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RESEARCH

Serotonin syndrome: A pharmacovigilance comparative study of drugs affecting serotonin levels

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Abstract

Background Serotonin syndrome is a rare and potentially fatal adverse drug reaction caused by serotonergic drugs and is due to an increase in serotonin concentration or activation of the 5-HT receptor in the central nervous system. We analysed adverse events in the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) data set to investigate the main drug classes related to reports of serotonin syndrome and the reporting risk in relation to age and sex.

Methods We analysed data from the FAERS database to evaluate the main drug classes related to reports of the serotonin syndrome, and the reporting risk in relation to age and sex.

Results We found 8,997 cases of serotonin syndrome; selective serotonin reuptake inhibitors (SSRIs) was the class of drugs with most reports, followed by opioids and other antidepressants. The highest Reporting Odds Ratios (ROR) for drug classes was for monoamine oxidase (MAO) inhibitors (45.99, 95% confidence interval (CI): 41.21–51.33) and SSRIs (32.66, 95% CI: 31.33–34.04), while the ten active substances with the highest ROR were moclobemide, isocarboxazid, oxitriptane, tranylcypromine, melitracen, phenelzine, linezolid, amoxapine, reboxetine and tryptophan; with values of ROR ranging from 44.19 (95% CI: 25.38–76.94) of tryptophan to 388.36 (95% CI: 314.58-479.46) of moclobemide. The ROR for the most commonly involved drugs was higher in the group of older adults (65 > years old), and higher in males.

Conclusion Prescribers need to be vigilant about drugs that can raise serotonin concentration or influence serotonergic neurotransmission, also when using drugs with less well-known risk for serotonin syndrome, like linezolid and triptans.

Keywords Serotonin syndrome · Serotonergic drugs · Pharmacovigilance · Adverse drug reaction · Drug safety

Introduction

Serotonin syndrome is a rare and potentially fatal adverse drug reaction (ADR) caused by drugs with serotonergic properties and is due to increases in serotonin concentration or activation of the 5-HT, principally central postsynaptic 5HT-$_{1\,A}$ and, most notably, 5HT-$_{2\,A}$ receptors in the central nervous system. The syndrome is also called serotonin toxicity and severity depends on the amount of increased serotonin. Serotonin syndrome presents a classic triad of clinical symptoms: neuromuscular hyperactivity (such as clonus, myoclonus, tremor, hyperreflexia, rigidity), autonomic nervous system excitation (such as hyperthermia, tachycardia, diaphoresis) and altered mental state (agitation, confusion) [1–3].

Severe events can occur after stimulation of 5-HT receptors by drugs that increase serotonergic effects [1] (such as tryptophan, a serotonin precursor), drugs causing serotonin release (such as fenfluramine, sibutramine and amphetamines) or drugs that inhibit serotonin reuptake (such as selective serotonin reuptake inhibitors, SSRIs; serotonin and norepinephrine reuptake inhibitors, SNRIs, linezolid and monoamine oxidase (MAO) inhibitors). Many opioids may also block serotonin and noradrenaline reuptake, causing the serotonin syndrome [4]. Recent reports have also suggested that antiemetics and antinauseants acting as 5-HT$_3$ antagonists can contribute to serotonin syndrome, through the excessive stimulation of other serotonin receptors, such

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as 5-HT_{1A} and 5-HT_{2A}, as a result of increased levels of serotonin due to 5-HT_3 receptor antagonism [5].

Serotonin syndrome is only described in some case reports, but no epidemiological studies have investigated the drug classes most closely related to the syndrome and the frequency of this ADR in relation to age and sex. Again, the causal relationship with some medications (e.g. triptans or linezolid) is still not clear [6, 7].

We analysed adverse events in the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) data set to investigate: (i) the main drug classes and active substances related to reports of serotonin syndrome; (ii) the reporting risk in relation to age and sex.

Methods

We ran a disproportionality analysis based on data from the FAERS database to assess whether there was any disproportion in the numbers of reports of serotonin syndrome in patients receiving drugs causing serotonin release or affecting serotonin reuptake. Reports were extracted from inception (1 January 2004) up to 30 September 2022. The FAERS database is a global repository for post-marketing safety reports, and pharmacovigilance using this database provides a warning of potential issues with marketed drugs [8, 9].

We used the online tool OpenVigil 2.1 (https://openvigil.sourceforge.net/) to query the FAERS database. OpenVigil 2.1 is a pharmacovigilance tool for data extraction, cleaning, mining and analysis on the FAERS database [10, 11]. OpenVigil 2.1 has already mapped arbitrary drug names (such as brand names, generic names, abbreviations, misspelt names, ecc.) to single names and allow one to query the database also through the Anatomical Therapeutic Chemical (ATC) Classification System of drugs.

Thus, we first identified each drug according to its ATC code, as reported in Supplementary Table S1. In the FAERS database, adverse events are coded according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology. We detected all adverse events according to the Preferred Terms (PTs) from the MedDRA dictionary using the definition "Serotonin Syndrome" suggested by the tool, and for each report we selected the most recent version of reported cases.

Results are presented as Reporting Odds Ratios (ROR) [12, 13], a ratio similar to the odds ratio in case-control studies with their 95% confidence interval, calculated to establish the association between drugs investigated and the occurrences of serotonin syndrome reported events. The ROR is the ratio of the odds of reporting of one specific event (serotonin syndrome for a given drug) versus all other events compared to this reporting odds for all other drugs present in the database and registered during the same period. So the ROR compared cases and non-cases and a signal is considered when the lower limit of the 95% confidence interval (CI) of the ROR is greater than one [14]. A higher ROR indicates a stronger relation and any consideration was accorded to the criteria of Evans [15]. Institutional review board approval was not required because FAERS is an anonymized database open to pharmacovigilance centers.

Results

We found 8,997 cases of reported serotonin syndrome in 18 years of post-marketing safety reports of FAERS. SSRIs was the class of drugs with most reports of serotonin syndrome (4,548), followed by opioids (3,159) and other antidepressants (2,145). Table 1 shows the numbers of cases and the ROR regarding each class of drugs related to serotonin syndrome and individual substances. At class level the highest ROR were found for MAO inhibitors (45.99, 95% CI: 41.21–51.33) and SSRIs (32.66, 95% CI: 31.33–34.04).

The ten active substances with the highest ROR were moclobemide, isocarboxazid, oxitriptane, tranylcypromine, melitracen, phenelzine, linezolid, amoxapine, reboxetine and tryptophan, with values of ROR ranging from 44.19 (95% CI: 25.38–76.94) of tryptophan to 388.36 (95% CI: 314.58-479.46) of moclobemide.

Among the classes with highest number of reported cases of serotonin syndrome, the ROR was similar for the individual substances of the SSRIs, ranging from 18.06 (95% CI: 16.82–19.39) for citalopram to 33.33 (95% CI: 27.54–40.34) for fluvoxamine. Differently, among the opioids the ROR ranged from 0.45 (95% CI: 0.19–1.09) for oxymorphone to 17.75 (95% CI: 15.24–20.67) for tapentadol.

Among the 6,938 cases with complete information on age, 526 (7.6%) were patients under 17 years of age; 5,010 (72.2%) were adults between 18 and 64 years; and 1402 (20.2%) were over 65 years. The ROR for the most commonly involved drugs was higher in the group of older adults (Table 2). The risk was higher for opioids; tricyclic and tetracyclic antidepressants; triptans; linezolid and methylphenidate.

Among the 7,891 cases with complete information on sex, 4,633 (58.7%) of cases were female, but ROR for the most commonly involved drugs was higher in males (Table 3). For example, ROR for SSRIs were 41.15 (male) vs. 28.09 (female); for SNRIs were 26.68 vs. 21.70; for tricyclic and tetracyclic antidepressants were 20.04 vs. 12.67. In contrast, the ROR was higher in females for linezolid (61.32 vs. 43.27) and MAO inhibitors (48.08 vs. 35.12).

Table 1 Main drug classes and substances related to serotonin syndrome

Class of drugs	No. of cases [b]	Reporting Odds Ratio (ROR) (95% confidence interval)
SSRIs	4548[b]	32.66 (31.33–34.04)
Escitalopram	1592	19.14 (18.12–20.21)
Sertraline	1332	18.97 (17.89–20.11)
Fluoxetine	1022	22.96 (21.49–24.52)
Citalopram	856	18.06 (16.82–19.39)
Paroxetine	814	18.29 (17.01–19.67)
Fluvoxamine	110	33.33 (27.54–40.34)
Opioids	3159 [b]	5.52 (5.29–5.77)
Tramadol	1223	17.09 (16.08–18.15)
Codeine	965	2.19 (2.05–2.34)
Fentanyl	636	10.17 (9.38–11.03)
Oxycodone	371	1.99 (1.79–2.21)
Morphine	198	2.21 (1.92–2.55)
Dextromethorphan	189	13.63 (11.79–15.75)
Methadone	175	6.88 (5.92–7.99)
Hydromorphone	173	2.41 (2.07–2.80)
Tapentadol	171	17.75 (15.24–20.67)
Buprenorphine	110	1.65 (1.37–1.99)
Pethidine	81	15.76 (12.65–19.65)
Oxymorphone	5	0.45 (0.19–1.09)
Other antidepressants[a]	2145 [b]	15.55 (14.81–16.33)
Bupropion	708	12.45 (11.52–13.44)
Mirtazapine	665	21.55 (19.90-23.33)
Trazodone	661	18.52 (17.10-20.06)
Vortioxetine	163	15.99 (13.68–18.69)
Agomelatine	18	26.75 (16.76–42.71)
Mianserine	18	11.29 (7.09–17.96)
Oxitriptane	15	127.69 (74.84-217.86)
Nefazodone	15	8.89 (5.35–14.78)
Reboxetine	13	44.19 (25.38–76.94)
Triptofan	12	44.53 (25.00-79.31)
SNRIs	1258 [b]	24.14 (22.73–25.63)
Desvenlafaxine	1403	21.57 (20.37–22.85)
Venlafaxine	1258	24.14 (22.73–25.63)
Duloxetine	1083	17.12 (16.06–18.25)
Tricyclic and tetracyclic antidepressants	764 [b]	15.09 (14.01–16.26)
Amitriptyline	492	15.10 (13.78–16.55)
Clomipramine	126	37.51 (31.38–44.85)
Nortriptyline	48	6.12 (4.60–8.13)
Doxepin	37	6.60 (4.78–9.13)
Trimipramine	36	11.25 (8.09–15.62)
Imipramine	31	12.16 (8.53–17.33)
Desipramine	11	15.39 (8.48–27.91)
Amoxapine	10	45.44 (24.14–85.54)
Opipramol	8	18.32 (9.11–36.85)
Melitracen	5	89.76 (36.10-223.19)
Linezolid	475	53.46 (48.65–58.75)
Antiemetics and antinauseants(serotonin ($5HT_3$) antagonists)	427 [b]	9.39 (8.52–10.35)
Ondansetron	378	9.55 (8.61–10.59)
Granisetron	46	1.55 (8.63–15.46)
Palonosetron	4	1.60 (0.60–4.26)
Dolasetron	2	4.08 (1.02–16.36)

Table 1 (continued)

Class of drugs	No. of cases [b]	Reporting Odds Ratio (ROR) (95% confidence interval)
MAO inhibitors	344 [b]	45.99 (41.21–51.33)
Moclobemide	117	388.36 (314.58-479.46)
Rasagiline	87	24.22 (19.56–29.98)
Phenelzine	61	57.08 (44.10-73.88)
Tranylcypromine	56	97.39 (74.07-128.04)
Selegiline	22	11.91 (7.82–18.14)
Safinamide	9	23.74 (12.26–45.95)
Isocarboxazid	4	137.07 (48.55-386.99)
Lithium	336	18.78 (16.82–20.95)
Triptans	219 [b]	6.83 (5.97–7.82)
Sumatriptan	119	5.63 (4.70–6.75)
Rizatriptan	42	9.18 (6.77–12.45)
Eletriptan	27	6.98 (4.78–10.20)
Zolmitriptan	21	7.40 (4.81–11.37)
Almotriptan	9	25.65 (13.24–49.68)
Naratriptan	7	8.07 (3.84–16.98)
Metoclopramide	215	6.98 (6.10–7.99)
Buspirone	203	7.44 (6.47–8.55)
Methylphenidate	194	6.07 (5.27–7.01)
Amphetamine	77	3.95 (3.15–4.94)
Methamphetamine	58	16.92 (13.04–21.94)
Cocaine	42	7.16 (5.28–9.70)
Sibutramine	5	4.52 (1.88–10.88)
Phentermine	4	1.14 (0.43–3.03)

[a] Antidepressants excluded SSRI, SNRI, MAO inhibitors, tricyclic and tetracyclic antidepressant

[b] For each class the number of cases can be lower than the sum of each active substance due to the possibility that a spontaneous reporting of adverse drug reaction is referred to more than one active substance

Discussion

This study investigated the classes of drug and active substances most at risk for serotonin syndrome reporting in clinical practice. The number of cases between 2004 and 2022 was highest for SSRIs, followed by opioids and SNRIs, while MAOi was the class with the highest risk of serotonin syndrome reporting risk. Again, the serotonin syndrome reporting risk was generally higher in older adults and the number of cases were similar for males and females, but the reporting risk was higher in males, who could be at higher risk for this severe central nervous system ADR. Even though our study confirms that ADR are more frequent in older adults, for this suspected adverse reaction we did not find a definite higher prevalence in women than men, as suggested by some pharmacovigilance studies [16, 17].

Our study confirms that among the opioids those classified as high-medium risk of serotonin toxicity, such as tramadol, fentanyl, dextromethorphan, tapentadol and pethidine, [4] had the highest relation with the risk of serotonin syndrome. In fact, many opioids, in particular synthetic opioids, have actions on other targets, for example blocking serotonin reuptake or having affinity with postsynaptic receptors 5-HT_{1A} and 5-HT_{2A} [18].

A recent review found a lack of data supporting severe consequences of serotonin toxicity for linezolid [7], but we found that linezolid was strictly related with serotonin syndrome despite the small number of cases reported. The study also found several reports of serotonin syndrome for triptans, though the relation is not clear because of the lack of biological plausibility since triptans do not act on 5-HT_{2A} receptors and very little on 5-HT_{1A} [6], and the number of published cases reported is small. Similarly, a significantly higher reporting risk was found for the 5-HT_3 antagonists, although these medications do not have the pharmacological properties necessary to contribute to serotonergic effects. However, as the WHO report suggested, there may be greater vulnerability with the concomitant use of 5-HT_3 antagonists and some serotonergic drugs, for the increased availability of serotonin (which can stimulate 5-HT_{1a} and 5-HT_{2a} receptors) due to 5-HT_3 receptor antagonism [5].

The main strength of this study is that, as far as we know, it is the first systematic investigation of the association between different medications acting on serotonin receptors and serotonin syndrome reports, using real world data. With a validated method to detect differences in ADR reports, our analysis shows the medications at greater risk of serotonin syndrome reporting rates, as well as the reporting risk in relation to age and sex. Again, a selection bias can be excluded since we used all records available, even if under reporting or selective reporting cannot be excluded.

Table 2 Drugs related to serotonin syndrome stratified by age groups

	Number of cases	Reporting Odds Ratio (ROR) (95% confidence interval)
SSRIs		
0–17 years	343	36.54 (30.52–43.76)
18–64 years	2547	21.64 (20.47–22.88)
> 65 years	779	44.57 (40.10-49.54)
Opioids		
0–17 years	137	3.32 (2.73–4.03)
18–64 years	1848	5.43 (5.12–5.75)
> 65 years	576	7.47 (6.71–8.31)
Other antidepressants		
0–17 years	91	12.90 (10.28–16.21)
18–64 years	1244	10.89 (10.21–11.61)
> 65 years	327	17.23 (15.22–19.51)
SNRIs		
0–17 years	70	20.04 (15.53–25.86)
18–64 years	1465	16.27 (15.31–17.30)
> 65 years	315	22.85 (20.14–25.92)
Tricyclic and tetracyclic antidepressants		
0–17 years	17	6.95 (4.27–11.30)
18–64 years	524	11.33 (10.35–12.42)
> 65 years	109	12.95 (10.64–15.76)
Linezolid		
0–17 years	12	13.28 (7.45–23.69)
18–64 years	216	33.91 (29.49–38.99)
> 65 years	114	53.79 (44.27–65.36)
Antiemetics and antinauseants		
0–17 years	32	8.31 (5.79–11.90)
18–64 years	254	8.71 (7.67–9.89)
> 65 years	69	7.77 (6.09–9.90)
MAO inhibitors [a]		
0–17 years	1	17.53 (2.39-128.57)
18–64 years	151	42.90 (36.30–50.70)
> 65 years	92	42.91 (34.63–53.17)
Lithium		
0–17 years	32	20.48 (14.24–29.45)
18–64 years	232	12.42 (10.87–14.18)
> 65 years	28	16.13 (11.07–23.50)
Triptans		
0–17 years	5	4.66 (1.92–11.27)
18–64 years	136	5.21 (4.39–6.19)
> 65 years	19	12.41 (7.88–19.56)
Metoclopramide		
0–17 years	4	3.56 (1.33–9.55)
18–64 years	143	11.28 (9.53–13.33)
> 65 years	33	9.01 (6.37–12.74)
Buspirone		
0–17 years	7	4.48 (2.12–9.46)
18–64 years	136	7.07 (5.96–8.39)
> 65 years	23	4.63 (3.06–6.99)
Methylphenidate		
0–17 years	58	3.24 (2.46–4.25)
18–64 years	87	7.34 (5.93–9.08)
> 65 years	13	22.38 (12.90-38.81)
Amphetamine[a]		
0–17 years	2	1.13 (0.28–4.53)
18–64 years	51	3.81 (2.89–5.02)
> 65 years	12	39.82 (22.37–70.90)

[a] According to the criteria of Evans 2001 (n > 2, chisq > 4, PRR > 2) this combination of drug(s) and adverse event(s) among 0–17 years old patients is probably not related

Reporting Odds Ratios were not calculated for sibutramine and phentermine because of the small number of cases reported (respectively 4 and 1). Reporting Odds Ratios were not calculated for cocaine and methamphetamine because all the cases except one were in the 18–64 years group

Table 3 Drugs related to serotonin syndrome stratified by sex

	Number of cases	Reporting Odds Ratio (ROR) (95% confidence interval)
SSRIs		
female	2339	28.09 (26.51–29.76)
male	1737	41.15 (38.40–44.10)
Opioids		
female	1663	5.95 (5.60–6.31)
male	1146	4.83 (4.50–5.19)
Other antidepressants		
female	1169	14.51 (13.58–15.51)
male	729	16.35 (15.05–17.76)
SNRIs		
female	1339	21.70 (20.36–23.13)
male	736	26.68 (24.56–28.98)
Tricyclic and tetracyclic antidepressants		
female	397	12.67 (11.43–14.05)
male	301	20.04 (17.78–22.59)
MAO inhibitors		
female	158	48.08 (40.90-56.52)
male	128	35.12 (29.35–42.02)
Linezolid		
female	197	61.32 (52.98–70.96)
male	187	43.27 (37.24–50.29)
Antiemetics and antinauseants		
female	194	7.59 (6.57–8.76)
male	162	10.33 (8.82–12.11)
Lithium		
female	149	16.47 (13.97–19.41)
male	157	21.31 (18.13–25.05)
Triptans		
female	170	7.11 (6.09–8.29)
male	37	7.68 (5.55–10.63)
Metoclopramide		
female	129	7.28 (6.10–8.67)
male	57	5.94 (4.57–7.73)
Buspirone		
female	118	7.00 (5.83–8.41)
male	64	7.44 (5.80–9.53)
Methylphenidate		
female	62	5.74 (4.47–7.38)
male	115	7.19 (5.97–8.70)
Amphetamine		
female	37	3.59 (2.60–4.96)
male	34	5.02 (3.58–7.05)
Methamphetamine		
female	9	7.48 (3.88–14.42)
male	47	23.78 (17.78–31.82)
Cocaine		
female	27	15.09 (10.31–22.09)
male	10	2.77 (1.49–5.15)

Reporting Odds Ratios were not calculated for sibutramine and phentermine because of the small number of cases reported (respectively 5 and 3)

This work has some limitations inherent to the method, like every pharmacovigilance study [19]: the lack of systematic recording of drug exposure duration or drug doses meant we could not discuss the role of higher doses of the different medications in the occurrence of serotonin syndrome. Because FAERS is an adverse events database, our analysis can only show an increase in the frequency of reports of serotonin syndrome among all reported adverse events, with no direct comparison of classes of medication.

Our study suggests that some signals, especially those found for drugs with a small number of cases reported, should be more carefully analysed in larger pharmaco-epidemiological studies and that future studies should compare the risk of serotonin syndrome between the different active substances among the same drug class.

Conclusions

Prescribers need to be vigilant about drugs that can raise serotonin concentrations or influence serotonergic neurotransmission, such as SSRIs, opioids, SNRIs and MAOi, particularly in older adults and male patients. Clinicians should be careful when using drugs with less well-known risk for serotonin syndrome, like linezolid and triptans, and must take account of the risk of serotonin syndrome in their risk-benefit analysis.

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Data availability The data are openly available in the FDA Adverse Event Reporting System Public Dashboard at https://openvigil.sourceforge.net/.

Declarations

Conflict of interest The authors have no conflicts of interest directly relevant to the content of this manuscript.

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