

Concomitant Use of Serotonergic Drugs with Zolmitriptan in a One-year Safety Trial

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Introduction and Objectives

- Serotonin syndrome is a potentially life-threatening set of symptoms caused by serotonin toxicity.
- It is defined as excessive serotonergic activity in the central and peripheral nervous systems. It results from increased serotonergic neurotransmission, primarily due to use of synergistic serotonergic medications¹ (Figure 2).
- Symptoms include any of the following²:

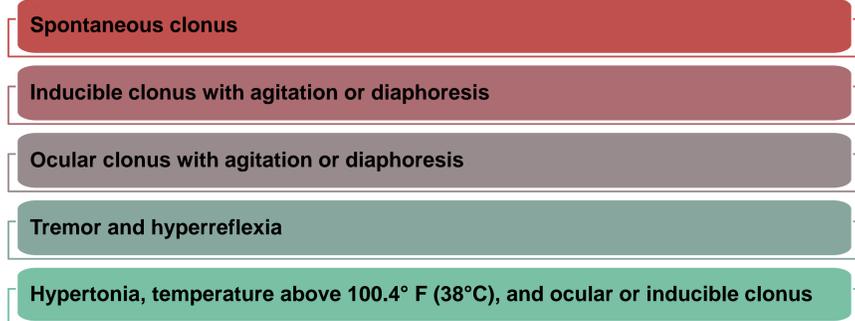


Figure 1. Hunter Serotonin Toxicity Criteria

Amphetamines and derivatives	Analgesics	Antidepressants/Mood Stabilizers
<ul style="list-style-type: none"> •Dextroamphetamine •3,4-methylenedioxymethamphetamine •Methamphetamine •Sibutramine 	<ul style="list-style-type: none"> •Cyclobenzaprine •Fentanyl •Meperidine 	<ul style="list-style-type: none"> •Buspirone •Lithium •Monoamine oxidase inhibitors •Selective serotonin reuptake inhibitors •Serotonin-norepinephrine reuptake inhibitors •Serotonin 2A receptor blockers •St. John's wort •Tricyclic antidepressants
Antimigraine drugs	Antiemetics	Additional
<ul style="list-style-type: none"> •Carbamazepine •Ergot alkaloids •Triptans •Valproic acid 	<ul style="list-style-type: none"> •Metoclopramide •Ondansetron 	<ul style="list-style-type: none"> •Cocaine •Dextromethorphan •Linezolid •L-tryptophan •5-hydroxytryptophan

Figure 2. Medications that May Contribute to Serotonin Syndrome¹

- In the United States, all triptans carry a warning against concomitant use with serotonergic medications, specifically selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitor (SNRIs), in the Warnings and Precautions section of the package insert.
- Similarly, many serotonergic drugs carry a warning against concomitant use with triptans.
- Despite these warnings, some believe that the risk of serotonin syndrome resulting from concomitant use of triptans with SSRIs and SNRIs is not supported by reliable data, and that those with coexisting affective conditions and migraine need not forgo management of one condition to treat the other.³
 - In a data registry study of nearly 50,000 patients prescribed triptans, 21-29% were co-prescribed an SSRI or SNRI. The incidence of serotonin syndrome was 0-4 cases per 10,000 person-years of exposure.³
 - In this study, prescriptions spanned a 14-year period; co-prescription of triptans and SSRIs or SNRIs was found to be common and not to taper following the FDA issuance of an advisory in 2006.³
- Adhesive Dermal-Applied Microarray (ADAM) is an investigational system that provides intracutaneous drug administration.
- ADAM zolmitriptan 2 X 1.9 mg (Qtrypta™) uses ADAM to administer zolmitriptan for the acute treatment of migraine
- In a pivotal phase 2b/3 randomized, double-blind, placebo-controlled study (ZOTRIP), ADAM zolmitriptan 2 X 1.9 mg met both co-primary endpoints of pain freedom and freedom from patients' usual other most bothersome symptom (MBS) two hours post-dose⁴
- A long-term safety study of ADAM zolmitriptan 2 X 1.9 mg was recently completed (see Nahas et al. Long-term Safety of Qtrypta™ for the Acute Treatment of Migraine – 1-year Safety Results of Nearly 6,000 Treated Attacks; present at this meeting).
- Though some serotonergic medications were not allowed during the trial, several subjects initiated one of these drugs at some point in the trial.
- We sought to analyze whether concomitant use of these medications affected the safety of the study drug with regard to serotonin syndrome.

Methods

- This was an open-label, 12-month, long-term safety study of ADAM zolmitriptan (M207) for the acute treatment of migraine (NCT03282227).
- Adults were eligible to participate if:
 - They had a ≥1 year history of episodic migraine
 - In the last 6 months they experienced 2 to 8 migraines per month with no more than 15 headache days per month
- Subjects self-administered ADAM zolmitriptan 2 X 1.9 mg to treat a qualifying migraine. Subjects were expected to treat multiple migraine attacks.
- The primary outcome measure was long-term safety as measured by incidence of adverse events and other safety measures over a 12 month period.
- We analyzed the study medication database for known serotonergic drugs. In addition, the adverse event database was queried for terms (per MedDRA 20.0) corresponding to Hunter Criteria for the diagnosis of serotonin syndrome⁵ (clonus, agitation, diaphoresis, tremor, hyperreflexia, hypertonia or fever). The frequency of these terms was compared between the two groups.

Results

- A total of 342 subjects were enrolled, 335 treated at least 1 migraine (safety population), 257 completed 6 months of the study and 127 completed 12 months.
- Demographics and baseline characteristics are shown in Table 1.
- The average (SD) number of treatments per month was 1.8 (0.9).
 - The number of subjects who treated on average 2 or more headaches per month (≥2 doses) for the first 6 months was 162 (48%).
 - The number of subjects who treated on average 2 or more headaches per month (≥2 doses) for the first 12 months was 89 (27%).
- A total of 96 subjects treated at least 25 migraine attacks and had post-treatment observations.
- In all 5963 migraine attacks were treated and more than 98,000 application site assessments were recorded by subjects.

Table 1. Patient Demographics and Baseline Characteristics (Safety Population, n = 335)

Mean (SD) Age, years	42.9 (12.1)
Female, n (%)	297 (88.7%)
Race, n (%)	
White	265 (79.1%)
Black or African American	55 (16.4%)
Other ^a	15 (<1%)
Mean (SD) BMI	29.2 (7.2)

^a includes Asian, native Hawaiian or other Pacific Islander, multiracial, other
BMI: body mass index, SD: standard deviation

- Twenty-two subjects (6.6%) reported being on serotonergic drugs while treating their migraines (Table 2).

Table 2. Serotonergic Drugs Taken Concomitantly^a with ADAM zolmitriptan 2 X 1.9 mg

Medication	n
TRAZODONE	8
TRAMADOL	6
NORTRIPTYLINE	3
AMITRIPTYLINE HYDROCHLORIDE	1
VENLAFAXINE HYDROCHLORIDE	1
SERTRALINE HYDROCHLORIDE	1
ESCITALOPRAM OXALATE	1
MIRTAZAPINE	1
VILAZODONE HYDROCHLORIDE	1

^aUsed while dosing with the study drug. One subject received more than one serotonergic medication.

- Table 3 shows adverse events occurring in >5% of subjects who took concomitant serotonergic drugs.
- None of the serotonin syndrome diagnostic terms were reported among subjects who were prescribed serotonergic drugs (nor in those who did not receive them).
- There were no reports of serotonin syndrome.

Table 3. Treatment-Emergent Adverse Events^a Occurring in >5% of Subjects who took Concomitant Serotonergic Drugs^b (n = 22)

Adverse Event	n (%)	Adverse Event	n (%)
Application site erythema	21 (96)	Pneumonia	2 (9)
Application site swelling	19 (87)	Sinusitis	2 (9)
Application site haemorrhage ^c	18 (82)	Upper respiratory tract infection	2 (9)
Application site bruise	12 (55)	Contusion	2 (9)
Application site pain	8 (36)	Ligament sprain	2 (9)
Application site discoloration	4 (18)	Anxiety	2 (6)
Nausea	2 (9)	Paraesthesia	2 (9)
		Pain in extremity	2 (9)

^a MedDRA 20.0 ^bUsed while dosing with the study drug ^cMost consisted of "pink color on skin" or "visible blood drop".

Conclusions and Discussion

- The results of this analysis suggest that a certain proportion of migraine patients will be prescribed triptans and serotonergic drugs concurrently, despite the warnings in the respective package inserts.
- However, in this limited sample there were no reported cases of serotonin syndrome, presumably the most serious complication of concomitant use.
- These findings lend further support to the argument that the risk of serotonin syndrome with concomitant use of triptans and serotonergic medications may be overstated.

References

1. Ables AZ, Nagubilli R. American Family Physician. 2010; 81(9):1139-1142
2. Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. QJM: monthly journal of the Association of Physicians. 2003; 96:635-642.
3. Orlova Y, Rizzoli P, Loder E. JAMA neurology. 2018; 75:566-572. <https://www.fda.gov/downloads/drugs/guidances/ucm419465.pdf>
4. Spierings EL, Brandes JL, Kudrow DB, Weintraub J, Schmidt PC, Kellerman DJ, et al. Cephalalgia: an international journal of headache. 2017

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