



## RESEARCH ARTICLE

# Serotonin Syndrome in Children and Adolescents Exposed to Selective Serotonin Reuptake Inhibitors – A Review of Literature

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### Abstract

**Objective:** The use of selective serotonin reuptake inhibitors (SSRIs) in children and adolescents is increasing in Canada and internationally. While SSRIs are known for their generally well tolerated side effect profile, serotonin syndrome can arise as a severe complication. The objective of this study is to review literature on SSRI-related serotonin syndrome in the pediatric population. **Methods:** An extensive review of literature on “serotonin syndrome” is conducted using PubMed from inception to March 2019, focusing on subjects zero to 18 years of age. Descriptive statistics are used for data analysis. **Results:** The search yielded  $N=338$  references and  $N=18$  studies are included, all of which are case reports. The cases encompass ethnically diverse subjects ranging from 4 to 18 years of age, diagnosed with serotonin syndrome after exposure to SSRI agents. Most common presenting symptoms are confusion, agitation, tachycardia, hypertension, hyperreflexia, rigidity, and tremor. Serotonin syndrome manifested from SSRI monotherapy (7/18; 3 after first dose), when SSRI was combined with another serotonergic agent (6/18), or after an overdose (5/18). Risk factors include high starting doses and co-prescription. Changing multiple medications at the same time adds to diagnostic challenges. **Conclusions:** Serotonin syndrome is a severe adverse drug reaction associated with SSRI, and can be associated with diverse presentations in the pediatrics population and diagnostic challenges. Clinicians are recommended to be vigilant in the monitoring and recognition of serotonin syndrome.

**Key Words:** serotonin syndrome, selective serotonin reuptake inhibitor, review, child

### Résumé

**Objectif:** L'utilisation des inhibiteurs sélectifs du recaptage de la sérotonine (ISRS) chez les enfants et les adolescents est en croissance au Canada et sur la scène internationale. Bien que les ISRS soient connus pour leur profil d'effets secondaires généralement bien toléré, le syndrome sérotoninergique peut survenir comme complication grave. La présente étude a pour objectif d'examiner la littérature sur le syndrome sérotoninergique lié aux ISRS dans la population pédiatrique. **Méthodes:** Une vaste revue de la littérature sur le « syndrome sérotoninergique » est menée à l'aide de PubMed du début à mars 2019, portant sur les sujets de 0 à 18 ans. Des statistiques descriptives servent à l'analyse des données.

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Submitted: March 26, 2020; Accepted: March 10, 2021

**Résultats:** La recherche a donné  $N = 338$  références et  $N = 18$  études sont incluses qui sont toutes des études de cas. Les cas comprennent des sujets de différentes ethnies qui ont de 4 à 18 ans, et ont reçu un diagnostic de syndrome sérotoninergique après une exposition à des ISRS. Les symptômes communs les plus présentés sont la confusion, l'agitation, la tachycardie, l'hypertension, l'hyperréflexie, la rigidité et le tremblement. Le syndrome sérotoninergique se manifestait après la monothérapie d'ISRS, (7/18; 3 après la première dose), quand les ISRS étaient combinés avec un autre agent sérotoninergique (6/18), ou après une surdose (5/18). Les facteurs de risque comprennent des doses de départ élevées et la co-prescription. Changer de multiples médicaments à la fois ajoute aux difficultés diagnostiques.

**Conclusions:** Le syndrome sérotoninergique est une réaction indésirable grave à un médicament associé aux ISRS, et peut être associé à diverses présentations dans la population pédiatrique et à des difficultés diagnostiques. On recommande aux cliniciens d'être vigilants pour surveiller et reconnaître le syndrome sérotoninergique.

**Mots clés:** *syndrome sérotoninergique, inhibiteur sélectif du recaptage de la sérotonine, revue, enfant*

## Introduction

The use of psychotropic medications in the child and adolescent population has been rising (Steinhausen, 2015; Zito et al., 2002). In Canada, between 2005 and 2009, prescriptions of selective serotonin reuptake inhibitors (SSRIs) by pediatricians increased by 39%, and recommendations of SSRIs by pediatric specialists increased by 44% (Lam, Gorman, Patten, & Pringsheim, 2013). A more recent analysis of data from the Canadian Primary Care Sentinel Surveillance Network between 2009 and 2014 found a steady increase in antidepressant prescriptions, 83% of which included SSRIs, for children and adolescents (Morkem et al., 2017). The trend, echoed by numerous other countries, may be a response to the growing rates of pediatric mental health conditions or lack of other appropriate pathways of care (Twenge, Cooper, Joiner, Duffy, & Binau, 2019; von Soest & Wichstrøm, 2014).

SSRIs are a class of medications that selectively inhibit the reuptake of serotonin in the presynaptic neurons resulting in postsynaptic effects. The class typically includes fluoxetine, sertraline, citalopram, escitalopram, fluvoxamine, and paroxetine (Korczak, 2013). Health Canada has not authorized the use of any SSRIs for individuals under 18 years of age (Health Canada, 2004). Canadian clinical practice guidelines recommended psychotherapy over pharmacotherapy as first-line treatment of pediatric mood and anxiety disorders and identified the use of fluoxetine for the treatment of pediatric major depressive disorder and social anxiety disorder as level 1 evidence (Katzman et al., 2014; MacQueen et al., 2016). In contrast, the U.S. Food and Drug Administration (FDA) has approved select SSRIs for the treatment of pediatric major depressive disorder and obsessive-compulsive disorder (OCD) (U.S. Food and Drug Administration, 2017 & 2019). The American Academy of Child and Adolescent Psychiatry (AACAP) recommended SSRIs as the medication of choice for pediatric anxiety disorders (Connolly & Bernstein, 2007).

Adverse effects of SSRIs include nausea, dry mouth, headache, dizziness, sweating, sexual dysfunction, sleep disturbances, increased risk of bleeding, agitation, manic switch, and suicidal behaviour (Cheung, Emslie, & Mayes, 2005; Kennedy et al., 2016). It is thought that children and adolescents experience similar adverse effects to adults with use of SSRIs, and serious adverse events are rare (Cheung et al., 2005). One of the serious clinical complications is serotonin syndrome or serotonin toxicity, and the classic presentation involves the triad of altered mental status, autonomic hyperactivity, and neuromuscular abnormalities (Volpi-Abadie, Kaye, & Kaye, 2013). Clinical diagnosis is established by exclusion and primarily based on the history of use of a serotonergic drug and the physical examination (Martin, 1996; Volpi-Abadie et al., 2013).

Multiple criteria exist to aid clinicians in the diagnosis of serotonin syndrome, though none are based on a pediatric population. The original Sternbach criteria were based on 38 established serotonin syndrome cases 20 to 68 years of age and are defined by the presence of three or more of the ten most common clinical features in these cases (Sternbach, 1991). More recently, the Hunter Serotonin Toxicity Criteria (HSTC) was developed and was based on over two thousand cases of serotonergic drug overdose, including a learning dataset of 473 SSRI-alone overdoses (Dunkley, Isbister, Sibbritt, Dawson, & Whyte, 2003). Demographic information, such as the age of included cases, was not reported. The HSTC involves a set of six decision rules and identifies clonus as the cardinal finding in establishing the serotonin syndrome diagnosis (Boyer & Shannon, 2005; Dunkley et al., 2003).

While serotonin syndrome is accepted as a theoretical risk in children and adolescents receiving SSRI treatment, there is scarce summative information on serotonin syndrome in the pediatric population (Figueroa, Rosenberg, Birmaher, & Keshavan, 1998). According to the Canadian Vigilance Adverse Reaction Online Database, only 10 cases of serotonin syndrome involving SSRI were recorded from 1965 to 2020

among individuals up to 18 years of age (Health Canada, 2020). The objective of this study is to comprehensively review the existing literature landscape on SSRI-induced serotonin syndrome pertaining to children and adolescents 0 to 18 years of age, describe their clinical manifestations, and highlight any knowledge gaps. To the best of our knowledge, this is the first review that focuses on published data of serotonin syndrome in the pediatric population.

## Methods

### Search strategy

An extensive review of literature was conducted using PubMed from inception to March 2019. The keyword/subject heading “serotonin syndrome” was used, and, exploded after verifying its definition and any umbrella terms. The search was limited to human subjects 0 to 18 years of age, but, was not limited to language of study or publication type, including case reports, letters to editors, and brief communications. All titles and abstracts of identified studies were examined. References of included studies were hand searched to identify additional publications.

### Inclusion/exclusion criteria

Studies were included if they met the following criteria: (1) contained original data that were published in a peer-reviewed journal; (2) involved any human subjects zero to 18 years of age; (3) subjects were exposed to any SSRI(s); and 4) included a clinical diagnosis of serotonin syndrome while exposed to the SSRI(s).

Studies were excluded if: (1) subjects received SSRI(s) through prenatal or antenatal exposure (i.e. through pregnancy or breastfeeding); (2) serotonin syndrome was related to infantile accidental ingestion of SSRI(s); (3) subjects were not taking any SSRI and serotonin syndrome was solely related to other serotonergic agents, such as pain medications, recreational substances, and complementary/alternative medicines; and (4) the clinical diagnosis was unclear/unestablished or mimicked serotonin syndrome (e.g. neuroleptic malignant syndrome).

### Data extraction and analysis

Study characteristics, including year of publication and country of study, were extracted. Pertinent subject information included age, sex, ethnicity, primary psychiatric diagnoses and co-morbidities. Pertinent medication information included the name(s), doses(s) and administration route(s) of the SSRI(s) and any co-prescribed medication(s). Clinical symptoms and the timing of their onset upon receiving the SSRI(s), if available, were further extracted. Descriptive statistics are used for data analysis.

## Results

The search strategy yielded 338 references, and 320 were excluded based on exclusion criteria and duplications. Eighteen studies are included in the final review. The studies were published between 1994 and 2016, and based in 9 countries across North America, Europe, Asia, the Middle East (Table 1). All were either case reports or letters/brief communications in format, and identified 18 distinct subjects/episodes of serotonin syndrome. Despite our best efforts, including contacting academic libraries and original authors, two full-texts (one in English and one in Japanese) could not be retrieved and therefore data was extracted from their abstracts alone (Ghanizadeh, Ghanizadeh, & Seifoori, 2008; Kawano et al., 2011).

### Subject characteristics

The study subjects included 11 males and 7 females ranging from 4 to 18 years of age, with the median age being 13 years of age and average age being 12 years of age. Identified ethnicities included Caucasian, Hispanic and East-Asian.

Psychiatric diagnoses for which the subjects were being treated with SSRIs included depression or dysthymia ( $N = 8$ ), anxiety-spectrum disorders including specific phobia and panic disorder ( $N = 3$ ), OCD ( $N = 2$ ), post-traumatic stress disorder or acute stress disorder ( $N = 2$ ), attention deficit hyperactivity disorder ( $N = 2$ ), eating disorder ( $N = 1$ ) and behavioural problem ( $N = 2$ ). Five subjects had more than one psychiatric diagnosis. In one case, a child without a formal diagnosis was administered a one-time dose of SSRI that was prescribed for a family member to “calm down” (Mullins, 1999). All subjects were seen in outpatient settings prior to the onset of serotonin syndrome, except one who was hospitalized for spinal cord injury, and one who was post-operative from an elective surgery (Jahr, Pisto, Gitlin, & O’Neill, 1994; Satoh, Takano, Onogi, Ohtsuki, & Kobayashi, 2006).

### Medication characteristics

SSRIs associated with the serotonin syndrome episodes included sertraline ( $N = 9$ ), fluoxetine ( $N = 4$ ), paroxetine ( $N = 3$ ) and fluvoxamine ( $N = 2$ ). No case reports were found on either citalopram or escitalopram and serotonin syndrome in the pediatric population.

Five cases occurred in the context of an overdose (intentional or accidental) (Grenha, Garrido, Brito, Oliveira, & Santos, 2013; Kaminski, Robbins, & Weibley, 1994; Kawano et al., 2011; Lee-Kelland, Zehra, & Mappa, 2018; Pitzianti, Marciano, Minnei, Baratta, & Pasini, 2016). Six cases reported serotonin syndrome from the combination of

SSRI and another medication (Jahr et al., 1994; Lee & Lee, 1999; Likasitwattanakul, 2005; Park & Jung, 2010; Thomas, Rosenberg, Blythe, & Meyer, 2004; Türkoglu, 2015). The postulated mechanisms varied, including the inhibition of CYP3A4 activity and SSRI metabolism (erythromycin), the increase of free SSRI fraction due to displacement from plasma proteins (lidocaine, midazolam, fentanyl), and the additive serotonergic effect (methylphenidate, clomipramine, linezolid) (Jahr et al., 1994; Lee & Lee, 1999; Likasitwattanakul, 2005; Park & Jung, 2010; Thomas, Rosenberg, Blythe, & Meyer, 2004; Türkoglu, 2015).

The rest of the seven cases were in the context of SSRI monotherapy (Benzick, 2001; Gill, LoVecchio, & Selden, 1999; Ghanizadeh et al., 2008; Godinho, Thompson, & Bramble, 2002; Mullins & Horowitz, 1999; Phan et al., 2008; Satoh et al., 2006). Among them, three developed symptoms upon receiving the first SSRI dose (fluvoxamine 50 mg, sertraline 50 mg and sertraline 100 mg) (Gill et al., 1999; Mullins & Horowitz, 1999; Phan et al., 2008). All were considered to be higher than the recommended starting doses in the pediatric population (U.S. Food and Drug Administration, 2017 & 2019).

### Clinical presentation

Time to symptom onset or medical attention varied widely depending on the clinical scenario. Of the five cases of SSRI overdose, all presented within 24 hours of ingestion. For most other subjects, symptoms emerged within the first 48 hours ( $N = 7$ ) or within 3 to 6 days ( $N = 3$ ) after SSRI was either initiated, had its dosage increased, or was combined with another serotonergic medication. Of note, one male 18 years of age developed simultaneous mania and serotonin syndrome symptoms approximately one month after he began low-dose paroxetine and methylphenidate combination treatment (Park & Jung, 2010). In another case, one male 8 years of age came to clinical attention 33 days after initiating low-dose fluoxetine, and 7 days after stopping pimozide (Godinho et al., 2002).

The most prevalent presenting signs and symptoms of serotonin syndrome identified by this review are presented in Table 2.

Regarding altered mental status, many subjects were described to be agitated/poorly cooperative ( $N = 10$ ) and confused ( $N = 9$ ). Six subjects presented with significantly altered level of consciousness or in a comatose state (Gill et al., 1999; Jahr et al., 1994; Kawano et al., 2011; Likasitwattanakul, 2005; Phan et al., 2008; Türkoglu, 2015). Five presented with visual and/or auditory hallucinations and two experienced delusions of reference or grandeur (Ghanizadeh et al., 2008; Godinho et al., 2002; Grenha et al.,

2013; Kaminski et al., 1994; Park & Jung, 2010; Pitzianti et al., 2016; Türkoglu, S., 2005). Regarding autonomic hyperactivity, subjects commonly experienced tachycardia ( $N = 12$ ), hypertension ( $N = 10$ ) and hyperthermia ( $N = 9$ ). The highest rate of heart rate (over 200 beats per minute) was observed in a male 9 years of age (Kaminski et al., 1999). Three cases noted autonomic instability and dramatic fluctuations in heart rate and/or blood pressure measures (Gill et al., 1999; Godinho et al., 2002; Likasitwattanakul, 2005). Diaphoresis, mydriasis, gastrointestinal symptoms, and shivers were also common. Regarding neuromuscular abnormalities, the most prevalent presenting signs and symptoms were hyperreflexia ( $N = 11$ ), tremor ( $N = 10$ ), and rigidity ( $N = 9$ ). Other signs and symptoms not captured by Table 2 include clonus ( $N = 5$ ), flushing ( $N = 4$ ), seizures ( $N = 2$ ), hypersensitivity to noise ( $N = 2$ ), nystagmus ( $N = 2$ ), and ataxia ( $N = 2$ ). All subjects' symptoms subsided upon supportive care and discontinuation of causative agents, except one overdose case in which the subject presented with cardiopulmonary arrest and died despite intensive treatment (Kawano et al., 2011).

## Discussion

While generally well tolerated, SSRIs can be associated with the serious clinical complication of serotonin syndrome. Several case series describe and summarize the symptomatology of serotonin syndrome and their relative occurrence rate, however, almost all data have been based on adult cases with a mean/median between 30 to 40 years of age (Hilton, Maradit, & Möller, 1997; Isbister, Bowe, Dawson, & Whyte, 2004; Mason, Morris, & Balcezak, 2000; Radomski, Dursun, Reverley, & Kutcher, 2000).

There is a need to better understand the epidemiology and clinical manifestations of serotonin syndrome in children and adolescents. This is especially the case given the lack of summative data specific to this population, and the pattern of increasing SSRI prescriptions (Lam et al., 2013). This review is the first effort to summarize and analyze literature on pediatric incidents of SSRI-associated serotonin syndrome, and identified 18 unique cases involving individuals from 4 to 18 years of age in nine countries.

Consistent with existing literature, the majority of pediatric subjects developed serotonin syndrome symptoms within 24 hours following a dose increase or an overdose, or after one to two added doses of another serotonergic agent (Sun-Edelstein, Tepper, & Shapiro, 2008; Volpi-Abadie et al., 2013). However, in other cases, symptom manifestation was not apparent or did not reach clinical attention until more than one month after medication change (Godinho et al., 2002; Park & Jung, 2010). While serotonin syndrome is

Table 1. Demographic and medication-related information of 18 pediatric serotonin syndrome cases								
Study	Age	Sex	Ethnicity	Diagnoses	SSRI	SSRI dose	Other medications	Time to symptom onset
Benzick, 2001; USA	17	F	East Asian	PTSD	Paroxetine	10 mg		3 days after starting paroxetine
Ghanizadeh et al, 2008; Iran	AD	M		Depression	Fluoxetine			
Gill et al, 1999; USA	11	M		ADHD	Fluvoxamine	50 mg	Perphenazine, benzotropine, valproate (stopped 7 days prior)	1 hour after first dose
Godinho et al, 2002; UK	8	M		ADHD, ID	Fluoxetine	10 mg	Pimozide (stopped 7 days prior)	33 days after taking 10mg daily
Grenha et al, 2013; Portugal	8	F		Behavioral problem/ insomnia	Sertraline	50 mg x 30 tabs	Risperidone	Several hours after overdose
Jahr et al, 1994; USA	18	F		Depression	Sertraline	200 mg	Fentanyl, lidocaine, midazolam	Immediately after receiving fentanyl, lidocaine, and midazolam
Kaminski et al, 1994; USA	9	M			Sertraline	50 mg x unknown tabs	Methylphenidate (stopped 9 days prior)	2 hours after overdose
Kawano et al, 2011; Japan	15	M			Fluvoxamine	Overdose	Tandospirone	24 hours after overdose
Lee & Lee, 1999; USA	12	M		OCD, Phobia	Sertraline	37.5 mg	Erythromycin	4 days after starting erythromycin
Lee-Kelland et al, 2018; UK	14	M		Depression, anxiety	Fluoxetine	20 mg x 60 tabs		7 hours after overdose
Likasitwattanakul, 2005; Thailand	12	M		OCD	Sertraline	50 mg	Clomipramine	1 day after increasing sertraline from 25mg to 50mg
Mullins, 1999; USA	16	F	Hispanic		Sertraline	100 mg		Soon after first dose
Park & Jung, 2010; Korea	18	M	East Asian	Depression	Paroxetine	40 mg	Methylphenidate	One month after starting paroxetine and methylphenidate
Phan et al, 2008; USA	9	M		Behavioral problem	Sertraline	50 mg		2 hours after first dose
Pitzianti et al, 2016; Italy	16	F		Eating disorder, dysthymia, hypomania	Sertraline	20 mg x 100 tabs		13 hours after overdose
Satoh et al, 2006; Japan	18	M	East Asian	Depression, panic disorder	Paroxetine	10 mg	Fluvoxamine (stopped 1 day prior)	6 days after starting paroxetine

continued

Table 1. continued								
Study	Age	Sex	Ethnicity	Diagnoses	SSRI	SSRI dose	Other Medications	Time to Symptom Onset
Thomas et al, 2004; USA	4	F	Hispanic	Acute stress disorder	Fluoxetine	5 mg	Fentanyl, linezolid	2 days after starting linezolid and soon after receiving fentanyl
Türkoglu, 2015; Turkey	14	F		Depression	Sertraline	150 mg	Methylphenidate	2 days after starting methylphenidate

Abbreviations: AD = adolescent; ADHD = attention deficit hyperactivity disorder; ID = intellectual disability; OCD = obsessive compulsive disorder; PTSD = post-traumatic stress disorder; SSRI = selective serotonin reuptake inhibitor

typically thought to occur in overdoses or drug interactions, this review identified seven cases of serotonin syndrome from SSRI monotherapy. It is unclear whether this indicates a greater sensitivity in the pediatric population.

Clinical symptomatology among the pediatric cases overall presented in the classic triad of altered mental status, autonomic hyperactivity, and neuromuscular abnormalities, and reflected many outlined in the Sternbach criteria (Sternbach, 1991). In comparison to the frequency of serotonin syndrome symptoms described in adult populations, the pediatric cases exhibited high frequencies of altered level of consciousness or unresponsiveness, hypertension, mydriasis, and muscle rigidity (Mason et al., 2000; Sternbach, 1991). Several reports described their subjects to be hypersensitive to sound, a symptomatology that is not typically included in adult-based studies (Godinho et al., 2002; Türkoglu, S., 2005). This review further identified seven subjects who experienced psychosis in the form of either hallucinations or delusions. This is in contrast to only one case involving psychosis among the 62 cases reviewed by Radomski et al. (2000). Due to the non-specific nature of serotonin syndrome symptoms, many reports noted the diagnostic difficulties and/or overlap with other syndromes such as mania, neuroleptic withdrawal, neuroleptic malignant syndrome, and anticholinergic toxidrome (Gerardi et al., 2015; Godinho et al., 2002; Kaminski et al., 1994; Park & Jung, 2010).

## Limitations

Limitations of this review include that all included studies are case reports, and therefore there may be inherent biases and risk of over-/under-reporting. Because of the small number of cases, the rates of symptomatology may be artificially inflated, and true differences from the adult population can only be speculated on and not formally tested. Relative toxicity of SSRIs could not be established, and no cases involving citalopram or escitalopram were found,

but this finding does not imply that citalopram and escitalopram are free of risk for serotonin syndrome. This review does not include information on the subjects' laboratory investigations and management plans, which were mostly conducted in emergency departments and medical inpatient settings including intensive care units. The goal of the review is intended to help clinicians in mental health settings to be more aware of its manifestations, rather than to guide acute management.

Overall, we recognize that due to the lack of literature on SSRI-induced serotonin syndrome in the pediatric population, it remains challenging to ascertain any patterns based on a small number of case studies. Rather, this review suggests the breadth of possible etiologies and presentations highlighting the many more unknowns of this topic. Specifically, the incidence of serotonin syndrome in the pediatric population is unestablished. Moreover, the existing diagnostic criteria for serotonin syndrome are primarily based on the adult population (Dunkley et al., 2003; Sternbach, 1991). It is unclear whether the adult criteria are misapplied or overemphasized. The diagnostic uncertainty is further complicated by children's poor subjective reporting, adolescents' guardedness of using serotonergic recreational substances, the vague nature of serotonin syndrome symptoms, such that the presentation may be dismissed or misattributed (Boyer & Shannon, 2005; Ganetsky & Brush, 2005).

## Clinical implications

Serotonin syndrome related to SSRI use has been identified in the pediatric population. If SSRI treatment is indicated, clinicians are recommended to provide psychoeducation on serotonin syndrome to children, adolescents and their parents/caretakers. SSRIs should be started at a low dose and titrated upward slowly, as starting doses considered routine practice for adults are found to be associated with serotonin syndrome in children in some scenarios.

**Table 2. Rate of the most common presenting symptoms in 18 pediatric serotonin syndrome cases**

	Altered Mental Status					Autonomic Hyperactivity					Neuromuscular Abnormalities				
	Agitation	Confusion	Psychosis	Altered LOC	HR*	BP*	Hyper-thermia*	Dia-phoresis	Mydriasis	N/V/D	Shivers	Hyper-reflexia	Tremors	Rigidity	Myo-clonus
Total Number	10	9	7	6	12	10	9	9	8	6	6	11	10	9	7
Benzick, 2001; USA					✓		✓					✓	✓	✓	
Ghanizadeh et al, 2008; Iran	✓	✓	✓					✓		✓					
Gill et al, 1999; USA	✓			✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
Godinho et al, 2002; UK	✓	✓	✓		✓	✓	✓	✓	✓	✓		✓			
Grenha et al, 2013; Portugal	✓	✓	✓		✓	✓	✓	✓				✓	✓	✓	✓
Jahr et al, 1994; USA				✓											✓
Kaminski et al, 1994; USA	✓		✓		✓		✓	✓	✓	✓		✓			
Kawano et al, 2011; Japan				✓			✓							✓	
Lee & Lee, 1999; USA	✓	✓											✓		
Lee-Kelland et al, 2018; UK		✓			✓	✓		✓	✓	✓		✓	✓		
Liksitwattanakul, 2005; Thailand				✓		✓	✓	✓	✓			✓		✓	
Mullins, 1999; USA					✓	✓						✓	✓	✓	
Park & Jung, 2010; Korea		✓	✓		✓	✓	✓	✓				✓	✓	✓	✓
Phan et al, 2008; USA	✓	✓		✓	✓		✓	✓	✓	✓		✓	✓	✓	
Pizzianti et al, 2016; Italy	✓		✓		✓	✓		✓	✓	✓		✓	✓		
Satoh et al, 2006; Japan	✓	✓			✓	✓	✓	✓							✓
Thomas et al, 2004; USA									✓						✓
Türkoglu, 2015; Turkey	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓

BP = blood pressure; HR = heart rate; LOC = level of consciousness; N/V/D = nausea/vomiting/diarrhea

\* Hyperthermia as defined by case report or by Hamilton & John, 2013; increased blood pressure (hypertension) and heart rate (tachycardia) defined by case report or by Disque, 2016

Serotonin syndrome is associated with many other drug classes in addition to SSRIs, and clinicians should be aware of patients' other prescription and over-the-counter medications by conducting medication reconciliation frequently. Classes particularly relevant to the pediatric population include antiemetic agents, antibiotics, tramadol, over-the-counter cough remedies (e.g. dextromethorphan), and drugs of abuse (Boyer & Shannon, 2005). Serotonin syndrome can manifest in diverse presentations, and do not always present immediately upon medication changes. Therefore, clinicians are recommended to familiarize themselves with its symptomatology, remain vigilant, and not misattribute symptoms such as irritability, agitation and anxiety to patients' psychopathology (Boyer & Shannon, 2005). Changing two medications in the same time period is discouraged as it may lead to diagnostic uncertainty (Godinho et al., 2002). This review suggests that the establishment of a registry of confirmed serotonin syndrome cases may be an important future direction to aid clinicians in recognizing serotonin syndrome and understanding its prospective epidemiology in the pediatrics population.

## Conflicts of interest

The authors have neither financial nor other competing interests to disclose.

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