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Use of a Bioinformatics-Based Toxicity Scoring System to Assess Serotonin Burden and Predict Population-Level Adverse Drug Events from Concomitant Serotonergic Drug Therapy

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Abstract

Study Objective—Numerous medications interact at serotonin (5-hydroxytryptamine [5-HT]) receptors directly or through off-target interactions, causing mild to severe serotonergic adverse drug events (ADEs), particularly among the elderly. Our objective was to develop a novel molecular-based toxicity scoring system to assess serotonergic burden resulting from concurrently administered drugs. Quantitative methods to assess serotonergic burden may provide a useful clinical tool for improving pharmacotherapy.

Design—Retrospective cohort study.

Data Sources—PharMetrics Legacy health claims database (January 2001–December 2013) and ChEMBL bioactivity database.

Patients—A 2-serotonergic drug exposure cohort (78,172 patients) and a 3-serotonergic drug exposure cohort (19,900 patients) were generated, and population-level statistics were collected. Nonexposure cohorts were created for each drug exposure cohort and matched in a 4:1 ratio for age, sex, and length of enrollment.

Measurements and Main Results—Eight 5-HT medications were screened against multiple bioactivity databases to identify their off-target interactions at 5-HT receptors and serotonin reuptake transporter protein. A computational serotonin burden score (SBS) was derived from the receptor-specific interaction propensities reported from the comprehensive bioactivity screen. Linear regression was used to characterize associations between SBSs and combined total ADE incidence rate detected by *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis codes. A significantly greater incidence of 17 potential 5-HT-related ADEs

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was seen in exposed serotonergic drug cohorts ($p < 0.05$). A positive correlation between SBS and overall ADE incidence rate in the 2-serotonergic drug exposure cohort ($R^2 = 0.69$, $p < 0.34$), and 3-drug cohort ($R^2 = 0.85$, $p < 0.01$) was observed. When both drug cohorts were combined, total drug SBSs strongly correlated with the composite 5-HT adverse event rate ($R^2 = 0.92$, $p < 0.0001$). Despite an increasing burden of illness, these data suggest that drug combinations with higher SBSs are associated with a higher rate of potential serotonergic ADEs.

Conclusion—In this test-of-concept, positive associations between SBSs and serotonin-related ADEs suggest that it may offer a pharmacologic-based foundation for developing risk assessment tools to assist in optimizing pharmacotherapy.

Keywords

serotonin; serotonin toxicity; serotonergic adverse drug events; serotonin receptors

Serotonin (5-hydroxytryptamine [5-HT]) toxicity is most commonly reported in the clinical setting of serotonin syndrome, a rare but potentially fatal adverse drug event (ADE) resulting from excessive accumulation at serotonergic receptors. A classic triad of symptoms involving behavioral changes, autonomic dysfunction, and somatic symptoms is now well described, and specific criteria are available to assist clinical diagnosis^{1–3}.

Very little is known, however, about less serious forms of serotonin-mediated toxicity that may include milder manifestations of agitation, tremor, irritability, muscular incoordination, diarrhea, or confusion. Our previous work has characterized the potential interactions of 71 United States Food and Drug Administration–approved drugs at one or more serotonin receptor subtypes and off-target neurotransmitter activity⁴. These drugs encompass multiple therapeutic categories and tend to be commonly prescribed. For example, two of the most commonly prescribed serotonergic drug classes, tricyclic antidepressants (TCAs) and serotonin reuptake inhibitors (SRIs), which include selective SRIs (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), accounted for use by 1 in 10 persons aged 12 years and older in the United States in 2011⁵. Thus, concurrent administration of drugs with either known or off-target serotonergic activity is likely but may go unrecognized.

A clinical review of SSRI adverse effects and tolerability lists 37 potential serotonin-mediated ADEs⁶, and a meta-analysis comprising 84 well-controlled studies reports 18 adverse drug events associated with TCAs and SRIs, suggesting that ADEs are common. A crude ADE rate of greater than 10% was reported for 14 of 18 adverse effects for SSRIs and 11 of 18 for TCAs⁷. Currently, to our knowledge, no method exists for assessing cumulative toxicity resulting from combinations of serotonergic medications. Moreover, mild serotonin-mediated ADEs may be difficult to distinguish from disease-related manifestations, especially mental health disorders. The health care consequences arising from undetected mild toxicity may be significant, including addition of medications to treat drug-induced ADEs (i.e., polypharmacy), additional clinic and hospital costs, and poor quality of life. Methods are needed to investigate the potential for cumulative toxicity arising from concurrently administered serotonergic agents and eventually develop clinical tools for estimating individual patient risk.

This investigation was undertaken to assess potential mild to moderate serotonin-related toxicity resulting from concurrently administered serotonergic drugs. The serotonin burden score (SBS), derived from interactions at eight therapeutically relevant serotonergic receptor subtypes, was used to predict a composite ADE endpoint using a commercial health care claims database.

Methods

Serotonin Receptor Interactions

This study builds on our earlier work in which the Serotonin Expanded Biomedical Matrix (SEBM) was developed to characterize serotonergic drug interactions at 13 serotonin receptor subtypes, serotonin and norepinephrine transporter proteins, and antimuscarinic receptors⁴. An in-house bioinformatics Web service, TargetSearch (<http://dxulab.org/software>) was developed to mine publicly available ChEMBL, a pharmacologic database for relevant drug-receptor interactions and functional activity⁸. The TargetSearch bioinformatics approach leverages large bioactivity databases and advanced molecular fingerprinting algorithms to detect and evaluate known interactions and off-target poly-pharmacology in a rapid and systematic fashion.

For the purposes of this preliminary investigation, a subset of eight receptor targets was used. Each drug's molecular structure was retrieved from the DrugBank database⁹ and used as TargetSearch queries to search ChEMBL for known and off-target interactions with 5-HT receptors (1A-B, 2A-C, 6, and 7), serotonin reuptake transporter (SERT) protein. The widely used rapid overlay of chemical structures (ROCS) algorithm¹⁰ was used in the bioinformatics screening. A 10- μ M activity cutoff was used to ensure a high-level of confidence in identifying relationships within the human interactome. This computational approach efficiently accounts for the interaction of drugs at these receptors and has been shown to effectively capture drug off-target interactions¹¹ and measure drug-induced toxic burden^{12, 13}. The concordance of documented versus experimentally derived receptor interactions as been previously described⁴.

The relative strength of drug-receptor interactions—essentially how likely a molecule fits into the receptor complex—utilizes a continuous scale from 0 to 1.0 where a high-propensity interaction is equal to 1.0 and lower propensities are represented by scores <1.0. A zero denotes an inability to identify any similar molecular entity (out of 1.5 million molecular candidates) that possesses a known or inferred interaction at that specific receptor.

Study Design, Data Sources, and Data Collection

This retrospective cohort study used the PharMetrics Legacy health plans claims database, a longitudinal dataset comprising paid medical and pharmacy insurance claims from over 80 managed care programs throughout the United States and representing over 75 million unique patients. The data are considered representative of the U.S. commercially insured population with respect to age and sex.¹⁴ Variables available on each claim include up to four *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnostic codes; procedures; medications filled (drug code, days supplied); service

dates; place of service (inpatient, outpatient, emergency department); and type of provider. Demographic characteristics such as year of birth, sex, and region of residence are also available.

Comorbidities were assessed by using the Charlson Comorbidity Index (CCI)¹⁵ and the Chronic Disease Indicator (CDI)¹⁶ score. The CCI uses medical claims to assign a comorbidity score based on the number and severity of 19 predefined comorbid conditions. The CDI uses medication claims to determine the number of chronic diseases. Age in years (at the time of their earliest study medication fill), sex, region of residence (South, Midwest, West, East), and Medicare status (yes/no) were available for each patient.

A 10% random sample of the entire PharMetrics Legacy claims data from January 2001 through December 2013 was obtained by the study team and used to identify a retrospective cohort of patients exposed to study medications using the following criteria: (1) filled at least one of the eight selected 5-HT medications; (2) had at least one year of continuous health plan enrollment prior to and 3 months of continuous health plan enrollment following their earliest 5-HT medication fill; (3) had no 5-HT related ADEs during the 180 days prior to their earliest 5-HT medication fill; and (4) were aged 5 years or older at the time of their earliest study medication fill. This study received exempt status from the Idaho State University Institutional Review Board.

Exposure to Serotonergic Study Medications

A subset of eight serotonergic drugs were selected in order to limit the potential drug combinations to a manageable number (719 potential combinations). The eight drugs were chosen because they represent commonly prescribed medications from different therapeutic drug classes and a relatively uniform range of SBSs (1.0 to 7.5). The PharMetrics drug dispensing history extracted from computerized pharmacy records is an excellent source of medication data that is not subject to information bias and has high concordance with medication use as reported by patients¹⁷. The general product identifier (GPI-8) code of each drug was obtained from Find-A-Code (available from findacode.com). GPI-8 encodes hierarchical information regarding drug group, class, subclass, and name. Using GPI-8 allowed an efficient search by capturing all formulations, dosage forms, and strengths of a drug of interest. A 30-day window was searched for ICD-9-CM codes relating to potential serotonergic adverse effects after addition of each new study medication (e.g., drug start 2; drug start 3). Nonexposure cohorts were created for each drug exposure cohort and matched in a 4:1 ratio for age, sex, and length of enrollment. Both exposed and nonexposed cohorts may have included patients with other nonstudy serotonergic drugs, but it was assumed this drug use would occur in a random and normally distributed manner throughout each cohort. Figure 1A is a schematic of the study design, and Figure 1B lists the eight serotonergic drugs.

Potential Serotonin-Related Adverse Drug Events

Potential adverse drug effects representing milder presentations of serotonergic toxicity were taken from Sternbach's criteria in which a combination of three of a potential 10 adverse effects is needed to diagnosis serotonin syndrome (see Discussion section)². We

hypothesized that any of the 10 adverse effects occurring individually may represent an early or milder presentation. Therefore, we identified 17 ICD-9-CM codes closely matching Sternbach's 10 symptoms. Although confounding by indication is a potential concern for some symptoms, no attempt to control for this was made in order to determine if potential drug adverse effects could be differentiated from comorbidity-related symptoms (i.e., a real-world situation).

The first occurrence of each ADE during the follow-up period was captured. In order to define a broad spectrum of adverse drug effects, a composite incidence rate including any symptom or combination of symptoms was identified. For each patient, indicator (yes/no) variables were created for each of the 17 ADEs. The total number of distinct ADEs per patient was also calculated. Drug exposure cohorts were identified based on exposure to two or three serotonergic study drugs.

Serotonin Burden Score (SBS)

Given the paucity of clinical data relating specific adverse effects to individual serotonin receptors, all receptor interactions were given equal weighting, and a simple additive activity was assumed. Thus, an SBS score for each serotonergic drug was calculated by summing the interaction propensities at each of the eight sub-receptor types, and the eight drugs were selected because they represent a relatively uniform range of scores between 1.0 for trazodone and 7.5 for amitriptyline. The 2- and 3-drug cohorts were searched for one or more ADEs within the 30-day post-drug window following a new start of a study medication. Total SBS was calculated by summing individual drug scores (e.g., 3-drug cohort: $\text{total SBS} = \text{SBS}_{\text{Drug1}} + \text{SBS}_{\text{Drug2}} + \text{SBS}_{\text{Drug3}}$). For example, a total regimen SBS of 10 could arise from the combination of aripiprazole, sertraline, and cyclobenzaprine ($4.2 + 4.0 + 1.8 = \text{total regimen SBS of } 10$).

Statistical Analysis

Demographic and clinical information were compared by using analysis of variance tests for continuous variables, (e.g., age, length of follow-up) and a χ^2 test for categorical variables (e.g., sex, region). The incidence rates for the 17 identified adverse events were examined individually for differences between exposed and nonexposed cohorts, using a χ^2 test. To account for the multiple comparisons in Table 2, a Bonferroni correction was applied, resulting in a p value less than 0.003 being considered to indicate a statistically significant difference. To examine a dosing relationship between serotonin burden and incidence rate of adverse events, the data were binned by total SBS score for 2-drug and 3-drug combinations. Eight bins were created (1 to 2.99, 3.0 to 4.99, 5.0 to 6.99, etc.). An incidence rate was calculated within each bin. The relationship between SBS bin and the incidence of adverse events was evaluated by using a linear regression. The 2-drug and 3-drug cohorts were analyzed separately.

Although a potential limitation, adjustment for disease severity was not undertaken. Instead, within drug cohort, correlations were performed to evaluate the dose response effect within a lower disease severity group (i.e., 2-drug cohort) versus a higher disease burden (3-drug cohort) as measured by the CDI and CCI.

Results

Demographic and clinical characteristics of the study populations are presented in Table 1. Mean age of the 2-drug cohort was 43.7 years (range 5–84 yrs), 91.1% were aged < 65 years, and 61.7% were female. Similarly, the mean age of the 3-drug exposed cohort was 42.6 years (range 5–83 yrs), 94.1% were < 65 years, and 72.2% were female. The study population was predominantly non-Medicare (97%), reflecting the commercially insured data source.

Comorbidities were measured using the Chronic Disease Index (CDI) and Charlson Comorbidity Index (CCI). Patients in the 2-drug cohort had a mean CDI of 4.3 versus 2.4 for nonexposed matched patients ($p < 0.0001$) and a mean CCI of 1.2 versus 0.7 for nonexposed patients ($p < 0.0001$). Patients exposed to 3 serotonergic drug combinations had a mean CCI of 1.6 versus 0.7 ($p < 0.0001$) for nonexposed matched patients. Patients in the 2-drug and 3-drug cohorts had higher number of potential ADEs compared to the nonexposed cohorts.

As shown in Table 2, all 17 potential drug-related ADEs were associated with significantly higher rates in both 2-drug and 3-drug exposed cohorts versus nonexposed patients matched for age, sex, and length of enrollment. The most common ADEs were associated with a rate incidence of diarrhea of (11.2% vs 4.7%, $p < 0.0001$, 2-drug cohort) and (20.6% vs 6.3%, $p < 0.0001$, 3-drug cohort); abnormal gait (4.7% vs 1.8%, $p < 0.0001$, 2-drug cohort) (7.1% vs 2.0%, $p < 0.0001$, 3-drug cohort); and unspecified fever (3.7% vs 1.7%, $p < 0.0001$, 2-drug cohort) (6.2% vs 2.3%, $p < 0.0001$, 3-drug cohort). Myoclonus, a potential hallmark symptom of severe toxicity, was associated with a significantly higher rate in 2-drug exposed versus unexposed patients (0.2% vs. 0.0%, $p < 0.0001$) and 3-drug exposed patients (0.3% vs. 0.1%, $p < 0.0001$).

Figure 1B presents the eight serotonergic drugs and their individual 5-HT receptor subtype propensity scores as computed by SBS. A simple sum of the individual receptor scores was used to calculate the total SBS drug score. Upon identification of a potential ADE, the total regimen SBS (summed score of each individual drug) was reported.

Figure 2 shows the correlation coefficient after combining both the 2-drug and 3-drug cohorts. The total regimen SBS in 2-point increments is plotted against the composite ADE incidence rate. A strong positive correlation is observed ($R^2 = 0.92$, $p < 0.0001$).

The combination regimen SBS versus the composite ADE incidence rate correlation coefficients are presented in Figure 3 for the individual 2-drug cohort and Figure 4 for the 3-drug cohort. Within the patient cohort receiving 2 serotonergic drugs (SBS range 2–12), a modest positive correlation is seen ($R^2 = 0.69$, $p < 0.34$). Figure 3 represents a similar correlation when limited to the 3-drug patient cohort, where a strong positive correlation is observed ($R^2 = 0.85$, $p < 0.01$).

Discussion

A plethora of drug-drug interaction literature seeks to identify mechanisms that influence drug therapy through alterations in drug pharmacokinetics. Without question, understanding

these mechanisms has led to improved drug therapy and facilitated the development of safer medications. However, very little is known about pharmacodynamic drug-drug interactions where drugs acting at the same target receptor or through polypharmacologic targets may augment pharmacodynamic activity resulting in toxicity. Currently, the best example is toxicity resulting from cumulative anticholinergic (AC) drug therapy. Attempts to quantitate activity resulting from concurrently administered AC drugs has resulted in at least nine quantitative scales^{18, 19}. Despite their relatively subjective ranking of anticholinergic activity, concurrently administered AC drugs with higher AC scores have correlated with increasing severity of dementia^{20, 21}, cognitive impairment^{22, 23}, and fracture²⁴. Similarly, serotonergic drugs represent a diverse spectrum of therapeutic drug classes, and as observed from the number of patients receiving combinations of just eight drugs, concurrent administration is common.

Severe versus Mild Serotonin Toxicity

Two widely used serotonin toxicity criteria—Sternbach's criteria² and the Hunter Serotonin Toxicity Criteria²⁵—provide different approaches but useful guidance in the clinical diagnosis of serotonin syndrome. Hunter's criteria consists of an algorithm-like decision tree that targets spontaneous clonus as a hallmark sign followed by inducible or ocular clonus or tremor in conjunction with additional symptoms of agitation, diaphoresis, hypertonia with pyrexia, or hyperreflexia.²⁶ Alternatively, Sternbach's criteria lists 10 symptoms—mental status changes, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever; at least three of these 10 symptoms are required to denote a serotonin syndrome diagnosis. However, controversy remains as to which criteria provide the most accurate assessment of severe serotonin toxicity.

Recently, Werneke et al challenged the superiority of Hunter's criteria because it was derived solely from SSRI overdoses and called for more focus on potential etiologies²⁷. Analysis of the FDA Adverse Event Reporting System (FAERS) of serotonin syndrome cases by our group suggests that the two criteria differ substantially in their clinical application. This was evident from an additional 1100 FAERS cases identified by Sternbach but not Hunter's criteria⁴. Thus, Sternbach's inclusion of more nonspecific symptoms may result in identification of milder toxicity cases. Similarly, Radomski²⁸ and, later, Isbister²⁶ recognized that several states of serotonin-related toxicity existed: a mild state in which symptoms occurred within 4 weeks, were usually transient and resolved within one week; a full serotonin syndrome including mental, neurologic, and vegetative symptoms; and a toxic state with life-threatening symptoms manifesting as coma, seizures, and hyperpyrexia. Thus, differentiating patients with mild transient symptoms versus those that may progress to life-threatening toxicity is potentially an important clinical dilemma. Although application of the SBS model for assessing individual patient risk is likely to be complex, the potential to improve drug therapy is worthy of the effort.

Serotonin Receptors

Potential methods for quantifying relative 5-HT burden are daunting when confronted with the complex nature of serotonin pharmacology and numerous receptor subtypes. Receptor interactions at both presynaptic and postsynaptic sites often simultaneously involve agonism

at one receptor subtype and antagonism at another. Additionally, recent pharmacologic advances suggest that some receptors may possess functional selectivity processes such that agonists, for example, may act through a variety of conformational states to elicit a preferred signal pathway. Hence, two drugs acting as agonists at the same receptor may produce two different responses²⁹.

Which serotonin receptors are important in determining clinical manifestations of toxicity is an important area of study. Recently, Racz et al identified inhibition of serotonin transporter protein, agonism at 5-HT_{1A}, and antagonism at 5-HT_{2A} as the principal candidate receptors involved in severe serotonin syndrome cases present in FAERS³⁰. Whether milder toxicity involves different receptors is a question requiring further study. Our previous work suggests that off-target interactions at norepinephrine transporter protein and antimuscarinic activity may contribute to serotonin toxicity. Unfortunately, these findings were not available in time for inclusion in the current study design. Therefore, as an initial starting point, we undertook a simplified approach based on identified interactions at eight receptors generally representing those most commonly studied. Although a thorough understanding of pharmacodynamic effects of serotonergic drugs may not be within reach for some time, the current study provides some hope that even general approximations may provide some clinical utility.

Serotonin Burden Scores

Based on interaction scores at eight serotonin receptors, eight serotonergic drugs were chosen to represent a range of scores as well as diverse therapeutic drug classes. A subset of eight drugs was undertaken to limit the computational time required to calculate the various 2- and 3-drug combinations resulting from inclusion of all potential serotonergic agents. The strong correlation between SBS and the composite ADE endpoint seen in Figure 2 is likely due in part to the higher comorbidities associated with the 2-drug and 3-drug cohorts. Nevertheless, intracohort correlations (Figures 3 and 4 suggest that the increasing adverse event rates within each drug cohort is associated with drug combinations that have higher SBS scores. Thus, despite a higher background of potential comorbidity-related adverse events within each drug cohort, drug combinations with higher SBS scores were positively correlated with the composite event rate (2-drug cohort, $R^2 = 0.69$; and 3-drug cohort, $R^2 = 0.85$). Given the nonspecific and ubiquitous nature of serotonin toxicity, these data imply that differentiating between disease-related and drug-induced serotonergic symptoms may be a prudent and worthwhile endeavor.

Although the clinical utility of SBS in predicting individual patient risk is unknown and likely much more complicated, SBS offers a pharmacologic receptor-based and scientifically rational methodology from which to experiment with inclusion of additional pharmacokinetic parameters. Among these, drug dose and central nervous system penetrability are probably cornerstone requirements and ultimately might include pharmacogenetics parameters as well.

Study Limitations

The use of insurance claims databases is associated with several limitations including underreporting of adverse events or symptoms, and unmeasured or residual confounding that could have introduced bias in our estimates. Intracohort correlations were an attempt to minimize some of this potential bias. Specific serotonergic-related adverse effects are not well described in the clinical literature except as it relates to more severe cases such as serotonin syndrome. Therefore, we used ICD-9-CM codes representing these known symptoms but could have misrepresented some adverse events or excluded other potential ADEs. As noted above, the significantly higher comorbidities as measured by the CCI and CDI in serotonergic drug-exposed versus nonexposed patients may limit our findings, and additional research is needed validate this approach.

Conclusion

As an exploratory test-of-concept, we assessed the feasibility of a SBS for predicting serotonin toxicity. The large number of potential serotonergic drugs and frequent combinations of serotonergic agents from different therapeutic categories suggest an important clinical need for a tool to assess serotonergic burden. New clinical tools are needed to help estimate the relative serotonin burden induced by single or, more commonly, multiple serotonergic drugs administered concurrently. Although further research is needed to elucidate and validate its clinical utility, the SBS may offer a foundation from which risk assessment tools can be developed.

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1A.

1B. Serotonin Receptor Subtypes

Study Drugs	5HT-1 _A	5HT-1 _B	5HT-2 _A	5HT-2 _B	5HT-2 _C	5HT-6	5HT-7	SERT	Total SBS Score
Amitriptyline	1.00	1.00	1.00	1.00	1.00	1.00	0.5	1.00	7.5
Buspirone	1.00	1.00	1.00	1.00	1.00	0.00	0.37	0.00	5.4
Rizatriptan	0.65	1.00	1.00	0.50	0.50	0.50	0.50	0.00	4.7
Aripiprazole	1.00	0.37	1.00	0.00	1.00	0.00	0.40	0.39	4.2
Sertraline	0.00	0.00	1.00	1.00	1.00	0.00	0.00	1.00	4.0
Venlafaxine	1.00	1.00	0.00	0.00	0.00	0.00	0.00	1.00	3.0
Cyclobenzaprine	0.00	0.00	0.00	0.63	0.63	0.00	0.50	0.00	1.8
Tramadol	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	1.0

Figure 1.

(A) Study design representing the 2-serotonergic drug and 3-serotonergic drug cohorts.

When a potential adverse drug event (ADE) occurred within a 30-day window of a newly

added serotonergic study drug, the individual drug scores were summed to give a total

regimen serotonin burden score (SBS). (B) SBSs for the eight study drugs. Receptor scores

are the propensity score of a drug to fit into each receptor, where 1.0 equals high probability

and <1.0 represents lower probabilities. A threshold score for activity is unknown. ICD-9-

CM ADE code= *International Classification of Diseases, Ninth Revision, Clinical*

Modification; 5-HT = serotonin; SERT = serotonin reuptake transporter.

Figure 2. Serotonin burden score in the combined 2- and 3-serotonergic drug cohorts (98,072 patients) in 2-point increments versus the composite serotonin adverse drug event (ADE) rate.

Figure 3. Serotonin burden score in the 2-serotonergic drug cohort (78,172 patients) in 2-point increments versus the composite serotonin adverse drug event (ADE) rate.

Figure 4. Serotonin burden score in the 3-serotonergic drug cohort (19,900 patients) versus the composite serotonin adverse drug event (ADE) rate.

Table 1.

Demographic and Clinical Characteristics of the Serotonergic Drug–Exposed and Matched Nonexposed Cohorts

Characteristics	2-Drug Cohort			3-Drug Cohort		
	Exposed (n=78,172)	Nonexposed (n=312,688)	p-value	Exposed (n=19,900)	Nonexposed (n=79,600)	p-value
Demographic characteristics						
Age (yrs)						
Mean ± SD	43.7 ± 15.84	43.6 ± 15.94	0.6069	42.6 ± 14.45	42.6 ± 14.58	0.8019
Median, Range	44.0, 5–84	44.0, 4–84		43.0, 5–83	43.0, 4–83	
< 65	71,247 (91.1)	284,594 (91.0)	0.2699	18,724 (94.1)	74,786 (4.0)	0.4635
65	6,925 (8.9)	28,094 (9.0)		1,176 (5.9)	4,814 (6.0)	
Sex						
Female	48,229 (61.7)	192,916 (61.7)	1.0000	14,365 (72.2)	57,460 (72.2)	1.0000
Male	29,940 (38.3)	119,760 (38.3)		5,535 (27.8)	22,140 (27.8)	
Unknown	3 (0.0)	12 (0.0)		0 (0.0)	0 (0.0)	
Region						
East	14,737 (18.9)	68,787 (22.0)	<0.0001	3,534 (17.8)	16,233 (20.4)	<0.0001
Midwest	20,917 (26.8)	96,930 (31.0)		5,259 (26.4)	28,434 (35.7)	
South	32,146 (41.1)	93,847 (30.0)		8,547 (42.9)	23,066 (29.0)	
West	10,372 (13.3)	53,124 (17.0)		2,560 (12.9)	11,867 (14.9)	
Medicare						
No	75,869 (97.1)	304,161 (97.3)	0.0008	19,468 (97.8)	77,955 (97.9)	0.3574
Yes	2,303 (2.9)	8,527 (2.7)		432 (2.2)	1,645 (2.1)	
Clinical characteristics						
Chronic Disease Indicator score						
Mean ± SD	4.3 ± 2.71	2.4 ± 2.52	<0.0001	5.9 ± 2.71	2.9 ± 2.65	<0.0001
Median, Range	4.0, 0–15	2.0, 0–15		6.0, 0–15	2.0, 0–14	
Charlson Comorbidity Index score						
Mean ± SD	1.2 ± 2.10	0.7 ± 1.54	<0.0001	1.6 ± 2.37	0.7 ± 1.58	<0.0001
Median, Range	0.0, 0–26	0.0, 0–21		1.0, 0–20	0.0, 0–21	
Length of follow-up (days)						
Mean ± SD	951.0 ± 664.39	1103.4 ± 720.92	<0.0001	1500.9 ± 833.87	1545.9 ± 900.46	<0.0001
Median, Range	823.0, 3–4990	993.0, 2–5010		1418.0, 7–4988	1449.0, 3–4990	
No. of potential adverse events/patient						
Mean ± SD	0.3 ± 0.59	0.1 ± 0.37	<0.0001	0.5 ± 0.76	0.1 ± 0.41	<0.0001
Median, Range	0.0, 0–7	0.0, 0–6		0.0, 0–7	0.0, 0–6	
No. of potential adverse events in patients with 1 adverse event						
Mean ± SD	1.3 ± 0.59	1.2 ± 0.48	<0.0001	1.4 ± 0.68	1.2 ± 0.48	<0.0001
Median, Range	1.0, 1–7	1.0, 1–6		1.0, 1–7	1.0, 1–6	

Data are no. (%) of patients unless otherwise specified.

Table 2.

Summary of Potential Serotonin-Related Adverse Effects in the Serotonergic Drug–Exposed and Matched Nonexposed Cohorts

Potential serotonin-related adverse drug event (ICD-9-CM code)	2-Drug Cohort			3-Drug Cohort		
	Exposed (n=78,172)	Nonexposed (n=312,688)	p-value	Exposed (n=19,900)	Nonexposed (n=79,600)	p-value
Bipolar I disorder, single manic episode (296.00–06)	360 (0.5)	247 (0.1)	<0.0001	222 (1.1)	92 (0.1)	<0.0001
Bipolar I disorder, recurrent manic episode (296.10–296.16)	38 (0.0)	20 (0.0)	<0.0001	21 (0.1)	6 (0.0)	<0.0001
Psychogenic GI dysfunction including diarrhea (306.4)	139 (0.2)	273 (0.1)	<0.0001	44 (0.2)	112 (0.1)	0.0103 ^a
Mild cognitive impairment (331.83)	184 (0.2)	327 (0.1)	<0.0001	99 (0.5)	85 (0.1)	<0.0001
Essential and other forms of tremor (medication-induced and familial) (333.1)	629 (0.8)	988 (0.3)	<0.0001	279 (1.4)	267 (0.3)	<0.0001
Myoclonus (333.2)	131 (0.2)	119 (0.0)	<0.0001	69 (0.3)	52 (0.1)	<0.0001
Toxic gastroenteritis and colitis (558.2)	34 (0.0)	69 (0.0)	0.0010	14 (0.1)	18 (0.0)	0.0008
Diarrhea (787.91)	8,718 (11.2)	14,693 (4.7)	<0.0001	4,092 (20.6)	5,034 (6.3)	<0.0001
Fever, unspecified (780.60)	2,862 (3.7)	5,247 (1.7)	<0.0001	1,235 (6.2)	1,793 (2.3)	<0.0001
Chills (without fever) (780.64)	348 (0.4)	671 (0.2)	<0.0001	173 (0.9)	229 (0.3)	<0.0001
Generalized hyperhidrosis (780.8)	1,194 (1.5)	1,895 (0.6)	<0.0001	561 (2.8)	643 (0.8)	<0.0001
Abnormal involuntary movements (head, fasciculations, spasms, tremor) (781.0)	1,469 (1.9)	1,887 (0.6)	<0.0001	753 (3.8)	558 (0.7)	<0.0001
Abnormality of gait (781.2)	3,669 (4.7)	5,566 (1.8)	<0.0001	1,417 (7.1)	1,576 (2.0)	<0.0001
Lack of coordination (ataxia, muscular incoordination) (781.3)	1,060 (1.4)	1,559 (0.5)	<0.0001	456 (2.3)	470 (0.6)	<0.0001
Nervousness (799.2, 799.21)	99 (0.1)	120 (0.0)	<0.0001	81 (0.4)	36 (0.0)	<0.0001
Irritability (799.22)	74 (0.1)	85 (0.0)	<0.0001	45 (0.2)	31 (0.0)	<0.0001
Impulsiveness (799.23)	7 (0.0)	8 (0.0)	0.0098 ^a	2 (0.0)	1 (0.0)	0.0433 ^a

Data are no. (%) of patients.

ICD-9-CM = *International Classification of Diseases, Ninth Revision, Clinical Modification*; GI = gastrointestinal.

^aNot significant after Bonferroni correction.