for four prophylaxis studies and a synopsis of the fifth (JV15824).[5] The definition of NPAE is not provided in detail by Toovey et al.,[1] nor in the CSR protocols. However, the three broad classes of adverse events included in the Toovey et al.[1] definition are *nervous system disorders*, *psychiatric disorders* and *accidents/injuries*. The reporting of adverse events in the CSRs appears to have been based on a different system of classification where *nervous system disorders* were termed *neurological* and *accidents/injuries* were termed *injury and poisoning*. Table I shows the total numbers of patients with adverse events in the three broad classes by treatment group.

Given that the term neuropsychiatric implies a mental disorder attributable to the nervous system, psychiatric adverse events appear to be the most relevant. However it is possible that particular events classified as neurological or injury could be regarded as neuropsychiatric providing they were likely to have been the result of a nervous system-attributable mental disorder. Overall, the psychiatric (and neurological) adverse event data (table I) show a trend of higher proportion of events in the oseltamivir arm compared with the placebo arm that is consistent with the results of three prospective observational studies of NPAE events in Japanese children.[7-9] A meta-analysis of these three studies show pooled odds ratio for abnormal behaviours due to oseltamivir exposure

Table I. Number of patients with adverse events reported in clinical study reports of five prophylaxis randomized controlled trials

Adverse event category	Oseltamivir (N = 1662) [n (%)]	Placebo (N = 1128) [n (%)]
Psychiatric	31 (1.9)	13[a] (1.1)
Neurological	590 (35)	285 (25)
Injury and poisoning	49 (2.9)	32 (2.8)

a This number includes one patient who had concussion but was incorrectly classified as having confusion.

of 1.55 (95% CI 1.21, 1.98; p = 0.0005) without significant heterogeneity.[10]

Since NPAEs were not a defined category in the trial protocols, analysing NPAEs requires constructing *post hoc* definitions of which adverse events count as NPAEs (and which do not). This allows the possibility of choosing and selectively reporting adverse events based on the observed data (sometimes referred to as 'cherry picking'). In addition, the lumping together of adverse events from a number of heterogeneous categories risks swamping any potential signals of importance from being discovered. We request that Toovey et al.[1] provide further details on what events from the randomized controlled prophylaxis studies were included in their comparison of NPAE, including the list of 98 preferred terms they mention at the end of page 1100. In addition, and perhaps more importantly, they should clearly state which psychiatric adverse events were not included in their comparison.

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The Authors' Reply

We thank Dr Jones and colleagues[1] for their comments on our review,[2] and welcome the opportunity to address the points they raise in their correspondence. The reviewers pinpoint a major difficulty in addressing the issue of neuropsychiatric adverse events (NPAEs) when they state that

Table I. Preferred terms used to identify neuropsychiatric cases in the Roche Tamiflu Safety Database

Category	Preferred Terms
Delirium	Delirium
	Delirium febrile
Delusions/perceptual disturbance	Delusion
	Delusional perception
	Hallucination
	Hallucination, auditory
	Hallucination, visual
	Hallucinations, mixed
	Illusion
	Paranoia
Panic attack	Panic attack
	Panic reaction
Suicidal events	Completed suicide
	Self-injurious behaviour
	Self-injurious ideation
	Suicidal ideation
	Suicide attempt
Convulsions	Grand mal convulsion
	Clonic convulsion
	Convulsion
	Epilepsy
	Febrile convulsion
	Partial seizures
	Status epilepticus
	Tonic convulsion
Depressed level of consciousness	Altered state of consciousness
	Consciousness fluctuating
	Depressed level of consciousness
Loss of consciousness	Syncope
	Loss of consciousness
Parasomnia	Abnormal dreams
	Nightmare
	Parasomnia
	Sleep terror
	Sleep walking
	Sleep talking
Accident/injury	Fracture
	Brain contusion
	Concussion
	Accident
	Accident at home
	Fall
	Injury
	Road traffic accident
	Contusion
	Femur fracture
	Lower limb fracture
	Pelvic fracture
	Fractured coccyx
	Lumbar vertebral fracture
	Rib fracture
	Upper limb fracture
Cognition disturbance	Confusional state
	Disorientation
	Thinking abnormal
	Amnesia
	Global amnesia
	Memory impairment
	Cognitive disorder
	Disturbance in attention
	Mental impairment
	Incoherent
Abnormal behaviour	Abnormal behaviour
Encephalitis	Encephalitis
	Encephalopathy
Miscellaneous – Psych	Anxiety disorder
	Obsessive-compulsive disorder
	Agitation
	Anxiety
	Compulsions
	Nervousness
	Fear
	Restlessness
	Expressive language disorder
	Logorrhoea
	Depressed mood
	Depressive symptom
	Morose
	Affect lability
	Flat affect
	Inappropriate affect
	Anger
	Dysphoria
	Emotional disorder
	Emotional distress
	Euphoric mood

Continued

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Table I. Contd

Category	Preferred Terms
	Moaning
	Mood altered
	Affective disorder
	Apathy
	Listless
	Aggression
	Social avoidant behaviour
	Regressive behaviour
	Hyperventilation
	Choking sensation
	Irritability
	Psychomotor hyperactivity

NPAEs were not a defined category in the trial protocols for oseltamivir. Neuropsychiatric events became topical some years after the drug was approved, and then mainly in Japan. We state this in our article. Furthermore, we agree with Jones et al.[1] that this leads to difficulties when trying to revisit the data. It is quite incorrect, however, that the definition of NPAE is not provided in detail. The case definition used is clearly and unambiguously given in section 1.1 of the review. With hindsight, it may not be clear from the wording of section 2 that we were in fact using the same definition of NPAEs, and we apologise for this possible oversight. Of note, the event terms and categories used in the analyses reported in sections 1 and 2 were agreed in advance with the US FDA, and the list of preferred terms for reference are detailed in table I. We geared our search terms towards the type of events being reported in Japan, notably abnormal behaviour, delirium, seizures, hallucinations and accidental injury. Other preferred terms classified under the Psychiatric Disorders and Neurological Disorders System Organ Classes (SOCs) did not appear in the list. For example, on-treatment events in the Psychiatric Disorders SOC that were not encompassed by our analysis include serious mental illnesses such as depression, bipolar disorder and psychoses including schizophrenia. Jones et al.[1] have included all Psychiatric Disorder preferred terms, so it is perhaps not surprising that their totals of 31 and 13 patients are much higher than in our review.

We therefore stand by our analysis, and trust that this answers the concerns of Dr Jones and colleagues. Far from 'cherry picking', our retrospective analysis of the results of the oseltamivir studies referred to was intended to reflect real-world experience and was carried out in cooperation with regulatory authorities, to whom Roche continues to provide adverse event data.

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on behalf of the wider author team

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