

Research Submissions

Concomitant Use of Triptan, and SSRI or SNRI After the US Food and Drug Administration Alert on Serotonin Syndrome

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Objective.—The present study was designed to discern the prevalence of concomitant use of a 5-hydroxytryptamine receptor agonist (triptan), and a selective serotonin reuptake inhibitor (SSRI) or a selective serotonin/norepinephrine reuptake inhibitor (SNRI) after the US Food and Drug Administration issued an alert regarding serotonin syndrome in 2006 and to contrast findings with data published prior to the federal warning.

Background.—In July 2006, the US Food and Drug Administration warned patients and health-care professionals to be aware that use of a triptan in combination with an SSRI or SNRI may result in a potentially life-threatening problem known as serotonin syndrome. In 2010, the American Headache Society published a position paper noting that there existed conflicting and insufficient information to discern the risk of serotonin syndrome with the use of triptan, and SSRI or SNRI, and that said Class IV data were not to be used as the basis for limiting the prescribing of triptan with SSRI or SNRI (Level U). Clinicians were cautioned as to the seriousness of serotonin toxicity and that monitoring was warranted.

Methods.—We used weighted data from the US National Ambulatory Medical Care Survey for years 2007 and 2008 to derive national estimates of the number of office-based physician–patient encounters (visits), documenting the concomitant use of triptan, and SSRI or SNRI. Results are compared with previously published findings for the years 2003 and 2004.

Results.—During the time-frame 2007-2008, an annualized mean of 5,256,958 patients were prescribed a triptan (vs 3,874,367 in 2003-2004, a 35.7% increase), and 68,603,600 patients were prescribed an SSRI or SNRI (vs 50,402,149 in 2003-2004, a 36.1% increase). An annualized mean of 1,319,763 patients were simultaneously prescribed or continued use of triptan, along with SSRI or SNRI (vs 694,276 in 2003-2004, a 90.1% increase).

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Conclusion.—Our study documents that 1.8% (1,319,763/73,860,558) of patients in 2007-2008 were prescribed triptan, and SSRI or SNRI (vs 1.3% in 2003-04, an increase of 38.5%). While this is a small fraction overall, the actual number of patients on a nationwide basis is substantial. What remains missing from the literature is documentation as to the number of cases of serotonin syndrome and resulting consequences (clinical and economic) because of the concomitant use of triptan, and SSRI or SNRI in the time-frame 2007-2008. Absent in these data, it remains difficult to assess the risk benefit associated with the use of triptan, and SSRI or SNRI.

Key words: drug-drug interaction, serotonin syndrome, serotonin/norepinephrine reuptake inhibitor, selective serotonin reuptake inhibitor, 5-hydroxytryptamine receptor agonist, US National Ambulatory Medical Care Survey

Abbreviations: FDA Food and Drug Administration, NAMCS US National Ambulatory Medical Care Survey, NCHS US National Center For Health Statistics, SNRI serotonin/norepinephrine reuptake inhibitor, SSRI selective serotonin reuptake inhibitors, triptan 5-hydroxytryptamine receptor agonist

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Migraine is a pervasive disease state with a 1-year period prevalence in the USA of 11.7% (17.1% in women and 5.6% in men) among persons aged ≥ 12 years.¹ An additional 4.5% of Americans experience probable migraine, with 2% having chronic disease.² Epidemiologic studies document that migraine is often comorbid (and/or coexisting) with psychiatric disorders.^{3,4} Consequently, migraineurs who have been prescribed a 5-hydroxytryptamine receptor agonist (triptan) for acute migraine attacks may also have been prescribed a selective serotonin reuptake inhibitor (SSRI) or a selective serotonin/norepinephrine reuptake inhibitor (SNRI).^{5,6}

In July 2006, the US Food and Drug Administration (FDA) warned patients and health-care professionals to be aware that use of a triptan in conjunction with an antidepressant, inclusive of an SSRI or SNRI, may result in a potentially life-threatening problem known as serotonin syndrome.^{7,8} Serotonin syndrome is characterized by restlessness, hallucinations, loss of coordination, tachycardia, rapid blood pressure changes, increased body temperature, overactive reflexes, nausea, vomiting, and diarrhea, and can range from mild to fatal.^{9,10}

In 2010, the American Headache Society published a position paper noting that there existed conflicting and insufficient information to discern the risk of serotonin syndrome with the use of triptan, and SSRI or SNRI, and that said Class IV data were not to be used as the basis for limiting the prescribing of triptan with SSRI or SNRI (Level U). Clinicians were

cautioned as to the seriousness of serotonin toxicity and that monitoring was warranted.¹¹

The present study builds on previous research using the US National Ambulatory Medical Care Survey (NAMCS) and was designed to discern the prevalence of concomitant use of triptan, and SSRI or SNRI after the US FDA Alert was published in 2006 and to contrast findings with data published prior to the federal warning.¹²

METHODS

Data from the NAMCS for the years 2007 and 2008 were used for this analysis.¹³ The NAMCS is a national probability sample designed and conducted by the US National Center for Health Statistics (NCHS) of the US Centers for Disease Control and Prevention. Data are collected by the US Bureau of the Census. The 3-stage probability sampling procedure, sampling variation, and estimation procedures for the NAMCS have been described in detail elsewhere.¹⁴ Briefly, the basic sampling unit is the office-based physician-patient encounter (office-based visit). The sampling frame for each year of the NAMCS is composed of physician names, as documented in the files maintained by the American Medical Association and the American Osteopathic Association, and classified therein as being involved in "office-based, patient care." Physicians who are federally employed, hospital-based, or principally engaged in teaching, research, or administration are

excluded from the NAMCS, as are anesthesiologists, radiologists, and pathologists.

An initial probability sample is drawn from primary sampling units consisting of counties, groups of counties, county equivalents (ie, parishes or independent cities), or towns and townships. Second, a probability sample is drawn from practicing physicians from within each of these primary sampling units. Finally, a systematic sample of office-based visits to an individual physician during a randomly assigned 1-week reporting period is collected. In turn, these patient records are weighed by the NCHS based on the probability of selection, differences in response rates, and the physician specialty distribution so as to yield unbiased national estimate of office-based visits within a given year.

The US NAMCS data collection form requested extensive information regarding patient characteristics, physician's diagnoses, prescribed pharmacotherapy, and the specialty of the reporting physician. A maximum of three diagnoses were to have been reported by their *International Classification of Diseases, 9th Revision, Clinical Modification* codes.¹⁵ Physicians were instructed to record the specific brand or generic name for all new and continued medications. Code numbers corresponding to each brand and generic name were assigned from the US National Drug Code (NDC) Directory.^{16,17} The primary class of pharmacotherapy to which each medication entry belonged was assigned using the NDC Directory prior to 2005 and via Lexicon Plus® (Denver, CO, USA) thereafter.¹⁸

Using a method previously employed to analyze the NAMCS, survey years 2007 and 2008 were merged in order to enhance the sample size and stability of results.^{12,19-23} We report estimated annualized mean values for the 2 survey years. Data were analyzed using SAS® (Release 9.1.3, SAS Institute, Inc., Cary, NC, USA).

RESULTS

During the time-frame 2007-2008, an annualized mean of 5,256,958 patients were prescribed triptan (vs 3,874,367 in 2003-2004, a 35.7% increase), and 68,603,600 patients were prescribed SSRI or SNRI (vs 50,402,149 in 2003-2004, a 36.1% increase). An

annualized mean of 1,319,763 patients were simultaneously prescribed or continued use of triptan along with SSRI or SNRI in 2007-2008 (vs 694,276 in 2003-2004, a 90.1% increase) (Table).

The majority of the 1,319,763 patients who were simultaneously prescribed or continued use of triptan along with an SSRI or SNRI in 2007-2008 were female (85.7% vs 84.1% in 2003-2004) and white (89.2% vs 85.8% in 2003-2004), and 75.8% were aged ≥ 40 years (vs 65.8% in 2003-2004). Approximately one third (32.9%) of the patients were treated by a general or family practice physician. This latter finding is in sharp contrast with that observed in the time-frame 2003-2004, wherein 65.7% of patients were treated by a general or family practice physician (a decrease of 49.9%). The percentage of office visits wherein patients were seen by a neurologist or psy-

Table.—Characteristics of Office Visits Among Patients Who Were Prescribed Both a Triptan and a Selective Serotonin Reuptake Inhibitor (SSRI) or a Selective Serotonin/Norepinephrine Reuptake Inhibitor (SNRI). Annualized Mean, 2003-2004, and 2007-2008. Source: U.S. National Ambulatory Medical Care Survey (NAMCS)

Characteristic	2003-2004, n (%)	2007-2008, n (%)
Prescribed a triptan, [†] and an SSRI [‡] or SNRI [§]	694,276 (100)	1,319,763 (100.0)
Female	583,825 (84.1)	1,131,027 (85.7)
Age, years		
<20	25,725 (3.7)	16,602 (1.3)
20-39	211,555 (30.5)	302,219 (22.9)
40-59	339,507 (48.9)	867,285 (65.7)
60+	117,489 (16.9)	133,657 (10.1)
Race		
White	595,767 (85.8)	1,177,094 (89.2)
Nonwhite [¶]	98,509 (14.2)	142,669 (10.8)
Physician specialty		
General/family practice	456,160 (65.7)	433,643 (32.9)
Internal medicine	133,196 (19.2)	219,431 (16.6)
Neurology	54,977 (7.9)	232,953 (17.6)
Psychiatry	22,713 (3.3)	74,638 (5.7)
Other	27,230 (3.9)	359,098 (27.2)

[†]Triptans: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan.

[‡]SSRI: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline.

[§]SNRI: desvenlafaxine, duloxetine, venlafaxine.

[¶]Includes Hispanics.

chiatrist increased significantly between 2007-2008 and 2003-2004 (122.8% and 72.7%, respectively).

COMMENT

Our study documents that 1.8% (1,319,763/73,860,558) of patients in 2007-2008 were prescribed triptan, and SSRI or SNRI (vs 1.3% in 2003-2004, an increase of 38.5%). Previous research by Tepper et al²⁴ found that among patients who had filled 2 or more triptan prescriptions in a 6 month period, 21% were simultaneously prescribed an SSRI. By employing the methodology used by Tepper et al²⁴ and thus limiting our denominator to only patients prescribed with triptan, we found that 25.1% (1,319,763/5,256,958) of patients were simultaneously prescribed SSRI or SNRI in 2007-2008 (vs 17.9% in 2003-2004, an increase of 40.2%).

The actual number of patients experiencing characteristics of serotonin syndrome because of the concomitant use of triptan, and SSRI or SNRI is unknown.^{11,25} Moreover, reports of serotonin syndrome are rare.⁷⁻¹⁰ This may be a result of practitioners being unaware of serotonin syndrome.⁷⁻¹⁰ However, our results indicate there existed a significant decrease (49.9%) in the percent of general or family practice physicians who prescribed or continued patients on a regimen of triptan, and SSRI or SNRI in 2007-2008, relative to 2003-2004, while the percentage of physicians specializing in neurology or psychiatry were more likely to have done so. The observed changes in the prescribing pattern for migraineurs may well have been a result of the US FDA Alert. That said, the total number of patients prescribed with triptan, and SSRI or SNRI increased by 90.1% between 2003-2004 and 2007-2008.

Experts have been critical of the 2006 US FDA Alert regarding the use of triptan in conjunction with antidepressant, inclusive of SSRI or SNRI, and the stipulation that co-administration may result in a potentially life-threatening problem known as serotonin syndrome.¹¹ The fundamental criticism stems from the fact that the US FDA based the Alert on a small case series (29 total) and that when Sternbach Criteria for the diagnosis of serotonin syndrome was applied, only 10 of the 29 cases were validated.¹¹ Moreover, when applying the more robust Hunter Criteria, no

cases were validated.¹¹ Thus, debate persists as to whether the US FDA was prudent in issuing the 2006 Alert or overcautious. To date, the US FDA has not issued an update to the 2006 Alert nor have there been any case series published in the peer-reviewed literature regarding the use of triptan in conjunction with antidepressant, inclusive of SSRI or SNRI, and the validated occurrence of serotonin syndrome. Finally, it needs to be stated that while computerized decision support systems afford clinicians with immediate counsel regarding potential interactions with pharmacotherapy, our data suggest that clinicians have concluded the risk of serotonin syndrome because of the use of triptan in conjunction with antidepressant, inclusive of SSRI or SNRI, is negligible.²⁵

Although we were able to quantify the extent of concomitant use of a triptan and an SSRI or SNRI on a nationwide basis, limitations inherent to the NAMCS did not allow for the identification of acute adverse reactions, including characteristics of serotonin syndrome. What remains missing from the literature is documentation as to the number of cases of serotonin syndrome due to the concomitant use of triptan, and SSRI or SNRI, and the resulting consequences (clinical and economic) in the time-frame 2007-2008.^{11,12,25} Absent in these data, it remains difficult to accurately assess the risk benefit associated with the use of triptan, and SSRI or SNRI.

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