Serotonin Toxicity

Associated Agents and Clinical Characteristics

Michael J. Moss, MD,†*
and Robert G. Hendrickson, MD,‡§ on behalf of the Toxicology Investigators Consortium (ToxIC)

Abstract:

Background: Serotonin toxicity is a common cause of drug-induced altered mental status. However, data on the causes of serotonin toxicity, symptomatology, complications, and rate of antidotal treatment are limited.

Methods: This study evaluated cases of serotonin toxicity in the ToxIC registry, an international database of prospectively collected cases seen by medical toxicologists. Serotonin toxicity was diagnosed by bedside evaluation of medical toxicology specialists and explicit criteria were not used. The database was searched for "serotonin syndrome" between January 1, 2010, and December 31, 2016.

Results: There were 1010 cases included. Females made up 608 (60%) cases. Ages are as follows: younger than 2 years (3, 0.3%), 2 to 6 years (8, 0.8%), 7 to 12 years (9, 0.9%), 13 to 18 years (276, 27.3%), 19 to 65 years (675, 67%), older than 66 years (33, 3.4%), unknown (6, 0.6%). Reasons for encounter: intentional (768, 76%), adverse drug event/reaction (127, 12.6%), unintentional (66, 6%), and unknown (55, 5.4%). Signs/symptoms: hyperreflexia/clonus/myoclonus (601, 59.5%), agitation (337, 33.4%), tachycardia (256, 25.3%), rigidity (140, 13.9%), seizures (139, 13.7%), and hyperthermia (29, 2.9%). Complications: rhabdomyolysis (97, 9.7%), dysrhythmias (8, 0.8%), and death (1, 0.1%). Treatments: benzodiazepines 67% (677/1010), cyproheptadine 15.1% (153/1010). There were 192 different xenobiotics reported with 2046 total exposures. Antidepressants were most common (915, 44.7%) with bupropion the most frequent overall (147, 7.2%). Common non-antidepressants were dextromethorphan (95, 6.9%), lamotrigine (64, 3.1%), and tramadol (60, 2.9%).

Discussion: Serotonin toxicity most often occurred in adult patients with intentional overdose. Antidepressants were the most common agents of toxicity. Interestingly, bupropion, a norepinephrine/dopamine reuptake inhibitor, was the most frequently mentioned xenobiotic. Though often cited as a potential antidote, only 15% of patients received cyproheptadine. Severe toxicity was rare. A single death was reported.

Key Words: serotonin toxicity, serotonin syndrome, antidepressants, bupropion, cyproheptadine

(*J Clin Psychopharmacol* 2019;39: 628–633)

Serotonin toxicity is caused by an increase of serotonin in select areas of the central nervous system (CNS) resulting in a classic triad of altered mental status, neuromuscular effects, and autonomic hyperactivity.[1–4] Although the terms serotonin toxicity and serotonin syndrome are often used interchangeably, serotonin toxicity more accurately describes the condition as a spectrum of disease rather than a single set of clinical findings.[2] Population level data on serotonin toxicity are difficult to obtain. There is no specific code in the International Statistical Classification of Diseases for serotonin toxicity or serotonin syndrome. The US National Poison Data System also does not specifically track serotonin toxicity. However, the National Poison Data System does report that antidepressants as a category are in the top 5 for total exposures, year-to-year increase in exposures, and deaths.[5] Treatment of serotonin toxicity is largely supportive in nature. Cyproheptadine, an antihistamine with antiserotonergic effects, is often cited as a potential antidote though its use is only supported by case reports and case series.[6–9] Information on the agents associated with serotonin toxicity, rate of complications, and use pharmacologic treatment are based on smaller scale case reports, case series, and database studies.[2,3,10] We sought to report the clinical characteristics of serotonin toxicity and associated xenobiotics as diagnosed by medical toxicologists at the bedside from a large international database.

METHODS

The Toxicology Investigators Consortium (ToxIC) registry was established in 2009 by the American College of Medical Toxicology.[11] Toxicology Investigators Consortium is a registry of toxicology cases that are seen at the bedside by a medical toxicology consultant at greater than 50 geographically diverse locations. Entries are made by medical toxicology fellows or faculty only after bedside evaluation and not from phone or poison center consultations. The ToxIC database contained over 50,000 patient consultations during our study period.

The ToxIC database was searched for the term "serotonin syndrome" in the "Toxidrome" section for the 7-year period from January 1, 2010, to December 31, 2016. In this section, toxicologists may select from a list of several toxidromes at their discretion. Specific criteria for each toxidrome are not listed nor required to be entered, though signs and symptoms related to these toxidromes are listed elsewhere in the database. Cases were excluded if multiple toxidromes were listed (eg, anticholinergic, sympathomimetic, neuroleptic malignant syndrome) or if the case was marked "unlikely tox related" or "unknown if tox related." Cases were only required to have entered "serotonin syndrome" as the sole toxidrome and were still included if other information, symptoms, or outcomes were not recorded. If clinical signs and symptoms were not recorded, these were assumed to be absent. For instance, we did not assume the presence of tremor or hyperreflexia based on the diagnosis of serotonin toxicity alone if those findings were not separately documented. The following terms were analyzed: age, sex, primary reason for encounter (adverse drug event, adverse drug reaction, intentional exposure, unintentional exposure), specific agents, notable vital sign abnormalities (hypertension, tachycardia, hyperthermia), cardiovascular (dysrhythmias), neurologic symptoms (agitation, coma/CNS depression, delirium, hallucinations, hyperreflexia/myoclonus/clonus, rigidity, seizures), rhabdomyolysis, antidotes (cyproheptadine, other), pharmacologic support (benzodiazepines, other), and nonpharmacologic support (intubation/ventilation).

From the *Utah Poison Control Center, College of Pharmacy, †Division of Emergency Medicine, University of Utah, Salt Lake City, UT; ‡Oregon Poison Center; and §Department of Emergency Medicine, Oregon Health & Science University, Portland, OR.

Received May 14, 2019; accepted after revision September 3, 2019.

Reprints: Michael J. Moss, MD, Utah Poison Control Center, College of Pharmacy, 30 S 2000, E Suite 4540, Salt Lake City, UT 84112 (e-mail: mikemosstox@gmail.com).

ISSN: 0271-0749
DOI: 10.1097/JCP.0000000000001121

Xenobiotics listed under "Primary agent, most consequential" were compiled. Up to five "primary agents" are entered by the treating medical toxicologist and denotes the xenobiotics determined to be most associated or causative of the patients' symptoms. We did not include xenobiotics listed under "secondary agents." All xenobiotics listed as primary agents were counted for total number of mentions in the database. Cases with only a single agent listed and those coded as adverse drug event/adverse drug reaction were separately analyzed.

The database defines adverse drug event as a medication error resulting in harm, whereas an adverse drug reaction is an undesirable effect of a medication used in a normal dose. Intentional exposure refers to any deliberate exposure either for self-harm, misuse or abuse, or therapeutic use. Unintentional exposure includes accidental ingestions and exploratory pediatric ingestions. The database includes hyperreflexia/myoclonus/clonus and coma/CNS depression as single terms that clinicians select rather than individual signs. Complications were defined as intubation, rhabdomyolysis, and dysrhythmias. Death is the only outcome specifically reported in the database. Duration of symptoms is not specifically recorded in the database.

With the exception of the field "antidotes, other" all other analyzed variables and data are selected by the treating toxicologist from predefined menus rather than entered manually. Original hospital charts were not reviewed. Data were summarized with descriptive statistics.

The local institutional review board reviewed this study and found it exempt as it did not represent human research.

RESULTS

The initial search yielded 1214 cases with a final total of 1010 meeting all inclusion and exclusion criteria. Cases were excluded for the following reasons: "unlikely or unknown if tox related," multiple toxidromes listed (169). This represents 1.9% of cases in the registry. There were 353 cases with exposure to a single agent and 657 with exposure to multiple agents. Demographics and type of exposure are summarized in Table 1.

TABLE 1. Case Characteristics

Sex	n (%)
Male	402 (40%)
Female	608 (60%)
Age	
<2 years	3 (0.3%)
2–6	8 (0.8%)
7–12	9 (0.9%)
13–18	276 (27.3%)
19–65	675 (66.8%)
66–89	32 (3.2%)
Type of exposure	
Intentional exposure	768 (76%)
Reason for intentional exposure	
Self-harm	289 (28.6%)
Misuse/abuse	243 (24%)
Therapeutic	47 (4.7%)
Not reported	189 (18.7%)
Unintentional exposure	60 (6%)
Adverse drug event	23 (2%)
Adverse drug reaction	104 (10.3%)
Other/not reported	55 (5.4%)

TABLE 2. Signs, Symptoms, Outcomes, and Treatments

Signs/symptoms	n (%)
Hyperreflexia/clonus/myoclonus	601 (60%)
Agitation	337 (33%)
Delirium	276 (27%)
Coma/CNS Depression	254 (25%)
Rigidity	140 (14%)
Seizures	139 (14%)
Hallucinations	99 (10%)
Tachycardia (HR > 140 bpm)	256 (25%)
Hypertension (SBP > 200 and/or DBP > 120)	71 (7%)
Hyperthermia (T > 105)	29 (3%)
Symptoms per patient, median (range)	2 (1–8)
Complications/outcomes	
Intubation	160 (16%)
Rhabdomyolysis (CPK > 1000)	97 (10%)
Ventricular dysrhythmias	8 (0.8%)
Death	1 (0.1%)
Treatments	
Benzodiazepines	677 (67%)
Cyproheptadine	153 (15%)
Chlorpromazine	1 (0.1%)
Risperidone	1 (0.1%)

CPK indicates creatine phosphokinase; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

Signs, symptoms, complications, and treatments are summarized in Table 2. Rates of several measures of severe toxicity by reason for exposure are shown in Table 3.

Xenobiotics listed as primary agents of toxicity are summarized in Table 4. These are grouped by overall total number of times mentioned in the database, cases of a single xenobiotic implicated in toxicity, and those agents associated with adverse drug reactions, respectively. Percentages are shown for totals in each group. Multiple agents may be listed for a single case. On average, there were 2 agents listed per case. Antidepressants as a class were the most common agents listed in all categories. Other agents of note include opioids: sufentanil (1, 0.05%); remifentanil (1, 0.05%); and drugs of abuse: lysergic acid diethylamide (LSD) (7, 0.3%), 3-4, methylenedioxymethamphetamine (6, 0.3%), mephedrone (4, 0.2%), methamphetamine (4, 0.2%), 2-(4-iodo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine (25I-NBOMe) (3, 0.1%), psilocybin mushrooms (2, 0.1%), salvia divinorum (1, 0.05%), and methoxetamine (1, 0.05%), methylenedioxypyrovalerone (MDPV) (1, 0.05%), cathinone (1, 0.05%), and *N*,*N*-dimethyltryptamine (DMT) (1, 0.05%).

A summary of which patients received cyproheptadine is shown in Table 5. A comparison of clinical signs and symptoms among the most common xenobiotics in single-agent exposures is shown in Table 6.

DISCUSSION

Most cases of serotonin toxicity seen by medical toxicologists in this database were due to intentional overdoses of antidepressant medications in adults. Symptoms of serotonin toxicity reported in ToxIC cases are similar to those described previously[1,3] and reflect the common neuromuscular (eg, clonus and hyperreflexia), CNS (eg, delirium and agitation), and autonomic effects (eg, tachycardia). Severe outcomes, such as seizures,

TABLE 3. Reason for Encounter and Findings of Severe Serotonin Toxicity

Primary Reason for Encounter	Dysrhythmias	Hyperthermia	Intubation	Rhabdomyolysis	Seizures
Intentional exposures	7 (1%)	20 (3%)	140 (18%)	84 (11%)	121 (16%)
Self-harm	3 (1%)	2 (1%)	65 (23%)	33 (11%)	56 (20%)
Misuse/abuse	0 (0%)	0 (0%)	6 (9%)	7 (10%)	7 (10%)
Therapeutic	0 (0%)	1 (2%)	2 (3%)	5 (8%)	6 (10%)
Not reported	4 (2%)	17 (9%)	67 (35%)	39 (21%)	53 (28%)
Unintentional	1 (2%)	2 (3%)	8 (13%)	3 (5%)	7 (12%)
ADR	0 (0%)	5 (5%)	3 (3%)	3 (3%)	4 (4%)
ADE	0 (0%)	0 (0%)	0 (0%)	1 (4%)	1 (4%)
Other/not reported	0 (0%)	2 (4%)	9 (16%)	6 (11%)	5 (9%)

ADR indicates adverse drug reaction; ADE, adverse drug event.

rhabdomyolysis, and endotracheal intubation, occurred in about 10% to 15% of cases and may reflect some selection bias inherent in the registry. It is possible that this registry represents the most severely affected population because less severe cases may not require a bedside consultation and may not be reported here. Conversely, some outcomes may appear less frequently due to the strict definitions used in the registry (eg, hyperthermia is defined as a temperature >105° F/40.6°C, tachycardia is defined as a heart rate >140 bpm).

Patients with intentional exposures had a higher rate of severe effects (Table 3). Although not directly assessed, in cases of self-harm patients may have ingested a relatively larger dose of medication. The highest rate of severe effects was noted in a subgroup of intentional exposures where intent was unknown or not reported. This may reflect the difficulty in obtaining an ingestion history in the most severely affected patients and limits the ability to interpret these data.

Patients in this study were commonly treated with benzodiazepines (67%). Serotonin antagonists, such as cyproheptadine, risperidone, and chlorpromazine, were rarely used.[12,13] Cyproheptadine has been described in several case reports[7–9,14] but was only used in 15% of our patients. This is similar to a previous report of 473 cases of serotonin toxicity where only 9.3% received serotonin antagonists.[2] Although patients with more severe toxicity did receive cyproheptadine more often (Table 5), the majority of these cases were not given cyproheptadine. This suggests the need for a definitive trial on cyproheptadine use. Risperidone and chlorpromazine were only noted in the pharmacologic support-other or antidote-other categories. These agents are not listed as predetermined "antidotes" in the registry. Toxicologists would have had to type these agents into a free text area, and hence it is possible that our study missed some use of these agents.

It is not surprising that selective serotonin and serotonin-norepinephrine reuptake inhibitors were common causes of serotonin toxicity in our cases. However, bupropion, the most common agent noted, is a norepinephrine-dopamine reuptake inhibitor and has no direct effect on serotonin reuptake or serotonin receptors.[15–17] However, bupropion causes increases in serotonergic neuronal firing after continued use.[18,19] In one small (n = 6) study, bupropion produced a 2-fold increase in the hippocampal serotonin concentrations of rats after a single dose, but this was not a significant change. Bupropion has been previously implicated in several case reports of serotonin toxicity both alone and in combination with other serotonergic medications,[20–25] but has not been generally associated with serotonin toxicity as it is not a serotonin reuptake inhibitor.[26] There are several possible explanations for bupropion's ubiquity in these cases. It is possible that bupropion causes true serotonin toxicity via an unknown mechanism which may include a toxicodynamic, downstream, indirect effect, or the effects of bupropion metabolites. Alternatively, bupropion may produce symptoms that are similar to that of serotonin toxicity, but via a non-serotonin pathway. Bupropion is known to effect norepinephrine and dopamine pathways, which may lead to a sympathomimetic syndrome (eg, tachycardia, diaphoresis, altered mental status) with dopaminergic neuromuscular effects (eg, tremor, extrapyramidal effects) that mimic serotonin toxicity, or a serotonin-like toxicity. Further, it is possible that bupropion increases concentrations of other serotonergic

TABLE 4. Xenobiotics Associated With Serotonin Toxicity

	Total Mentions, n (%)	Single Mentions, n (%)	Total ADR Mentions, n (%)
1	Bupropion, 147 (7.2%)	Sertraline, 54 (15.3%)	Citalopram, 24 (7.7%)
2	Sertraline, 144 (7%)	Dextromethorphan, 45 (12.8%)	Fentanyl, 21 (6.8%)
3	Citalopram, 142 (6.9%)	Citalopram, 43 (12.2%)	Sertraline, 21 (6.8%)
4	Dextromethorphan, 95 (4.6%)	Bupropion, 30 (8.5%)	Trazodone, 17 (5.5%)
5	Fluoxetine, 87 (4.3%)	Fluoxetine, 19 (5.4%)	Lithium, 15 (4.8%)
6	Venlafaxine, 80 (3.9%)	Escitalopram, 15 (4.3%)	Bupropion, 15 (4.8%)
7	Escitalopram, 72 (3.5%)	Venlafaxine, 13 (3.7%)	Escitalopram, 13 (4.2%)
8	Lamotrigine, 64 (3.1%)	Tramadol, 11 (3.1%)	Venlafaxine, 13 (4.2%)
9	Tramadol, 60 (2.9%)	Paroxetine, 10 (2.8%)	Fluoxetine, 12 (3.9%)
10	Trazodone, 57 (2.8%)	Lithium, 8 (2.3%)	Tramadol, 11 (3.5%)
Total mentions	2046	353	310

Only the top 10 xenobiotics in each category are listed.

TABLE 5. Proportions of Patients that Received Cyproheptadine

Patient Characteristics	Received Cyproheptadine
All cases	153/1010 (15%)
Coma/CNS depression	45/254 (18%)
Delirium	47/276 (17%)
Hyperreflexia/clonus/myoclonus	30/176 (15%)
Hyperthermia ($T > 105$)	12/29 (41%)
Intubation	41/119 (26%)
Rhabdomyolysis	25/97 (26%)
Rigidity	36/140 (26%)
Seizures	26/139 (19%)

agents as bupropion metabolites are CYP2D6 inhibitors.[27–31] We attempted to minimize any potential clinical overlap of toxidromes by only including cases specifically diagnosed as "serotonin syndrome" by the treating toxicologist and excluding cases with multiple toxidromes listed (eg, anticholinergic, sympathomimetic). Other unrecognized serotonergic agents may have been present which were actually responsible for serotonin toxicity instead of bupropion. However, this seems unlikely to be the sole explanation with the large number of cases associated with bupropion. Whatever the mechanism, bupropion is associated with a similar constellation of symptoms as other agents in single-agent exposures (Table 6). Further research is required to evaluate the relationship between bupropion and these serotonin-like clinical effects. The ubiquity of bupropion in this study should not be construed to suggest that bupropion toxicity should be treated with serotonin antagonists. Until further research is performed, treatment of bupropion symptoms should remain supportive and benzodiazepines should remain first line.

There were several cases of serotonin toxicity from recreational drugs. Mephedrone, cathinone, and MDPV, which were commonly found in "bath salts" during the study period, were noted. Serotonin toxicity from mephedrone, methylone, and butylone has been reported in case reports.[32,33] Although mephedrone, methylone, and butylone interact with the serotonin system, cathinone and MDPV do not directly interact with the serotonin system and only act via the dopamine and norepinephrine transporter.[34] Methamphetamine and cocaine were also associated with serotonin toxicity in our study. The association between serotonin toxicity and cocaine has been noted previously.[35] Although some amphetamines, such as lisdexamphetamine[36] and 3-4, methylenedioxymethamphetamine,[37] have been associated with serotonin toxicity, methamphetamine use has not been associated previously and methamphetamine does not directly interact with the serotonin system.[34,38] Given the popularity of methamphetamine use, this association deserves further study. Several psychedelics were also reported in association with serotonin toxicity. There are previous reports of serotonin toxicity related to 25I-NBOMe and psilocybin,[39,40] but there are no reported cases associated with DMT, salvia divinorum, or methoxetamine. Consistently, NBOMs and tryptamines including psilocybin and DMT directly act on serotonin receptors.[41,42]

Dextromethorphan was one of the most common medications noted and was reported in cases of intentional overdose, drug abuse, and adverse drug reactions. Dextromethorphan inhibits the reuptake of serotonin and has been described as a cause of serotonin toxicity previously.[43] Fentanyl, remifentanil, and sufentanil were associated with 36 cases of serotonin toxicity. An association with fentanyls, as well as several other opioids and serotonin toxicity, has been described.[44–46] Given the frequency of fentanyl use in medical settings as well as its increase as a drug of abuse, medical toxicologists should be aware of this association and further studies would be appropriate.

About 35% of cases were attributed to a single-agent exposure. Though commonly associated with exposures to multiple serotonergic agents, serotonin toxicity has been reported with both therapeutic use and overdose of a single agent, which was common in our study.[47,48] Alternatively, some of these cases may not have identified other serotonergic agents or drug-drug interactions that were present.

LIMITATIONS

Our study does not establish a definitive cause and effect relationship between any of the xenobiotics and serotonin toxicity. However, all of the cases described here are patients who were diagnosed with serotonin toxicity at the bedside by medical toxicologists and report the xenobiotic that was most likely the causative agent in each case. Several xenobiotics in this database associated with serotonin toxicity lack serotonergic effects, most notably bupropion as discussed above. Given the small number of mentions of some other non-serotonergic agents (methamphetamine, cathinone, MDPV) these were more likely incorrectly identified as responsible. It is possible that an unknown and unreported substance may have caused the serotonin toxicity in these cases or that the medical toxicologist who entered the data may have incorrectly coded the case. Laboratory confirmation of xenobiotic exposure is infrequently reported in the registry and if made available could alter the diagnosis or responsible agents listed. Though we report both recorded treatments and outcomes, the registry does not make any assessment of efficacy. Additionally, the database does not require that any specific criteria be entered to diagnose serotonin toxicity and any associated signs and symptoms are entered voluntarily. We are unable to specifically compare cases in the database to established criteria for serotonin toxicity. Though toxicologists directly consult on these patients at the bedside, the diagnosis of serotonin toxicity may partially be made on findings reported by the patient or other providers that

TABLE 6. Signs and Symptoms Associated With Top 5 Single-Agent Exposures

	Bupropion	Citalopram	DXM	Fluoxetine	Sertraline
Hyperreflexia/myoclonus/clonus/tremor	20 (67%)	26 (60%)	28 (62%)	11 (58%)	42 (78%)
Agitation	12 (40%)	16 (37%)	12 (27%)	4 (21%)	19 (35%)
Seizures	11 (37%)	9 (21%)	1 (2%)	4 (21%)	3 (6%)
Hyperthermia	0 (0%)	3 (7%)	0 (0%)	1 (5%)	1 (2%)
Tachycardia	10 (33%)	11 (26%)	13 (29%)	6 (32%)	19 (35%)
Total cases	30	43	45	19	54

DXM indicates dextromethorphan.

had resolved by the time of consultation. Additionally, the database groups many criteria together as a single entry (eg, hyperreflexia/clonus/myoclonus) and very restrictively defines hyperthermia as a temperature greater than 105°F. Even so, the established criteria for the diagnosis of serotonin toxicity were derived from the opinion of toxicologists as the gold standard.[2,4]

CONCLUSIONS

Serotonin toxicity is seen in 2% of all bedside medical toxicology consultations. Serotonin toxicity is associated with exposure to antidepressants, mood stabilizers, opioids, and recreational stimulants. The most severe symptoms were seen in patients with intentional self-harm ingestions. The most common findings in serotonin toxicity are hyperreflexia, clonus, and myoclonus. Serotonin antagonists, such as cyproheptadine, are rarely used.

AUTHOR DISCLOSURE INFORMATION

The authors have no financial disclosures and there was no funding for this report.

REFERENCES

1. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med*. 2005;352:1112–1120.
2. Dunkley EJ, Isbister GK, Sibbritt D, et al. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *QJM*. 2003;96:635–642.
3. Isbister GK, Bowe SJ, Dawson A, et al. Relative toxicity of Selective Serotonin Reuptake Inhibitors (SSRIs) in overdose. *J Toxicol Clin Toxicol*. 2004;42:277–285.
4. Sternbach H. The serotonin syndrome. *Am J Psychiatry*. 1991;148:705–713.
5. Gummin DD, Mowry JB, Spyker DA, et al. 2016 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 34th Annual Report. *Clin Toxicol (Phila)*. 2017;55:1072–1252.
6. Gillman PK. The serotonin syndrome and its treatment. *J Psychopharmacol (Oxf)*. 1999;13:100–109.
7. Graudins A, Stearman A, Chan B. Treatment of the serotonin syndrome with cyproheptadine. *J Emerg Med*. 1998;16:615–619.
8. Lappin RI, Auchincloss EL. Treatment of the serotonin syndrome with cyproheptadine. *N Engl J Med*. 1994;331:1021–1022.
9. McDaniel WW. Serotonin syndrome: early management with cyproheptadine. *Ann Pharmacother*. 2001;35:870–873.
10. Abadie D, Rousseau V, Logerot S, et al. Serotonin syndrome: analysis of cases registered in the french pharmacovigilance database. *J Clin Psychopharmacol*. 2015;35:382–388.
11. Wax PM, Kleinschmidt KC, Brent J. The Toxicology Investigators Consortium (ToxIC) Registry. *J Med Toxicol*. 2011;7:259–265.
12. Nisijima K, Yoshino T, Ishiguro T. Risperidone counteracts lethality in an animal model of the serotonin syndrome. *Psychopharmacology (Berl)*. 2000;150:9–14.
13. Nisijima K, Yoshino T, Yui K, et al. Potent serotonin (5-HT)(2A) receptor antagonists completely prevent the development of hyperthermia in an animal model of the 5-HT syndrome. *Brain Res*. 2001;890:23–31.
14. Horowitz BZ, Mullins ME. Cyproheptadine for serotonin syndrome in an accidental pediatric sertraline ingestion. *Pediatr Emerg Care*. 1999;15:325–327.
15. Ascher JA, Cole JO, Colin JN, et al. Bupropion: a review of its mechanism of antidepressant activity. *J Clin Psychiatry*. 1995;56:395–401.
16. Cooper BR, Hester TJ, Maxwell RA. Behavioral and biochemical effects of the antidepressant bupropion (Wellbutrin): evidence for selective blockade of dopamine uptake in vivo. *J Pharmacol Exp Ther*. 1980;215:127–134.
17. Piacentini MF, Clinckers R, Meeusen R, et al. Effect of bupropion on hippocampal neurotransmitters and on peripheral hormonal concentrations in the rat. *J Appl Physiol*. 2003;95:652–656.
18. Dong J, Blier P. Modification of norepinephrine and serotonin, but not dopamine, neuron firing by sustained bupropion treatment. *Psychopharmacology (Berl)*. 2001;155:52–57.
19. El Mansari M, Ghanbari R, Janssen S, et al. Sustained administration of bupropion alters the neuronal activity of serotonin, norepinephrine but not dopamine neurons in the rat brain. *Neuropharmacology*. 2008;55:1191–1198.
20. Thorpe EL, Pizon AF, Lynch MJ, et al. Bupropion induced serotonin syndrome: a case report. *J Med Toxicol*. 2010;6:168–171.
21. Falls BA, Gurrera RJ. Serotonin syndrome in a patient on tramadol, bupropion, trazodone, and oxycodone. *Psychosomatics*. 2014;55:305–309.
22. Gollapudy S, Kumar V, Dhamee MS. A case of serotonin syndrome precipitated by fentanyl and ondansetron in a patient receiving paroxetine, duloxetine, and bupropion. *J Clin Anesth*. 2012;24:251–252.
23. Munhoz RP. Serotonin syndrome induced by a combination of bupropion and SSRIs. *Clin Neuropharmacol*. 2004;27:219–222.
24. Shahani L. Tramadol precipitating serotonin syndrome in a patient on antidepressants. *J Neuropsychiatry Clin Neurosci*. 2012;24:E52.
25. Alsukaiti WMB, Carptenter J, Dunkley C, et al. Serotonin syndrome resulting from bupropion overdose treated with cyproheptadine. *J Med Toxicol*. 2019:61.
26. Gillman PK. Bupropion, bayesian logic and serotonin toxicity. *J Med Toxicol*. 2010;6:276–277.
27. Greenblatt DJ, von Moltke LL, Harmatz JS, et al. Human cytochromes and some newer antidepressants: kinetics, metabolism, and drug interactions. *J Clin Psychopharmacol*. 1999;19(5 suppl 1):23s–35s.
28. Kotlyar M, Brauer LH, Tracy TS, et al. Inhibition of CYP2D6 activity by bupropion. *J Clin Psychopharmacol*. 2005;25:226–229.
29. Reese MJ, Wurm RM, Muir KT, et al. An in vitro mechanistic study to elucidate the desipramine/bupropion clinical drug-drug interaction. *Drug Metab Dispos*. 2008;36:1198–1201.
30. Richelson E. Pharmacokinetic drug interactions of new antidepressants: a review of the effects on the metabolism of other drugs. *Mayo Clin Proc*. 1997;72:835–847.
31. Steuer AE, Schmidhauser C, Tingelhoff EH, et al. Impact of cytochrome P450 2D6 function on the chiral blood plasma pharmacokinetics of 3,4-methylenedioxymethamphetamine (MDMA) and its phase i and ii metabolites in humans. *PLoS One*. 2016;11:e0150955.
32. Garrett G, Sweeney M. The serotonin syndrome as a result of mephedrone toxicity. *BMJ Case Rep*. 2010;2010.
33. Warrick BJ, Wilson J, Hedge M, et al. Lethal serotonin syndrome after methylone and butylone ingestion. *J Med Toxicol*. 2012;8:65–68.
34. Simmler LD, Buser TA, Donzelli M, et al. Pharmacological characterization of designer cathinones in vitro. *Br J Pharmacol*. 2013;168:458–470.
35. Tordoff SG, Stubbing JF, Linter SP. Delayed excitatory reaction following interaction of cocaine and monoamine oxidase inhibitor (phenelzine). *Br J Anaesth*. 1991;66:516–518.
36. Akingbola OA, Singh D. Dexmedetomidine to treat lisdexamfetamine overdose and serotonin toxidrome in a 6-year-old girl. *Am J Crit Care*. 2012;21:456–459.
37. Smilkstein MJ, Smolinske SC, Rumack BH. A case of MAO inhibitor/MDMA interaction: agony after ecstasy. *J Toxicol Clin Toxicol*. 1987;25:149–159.
38. Schep LJ, Slaughter RJ, Beasley DM. The clinical toxicology of metamfetamine. *Clin Toxicol (Phila)*. 2010;48:675–694.

39. Hill SL, Doris T, Gurung S, et al. Severe clinical toxicity associated with analytically confirmed recreational use of 25I–NBOMe: case series. *Clin Toxicol*. 2013;51:487–492.

40. Suzuki K. Three cases of acute serotonin syndrome due to psilocybin mushroom poisoning. *Chudoku Kenkyu*. 2016;29:33–35.

41. Rickli A, Luethi D, Reinisch J, et al. Receptor interaction profiles of novel N-2-methoxybenzyl (NBOMe) derivatives of 2,5-dimethoxy-substituted phenethylamines (2C drugs). *Neuropharmacology*. 2015;99:546–553.

42. Rickli A, Moning OD, Hoener MC, et al. Receptor interaction profiles of novel psychoactive tryptamines compared with classic hallucinogens. *Eur Neuropsychopharmacol*. 2016;26:1327–1337.

43. Sovner R, Wolfe J. Interaction between dextromethorphan and monoamine oxidase inhibitor therapy with isocarboxazid. *N Engl J Med*. 1988; 319:1671.

44. Ailawadhi S, Sung KW, Carlson LA, et al. Serotonin syndrome caused by interaction between citalopram and fentanyl. *J Clin Pharm Ther*. 2007;32: 199–202.

45. Kirschner R, Donovan JW. Serotonin syndrome precipitated by fentanyl during procedural sedation. *J Emerg Med*. 2010;38: 477–480.

46. Rickli A, Liakoni E, Hoener MC, et al. Opioid-induced inhibition of the human 5-HT and noradrenaline transporters in vitro: link to clinical reports of serotonin syndrome. *Br J Pharmacol*. 2018;175: 532–543.

47. Gill M, LoVecchio F, Selden B. Serotonin syndrome in a child after a single dose of fluvoxamine. *Ann Emerg Med*. 1999;33:457–459.

48. Kolecki P. Isolated venlafaxine-induced serotonin syndrome. *J Emerg Med*. 1997;15:491–493.

Erratum

The Editors received the following correction from the authors, Dr. Jay D. Amsterdam and Thomas T. Kim, for their article published in the July–August 2019 issue of the Journal.

We would like to bring to your readers' attention the presence of an error in our article in the Journal entitled "*Prior antidepressant treatment trials may predict a greater risk of depressive relapse during antidepressant maintenance therapy*" by Amsterdam JD and Kim TT (J Clin Psychopharmacol 2019; 39:344-350).

Specifically, we were informed by one of your nice journal readers that one of our Odds Ratios (OR) may have been incorrectly reported out, and that the reported OR value suggested a 'reduction', rather than an 'increase', in the likelihood of depressive relapse with each increase in the number of prior antidepressant treatment trials. We have examined this issue, and we agree with the reader.

The error occurred on page 47 of the article in the Results section, under the sub-heading: *Effect of Prior Antidepressant Treatment Trials on the Odds of Depressive Relapse. It is located in the last paragraph, stated verbatim as*:

> *"After controlling for age, sex, race, number of prior depressive episodes, number of prior hypomanic episodes, age of onset of first depression, age of onset of first hypomania, baseline HRSD, duration of current depressive episode, number of prior antidepressant trials, type of treatment condition, and rapid cycling status, only the number of prior antidepressant treatment trials was associated with an increased odds of relapse (OR = 0.38, z = 2.11, P = 0.04)."*

The OR value of 0.38 is incorrect. The **Correct OR value** should read **1.47.**

Thus, the correct sentence should read:

> *"After controlling for age, sex, race, number of prior depressive episodes, number of prior hypomanic episodes, age of onset of first depression, age of onset of first hypomania, baseline HRSD, duration of current depressive episode, number of prior antidepressant trials, type of treatment condition, and rapid cycling status, only the number of prior antidepressant treatment trials was associated with an increased odds of relapse (OR = 1.47, z = 2.11, P = 0.04)."*

Please note that this change does not otherwise alter the overall conclusions drawn from our study results.

Thank you for providing this correction to your readers.