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Serotonin toxicity from antidepressant overdose and its association with the T102C polymorphism of the 5-HT$_{2A}$ receptor.

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ABSTRACT

Serotonin toxicity results from serotonin excess in the central nervous system from serotonergic drugs. Previous studies suggest an association between T102C polymorphism of the serotonin 2A (5-HT2A) receptor gene and serotonergic adverse effects with serotonergic drugs. We aimed to determine if there is an association between the T102C polymorphism and serotonin toxicity in patients taking serotonergic drug overdoses. Ninety five patients presenting with serotonergic drug overdoses were examined for serotonin toxicity and had blood collected for DNA analysis. A diagnosis of serotonin toxicity was made in 14 patients (15%) based on the Hunter Serotonin Toxicology Criteria. Four of 14 patients (29%) with serotonin toxicity had the C/C genotype compared to 20/81 (25%) without serotonin toxicity. There were no differences in age or sex, but the median defined daily dose taken by patients with serotonin toxicity was 27(14–84) compared to 18(2–136) in patients without serotonin toxicity (p=0.06). There was no association between serotonin toxicity and the T102C polymorphism in patients taking a serotonergic drug overdose.

KEYWORDS: serotonin toxicity, serotonin syndrome, serotonin 2A receptor, 5HT2A, polymorphism, genotype
INTRODUCTION

The incidence of adults experiencing a mental health disorder sometime in their lifetime has been estimated to be approximately 45%. Depression is the commonest problem and antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs), are amongst the most commonly prescribed groups of medications. The SSRIs act by inhibiting the reuptake of serotonin (5-HT) and thus increase the concentration at the synaptic cleft. Increased 5-HT in the central nervous system and particularly increased agonism at the serotonin 1A receptors (5-HT1A) is thought to be the mechanism of action of most antidepressants in treating depression. However, greatly increased concentrations of 5-HT in the central nervous system can result in serotonin toxicity, a potentially severe adverse effect from drug treatment.

Literature suggests that the variation in effectiveness of antidepressants between individuals is thought to be, at least partly, under genetic influence. Specifically, the T102C polymorphism (rs6313) of the serotonin 2A receptor (5-HT2A) gene is associated with differential gene expression and has been studied in a number of neuropsychiatric disorders. There is no clear association with this polymorphism and depression, schizophrenia, or bipolar affective disorder, and also no association has been found with suicidal behaviour or ideation. However, this polymorphism has been shown to have an association with treatment outcomes following treatment with clozapine which modifies serotonergic activity in the brain, and the 5-HT2A polymorphism has also been investigated for a possible role in antidepressant treatment outcomes, but results to date have shown only marginal significance or no association. These polymorphisms may also be associated with the severity of adverse effects from the SSRI group of antidepressant medications.
Serotonin toxicity (or serotonin syndrome) results from excess serotonin in the central nervous system. Clinically, serotonin toxicity is characterised by a triad of clinical effects: 1) neuromuscular hyperactivity - clonus, myoclonus, tremor or hyperreflexia; 2) autonomic hyperactivity - diaphoresis, fever, tachycardia or mydriasis; 3) altered mental status - agitation, excitement or confusion. Defining diagnostic criteria for serotonin toxicity has been difficult. These were first described by Sternbach, then redefined by Radomski to include a severity score, and most recently by Dunkley et al. The Hunter Serotonin Toxicity Criteria described by Dunkley et al are more specific using signs and symptoms that occur almost exclusively with serotonin excess in the central nervous system. (Figure 1)

Although the pathophysiology of serotonin toxicity is not fully understood, it has been proposed that variation at the 5-HT2A gene locus is associated with a higher risk for developing symptoms of serotonin toxicity. A study in older, depressed patients reported that variation in the T102C single nuclear polymorphism (SNP) of the 5-HT2A gene had a major effect on the reported incidence of side effects and discontinuations following paroxetine therapy. This study included 246 patients in an 8-week, double blind, randomised, controlled trial with the SSRI paroxetine with increasing doses of up to 40 mg/day. There were significantly more discontinuations in the patients with the C/C genotype 19/41 (46.3%) compared to the T/T or T/C genotypes 13/81 (16%), suggesting that genetic variation in the 5-HT2A gene may be important in determining and predicting medication discontinuations in older patients treated with paroxetine.

The aim of our study was to investigate if there is an association between the T102C polymorphism in the 5-HT2A gene and a clinical diagnosis of serotonin toxicity in patients taking an overdose of serotonergic drugs.
METHODS

Study design and setting

We undertook a cohort study of patients taking overdoses of serotonergic antidepressant drugs to investigate the association between patient genotype for the T102C polymorphism in the 5-HT$_{2A}$ gene and the clinical occurrence of serotonin toxicity. The study was approved by the Human Research Ethics Committees of the Area Health Service and the University of Newcastle and all patients consented to the study.

The study was undertaken in a large regional toxicology unit which takes primary presentations and referrals for all overdose and poisoning patients in a population of over 500,000 people. A toxicology admission form is completed for all toxicology presentations. Information from this form and the medical record is prospectively entered into a clinical database by research assistants. The database includes patient demographic details, clinical effects, treatments and complications. The database contains all overdose and poisoning admissions from 1987 to the present time.

Participants

In this study we aimed to recruit patients who had taken an overdose of an antidepressant drug known to cause an increase in serotonin levels in the brain, and collect a blood sample for DNA analysis of the T102C SNP for the 5-HT$_{2A}$ gene. Groups of drugs included were those associated with causing serotonin toxicity as follows: selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). Drug overdose was defined as a quantity of drug in excess of the patient’s usual daily dose if applicable, and a dose in excess of the manufacturer’s recommended maximum daily dose for the medication. Doses were
converted to the defined daily dose equivalent (DDD) for the treatment of depression for the
particular medication to allow comparison of medications. The DDD for each serotonergic
drug included in the study was: citalopram 20 mg, escitalopram 10 mg, clomipramine 100
mg, venlafaxine 100 mg, desvenlafaxine 50 mg, duloxetine 60 mg, fluoxetine 20 mg,
fluvoxamine 100 mg, moclobemide 300 mg, paroxetine 20 mg and sertraline 50 mg
according to the World Health Organisation Collaborating Centre for Drug Statistics
Methodology. ²⁹

Potential participants were identified either prospectively from consecutive hospital
admissions between October 2008 and March 2010, or retrospectively from the toxicology
database. Retrospective identification of patients was done by random sampling from the
database of patients who had ingested a serotonergic drug. Patients who ingested an overdose
of a drug with the potential to cause serotonin toxicity were eligible to be included in the
study. Patients who consented to participate provided a blood sample for DNA analysis.

**Data Collection**

For patients recruited to the study, data was extracted from the toxicology database including,
demographic information (age, sex, ethnicity/place of birth), details of ingestion (estimated
dose converted to defined daily doses [DDD]), psychiatric diagnosis and serotonergic clinical
effects (hyperreflexia, tremor, diaphoresis, clonus [inducible or sustained ankle clonus, ocular
clonus], agitation/anxiety, hypertonia and hyperthermia [temperature > 38°C]). All medical
records were reviewed by a clinical toxicologist (GKI) with extensive experience in the
diagnosis and classification of serotonin toxicity to confirm the serotonergic signs and
symptoms documented by the treating doctors. Ten percent of the medical records were
reviewed by another researcher (JMC) with complete agreement. The diagnosis of serotonin
toxicity was made based on the Hunter Serotonin Toxicology Criteria. ²⁸ (Figure 1)
Psychiatric diagnosis was made by the liaison psychiatrist during the patient admission. Each patient had between 1 and 5 (median, 2) psychiatric diagnoses.

**DNA Analysis**

Blood was collected in EDTA tubes, centrifuged and stored at -80°C. Genomic DNA was extracted using the Gentra Puregene blood kit (Qiagen sample and assay technologies, [www.qiagen.com](http://www.qiagen.com)) and analysed for the T102C polymorphism in the 5-HT$_{2A}$ gene using polymerase chain reaction (PCR). 10 ng of DNA was added to a 10 μL SensitDt master-mix (Bioline, Australia) that contained Sito9 intercalating dye (1:10,000). PCR was performed on a 480 LightCycler® (Roche) with the following program: 95°C for 10 minutes; 12 cycles of 95°C for 10 seconds, 65°C to 55°C (0.7°C/step) for 20 seconds, 72°C for 80 seconds; 28 cycles of 95°C for 10 seconds; 55°C for 20 seconds, 72°C for 80 seconds; followed by a meltcurve of 95°C for 3 minutes, 40°C for 3 minutes, meltcurve data collection 15 acquisitions/sec to 95°C. Analysis was performed against known controls.

**Data Analysis**

The genotypes for the T102C polymorphism were determined and analysed against the presence or absence of serotonin toxicity in study participants. Researchers performing genetic analysis were blinded to the details and clinical diagnosis of study participants. The diagnosis of serotonin toxicity was also determined prior to comparison with the DNA analysis by one author (GKI).

Statistical analysis was performed using STATA 11.2 (StataCorp, Texas, USA [www.stata.com](http://www.stata.com)). Genetic frequencies were tested for Hardy-Weinberg equilibrium. Comparison of the distribution of genotypes and the association with serotonin toxicity was performed using Fisher’s exact test. Contingency tables were used to test for distributions of
sex, age and DDD, between the groups of patients who were diagnosed with serotonin toxicity and those without.
RESULTS

A total of 95 patients who took a single overdose of a serotonergic drug during were included. Table 1 shows the characteristics of the patients in the study and genotype results related to the diagnosis of serotonin toxicity using the Hunter Serotonin Toxicity Criteria. Psychiatric diagnoses and the frequency of these according to genotype are shown in Table 2. Although specific ethnicity data was not available, 86 patients were born in Australia (non-Aboriginal or Torres Strait Islander descent), four were Australian-indigenous and five were of European birth (Table 2).

The drugs included and the frequency of ingestion of each drug type is shown in parentheses: venlafaxine (19), sertraline (17), desvenlafaxine (16), escitalopram (12), fluoxetine (10), citalopram (10), duloxetine (3), fluvoxamine (3), paroxetine (3), clomipramine (1) and moclobemide (1). Fourteen of the 95 patients (15%) were given a diagnosis of serotonin toxicity.

The overall 5-HT$_{2A}$ T102C allele frequencies were C = 0.55 and T = 0.45. However, we found that genotype frequencies were not consistent with Hardy-Weinberg equilibrium (HWE) ($\chi^2 = 4.33$, p=0.04). We are not able to explain why this occurred in our sample of overdose patients, with two technicians performing the DNA analysis. Genotype frequencies are shown in table 1. We analysed the results by comparing patients with the C/C genotype to the others on the basis that this dichotomous outcome was used to predict discontinuations and adverse events from paroxetine therapy$^{24}$. There were no statistical differences between patients diagnosed with serotonin toxicity and those without diagnosed toxicity in sex, age and genotype frequency. The median dose (DDD) for patients with serotonin toxicity was 27 (IQR: 20–50; range: 14 to 84) compared to 18 (IQR: 10–30; range: 2 to 136) in patients without serotonin toxicity (p=0.06). For patients with diagnosed serotonin toxicity, 4/14
(29%) had the C/C genotype whereas 10/14 (71%) had the T/T or T/C genotypes. The genotype distribution in patients without diagnosed toxicity was 20/81 (25%) for the C/C genotype and 61/81 (75%) in the T/T and T/C genotypes. (Table 1)

The incidence of symptoms and the diagnosis of serotonin toxicity and patient genotype are summarised in table 3.
DISCUSSION

This study suggests that the T102C polymorphism of the 5-HT$_{2A}$ gene is unlikely to be associated with a greater risk of serotonin toxicity following an overdose with a serotonergic antidepressant drug. There was no significant difference in the proportion of patients with serotonin toxicity who had the C/C genotype compared to patients with the T/T and T/C genotypes. This is in contrast to a previous study of patients taking therapeutic doses of paroxetine, in which there was an association between the C/C genotype and increased serotonergic symptoms.$^{23}$

Murphy et al demonstrated a strong association between the C/C genotype and adverse events and discontinuation of paroxetine therapy in elderly depressed, non-demented patients.$^{24}$ Patients with the C/C genotype discontinued the treatment early in this 8-week double-blind study given escalating doses of paroxetine, and also experienced greater side effect severity. In another case report of serotonin toxicity induced by phenelzine alone, it was suggested that there was an association with the C/C genotype$^{22}$. However, this was only based on a single case of phenelzine (75mg/day), a non-selective monoamine oxidase inhibitor (MAOI) antidepressant, causing serotonin toxicity in a 39 year old female Caucasian with a history of bipolar disorder type II. These previous studies suggest that the association of serotonergic symptoms in patients on therapeutic doses of serotonergic drugs with the C/C genotype may have a different underlying mechanism to serotonin toxicity in overdose patients.

The exact pathophysiology of serotonin toxicity is still not fully understood, except that it occurs with an excess of serotonin in the central nervous system. Activation of the 5-HT$_{2A}$ receptors located on the post-synaptic neurones is thought to be involved, at least in part, with some of the adverse effects due to serotonin excess.$^{25,30}$ However, other receptors are likely to account for the observed variability. Differential activation of various receptor pathways...
may account for differences in receptor involvement and therefore genomic polymorphism may result in therapeutic adverse effects and serotonin toxicity from overdose.

Researchers have attempted to examine the role of the 5-HT$_{2A}$ receptor polymorphisms and their association with adverse effects from SSRIs, but the results have been disappointing. In two studies investigating the adverse effects of paroxetine therapy in Japanese populations, there was a significant incidence of severe nausea associated with the -1438 G/G polymorphism of the 5-HT$_{2A}$ gene. However a later study found no association with the incidence of nausea and the T102C polymorphism. Notably, the -1438G/A polymorphism has been reported previously to be in complete linkage disequilibrium with the T102C polymorphism on 5-HT$_{2A}$.

When the efficacy of antidepressants was investigated in relation to genetics in a large data set of European patients (1790 patients in 5 studies), screening for over half a million genetic markers, there was no single common genetic variant associated with antidepressant response shown at a clinically relevant level. Similarly, Peters et al has shown a possible link with the response to fluoxetine which is reported to involve three genes: 5-HT$_{2A}$, monoamine oxidase type A (MAOA) and tryptophan hydroxylase isoform-2 (TPH2). It is therefore likely the susceptibility to serotonin toxicity will also involve more than one polymorphism.

Previous work has also focused on polymorphisms in the cytochrome P (CYP) 450 metabolising enzyme systems, but to our knowledge there has been no research investigating this association with serotonin toxicity in overdose. There is also only one study that indicated a higher risk of gastrointestinal adverse effects with CYP-2D6 poor metaboliser status; most studies have shown no association with adverse effects caused by the SSRIs.
We acknowledge that ethnicity data was not available for all the participants in this study as this information is not routinely collected as part of the hospital admission. However, this is not of consequence in this study as we note that the rs6313 polymorphism displays similar distribution of genotype frequencies when examined across different ethnic groups.  

It is possible that the dose or the type of serotonergic drug itself may also influence the risk of developing serotonin toxicity. When we compared the DDDs for the agents ingested, the patients with serotonin toxicity had a higher median DDD (27) compared to patients without toxicity (18). Chan et al similarly showed that following intentional poisoning with either SSRIs or the serotonin noradrenaline reuptake inhibitor (SNRI) venlafaxine, the median DDD was higher in the venlafaxine group compared to the SSRI group (35 compared to 19). However the incidence of serotonin toxicity between the groups was not statistically significant (p=0.066). The genotype frequencies for the SSRIs versus the SNRIs is included in table 2 and they are similar. Other non-genetic factors which also warrant further study include pharmacokinetic and pharmacodynamic parameters such as age, sex, weight (body composition), disease states and co-ingested medications.

A limitation of our study was that we only investigated an association with serotonin toxicity and polymorphism of the T102C polymorphism of the 5-HT2A receptor, and no other polymorphisms. This was done because of a previous study that did show an association in therapeutic use between serotonergic adverse effects and discontinuations. We acknowledge that the study by Murphy et al. was a clinical trial in geriatric patients using therapeutic doses of paroxetine which examined discontinuations due to adverse events as the outcome measure and this polymorphism. In contrast, our study aimed to examine any possible relationship with the occurrence of serotonin toxicity in a population who had taken an overdose of a serotonergic medication with the same polymorphism. It is entirely possible that other
genetic associations may exist and further study is required to investigate other pharmacogenomic associations. This study does suggest that in overdose the dose is an important association, with higher doses taken in serotonin toxicity patients. Further investigation into specific agents is required to investigate any link between toxicity and the medication taken in overdose.

CONCLUSION

This study found no association between the clinical diagnosis of serotonin toxicity (‘Serotonin Syndrome’) and the T102C polymorphism in the 5-HT$_{2A}$ receptor in patients taking a serotonergic antidepressant overdose. Further studies are needed to investigate factors that are associated with a great risk of serotonin toxicity which may involve other genetic factors but also non-genetic factors such as dose of medication.
ACKNOWLEDGEMENTS

We thank Pavel Bitter from the Australian Cancer Research Foundation Unit (ACRF), Garvan Institute, Sydney, New South Wales, Australia for assistance with DNA analysis. The project was partly funded by a University of Newcastle grant in 2009. We thank Debbie Whyte and Antonia Nash for data entry in the clinical database. We thank Renai Kearney for administrative assistance and obtaining medical records.
CONFLICT OF INTEREST

All authors declare no conflicts of interest
REFERENCES


Table 1. The frequency and characteristics of patients, including demographics, dose and genotype results for the T102C SNP of 5-HT$_{2A}$, for those with and without serotonin toxicity.

<table>
<thead>
<tr>
<th></th>
<th>Serotonin Toxicity</th>
<th>No Serotonin Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>14 (15%)</td>
<td>81 (85%)</td>
</tr>
<tr>
<td>Female/Males</td>
<td>10 / 4</td>
<td>64 / 17</td>
</tr>
<tr>
<td>Age - median (IQR), range</td>
<td>28 (19 – 36), 17 – 76</td>
<td>32 (20 - 45), 16 – 84</td>
</tr>
<tr>
<td>DDD$^1$ - median (IQR), range</td>
<td>27 (20 – 50), 14 – 84$^2$</td>
<td>18 (10 – 30), 2 – 136$^3$</td>
</tr>
<tr>
<td>Genotype group: C/C</td>
<td>4 (29%)</td>
<td>20 (25%)</td>
</tr>
<tr>
<td>Genotype: Groups T/T &amp; T/C combined</td>
<td>10 (71%)</td>
<td>61 (75%)</td>
</tr>
<tr>
<td>Groups T/T</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Groups T/C</td>
<td>5</td>
<td>52</td>
</tr>
</tbody>
</table>

$^1$ DDD according to WHO Collaborating Centre for Drug Statistics Methodology

$^2$ one patient took an unknown quantity

$^3$ two patients took unknown quantities
Table 2. Distribution of gender, ethnicity, psychiatric diagnoses and drug types for all genotypes.

<table>
<thead>
<tr>
<th>Total (%)</th>
<th>C/C</th>
<th>T/T</th>
<th>T/C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>19 (26)</td>
<td>11 (15)</td>
<td>44 (59)</td>
</tr>
<tr>
<td>Male</td>
<td>5 (24)</td>
<td>3 (14)</td>
<td>13 (62)</td>
</tr>
<tr>
<td><strong>Ethnicity – Country of Birth:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australian birth</td>
<td>20 (23)</td>
<td>13 (15)</td>
<td>53 (61)</td>
</tr>
<tr>
<td>Australian – Indigenous</td>
<td>1 (25)</td>
<td>1 (25)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>European birth</td>
<td>3 (60)</td>
<td>0 (0)</td>
<td>2 (40)</td>
</tr>
<tr>
<td><strong>Major psychiatric diagnoses:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>substance related disorders</td>
<td>10 (17)</td>
<td>10 (17)</td>
<td>38 (66)</td>
</tr>
<tr>
<td>schizophrenia/psychotic disorder</td>
<td>1 (33)</td>
<td>0 (0)</td>
<td>2 (67)</td>
</tr>
<tr>
<td>depression/bipolar</td>
<td>19 (31)</td>
<td>7 (11)</td>
<td>36 (58)</td>
</tr>
<tr>
<td>anxiety disorders</td>
<td>3 (25)</td>
<td>2 (17)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>personality disorders</td>
<td>7 (30)</td>
<td>3 (13)</td>
<td>13 (57)</td>
</tr>
<tr>
<td><strong>Major drug types:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRI*</td>
<td>15 (27)</td>
<td>8 (15)</td>
<td>32 (58)</td>
</tr>
<tr>
<td>SNRI#</td>
<td>9 (24)</td>
<td>6 (16)</td>
<td>23 (60)</td>
</tr>
</tbody>
</table>

* SSRI – Selective serotonin reuptake inhibitor (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline)

# SNRI – serotonin-noradrenaline reuptake inhibitor (desvenlafaxine, duloxetine and venlafaxine)
**Table 3.** Incidence of symptoms and diagnosis of serotonin toxicity following drug overdose in participants related to genotype of T102C

<table>
<thead>
<tr>
<th>Genotype</th>
<th>C/C present (n=4)</th>
<th>C/C absent (n=20)</th>
<th>T/T present (n=5)</th>
<th>T/T absent (n=9)</th>
<th>T/C present (n=5)</th>
<th>T/C absent (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous clonus</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inducible clonus</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Ocular clonus</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Agitation</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Tremor</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>4</td>
<td>13</td>
<td>5</td>
<td>7</td>
<td>5</td>
<td>41</td>
</tr>
<tr>
<td>Hypertonia</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Temperature &gt;38°C</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Serotonin toxicity diagnosed according to the Hunter Serotonin Toxicity Criteria.\(^{28}\)
Figure 1. Flow diagram for the diagnosis of serotonin toxicity based on the Hunter Serotonin Toxicity Criteria; modified from Isbister et al and copyright WikiTox. 8