PSYCHOGERIATRICS
The Official Journal of the Japanese Psychogeriatric Society

doi:10.1111/psyg.12849 PSYCHOGERIATRICS 2022; 22: 502–508

ORIGINAL ARTICLE

Antidepressant-induced serotonin syndrome in older patients: a cross-sectional study

Neziha ERKEN [1a], **Derya KAYA** [2,3a], **Fatma Sena DOST** [2,3], **Esra ATES BULUT** [3,4] and **Ahmet Turan ISIK** [2,3]

[1]Department of Geriatric Medicine, Faculty of Medicine, Gaziantep University, Gaziantep, [2]Unit for Aging Brain and Dementia, Department of Geriatric Medicine, Faculty of Medicine, Dokuz Eylul University and [3]Geriatric Science Association, Izmir and [4]Department of Geriatric Medicine, Adana Numune Training and Research Hospital, Adana, Turkey

Correspondence: Ahmet Turan ISIK MD, Chair, Professor of Geriatric Medicine, Unit for Brain Aging and Dementia, Department of Geriatric Medicine, School of Medicine, Dokuz Eylul University, Izmir, Turkey. Email:atisik@yahoo.com

[a]Equally contributed.

Received 1 February 2022; revision received 13 April 2022; accepted 25 April 2022.

Abstract

Background: Widespread prescription of antidepressants and their resulting role in serotonin syndrome (SS) are of great importance for clinical practice in the elderly. This study aims to investigate possible associations of antidepressant drug-induced SS with related variables in these patients.

Methods: A total of 238 older adults using antidepressants were included. Patients who fulfilled the Hunter Serotonin Toxicity Criteria (HSTC) for SS were considered as the clinical groups (mild, moderate, or severe), and those who did not as the control group. We recorded all patients' demographic and clinical characteristics, including age, gender, comorbidity index, number of medications, daily equivalent dose of the relevant antidepressant according to fluoxetine per day, electrocardiogram test results, laboratory results, and management.

Results: The mean age of all patients was 75.4 ± 7.6 years and 63.4% were female. Sixty patients had SS, while 178 patients did not. There was a significant difference between those with and without SS in terms of gender, frequency of combination antidepressant therapy, and daily equivalent antidepressant dose ($P < 0.05$). The most common diagnostic findings in SS patients were tremor and hyperreflexia and 31.7% was mild, and moderate in 68.3% with higher median age and number of medications ($P < 0.041$). Antidepressants were discontinued in all patients regardless of severity, of whom 71.7% were treated with benzodiazepines and 36.7% with cyproheptadine. After adjusting for age and sex, association with use of SSRI + SNRI, use of any combination therapy, and daily equivalent dose remained significant.

Conclusions: The widespread single or combined use of antidepressants in older adults represents an increased clinical concern for SS and physicians should be aware of this drug-related complication in older patients.

Key words: *antidepressant, serotonin, serotonin syndrome, SNRI, SSRI, toxicity.*

INTRODUCTION

One of the most common prescriptions for older adults is antidepressant medication used for a variety of indications including depression, anxiety, sleep disorders, urinary incontinence, and neuropathic pain.[1] The risks and benefits of antidepressant drugs have been an intriguing area of research in older adults, a vulnerable population, as they are likely to be at increased risk for adverse events due to multimorbidity, cognitive impairment, drug–drug interactions, polypharmacy, and aging kidney. Therefore, assessing antidepressant drugs' risk of QTc prolonging effect,[2] bleeding, hyponatremia, sexual dysfunction, hypertension, seizure, and serotonin syndrome (SS) are of great importance in clinical practice.[3,4]

Among these adverse effects, SS is considered one of the potentially life-threatening entities. SS, also referred to as serotonin toxicity, is characterized by increased serotonergic activity in the peripheral and central nervous systems, depending on the level

of free serotonin (5-hydroxytryptamine (5-HT)), or 5-HT receptor activation, in particular the 5-HT_{1A} and 5-HT_{2A} subtypes.[4–6] The clinical findings, ranging from a clonus to a severe mental state change, require an established set of decision rules, and the Hunter Serotonin Toxicity Criteria (HSTC)[7] are the most commonly used diagnostic criteria for SS. Initiation of a serotonergic drug, increasing the therapeutic dose of a single serotonergic drug, or adding a second serotonergic one has been blamed in the aetiology.[4] Therefore, a thorough inquiry about all types of drugs, including over-the-counter drugs, dietary supplements, and illegal ones,[8,9] is crucial for differential diagnosis and management.

Furthermore, the true incidence of SS due to antidepressants is unknown because of several factors: (i) it has not been the primary outcome of controlled clinical antidepressant trials; (ii) its mild forms may easily be overlooked, or physicians may not be familiar with the entity.[10,11] On the other hand, apart from antidepressants, some analgesics and antiparkinsonian medications are other serotonergic agents commonly received by older adults. Given the aforementioned reasons, and the presence of comorbidities and factors that predispose to drug side effects such as age-related pharmacodynamic changes, antidepressant drug-induced SS in older adults certainly requires a better understanding; however, data on the subject is scarce in the literature. Therefore, we aimed to investigate the occurrence/rate of antidepressant drug-induced SS and its possible associations with related variables using HSTC in an effort to avoid the confounding effects of other serotonergic drugs by using a detailed drug history.

MATERIALS AND METHODS

Study population

Two hundred thirty-eight outpatients, aged 60 years and older, using antidepressants who were admitted to our geriatric department between June 2015 and June 2020 were included in this cross-sectional study. The study was conducted according to the Declaration of Helsinki and the Committee on Publication Ethics (COPE) guidelines and approved by the ethics committee of Dokuz Eylul University, Faculty of Medicine (IRB number: 2020/27–13). Informed consent was obtained for the study. All patients had a least one of the comorbidities common in older adults or geriatric syndromes, such as hypertension, diabetes mellitus, sleep disorder, chronic pain, osteoarthritis, cardio-cerebrovascular disease, osteoporosis, movement disorder, dementia, geriatric depression, urinary incontinence, as reflected in the Charlson comorbidity index shown in Table 1.

Patients using serotonergic agents other than antidepressants (e.g., tramadol, antiemetics, antipsychotics, monoamine oxidase inhibitors, fentanyl, levodopa, linezolid) were excluded from the study.[9,12–15] Criteria for inclusion in the SS clinical groups were a diagnosis of SS using the Hunter Serotonin Toxicity Criteria (HSTC),[7] which requires the presence of one of the following classic features or groups of traits in a subject using a serotonergic agent: spontaneous clonus; inducible clonus with agitation or diaphoresis; ocular clonus with agitation or diaphoresis; tremor and hyperreflexia; or hypertonia, plus temperature above 100.4° F (38°C) and ocular or inducible clonus. Further, those with SS were further divided into the three clinical groups of mild, moderate, and severe.[16] Those who used antidepressants and complied with the study pattern but were not diagnosed with SS according to HSTC were considered as the control group.

Measurements

For all patients, we recorded the following demographic and clinical characteristics: age; gender; comorbidity index; number of medications; 12-lead surface electrocardiogram (ECG) test results including heart rate, PR, QT and QTc interval, and QRS duration; laboratory results (sodium, potassium, magnesium, creatinine kinase); and management.

Classification and dosages of antidepressants

All patients were classified into six subgroups according to the type of antidepressants: (i) selective serotonin reuptake inhibitors (SSRIs) including citalopram, escitalopram, sertraline, paroxetine, fluoxetine, fluvoxamine; (ii) serotonin-noradrenaline reuptake inhibitors (SNRIs) including duloxetine and venlafaxine; (iii) noradrenaline and specific serotonergic antidepressants (NASSAs); (iv) serotonin antagonists and reuptake inhibitors (SARIs); (v) tricyclic antidepressants (TCAs); (vi) combination therapy. Since the main prescriptions for NASSAs and SARIs in our country are mirtazapine and trazodone, respectively, only the names of these two antidepressants will be used throughout the text.

Table 1 Demographic and clinical features of the study population

	Patients with SS (n=60)	Controls (n = 178)	P-value
Age	76.3 ± 8.0	75.1 ± 7.5	0.302
Sex, F *n* (%)	45 (75)	105 (59.3)	0.029*
CCI	4.5 ± 1.2	4.0 ± 1.7	0.147
Number of medication	6.5 ± 2.7	6.2 ± 2.2	0.868
Symptoms on admission/diagnosis *n* (%)			
Spontaneous clonus	9 (15)	–	
Inducible clonus and agitation or diaphoresis	19 (31.7)	–	
Ocular clonus and agitation or diaphoresis	6 (10)	–	
Tremor and hyperreflexia	53 (88.3)	–	
Hypertonia and temperature >38°C and ocular clonus or inducible clonus	1 (1.7)	–	
Use of any combination antidepressant therapy *n* (%)	28 (46.7)	49 (27.7)	0.007*
Antidepressive agent *n* (%)			
SSRI	29 (48.3)	105 (59.0)	
SSRI + trazodone	14 (23.3)	42 (23.6)	
SSRI + SNRI	5 (8.3)	1 (0.6)	
SSRI + mirtazapine	4 (6.7)	3 (1.7)	
SNRI	3 (5)	9 (5.1)	
Trazodone + mirtazapine	2 (3.3)	3 (1.7)	
SNRI + trazodone	1 (1.7)	2 (1.1)	
SSRI + SNRI + trazodone	1 (1.7)	0 (0)	
SSRI + SNRI + mirtazapine	1 (1.7)	0 (0)	
Trazodone	0 (0)	11 (6.2)	
Mirtazapine	0 (0)	2 (1.1)	
Equivalent dose,† mg/d	34.85 ± 18.38	28.17 ± 13.06	0.038*
ECG findings			
Heart rate	76.0 ± 21.2	71.2 ± 13.9	0.282
PR interval	159.1 ± 25.5	167.8 ± 30.5	0.077
QRS	91.4 ± 19.4	93.2 ± 18	0.348
QT	392.6 ± 30.8	400 ± 34.4	0.492
QTc	417.4 ± 20.3	419.5 ± 27.7	0.716
Laboratory			
Sodium, mmol/L	140 ± 3.8	139.8 ± 2.6	0.592
Potassium, mmol/L	4.1 ± 0.4	4.2 ± 0.3	0.06
Magnesium, mmol/L	0.83 ± 0.1	0.82 ± 0.08	0.114
Creatinine kinase, U/L	79.2 ± 57.9	87.6 ± 89.9	0.398

*P < 0.05 is considered statistically significant. † Dose equivalency of antidepressive agents was calculated according to fluoxetine per day. SS, serotonin syndrome; CCI, Charlson comorbidity index; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-noradrenaline reuptake inhibitor.

Combination therapy means the concurrent use of at least two different antidepressants.

SS patients' antidepressive agent dosage per day was provisionally calculated in accordance with Hayasaka *et al*.'s study of recommendations from randomized controlled trials. Following their study, dose equivalency of antidepressants was calculated using fluoxetine as the standard. Thus, fluoxetine 40 mg/day was accepted as equivalent to dosages of paroxetine 34 mg/day, escitalopram 18 mg/day, fluvoxamine 143 mg/day, mirtazapine 50 mg/day, sertraline 100 mg/day, trazodone 400 mg/day, and venlafaxine 150 mg/day, and with less consistent data, it was considered equivalent to duloxetine 60 mg/day and citalopram 40 mg/day.[17]

Statistical analysis

Statistical analyses were performed with IBM SPSS V.22.0 for Windows (SPSS, IBM Software Group, Chicago, IL, USA). Numerical variables were displayed as numbers of cases and percentages. For comparisons of common demographic and clinical data between the patients with and without SS, the Mann–Whitney *U*-test was used for continuous variables and the chi-squared test was adopted for categorical variables. Univariate logistic regression (odds ratio (OR) and 95% confidence

interval (CI)) analysis was carried out to examine the bivariate relationships between SS and variables. Then, a binary logistic regression (OR and 95% CI) analysis adjusted for age and sex was run to find the association for the related significant variables. A probability level of $P < 0.05$ was considered statistically significant.

RESULTS

The mean age of all patients was 75.4 ± 7.6 years and 63.4% were female. The mean number of medications was 6.3 ± 2.4, and the mean equivalent dose of antidepressants was 29.8 ± 14.8 mg/day. Out of 238 outpatients, 60 (25.2%) patients had SS, but 178 (74.8%) patients did not. Most of the patients were using SSRIs ($n = 134$, 56.3%), SSRIs plus trazodone ($n = 56$, 23.5%), and SNRIs ($n = 12$, 5%), whereas none were using TCAs. One hundred fifty-nine patients (66.8%) received only one antidepressant, and 79 patients (33.2%) combined two or three antidepressants. Those treated with combinations of three antidepressants (1 patient each for SSRI + SNRI + mirtazapine and SSRI + SNRI + trazodone) had SS.

There was a significant difference between those with and without SS in terms of gender, frequency of combination antidepressant therapy, and daily equivalent antidepressant dose ($P < 0.05$ for each); however, as seen in Table 1, there was no difference in terms of age, comorbidity index, number of drugs, laboratory results, and ECG findings.

The most common diagnostic findings in SS patients were tremor and hyperreflexia (88.3%). Of all patients with SS, 31.7% ($n = 19$) were grouped as mild, with a median age of 76 (60–90) years, and 68.3% ($n = 41$) as moderate, with a median age of 79 (62–93) years ($P = 0.040$). There was no severe case in our study population. The median number of medications was higher in those with moderate compared with mild severity, 5 (range 2–13) versus 6 (range 3–13), respectively ($P = 0.019$). Antidepressants were discontinued in all patients with SS, regardless of severity, of whom 71.7% ($n = 43$) were treated with benzodiazepines and 36.7% ($n = 22$) with cyproheptadine (12 mg/day initially, then 2 mg every 2 h until symptoms resolved).

Table 2 shows the bivariate relationships between SS and the SS patients' variables. At the univariate level performed with logistic regression analysis, SS was associated with female gender, with combination therapy (at least any two antidepressive agents) including particularly SSRI + mirtazapine and the combination of SSRI + SNRI, and with daily equivalent dose.

Table 2 Bivariate relationships between serotonin syndrome and variables of the patients

Variables	OR (95% CI)	*P*-value
Age (years)	1.020 (0.982–1.061)	0.304
Sex (female)	2.13 (1.09–4.17)	0.027*
CCI	1.182 (0.976–1.431)	0.087
Number of drugs	1.041 (0.920–1.176)	0.526
Any combination therapy	2.17 (1.19–3.98)	0.011*
SSRI	1.207 (0.307–4.74)	0.788
SSRI + SNRI	18.10 (2.03–161.12)	0.009*
SSRI + trazodone	1.207 (0.581–2.508)	0.614
SSRI + mirtazapine	4.82 (1.022–22.79)	0.047*
Trazodone + mirtazapine	2.41 (0.38–15.38)	0.347
Equivalent dose† (mg/d)	1.030 (1.010–1.050)	0.003*

* $P < 0.05$. † Dose equivalency of antidepressive agents was calculated according to fluoxetine per day. The reference category is older adults without serotonin syndrome (controls). OR, odds ratio; CI, confidence interval; CCI; Charlson comorbidity index; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-noradrenaline reuptake inhibitor.

The associations with use of SSRI + SNRI (OR 17.26, 95% CI 1.86–159.69), use of any combination therapy (OR 1.937, 95% CI 1.041–3.605), and daily equivalent dose (OR 1.025, 95% CI 1.005–1.046) remained significant after adjusting for age and sex (Table 3).

DISCUSSION

This cross-sectional and case–control study demonstrated that antidepressant-related SS in older adults was closely associated with SSRI + SNRI, daily equivalent-dose antidepressant use, and combination therapy, regardless of age or gender. Additionally, more than half of the patients with SS were moderately severe, older, and had a higher mean drug count than patients with mild SS.

Table 3 Age and gender-adjusted logistic regression analysis to evaluate the association between serotonin syndrome and the clinical parameters

	OR (95% CI)	*P*-value
Any combination therapy	1.937 (1.041–3.605)	0.037*
SSRI + SNRI	17.26 (1.86–159.69)	0.012*
SSRI + mirtazapine	3.75 (0.77–18.15)	0.100
Equivalent dose† (mg/d)	1.025 (1.005–1.046)	0.014*

* $P < 0.05$. † Dose equivalency of antidepressive agents was calculated according to fluoxetine per day. The reference category is older adults without serotonin syndrome (controls). The model is adjusted for age (years) and gender (male and female). OR, odds ratio; CI, confidence interval; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-noradrenaline reuptake inhibitor.

The prevalence of SS is not precisely known because it varies over a wide range depending on which diagnostic criteria are used for assessment, the setting, and the medication group.[18–20] The prevalence was 25% in the present study. Generally speaking, it is not uncommonly reported in older adults.[21] The reason for the higher prevalence in the elderly may be drug–drug interaction due to multidrug use, drug-disease interaction due to multiple diseases at the same time, or pharmacokinetics in this risky population. Besides, it is known that the addition of a second serotonergic agent increases the risk.[9] Accordingly, we found that SS was associated with the simultaneous administration of SSRIs and mirtazapine, and of SSRIs and SNRIs. However, after adjusting for age and sex, only the combined use of SSRIs and SNRIs remained relevant for SS. The additive effect of combined serotonin reuptake inhibition, rather than activation of 5-HT_{1A} receptors by mirtazapine with SSRI use, appears to be more notable for the development of SS. This may be due to the monoamine summation effect[22] of concomitant use of SNRIs and SSRIs, or the sedation or H1-antihistamine effect due to mirtazapine's high affinity for H1-histaminic receptors. However, this point needs to be explored in another study.

The most common finding of SS was neuromuscular hyperactivity, including hyperreflexia, clonus, and tremor, which could easily be overlooked if not examined in a patient receiving antidepressant medication.

Also, even when detected, this neuromuscular hyperreactivity may be attributed to other causes such as thyroid storm, essential tremor, or post-stroke sequelae in older adults. Awareness of the syndrome would lead to an increase in patients diagnosed with mild SS. On the other hand, some authors report that for patients with mild SS it may be considered that when the beneficial effect of the agent outweighs the side effects of serotonergic administration, this should be the focus of decision-making. In our study, one third of the patients with SS were mild and the rest were moderate, but antidepressants were discontinued in all SS patients, regardless of severity. In our clinical practice we discontinue serotonergic medication for all patients with SS because (i) the exact transition point between tolerable side effects of serotonergic administration and a toxic SS requiring withdrawal of medication is not known; and (ii) continuing the medication with close observation is not feasible in older patients in real life.

Overall prognosis in our patients was favourable, and we did not observe any severe complications such as rhabdomyolysis, liver damage, or seizure. None of our patients had severe SS, probably because severe cases may have presented to the emergency services rather than the outpatient clinic.

Previous studies of SS in older adults were either based on case reports or clinical studies conducted in the general population, or included all SS related to the causative agent.[23,24] Therefore, this study evaluating antidepressant-induced SS in older adults is unique as far as we are concerned. In this study, no patients received TCA and monoamine oxidase inhibitors, but all patients received predominantly SSRIs and other classes of antidepressants, including SSRIs combined with trazodone. Furthermore, when we compared the doses of antidepressants with respect to the daily dose of fluoxetine, we found that the equivalent daily dose of fluoxetine was associated with SS, and the SS was 1.09 times higher for each unit increase in the corresponding antidepressant dose. While it is not surprising that high doses of antidepressants are associated with SS, our results should alert healthcare professionals to the fact that the higher the dose of antidepressants, the higher the risk of SS in the elderly. On the other hand, it should be kept in mind that fatal SS may develop even with one or two serotonergic drugs at therapeutic doses.[24,25]

There is no consensus on the use of cyproheptadine in the management of SS. In a recent systematic review, cyproheptadine use was reported to be 16% among 56 SS patients with a mean age of 42.[24] In contrast, in another previous study, 23% of 288 patients (mean age 49.7) were treated with cyproheptadine and reported no benefit for worse outcomes of SS in patient populations, concluding that the use of cyproheptadine is questionable.[26] Accordingly, in this study, 37% of patients with SS received cyproheptadine more frequently than in previous reports, and this might be the reason why none of our patients progressed severely. Consequently, the use of cyproheptadine in SS needs to be further evaluated in randomized controlled trials.

The study has several strengths. To begin with, this is the first study to the best of our knowledge on

SS exclusively associated with exposure to antidepressant drugs in older adults. In addition, excluding confounding agents and using established diagnostic criteria allowed us to more accurately search for associations. Furthermore, we had a control group in the study who used antidepressants and did not meet the diagnostic criteria for SS. Accordingly, comorbidities and the number of drugs that may play an important role in the development of vulnerability with age in the SS patients could be evaluated. On the other hand, the study also had several limitations to consider. Specifically, the retrospective design and the small number of patients receiving certain classes of antidepressants did not allow for a comparison between subgroups. Nevertheless, we tried to make a comparable dose equivalence between them. Therefore, larger, prospective follow-up studies are needed to clarify the details of the relationship in the elderly.

CONCLUSION

The widespread single or combined use of antidepressants in older adults represents an increased clinical concern for SS. Therefore, physicians should be aware of this drug-related complication in older patients receiving serotonergic agents, especially antidepressants. Moreover, SS should be considered in older patients showing tremor and hyperreflexia, especially in females, those using any combination therapy and particularly SSRI with SNRI, and those using higher doses of antidepressant. Thus, early detection of this potentially life-threatening and easily recognizable complication can prevent these vulnerable patients from unnecessary interventions, polypharmacy, prescribing cascade, or even morbidity and mortality.

ACKNOWLEDGMENTS

We would like to thank Ayse Fadiloglu, Acelya G Yildirim, Mustafa Yildirim, Hemrin Kavak, Burak Karakaya for assisting the data collection.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1 Noordam R, Aarts N, Verhamme KM, Sturkenboom MC, Stricker BH, Visser LE. Prescription and indication trends of antidepressant drugs in The Netherlands between 1996 and 2012: a dynamic population-based study. *Eur J Clin Pharmacol* 2015; **71**: 369–375. https://doi.org/10.1007/s00228-014-1803-x.
2 Rochester MP, Kane AM, Linnebur SA, Fixen DR. Evaluating the risk of QTc prolongation associated with antidepressant use in older adults: a review of the evidence. *Ther Adv Drug Saf* 2018; **9**: 297–308. https://doi.org/10.1177/2042098618772979.
3 Wang SM, Han C, Bahk WM *et al*. Addressing the side effects of contemporary antidepressant drugs: a comprehensive review. *Chonnam Med J* 2018; **54**: 101–112. https://doi.org/10.4068/cmj.2018.54.2.101.
4 Scotton WJ, Hill LJ, Williams AC, Barnes NM. Serotonin syndrome: pathophysiology, clinical features, management, and potential future directions. *Int J Tryptophan Res* 2019; **12**: 1178646919873925. https://doi.org/10.1177/1178646919873925.
5 Isbister GK, Buckley NA. The pathophysiology of serotonin toxicity in animals and humans: implications for diagnosis and treatment. *Clin Neuropharmacol* 2005; **28**: 205–214. https://doi.org/10.1097/01.wnf.0000177642.89888.85.
6 Mignon L, Wolf WA. Postsynaptic 5-HT(1A) receptors mediate an increase in locomotor activity in the monoamine-depleted rat. *Psychopharmacology* 2002; **163**: 85–94. https://doi.org/10.1007/s00213-002-1121-3.
7 Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The hunter serotonin toxicity criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *QJM* 2003; **96**: 635–642. https://doi.org/10.1093/qjmed/hcg109.
8 Buckley NA, Dawson AH, Isbister GK. Serotonin syndrome. *BMJ* 2014; **348**: g1626. https://doi.org/10.1136/bmj.g1626.
9 Boyer EW, Shannon M. The serotonin syndrome [published correction appears in N Engl J med. 2007 Jun 7;356(23):2437] [published correction appears in N Engl J med 2009 Oct 22; 361(17):1714]. *N Engl J Med* 2005; **352**: 1112–1120. https://doi.org/10.1056/NEJMra041867.
10 Werneke U, Jamshidi F, Taylor DM, Ott M. Conundrums in neurology: diagnosing serotonin syndrome - a meta-analysis of cases. *BMC Neurol* 2016; **16**: 97. https://doi.org/10.1186/s12883-016-0616-1.
11 Mackay FJ, Dunn NR, Mann RD. Antidepressants and the serotonin syndrome in general practice. *Br J Gen Pract* 1999; **49**: 871–874.
12 Finberg JP, Rabey JM. Inhibitors of MAO-A and MAO-B in psychiatry and neurology. *Front Pharmacol* 2016; **7**: 340. https://doi.org/10.3389/fphar.2016.00340.
13 Francescangeli J, Karamchandani K, Powell M, Bonavia A. The serotonin syndrome: from molecular mechanisms to clinical

practice. *Int J Mol Sci* 2019; **20**: 2288. https://doi.org/10.3390/ijms20092288.
14 Sun-Edelstein C, Tepper SJ, Shapiro RE. Drug-induced serotonin syndrome: a review. *Expert Opin Drug Saf* 2008; **7**: 587–596. https://doi.org/10.1517/14740338.7.5.587.
15 Volpi-Abadie J, Kaye AM, Kaye AD. Serotonin syndrome. *Ochsner J* 2013; **13**: 533–540.
16 Wang RZ, Vashistha V, Kaur S, Houchens NW. Serotonin syndrome: preventing, recognizing, and treating it. *Cleve Clin J Med* 2016; **83**: 810–817. https://doi.org/10.3949/ccjm.83a.15129.
17 Hayasaka Y, Purgato M, Magni LR *et al*. Dose equivalents of antidepressants: evidence-based recommendations from randomized controlled trials. *J Affect Disord* 2015; **180**: 179–184. https://doi.org/10.1016/j.jad.2015.03.021.
18 Prakash S, Rathore C, Rana K. The prevalence of serotonin syndrome in an intensive care unit: a prospective observational study. *J Crit Care* 2021; **63**: 92–97. https://doi.org/10.1016/j.jcrc.2020.12.01.
19 Lejoyeux M, Rouillon F, Adès J. Prospective evaluation of the serotonin syndrome in depressed inpatients treated with clomipramine. *Acta Psychiatr Scand* 1993; **88**: 369–371. https://doi.org/10.1111/j.1600-0447.1993.tb03475.x.
20 Kaneda Y, Ishimoto Y, Ohmori T. Mild serotonin syndrome on fluvoxamine. *Int J Neurosci* 2001; **109**: 165–172. https://doi.org/10.3109/00207450108986532.
21 Poeschla BD, Bartle P, Hansen KP. Serotonin syndrome associated with polypharmacy in the elderly. *Gen Hosp Psychiatry* 2011; **33**: 301.e11. https://doi.org/10.1016/j.genhosppsych.2010.11.015.
22 Zhang ZH, Yang SW, Chen JY, Xie YF, Qiao JT, Dafny N. Interaction of serotonin and norepinephrine in spinal antinociception. *Brain Res Bull* 1995; **38**: 167–171. https://doi.org/10.1016/0361-9230(95)00084-r.
23 Moss MJ, Hendrickson RG. Toxicology investigators consortium (ToxIC). Serotonin toxicity: associated agents and clinical characteristics [published correction appears in J Clin Psychopharmacol. 2021 mar-Apr 01;41(2):226]. *J Clin Psychopharmacol* 2019; **39**: 628–633. https://doi.org/10.1097/JCP.0000000000001121.
24 Prakash S, Rathore C, Rana K, Prakash A. Fatal serotonin syndrome: a systematic review of 56 cases in the literature. *Clin Toxicol (Phila)* 2021; **59**: 89–100. https://doi.org/10.1080/15563650.2020.1839662.
25 Abadie D, Rousseau V, Logerot S, Cottin J, Montastruc JL, Montastruc F. Serotonin syndrome: analysis of cases registered in the French pharmacovigilance database. *J Clin Psychopharmacol* 2015; **35**: 382–388. https://doi.org/10.1097/JCP.0000000000000344.
26 Nguyen H, Pan A, Smollin C, Cantrell LF, Kearney T. An 11-year retrospective review of cyproheptadine use in serotonin syndrome cases reported to the California poison control system. *J Clin Pharm Ther* 2019; **44**: 327–334. https://doi.org/10.1111/jcpt.12796.