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Original Research

Assessment and management of serotonin syndrome in a simulated patient study of Australian community pharmacies

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ABSTRACT*

Background: The incidence of serotonin syndrome is increasing due to the widening use of serotonergic drugs. Identification of serotonin syndrome is challenging as the manifestations are diverse. Misdiagnosis can lead to delay in care and inappropriate treatment.

Objectives: The objectives of this study were to determine if staff of community pharmacies in Australia could identify the symptoms of serotonin syndrome in simulated patients and recommend an appropriate course of action.

Methods: Agents acting on behalf of a simulated patient were trained on a patient scenario that reflected possible serotonin syndrome due to an interaction between duloxetine and recently prescribed tramadol. They entered 148 community pharmacies in Australia to ask for advice about a 60 year old male simulated patient who was 'not feeling well'. The interaction was audio recorded and analysed for degree of access to the pharmacist, information gathered by pharmacy staff, management advice given and pharmacotherapy recommended.

Results: The simulated patient's agent was consulted by a pharmacist in 94.0% (139/148) of cases. The potential for serotonin syndrome was identified by 35.1% (52/148) of pharmacies. Other suggested causes of the simulated patient's symptoms were viral (16.9%; 25/148) and cardiac (15.5%; 23/148). A total of 33.8% (50/148) of pharmacies recommended that the simulated patient should cease taking tramadol. This advice always came from the pharmacist. Immediate cessation of tramadol was advised by 94.2% (49/52) of pharmacists correctly identifying serotonin syndrome. The simulated patient was advised to seek urgent medical care in 14.2% (21/148) of cases and follow up with a doctor when possible in 68.2% (101/148) of cases. The majority of pharmacies (87.8%; 130/148) did not recommend non-prescription medicines.

Conclusion: While not identifying the cause of the simulated patient's symptoms in the majority of cases, community pharmacies recommended appropriate action to minimise the health impact of serotonin syndrome by advising to cease tramadol and/or referring to a doctor and not recommending non-prescription medicines to treat symptoms. Raising pharmacists' awareness of the signs and symptoms of serotonin syndrome, and the importance of taking a comprehensive medication history when assessing a set of symptoms, may help community pharmacies further reduce serotonin syndrome toxicity.

Keywords: Serotonin Syndrome; Community Pharmacy Services; Pharmacies; Patient Simulation; Professional Practice; Australia

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INTRODUCTION

Serotonin syndrome is a toxic state caused by increases in serotonin in the central nervous system. It is characterised by neuromuscular excitation, and autonomic and central nervous system effects including mental state changes. It is caused by serotonergic drugs including serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors, other antidepressants, stimulants and opioid analgesics such as tramadol. Interaction between these can also lead to serotonin syndrome. Serotonin toxicity can be reversed and the clinical outcome improved if the serotonergic agent is ceased in a timely manner.[1]

The incidence of serotonin syndrome is increasing, potentially in line with increasing use of serotonergic drugs.[2] Research in an Australian veteran population indicated that 8% of patients had the potential for concomitant use of serotonergic drugs and 0.7% took potentially life-threatening combinations.[3]

Tramadol is a unique analgesic as it is an opioid and both a noradrenaline and serotonin reuptake inhibitor. It is an attractive analgesic clinically as it causes less respiratory depression and addiction than other conventional opioids.[1] The increased use of tramadol for pain management has seen a number of case reports of serotonin syndrome involving tramadol come to light.[4-7] Analysis of the French pharmacovigilance database (1985-2013) revealed that opioids were involved in 14.8% of cases of serotonin syndrome and most of these were due to the use of tramadol in combination with an SSRI.[8] Eighty-four per cent of cases of serotonin syndrome were subsequent to a change in therapy involving drug initiation, dose escalation or drug overdose.

Although serotonin toxicity is well described, clinical presentation can be highly variable and non-specific, with severity ranging from mild to life threatening.[9-11] The exact incidence of serotonin syndrome is difficult to determine. This may be because the diverse manifestations of serotonin syndrome can lead to misdiagnosis.[9] There are a number of case reports of patients with serotonin syndrome being misdiagnosed in hospital emergency departments with conditions such as epileptic seizure, drug overdose, anxiety, gastroenteritis, sepsis, psychiatric illness and fibromyalgia.[12-14] In these cases, misdiagnosis led to delay in receiving appropriate care for serotonin syndrome, provision of unnecessary hospital

Table 1. Attributes of the simulated patient.	
Age	60 years
Sex	Male
Symptoms	His skin feels a little clammy and he is flushed in the face. His hands are shaking. He had trouble sleeping last night. He does NOT have: stiff muscles, eye problems, fever or a racing heart. He does NOT appear agitated or confused.
Symptom duration	Symptoms started last night
Co-morbidities	Back pain (1 week) Depression Osteoarthritis of the right knee Gastric reflux Gastric ulcer (5 years ago)
Other medicines	Duloxetine (60 mg in the morning – has been taking this for 12 months) Esomeprazole 40 mg daily Modified release paracetamol (665 mg 3 times daily) Tramadol (prescribed for back pain - 50-100 mg 3 times daily – taken for 48 hours – last confirmed dose 100 mg on the morning of the pharmacy visit)

services and administration of inappropriate drugs with their own associated risks.

As the incidence of serotonin syndrome is increasing, health professionals must develop an increased awareness of the signs and symptoms to expedite access to treatment.[15] It is currently not known how well staff of community pharmacies can identify potential serotonin syndrome and recommend an appropriate course of action to minimise toxicity. Appropriate action would include advice to cease the causative agent immediately and/or referring the patient to a doctor in a timely fashion. Recommendation of over the counter medicines for the treatment of the symptoms of serotonin syndrome is not necessary and may be harmful. The objectives of this study were to determine if pharmacies accredited under the Pharmacy Guild of Australia's quality assurance program (the Quality Care Pharmacy Program – QCPP) identified serotonin syndrome and recommended appropriate action in a clinical simulated patient setting.

METHODS

In March 2014, an agent of the simulated patient entered 148 metropolitan and regional QCPP accredited pharmacies in five Australian states and the Northern Territory. The agent made the following request on behalf of the simulated patient: 'Hi. My dad is not feeling very well and I'm just after some advice.' The attributes for the simulated patient related to the presentation are listed in Table 1. The simulated patient attributes were constructed into a scenario intended to represent the type of interaction that typically occurs in community pharmacies. The agent could receive counselling from pharmacists (either directly or following referral from non-pharmacist support staff) or from non-pharmacist support staff without pharmacist involvement.

The agent was different in each of the six jurisdictions (two each in Victoria and Western Australia and one in South Australia, New South Wales, Tasmania and the Northern Territory). The agent was trained to divulge the attributes of the simulated patient when specifically questioned by pharmacy staff or at such a time as to ensure the natural flow of the conversation without appearing contrived. They were instructed on standardised responses to give when pertinent questions were asked by staff. They were instructed to refrain from adding details not covered in the scenario and respond with "not sure" if the interaction varied from the scenario notes. The agent carried a written list of the medicines taken by the simulated patient and showed it to pharmacy staff when asked about medicines being taken.

Scenario attributes were determined by the co-ordinating pharmacist at the Australian College of Pharmacy (the College) and reviewed by pharmacists from the Pharmacy Guild of Australia (PGoA) for face validity. The scenario was workshopped with field staff by teleconference prior to training of the agent. All agents and their supervisors received standardised training to minimise inter-rater variability.

Agents had permission to enter pharmacies under the pre-existing QCPP terms and conditions. Pharmacies accredited under QCPP, against the Australian standard (AS85000:2011), are assessed on requirements for the supply of non-prescription medicines under the Standards Maintenance Assessment (SMA) program. All pharmacies had also given permission for staff to be audio taped as part of their accreditation (permission could be removed prior to the visit). Pharmacies were randomly selected from the database of QCPP accredited pharmacies (approximately 95% of Australia's 5600 pharmacies) as determined by the SMA visit schedule. Participating pharmacies were sent written notification they would receive a visit in the ensuing six months. The date and details of the scenario were not divulged to the QCPP accredited pharmacy prior to the visit.

Audio recordings were analysed by a pharmacist assessor at the College for appropriateness of the agent's responses to questions asked as per the investigation protocol, degree of access to the pharmacist, information gathered by pharmacy staff, management advice given and pharmacotherapy recommended. The assessor was instructed to identify agents not adhering to the study protocol. Data collection utilised the validated protocol of Benrimoj *et al*. (2008).[16] Information gathered and

Table 2. Details of information gathered and management advice given by the pharmacy staff.

N=148	Frequency % (n)
Information gathered	
Investigation of the symptoms	98.6 (146)
Duration of the symptoms	79.1 (117)
Other medicines taken	71.6 (106)
Other co-morbidities	75.0 (111)
Suggested possible cause of the symptoms given^	
Serotonin syndrome/related to serotonin/tramadol	35.1 (52)
Virus	16.9 (25)
Other infection	2 (3)
Cardiac cause	15.5 (23)
Blood glucose	3.4 (5)
Anxiety	2.0 (3)
Dehydration	0.7 (1)
No suggestion of possible cause given	31.8 (47)
Management advice given	
Cease tramadol immediately (total)	33.8 (50)
Cease tramadol immediately (when serotonin syndrome identified)	94.2 (49/52)
Doctor may cease tramadol	2.0 (3)
Seek medical advice immediately	14.2 (21)
Follow up with doctor when possible	68.2 (101)
No advice on tramadol given	64.2 (95)
No advice on tramadol, but refer to a doctor	79.0 (75/95)
Pharmacotherapy recommended	
Maintain the patient's existing paracetamol	18.2 (27)
Change the patient's paracetamol to paracetamol/codeine	4.1 (6)
NSAIDs	4.1 (6)
Maintain adequate hydration	11.5 (17)
Cold and flu tablets	2.0 (3)
Complementary medicines	2.0 (3)
No non-prescription medicine sold	87.8 (130)
The staff member advising the agent	
Pharmacist involvement	94.0 (139)*
Non-pharmacist support staff only (no pharmacist involvement)	6.0 (9)

^Some pharmacy staff suggested multiple possible causes for the symptoms of the simulated patient.
*The agent of the simulated patient was referred to the pharmacist by non-pharmacist support staff in 67.6% of pharmacies (100/148).

counselling were assessed and entered into a database.

RESULTS

The pharmacist assessor determined that agents communicated the attributes of the simulated patient as per the study protocol during all pharmacy visits.

The percentage of pharmacy staff gathering information, providing advice and making recommendations is presented in Table 2. The clinical process pertinent to limiting the toxicity caused by serotonin syndrome undertaken by pharmacy staff is outlined in Figure 1. Investigation of the simulated patient's symptoms was undertaken by staff in 98.6% (146/148) of pharmacies. Ninety-four per cent (139/148) were consulted by a pharmacist (28% of these were directly consulted by a pharmacist and 72% were referred to a pharmacist by non-pharmacist support staff) and 6% (9/148) were consulted by non-pharmacist support staff without a pharmacist.

Symptom duration was discussed in 79.1% (117/148) of cases. A medication history was taken by 71.6% (106/148). The symptoms of the simulated patient were identified as potential serotonin syndrome by pharmacists in 35.1% (52/148) of pharmacies. Other suggested causes for the symptoms of the simulated patient were viral (16.9%; 25/148) and cardiac (15.5%; 23/148). No suggestion of the possible cause of the symptoms was made in (31.8%; 47/148) of pharmacies. The simulated patient was advised to cease the tramadol immediately in 33.8% (50/148) of all cases. Pharmacies advised the simulated patient should seek medical advice immediately in 14.2% (21/148) of all cases and seek medical advice when possible in 68.2% (101/148) of all cases. When potential serotonin syndrome was correctly identified, 94.2% (49/52) of pharmacists recommended an appropriate course of action advising that the simulated patient should cease tramadol immediately.

Tramadol use was not addressed in 64.2% (95/148) of cases; however, 79.0% (75/95) of these pharmacies advised the simulated patient to visit a doctor (18.7% of these suggested the simulated patient seek medical advice immediately while 81.3% suggested medical follow up when possible). The majority of pharmacies (87.8%; 130/148) did not recommend any non-prescription medicines for the simulated patient.

Although not an aim of the study, it was determined that there was a statistically significant difference between the jurisdictions in the identification of serotonin syndrome (chi-square=12.5, df=5, $p<0.05$). This was driven by an identification rate of 50% in Western Australia, contrasting with only 11% in New South Wales. Reviewing the audiotapes provided no indication that the agents of the

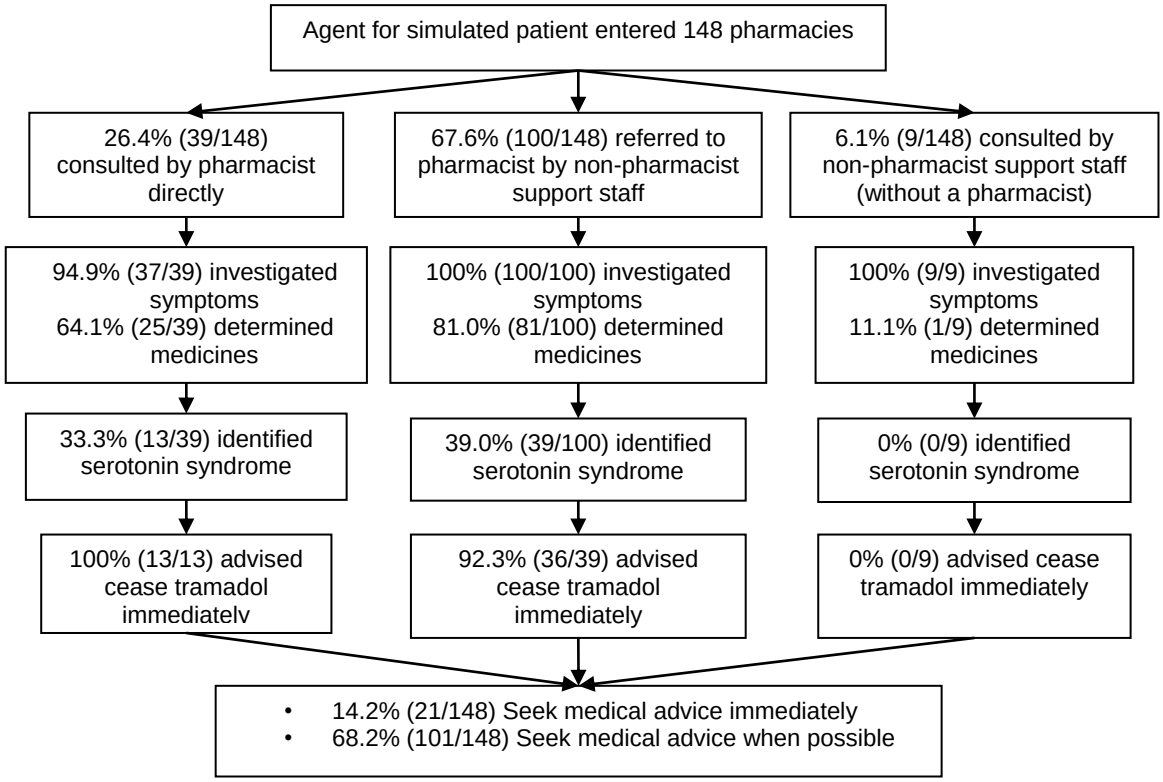

Figure 1: Assessment process undertaken by pharmacy staff and recommendations for management of serotonin syndrome made.

simulated patients in Western Australia disclosed any more information than elsewhere.

DISCUSSION

The percentage of pharmacy staff investigating the symptoms of the simulated patient was similar to another simulated patient community pharmacy study involving a request to treat reflux where 95% of pharmacies investigated the symptoms.[17] In another study involving a request for pain management in a patient taking warfarin, 88.2% investigated symptoms of the simulated patient.[18]

There was a distinct difference between the present study and the reflux study in the request made by the agent. In the present study the agent asked for advice while in the reflux study the agent requested treatment i.e. 'something for reflux'. It has been previously suggested that requests for non-prescription medicines by brand name are treated differently by pharmacy staff to requests for treatment of symptoms.[19] This was further highlighted by an investigation involving a request for a non-prescription sleeping preparation by brand name, that found only approximately 40% of pharmacies asked about the symptoms of the simulated patient.[20] While another Australian simulated patient study involving a request by brand name for an oral or topical vaginal thrush treatment resulted in an incidence of assessment of only 14% and 30% respectively.[21] The effect of request type was not investigated here; however, the percentage of pharmacy staff enquiring about symptoms was similar to other studies involving a request to treat symptoms rather than a request for medicines by brand name.

Investigation of the duration of the simulated patient's symptoms was important as this enabled pharmacy staff to identify that the symptom onset was related to initiation of tramadol therapy and potentially pointed to the tramadol as the cause of the symptoms. In the current study, discussion of symptom duration (79.1%) was more frequent than in the reflux study (58%) and the analgesics with warfarin study (47.6%).[17,18] This potentially indicates that the acute nature and severity of the symptoms in this serotonin syndrome scenario prompted more in depth investigation by pharmacy staff.

Identification of other medicines taken by the simulated patient was a key to determining the potential for serotonin syndrome. The percentage of pharmacy staff determining other medicines taken (71.6%) was similar to the reflux study (69%) and the insomnia symptoms study (approximately 75%) however greater than the brand name vaginal thrush treatment study (44% and 28%).[18,20,21] However, not identifying the other medicines the simulated patient was taking potentially prevented 28.4% of pharmacies from determining the simulated patient was experiencing serotonin syndrome. In most cases this did not prevent the simulated patient from receiving care, as in 78.6% (33/42) of cases when a medication history was not taken, pharmacy staff advised that the simulated patient should seek advice from a doctor. There were only 6.1% of all cases when neither a medication history was taken nor a doctor referral made by pharmacy staff.

The results highlight that taking a comprehensive medicines history can be overlooked by pharmacy staff when they are faced with determining the cause of a set of symptoms (98.6% of pharmacies discussed symptoms whereas only 71.6% took a medicines history). In the case of serotonin syndrome, a medicines history is an important part of the clinical workup and the results of this study indicate that pharmacy staff need to focus on both medicines and symptoms in order to elucidate the full picture.

The other most commonly suggested causes for the simulated patient's symptoms were viral and cardiac e.g. blood pressure or heart attack. Some pharmacies suggested the simulated patient should be investigated by a doctor for a range of potential causes including blood pressure, blood glucose and viral illness. Given the number of case reports of misdiagnosis of serotonin syndrome in the literature it is not unrealistic that these potential causes for the simulated patient's symptoms were suggested. The level of awareness of serotonin syndrome by other health professionals has also been reported to be low. A 1999 English study found that 85% of general practice doctors self-reported that they were not aware of serotonin syndrome.[22] While the clinical incidence of misdiagnosis of serotonin syndrome is not known, the current study indicated that community pharmacists identified the symptoms of serotonin syndrome in 35.1% of cases. The reason for the observed difference between the jurisdictions in the identification of serotonin syndrome is unknown.

A potential cause for the simulated patient's symptoms was not given in 31.8% of pharmacies. Most commonly this was associated with a suggestion that the simulated patient should have their symptoms assessed by a doctor. This may indicate that pharmacy staff are aware of their own uncertainty over symptoms that reflect serotonin syndrome and appropriately refer patients to a doctor for diagnosis if they cannot identify the condition themselves.

Ceasing the implicated serotonergic agent is identified as the ideal approach to controlling serotonin syndrome.[1] In the cases when the pharmacist correctly identified serotonin syndrome, 94.2% advised the simulated patient should cease tramadol immediately. Therefore, pharmacists take appropriate action when serotonin syndrome is identified. Pharmacy staff advised that the simulated patient should cease the tramadol immediately in 33.8% of all cases. A further 2.0% advised that, if consulted, the simulated patient's doctor would possibly recommend they cease tramadol. All pharmacists advising the simulated patient to cease tramadol recommended they follow up with a doctor. An urgent referral to a doctor, emergency department or ambulance service was made in 14.2% of cases. While the symptoms of the simulated patient did not represent severe serotonin syndrome, referral to emergency care was an appropriate action considering the potential for clinical deterioration.

The simulated patient's tramadol use was not addressed in 64.2% of cases. This is partly explained by the fact that the simulated patient's medication history was not determined by 28.4% of pharmacies. Even though staff in these 95 pharmacies did not directly address the simulated patient's tramadol use, they advised that the simulated patient should follow up with a doctor when possible in 79.0% (75/95) of cases.

Standard management of serotonin syndrome is to cease the causative agent and provide supportive therapy if required. There is no antidote to serotonin syndrome. Only 12.2% of pharmacies recommended a non-prescription medicine to treat the symptoms. These medicines were primarily alternative analgesics to the paracetamol the simulated patient was already taking. Three pharmacies recommended oral phenylephrine for cold and flu symptoms, which has the potential to further contribute to serotonin syndrome.

The agent was consulted by the pharmacist in 94.0% of cases. This compared favourably to the analgesics with warfarin study where 97% of consultations were undertaken by the pharmacist.[17] In the Kayshap *et al*. study involving a request for treatment of insomnia, only 24% were addressed by the pharmacist.[20] In Australia, non-pharmacist support staff receive formalised training including how to determine when it is necessary to refer health consumers to the pharmacist. QCPP standards require that non-pharmacist support staff refer health consumers to the pharmacist when they take other medicines, have other health conditions or when treatment for the medical condition presented is outside of their scope of training. Ninety-two per cent (100/109) of non-pharmacist support staff referred the agent to the pharmacist when they were the first point of contact. This indicates that non-pharmacist support staff are capable of identifying when it is necessary to refer health consumers to the pharmacist. It also reflects the high degree of access that health consumers have to the trained medicines experts in community pharmacies in Australia when they require expert advice.

There are limitations in investigating clinical assessment and counselling in a simulated patient environment. The individual is an actor constrained to a set of attributes. They do not have English language barriers or poor hearing. They are aware of the interaction between the two medicines the simulated patient is taking and of the expected outcome of the interaction. Finally, despite thorough and ongoing training, not all simulated patients behave uniformly.

CONCLUSIONS

While not identifying the cause of the simulated patient's symptoms in the majority of cases, community pharmacies contributed to the appropriate management of serotonin syndrome. They either took direct action to minimise harm to the patient by advising to cease the causative agent or referred the patient to a doctor for assessment.

Of the pharmacists who identified serotonin syndrome, 94.2% advised the patient to cease tramadol immediately. They rarely sold non-prescription medicines to control symptoms of serotonin syndrome. Pharmacies could more effectively limit serotonin syndrome toxicity by routinely taking a comprehensive medicines history. Potential future directions for the research would be to deliver targeted serotonin syndrome training to pharmacy staff and assess the scenario again in this cohort.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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