

# AHS Position Paper

## The FDA Alert on Serotonin Syndrome With Use of Triptans Combined With Selective Serotonin Reuptake Inhibitors or Selective Serotonin-Norepinephrine Reuptake Inhibitors: American Headache Society Position Paper

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**Background.**—In 2006, a US Food and Drug Administration (FDA) alert warned about the potential life-threatening risk of serotonin syndrome when triptans are used in combination with selective serotonin reuptake inhibitors (SSRIs) or selective serotonin/norepinephrine reuptake inhibitors (SNRIs). This American Headache Society Position Paper further reviews the available evidence of the potential risk of combining triptans with other serotonergic agents.

**Methods.**—Using the Sternbach Criteria or the Hunter Serotonin Toxicity Criteria, the 29 cases used as the basis for the FDA alert were assessed in addition to a more recently published clinical review of 11 case reports of serotonin syndrome resulting from monotherapy, and one report of combination serotonergic agents. Evidence was evaluated according to the American Academy of Neurology Clinical Practice Guideline Process Manual.

**Results.**—Collectively, 40 case reports are available in the literature for subjects receiving either combination or monotherapy of serotonin agonists, all of which are limited to Class IV level of evidence. Of the 29 cases used as the basis for the FDA alert, 10 cases actually met the Sternbach Criteria for diagnosing serotonin syndrome. No cases fulfilled the Hunter Criteria for serotonin toxicity. One case published since the original report does not meet either criteria, and subsequently reported cases involving triptan monotherapy include insufficient details to confirm a diagnosis of serotonin syndrome.

**Recommendations.**—With only Class IV evidence available in the literature and available through the FDA registration of adverse events, inadequate data are available to determine the risk of serotonin syndrome with the addition of a triptan to SSRIs/SNRIs or with triptan monotherapy. The currently available evidence does not support limiting the use of triptans with SSRIs or SNRIs, or the use of triptan monotherapy, due to concerns for serotonin syndrome (Level U). However, given the seriousness of serotonin syndrome, caution is certainly warranted and clinicians should be vigilant to serotonin toxicity symptoms and signs to insure prompt treatment. Health care providers should report potential cases to MedWatch and consider submitting them for publication.

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On July 19, 2006, the United States Food and Drug Administration (FDA) issued an alert, "Potentially Life-Threatening Serotonin Syndrome with Combined Use of SSRIs or SNRIs and Triptan Medications."<sup>1</sup> (An update was issued on November 24, 2006 adding sibutramine).<sup>2</sup> The FDA reported that there is the potential for life-threatening serotonin syndrome in patients taking 5-hydroxytryptamine receptor agonists (triptans) and concomitantly taking selective serotonin reuptake inhibitors (SSRIs) or selective serotonin/norepinephrine reuptake inhibitors (SNRIs) (listed in Table 1).

As summarized in the FDA alert, the recommendation is based on 29 case reports of serotonin syndrome that occurred in patients concomitantly treated with triptans and SSRIs/SNRIs, with the assumption of biological plausibility of such a reaction in persons receiving 2 serotonergic medications.<sup>1</sup> The FDA recommended that patients receiving a triptan and SSRI/SNRI medications be informed of the possible risk of serotonin syndrome.<sup>1</sup> The FDA now requires that this information be included as part of the prescribing information for triptans.

Based upon this alert, numerous patients and physicians have received warnings or recommendations from pharmacists that at least one of the medications (triptan or SSRI/SNRI) be discontinued. However, this recommendation is based on a limited number of anecdotal clinical reports. Consequently, using established criteria for diagnosing serotonin syndrome (eg, Sternbach Criteria and Hunter Serotonin Toxicity Criteria), an evidence-based review of the published clinical reports available to date is clearly warranted and provided below.

## BACKGROUND

**Migraine Is Co-Morbid With Depression, Anxiety, Panic, and Bipolar Disorder.**—Migraine is a very common disease with a 1-year period prevalence in the USA among those age 12 years and older of 11.7% (17.1% in women and 5.6% in men).<sup>3</sup> An additional 4.5% have probable migraine and 2% have chronic migraine.<sup>4</sup> Epidemiological studies also show that migraine is co-morbid (and/or coexisting) with various psychiatric disorders.<sup>5,6</sup> Specifically, these studies show that migraineurs are 2.2-4.0 times more

**Table 1.—Serotonergic Agents Affected by the FDA Alert**

| SSRIs or a combination drug containing an SSRI | SNRIs                      | Triptans or a combination drug containing a triptan |
|--|----------------------------|---|
| Celexa® (citalopram)                           | Cymbalta® (duloxetine)     | Amerge® (naratriptan)                               |
| Lexapro® (escitalopram)                        | Effexor® (venlafaxine)     | Axert® (almotriptan)                                |
| Luvox® (fluvoxamine)                           | Meridia® (sibutramine)†    | Frova® (frovatriptan)                               |
| Paxil® (paroxetine)                            | Pristiq® (desvenlafaxine)‡ | Imitrex® (sumatriptan)                              |
| Prozac® (fluoxetine)                           | Savella® (milnacipran)‡    | Maxalt® and Maxalt MLT® (rizatriptan)               |
| Symbyax® (olanzapine/fluoxetine)               |                            | Relpax® (eletriptan)                                |
| Zoloft® (sertraline)                           |                            | Sumavel DosePro®‡ (sumatriptan)                     |
|  |                            | TREXIMET®‡ (sumatriptan/naproxen sodium)            |
|  |                            | Zomig® and Zomig ZMT® (zolmitriptan)                |

†Added in updated 11/24/06 Alert.

‡New drugs since the issue of the Alert<sup>1</sup> that carry the warning.

SNRI = serotonin/norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

likely to have depression and are more likely to have generalized anxiety disorder (odds ratio [OR] 3.5-5.3), panic disorder (OR 3.7), and bipolar disorder (OR 2.9-7.3). Given these statistics, it is not surprising that some migraineurs who take triptans for acute migraine attacks also may be taking SSRIs and SNRIs for their co-morbid psychiatric disorders.

In an attempt to further assess the frequency of patients who require treatment with triptans and SSRIs, Shapiro and Tepper extrapolated co-prescription information using a large national pharmacy database.<sup>7</sup> The authors estimated that more than 185,000 Americans were exposed to co-treatment with a triptan and an SSRI for over a 1-month or greater period during 2000-2001.<sup>7</sup> Based on this extrapolation, and assuming that the 2000-2001 data are fairly representative of the years 1998-2002, nearly 1 million relevant patient-month exposures occurred with the combination of triptans and SSRIs during the period of the 29 reported FDA cases. Sclar and colleagues<sup>8</sup> further estimated that, during 2003-2004, an annualized mean of 694,276 patients were simultaneously prescribed or continued use of a triptan along with an SSRI or an SNRI.

**Defining and Recognizing Serotonin Syndrome.**—Serotonin syndrome is an adverse drug reaction resulting from increased serotonin levels, which stimulate central and peripheral postsynaptic serotonin receptors, in particular serotonin 5-HT<sub>2A</sub> receptors. Prior to the FDA alert, selected medications associated with serotonin syndrome or toxicity have included SSRIs, SNRIs, monoamine oxidase inhibitors, tricyclic antidepressants, opiate analgesics, over-the-counter cough medicines, antibiotics, weight-reduction agents, anti-emetics, drugs of abuse, and herbal products.<sup>9</sup> As an example, the incidence of serotonin syndrome among patients on monotherapy with the SSRI, nefazodone, has been estimated to be 0.4 cases per 1000 patient-months of treatment.<sup>10</sup>

Serotonin syndrome presents with 1 or more clinical features including a potential triad of mental status changes, dysautonomia, and neuromuscular dysfunction.<sup>9,11,12</sup> The mental status changes are diverse and may include anxiety, agitation, confusion, delirium and hallucinations, drowsiness, seizures, and coma. Severity of these symptoms may be mild to

severe. Autonomic hyperactivity occurs in about 50% of patients and may include hyperthermia, diaphoresis, sinus tachycardia, hypertension, hypotension, flushing of the skin, diarrhea, mydriasis, or vomiting. The neuromuscular dysfunction can include akathisia, myoclonus, hyperreflexia, muscle rigidity, tremor, nystagmus, and severe shivering.<sup>9,11,12</sup> Symptoms and signs may range from diarrhea and tremor in mild cases to life-threatening complications such as seizures, coma, rhabdomyolysis, and disseminated intravascular coagulation.

Sixty percent of patients with serotonin syndrome present within 6 hours of medication initiation, overdose, withdrawal, or change in dosage and 74% present within 24 hours.<sup>13</sup> As excess serotonin levels can present with a spectrum of toxicity from mild cases in which medication(s) can be continued with close observation, to severe and life-threatening cases requiring cessation of the medication(s), depending upon the intrasynaptic concentration, some authors prefer the term “serotonin toxicity” to serotonin syndrome.<sup>14</sup>

The diagnosis of serotonin syndrome is based upon the history of medication use, the physical examination, and exclusion of other neurological disorders such as meningoencephalitis, delirium tremens, heat stroke, neuroleptic malignant syndrome, malignant hyperthermia, and poisoning from anticholinergic drugs (summarized in Table 2). The diagnosis is suggested with a sensitivity of 84% and specificity of 97% (as compared to the gold standard of diagnosis by a medical toxicologist in patients who overdosed on a serotonergic drug) by the Hunter Serotonin Toxicity Criteria (Box 1).<sup>14</sup>

#### **Box 1.—Hunter Serotonin Toxicity Criteria<sup>14</sup>**

In the presence of a serotonergic agent and one of the following symptoms:

- Spontaneous clonus
- Inducible clonus and agitation or diaphoresis
- Ocular clonus and agitation or diaphoresis
- Ocular clonus or inducible clonus
- Tremor and hyperreflexia
- Hypertonia and temperature >38°C and ocular clonus or inducible clonus

Table 2.—Manifestations of Severe Serotonin Syndrome and Related Clinical Conditions†

| Condition                      | Medication history      | Time needed for condition to develop  | Vital signs  | Pupils    | Mucosa     | Skin                            | Bowel sounds        | Neuromuscular tone                                | Reflexes   | Mental status              |
|--------------------------------|-------------------------|---|--|-----------|------------|---------------------------------|---------------------|---|--|----------------------------|
| Serotonin syndrome             | Pro-serotonergic drug   | <12 hours   | Hypertension, tachycardia, tachypnea, hyperthermia (>41.1°C)                         | Mydriasis | Sialorrhea | Diaphoresis                     | Hyperactive         | Increased, predominantly in lower extremities     | Hyperreflexia, clonus (unless masked by increased muscle tone) | Agitation, coma            |
| Anticholinergic "toxidrome"    | Anticholinergic agent   | <12 hours   | Hypertension (mild), tachycardia, tachypnea, hyperthermia (typically 38.8°C or less) | Mydriasis | Dry        | Erythema, hot and dry to touch  | Decreased or absent | Normal  | Normal   | Agitated delirium          |
| Neuroleptic malignant syndrome | Dopamine antagonist     | 1-3 days  | Hypertension, tachycardia, tachypnea, hyperthermia (>41.1°C)                         | Normal    | Sialorrhea | Pallor, diaphoresis             | Normal or decreased | "Lead-pipe" rigidity present in all muscle groups | Bradyreflexia  | Stupor, alert mutism, coma |
| Malignant hyperthermia         | Inhalational anesthesia | 30 minutes to 24 hours after administration of inhalational anesthesia or succinylcholine | Hypertension, tachycardia, tachypnea, hyperthermia (can be as high as 46.0°C)        | Normal    | Normal     | Mottled appearance, diaphoresis | Decreased           | Rigor mortis-like rigidity                        | Hyporeflexia   | Agitation                  |

†From Boyer et al<sup>9</sup> with permission.

The Hunter criteria have not been validated in patients who develop serotonin toxicity on therapeutic doses of serotonergic agents (either single agents or as a drug interaction). Other diagnostic criteria have been proposed that might better detect the full range of mild to severe cases, but are not completely validated.<sup>15,16</sup>

A second validated set of diagnostic criteria is the Sternbach Criteria (Box 2).<sup>17</sup>

**Box 2.—Sternbach Criteria for Serotonin Syndrome<sup>17</sup>**

1. Recent addition or increase in a known serotonergic agent
2. Absence of other possible etiologies (eg, infection, substance abuse, withdrawal, etc)
3. No recent addition or increase of a neuroleptic agent
4. At least 3 of the following symptoms: Mental status changes (confusion, hypomania), agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, or fever

Following an overdose of a serotonergic drug, the Sternbach Criteria suggest a serotonin syndrome diagnosis with a sensitivity of 75% and a specificity of 96%.<sup>14</sup> Despite these validated criteria, serotonin syndrome often remains underdiagnosed – perhaps because of its variable clinical manifestations and a general lack of awareness of the syndrome among clinicians.

Management of serotonin toxicity varies depending upon the severity of symptoms. Standard approaches may include<sup>18</sup>:

- Remove or modify responsible medications
- Provide supportive care
- Administer cyproheptadine (a 5-HT<sub>2A</sub> antagonist)
- Control agitation (if needed [eg, benzodiazepines])

- Treat autonomic dysfunction and/or hyperthermia (if needed)

With appropriate management, symptoms resolve within 24 hours for about 60% of patients, but drugs with long durations of action or active metabolites may cause prolonged symptoms.<sup>9</sup>

There is discussion regarding the exact transition point between tolerable side effects of serotonergic administration and a toxic serotonin syndrome requiring withdrawal of medication. Some patients with stable mild subacute or chronic symptoms fulfilling criteria for serotonin syndrome (such as mild tremor and hyperreflexia) might safely continue the medication with close observation.<sup>18,19</sup>

## DESCRIPTION OF THE ANALYTIC PROCESS

Under the direction of American Headache Society Clinical Action Team Chair, Gretchen E. Tietjen, MD, the physicians participating in this project were selected based on their expertise in the field of migraine and headache management. All participants had previously published on serotonin syndrome and toxicity. A PubMed search was performed from inception through March, 2010, using the recognized search terms triptans, serotonin syndrome, and serotonin toxicity. Supplemental literature search was done by reviewing the cited publications from selected relevant articles. The authors identified the selected publications and further extrapolated and interpreted relevant published data based upon serotonin toxicity syndrome criteria.

## ANALYSIS OF EVIDENCE

**Concomitant Administration of Triptans and Serotonin Agonists.**—The July 19, 2006 FDA alert reported the following findings:

The FDA has reviewed 27 reports of serotonin syndrome reported in association with concomitant SSRI or SNRI and triptan use. Two reports described life-threatening events and 13 reports stated that the patients required hospitalization. Some of the cases occurred in patients who had previously used concomitant SSRIs or SNRIs and triptans without experiencing serotonin syn-

drome. The reported signs and symptoms of serotonin syndrome were highly variable and included respiratory failure, coma, mania, hallucinations, confusion, dizziness, hyperthermia, hypertension, sweating, trembling, weakness, and ataxia. In 8 cases, recent dose increases or addition of another serotonergic drug to an SSRI/triptan or SNRI/triptan combination were temporally related to symptom onset. The median time to onset subsequent to the addition of another serotonergic drug or dose increase of a serotonergic drug was 1 day, with a range of 10 minutes to 6 days.<sup>1</sup>

This report sparked a series of further inquiries into the case reports and upon further review, it was noted that specific information about the reported cases was not available through standard published resources. Therefore, R. Evans requested that a complete report of the possible serotonin syndrome cases (plus 2 more than described in the original alert;  $n = 29$ ) be made available for public review under the Freedom of Information Act. Of the cases, 8 were published in the medical literature, and the other 21 cases were filed with the FDA through the MedWatch reporting system. No further description of the FDA's analytical process, diagnostic criteria used, or how its conclusions were reached have been made public regarding the 21 cases used as the basis for the alert.

**Evaluation of 29 FDA Cases Used as the Basis for the FDA Serotonin Syndrome Alert.**—In response to the request for information on these cases, a summary of the 29 cases was published elsewhere, including an overall rating of the quality of the cases based upon the information provided.<sup>20</sup> Additionally, these cases were further analyzed to determine if they met the Sternbach and/or Hunter diagnostic criteria for serotonin syndrome.

All of the cases reviewed were case reports and therefore are considered Class-IV evidence, as established by the American Academy of Neurology Clinical Practice Guideline Process Manual (2004 Edition).<sup>21</sup> The quality of the information substantiating many of the FDA cases reports is incomplete or anecdotal. Specifically, for 3 cases, pharmaceutical representatives submitted reports of putative inci-

dents; 1 case alleges only bilateral retinal detachments and clearly does not represent serotonin syndrome; and 2 of the published cases (26 and 28) failed to include important information such as vital signs or detailed neurological exams so the Hunter criteria could not be applied. Table 3 provides a limited overview of several cases and their documentation, which illustrates the format in which the cases were reviewed and the variability in case information reporting.

Of the 29 cases, 10 met the Sternbach Criteria, and none met the Hunter Criteria.<sup>20</sup> Even among those cases meeting the Sternbach Criteria, some questions arise with several of the cases. The Sternbach Criteria require exclusion of other disorders, which was lacking in 6 of the 29 cases (21%). For example, Case 1 appears to meet Sternbach Criteria, but the physicians diagnosed conversion disorder, and the noted serotonin syndrome symptoms occurred later, when the patient was not actually taking sumatriptan. Moreover, this patient also had symptoms of hives and wheezing, which while not exclusionary criteria for making the diagnosis of serotonin syndrome, also raise consideration of other diagnoses. Therefore, Case 1 was rated as not meeting either set of diagnostic criteria.

Case 24 met Sternbach Criteria, but the patient was noted to have had 2 prior similar episodes associated with the use of metoclopramide and naproxen for migraine. In addition, she was taking only sumatriptan and metoclopramide but was not taking an SSRI or SNRI.

Case 28 may very well be serotonin syndrome, but based on the limited information provided, does not meet established diagnostic criteria for serotonin syndrome. Subsequent to the FDA alert, Bonetto and colleagues reported what they described as a case of serotonin syndrome in a patient on eletriptan and fluoxetine, but this case also met neither Sternbach nor Hunter Criteria.<sup>2,22,23</sup>

**Triptan Monotherapy and Serotonin Syndrome.**—In a letter to the editor, Soldin and Tønning reported that triptans alone can cause serotonin syndrome based upon 11 clinical cases found from their search of the FDA's Adverse Event Reporting System.<sup>24</sup> The mean age of the patients was 39.9 years, with 3

Table 3.—Summary of Selected Cases Reported by FDA Alert<sup>1</sup>

| Reference case<br>Medications   | Case summary  | Quality rating of case <sup>†</sup><br>Sternbach <sup>17</sup> Criteria<br>Hunter <sup>14</sup> Criteria |
|---|---|--|
| Case 4<br>Sumatriptan tablets (dose NS)<br>Paroxetine (dose NS)   | Physician told sales representative that a patient (unspecified gender and age) developed medically serious serotonin syndrome. No details provided. Medications continued and symptoms resolved.   | ‡<br>Sternbach Criteria – No<br>Hunter Criteria – No   |
| Case 17<br>Sumatriptan 100 mg<br>Fluoxetine 20 mg/d   | 34 y woman. Several hours following administration of sumatriptan 100 mg and a second dose of sumatriptan 50 mg and fluoxetine, she experienced tightness of the chest and palpitations. Treatment with sumatriptan and fluoxetine was continued. Events were reported as resolved.   | §<br>Sternbach Criteria – No<br>Hunter Criteria – No   |
| Case 18<br>Rizatriptan 10 mg<br>Citalopram 20 mg/d; 4 mo  | 37 y woman. Patient took rizatriptan followed with symptoms of palpitation, tachycardia, tremor, “close syncope,” vomiting, diarrhea, and hyperthermia. Patient was not hospitalized. Rizatriptan discontinued. Patient had received medications prior without adverse reactions.   | §<br>Sternbach Criteria – Yes<br>Hunter Criteria – No  |
| Case 23 <sup>35</sup><br>Sumatriptan 6 mg sc<br>Sertraline 100 mg/d<br>Propranolol (dose NS)                      | 48 y woman. Ten minutes after administering sumatriptan sc for the first time, she became anxious, agitated, disoriented, and diffusely weak. She could not walk without assistance. In the emergency room, pulse was 120 with normal blood pressure and temperature. She was anxious and easily excitable with weakness, incoordination, and hyperreflexia in all 4 limbs. EKG and EEG were normal. Improvement in her mental status, speech, and motor control began within 3 hours of symptom onset and complete recovery within 24 hours. Sertraline was discontinued. When sumatriptan was combined with nortriptyline, she had no similar events. | ¶<br>Sternbach Criteria – Yes<br>Hunter Criteria – No  |
| Case 25 <sup>36</sup><br>Zolmitriptan tablets (dose NS)<br>Paroxetine 2X/d (dose NS)<br>Indoramine 2X/d (dose NS) | 25 y woman with migraine and depression. Patient took zolmitriptan for the first time and was pain free in 1 h. The next afternoon, she had a migraine and took 1 zolmitriptan and 1 paroxetine together. During the night, she developed diffuse sweating, hypertonia and myoclonus of the forelimbs, which resolved by morning. She discontinued indoramine but took another tablet of paroxetine 2 d after the prior dose. Patient was hospitalized after developing same symptoms and tachycardia, hyperreflexia, diarrhea, and agitation. All symptoms resolved in 3 days.   | ¶<br>Sternbach Criteria – Yes<br>Hunter Criteria – No  |
| Case 29 <sup>37</sup><br>Sumatriptan 25 mg pr<br>Paroxetine 20 mg/d (4 y)   | 65 y woman. Several hours after receiving sumatriptan suppository, she experienced tachycardia, agitation, hyperthermia, hypertension, and confusion. She was hospitalized and a diagnosis of serotonin syndrome was made. She made a full recovery within 48 hours.  | ¶<br>Sternbach Criteria – Yes<br>Hunter Criteria – No  |

<sup>†</sup>Quality of evidence rating: ‡ = poor; § = fair; ¶ = good; †† = excellent.

d = day(s); mo = month(s); NS = not specified; pr = rectal suppository; sc = subcutaneous; SNRI = serotonin norepinephrine-reuptake inhibitor; SS = serotonin syndrome; SSRI = selective serotonin-reuptake inhibitor; tab = tablet; y = year(s).

patients specifically coded as serotonin syndrome and 8 coded with additional terms indicative of the triad of clinical features of the serotonin syndrome.

These authors did not provide details of the cases, or an analysis of whether they met the Sternbach or

Hunter Criteria. In addition, the authors commented that symptoms in some of these cases usually resolved over several hours either with or without supportive treatment such as intravenous diphenhydramine. Since diphenhydramine is commonly used to treat

cholinergic and extrapyramidal toxicity, is not a standard treatment for serotonin syndrome, and in fact may actually exacerbate serotonin syndrome via inhibition of serotonin reuptake, assignment of the diagnosis of serotonin syndrome in some of these cases is suspect.

Full publication of the details of Soldin and Toning's cases would be of interest and potentially clarifying.<sup>25</sup> Their conclusions from these 11 case reports arise after over 10 million patients have used triptans worldwide since the launch of the first triptan (sumatriptan) in 1991.<sup>26</sup> Moreover, a prospective post-marketing safety study of the use of subcutaneous sumatriptan for up to 1 year among 12,339 migraineurs, including 1784 also taking SSRIs, found no cases of serotonin syndrome.<sup>27</sup>

## RECOMMENDATIONS

**Summary.**—Insufficient data are available to determine the risk of serotonin syndrome with the addition of a triptan to SSRIs/SNRIs or with triptan monotherapy. The currently available Class IV evidence does not support limiting the use of triptans with SSRIs or SNRIs, or the use of triptan monotherapy, due to concerns for serotonin syndrome. (Class IV evidence is based on uncontrolled studies, case series, case reports, or expert opinion.<sup>21</sup>)

**Conclusion.**—Level U.<sup>21</sup> Data are inadequate or conflicting. Given current knowledge on the risks of combining triptans with SSRIs/SNRIs, increased risks of serotonin syndrome are unproven.

**Recommendation.**—None. An evidence-based recommendation cannot be made at this time.<sup>21</sup>

## DISCUSSION

Given the seriousness of serotonin syndrome, caution is certainly warranted; clinicians should be vigilant to its symptoms and signs to ensure prompt treatment when an appropriate diagnosis is made.

It is possible that additional definite cases of serotonin syndrome may be reported by improving awareness of the syndrome and these risks of these potential drug interactions. If a health care provider has seen or sees a patient with serotonin syndrome due to triptans alone or in combination with SSRIs or SNRIs meeting criteria for the syndrome, they

should submit the case to the FDA on-line through MedWatch (<http://www.fda.gov/medwatch>), by fax, by mail, or by telephone (1-800-FDA-1088), and also consider submitting the case for publication in relevant medical journals. Post-marketing surveillance is certainly a challenge for all medications and various suggestions have been made for improvements.<sup>28</sup>

Given that patients now routinely receive warnings from their pharmacists when filling prescriptions for SSRIs, SNRIs and/or triptans, it would be prudent to avoid undue alarm by specifically discussing serotonin syndrome with patients when prescribing these medications. Compliance may also be increased by disclosing that an elevated risk of experiencing serotonin syndrome with triptans is currently unproven.

**Pharmacological Plausibility of Triptan Involvement in Inducing Serotonin Syndrome.**—Based upon their pharmacology, the involvement of triptans in contributing to a serotonin syndrome, either alone or in combination with other medications, seems implausible.<sup>7,29</sup> Triptans are high-affinity agonists at 5-HT<sub>1B</sub>/5-HT<sub>1D</sub>/5-HT<sub>1F</sub> subtype receptors with lower affinity for 5-HT<sub>1A</sub> receptors. Available evidence supports a model of serotonin syndrome due to activation of 5-HT<sub>2A</sub> receptors, with some questionable involvement of 5-HT<sub>1A</sub> receptors.<sup>19,30</sup> Sumatriptan and zolmitriptan acutely decrease 5-HT synthetic rate in several brain regions via the activation of 5-HT<sub>1</sub> autoreceptors that inhibit serotonin release.<sup>31</sup> Sumatriptan has been shown to inhibit release of serotonin from dorsal raphe nucleus in rat brain slices.<sup>32,33</sup> Zolmitriptan may also activate prejunctional 5-HT<sub>1B/1D</sub> autoreceptors, thereby lowering central serotonin release.<sup>34</sup> Collectively, these studies do not support the assertion that triptans increase serotonin levels.<sup>1</sup>

## CONCLUSIONS

It is not clear at this time what role, if any, triptans might play in contributing to serotonin syndrome with or without SSRIs or SNRIs. Of the 29 cases obtained from the FDA, only 10 cases actually met the Sternbach Criteria for diagnosing serotonin syndrome, and none met the Hunter Criteria.<sup>20</sup> One case published since the original alert met neither crite-

ria.<sup>22</sup> Putative cases of serotonin syndrome involving triptan monotherapy include insufficient details to confirm the diagnosis.<sup>25</sup> This review demonstrates that standardized criteria are warranted for evaluating serotonin syndrome in patients using triptan monotherapy, or using triptans in combination with drugs that increase cerebral serotonin. We suggest that newly published cases use both Sternbach and Hunter Criteria when documenting clinical reports on serotonin syndrome.

The July 2006 FDA alert stated: “This information reflects FDA’s preliminary analysis of data concerning this drug. FDA is considering, but has not reached a final conclusion about this information. FDA intends to update this sheet when additional information or analyses become available.” We propose that our current analyses warrant such an update. We urge the FDA to assemble an impartial advisory panel to review the available evidence and to consider whether the alert, and the resulting cautionary language in triptan prescribing information, should be rescinded or revised.

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