Title

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Journal

Annals of Pharmacotherapy, 49(12)

ISSN

1060-0280

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Publication Date

2015-12-01

DOI

10.1177/1060028015604631

Peer reviewed

Annals of Pharmacotherapy
1–6

DOI: 10.1177/1060028015604631
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Comparative Toxicity of Tapentadol and Tramadol Utilizing Data Reported to the National Poison Data System

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Abstract

Background: Tapentadol (TAP) and tramadol (TRA) provide pain relief through similar monoaminergic and opioid agonist properties. **Objective:** To compare clinical effects and medical outcomes between TAP and TRA exposures reported to the National Poison Data System of the American Association of Poison Control Centers. **Methods:** A retrospective cohort study was conducted analyzing national data for single medication TAP or TRA cases reported from June 2009 through December 2011. Case outcomes, dichotomized as severe versus mild; clinical effects; and use of naloxone were compared. **Results:** There were 217 TAP and 8566 TRA cases. Significantly more severe outcomes were associated with TAP exposures for an all-age comparison (relative risk [RR] = 1.24; 95% CI = 1.04-1.48), and for the <6-year-old age group (RR = 5.76; 95% CI = 2.20-15.11). Patients with TAP exposures had significantly greater risk of respiratory depression (RR = 5.56; 95% CI = 3.50-8.81), coma (RR = 4.16; 95% CI = 2.33-7.42), drowsiness/lethargy (RR = 1.38; 95% CI = 1.15-1.66), slurred speech (RR = 3.51; 95% CI = 1.98-6.23), hallucination/delusion (RR = 7.25; 95% CI = 3.61-14.57), confusion (RR = 2.54; 95% CI = 1.56-4.13) and use of naloxone (RR = 3.80; 95% CI = 2.96-4.88). TRA exposures had significantly greater risk of seizures (RR = 7.94; 95% CI = 2.99-20.91) and vomiting (RR = 1.96; 95% CI = 1.07-3.60). **Conclusion:** TAP was associated with significantly more toxic clinical effects and severe outcomes consistent with an opioid agonist. TRA was associated with significantly higher rates of seizures and vomiting.

Keywords

tapentadol, tramadol, toxicity, adverse effects

Background

Pain is a complex experience that is modulated through several mechanisms.[1] Tramadol (TRA) and tapentadol (TAP) are novel analgesics that provide pain relief through monoaminergic pathways by blockade of the reuptake of norepinephrine and serotonin as well as through opioid agonist properties.[2-5]

Tramadol (Ultram® by Janssen Pharmaceuticals, Inc.) is a bicyclic synthetic 4-phenyl-piperidine analog of codeine, with low affinity for the μ-opioid receptor. It is a racemic mixture and has an active metabolite. TRA has been approved to treat moderate to moderately severe pain in adults. Commonly reported adverse events from clinical trials with TRA include dizziness, nausea, dry mouth, and sedation.[6] Two observational studies of single-agent TRA exposures reported to poison control centers (PCCs) revealed a higher prevalence of seizures, tachycardia, and agitation compared with the frequency of cases of coma and respiratory depression.[7,8] TRA was recently rescheduled to a schedule IV substance under the Federal Controlled Substances Act.

Tapentadol (Nucynta® by Depomed, Inc.) is an orally active, centrally acting synthetic analgesic that acts via μ-opioid receptor agonism and norepinephrine reuptake inhibition. It exerts analgesic effects without a pharmacologically active metabolite. Commonly reported adverse events from clinical trials with TAP include nausea, vomiting, constipation, dizziness, somnolence, headache, and pruritus.[5] Reports of serious adverse effects are limited to

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forensic cases.[9,10] TAP is approved for the treatment of moderate to severe pain in adults and is a schedule II substance.

PCCs provide treatment advice and referral assistance to the public and health care professionals through toll-free emergency hotlines 24 hours a day. Each reported case is entered into a clinical database by trained specialists in poison information (SPIs). SPIs are health care providers with specialized training in clinical toxicology. SPIs enter into a database symptoms and treatment and outcome codes according to American Association of Poison Control Centers (AAPCC) criteria for each case. The National Poison Data System (NPDS) is managed by the AAPCC and contains the data from poison exposures and information calls from patients and health care providers to all PCCs across the United States. From mid-2009, 61 PCCs and 60 PCCs in 2010 and 57 in 2011 transmitted approximately 6 200 000 human case records to the NPDS.[11-13]

Objective

A review of the literature found no published clinical studies describing overdose or exposures of TAP or studies comparing the toxicity profiles of these two medications. The objective of this study was to compare differences in the reported toxicity of TAP and TRA by analyzing reports of exposures to the NPDS of the AAPCC. Although these medications have similar mechanisms of action, it would be beneficial to compare their toxicities to determine if there may be more potential for opioid-related toxicity as well as other non–opioid-related adverse effects between these medications.

Methods

A retrospective analysis of single-medication TAP or TRA exposure cases reported to the NPDS from June 2009 through December 2011 was conducted.

Data regarding clinical effects and outcomes were identified via codes assigned to cases designated by the SPI. Free text narratives were not available for evaluation. Outcomes were classified according to severity and defined by AAPCC criteria.[11-13] Cases were coded for outcome as follows: no effect; minor effect; moderate effect; major effect; death; not followed, judged as nontoxic; not followed, minimal clinical effects possible; unable to follow, judged as a potentially toxic exposure; confirmed nonexposure; unrelated effect; and death, indirect report.

Cases included in the study were any patient with a reported sole ingestion of TAP or TRA coded with a known outcome. Cases excluded from the analysis were those with a noningestion route; with outcomes that were unrelated; with confirmed nonexposure; not followed to a known medical outcome, which includes judged as nontoxic or minimal clinical effects possible, or if they were lost to follow-up, which includes unable to follow, judged as potentially toxic exposure.

Data were analyzed for age, gender, medication ingested, reason for exposure, clinical effects, use of naloxone, and medical outcome. Ages were categorized as <6, 6 to 12, 13 to 19, >19 years, and unknown age. These age groupings are the same as those used by the NPDS. Reasons for exposure include unintentional (unintentional general, therapeutic errors, unintentional misuse, and unknown), intentional (suspected suicides, misuse, abuse, and unknown), adverse reaction, unknown, and other. Clinical effects were coded as specific signs and symptoms and assessed by SPIs as related, unknown if related, or unrelated. Clinical effects coded as unknown if related or unrelated were excluded from the analyses.

This study was approved by the University of California, San Francisco Committee on Human Research and was granted exempt status. Statistical analysis was performed using OpenEpi version 3.03. Mean age data were compared using the *t* test. Gender, site of management, frequency of medical outcomes, clinical effects, and use of naloxone for TAP and TRA were compared by the Fisher exact test. Relative risk (RR) ratios and 95% CIs were also calculated. Bonferroni correction was applied to multiple comparisons. Medical outcomes were collapsed into two groups for comparison. One group was deemed mild outcome and included cases with medical outcome coded as no effect and minor effect. The other group was deemed as severe outcome and included cases with medical outcomes coded as moderate effect, major effect, and death. This approach was taken because of the small number of patients within each outcome category of moderate effect, major effect, or death as well as the small number of patients in the TAP group as compared with the TRA cohort.

Results

A retrospective search of the NPDS identified 1101 TAP and 56 739 TRA cases during the study period, June 2009 through December 2011. Figure 1 is an algorithm of evaluable cases and provides a summary of reasons for exclusion of cases. A total of 217 TAP and 8566 TRA cases met inclusion criteria.

Baseline characteristics of the 2 groups are contained in Table 1. There was a significant difference in mean age: 37.6 years for TAP (range = 9 months to 92 years) and 27.4 years for TRA (range = 6 days to 98 years); $P < 0.001$. The majority of exposures occurred in adults, age >19 years old—TAP, 81.6% (n = 177) and TRA, 64.1% (n = 5491)—followed by pediatric patients <6 years of age—TAP, 14.3% (n = 31) and TRA, 20.8% (n = 1785). There were very few TAP patients in the age groups 6 to 12 years and 13 to 19 years, making it difficult to draw any conclusions about these groups.

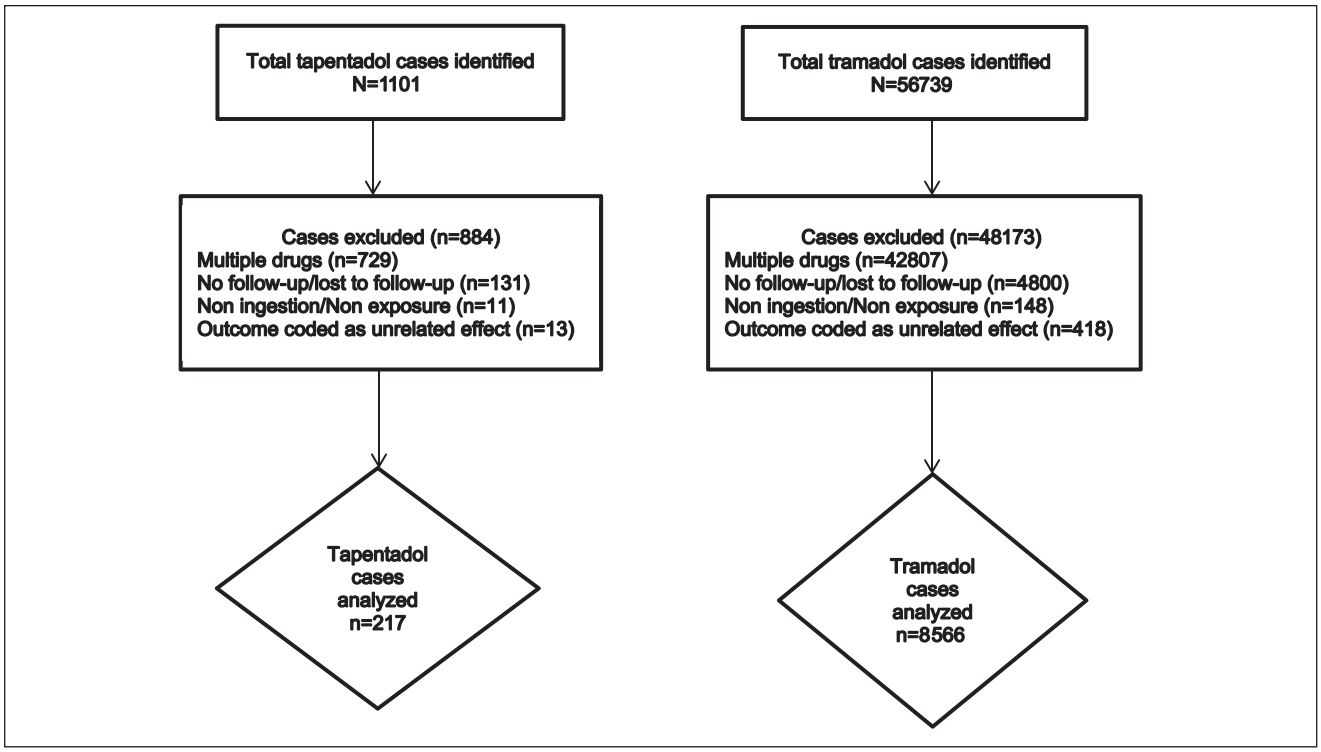

Figure 1. Study flowchart of evaluable cases.

Table 1. Comparison of Demographics and Site of Patient Management Between Tapentadol Exposures and Tramadol Exposures Reported to Poison Centers in the United States.

	Tapentadol (n = 217)	Percentage	Tramadol (n = 8566)	Percentage	*P* Value
Gender					
Male	84	38.7%	3731	43.6%	
Female	133	61.3%	4827	56.4%	$P = 0.17$
Unknown			8	0.1%	
Age					
Mean age, years (standard deviation, SD)	37.6 (SD = 21.3)		27.4 (SD = 19.9)		$P < 0.001$
<6 Years	31	14.3%	1785	20.8%	
6 to 12 Years	4	1.8%	178	2.1%	
13 to 19 years	5	2.3%	1088	12.7%	
>19 years	177	81.6%	5491	64.1%	
Unknown age			24	0.3%	
Site of management					
Health care facility[a]	161	74.2%	6548	76.4%	$P = 0.49$
Non–health care site	56	25.8%	2018	23.6%	

[a]Cases managed in a health care facility were treated/evaluated and released, admitted to a critical care unit, admitted to a noncritical care unit, or admitted to a psychiatric facility.

The most common reason for exposure for TAP and TRA was suspected suicide: TAP, 26.7% (n = 58), and TRA, 34.5% (n = 2956). In patients >19 years old, the most common reason for exposure was suspected suicide for TAP (31.6%, n = 56) followed by therapeutic error (24.9%, n = 44). For TRA, the most common reason was suspected suicide (43.4%, n = 2383) followed by intentional misuse (16.4%, n = 898). In patients <6 years old, unintentional ingestion accounted for 96.8% (n = 30) of TAP exposures and 97.9% (n = 1747) of TRA exposures.

The majority of patients in both groups experienced a mild outcome (TAP 62.7%, n = 136; TRA 69.8%, n = 5982).

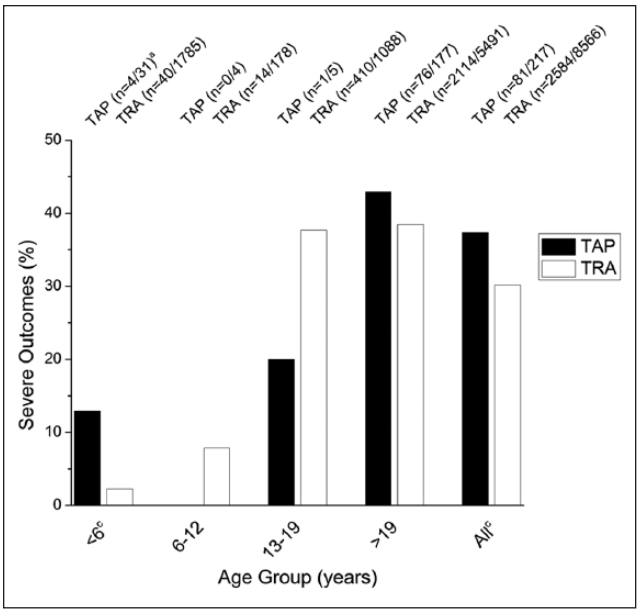

Figure 2. Comparison of severe outcomes[b] by age group between tapentadol (TAP) and tramadol (TRA) exposures.
[a]n, severe outcomes/total exposures.
[b]Severe outcome = sum of moderate effect, major effect, and death coded outcomes.
[c]Statistically significant relative risk (RR), 95% CI for risk of severe outcomes for TAP exposures: <6 years (RR = 5.76; 95% CI = 2.20-15.11), $P = 0.012$; all ages (RR = 1.24; 95% CI = 1.04-1.48), $P = 0.031$.

The coded outcomes were as follows: no effect (TAP 27.6%, n = 60; TRA 37.3%, n = 3195), minor effect (TAP 35.0%, n = 76; TRA 32.6%, n = 2787). TAP exposures had a greater risk of a severe outcome for an all-age comparison (RR = 1.24; 95% CI = 1.04-1.48; $P = 0.031$). The coded outcomes were as follows: moderate effect (TAP 31.8%, n = 69; TRA 25.2%, n = 2160), major effect (TAP 5.1%, n = 11; TRA 4.8%, n = 414), death (TAP 0.5%, n = 1; TRA 0.1%, n = 10). Outcome stratified by age group showed that patients <6 years old had greater risk for a severe outcome from TAP exposure (RR = 5.76; 95% CI = 2.20-15.11; $P = 0.012$). The coded outcomes were as follows: moderate effect (TAP 6.5%, n = 2; TRA 2.1%, n = 37), major effect (TAP 6.5%, n = 2; TRA 0.2%, n = 3), death (TAP 0.0%, n = 0; TRA 0.0%, n = 0). No statistically significant risk differences were observed for outcomes in the other age groups because of small sample size. A comparison of severe outcomes by age group is illustrated in Figure 2.

Clinical effects that occurred in >1% of patients were evaluated and are listed in Table 2. For TAP exposures, there was significantly greater risk of developing respiratory depression (RR = 5.56; 95% CI = 3.50-8.81; $P < 0.001$), coma (RR = 4.16; 95% CI = 2.33-7.42; $P < 0.001$), drowsiness/lethargy (RR = 1.38; 95% CI = 1.15-1.66; $P = 0.002$), slurred speech (RR = 3.51; 95% CI = 1.98-6.23; $P < 0.001$), hallucination/delusion (RR = 7.25; 95% CI = 3.61-14.57; $P < 0.001$), and confusion (RR = 2.54; 95% CI = 1.56-4.13; $P = 0.002$). Patients with TRA exposures had significantly greater risk of having seizures (RR = 7.94; 95% CI = 2.99-20.91; $P < 0.001$) and vomiting (RR = 1.96; 95% CI = 1.07-3.60; $P = 0.023$).

The frequency of naloxone use was significantly higher for TAP exposures as compared with TRA: 24.0% (n = 52) and 6.3% (n = 540), respectively (RR = 3.80; 95% CI = 2.96-4.88, $P < 0.001$). A significantly higher frequency of naloxone use was also observed in those <6 years old (RR = 5.40; 95% CI = 2.53-11.52; $P = 0.002$) and >19 years old (RR = 3.58; 95% CI = 2.73-4.69; $P < 0.001$) for TAP.

Discussion

In this study, TAP exposure was associated with a significantly greater risk of having a severe outcome. TAP was associated with significantly higher rates of respiratory depression, coma, drowsiness/lethargy, slurred speech, hallucination/delusion, and confusion. The use of naloxone was also significantly higher for TAP compared with TRA exposures. TRA was associated with higher rates of seizures and vomiting.

In a study by Spiller et al,[7] seizures occurred in 8%, vomiting in 6%, coma in 5%, and respiratory depression in 2% of their TRA patients. Marquardt et al[8] reported seizures in 13.7%, vomiting in 21.1%, coma in 1.6%, and respiratory depression in 0.5% of their TRA-exposed patients. Our TRA patients had rates of seizures of 14.6%, vomiting 9.0%, coma 1.3%, and respiratory depression 1.6%. These rates are consistent with those in prior reports. Our TAP patients had a much lower seizure rate of 1.8% and a diminished rate of vomiting at 4.6%. TAP exposures had a 5.5% incidence of coma and 8.8% rate of respiratory depression. TAP-associated respiratory depression occurred at a much greater rate than that for TRA in the present study as well as compared with the reported rates in the 2 prior TRA studies.

Spiller et al[7] attributed much of their observed TRA toxicity to monoamine uptake inhibition rather than its opioid effect. TRA's analgesia comes from relatively weak μ-opioid receptor agonism and norepinephrine and serotonin reuptake inhibition.[2] TRA is a racemic mixture. The (+) enantiomer possesses weak μ-opioid receptor activity and provides serotonin reuptake inhibition.[2,3] The (−) enantiomer provides norepinephrine inhibition.[2,3] TRA undergoes cytochrome P450 metabolism, predominantly via CYP2D6, which has pronounced genetic polymorphism, to its active metabolite, *O*-desmethyl TRA. This metabolite possesses greater μ-opioid receptor affinity than its parent but has lower central nervous system penetration.[2] TAP is itself pharmacologically active. It has much greater μ-opioid receptor potency than TRA and much greater central nervous system penetration than *O*-desmethyl TRA.[2] TAP's norepinephrine reuptake inhibition activity is similar to that of TRA, whereas its serotonin reuptake inhibition is weak.[2] TAP avoids

Table 2. Comparative Clinical Effects Associated With Tapentadol and Tramadol Exposures.

	Tapentadol		Tramadol				
	Total (n = 217)		Total (n = 8566)				
Clinical Effect	n	Percentage	n	Percentage	Relative Risk	95% CI	*P* Value
Drowsiness/Lethargy[a]	76	35.0	2178	25.4	1.38	1.15-1.66	0.002
Respiratory depression[a]	19	8.8	135	1.6	5.56	3.50-8.81	<0.001
Confusion[a]	16	7.4	249	2.9	2.54	1.56-4.13	0.002
Slurred speech[a]	12	5.5	135	1.6	3.51	1.98-6.23	<0.001
Coma[a]	12	5.5	114	1.3	4.16	2.33-7.42	<0.001
Hallucination/Delusion[a]	9	4.2	49	0.6	7.25	3.61-14.57	<0.001
Seizures[b]	4	1.8	1249	14.6	7.94	2.99-20.91	<0.001
Vomiting[b]	10	4.6	773	9.0	1.96	1.07-3.60	0.023
Tachycardia	31	14.3	1415	16.5	0.86	0.62-1.20	0.44
Dizziness/Vertigo	14	6.5	552	6.4	1.00	0.60-1.67	>0.99
Nausea	13	6.0	722	8.4	0.71	0.42-1.21	0.24
Hypertension	13	6.0	530	6.2	0.97	0.57-1.65	>0.99
Agitated/Irritable	12	5.5	467	5.5	1.01	0.58-1.77	>0.99
Tremor	8	3.7	209	2.4	1.51	0.76-3.02	0.34
Miosis	6	2.8	110	1.3	2.15	0.96-4.84	0.13
Hypotension	5	2.3	125	1.5	1.58	0.65-3.82	0.44
Pruritis	5	2.3	88	1.0	2.24	0.92-5.47	0.16
Dyspnea	5	2.3	83	1.0	2.38	0.97-5.80	0.13
Headache	3	1.4	96	1.1	1.23	0.39-3.86	0.89
Diaphoresis	2	0.9	207	2.4	0.38	0.095-1.53	0.21
Electrolyte abnormality	1	0.5	112	1.3	0.35	0.049-2.51	0.45

[a]Significantly higher rate of clinical effect in the tapentadol group.
[b]Significantly higher rate of clinical effect in the tramadol group.

the potential variable response patients have to TRA because of genetic variability in metabolism or drug-drug interactions. These pharmacological and pharmacokinetic differences may explain the higher rates of opioid effect caused by TAP.

The pharmacological reasons for the higher seizure risk with TRA are unclear. There are human cases and animal models that attempt to characterize this adverse effect.[7,14-20] In a rat and a mouse model, TRA, its enantiomers, and active metabolite were shown to induce seizures in rats with a lowered seizure threshold and at a seizure dose to antinociceptive dose ratio similar to that of codeine.[14,15] TRA has structural similarities and may possess some antidepressant activity similar to venlafaxine, which has been associated with seizures in several studies.[16-20]

Those younger than 6 years who have been exposed are a critical group to evaluate because of their susceptibility to the toxic effects of opiates and opioids. In human exposure cases involving both pharmaceuticals and nonpharmaceuticals, they make up almost half of the cases reported to the NPDS.[11-13] They account for >60 000 emergency department visits annually.[21] In this study, the reasons for exposure to both TAP and TRA in the age group <6 years were mainly unintentional. TAP patients aged <6 years old had a significantly higher risk of having a severe outcome. The limited number of cases precludes comparing individual clinical effects between TAP and TRA for this age group. Because of the potential for a severe outcome and until more data are available to define a minimally toxic dose in pediatric patients, patients <6 years of age with an unintentional exploratory ingestion of TAP should be referred to an emergency department for evaluation and observation.

Limitations of using NPDS data include missing or inaccurate information, coding errors, the inability to confirm exposure with blood levels or rule out coingestants, inability to read the free text field to more accurately characterize the circumstances of the exposure, and reporting bias. The rationale for comparing 2 different medications from the same database was that some of these limitations might be mitigated. Yet the mean age of the TAP group was higher than the mean age for the TRA cohort, a limitation of the study. Other limitations of the data are the large number of excluded cases and the difference in the cohort sizes.

The use of naloxone was observed to be significantly higher for TAP exposures as compared with TRA. Clinicians may not routinely consider naloxone for TRA cases because of risks of inducing seizures or are unclear of its efficacy. Also, the use of naloxone may or may not have been warranted. These are further limitations to the analysis.

Pharmacologically, there are plausible explanations for the increased opioid-like effects seen with TAP. Further prospective evaluation of TAP, its clinical effects, and toxic range, especially in pediatric patients, would be helpful in developing poison center triage guidelines.

Conclusion

Although these medications have similar mechanisms of action, TAP was associated with significantly more toxic clinical effects, which included respiratory depression and coma, and severe outcomes consistent with an opioid agonist. TRA was associated with significantly higher rates of seizures and vomiting.

Acknowledgment

The authors gratefully acknowledge Sylvia Hu, PhD, for providing statistical review.

Authors' Note

The data were previously presented as a poster at the 2012 Annual Meeting of the North American Congress of Clinical Toxicology. The views expressed by Dr Fung are her own and do not represent the views of either Genentech or Roche.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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