Journal Pre-proof

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PII: S2667-1182(26)00008-5
DOI: https://doi.org/10.1016/j.etdah.2026.100278
Reference: ETDAH 100278

To appear in: *Emerging Trends in Drugs, Addictions, and Health*

Received date: 25 October 2025
Revised date: 26 June 2026
Accepted date: 8 July 2026

Please cite this article as: Rokhsareh Meamar Associate Professor , Farhad Kiani Medical Doctor , Ali Karami Nogourani Medical Doctor , Shiva Samsamshariat Assistant Professor , Nastaran Eizadi-Mood Professor , Clinical Toxicity and Management of Selective Serotonin Reuptake Inhibitor (SSRI) Poisoning: A Comprehensive Review, *Emerging Trends in Drugs, Addictions, and Health* (2026), doi: https://doi.org/10.1016/j.etdah.2026.100278

Clinical Toxicity and Management of Selective Serotonin Reuptake Inhibitor (SSRI) Poisoning: A Comprehensive Review

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Abstract

Introduction: Selective Serotonin Reuptake Inhibitors (SSRIs) are widely prescribed. With the global rise in SSRI prescriptions, the incidence of overdose has increased. SSRI overdose can result in severe toxicity, including serotonin syndrome, seizures, and QT interval prolongation. This review summarizes the clinical features, management, and outcomes associated with SSRI poisoning.

Methods: A narrative review was conducted using a structured search in PubMed, Web of Science, Embase, and Scopus through January 2025. Fifteen studies, including case reports and cohort studies, were identified. The results of SSRI exposure, clinical symptoms (cardiac, neurologic), treatment, and outcome are summarized.

Results: SSRI overdose most commonly results in mild symptoms, such as nausea, vomiting, and drowsiness. Serious complications are less frequent and include serotonin syndrome (up to 19.3%), seizures (1-8%), and QT prolongation (3-50.5%), particularly following citalopram overdose. Management is primarily supportive, with activated charcoal and benzodiazepines used when indicated. Intensive care unit admission (2.3-11.4%) and mortality (<0.1%) are uncommon, and most patients recover within 24 h.

Discussion: Among SSRIs, citalopram is associated with a higher risk of severe neurological and cardiac complications. Variability in diagnostic criteria and dose reporting across studies limits direct comparisons and highlights the need for standardized reporting.

Conclusion: SSRI poisoning is generally associated with favorable outcomes; however, continuous monitoring is essential for early detection of serious complications. Clinicians should remain vigilant for neurological and cardiac toxicity, particularly in citalopram overdose, where electrocardiographic monitoring is crucial for identifying QTc prolongation.

Keywords: SSRI, Toxicity, Overdose, Outcome, Review

Introduction

Selective Serotonin Reuptake Inhibitors (SSRIs) are widely recognized as first-line pharmacological treatments for depression (1). Since fluoxetine was first introduced in the United States in 1988, SSRIs have rapidly become the mainstay of treatment for various

psychiatric disorders, including depression, anxiety disorders, obsessive-compulsive disorder, and other related conditions (2-4). Beyond psychiatric indications, SSRIs are prescribed for panic disorders, pain syndromes, and other non-psychiatric conditions (5).

Over the past three decades, SSRI prescriptions have increased substantially worldwide, with the United States showing one of the most significant increases in antidepressant utilization (6). Consequently, SSRIs have emerged as one of the most frequently implicated agents in both intentional and unintentional overdose cases (7).

Recent studies of SSRI cases reported to U.S. poison centers have shown a 19.9% increase in calls between 2015 and 2020, with sertraline being the most frequently reported (8). In Iran, SSRI poisoning accounts for approximately 1.3% of acute toxicological presentations (9). The increasing availability of SSRIs has been accompanied by increasing rates of intentional self-poisoning, specifically in individuals already prescribed these medications (10).

Although SSRIs are generally considered safer than older antidepressants, such as tricyclic antidepressants (TCAs), they may have some toxic effects (9, 11). SSRIs are associated with higher patient adherence, mainly because of their more favorable side effect profile and lower lethality in overdose (2, 12, 13).
Most SSRI overdoses are clinically mild and present with gastrointestinal symptoms, drowsiness, tremors, or tachycardia (9, 14). Nevertheless, SSRIs may cause severe complications, including QT prolongation, life-threatening arrhythmias, seizures, and serotonin syndrome (15-19).

Given the increasing use of SSRIs and the corresponding rise in SSRI toxicity cases, this review specifically consolidates data until 2025, focusing on the management of massive overdoses and refractory complications, especially cardiac and neurologic, based on the most recent clinical data, which are underrepresented in earlier comprehensive works.

Methods

We conducted a structured narrative review by searching PubMed, Web of Science, Embase, and Scopus for studies published until January 2025. The search strategy combined terms associated with selective serotonin reuptake inhibitors and poisoning manifestations (Supplementary 1).

The inclusion criteria were case reports, case series, cohort studies, and cross-sectional studies that evaluated the clinical manifestations, management strategies, or outcomes of SSRI poisoning in both adult and pediatric patients, particularly those that included cardiovascular and neurological findings. Only studies written in English were included in this review.

Studies were excluded if they did not specifically address SSRI toxicity or poisoning, including the ones focused on the therapeutic use of SSRIs, treatment of depression or anxiety disorders, or long-term adverse effects unrelated to overdose. In addition, pharmacokinetic, receptor-binding, or mechanistic studies without clinically relevant toxicity findings were excluded, as were studies lacking sufficient details regarding SSRI exposure, ingested dose, clinical manifestations, management, or outcomes. Gray literature, including conference abstracts, unpublished reports, and theses, was explicitly excluded. Finally, studies involving mixed-drug poisoning were excluded if the SSRI-specific data were not separately identifiable.

Five reviewers fully completed the literature search in January 2025 and independently screened the databases before comparing the retrieved records. Conflicts, if any, were discussed amongst the reviewers and resolved via adjudication by Professor Izadi-Mood when required. The search yielded 15 studies (4 case reports, 3 cross-sectional and 8 cohort studies) that described clinical cases of SSRI toxicity, including case reports and larger observational cohorts with extractable treatment and outcome data. The concordant PRISMA diagram is available in Supplementary 2.

The main findings of the included studies are summarized in the following tables. Table 1 outlines the study characteristics and reported SSRI exposures, while Table 2 outlines the clinical manifestations (cardiac and neurological symptoms), treatments, and outcomes associated with SSRI poisoning. Cardiac manifestations included prolonged QT interval, bradycardia, tachycardia, arrhythmia, conduction block or disturbance, negative T-waves, and cardiac arrest. QTc prolongation in each study is indicated in Table 2. The Bazett formula was used to derive QTc from QT in some studies,(18-22) whereas in others, the method was unknown (3, 13, 15, 23). Neurological manifestations consisted of agitation, ataxia, coma, confusion, dizziness/vertigo, drowsiness/lethargy, hallucinations/delusion, seizures, status seizures, serotonin syndrome, restlessness, fatigue, and confusion.

Table 1. Characteristics of Included Studies and Selective Serotonin Reuptake Inhibitors (SSRIs) **Exposure Data**

Author (Year)	Country	Study Design	Sample Size	Dosage	Single / Multi Substance
Whyte et al. (2003) [24]	Australia	Prospective cohort	538 (233 with SSRI poisoning)	Dosage not reported	Multi-Substances; Mixed SSRIs
Kelly et al. (2004) [15]	United Kingdom	Retrospective observational	225 (88 with SSRI poisoning)	Mean dose 449.74 mg	Single Substance: Citalopram
Isbister et al. (2004) [13]	Australia	Prospective observational cohort	469 (Subset 1)	Dosage not reported	Multi Substances: Fluoxetine (75 cases), Citalopram (96 cases), Sertraline (156 cases), Paroxetine (119 cases), Fluvoxamine (23 cases);
Isbister et al. (2004) [13]	Australia	Prospective observational cohort	297 (Subset 2*)	Fluoxetine (median 16 DDD; ≈ 320 mg), Citalopram (median 16 DDD; ≈ 320 mg), Sertraline (median 24 DDD; ≈ 1200 mg), Paroxetine (median 15 DDD; ≈ 300 mg), Fluvoxamine (median 15 DDD; ≈ 1500 mg) ¶	Multi Substances; Fluoxetine (42 cases), Citalopram (57 cases), Sertraline (103 cases), Paroxetine (78 cases), Fluvoxamine (17 cases)
De Boer et al. (2005) [18]	Netherlands	Case report	1	Sertraline; total dose 2250 mg	Single Substance: Sertraline
Suchard (2008) [14]	USA	Case report	1	Fluoxetine; total dose 1400 mg	Single Substance: Fluoxetine
White et al. (2008) [25]	USA	Cross-sectional	82802 (36893 with SSRI poisoning)	Dosage not reported	Multi Substances; Fluoxetine (7008 cases), Citalopram (5251 cases), Escitalopram (3008 cases), Sertraline (12002 cases), Paroxetine (9258

					cases), Fluvoxamine (366 cases)
Hayes et al. (2010) [3]	USA	Retrospective observational	795	Escitalopram (mean dose 199.2 mg); Citalopram (mean dose 426.1 mg)	Multi Substances; Escitalopram (421 cases), Citalopram (374 cases)
Yilmaz et al. (2010) [23]	Germany, Austria, Switzerland	Retrospective observational	379	Citalopram mean dose 712 mg; Escitalopram mean dose 322 mg	Multi Substances; Citalopram (316 cases); Escitalopram (63 cases)
Acikalin et al. (2010) [19]	Turkey	Retrospective observational	96 (21 with SSRI poisoning)	Dosage not reported	Multi Substances; Fluoxetine (3 cases), Citalopram (2 cases), Sertraline (16 cases)
Chan et al. (2010) [20]	Australia	Retrospective cohort	80 (44 with SSRI poisoning)	Other substances. Dosage not reported	Multi Substances: Fluoxetine, Citalopram, Sertraline, Paroxetine, Fluvoxamine
Groot et al. (2018) [21]	Netherlands	Case report	1	Fluoxetine Total dose2800 mg	Multi Substances
Overberg et al. (2019) [17]	USA	Retrospective observational	30026 (26522 with SSRI poisoning)	Dosage not reported	Fluoxetine (7395 cases), Citalopram (3385 cases), Escitalopram (4036 cases), Sertraline (8969 cases), Paroxetine (920 cases), Fluvoxamine (113 cases), Other SSRIs (1704)
Koshy et al. (2023) [16]	India	Case report	1	Total dose 200 mg	Single Substance: Escitalopram
Eizadi-Mood et al. (2024) [9]	Iran	Cross-sectional	199	Mean Citalopram dose 373 mg, mean total SSRIs dose 562 ± 575 mg	Multi Substances; Fluoxetine (33 cases), Citalopram (76 cases), Sertraline (67 cases), Paroxetine (1 case), Fluvoxamine (10 cases), Escitalopram (6 cases), Mixed SSRIs (6 cases)

Meamar et al. (2025) (22)	Iran	Cross-sectional	101	Dosage not reported	Fluoxetine (19 cases), Citalopram (18 cases), Escitalopram (15 cases), Sertraline (44 cases), Paroxetine (1 case), Fluvoxamine (4 cases)

1 Cardiac toxicity analysis,*

¶ Doses in Isbister et al. (2004, Subset 2) are reported as Defined Daily Doses (DDD). Mg equivalents were calculated using WHO ATC/DDD values: sertraline 50 mg, paroxetine 20 mg, fluvoxamine 100 mg, fluoxetine 20 mg, and citalopram 20 mg.

Table 2. Cardiac and Neurological Manifestations, Treatment, and Outcomes of Selective Serotonin Reuptake Inhibitors (SSRIs) **Poisoning**

Author (Year)	Cardiac manifestations n (%)	Neurological manifestations n (%)	Treatment	Outcome n (%)
Whyte et al. (2003) [24]	Life-threatening arrhythmias: 1 (0.4); QRS >100 ms: 43 (24.2).	Seizures: 3 (1.3); Coma: 3 (1.3). Serotonin toxicity: 45 (19.3).	-----	ICU admission: 17 (7.3) All patients recovered
Kelly et al. (2004) [15]	Prolonged QT interval: QTc > 450ms: 7 (7.9)	Seizure: 5 (5.7)	-----	ICU admission: 2 (2.3) All patients recovered.
Isbister et al. (2004, Subset 1) [13]	Prolonged QT interval: QTc > 440ms: 150 (50.5); Bradycardia: 25 (8.4); Tachycardia: 45 (15.2); Arrhythmia/conduction block: 2 (0.6).	Seizures: 9 (1.9); Coma: 11 (2.4). Serotonin syndrome: 67 (14.3).	-----	ICU admission: 30 (6.4) All patients recovered
De Boer et al. (2005) [18]	Prolonged QT interval: QTc= 525 ms; negative T-waves in V1–V3.	Fatigue; Drowsiness.	Sodium-sulfate, Activated charcoal	ICU admitted and discharged
Suchard (2008) [14]	Sinus tachycardia.	Tonic-colonic seizure.	Phenobarbital	ICU admitted and discharged
White et al. (2008) [25]	Bradycardia: 110 (0.3); Tachycardia: 3279 (8.8); Cardiac arrest‡: 5 (0.01); Conduction disturbance: 145 (0.4); Dysrhythmia (VT/VF) ‡: 5 (0.01).	Agitated/irritable: 1245 (3.4); Ataxia: 206 (0.5); Coma: 135 (0.4); Confusion: 358 (1.0); Dizziness/vertigo: 839 (2.3); Drowsiness/lethargy: 5594 (15.2); Hallucinations/delusion: 133 (0.4); Seizures (single): 339 (0.9); Seizures (multi): 101 (0.3); Seizures (status): 29 (0.1).	-----	Death: 8 (0.1).

Hayes et al. (2010) **(3)**	Escitalopram: Tachycardia: 82 (19.5); Prolonged QT interval (men's QTc > 440 ms, women's QTc > 460 ms): 7 (1.7).	Escitalopram: Seizure: 1 (0.2); Drowsiness: 63 (15.0); Agitation: 16 (3.8); Dizziness/ataxia: 17 (4.0); Coma: 2 (0.5).	Activated charcoal: 272 (64.6), Benzodiazepine: 14 (3.3), Intubation: 1 (0.2)	All patients recovered. Severity✦: No effect: 214 (50.8); Minor: 182 (43.2); Moderate: 24 (5.7); Major: 1 (0.2).
Hayes et al. (2010) (3)	Citalopram: Tachycardia: 93 (24.9); Prolonged QT interval (men's QTc> 440 ms, women's QTc > 460 ms): 14 (3.7).	Citalopram: Seizure: 30 (8.0); Drowsiness: 76 (20.3); Agitation: 21 (5.6); Dizziness/ataxia: 12 (3.2); Coma: 2 (0.5); Nystagmus: 3 (0.8).	Activated charcoal: 255 (68.2), Benzodiazepine: 30 (8.1), Intubation: 6 (1.6), Cyproheptadine: 1 (0.2)	All patients recovered. Severity✦: No effect: 167 (44.6); Minor: 140 (37.4); Moderate: 54 (14.4); Major: 13 (3.5).
Yilmaz et al. (2010) **(23)**	Citalopram: Prolonged QT interval (men's QTC > 390 ms, women's QTc >440 ms)⁚ 27 (9); Tachycardia: 54 (17); AV-Block: 2 (0.6). Escitalopram: Prolonged QT interval (men's QTc > 390 ms, women's QTc >440 ms)⁚ 5 (8.0); Tachycardia: 7 (11.0).	Citalopram: Coma: 8 (2.5); Seizures: 43 (14); Dizziness: 25 (7.9); Restlessness: 11 (3.5); Agitation: 13 (4.1). Escitalopram: Coma: 1 (1.6); Seizures: 1 (2.0); Dizziness: 2 (3.1); Restlessness: 2 (3.1); Agitation: 4 (6.3).	Gastric lavage and activated charcoal were administered.	All patients recovered
Acikalin et al. (2010) **(19)**	Sinus tachycardia: 11 (52.4%); Prolonged QT interval (QTc >400 ms): 13 (61.9%); QTc >500 ms: 1 (4.8%).	-----	IV fluids, Sodium bicarbonate	All patients recovered
Chan et al. (2010) **(20)**	Tachycardia: 7 (15.9); Arrhythmia: 0; Prolonged QT interval – QT: 367.7 ± 34.6 ms, QTc: 425.3 ± 24.3 ms; QRS >100 ms: 3 (6.8).	Agitation: 3 (6.8); Restlessness: 1 (2.3); Coma: 1 (2.3); Seizures: 1 (2.3). Serotonin toxicity: 6 (13.6).	Intubation: 1 (2.3), psychiatric admission: 13 (29.5)	ICU admission: 1 (2.3), All patients recovered
Groot et al. (2018) **(21)**	Prolonged QT interval: QT= 503ms	-----	IV fluids, Magnesium sulfate, Serial ECG	ICU admitted and discharged

Overberg et al. (2019) [17]	Tachycardia: 6295 (22.3); Conduction disturbance: 948 (3.4).	Drowsiness: 3349 (11.9); Agitated/Irritable: 1062 (3.8); Dizziness/Vertigo: 1177 (4.2); Seizure (single): 429 (8.5).	Activated charcoal: 4846 (18.5), ICU admission: 3010 (11.4), Benzodiazepines: 1430 (5.4), Intubation: 71 (0.2), Ventilator: 66 (0.2), Anticonvulsants: 19 (0.1), Vasopressors: 6 (0.1)	All patients recovered. Severity✦: No effect: 9234 (34.8); Minor: 8804 (33.2); Moderate: 4767 (18); Major: 260 (0.98).
Koshy et al. (2023) [16]	T-wave inversion	Agitation.	Supportive care, Gastric lavage, Benzodiazepine	ICU admitted and discharged
Eizadi-Mood et al. (2024) [9]	Tachycardia: 62 (31.2).	Drowsiness: 74 (37.2); Agitation: 9 (4.5); Headache: 22 (11.1); Vertigo: 59 (29.6); Seizure: 7 (3.5). Serotonin toxicity: 6 (3.0).	Activated charcoal: 194 (97.5), Intubation: 1 (0.5)	All patients recovered. Severity✦: Mild: 174 (87.4); Moderate: 25 (12.6); Severe: 0.
Meamar et al. (2025) [22]	Prolonged QT interval (men's QTc > 430 ms, women's QTc >450 ms): 32 (31.6); Arrhythmia: 4 (3.9).	Seizure†: 1 (1.0); Agitation: 3 (3.0); Fatigue: 16 (15.8); Vertigo: 10 (9.9). Serotonin toxicity:6 (5.9).	Activated charcoal: 100 (99), Gastric lavage: 77 (76.2), Benzodiazepine: 10 (9.9), Cyproheptadine: 6 (5.9)	All patients recovered

2✦A "minor" effect was defined as evidence of clinical toxicity, including hypertension, tachycardia, nausea, vomiting, agitation, drowsiness, dizziness, headache, mydriasis and diaphoresis. Hypertension was defined as systolic pressure ≥ 140 mm Hg or diastolic pressure ≥ 90 mm Hg, and tachycardia was defined as heart rate ≥ 100 beats/min. A "moderate" effect was defined as minor effects plus hypotension (that rapidly responded to treatment), single seizure, conduction disturbance (without hypotension), tremor, or coma. Conduction disturbances were defined as QTc prolongation > 440 ms for males and > 460 ms for females or QRS interval widening >100 ms. Patients with a "major" effect had multiple seizures or met more than one "moderate" criterion, in addition to any minor effects.

† Seizures were reported in only one patient with sertraline overdose.

‡ Cardiac arrest occurred only in patients with a citalopram overdose. VF: Ventricular Fibrillation / VT: Ventricular Tachycardia

Note: The data presented in this table are not directly comparable due to differences in study methods and designs.

Pharmacological Overview of SSRIs

Selective serotonin reuptake inhibitors (SSRIs) exert their therapeutic effects primarily by inhibiting the serotonin transporter (SERT) in the presynaptic membrane, thereby increasing serotonin concentrations in the synaptic cleft and raising serotonergic neurotransmission (2, 26). This mechanism underlies their therapeutic effects in major depressive disorder, anxiety disorders, and several related psychiatric conditions (27, 28).

The most commonly prescribed SSRIs are fluoxetine, citalopram, escitalopram, paroxetine, sertraline, and fluvoxamine (2). Although these agents share a common mechanism of action, they differ substantially in receptor-binding profiles, pharmacokinetic properties, metabolism, and adverse effect patterns, which may contribute to variations in toxicity during overdose (29).

Among SSRIs, fluvoxamine has distinct secondary pharmacologic properties that may influence its clinical adverse effect profile (30-32). Clinically, nausea is the most frequently reported adverse effect, while somnolence, headache, and asthenia are also common (33, 34). Unlike several other SSRIs, fluvoxamine lacks clinically significant active metabolites (35). The absence of active metabolites may result in a shorter duration of toxicity in overdose compared with agents such as fluoxetine. In addition, the sedative adverse effect profile may partially explain the frequent occurrence of central nervous system depression in some fluvoxamine intoxications (35).

Paroxetine is associated with mild anticholinergic effects and sedation compared with other SSRIs (36). In addition, it demonstrates modest inhibition of norepinephrine reuptake and is associated with a relatively high incidence of discontinuation symptoms (37, 38). Similar to fluvoxamine, paroxetine does not form active metabolites (35).

Fluoxetine has activating pharmacologic properties that may increase the neurotransmission of norepinephrine and dopamine (39). It is characterized by activating effects, a long elimination half-life, and the formation of the active metabolite norfluoxetine, all of which may affect both therapeutic persistence and the duration of toxicity (35). In overdose settings, the prolonged half-life of fluoxetine and norfluoxetine may result in delayed recovery and persistence of serotonergic or neurologic symptoms for several days after ingestion (35).

Sertraline demonstrates modest dopaminergic activity compared with several other SSRIs (29, 40). It also produces an active metabolite, although this metabolite has weaker pharmacological activity than the parent compound (41). Although sertraline overdose is often clinically mild, dopaminergic activity may contribute to agitation, tremors, or neurological manifestations in susceptible patients (29).

Citalopram is considered one of the most selective SSRIs for serotonin reuptake inhibition and forms multiple active metabolites (42, 43). Escitalopram, the S-enantiomer of citalopram (44), has reduced H_1 receptor affinity, no significant activity on noradrenaline or dopamine transporters (45), and has two active metabolites (46).

Stereochemistry plays a crucial role in SSRI pharmacology (47). Citalopram is a racemic mixture containing both R- and S-enantiomers (48). The S-enantiomer is primarily responsible for therapeutic efficacy, whereas the R-enantiomer may contribute to adverse effects (49). This stereochemical distinction may partly explain the higher toxicity associated with citalopram overdoses (3).

Escitalopram consists only of the S-enantiomer, which is approximately 150 times more potent at the serotonin receptor than the R-enantiomer (45) and about twice as potent in inhibiting serotonin reuptake compared with racemic citalopram (23). These pharmacological differences are reflected in therapeutic dose ranges, with citalopram typically prescribed at 20-60 mg/day and escitalopram at 10-20 mg/day (50), and may also underlie differences in toxicity profiles between the two agents (3).

Pharmacokinetics and Toxicokinetics of SSRIs

SSRIs are generally well absorbed following oral administration and exhibit high bioavailability, extensive tissue distribution, and substantial plasma protein binding (4, 12, 29). Their large volumes of distribution contribute to extended persistence in the body and limit the effectiveness of extracorporeal elimination techniques such as hemodialysis (51).

All SSRIs undergo extensive hepatic metabolism through cytochrome P450 (CYP450) enzymes, although the dominant metabolic pathways vary between agents. Elimination occurs through both renal and biliary routes (2, 4, 29, 52). Fluoxetine and paroxetine are among the strongest

CYP2D6 inhibitors, increasing the potential for clinically significant drug interactions (53). Citalopram is metabolized primarily by CYP2C19, CYP3A4, and CYP2D6 to demethylated metabolites that retain partial pharmacological activity (13).

The pharmacokinetic characteristics of SSRIs differ substantially. Paroxetine has an elimination half-life of approximately 21 hours, citalopram 26–35 hours, and fluoxetine 1–4 days at steady state (2, 13, 54). Norfluoxetine, the active metabolite of fluoxetine, has a considerably longer half-life of approximately 7–15 days, causing prolonged clinical effects and delayed clearance in overdose situations (2, 55).

Differences in pharmacokinetic linearity may likewise influence overdose severity. Fluoxetine, fluvoxamine, and paroxetine exhibit nonlinear pharmacokinetics, whereas sertraline and citalopram more closely follow linear elimination kinetics at therapeutic concentrations (2, 54). During overdose, saturation of hepatic metabolic pathways may occur, resulting in disproportionate increases in serum concentrations, prolonged elimination, and extended toxicity duration (56, 57). This is particularly pertinent in massive SSRI overdoses, where small incremental increases in dose produce disproportionately high serum drug concentrations as metabolic capacity becomes saturated (57). Consequently, drug clearance may be prolonged for days due to neurologic loading that extends antiarrhythmic and cardiovascular toxicity well beyond the timeframe of normal therapeutic elimination (56, 57).

These toxicokinetic changes are particularly important in citalopram poisoning, where elevated serum concentrations are associated with seizures, QT interval prolongation, and ventricular arrhythmias (9, 58). Several studies have reported that seizures following citalopram overdose may occur in a delayed manner, sometimes hours after the initial presentation, likely because of ongoing absorption and saturation of metabolic pathways at high serum concentrations (13). This delayed neurotoxicity is clinically important because patients who at first appear stable may subsequently deteriorate with seizures or cardiac conduction abnormalities during observation. Escitalopram appears to produce fewer seizures and less severe cardiotoxicity compared with citalopram in overdose, although significant toxicity may still occur at high doses (3, 23). Accordingly, prolonged cardiac and neurological monitoring has been recommended after significant citalopram or escitalopram overdose, particularly in patients with large ingestions, electrocardiographic abnormalities, or neurologic manifestations (3, 15, 23). Continuous ECG

monitoring is especially important because QT prolongation and ventricular dysrhythmias may develop several hours after ingestion (18). Similarly, fluoxetine overdose may produce prolonged toxicity because of the extended half-lives of both fluoxetine and norfluoxetine (59).

In spite of these pharmacological and toxicokinetic differences, SSRIs generally possess a wider therapeutic index than tricyclic antidepressants. Many overdoses involving less than 30 times the therapeutic dose result in mild or self-limited symptoms, whereas massive ingestions may lead to seizures, serotonin toxicity, cardiac conduction abnormalities, and central nervous system manifestations (11).

Toxic Doses and Risk Factors

SSRI overdose generally refers to ingestion exceeding the recommended therapeutic dose; however, the severity of toxicity varies considerably between agents and individuals, and no absolute toxic dose threshold has been established for most SSRIs (11). Many ingestions exceeding therapeutic doses produce only mild or self-limited symptoms. In contrast, severe toxicity is more likely with large overdoses, co-ingestions, underlying comorbidities, or agents with greater intrinsic toxicity, such as citalopram (11)**.** Therapeutic daily doses commonly cited in the literature include fluoxetine ≤60 mg, fluvoxamine ≤200 mg, paroxetine ≤60 mg, sertraline ≤200 mg, and citalopram ≤60 mg (13, 22).

Reported quantities in studies vary widely. In one cohort of SSRI overdoses, the median ingestion corresponded to 19.4 defined daily doses (DDD) (interquartile range: 7.3-29.5) (20). Drug-specific data indicate median ingestion levels of 130 mg for escitalopram (mean 199.2 ± 234.7 mg) and 310 mg for citalopram (mean 426.1 ± 391.3 mg) (3). Larger case series have documented citalopram overdoses ranging from 80 to 4200 mg (mean 712 mg; mean S-enantiomer dose 356 mg) and escitalopram from 40 to 1860 mg (mean 322 mg) (23). Case reports also describe extreme ingestions, such as 2250 mg of sertraline co-ingested with benzodiazepines (18) and 1400 mg of fluoxetine with alcohol (14).

Current evidence indicates that SSRI toxicity should be viewed sequentially along a continuum rather than defined by a specific toxic threshold, with neurologic and cardiac complications increasing in frequency at higher ingestions(11)**.**

Compared with other SSRIs, citalopram is most closely associated with dose-dependent seizures, with events observed as low as 280-400 mg. The risk is saturated at high doses, reaching about 3% for <600 mg, 11.6% for 600-1900 mg, and nearly 75% for ≥1900 mg (3). A similar trend has been observed with escitalopram, where the frequency of seizures increases progressively at higher doses(23). Cardiac manifestations, particularly QT interval prolongation and conduction abnormalities, also become more common with increasing exposure, especially following citalopram and escitalopram overdose(13, 60). Taken together, these findings indicate that SSRI toxicity is better viewed as a spectrum that intensifies with increasing dose rather than as a condition defined by a single toxic cutoff value (3, 13, 60).

Kelly et al. documented seizures in patients ingesting citalopram, with requirements for airway or ventilatory support occurring at doses between 120 and 3000 mg (15). Similarly, Yilmaz et al. observed a graded seizure risk with increasing ingestion of the S-enantiomer (escitalopram): 11% at 200-400 mg, 27% at 401-600 mg, 41% at 601-800 mg, and 52% at >800 mg (23).

Age should be considered when evaluating poisoning severity and planning patient monitoring(13, 61, 62). It can influence the clinical course of SSRI poisoning through changes in hepatic enzyme activity, leading to variability in drug clearance across age groups (61, 62). Older children may eliminate some SSRIs more efficiently than adults, whereas immature metabolic pathways in infants can increase vulnerability to toxicity(61, 62). Among adults, particularly the elderly, concurrent illnesses, multiple medications, a higher rate of intentional toxicity, and age-related physiological changes may contribute to a greater risk of adverse outcomes(13, 61, 62).

Genetic polymorphisms affecting CYP2C19 activity may also alter SSRI toxicity, particularly for citalopram and escitalopram, which rely substantially on CYP2C19 metabolism. Poor metabolizers may develop higher serum drug concentrations and greater risks of QT prolongation or neurologic toxicity at comparable doses (63).

Risk factors associated with more severe SSRI toxicity include advanced age, low body weight, hyponatremia (especially in patients with baseline low sodium levels or concomitant use of hyponatremia-inducing medications), severe comorbid illness, and delayed presentation after overdose(2, 64).

Co-ingestions are frequent and add to the complexity of toxicity; common agents include benzodiazepines, alcohol, other antidepressants, antipsychotics, stimulants, and central nervous system depressants (11, 65). Co-ingestion of other QT-prolonging agents may further increase the risk of cardiac conduction abnormalities during SSRI overdose, particularly with citalopram and escitalopram (13, 66, 67).

Pathophysiology of SSRI Toxicity

SSRI toxicity primarily reflects excessive serotonergic activity in the central and peripheral nervous systems. Serotonin syndrome is the most characteristic manifestation, arising from the overstimulation of central and peripheral serotonin receptors, particularly 5-HT1A receptors, following high-dose ingestion or co-exposure to other serotonergic agents (2, 9, 68). This serotonergic excess disrupts thermoregulation, autonomic function, and neuromuscular control, yielding the characteristic triad of altered mental status, autonomic instability, and neuromuscular hyperactivity observed in serotonin toxicity (68, 69).

Cardiac complications represent another major concern in SSRI poisoning. These are predominantly due to ion channel disturbances, particularly potassium channel blockade, which prolongs cardiac repolarization and predisposes patients to QT prolongation and potentially life-threatening arrhythmias, such as Torsades de Pointes (TdP) (2, 3, 16). Citalopram and escitalopram appear to be particularly associated with these effects, likely due to greater cardiotoxic potential at high serum concentrations (13).

Seizures associated with SSRI toxicity are multifactorial but are primarily related to excessive serotonergic stimulation and disruption of neuronal excitatory–inhibitory balance. Proposed mechanisms include ion channel dysfunction, impairment of inhibitory neurotransmission via GABA and glycine pathways, and enhanced excitatory neurotransmission, all of which increase neuronal excitability and lower the seizure threshold (64, 70-72). Elevated hippocampal serotonin concentrations and activation of 5-HT1A receptors may further contribute to seizure susceptibility (9).

In citalopram overdose, seizure and QT prolongation risk may be further enhanced by the pharmacologic effects of the R-enantiomer, including inhibition of G-protein-coupled inwardly

rectifying potassium (GIRK) channels (3). This mechanism may partly explain the relatively greater neurotoxicity and cardiotoxicity observed with citalopram compared to several other SSRIs (3). Importantly, seizures may occur independently of serotonin syndrome and have been documented in patients without marked autonomic instability or neuromuscular rigidity (14).

Additional secondary pharmacologic properties of SSRIs may contribute to toxicity manifestations in overdose. These include antihistaminergic, anticholinergic, and dopaminergic effects, which may contribute to sedation, altered mental status, or hemodynamic instability in susceptible patients (35). In addition, serotonergic stimulation of antidiuretic hormone release may induce the syndrome of inappropriate antidiuretic hormone secretion (SIADH), resulting in hyponatremia, mainly in older adults and vulnerable populations (2, 64).

Serotonin Syndrome

Serotonin syndrome frequently arises after SSRI overdose or co-exposure to other serotonergic agents (2, 29). Its incidence has risen in parallel with the increasing prescription of SSRIs (2).

The reported prevalence varies according to diagnostic criteria and study population. In one cohort, 13.6% of SSRI overdoses met the Hunter criteria (20). Another study, using the Sternbach criteria and clinician diagnosis, reported a prevalence of 14%, with cases predominantly mild and non-life-threatening (13). A large Australian series demonstrated that SSRIs were more strongly associated with serotonin toxicity than tricyclic antidepressants (TCAs), with a prevalence of 19.3% (24). Compared with TCAs, SSRIs generally produce serotonin toxicity more frequently because of their more selective serotonergic effects, although severe cardiotoxicity and fatal arrhythmias occur less commonly than with TCA overdose (24, 33, 34). Serotonin toxicity may also occur with serotonin–norepinephrine reuptake inhibitors (SNRIs), particularly venlafaxine, which has been associated with higher rates of seizures and severe toxicity in overdose compared with many SSRIs (20, 24). Risk appears to be higher with sertraline, paroxetine, and fluvoxamine, and lower with citalopram and fluoxetine (13).

A triad of mental status changes, autonomic instability, and neuromuscular hyperactivity characterizes the clinical presentation. Onset is usually rapid, often within six hours and almost always within 24 hours of ingestion (4, 12). Diagnosis is most accurately established using the

Hunter serotonin toxicity criteria (4, 20), although the Sternbach criteria have been employed in earlier literature (13). The Hunter diagnostic criteria encompass characteristic signs such as hyperreflexia, clonus (often ankle clonus), tremor, myoclonus, fever, and hypertension (22, 69). However, interpreting the prevalence of serotonin syndrome across studies continues to be challenging because diagnostic methods were not uniform: some studies applied formal Hunter or Sternbach criteria, while others relied on retrospective chart review or clinician assessment alone (9, 13, 20, 22, 24). This variation likely contributes to variation in reported estimates of incidence and severity and represents an important limitation in the current literature.

Management of serotonin syndrome varies according to clinical severity, with mild cases often responding to discontinuation of the offending agent and close monitoring, whereas moderate to severe cases necessitate aggressive supportive interventions (73, 74). Supportive measures include hemodynamic stabilization, sedation, temperature control, and hydration(75). In severe cases, benzodiazepines, intubation, neuromuscular paralysis, and active cooling may be necessary (76). Although serotonin antagonists such as cyproheptadine are commonly administered, their efficacy remains largely supported by case-based evidence and clinical experience rather than high-quality controlled trials (74, 75). Early recognition and proper management are key for favorable outcomes in serotonin syndrome (77).

Clinical Features of SSRI Poisoning

The clinical manifestations of SSRI poisoning are generally milder compared with tricyclic antidepressant (TCA) toxicity, with a predominance of gastrointestinal and neurological symptoms (25, 29). Clinical presentation can be generally classified as mild, moderate, or severe toxicity, although substantial overlap exists depending on the ingested dose, co-exposures, and patient-related risk factors.

Mild Toxicity

Mild SSRI toxicity most commonly involves gastrointestinal symptoms and minor neurologic manifestations. Gastrointestinal manifestations are among the most frequently reported features

and typically include nausea, vomiting, diarrhea, and abdominal discomfort (9, 22, 25, 29). In a large study of more than 36,800 overdose cases, nausea occurred in 5.6%, vomiting in 9.6%, and diarrhea in 0.6% of patients (25). Drug-specific data showed nausea and vomiting in 7.8% and 7.4% of escitalopram overdoses (3) and in 17.7% and 10.1% of citalopram intoxications, respectively (23). More recent cross-sectional evidence confirmed this pattern, with nausea and vomiting present in nearly half of the cases (48.2%) (9).

Neurologic symptoms in mild poisoning commonly include drowsiness, dizziness, tremor, agitation, and confusion (25, 29). In one cross-sectional study, drowsiness was documented in 15.2%, dizziness in 2.3%, confusion in 1%, and agitation in 3.4% of patients (25). Recent examinations have shown similar findings, with drowsiness occurring in 37.2% of cases (9).

Moderate Toxicity

Moderate toxicity is characterized by more pronounced neurologic or autonomic manifestations, including serotonin toxicity and cardiac conduction abnormalities. In SSRI overdose, serotonin syndrome typically presents with agitation, tremor, hyperreflexia, clonus, myoclonus, and diaphoresis (12, 20). Other cohorts reported serotonin toxicity in up to 19.3% of patients (13, 15, 23, 24).

Cardiac effects are also an important feature of moderate toxicity, particularly QT interval prolongation, which is most strongly associated with citalopram and, to a lesser extent, escitalopram (66, 67) The risk appears dose-dependent and is amplified in elderly individuals or those suffering from underlying cardiac disease (67). However, findings are not entirely consistent, as some studies did not observe an increased risk in geriatric populations (78). Current FDA recommendations limit citalopram dosing to a maximum of 20 mg per day in older or high-risk individuals and advise electrocardiogram (ECG) monitoring when indicated (2, 67).

We reported QT prolongation rates ranging from 3% to 50.5% in our review. The reported prevalence of QT prolongation ranges from 3–9% in citalopram/escitalopram cohorts (3, 23) to 24.2% in a prospective study (24), 7.9% in a retrospective series (15), and as high as 50.5% in a large observational analysis (13). The high variability likely reflects substantial heterogeneity in study design, patient selection, ECG surveillance intensity, baseline ECG absence, selection bias

in cardiac-focused studies, and QTc threshold definitions rather than a true variation in risk across comparable patient populations.

QT prolongation is most often associated with citalopram or escitalopram and may be accompanied by conduction disturbances such as AV block and torsades de pointes (4, 12, 22). More broadly, across SSRI overdoses, additional rhythm abnormalities have been reported, including tachycardia (22.3%), conduction abnormalities (3.4%) (17), atrioventricular block (0.6%) (23), and ventricular arrhythmias (25).

Severe Toxicity

Severe SSRI toxicity is less common but may involve seizures, severe serotonin syndrome, coma, hyperthermia, shock, or malignant cardiac arrhythmias. Seizures occur in approximately 1-8% of all SSRI overdoses (13, 22, 24), but are significantly more frequent with citalopram poisoning (5.7-14%) compared with escitalopram (0.2-3%) (3, 15, 23). They are typically generalized, brief, and self-limiting, often occurring within 1-13 hours of ingestion (6).

Severe serotonin toxicity may progress to coma (1-2.5%, often related to sedative co-ingestants) (23, 24), hyperthermia with shock, cardiomyopathy (4), or torsades de pointes in the setting of marked QT prolongation (4, 12).

Drug-Specific Toxicity Patterns

Certain SSRIs show unique toxicity profiles in overdose**.** Citalopram and escitalopram are more strongly associated with QT prolongation, seizures, and ventricular dysrhythmias (3, 15, 23, 66, 67). Sertraline and fluoxetine are generally associated with milder cardiovascular toxicity, although serious complications may still occur in massive overdoses or mixed ingestions (14, 18).

Extrapyramidal symptoms (EPS), such as dystonia, parkinsonism, dyskinesia, and akathisia, have been reported, mainly within the first month of treatment or after dose escalation (79-81). Citalopram, escitalopram, fluoxetine, and sertraline are most often implicated, as highlighted in an analysis of 86 case reports (79).

Finally, other less frequent toxic effects include rash (occasionally severe cutaneous reactions), congenital malformations (particularly cardiac, when exposure occurs in utero), hyponatremia, and cataracts (2).

Diagnosis

The diagnosis of SSRI toxicity is primarily clinical and is determined by a detailed history of ingestion, assessment of prescribed and co-ingested medications, and recognition of characteristic toxidrome features (2, 6, 12, 29). Physical examination is necessary, particularly to detect signs of serotonin syndrome, such as hyperreflexia and clonus (2, 22). Although no laboratory test can directly confirm SSRI toxicity, laboratory investigations play an important role in excluding alternative diagnoses, identifying complications such as electrolyte disturbances or rhabdomyolysis, and identifying possible co-ingestants (29). Laboratory investigations often include serum electrolytes, renal and hepatic function tests, complete blood count (CBC), and coagulation parameters. In selected cases, cardiac biomarkers such as BNP, proBNP, creatine kinase (CK), and CK-MB may be measured to evaluate potential myocardial injury or severe system-wide toxicity (4, 22). Measurement of serum SSRI concentrations has a limited clinical role. It is generally not recommended for routine management, as serum levels correlate poorly with symptom severity and are often unavailable in acute care settings (2, 6).

ECG monitoring is an essential component of the diagnostic approach, particularly for detecting QTc prolongation and conduction abnormalities (3, 13). Serial ECG monitoring is especially important in citalopram and escitalopram overdoses because cardiotoxic manifestations and delayed seizures may occur several hours after ingestion (14, 16, 21, 58). Current toxicology literature supports prolonged cardiac monitoring in patients with significant citalopram exposure, particularly doses exceeding 600 mg, or in those with abnormal QT intervals, electrolyte disturbances, co-ingestion of QT-prolonging agents, or clinical evidence of serotonin toxicity (58, 66). Repeated ECGs are therefore recommended until QT intervals normalize and the patient remains clinically stable (18, 19, 21) .

Toxicology screening may assist in identifying co-ingested substances such as benzodiazepines, ethanol, or barbiturates (14, 16). Brain MRI can be considered in atypical presentations, such as dystonia, to rule out structural abnormalities (16).

Finally, severity grading is commonly performed using the American Association of Poison Control Centers' National Poison Data System (NPDS) criteria (3).

Management and Treatment

The management of SSRI toxicity is primarily supportive care, with key priorities including prompt discontinuation of the offending agent, airway protection, circulatory stabilization, seizure control, and close monitoring for complications. Intravenous fluids are commonly administered as part of initial resuscitation (2, 4, 12, 74). Most patients with isolated mild SSRI overdose remain clinically stable and recover with observation and supportive care alone (11, 13, 22) .

Decontamination measures are most effective when implemented early (4). Routine gastric lavage is not recommended in modern toxicology practice because potential complications generally outweigh clinical benefit, particularly in mild-to-moderate overdoses (4, 12). Gastric lavage and activated charcoal should also be used selectively rather than routinely and may be considered within 1–2 hours of ingestion in cooperative patients with a protected airway, particularly after large citalopram or escitalopram overdoses associated with delayed toxicity (4, 12, 16, 22).

The evidence supporting management strategies in SSRI poisoning is not uniform. Supportive care, ECG monitoring, benzodiazepines, and selective use of activated charcoal are supported by observational studies and toxicology guidelines(13, 60, 69, 82). In contrast, interventions such as cyproheptadine for severe serotonin syndrome are based largely on case reports and small case series(15, 83, 84). Therefore, these treatments should be individualized according to the patient's clinical presentation.

Pharmacokinetic-pharmacodynamic modeling of QT interval prolongation following citalopram overdose (84). Recommendations for observation and monitoring depend on the ingested agent, dose, and clinical presentation. Asymptomatic patients with mild isolated SSRI ingestion

generally require a shorter observation period, whereas symptomatic patients or those with significant citalopram or escitalopram exposure require prolonged monitoring (13, 58). Because delayed seizures and QT prolongation may occur after citalopram overdose, continuous cardiac monitoring and serial ECG assessment are recommended in patients ingesting more than 600 mg of citalopram or in those with ECG abnormalities, co-ingestants, or ongoing symptoms (13, 58, 81).

Serotonin syndrome requires immediate discontinuation of all serotonergic agents and provision of supportive care. Benzodiazepines are indicated for agitation and muscle rigidity in moderate-to-severe cases. If symptoms persist or worsen, cyproheptadine, a serotonin receptor antagonist, may be applied to diminish serotonergic activity. However, the evidence supporting cyproheptadine is derived mainly from case reports and observational experience rather than randomized clinical trials (74, 77).

QT prolongation necessitates ECG monitoring, avoidance of concomitant QT-prolonging drugs, and dose reduction or discontinuation if significant prolongation occurs (4, 12). If torsades de pointes develops, management follows advanced cardiac life support guidelines, including administration of intravenous magnesium sulfate (12).

Seizures are treated first-line with benzodiazepines (3, 6, 12), followed by phenobarbital if necessary (6). Refractory cases may require propofol, while phenytoin is not recommended for drug-induced seizures (6).

Hyponatremia, especially when caused by SIADH, is managed with serial serum sodium monitoring, fluid restriction, and discontinuation of the SSRI if symptoms develop (4, 12).

Reported treatment patterns vary across the literature. Activated charcoal was the most frequently documented intervention, ranging from 18.5% in large retrospective cohorts to 99% in smaller cross-sectional studies (17, 22). Gastric lavage was used less often, ranging from 76.2% of cases in some reports to isolated use in individual cases (16, 22). Benzodiazepine use varied widely across cohort studies, with percentages ranging from 3.3% to 9.9% (3, 16, 22). Intubation was infrequent (0.2–2.3%) and generally reserved for patients with severe neurologic compromise. Cyproheptadine was used occasionally (0.2–5.9%) (3, 22). Rates of ICU admission varied widely across studies (2.3% to 11.4% in large cohorts), and case reports described ICU monitoring for safety (15, 17, 21). Importantly, many of the interventions reported in case reports

are co-ingestions or reflect institutional practice patterns that may affect individualized management decisions, rather than standardized, evidence-based recommendations or treatment intensity.

Outcome and Prognosis

The prognosis of isolated SSRI overdose is usually good, and most patients recover completely with appropriate supportive care (4, 12, 29). Mortality is rare and is typically associated with severe cardiotoxicity, refractory arrhythmias, co-ingestion of multiple agents, or fulminant serotonin syndrome (4).

Grading of clinical effect demonstrates that outcomes categorized as "no effect" range from 34.8% to 50.8%, "minor effects" from 33.2% to 43.2%, and "moderate effects" from 5.7% to 18%. "Major effects" are rare, reported in only 0.1% to 3.5% of cases (3, 17) Smaller clinical series likewise report predominantly mild courses, with 87.4% of cases classified as mild and 12.6% as moderate, and no severe outcomes documented (9).

Mortality data from poison center registries confirm the low fatality rate of SSRIs. The agent-specific mortality rate is: 57 for citalopram, 0 for escitalopram, 14 for fluoxetine, 273 for fluvoxamine, 22 for paroxetine, and 8 for sertraline in a 100000 population during five years (25). Reported fatality rates were extremely low across all agents. However, interpretation of these fatality data requires caution because poison center registries frequently include mixed overdoses, incomplete dose verification, and variable follow-up quality. Many fatal cases reported in the literature involved co-ingested substances, making attribution of mortality solely to SSRIs difficult (11, 25). Hospital-based series provide further support for the generally favorable prognosis, reporting no fatalities across several cohorts and observational studies (9, 13, 19, 22, 24).

The hospital course is usually short, with most patients discharged within 24 hours and almost half within 12 hours in one cohort (22). Other series report hospitalizations of 1.6 days (19) or a median of 15.3 hours (24). Cardiac conduction abnormalities, including QT prolongation, generally revert to normal before discharge (15, 16, 18, 21). Seizures are usually brief and self-limiting, and rarely progress to status epilepticus (6, 14). However, delayed complications can

occur in citalopram overdose, which warrants prolonged observation in selected high-risk patients (21, 58).

Risk factors for poor outcomes include ingestion of higher doses, co-ingestion of other serotonergic or proconvulsant substances, delayed medical presentation, and significant comorbidities (2, 3, 6). Among SSRIs, citalopram overdose with QT prolongation or seizures represents the most common severe clinical presentation (15, 16).

Several important limitations should be considered when interpreting outcome data in SSRI poisoning studies. Poison center databases are subject to underreporting, reporting bias, and incomplete clinical follow-up, which could result in underestimation of severe outcomes or delayed complications. In many retrospective studies, ingested doses were self-reported and could not be independently verified, limiting the accuracy of dose-response analyses. Furthermore, the predominance of retrospective observational designs introduces selection bias and variability in recording quality, monitoring practices, and outcome classification across studies (3, 15, 17, 19, 20, 23).

Discussion

SSRIs remain central to depression treatment, yet increased reports of overdose and toxicity have accompanied their growing use. This review illustrates the heterogeneous clinical presentations of SSRI poisoning, spanning from mild symptoms to life-threatening complications. This review includes both large-scale cohort studies and individual case reports to provide a comprehensive clinical perspective**.** While cohort studies provide strong data on the incidence and frequency of common toxic effects, case reports are necessary to identify rare but clinically significant adverse events and illustrate the management of severe complications that may be underrepresented in aggregate data.

Overall, the available evidence supports the relative safety of SSRIs compared with older antidepressants such as TCAs, although important differences exist within the SSRI class itself (13, 24). Among the adverse effects associated with SSRI overdose, QT prolongation and seizures warrant particular attention owing to their clinical severity. While both citalopram and

escitalopram are implicated in these complications, citalopram regularly demonstrates a higher risk, especially in a dose-dependent manner (2, 3, 9). Escitalopram appears comparatively safer but is not devoid of risk at higher exposures (3, 23). The greater cardiotoxicity of citalopram is understood to result primarily from blockade of cardiac potassium channels, particularly the hERG (human Ether-à-go-go-Related Gene) channel, leading to delayed ventricular repolarization and QT interval prolongation (66, 85). This mechanism likely explains the higher incidence of torsades de pointes, conduction abnormalities, and delayed cardiac toxicity observed with citalopram overdose compared with other SSRIs (13, 58). The distinction in neurotoxicity and cardiotoxicity between these agents stresses the importance of dose awareness, early monitoring, and individualized risk assessment in overdose scenarios (3, 12). From a clinical perspective, these findings support more prolonged ECG monitoring and lower thresholds for hospital observation in cases of significant citalopram ingestion (13, 58).

A diagnosis of serotonin syndrome was common in these cases. It was possible that between 10% and 20% of people might qualify as having serotonin syndrome based on various diagnostic criteria. There is an obvious need for screening and careful monitoring when dealing with a condition that can easily be confused with other neurological issues. Variability in the prevalence rate of serotonin syndrome may have been caused by differing methods used to diagnose it (74, 77).

The treatment strategies adopted across all the research papers discussed followed a similar pattern, in which supportive measures predominated over more forceful strategies. Charcoal and benzodiazepines were used in most cases; however, in severe cases of serotonin syndrome, antidotes like cyproheptadine were mainly preferred (4, 12). The low proportion of patients admitted to the ICU serves as a confirmation of the general safety of SSRIs in cases of isolated overdosing (15, 17). It is important to emphasize that most of the serious cases reported involved patients exposed to mixed overdoses, hence the need for a comprehensive assessment of co-ingestants (11, 13).

In comparison with tricyclic antidepressants (TCAs), SSRIs show significantly reduced cardiotoxicity, coma, and fatal arrhythmias; these factors are due mainly to the absence of sodium channel blocking effect in SSRIs compared with TCAs (6, 33). However, citalopram reduces the benefits of this safety factor by causing QT prolongation(13, 58). The serotonin and

norepinephrine reuptake inhibitor (venlafaxine) could show higher levels of toxicity than the majority of SSRIs, especially concerning convulsions and cardiovascular disorders(20, 24).

The results also have implications for prescribing practices. In patients at elevated risk for self-poisoning, cardiac disease, electrolyte abnormalities, or concomitant QT-prolonging medications, clinicians may consider SSRIs with lower cardiotoxic potential over citalopram when clinically appropriate (13, 66, 67). Similarly, awareness of dose-dependent toxicity may support more cautious prescribing, closer follow-up, and patient education regarding overdose risk, notably in vulnerable psychiatric populations (11, 58).

Other important findings include the large degree of heterogeneity between the papers studied. Methods used varied widely, from the analysis of poison control center registries and retrospective hospital cohort studies to case reports, each with specific advantages and drawbacks. While registries provided an extensive picture of the epidemiology of the problem, they often lacked data on doses, standardized diagnostic assessments, and long-term follow-up. On the other hand, case studies provided more clinical details, although they usually selected cases of higher severity. Another factor that contributed to differences between the studies analyzed is the large variation in the doses associated with the development of serotonin syndrome, the use of ECG monitoring, and the definition of severe outcomes.

Limitations

There were several shortcomings of the existing evidence base that should be addressed. Firstly, there was notable heterogeneity among the studies in patient inclusion criteria, definitions of overdose, diagnostic criteria, outcome reporting, and management protocols, which precluded comparative analysis of the data. Secondly, the majority of serious adverse events were derived from either case reports or poison control data, both of which are known for the high risk of selection and publication biases as well as overestimation of rare and severe outcomes. Thirdly, definitions of serotonin syndrome varied: some studies used the Hunter criteria, others used the Sternbach criteria, and a few did not apply any validated criteria and relied solely on retrospective clinical judgment. Fourthly, the lack of meta-analysis precluded the development of reliable statistics and dose-response relations. Lastly, although regional differences in prescribing

practices, SSRI availability, and healthcare systems may influence reported outcomes, the available evidence was insufficient and too heterogeneous to permit meaningful geographic comparisons.

Conclusion

In conclusion, a good prognosis characterizes an SSRI overdose in most situations and requires observation rather than aggressive intervention. But the physician must be on guard against more severe neurologic and cardiac complications, particularly following citalopram and escitalopram overdoses, which seem to have a more pronounced association with convulsions and prolongation of the QT interval. It is imperative to conduct electrocardiographic examinations, particularly in citalopram overdose cases, where ECGs help in detecting conduction defects and arrhythmias. Early recognition of serotonin syndrome and supportive treatment, and close monitoring make up the key aspects of therapy. The risk factors for a more complicated clinical course include the amount of drug ingested, concomitant medications, underlying conditions, and ECG findings that can inform decisions to prolong observation or admit the patient to the ICU. Standardization of diagnostic procedures and improved documentation of toxicity cases will further contribute to the body of evidence.

Acknowledgements

The authors acknowledge the use of ChatGPT-5 (OpenAI) for language refinement of the manuscript. All AI-assisted content was critically reviewed and verified by the authors for accuracy.

Use of Artificial Intelligence (AI) Tools

Artificial intelligence (AI) tools were used solely to assist with language editing and grammar refinement. No AI tools were used for data extraction, data analysis, interpretation of findings, reference generation, or scientific decision-making. All intellectual content, critical interpretation, and final manuscript preparation were performed and verified by the authors, who

take full responsibility for the accuracy and integrity of the work. This paper follows the journal policy on AI acknowledgment placement.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of Interest

The authors declare no conflicts of interest.

Ethical Approval

This study was approved by the Ethics Committee of Isfahan University of Medical Sciences (Ethical Code: IR.MUI.MED.REC.1403.511).

Data Availability Statement

All data supporting the findings of this review are derived from published literature cited in the article.

Author Contribution

RM: Author contribution: Conceptualization, Methodology, Supervision, Writing – Review & Editing.

FK: Investigation, Data Curation, Formal Analysis, Writing – Original Draft.

AK: Writing- Original Draft, Review & Editing.

SS: Investigation, Project Administration, Writing – Original Draft, Visualization

NE: Methodology, Validation, Resources, Writing, Supervision – Review & Editing.

Supervision

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Declaration of Interest Statement

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for this journal and was not involved in the editorial review or the decision to publish this article.

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