

ORIGINAL ARTICLE

Pregabalin poisoning: Evaluation of dose-toxicity relationship

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Context: Pregabalin poisoning is mostly benign, although coma and convulsions occasionally occur.

Aim: To determine the dose-toxicity relationship of pregabalin.

Methods: Dose-toxicity data of isolated pregabalin poisonings were collected from (1) a prospective study performed by the Dutch Poisons Information Centre (4 April 2014 to 4 October 2016) and from (2) case reports and case series reported in literature. Poisonings were graded using the Poisoning Severity Score (PSS) and the relationship between dose (mg kg^{-1}) and PSS was evaluated.

Results: In our study ($n = 21$ patients), the most commonly observed symptoms were drowsiness (62%), confusion (29%) and apathy (24%). PSS was none in three (14%), minor in 15 (71%), and moderate in three patients (14%). Most case series also reported a PSS of none to minor in the majority of poisonings (69–100%). For 34 individual patients (21 from our study and 13 from literature), detailed data on dose and clinical course were available to examine the dose-toxicity relationship.

The median dose was significantly lower in the PSS none-minor group (“benign”) (8.6 mg kg^{-1} , interquartile range (IQ25–75) $5.0\text{--}17.6 \text{ mg kg}^{-1}$) than in the PSS moderate-severe group (“significant toxicity”) (46.7 mg kg^{-1} , IQ25–75 $21.3\text{--}64.3 \text{ mg kg}^{-1}$); estimate of the median difference = 27.3 mg kg^{-1} (95% confidence interval (CI): $10\text{--}48.6$).

Conclusions: In general, higher pregabalin doses result in more severe poisonings. Below 20 mg kg^{-1} the majority of patients (83%) only suffer from mild poisoning. However, large interindividual differences exist in pregabalin-induced toxicity. Therefore, pre-hospital triage should not only include pregabalin dose, but also underlying illnesses, co-exposures and reported symptoms.

KEYWORDS

clinical toxicology, intoxication, overdose, poisoning, pregabalin, toxicity

The authors confirm that the PI for this paper is Prof. D W de Lange, head of the Dutch Poisons Information Center (DPIC), MD, PhD. The DPIC has no direct patient contact, but provides information to medical professionals on the treatment of poisoned patients. The medical professionals that consult the DPIC have direct clinical responsibility for the patients.

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1 | INTRODUCTION

Pregabalin is prescribed for several disorders, including partial seizures, central and peripheral neuropathic pain, and generalized anxiety disorder.^{1–3} The number of pregabalin prescriptions has greatly increased worldwide in the last decade; up to 10-fold rises in prescriptions have been reported in several European countries.⁴ The higher prescription rate of pregabalin increases the likelihood of intentional and unintentional overdoses. Moreover, pregabalin abuse has been increasingly reported.⁵

Despite the increasing therapeutic use and abuse of pregabalin, only a few studies are available on the dose-toxicity relationship of pregabalin. A large study in 126 children ≤ 6 years old showed that most children (98%) remain asymptomatic or develop minor symptoms such as drowsiness, ataxia and restlessness after isolated pregabalin overdose. Hospital-based surveillance for healthy children was suggested from a pregabalin dose of 19.4 mg kg⁻¹ or higher.⁶ Another study reported similar effects for adolescent and adult patients (≥ 15 years old, $n = 59$ isolated pregabalin poisonings), although around 7% developed a moderate to severe poisoning, including seizures and coma. No dose-related criteria for pre-hospital triage were suggested in this study.⁷ Although rare, several additional case reports indicated serious life-threatening effects such as coma^{7,8} and seizures^{7,9,10} following relatively high doses of pregabalin.

While the clinical effects following pregabalin overdose are known, the dose-toxicity relationship of pregabalin is less clear. Therefore, we determined the relationship between pregabalin dose and poisoning severity in a prospective follow-up study on isolated paediatric and adult pregabalin overdoses reported to the Dutch Poisons Information Center (DPIC). In addition, we reviewed the available literature on isolated pregabalin overdose, focused on the poisoning severity related to pregabalin dose.

2 | METHODS

2.1 | Prospective DPIC study on pregabalin poisoning

The DPIC provides a 24/7 telephone information service to healthcare professionals on the management of (suspected) poisonings. We performed a prospective follow-up study on human isolated pregabalin overdoses reported to the DPIC between 4 April 2014 and 4 October 2016 (2.5 years). “Isolated” was defined as an exposure to pregabalin only, or to pregabalin and a nonrelevant co-exposure (eg, therapeutic use of other medications). We excluded chronic poisonings, cases with unknown dose, and cases with non-oral routes of exposure.

Data were collected by interviewing the consulting physician and/or the patient by telephone. The parent/caregiver was interviewed when patients < 16 years were involved. Physicians who were consulted by the patient by telephone, but did not examine the patient, were excluded. In these specific cases, only the (parent/caregiver of the) patient was asked to participate.

What is already known about this subject

- Isolated pregabalin overdose generally causes mild symptoms, although seizures and coma have been rarely reported.
- Despite the increasing therapeutic and recreational use of pregabalin, there is limited research studying the dose-toxicity relationship of pregabalin.

What this study adds

- Some patients develop moderate symptoms at therapeutic pregabalin doses, while others remain asymptomatic at high doses, indicating large interindividual differences.
- The majority of patients (83%) only suffer from mild poisoning at pregabalin doses < 20 mg kg⁻¹.
- Pre-hospital triage of patients with pregabalin overdose should include dose, underlying illnesses and reported symptoms.

During the study, physicians were informed on the possible clinical effects and treatment according to the standard DPIC procedure. At this stage, the patient's identity was unknown to the DPIC, except for sex, age and bodyweight. Subsequently, the DPIC requested the participation of physicians in a follow-up interview by telephone. Patients were asked by their physician to participate in the study. Only after patient agreement, physicians provided us with the patients' personal details and contact information (identifiable data were omitted before analysis). Before the patient interview, informed consent was obtained by telephone (and voice recorded) after information was provided on the content, duration and confidentiality of the interview and the anonymous processing of the data. Information on patients who were lost to follow-up was obtained from the recording of the initial DPIC telephone inquiry. The accredited Medical Research Ethics Committee of the University Medical Center Utrecht decided that the Dutch Medical Research Involving Human Subjects Act did not apply to this study (no. 14/146).

The interviews were conducted using standardized questionnaires tailored to patients or physicians. Although we aimed to conduct the interviews within one week after DPIC consultation, the median timespan between pregabalin exposure and the interview was 11 days (interquartile range (IQ25–75) 3–17 days). Questionnaires contained specific questions on patient characteristics (eg, age, gender, bodyweight, pregabalin user/nonuser), pregabalin exposure (eg, self-reported dose), exposure circumstances (eg, [un]intentional exposure), clinical course (eg, symptoms, ECG and laboratory results), use of healthcare (ie, general practitioner visit, emergency department [ED] visit, hospitalization) and treatment (eg, gastrointestinal

decontamination measures). The most abnormal vital signs and laboratory results were registered.

2.2 | Review of the literature on pregabalin poisoning

PubMed and EMBASE were queried for literature on pregabalin overdose up to 4 June 2021 using the following string: pregabalin [title/abstract] AND (toxicity [title/abstract] or poisoning [title/abstract] or overdose [title/abstract] or intoxication [title/abstract] or intoxicated [title/abstract]), filtered for human studies published in English language. Reference lists of included articles were checked to identify additional relevant publications. We included all case reports and case series of acute isolated pregabalin overdose in adult and paediatric patients (both pregabalin naïve and non-naïve patients). Individual patients described in case series, with detailed data on dose and clinical course, were also added as case reports. We excluded chronic poisonings, cases with unknown dose and cases with non-oral routes of exposure. Extracted data included gender, age, body weight, reported pregabalin dose, prescription for pregabalin, symptoms, gastrointestinal decontamination measures and hospital admission.

2.3 | Poisoning severity score

The observed severity of each pregabalin poisoning (ie, cases from our study and from literature) was graded by two experienced clinical toxicologists using the Poisoning Severity Score (PSS). The PSS is a scoring system that classifies the severity of poisoning in a standardized manner, including five severity grades: none: no symptoms or signs related to poisoning; minor: mild, transient and spontaneously resolving symptoms; moderate: pronounced or prolonged symptoms; severe: severe or life-threatening symptoms; fatal: death.¹¹ The Delphi method was applied in the process of scoring.¹² Inter-rater agreement on the PSS was evaluated using Cohen's kappa.¹³ The strength of agreement was substantial (Cohen's kappa: 0.78).

2.4 | Statistical analysis

Age and dose are presented as medians with interquartile ranges (IQ25-75) and full ranges. When body weight data were unavailable, a weight of 70 kg was assumed for adult patients. Individual poisonings, with detailed data on dose and severity, were grouped based on the assigned PSS as PSS none-minor ("benign") or PSS moderate-severe ("significant toxicity") (no fatal cases reported). Doses at different severity grades of the PSS showed a skewed distribution and are therefore presented as median doses. We computed the Independent-Samples Hodges-Lehmann estimator with 95% confidence interval (CI) for the difference in the median dose of the PSS none-minor group ("benign") vs PSS moderate-severe group

("significant toxicity"). Calculations were performed before and after exclusion of extreme values for "dose", defined as values more than 3 IQR from the 75th percentile. Statistical analysis was performed using IBM SPSS Statistics (version 25.0).

3 | RESULTS

3.1 | DPIC study

3.1.1 | Patient and exposure characteristics

We included 49 acute isolated pregabalin overdoses, of which 21 were followed up and included in analysis (Table 1). Interviews were conducted with both the physician and the patient ($n = 3$), only the physician ($n = 10$) or only the patient ($n = 8$, of whom seven were managed at home). The median age of the patients with follow-up was 26 years (IQ25-75 9-57 years, range 2-83 years). Exposure was unintentional in 62% of the pregabalin poisonings ($n = 13$), caused by medication errors ($n = 7$, 54%) or exploring behaviour in children ($n = 6$, 46%). The median self-reported pregabalin dose was 8.8 mgkg⁻¹ (IQ25-75 4.4-31.0 mg kg⁻¹, range 2.0-210.0 mg kg⁻¹).

3.1.2 | Symptoms and hospital admission

The most commonly reported symptoms were drowsiness ($n = 13$, 62%), confusion ($n = 6$, 29%), apathy ($n = 5$, 24%), dizziness ($n = 4$, 19%) and nausea ($n = 5$, 24%). Three patients (14%) remained asymptomatic, 15 patients (71%) developed mild symptoms and three patients (14%) developed moderate symptoms. No severe, life-threatening effects, such as coma or seizures, were reported in our study. Detailed information per patient is presented in Table 1 (ranked from lowest to highest self-reported pregabalin dose). Six patients (29%) were examined by a general practitioner, six patients (29%) presented to an ED and five patients (24%) were admitted to hospital of whom two patients were admitted to the intensive care unit (ICU). Gastrointestinal decontamination was performed in one patient, ie, gastric lavage and administration of activated charcoal in a 2-year-old boy after ingestion of 50 mg kg⁻¹ pregabalin (Table 1).

3.1.3 | Cases lost to follow-up

Twenty-eight patients were lost to follow-up (see Supporting Information Table S1). The median age of the patients who were lost to follow-up was 51 years and exposure was intentional in 79% of the cases. Although severe toxicity or mortality after DPIC consultation could not be verified, in most patients only mild symptoms such as sleepiness, dizziness and vomiting were reported during the initial consultation of the DPIC. One patient, a 51-year-old man, developed reduced consciousness (limited response to pain stimulus) after ingestion of 9.1 mg kg⁻¹ pregabalin.

TABLE 1 Acute isolated pregabalin overdose: cases from the prospective DPIC study, ranked from lowest to highest self-reported dose

Age, sex	Prescr.	Dose (mg)	Dose (mg kg ⁻¹)	Symptoms	Admission	PSS
12, M	No	75 ^a	2.0	Mydriasis	No	Minor
3, M	No	75 ^a	3.0	Confusion, drowsiness, headache, dizziness, mydriasis, nausea	No	Minor
13, M	No	150 ^a	3.0	Drowsiness, dizziness, tachycardia, angina pectoris, muscle twitching, nausea, stomach ache	No	Minor
77, F	Yes (first use)	300 ^a	3.1	Confusion, ataxia, dysarthria, apathy, drowsiness, sopor, dizziness, amnesia, blurred vision, diplopia, muscle twitching, nausea	No	Moderate
15, F	No	300 ^{b,c}	3.8	Drowsiness, headache, dizziness, nausea	ED only	Minor
12, F	No	300 ^a	5.0	Blurred vision	No	Minor
66, F	Yes	300 ^a	5.1	Asymptomatic	No	None
2, F	No	75 ^a	6.3	Asymptomatic	No	None
4, M	No	150 ^a	8.3	Ataxia	No	Minor
78, F	Yes	600 ^{a,d}	8.6	Drowsiness	No	Minor
72, F	Yes	525 ^{a,e}	8.8	Asymptomatic	No	None
31, F	Yes	1200 ^b	15.7	Apathy, drowsiness	Yes	Minor
26, M	No	1200 ^b	16.0	Confusion, apathy, drowsiness	No	Minor
33, F	No	1050 ^{a,f}	17.5	Confusion, apathy, drowsiness, nausea	No	Minor
5, F	No	300 ^a	17.6	Dysarthria, perspiration, stomach ache	No	Minor
27, M	Yes	1500 ^b	25.0	Confusion, dysarthria	ED only	Minor
20, M	Yes	2700 ^{b,g}	37.0	Drowsiness, mild hyperthermia (37.8 °C), hypertension (145/87 mmHg), no ECG abnormalities	Yes	Minor
28, F	Yes	4200 ^b	46.7	Drowsiness, hypothermia (34.8 °C), bradypnea (10/min), mild hypokalaemia (3.4 mmol/L). ECG: T-wave inversion (III and VI leads), normal conduction times	Yes	Moderate
2, M	No	600 ^a	50.0 ^h	Restlessness, drowsiness	Yes	Minor
48, F	Yes	3750 ^b	55.6	Apathy, drowsiness, no ECG abnormalities	Yes	Minor
83, F	Yes (first use)	10 500 ^b	210.0	Confusion, drowsiness, unconsciousness, headache, no ECG abnormalities	ED only	Moderate

ED, emergency department; F, female; M, male; Prescr., pregabalin prescription; PSS, Poisoning Severity Score.

^aUnintentional pregabalin exposure.

^bIntentional pregabalin exposure.

^cCo-exposure: 2000 mg of paracetamol.

^d600 mg of pregabalin in a span of 3 h.

^e525 mg of pregabalin in a span of 1.5 h.

^fCo-exposure: 200-250 mg of diclofenac.

^g2700 mg of pregabalin in a span of 4 h.

^hGastric lavage and activated charcoal (within 1 h post ingestion).

3.2 | Review of the literature on pregabalin overdose

3.2.1 | Case reports and case series

The literature search identified 14 reports, ie, six conference abstracts and eight articles, that met our inclusion criteria (six case reports and eight case series). From the case series, seven individual patients were described in detail (dose and clinical course). Individual patients are presented in Table 2 (dose-ranked).^{6-10,14-17} Case series are presented in Table 3, including data on study population, number of

patients included, pregabalin dose, clinical course and hospitalization.^{6,7,15,18-22}

In general, most common symptoms after pregabalin overdose were drowsiness and dizziness. Ataxia, tremor and cardiovascular symptoms (eg, tachycardia) were occasionally reported. Serious, life-threatening effects, such as coma or seizures, were rarely reported (Table 3). Most case series report no or minor symptoms following pregabalin poisoning in the majority of cases, varying from 69% to 100% (Table 3). One smaller study reported a relatively high proportion of moderate intoxications (44%), but this study only included hospitalized patients (n = 23).²²

TABLE 2 Acute isolated pregabalin overdose: cases from literature, ranked from lowest to highest self-reported dose

Ref.	Age, sex	Prescr.	Dose (mg)	Dose (mg kg ⁻¹)	Symptoms	Admission	PSS
Parekh 2017 ¹⁷	76, M	Yes	450 ^a	6.4 ^b	Drowsiness, confusion	Yes	Minor
Isoardi 2020 ⁷	Adult	NR	600	10.3 ^c	Seizure (1 min, self-limited) (pre-existing seizure disorder)	ED/short stay ward only	Moderate
Isoardi 2020 ⁷	Adult	NR	900	12.9 ^b	Seizure (1 min, self-limited)	ED/short stay ward only	Moderate
Dufayet 2020 ⁶	3, F	No	300	21.3 ^d	Ataxia, miosis, coma (GCS 9)	Yes	Moderate
Isoardi 2020 ⁷	Adult	No	2400	28.6 ^c	Coma (GCS 6)	ED/short stay ward only	Severe
Isoardi 2020 ⁷	Adult	NR	1800	31.6 ^c	Seizure (1 min, self-limited)	ED/short stay ward only	Moderate
Dufayet 2020 ⁶	6, F	No	600	31.6	Confusion, drowsiness, agitation, hallucinations	Yes	Moderate
Siocum 2018 ⁹	54, F	Likely ^e	3825	54.6 ^b	Obtundation, nystagmus, seizure (1.5 min, self-limited), hypertension (170/120 mmHg), tachycardia (140/min)	Yes	Moderate
Bellis 2018 ¹⁴	37, M	NR	4000 ^f	57.1 ^b	Seizures, drowsiness	Yes	Moderate
Ocak 2019 ¹⁶	23, M	No	4200	60.0 ^{b,g}	Metabolic acidosis (pH 7.16), seizure (2 min), unconsciousness (GCS NR)	Yes	Moderate
Tanyildiz 2018 ¹⁰	24, F	NR	4500	64.3 ^b	Tachycardia (165/min), tachypnea (34/min), loss of consciousness, severe metabolic acidosis (pH 6.79), seizures, bilateral serous macular detachment	Yes	Severe
Lackey 2012 ¹⁵	Adult	NR	4500	64.3 ^b	Respiratory depression	NR	Severe
Wood 2010 ⁸	54, M	Likely ^h	8400	120.0 ^{b,i}	Coma (GCS 4)	Yes	Severe

ED, emergency department; F, female; GCS, Glasgow Coma Scale; M, male; NR, not reported; Prescr., pregabalin prescription; PSS, Poisoning Severity Score.

^a450 mg of pregabalin in a span of 8 h.

^bUnknown bodyweight. Dose in mg kg⁻¹ calculated using a bodyweight of 70 kg.

^cDose in mg kg⁻¹ calculated based on bodyweight received by personal communication.

^dActivated charcoal (approximately 2 h post ingestion, vomited immediately after administration).

^eNot exactly specified. Past medical history of chronic back pain.

^fUrine drug screen positive for opioids (history of opioid abuse).

^gGastric lavage and activated charcoal (time post ingestion unclear).

^hNot exactly specified. Past medical history of peripheral neuropathy.

ⁱActivated charcoal (within 1 h post ingestion).

TABLE 3 Acute isolated pregabalin overdose: case series

Ref.	Study population	Number of patients (age range)	Median pregabalin dose (range) ^b	Symptoms	PSS	GIDC	Admission	Dose-toxicity
Browne 2009 ¹⁸	PCC ^a	n = 57 (3 mo-5 y)	Median/mean dose NR (25-400 mg)	Lethargy 10% Ataxia 7%	None 89% Minor 11%	AC 21%	ED only 68% Admitted to hospital 7%	NR
Sjoberg 2010 ¹¹	Patients presenting to hospital	n = 42 (15-61 y)	4200 mg (750-30 000 mg)	Mild CNS depression 48% Tachycardia 24% Tremor/muscle twitching 17% Seizures 12% Unconsciousness 10%	Minor 69% Moderate 26% Severe 2% (n = 1, related to aspiration)	NR	NR	<3000 mg: mild symptoms in most patients >3700 mg: seizures
Lackey 2011 ¹⁹	PCC ^a	n = 80 (8 mo-6 y)	Mean 106 mg (25-450 mg)	Drowsiness 5% Dizziness 3% Vomiting: 1%	None 91% Minor 9%	AC 10%	ED only 28% Admitted to hospital 0%	≤450 mg: mild symptoms
Lackey 2012 ¹⁵	PCC ^a	n = 147 (22-99 y)	Mean 762 mg (25-9000 mg)	Drowsiness 24% Dizziness 10% Tremor 7% Nausea/vomiting 2% Respiratory depression 0.7% (n = 1)	None 67% Minor 26% Moderate 7% Severe 0.7%	AC 8%	ED only 17% Admitted to hospital 0%	No clear correlation between dose and toxicity 4500 mg: respiratory depression (rare, n = 1)
Wills 2014 ²²	Patients treated in healthcare facility	n = 23 (16-85 y)	2375 mg (100-9000 mg)	Effects only reported as categories Neuromuscular 17% CNS 35% Gastrointestinal 13% Cardiac 22% Blood pressure 4% Metabolic 4%	None 35% Minor 22% Moderate 44%	NR	Only hospitalized patients were included	NR
Prasa 2014 ²⁰	PCC ^a	n = 133 (3 wk-90 y)	Median/mean dose NR Children (≤13 y) 15-1350 mg or 5.6-30.6 mg kg ⁻¹ Adolescents/adults (≥14 y) 75-13 500 mg	Somnolence 26% Fatigue 7% Drowsiness 7% Dizziness 12% Ataxia 10% Myoclonus 6% Nausea/vomiting 9% Infrequently (% not reported): seizures, respiratory insufficiency, tachycardia, bradycardia, hypertension	Children: none 52% minor 48% Adolescents/adults: none 23% minor 63% moderate 14%	NR	NR	No clear correlation between dose and toxicity Children ≥ 75 mg (2.7 mg kg ⁻¹): mild symptoms, highest dose with asymptomatic course 300 mg (30.6 mg kg ⁻¹) Adolescents/adults ^c : ≥225 mg mild symptoms, ≥200 mg moderate symptoms, highest dose with asymptomatic course 4200 mg

(Continues)

TABLE 3 (Continued)

Ref.	Study population	Number of patients (age range)	Median pregabalin dose (range) ^b	Symptoms	PSS	GIDC	Admission	Dose-toxicity
Isoardi 2020 ⁷	Patients presenting to hospital	n = 59 (20-76 y)	1500 mg (125-16 800 mg)	Seizures (n = 3, 5%), coma (n = 1, 2%)	Moderate 5% Severe 2%	NR	ED only 36% Short stay ward 64%	2400 mg (28.6 mg kg ⁻¹); severe symptoms (coma, n = 1) 600 mg (10.3 mg kg ⁻¹), 900 mg and 1800 mg (31.6 mg kg ⁻¹); moderate symptoms (self-limited short lasting seizures)
Dufayet 2020 ⁶	PCC ^a	n = 126 (≤ 6 y)	75 mg (5-750 mg) 6.4 mg kg ⁻¹ (0.5-41.7 mg kg ⁻¹)	Drowsiness 13% Ataxia 8% Restlessness 5%	None 77% Minor 21% Moderate 2%	NR	ED 49% Admitted to hospital: NR	Strong correlation between dose and PSS
Rietjens 2021	PCC ^a	n = 21 (2-83 y)	8.8 mg kg ⁻¹ (2.0-210.0 mg kg ⁻¹)	Drowsiness 62% Confusion 29% Apathy 24% Nausea 24% Dizziness 19%	None 14% Minor 71% Moderate 14%	GL and AC 5%	ED only 5% Admitted to hospital 24%	≥2.0 mg kg ⁻¹ : mild symptoms ≥ 3.1 mg kg ⁻¹ : moderate symptoms Median dose: none 6.3 mg kg ⁻¹ minor 15.7 mg kg ⁻¹ moderate 46.7 mg kg ⁻¹

AC, activated charcoal; CNS, central nervous system; ED, emergency department; GIDC, gastrointestinal decontamination; GL, gastric lavage; NR, not reported; PCC, Poison Control Center; PSS, Poisoning Severity Score.

^aStudy population involves patients with a pregabalin exposure reported to a PCC.

^bUnless otherwise reported.

^cTwo elderly patients developed moderate symptoms at a (therapeutic) dose of 75 mg (specific details on the clinical course are lacking).

3.2.2 | Dose-toxicity relationship

For 34 patients the reported pregabalin dose (mg kg^{-1}) and the PSS was plotted, ie, 21 patients from our study and 13 patients described in case reports and case series (Figure 1). One extreme dose value was observed (210.0 mg kg^{-1}). This concerned a 83-year-old woman who developed moderate symptoms after ingestion of a reported dose of 10.5 g of pregabalin (see Table 1). Mild symptoms were reported from 2.0 mg kg^{-1} and the median dose in minor poisonings was 12.2 mg kg^{-1} ($n = 16$; Figure 1). Moderate symptoms were reported from 3.1 mg kg^{-1} and the median dose in moderate cases was 31.6 mg kg^{-1} ($n = 11$). Severe symptoms were reported from 28.6 mg kg^{-1} ; an adult patient developed coma after ingestion of 2400 mg. The median dose in severe cases was 64.3 mg kg^{-1} ($n = 4$). The median dose was significantly lower in the PSS none-minor group ("benign") (8.6 mg kg^{-1} , IQ25-75 $5.0\text{--}17.6 \text{ mg kg}^{-1}$) than in the PSS moderate-severe group ("significant toxicity") (46.7 mg kg^{-1} , IQ25-75 $21.3\text{--}64.3 \text{ mg kg}^{-1}$); the estimate of the median difference was 27.3 mg kg^{-1} (95% CI: $10\text{--}48.6$) before exclusion and 25.3 mg kg^{-1} (95% CI: $8.3\text{--}46.3$) after exclusion of the outlier.

4 | DISCUSSION

We reviewed the literature on isolated pregabalin poisoning to explore the relationship between the dose and the severity of the poisoning. In line with earlier reports, we found that isolated pregabalin overdose mainly causes mild symptoms, such as drowsiness and dizziness. However, serious effects such as seizures and

coma are rare, but can occur, especially at higher reported doses (Figure 1).

In line with the study of Dufayet et al,⁶ we also show that moderate to severe effects following pregabalin overdose are uncommon in children (Tables 1 and 3, no additional moderate or severe cases were reported in children). This is likely explained by the predominance of unintentional exposures to relatively low pregabalin doses, caused by exploratory behaviours in children and/or lack of parental supervision. Notably, two children (<1%) in the study of Dufayet et al did develop a moderate to severe clinical course, ie, coma in a 3-year-old girl (21.3 mg kg^{-1}) and confusion, drowsiness, agitation and hallucination in a 6-year-old girl (31.6 mg kg^{-1}) (Table 2).⁶ Dufayet et al suggested a hospital-based surveillance for children ≤ 6 years old with no underlying neurological/cardiac disease if the ingested pregabalin dose is $\geq 19.4 \text{ mg kg}^{-1}$.⁶ Applying this dose threshold of 19.4 mg kg^{-1} to our data set (involving children and adults) to predict the need for hospital referral showed a sensitivity of 80% (95% CI: $0.51\text{--}0.95$) and specificity of 79% (95% CI: $0.54\text{--}0.93$). For this, the need for hospital referral was defined as a PSS of moderate or severe, while hospital referral was deemed unnecessary for patients with a PSS of none or mild.

We show that below 20 mg kg^{-1} pregabalin (18 out of 34 patients), the majority of patients (83%, 15 out of 18 patients) only suffer from mild poisoning. Three cases in our review developed a moderate poisoning below 20 mg kg^{-1} . A 77-year-old woman received a too-high initial dose of pregabalin (300 mg , 3.1 mg kg^{-1}) and developed moderate symptoms, ie, confusion, ataxia, sopor and amnesia. An adult patient developed self-limiting seizures of 1 minute duration after ingestion of 600 mg pregabalin (10.3 mg kg^{-1}), but had a pre-existing seizure disorder, possibly increasing sensitivity for toxicity. Another adult patient also developed self-limiting seizures of 1 minute duration after ingestion of 900 mg pregabalin (12.9 mg kg^{-1}). Prasa et al also report moderate toxicity at low, even therapeutic, pregabalin doses, ie, in adolescents and adults at pregabalin doses from 200 mg and in two elderly people at a dose of 75 mg ²⁰ (therapeutic adult pregabalin dose 150–600 mg/day divided into two or three doses). Since specific details on the clinical course are lacking, these patients are not presented in Table 2 and Figure 1. In contrast, pregabalin overdoses with an asymptomatic course have been described up to 30.6 mg kg^{-1} in children and up to 4200 mg in adolescents/adults ($\sim 60 \text{ mg kg}^{-1}$).²⁰ This indicates large interindividual differences in response to pregabalin overdose.

Due to these interindividual differences, pre-hospital triage should not only include pregabalin dose and underlying diseases, but also instructions should be provided to patients on when to seek medical assistance. These should include the occurrence of depression of consciousness or tremor. The risk of possible co-exposures should also be evaluated, as this can influence the clinical course. For example, coma and overdose deaths are more common in patients ingesting pregabalin in combination with sedating agents, such as opioids and benzodiazepines.^{5,7}

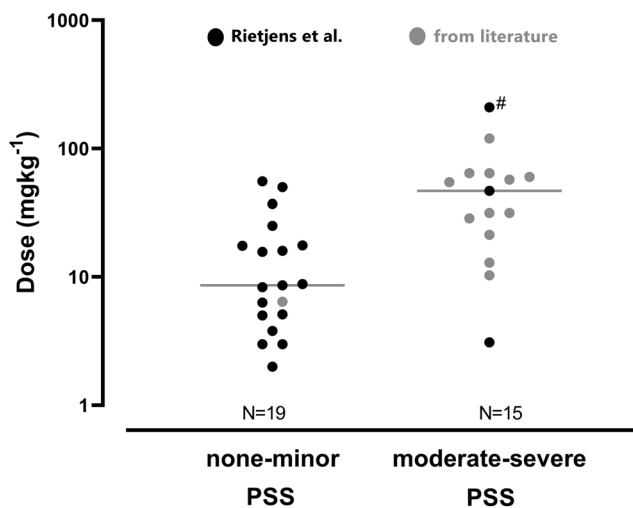


FIGURE 1 Scatterplots depicting pregabalin dose (mg kg^{-1}) (including median) in 34 patients stratified in two groups: "benign" (Poisoning Severity Score [PSS] none-minor) and "significant toxicity" (PSS moderate-severe). Black data points: cases from the prospective Dutch Poisons Information Center (DPIC) study. Grey data points: cases from literature. #, outlier

4.1 | Limitations

In our study, pregabalin exposure was not analytically confirmed in biological specimens and we did not aim to investigate the correlation between pregabalin blood concentrations and toxicity. The exact amount of pregabalin ingested is often uncertain because of self-reported doses, which could contribute to the interindividual differences observed in response to pregabalin overdose. Our study sample is relatively small and the estimated bodyweight in some cases could lead to under- or overestimation of the dose in mg kg⁻¹. Moreover, specific details on gastrointestinal decontamination measures are not always provided. Including cases with effective decontamination measures may confound the assessment of the dose-toxicity relationship, as these treatments will reduce the total amount of pregabalin absorbed. Furthermore, publication bias is probable, as severe poisonings are more likely to be published compared to mild cases. In our study, a relatively high percentage of cases (57%) was lost to follow-up, although this would not influence the dose-toxicity relationship of the cases with follow-up.

5 | CONCLUSIONS

Pregabalin poisoning usually results in mild symptoms, especially below 20 mg kg⁻¹. However, coma and seizures are occasionally reported. Overall, higher doses result in more severe poisonings, but large interindividual differences exist in the response to pregabalin. Therefore, pre-hospital triage of patients with pregabalin overdose should not only be based on pregabalin dose. Underlying illnesses, co-exposures and reported symptoms should also be taken into account, as should instructions on when to seek medical assistance.

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COMPETING INTERESTS

The authors report no conflict of interest.

CONTRIBUTORS

S.J.R., L.H. and D.W.L. designed the study. S.J.R. and L.H. collected and analysed the data. S.J.R. and M.A.S. graded the severity of each poisoning using the Poisoning Severity Score. C.C.H. performed the statistical analyses. S.J.R. drafted the manuscript and all authors contributed substantially to its revision. S.J.R. takes responsibility for the paper as a whole.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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