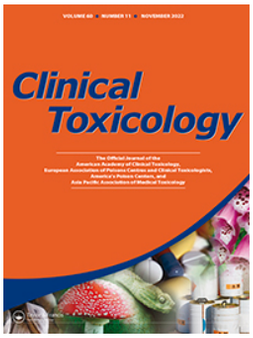

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CLINICAL RESEARCH

Predicting serotonin toxicity in serotonin reuptake inhibitor overdose

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ABSTRACT

Aims: We aimed to investigate the frequency of serotonin toxicity following overdose of antidepressants that inhibit serotonin reuptake and the factors that influence the probability of serotonin toxicity occurring.

Methods: This was a retrospective cohort study of overdoses that included selective serotonin reuptake inhibitors (SSRIs) (70%) and serotonin norepinephrine reuptake inhibitors (SNRIs) (30%) admitted to a tertiary toxicology unit over 23 years. A multivariate mixed effects logistic regression model using NONMEM (7.2.0) was used to determine factors that influenced the probability of serotonin toxicity occurring.

Results: There were 1978 overdoses in 1520 patients; median age 33 y (range: 13–86 years) and 64% female. Median defined daily dose equivalent (DDD) was 15 (1–420). Co-ingestants were taken in 1678/1978 (85%) overdoses: 11 co-ingested the monoamine oxidase-A inhibitor (MAOI) moclobemide, 99 (5%) co-ingested olanzapine, 58 (3%) co-ingested risperidone and 417 co-ingested a benzodiazepine (21%). Serotonin toxicity occurred in 269 overdoses (13.6%). The probability of serotonin toxicity increased slightly per 10 DDD units dose [OR, 1.01; 95% confidence intervals (CIs): 0.93–1.10], increased for an SNRI *vs.* an SSRI [OR, 1.07; 95% CI: 0.99–1.15], and markedly increased with co-ingestion of moclobemide [OR, 33.12; 95% CI: 7.5–147]. The probability decreased per 10 y age [OR, 0.84; 95% CI: 0.74–0.95], and with co-ingestion of the serotonin 2 A receptor (5-HT_{2A}) antagonists olanzapine [OR, 0.40; 95% CI: 0.17–0.94] or risperidone [OR, 0.13; 95% CI: 0.02–0.99]. The probability of serotonin toxicity was 12.5% at 1 DDD (therapeutic), 12.7% at 15 DDDs and 19% at 420 DDDs. In overdoses of the median dose of 15 DDDs, co-ingestion of moclobemide increased the probability to 83%, and co-ingestion of olanzapine or risperidone decreased it to 5.5% and 1.8%, respectively.

Conclusions: Serotonin toxicity is common following SSRI/SNRI overdose. Although dose increases probability, this was only a small effect. Co-ingestion with olanzapine or risperidone reduced the risk 2–6-fold, and moclobemide increased the risk 5-fold.

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Serotonin toxicity; serotonin syndrome; antidepressant; overdose; SSRI; SNRI; poisoning

Introduction

Serotonin toxicity, often termed serotonin syndrome, is a constellation of clinical effects associated with an excess in serotonin concentrations in the central nervous system causing increased stimulation at the serotonin receptors [1]. It typically occurs following ingestion of a drug in overdose, or sometimes with two or more drugs taken therapeutically, which have the potential to cause an increase in serotonin [2]. Serotonin toxicity presents as a triad of clinical effects, with neuromuscular and autonomic hyperactivity, and altered mental status [3,4].

The most common medications resulting in serotonin toxicity are the widely prescribed selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Other medications implicated include serotonin precursors, monoamine oxidase inhibitors (MAOIs), serotonin agonists and drugs that cause serotonin release. Diagnosis of serotonin toxicity has been problematic, initially with Sternbach's over-inclusive criteria [5]. In 2003, Dunkley et al. published the Hunter serotonin toxicity criteria based on a review of over 2000 cases following SSRI overdose which provided more specific and sensitive criteria for diagnosis [6]. Serotonin toxicity results in neuromuscular excitation, seen as clonus, myoclonus, hyper-reflexia and/or tremor; autonomic hyperactivity including tachycardia, diaphoresis, fever and/or mydriasis; and altered mental state such as confusion, excitement and/or agitation [6].

The pathophysiology of serotonin toxicity is not fully understood, except for life-threatening hyperthermia and increased tone, which appear to be due to excess serotonin at the synaptic cleft acting at the 5-hydroxytryptamine 2 A receptor (5-HT_{2A}) [1,7]. Severe serotonin toxicity is generally the result of a combination of two or more serotonergic drugs acting *via* different mechanisms, most commonly an SSRI or SNRI and a MAOI [2,4,8]. Deaths from antidepressant

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overdoses resulting in serotonin toxicity are characterised by rapidly rising temperature over 40 °C and increased tone leading to multiorgan failure [2,4,6,9–11].

The incidence of serotonin toxicity in SSRI and SNRI overdoses has been reported to be approximately 15% [2], which may be higher for the SNRI, venlafaxine [12,13]. Milder serotonergic signs and symptoms are well recognised and reported following therapeutic use of SSRIs and SNRIs, particularly following initiation of treatment or following dose increase. Discontinuation of antidepressant treatment due to adverse effects is recognised. A meta-analysis of 67 trials reported a discontinuation rate of 19.4% due to any side effect in patients treated with SSRIs [14]. Neurological adverse effects, likely attributed to serotonin excess, including tremors, headaches and dizziness were reported in 30% of patients who self-reported on their adherence to antidepressant treatment, with 20% also reporting anxiety, restless and agitation [15]. Similarly, the placebo-adjusted incidence rates for adverse effects that included anxiety, agitation or hostility, CNS stimulation or akathisia were 11%, 14.3% and 16.4% following therapeutic treatment of major depressive disorder with fluoxetine, paroxetine and sertraline, respectively, with reported rates of insomnia for these same three SSRIs of 6.7%, 7.1% and 7.6%, respectively [16]. It remains unclear why some patients experience serotonin-mediated adverse effects resulting from therapeutic treatment, or with symptoms of serotonin toxicity following SSRI or SNRI overdose, whilst others display mild or no symptoms. Genetic variation has been suggested as a factor, but published evidence is lacking particularly in the overdose population. Studies examining cytochrome P450 metaboliser status have mainly shown little or no association of this with serotonergic adverse effects from serotonergic antidepressants [17–19]. In addition, there is conflicting evidence seen with adverse effects of SSRIs at therapeutic doses and the association with polymorphisms of the 5-HT_{2A} receptor [20–22]. We previously found no association with serotonin toxicity and the T102C polymorphism of the 5-HT_{2A} receptor following overdose with serotonin reuptake inhibitors [23].

From a clinical perspective, it is important to understand what other factors influence the development of serotonin toxicity particularly following SSRI or other serotonergic overdose. There are a few studies examining the pharmacokinetics of SSRIs and SNRIs in overdose [24–27], but a lack of published evidence examining the pharmacodynamics of serotonergic antidepressants and serotonin toxicity. Combinations of factors, such as patient age and sex, the ingested dose, type of antidepressant, and any co-ingested medicines may impact on the frequency of serotonin toxicity following overdose. It remains unclear as to how important ingested dose is, because large SSRI overdoses often do not cause serotonin toxicity. However, combinations of therapeutic serotonergic drugs, such as an SSRI and a MAOI can cause severe serotonin toxicity [3,4]. It is therefore important to determine if, and by how much, does the dose ingested influence the risk of serotonin toxicity.

Non-specific 5-HT_2 antagonists, such as chlorpromazine and cyproheptadine have been used in the treatment of serotonin toxicity [28–30]. Other antipsychotics that antagonise the 5-HT_{2A} receptor, such as risperidone and olanzapine, are also potent inhibitors of this receptor, but are a relatively common co-ingestants in SSRI overdoses [30,31]. Therefore, examining the influence of co-ingestant drugs with affinity to block these receptors on the outcome and severity of serotonin toxicity may provide some insight into their effectiveness as treatments.

The aim of this study was to determine the factors that affect the frequency of serotonin toxicity in patients following SSRI and SNRI antidepressant overdoses, with a focus on the dose of SSRI/SNRI ingested.

Methods

Study design and setting

This was a retrospective review of a prospective cohort of SSRI/SNRI overdoses presenting to a toxicology service. The study was conducted at the Hunter Area Toxicology Service (HATS), a regional toxicology service based at the Calvary Mater Newcastle, Australia, which accepts primary presentations and referrals from a population of over 500,000 people. The study was approved by the Human Research Ethics Committees of the Area Health Service and the University of Newcastle, Australia. In this study, we investigated the frequency of serotonin toxicity and factors that influence the risk of serotonin toxicity occurring, using logistic regression.

Participants

Patients who took an overdose of an SSRI or SNRI between May 1990 and April 2013 were included in the study. Retrospective identification of cases was performed by searching fields in the toxicology database for the type of SSRI (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) or SNRI (desvenlafaxine and venlafaxine). There were no admissions that included duloxetine.

Data collection

The toxicology service collects data for all overdose and poisoning presentations on admission using a specially designed data collection form, and together with information from the patient medical record, is prospectively entered into a clinical research database by trained personnel blinded to any study hypotheses. The database includes patient demographics, overdose type, dose and timing, clinical effects, treatments, complications and outcome information. Serotonin toxicity is one of the major complications of overdose that is recorded by the database and is based on the diagnosis made by the attending clinical toxicologist during the admission. This, like other data elements, is reviewed at a weekly meeting. This clinical diagnosis has been previously used to develop the Hunter Serotonin Toxicity Criteria [6].

For this study, we first identified patients in the database that had ingested a single SSRI (fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram and escitalopram) or SNRI

(venlafaxine and desvenlafaxine) as part of their overdose, and the dose was known. Cases in which more than one SSRI or SNRI were ingested were excluded. The following data was then extracted from the database: patient demographic details (age, sex and date of admission), antidepressant drug ingestion information (type, dose ingested and whether the antidepressant was prescribed); the presence of co-ingestants and specifically whether the co-ingestant was the reversible MAOI moclobemide, or an irreversible MAOI (phenelzine or tranylcypromine); if an atypical antipsychotic was co-ingested which antagonises the 5-HT_{2A} receptor (i.e. risperidone or olanzapine); if chlorpromazine was co-ingested which antagonises 5-HT_2 receptors; and if a benzodiazepine was co-ingested; and the diagnosis of serotonin toxicity.

The dose of SSRI or SNRI was converted to the defined daily dose equivalent (DDD) for the treatment of depression for each specific medication to allow comparison between agents. The DDD unit used for each serotonergic drug included in the study were: citalopram 20 mg, escitalopram 10 mg, fluoxetine 20 mg, fluvoxamine 100 mg, paroxetine 20 mg, sertraline 50 mg, desvenlafaxine 50 mg and venlafaxine 100 mg, according to the World Health Organisation Collaborating Centre for Drug Statistics Methodology [32].

Outcomes

The primary outcome measured was the occurrence of serotonin toxicity following overdose. The diagnosis of serotonin toxicity was made by the attending medical officer during the admission and was a clinical diagnosis, rather than any of the published criteria. This was because the recording of this data element in the database as serotonin toxicity has not changed over the 23 years used in the study.

Analysis

Initially, a univariate analysis was performed to identify which factors were associated with serotonin toxicity. Covariates considered were dose (in DDD units), age (years), sex, type of antidepressant (SSRI or SNRI), whether the antidepressant was prescribed prior to overdose, presence of any co-ingestant, and the specific co-ingestants: MAOIs, risperidone and olanzapine. Because dose was the primary covariate we were interested in, we only included a limited number of other covariates: co-ingestion of risperidone, olanzapine and moclobemide. We did not include chlorpromazine because there were only 18 patients co-ingesting chlorpromazine, three also co-ingesting olanzapine or risperidone and four co-ingesting benzodiazepines. We also did not include benzodiazepines, because although they are used for the treatment of serotonin toxicity, they are not 5HT_2 antagonists. Subsequently, a multivariate logistic regression model was developed, using the predictor variables that indicated statistical significance from the univariate analysis. A stepwise covariate model-building approach was used with forward addition ($p < 0.05$) followed by backward elimination ($p < 0.01$). Statistical significance was determined using the likelihood ratio test for nested models.

Descriptive statistics were used to summarise the results with means and standard deviations for normally distributed data, and medians with interquartile ranges for non-parametric data. Fisher's exact test and Chi-squared analysis were performed using GraphPad Prism version 7.01 for Windows (GraphPad Software, La Jolla, CA, www.graphpad.com). Univariate and multivariate analyses were performed using logistic regression in NONMEM version 7.2.0 (ICON plc, Dublin, Ireland).

Results

There were 2237 admissions to the toxicology service between May 1990 and April 2013 with an overdose that included an SSRI or SNRI antidepressant. There was no reported dose in 194 admissions, two different SSRI/SNRIs ingested in 57 and three different SSRI/SNRIs ingested in eight. This left 1978 admissions in 1520 patients, with a median age of 33 years (range 13–86 years) and 976 females (64%). Of the 1978 admissions, 70% (1388/1978) involved an SSRI and 30% (590/1978) an SNRI. The antidepressant had been prescribed in 93% (1841/1978) of admissions prior to the overdose event. A co-ingestant was present in 85% (1678/1978) of overdoses. The reversible MAOI moclobemide was present in 0.6% (11/1978) of admissions co-ingested with all SSRIs or SNRIs, with the exception of paroxetine, escitalopram and desvenlafaxine. Only one patient took the irreversible MAOI phenelzine, co-ingested with sertraline, which was excluded in subsequent analysis to reduce bias in the results. In 99/1978 (5%) of admissions olanzapine was co-ingested, in 58/1978 (3%) risperidone was co-ingested and in 18/1978 (0.9%) chlorpromazine was ingested. A benzodiazepine was co-ingested in 417/1978 (21%) of admissions. Other common co-ingested drugs were paracetamol, codeine, valproate, quetiapine and ibuprofen (Supplementary Table 1). Serotonin toxicity was diagnosed by the attending clinical toxicologist in 269 of 1978 (13.6%) of admissions (Table 1).

Predictors of serotonin toxicity

The associations between different covariates and the occurrence of serotonin toxicity obtained from univariate logistic regression are shown in Table 2. The most important covariates were dose (OR:1.02), age (OR:0.87) the type of serotonin reuptake inhibitor, i.e. SSRI or SNRI (OR: 1.07), and the co-ingestants moclobemide (OR: 29.37), olanzapine (OR:0.40) and risperidone (OR:0.11).

The final multivariate model contained six predictor variables: dose (DDD units), age, SSRI/SNRI type and the presence of moclobemide, risperidone and olanzapine as separate dichotomous covariates for each specific co-ingestant. There was no influence from interaction terms for dose, age and sex, so the terms for covariates were entered independently. The only covariates that were not significant in the full model compared to the univariate analysis were sex, whether the antidepressant had been prescribed prior to the overdose, and the presence of any co-ingestant (but we note

Table 1. Demographics and characteristics of overdose presentations.

Characteristics *N* (%)	Total	No serotonin toxicity	Serotonin toxicity
Sex:			
Male	544 (27.5)	463 (85.1)	81 (14.9)
Female	1434 (72.5)	1246 (86.9)	188 (13.1)
Total	1978	1709 (86.4)	269 (13.6)
Age (years; median [IQR])	33 [22–43]	33 [23–43]	29 [22–40]
Overdose SSRI/SNRI type: *n* (%)			
SSRI (all):	**1388 (70)**	**1215 (87.5)**	**173 (12.5)**
Citalopram	261 (13)	232 (88.9)	29 (11.1)
Escitalopram	147 (7)	133 (90.5)	14 (9.5)
Fluoxetine	201 (10)	187 (93.0)	14 (7.0)
Fluvoxamine	93 (5)	82 (88.2)	11 (11.8)
Paroxetine	241 (12)	206 (85.5)	35 (14.5)
Sertraline	445 (23)	375 (84.3)	70 (15.7)
SNRI (all):	**590 (30)**	**494 (83.7)**	**96 (16.3)**
Desvenlafaxine	59 (3)	50 (84.7)	9 (15.3)
Venlafaxine	531 (27)	444 (83.6)	87 (16.4)
SSRI/SNRI prescribed:			
Yes	1841 (93.1)	1596 (86.7)	245 (13.3)
No	137 (6.9)	113 (82.5)	24 (17.5)
Co-ingestants (all)	1678 (85)	1464 (87.2)	214 (12.8)
MAOI [phenelzine]	1 (0.05)	0 (0)	1 (100)
RIMA [moclobemide]	11 (0.56)	2 (18.2)	9 (81.8)
Olanzapine	99 (5)	93 (93.9)	6 (6.1)
Risperidone	58 (3)	57 (98.3)	1 (1.7)
Chlorpromazine	18 (0.9)	18 (100)	0
Benzodiazepine	417 (21)	384 (92)	33 (8)
Number of presentations: total, median [range; IQR]	1978, 2 [1–17; 1–10]		

IQR: interquartile range; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin norepinephrine reuptake inhibitor; MAOI: monoamine oxidase inhibitor (non-selective); RIMA: reversible inhibitor of monoamine oxidase type A
The bold indicates each of the SSRI and SNRI as a group.

Table 2. Univariate and multivariate analysis of Serotonin toxicity against each predictor, showing odds ratio and 95% confidence interval.

Predictor	Univariate analysis Odds ratio (95% CI)	Multivariate analysis adjusted OR (95% CI)
Dose (per DDD increase)	1.02 (1.01 – 1.03)	1.01 (0.93 – 1.10)
Age (per 10 y increase)	0.87 (0.79 – 0.96)	0.84 (0.74 – 0.95)
SSRI/SNRI type	1.07 (1.00 – 1.15)	1.07 (0.99 – 1.15)
SSRI (reference)		
SNRI		
Moclobemide	29.37 (6.3 – 136.5)	33.12 (7.5–147)
No (reference)		
Yes		
Risperidone	0.11 (0.01 – 0.83)	0.13 (0.02 – 0.99)
No (reference)		
Yes		
Olanzapine	0.40 (0.17 – 0.94)	0.40 (0.17 – 0.94)
No – reference		
Yes		
Sex	1.16 (0.80 – 1.69)	–
Male (reference)		
Female		
SSRI/SNRI prescribed	0.72 (0.45 – 1.15)	–
No (reference)		
Yes		
Co-ingestant (all)	0.65 (0.47 – 0.95)	–
No (reference)		
Yes		

DDD: defined daily dose equivalent; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin norepinephrine reuptake inhibitor; CI: confidence interval

that specific co-ingestants were retained). The adjusted ORs and corresponding 95% CIs are shown in Table 2.

From the final model we calculated the probability of developing serotonin toxicity for specified predictor variables, including for increasing dose, different co-ingestants and increasing age (Figures 1 and 2). The probability of serotonin toxicity occurring at 1 DDD (therapeutic dose) was 12.5%, at 15 DDDs (median overdose) was 12.7%, and at 420 DDDs (maximum overdose ingested) was 19%. In patients taking the median dose of 15 DDDs, co-ingestion of moclobemide increased the probability of serotonin toxicity to 83%, and co-ingestion of the 5-HT_{2A} antagonists olanzapine or risperidone decreased the probability of serotonin toxicity occurring to 5.5% and 1.8%, respectively (Figure 1).

Antidepressant type was examined to assess for a correlation between individual agents or groups of medicines. Comparing all antidepressant agents, there was a statistically significant difference between those who developed serotonin toxicity and those that did not (χ^2 [7] = 16.77, $p = 0.02$). In addition, there was also a significant difference between

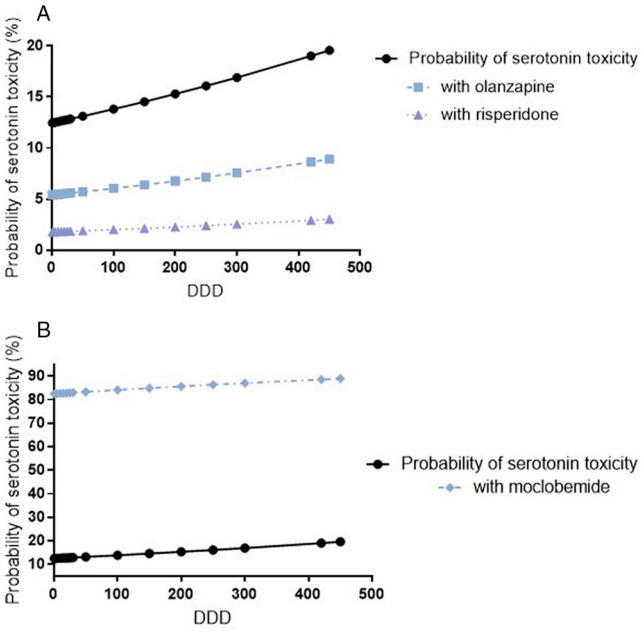

Figure 1. Predicted probability of serotonin toxicity *vs.* defined daily dose equivalent (DDD) after ingestion of a serotonin reuptake inhibitor alone, and with the co-ingestants olanzapine or risperidone (A) and with moclobemide (B).

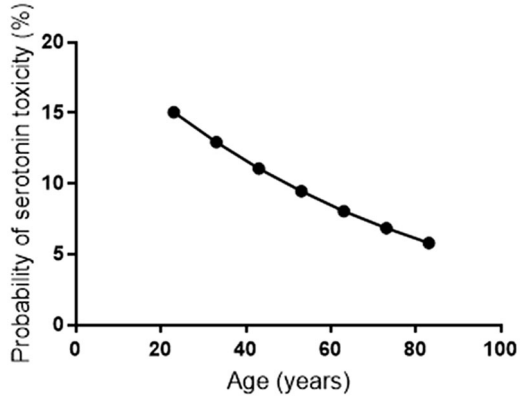

Figure 2. Predicted probability of serotonin toxicity *vs.* age of patient, ingesting the median dose of 15 DDD units of a serotonin reuptake inhibitor.

Table 3. Frequency of serotonin toxicity based on antidepressant type.

Drug (*n*)	Median DDD ingested (range; IQR)	Serotonin toxicity % (*n*)
SSRI (1388)	–	**12.5 (173)**
Citalopram (261)	14 (1–150; 8 – 26.5)	11.1 (29)
Escitalopram (147)	14 (1–225; 8–28)	9.5 (14)
Fluoxetine (201)	14 (1–420; 6.5 – 24.5)	7.0 (14)
Fluvoxamine (93)	11 (1–45; 6 – 15.5)	11.8 (11)
Paroxetine (241)	12 (0.5–200; 8–21)	14.5 (35)
Sertraline (445)	20 (1–180; 8–30)	15.7 (70)
SNRI (590)	–	**16.3 (96)**
Desvenlafaxine (59)	20 (3–112; 12–28)	15.3 (9)
Venlafaxine (531)	15 (0.75–135; 6–30)	16.4 (87)
Total (1978)	**15 (1–420; 8–27)**	**13.6 (269)**

DDD: defined daily dose equivalent; IQR: interquartile range; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin norepinephrine reuptake inhibitor The bold indicates each of the SSRI and SNRI as a group.

patients that took a SNRI and those that took an SSRI in the occurrence of serotonin toxicity (Fischer's exact test, $p = 0.03$). The frequency of serotonin toxicity is shown in Table 3 for each type of SSRI or SNRI.

Discussion

Serotonin toxicity is a recognised complication following serotonergic antidepressant overdose and we found that the frequency of serotonin toxicity was similar to that reported previously [2,12], with an overall frequency of 13.6% (Table 3). The ingested dose ranged from therapeutic (1 DDD) to large overdoses of hundreds times the DDD. Although dose was a significant covariate, the actual probability of serotonin toxicity occurring did not change much from therapeutic ingestions to overdose. We identified other factors that were associated with an increased (moclobemide co-ingestion) and decreased (olanzapine, risperidone and increasing age) probability of serotonin toxicity occurring. Importantly, the co-ingestion of olanzapine or risperidone decreased the risk of serotonin toxicity considerably more than a decrease in dose. The incidence of serotonin toxicity was slightly more likely to occur in patients that took a SNRI (16.3%), i.e. venlafaxine or desvenlafaxine, compared to an SSRI (12.5%), which is in agreement with the literature [2,12].

An unusual finding was that increasing age was associated with a decreased likelihood of serotonin toxicity occurring (Figure 2); a potentially protective effect (Table 2). A possible reason for this is that we would predict that older people would have more co-morbidities and may take more medicines. Therefore, age could be a confounder in that symptoms and signs of serotonin toxicity may be more difficult to detect and diagnose.

We calculated the OR in our multivariate analysis (Table 2), but in order to better describe the effects clinically we calculated the probability of developing serotonin toxicity from our final logistic regression model. We found the probability of developing serotonin toxicity increased with the dose of SSRI/SNRI (Figure 1). However, the magnitude of this effect was only small, with there being an already considerable risk of serotonin toxicity (12.5%) for a therapeutic dose, which increased little for the median overdose amount (12.7%). Even with a massive overdose (420 DDD), the probability (19%) was not doubled. This differs to most other pharmacodynamic outcomes in overdose studies, where dose has a much larger effect, such as in delirium in promethazine overdose [33], seizures in venlafaxine overdose [34], or the probability of requiring intubation following quetiapine overdose [35]. This means that there remains unexplained predictors of serotonin toxicity, such as genetic predisposition, although the specific genes or polymorphisms remain to be identified. Our reported probability for serotonin toxicity at therapeutic doses is not dissimilar to reported frequencies of adverse effects likely attributed to serotonin excess seen in therapeutic dosing [14–16].

The effect of co-ingestants was much larger than dose, particularly for co-ingestion of moclobemide, which increased the risk about five-fold to over 80% even with only therapeutic doses of SSRI/SNRI. This is consistent with the literature and clinical experience, in which fatalities from this combination are reported for both therapeutic and overdose amounts [36]. The co-ingestion of 5-HT_{2A} antagonists, olanzapine and risperidone decreased the risk of serotonin toxicity, and again this was a much more important covariate than

dose, decreasing the probability by 2-fold and 6-fold, respectively (Figure 1). These agents possess anti-serotonergic action particularly at the 5-HT_{2A} receptors and demonstrate a protective effect in the development of serotonin toxicity [37]. Schotte et al. and Richelson and Souder have independently shown that risperidone has a higher potency for occupying $5HT_{2A}$ receptors, than olanzapine, and thus protective of the development of serotonin toxicity [38,39]. Our results reflect this, with the probability of serotonin toxicity being approximately 1.8% if risperidone is part of an overdose (15 DDDs) with an SSRI or SNRI, and 5.5% with olanzapine. This apparent protective effect of co-ingesting a 5-HT_{2A} antagonist suggests that these agents may also be beneficial in treating serotonin toxicity. However, it cannot be assumed that co-ingesting an antagonist is equivalent to treating with an antagonist after the development of serotonin toxicity. Further investigation of treatment of serotonin toxicity with olanzapine or risperidone is required.

There are a number of limitations to our study. The data included all SSRI and SNRI antidepressants taken as part of an overdose in the study period, and in a small number of patients these agents were not taken in overdose amounts (being any amount in excess of the manufacturers recommended maximum daily dose). These factors may potentially bias our findings and underestimate the probability of serotonin toxicity, but we assume this effect to be small based on the range of DDDs. Ingestion of the SSRI, SNRI or co-ingestants was not confirmed analytically, and was based on patient history. We have shown numerous times in the past that patient history is accurate for the drug ingested and reported dose is a reasonable estimate of the actual dose ingested [40]. In addition, we did not examine all of the effects of co-ingestants on the development of serotonin toxicity, including potential pharmacokinetic interactions. Similarly, we only included a few individual co-ingestants in the logistic regression. Any more would have increased the complexity of the model, due to potential pharmacokinetic and pharmacodynamic interactions between the SSRI/SNRI and multiple co-ingestants.

Conclusions

The frequency of serotonin toxicity in the population following an overdose that includes an SSRI or SNRI is 13.6% and does not change much for increasing doses ingested, but is increased for an SNRI *vs*. an SSRI. Moclobemide increases the risk of serotonin toxicity when co-ingested with an SSRI or SNRI. Serotonin receptor antagonists, particularly risperidone and olanzapine, appear to have protective effects against the development of serotonin toxicity, when ingested with an SSRI or SNRI. Further exploration of genetic pre-disposition for serotonin toxicity will hopefully assist in identified patients most at risk.

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Author contributions

GI, JC and SD designed the study; GI and JC identified patients; GI and JC did the data extraction; JC carried out the analysis of the data; JC did the literature review; JC drafted the manuscript. All authors read and approved the final manuscript. GI is guarantor of the article.

Disclosure statement

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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