Extracorporeal Treatment for Gabapentin and Pregabalin Poisoning: Systematic Review and Recommendations From the EXTRIP Workgroup

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Toxicity from gabapentin and pregabalin overdose is commonly encountered. Treatment is supportive, and the use of extracorporeal treatments (ECTRs) is controversial. The EXTRIP workgroup conducted systematic reviews of the literature and summarized findings following published methods. Thirty-three articles (30 patient reports and 3 pharmacokinetic studies) met the inclusion criteria. High gabapentinoid extracorporeal clearance (>150 mL/min) and short elimination half-life (<5 hours) were reported with hemodialysis. The workgroup assessed gabapentin and pregabalin as "dialyzable" for patients with decreased kidney function (quality of the evidence grade as A and B, respectively). Limited clinical data were available (24 patients with gabapentin toxicity and 7 with pregabalin toxicity received ECTR). Severe toxicity, mortality, and sequelae were rare in cases receiving ECTR and in historical controls receiving standard care alone. No clear clinical benefit from ECTR could be identified although major knowledge gaps were acknowledged, as well as costs and harms of ECTR. The EXTRIP workgroup suggests *against* performing ECTR in addition to standard care rather than standard care alone (weak recommendation, very low quality of evidence) for gabapentinoid poisoning in patients with normal kidney function. If decreased kidney function and coma requiring mechanical ventilation are present, the workgroup suggests performing ECTR in addition to standard care (weak recommendation, very low quality of evidence).

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Introduction

The gabapentinoids gabapentin and pregabalin are among the most prescribed drugs in the United States,[1] and are increasingly misused recreationally.[2,3] Treatment of patients with gabapentinoid toxicity is supportive, but the role of extracorporeal treatment (ECTR) is debated. The Extracorporeal Treatments in Poisoning (EXTRIP) workgroup (www.extrip-workgroup.org) is composed of international experts representing diverse specialties and professional societies (Item S1). Its mission is to provide recommendations on the use of ECTRs in poisoning.[4-8] The objective of this article is to present EXTRIP's systematic review of the literature and recommendations for the use of ECTR in patients poisoned from gabapentin or pregabalin.

Clinical Pharmacology and Toxicokinetics

Gabapentin and pregabalin are structurally similar to gamma aminobutyric acid (GABA) but have little to no activity on the GABAergic system. Instead, they inhibit the α_2-δ subunit of P/Q-type voltage-gated calcium channels, thereby reducing presynaptic calcium influx and thus subsequent release and activity of excitatory neurotransmitters such as glutamate and substance P.[9] Gabapentin was approved in the United States in 1994 for treatment of partial seizures, and pregabalin in 2004 for treatment of neuropathic pain. They both have extensive on-label and off-label use, including for neuropathic pain, partial seizures, migraine, perioperative pain, and substance abuse disorders, as well as muscle cramps, restless leg syndrome, and pruritus in patients on maintenance dialysis.[9-11]

Gabapentin and pregabalin share many physicochemical and pharmacologic properties (Table 1). Both are rapidly absorbed with maximal concentration reached within 1-4 hours.[12-19] The oral bioavailability of therapeutic dose gabapentin is approximately 50%[15,20] although absorption is reduced at higher doses because of saturable intestinal transport mechanisms.[20-24] In comparison, oral bioavailability of pregabalin is 90% and is not dose dependent.[17] Neither gabapentinoid is significantly bound to plasma proteins,[12] and their volumes of distribution are <1 L/kg. They are not metabolized and are eliminated unchanged by the kidneys, with total body clearance equivalent to renal clearance.[13,17] The terminal elimination half-life of gabapentinoids is approximately 6 hours and can increase up to 12 hours in overdose[25-30] and up to 10-fold in patients with decreased kidney function.[31-33] Both drugs are available in sustained-release formulations although overdose data with these preparations are limited.[19,34-36]

Overview of Toxicity

Publications of poisoning from gabapentinoids, either from suicidal intent, misuse, or therapeutic errors, have increased dramatically over the last decade in many regions including Europe,[37-42] Australia,[43-45] and the United States.[46-50]

Isolated gabapentin and pregabalin poisoning share similar effects, usually limited to somnolence. In large cohorts, severe clinical effects occur in less than 5% of patients, and include coma,[45,51-54] bradycardia,[51,55,56] hypotension,[45,51] and respiratory failure requiring intubation.[51,55-60] Seizures also occur[45,51,53-55,57,58] and are characteristically a

Table 1. Physicochemical Properties and Pharmacokinetics of Gabapentin and Pregabalin

	Gabapentin		Pregabalin	
Characteristic	**Value**	**References**	**Value**	**References**
Molecular weight, Da	171		159	
pKa	3.7		4.2	
Protein binding	<5%	12	0%	149
Volume of distribution, L/kg[a]				
Normal GFR	0.6-0.8 (higher in children)	12-14, 24, 32, 150	0.4-0.6	17, 19, 31, 112, 151
CKD/maintenance dialysis	0.4-0.6			
Oral bioavailability	45%-60% (lower at higher doses)	13, 15, 16, 22, 24, 152	90% (independent of dose)	17
Half-life, h				
Normal GFR	5-8	12-14, 16, 25-27, 32, 33, 66, 117, 150, 152-158	4-9	17-19, 28-31
Overdose	5-10		10-12	
CKD stage 3 (GFR 30-60 mL/min)	10-15		15-20	
CKD stage 4 (GFR 15-30 mL/min)	15-35		20-30	
CKD stage 5 (GFR <15 mL/min)	60-200		45-60	
Total body and renal clearance, mL/min[a]				
Normal GFR	80-120	12-14, 16, 24, 117, 150, 152	70-90	17, 19, 31, 151
CKD stage 3 (GFR 30-60 mL/min)	30-40		15-30	
CKD stage 4 (GFR 15-30 mL/min)	10-20		10-15	
CKD stage 5 (GFR <15 mL/min)	<10		<10	
Serum therapeutic range, mg/L	2-20	147	0.2-7.5	147, 148

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
[a]Total body clearance and volume of distribution were obtained from intravenous data. If these data were unavailable but reported for oral data (ie, as V/F or CL/F), then values were adjusted for bioavailability (gabapentin = 50%, pregabalin = 90%)

single, short, self-limited episode.[45,61] The length of toxic effects from gabapentinoids is invariably short (<24 hours),[45,51] and admission to a critical care unit is seldom required.[45,48,49,51,54,58,62,63] Gabapentinoid toxicity is milder than that observed with other anticonvulsants such as carbamazepine and valproic acid.[55,57]

Larger ingestions of either gabapentinoid are associated with a greater likelihood of toxicity,[42,45,53,60,64] although this finding was not confirmed in some cohorts.[52,57,62] A threshold dose-relationship is described for myoclonus.[65,66] There are numerous reports of healthy patients ingesting up to 35 g of either gabapentin[51,52] or pregabalin[53,56] with uncomplicated outcomes. Exploratory ingestions in young children typically only cause mild toxicity.[42,51,63]

There appears to be a concentration-response relationship[60]: patients who were symptomatic from gabapentin had a statistically higher serum gabapentin concentration than asymptomatic patients (29.1 ± 2.5 vs 19.9 ± 1.3 mg/L, respectively, $P < 0.01$). This relationship exhibits large interpatient variability: patients can be symptomatic at a gabapentin concentration of 15 mg/L,[60,67] and be minimally affected at concentrations over 75 mg/L.[60,68,69]

Patients with decreased kidney function are particularly susceptible to gabapentinoid toxicity[60,70,71] especially those who are receiving maintenance dialysis.[60] Kidney disease is associated with a relative risk of 1.68 (95% CI, 1.27-2.22) of hospitalization from altered consciousness within 30 days of gabapentin initiation.[70] Significant alteration in mental status is reported after a single therapeutic dose of gabapentinoids in maintenance dialysis patients.[31,67,72] At similar gabapentinoid concentrations, patients with a lower glomerular filtration rate (GFR) have more central nervous system symptoms from gabapentin than those with a normal GFR.[60,73]

Almost all fatalities associated with gabapentin and pregabalin occur in a context of coingestion and polysubstance use.[43,48,54,59,74-79] Death from isolated gabapentinoid ingestion is described but is extremely uncommon[43,49,57,59,62] and generally occurred in patients who did not reach a health care facility.[48,74,80]

Patients on long-term gabapentinoid therapy develop tolerance.[3,64] Additionally, cessation of gabapentinoids after long-term therapy may lead to withdrawal symptoms, even when the dose is gradually decreased.[81,82] As opposed to GABA agonists such as baclofen and benzodiazepines, symptoms of gabapentinoid withdrawal are rarely life threatening[83-85] and include anxiety, hypertension, palpitations, and diaphoresis.[86-88] In rare cases, status epilepticus, respiratory failure, severe abdominal pain, and delirium are reported.[81,82,86,89,90]

The standard care of patients with gabapentinoid poisoning is mainly supportive and includes drug discontinuation, mechanical ventilation, fluid resuscitation, vasopressors, and gastrointestinal decontamination, depending on the severity and timing of the ingestion (Item S1).[91,92] There is no specific antidote currently available.

Methodology for EXTRIP Evaluation

The workgroup developed recommendations following the previously published[6] EXTRIP methodology with modifications, updates, and clarifications. The methods are presented fully in Item S1. In accordance with Institute of Medicine standards,[93] EXTRIP clinical practice guidelines include recommendations intended to optimize patient care by assisting decision-making.[4]

Systematic Review of Evidence

The systematic review of the literature was developed in accordance with the PRISMA-P 2015 statement,[94] and its objectives were to (1) summarize the balance of benefits and harms of ECTR on patient-important outcomes, and (2) describe the toxicokinetic outcomes of ECTR in the context of severe toxicity to gabapentinoids. The databases used and search strategy are presented in Item S1.

The eligibility criteria were based on the following inclusion criteria: (1) study design to include all types; (2) participants to include all patients with poisoning to gabapentinoids, stratified for presence or absence of decreased kidney function, defined as chronic kidney disease (CKD) GFR stages 3b, 4, or 5 or acute kidney injury (AKI) stage 2 or 3 using the KDIGO (Kidney Disease: Improving Global Outcomes) criteria (Item S2); (3) interventions comprising all types of ECTR if instituted at least partially for the purpose of poison removal; (4) comparator of standard care without ECTR; (5) patient-important outcomes comprising all outcomes judged "critical" or "important" for decision-making, as well as dialyzability (surrogate marker) (Item S1).

The screening process was performed independently in duplicate: screening of the study titles and abstracts for eligibility (CY and MG), and screening of full texts (CY and MG). Disagreements were resolved by consensus or by the methodologist (VL). Three members (CY, JB, and MG) extracted the data into a standardized data extraction tool; a fourth member (DPC) and the methodologist (VL) resolved inconsistencies.

Data Analysis

Dialyzability was categorized semiquantitatively[6] (Item S1). Two workgroup members (DR and MG) performed a modeling scenario to estimate time from an initial serum gabapentin concentration = 100 mg/L to the upper therapeutic concentration (20 mg/L) from first-order decay (Table 2) under various operating conditions using Microsoft Excel. New gabapentin concentrations (C_1) were calculated at a specific time (T_1) from the previous point (C_0, T_0) using derived half-lives ($T_{1/2}$) under different operating conditions (Table 2) with the following calculation: $X_1 = EXP(Ln(C_0) - ([T_1\text{-}T_0] \times [0.693/T_{1/2}])$.

Summary of Evidence and Quality of Evidence

Evidence summaries for each question were prepared by the assigned workgroup members in collaboration with

Table 2. Summary of the Pharmacokinetics and Toxicokinetics of Gabapentinoids During ECTR

	Gabapentin					Pregabalin				
	N	$T_{1/2}$, h	N	Clearance, mL/min	References	N	$T_{1/2}$, h	N	Clearance, mL/min	References
ECTR										
HD	19	4.0 (2.4-7.4)	18	156.6 (78-225)[a]	26, 32, 33, 107, 112, 117, 120	13	3 (2-3)	13	227 (89-227)	31, 108
CKRT	1	18.2	1	41.1						
HP-HD	1	3.5	1	64.5[b]						
PD	2	35.2 (29.1-41.3)	1	6.5						
Endogenous										
Normal kidney function		5-8		80-120			4-9		70-90	
AKI or CKD		10-200		0-40			10-60		0-30	

N indicates number of patients; other values given as median, median (range), or range, except as indicated. Decreased kidney function defined as chronic kidney disease stages 3b, 4, or 5 or acute kidney injury stages 2-3. Abbreviations: CKRT, continuous kidney replacement therapy; ECTR, extracorporeal treatment; HD, hemodialysis; HP-HD, hemoperfusion-hemodialysis in series; PD, peritoneal dialysis; $T_{1/2}$, half-life

[a]Clearance by arteriovenous difference and dialysate recovery were averaged.

[b]Maximum value.

the methodologist. In the absence of a direct comparison between the intervention and comparator, the members selected the publications reporting controls that most closely resembled patients from the ECTR group.

The quality of the evidence was assessed as per the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.[95,96] For each outcome and recommendation, the quality of evidence was assessed across the domains of risk of bias, consistency, directness, precision, publication bias, and additional domains where appropriate. Quality was adjudicated as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), or very low (very uncertain about the estimate of effect) (Item S1).

Development of Recommendations

The workgroup considered core elements of the GRADE evidence in the decision process, including the quality of evidence and balance between desirable and undesirable effects (Item S1). Additional domains were acknowledged when applicable (feasibility, resource use, acceptability). For all recommendations, the workgroup members voted to reach agreement for final recommendations (Item S1). All recommendations were labeled as either strong ("we recommend") or weak ("we suggest") according to the GRADE approach. A "strong" recommendation implies that most individuals in this situation would want the recommended course of action, while a "weak" recommendation means that a majority of individuals in this situation would want the suggested course of action, but many would not. High-quality evidence was expected to be lacking for the majority of recommendations. According to GRADE guidance on discordant recommendations,[97] strong recommendations in the setting of lower-quality evidence were only assigned when the workgroup members believed they conformed to one of the paradigmatic conditions, such as (1) low-quality evidence suggested benefit in a life-threatening situation (with evidence regarding harms being low or high), or (2) low-quality evidence suggested benefit and high-quality evidence suggested harm.

Results of the Literature Search

The results of the literature search (first performed on March 1, 2019, and last updated November 10, 2020) are presented in Figure 1. A total of 828 articles were identified after removal of duplicates. In the final analysis, 33 publications were included for qualitative analysis, including 30 case reports or case series[26,67,72,98-124] and 3 pharmacokinetic studies in maintenance dialysis patients.[31-33] No randomized controlled trials or observational studies were identified.

Summary of Dialyzability Evidence

Gabapentin and pregabalin have ideal characteristics for removal via ECTR, including absence of protein binding, small molecular weight, and low volume of distribution and endogenous clearance.[125] This theoretical high dialyzability is supported by pharmacokinetic and toxicokinetic data, which includes 36 patients (23 for gabapentin and 13 for pregabalin) (Table 2). Two well-conducted pharmacokinetic experiments in maintenance dialysis patients on gabapentin (18 patients) showed a hemodialysis clearance surpassing 100 mL/min, >95% reduction in half-life during hemodialysis, and removal of 17% to 55% of an ingested dose (higher if accounting for bioavailability) during a 3-4 hour session.[32,33] One study

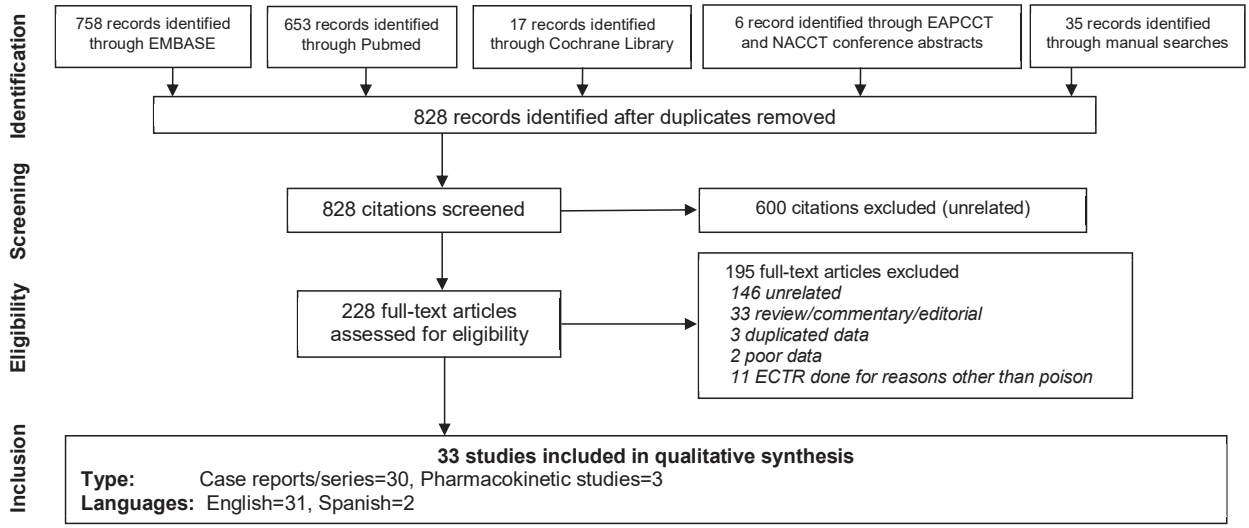

Figure 1. Process of selection and inclusion of studies in the review. Abbreviation: ECTR, extracorporeal treatment.

Table 3. Final Dialyzability Grading Based on the Number of Patients for Gabapentin and Pregabalin According to EXTRIP Criteria

	Gabapentin		Pregabalin
	HD	PD	HD
No. of patients per dialyzability grading			
Dialyzable	18	0	12
Moderately dialyzable	2[a]	0	0
Slightly dialyzable	0	1	0
Not dialyzable	0	0	0
Final grading (level of evidence)			
Normal kidney function	Moderately dialyzable (D)		
Decreased kidney function	Dialyzable (A)	Slightly dialyzable (D)	Dialyzable (B)

Levels of dialyzability are defined in Item S1. Abbreviations: EXTRIP, Extracorporeal Treatments in Poisoning Workgroup; HD, hemodialysis; PD, peritoneal dialysis.
[a]One patient had normal kidney function. Decreased kidney function is defined as chronic kidney disease stages 3b, 4, or 5 or Kidney Disease: Improving Global Outcomes acute kidney injury stages 2-3.

including 12 maintenance dialysis patients taking a therapeutic dose of pregabalin reported hemodialysis clearance of >200 mL/min, a half-life reduction from 55 hours off hemodialysis to 3 hours during hemodialysis, and removal of >50% of an ingested dose during a 4-hour session.[31] As expected, clearances for gabapentin and pregabalin are high with hemodialysis[108,117] and lower with continuous kidney replacement therapy (CKRT) and peritoneal dialysis (PD).[112,120] Toxicokinetic data from overdose cases in patients with normal kidney function are limited in number and in quality for gabapentin, but confirm pharmacokinetic findings. Data were absent for pregabalin. Combined hemoperfusion and hemodialysis in series yielded a maximum gabapentin clearance of 64.5 mL/min.[26] No toxicokinetic data are available for exchange transfusion, liver support devices, and therapeutic plasma exchange, but they would not be expected to confer any advantage over hemodialysis at eliminating gabapentin and pregabalin because of their negligible protein binding.

As kidney function declines, renal clearance—and hence endogenous clearance of gabapentin and pregabalin—is reduced, thereby increasing the relative contribution of ECTR to total clearance. Gabapentin was assessed as "dialyzable" by hemodialysis (level of evidence: A) and "slightly dialyzable" by PD (level of evidence: D) in patients with decreased kidney function (Table 3). There was only 1 patient with normal kidney function who underwent hemodialysis, and gabapentin was assessed as "moderately dialyzable" (level of evidence: D) for this patient. Based on 1 pharmacokinetic study (12 patients on maintenance dialysis in whom hemodialysis was performed), pregabalin was assessed as dialyzable in patients with decreased kidney function (level of evidence: B); dialyzability for pregabalin was not assessable in patients with normal kidney function. Because of the small volume of distribution of both drugs, the "rebound" increase in serum gabapentinoid concentrations after ECTR only reached a median of 30%.[26,31-33]

Although there are scant toxicokinetic data in patients with normal kidney function, it is possible to estimate dialyzability given the predictable pharmacokinetics of

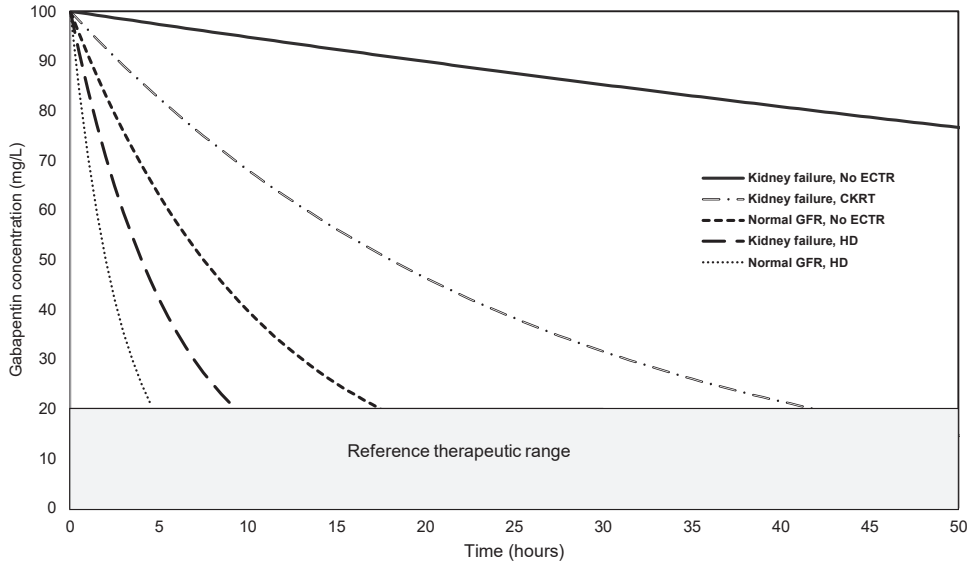

Figure 2. Modeling scenario of gabapentin concentrations under 5 different conditions. Assumptions: first order decay, initial concentration = 100 mg/L, therapeutic concentration = <20 mg/L. **Based on a 70-kg man, V_D = 0.7 L/kg, Total clearance = Endogenous + HD clearance = 300 mL/min, $T_{1/2}$ was calculated as (0.693 × Weight × V_D) / Total Clearance. Abbreviations: AKI, acute kidney injury; CKRT, continuous kidney replacement therapy; ECTR, extracorporeal treatments; GFR, glomerular filtration rate; HD, hemodialysis.

both drugs, even in overdose. The previously described modeling scenario for gabapentin suggests that time to achieve a therapeutic concentration would be 4.6 hours if hemodialysis is used in a patient with normal kidney function (Fig 2), compared with 17 hours in a same patient without ECTR and 300 hours in an anuric patient (without ECTR). This pharmacokinetic benefit would be reduced if the initial serum gabapentinoid concentration was lower. Although these predictions may not inform the duration of clinical indicators such as coma or respiratory failure, this model suggests a minor temporal impact of hemodialysis at enhancing elimination of gabapentinoids in patients with normal kidney function but a much larger one in patients with decreased kidney function.

Summary of Clinical Evidence

The available evidence of a clinical effect for ECTR in gabapentinoid poisoning consists of 29 case reports (including 6 conference abstracts and 8 letters to the editor) for a total of 24 patients poisoned with gabapentin and 7 with pregabalin. There were only 3 patients with normal kidney function (2 for gabapentin and 1 for pregabalin). These patient reports were considered of very low methodological quality; lack of reporting of critical information

Table 4. Clinical Summary of Included Cases of Gabapentinoid Toxicity

	Gabapentin		Pregabalin	
	Normal Kidney Function (n = 2)	Decreased Kidney Function (n = 22)	Normal Kidney Function (n = 1)	Decreased Kidney Function (n = 6)
Patient characteristics				
Age, y	26 [21-31]	56 [48-68]	23	52 [47-64]
Female sex	50%	68%	0%	67%
Maintenance dialysis	0%	55%	0%	100%
AKI	0%	45%	0%	0%
Poisoning information				
Self-harm	100%	0%	100%	0%
Dose, g	35 [16-54]		4.2	
Duration of exposure if taken long-term, d	NA	6 [2-550]	NA	5 [5-14]
Peak serum concentration, mg/L	93.7 [60.6-126.8]	26.8 [15.8-42.6]	NR	13
Signs/symptoms				
Coma	100%	27%	100%	0%
Altered consciousness	100%	86%	100%	33%
Respiratory depression	100%	9%	0%	0%
Myoclonus	NR	83%	0%	100%
Seizure	0%	0%	100%	20%
Hypotension	100%	14%	0%	17%
Other treatments				
Activated charcoal	50%	0%	0%	0%
Mechanical ventilation	100%	5%	0%	0%
Vasopressors	100%	5%	0%	0%
ECTR				
Hemodialysis	0%	73%	100%	50%
Therapeutic plasma exchange	50%	0%	0%	0%
CKRT	0%	14%	0%	0%
Peritoneal dialysis	0%	14%	0%	50%
More than one ECTR	50%	0%	0%	0%
Outcome				
Length of hospital stay, d	17	3 [1-4]	4	NR
Length of ICU stay, d	NR	1 [1-4]	NR	NR
Length of encephalopathy after drug discontinuation, h	NR	24 [24-48]	1	81 [72-90]
Length of myoclonus, h	NR	48 [34-120]	NR	48 [48-66]
Length of mechanical ventilation, h	17 [8-27]	<24	NR	NR
Death	0%	5%[a]	0%	0%

Values for continuous variables given as median [interquartile range]. Decreased kidney function is defined as chronic kidney disease stages 3b, 4, or 5 or Kidney Disease: Improving Global Outcomes acute kidney injury stages 2-3. Abbreviations: AKI, acute kidney injury; CKRT, continuous kidney replacement therapy; ECTR, extracorporeal treatment; ICU, intensive care unit, NR, not reported; NA, not applicable.
[a]One patient died of pneumonia on day 4, unclear if related (no coma or mechanical ventilation).

was noted, particularly with regard to ECTR parameters and outcomes.[126] The demographics, clinical findings, management, and outcomes of patients receiving ECTR for gabapentinoid poisoning are listed in Table 4. One death (unclear if related to gabapentin) was identified, and no cases of permanent sequelae were otherwise reported in survivors.

An attempt was made to compare the cohort of patients receiving ECTR to historical cohorts who did not receive ECTR. This analysis is limited because of several factors: (1) there were only 3 patients with normal kidney function receiving ECTR after overdose (underpowered analysis), 2 of whom were confounded by coingestants that depress the central nervous system; (2) approximately two-thirds of included patients in the ECTR group were receiving maintenance dialysis, and such patients cannot be used as controls as they already receive ECTR for kidney failure; and (3) patients had few features of serious toxicity—out of the 28 patients with kidney disease, only 6 were comatose, and only 1 required mechanical ventilation.

Despite these confounders, patient cohorts with isolated gabapentinoid poisoning and normal kidney function report excellent outcomes such as short duration of toxicity, low mortality, and infrequent sequelae.[41,45,48,49,52-59,62] This is also confirmed in reports containing patient-level data (excluding cases in which coingestants were considered responsible for clinical symptoms).[30] In these reports, the duration of mental status alteration and mechanical ventilation, when present, was < 26 hours for all cases, for both gabapentin (median dose, 54 g; median peak serum gabapentin concentration, 62 mg/L)[25,27,127-131] and pregabalin (median dose, 3.9 g; median peak serum pregabalin concentration, 36 mg/L).[29,61,132-135] Although limited, these data are comparable to patients receiving ECTR (Tables 4 and 5).

There are few publications that detail the effects and outcomes of gabapentinoid toxicity without ECTR in patients with decreased kidney function: most only report mild symptoms (asterixis, myoclonus), and none had severe features such as coma, seizures, or respiratory depression for either gabapentin[66,69,119,136-139] or pregabalin.[28,111,140] One patient with CKD had complete atrioventricular block with a therapeutically adjusted dose of pregabalin,[141] with partial and complete resolution at 4 and 7 days, respectively. Duration of altered consciousness and myoclonus in controls lasted on average 1-2 days,[28,66,69,137,139] similar to that observed in the ECTR cohort (Table 4). However, the historical cohort had few patients and less severely decreased kidney function than those receiving ECTR.

Compared with more efficient techniques such as hemodialysis, slower improvement of mental status alteration was reported with PD for both gabapentin (medians of 24 hours and 48 hours, respectively)[107,115,120] and pregabalin (medians of 72 hours and 90 hours, respectively).[104,114,118] This analysis was underpowered although the differences are less than those expected based on achievable clearances for both ECTRs.

One patient developed complications of ECTR, namely thrombocytopenia from hemoperfusion-hemodialysis and a hematoma from catheter insertion.[26] ECTR is known to be associated with significant costs[142] and potential for complications related to the insertion of central venous catheter and the extracorporeal procedure.[8,143-145] No patients with gabapentinoid withdrawal were reported after ECTR.

In summary, severe poisoning from isolated gabapentinoid ingestion is rare and relatively short-lived. ECTR is not expected to reduce the length or magnitude of toxicity to any clinically relevant extent in patients with normal kidney function. The lack of sufficient controls with severe clinical features in patients with decreased kidney function precludes reliable analysis of the impact of ECTR in this subgroup. However, favorable pharmacokinetic data in this subgroup of patients suggest gabapentinoid removal via hemodialysis can be accomplished and may be useful in individual cases such as comatose patients with decreased kidney function on mechanical ventilation.

Recommendations

Recommendations are summarized in Box 1. For all recommendations, as stated previously, the quality of the evidence regarding the use of ECTR for gabapentinoid poisoning was regarded as very low due to the poor overall methodological quality of the best available literature (uncontrolled case series).

Box 1. Summary of Recommendations for Extracorporeal Treatment (ECTR) in Gabapentinoid Poisoning

General Recommendations and Indications for ECTR

1.1: In patients severely poisoned with gabapentinoids and normal kidney function, ***we suggest against*** performing ECTR in addition to standard care rather than standard care alone (weak recommendation, very low quality of evidence).

1.2: In patients severely poisoned with gabapentinoids and coexisting kidney impairment, ***we suggest*** performing ECTR in addition to standard care rather than standard care alone, especially in the presence of associated coma requiring mechanical ventilation (weak recommendation, very low quality of evidence).

Type of ECTR

2.1: In patients severely poisoned with gabapentinoids requiring ECTR, when all modalities are available, ***we recommend*** using intermittent hemodialysis rather than any other type of ECTR (strong recommendation, very low quality of evidence).

Cessation of ECTR

3.1: In patients severely poisoned with gabapentinoids requiring ECTR, ***we recommend*** stopping ECTR based on clinical improvement (strong recommendation, very low quality of evidence).

For the purpose of recommendations, the workgroup decided to combine both drugs together as "gabapentinoids."

Table 5. Extracorporeal Treatments and Standard Care Compared With Standard Care Alone in Patients Severely Poisoned With Gabapentinoids

	Study Design and No. of Studies	Quality Assessment					Summary of Findings				
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	ECTR + Standard Care	Standard Care (Controls)	Effect	Quality	Importance
Mortality											
Gabapentin, normal kidney function	Observational studies (n = 7)[a]	Very serious[b]	Not serious	Serious[c]	Very serious[d]	Publication bias strongly suspected[e]	0/2 (0%)	Overall: 23/27,227 (0.08%)[f] Each study: 0/48[52]; 0/1,707[58]; 3/424[48]; 19/22,737[49]; 1/2,195[59]; 0/116 [57] Admitted to ICU: 19/2,050 (0.9%)[49]	Groups not comparable	⊕◯◯◯ Very low	Critical
Gabapentin, decreased kidney function	Observational studies (n = 7)[g]	Very serious[b]	Not serious	Serious[c]	Very serious[h]	Publication bias strongly suspected[e]	1/22 (4.5%)	Overall: 0/7 (0%)[66,69,119,136,137,139]	Groups not comparable	⊕◯◯◯ Very low	Critical
Pregabalin, normal kidney function	Observational studies (n = 9)[i]	Very serious[b]	Not serious	Serious[c]	Very serious[d]	Publication bias strongly suspected[e]	0/1 (0%)	Overall: 0/577 (0%)[f] Each study: 0/50[41]; 0/42[53]; 0/21[55]; 0/147[62]; 0/133[56]; 0/103[54]; 0/58[45]; 0/23[57]	Groups not comparable	⊕◯◯◯ Very low	Critical
Pregabalin, decreased kidney function	Observational studies (n = 4)[j]	Very serious[b]	Not serious	Serious[c]	Very serious[h]	Publication bias strongly suspected[e]	0/6 (0%)	Overall: 0/3 (0%)[28,111,140]	Groups not comparable	⊕◯◯◯ Very low	Critical
Length of Mechanical Ventilation											
Gabapentin, normal kidney function	Observational studies (n = 3)[k]	Very serious[b]	Not serious	Serious[c]	Very serious[l]	Publication bias strongly suspected[e]	Median: 17 h (n = 2)	Median: 20 h (n = 2)[127,131]	Groups not comparable	⊕◯◯◯ Very low	Critical
Gabapentin, decreased kidney function	Observational studies (n = 1)[m]	Very serious[b]	Not serious	Serious[c]	Very serious[l]	Publication bias strongly suspected[e]	Median: <24 h (n = 2)	No data	No comparison possible (lack of data in control group)	⊕◯◯◯ Very low	Critical
Pregabalin, all							No data	No data	No comparison possible (lack of data)		Critical
Length of Encephalopathy											
Gabapentin, decreased kidney function	Observational studies (n = 5)[n]	Very serious[b]	Not serious	Serious[c]	Very serious[l]	Publication bias strongly suspected[e]	Median: 1 d (n = 19)	Median: 1 d (n = 4)[66,69,137,139]	Groups not comparable	⊕◯◯◯ Very low	Important

(Continued)

Table 5 (Cont'd). Extracorporeal Treatments and Standard Care Compared With Standard Care Alone in Patients Severely Poisoned With Gabapentinoids

	Study Design and No. of Studies	Quality Assessment					Summary of Findings				
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	ECTR + Standard Care	Standard Care (Controls)	Effect	Quality	Importance
Pregabalin, decreased kidney function	Observational studies (n = 2)[o]	Very serious[b]	Not serious	Serious[c]	Very serious[l]	Publication bias strongly suspected[e]	Median: 3.3 d (n = 2)	Median: 2 d (n = 1)[28]	Groups not comparable	⊕◯◯◯ Very low	Important
Gabapentin/ pregabalin, normal kidney function							No data	No data	No comparison possible (lack of data)		Important
Length of Hospital Stay											
Gabapentin, normal kidney function	Observational studies (n = 6)[p]	Very serious[b]	Not serious	Serious[c]	Very serious[l]	Publication bias strongly suspected[e]	Median: 17 d (n = 1)	Mean: 22 d (n = 21)[55]; Median: 4 d (n = 4)[127,129,159,160]	Groups not comparable	⊕◯◯◯ Very low	Important
Gabapentin, decreased kidney function	Observational studies (n = 1)[q]	Very serious[b]	Not serious	Serious[c]	Very serious[l]	Publication bias strongly suspected[e]	Median: 3 d (n = 9)	No data	Groups not comparable	⊕◯◯◯ Very low	Important
Pregabalin, normal kidney function	Observational studies (n = 2)[r]	Very serious[b]	Not serious	Serious[c]	Very serious[l]	Publication bias strongly suspected[e]	Median: 4 d (n = 1)	Median: 0.5 d (n = 58)[45]	Groups not comparable	⊕◯◯◯ Very low	Important
Pregabalin, decreased kidney function	Observational studies (n = 6)[s]	Very serious[b]	Not serious	Serious[c]	Very serious[l]	Publication bias strongly suspected[e]	No data	Median: 1 d (n = 8)[30,61,132-134,161]	No comparison possible (lack of data in ECTR group)	⊕◯◯◯ Very low	Important
Serious Complications of Catheter Insertion[t]											
All	Observational studies (N = 5)[u]	Not serious	Not serious[v]	Not serious[w]	Not serious[x]	Strong association[y]	Rate of serious complications of catheter insertion: 0.1%-2.1%	≈0	Absolute effect estimated at 1-21 more serious complications per 1,000 pts in ECTR group	⊕⊕⊕◯ Moderate	Critical
Serious Complications of ECTR[z]											
All	Observational studies (N = 4)[A]	Not serious	Not serious	Not serious	Not serious	Strong association[B]	Rate of serious complications of ECTR varies by type, from 0.005% (IHD and CKRT) up to 1.9% (HP)	≈0	Absolute effect estimated at >0-19 more serious complications per 1,000 pts in ECTR group depending ECTR type	⊕⊕⊕◯ Moderate	Critical

"Withdrawal" and "length of ICU stay" were outcomes ranked important although data were extremely limited. Decreased kidney function defined as chronic kidney disease 3b, 4, or 5 or Kidney Disease: Improving Global Outcomes acute kidney injury stages 2-3. Abbreviations: CKRT, continuous kidney replacement therapy; ECTR, extracorporeal treatments; HP, hemoperfusion; ICU, intensive care unit; IHD, intermittent hemodialysis; NA, not applicable; pts, patients.

[a]Includes our systematic review of the literature on ECTR and 6 cohorts on standard care alone.

[b]Case reports published on effect of ECTR. Uncontrolled and unadjusted for confounders such as severity of poisoning, coingestions, supportive and standard care, and cointerventions. Confounding by indication is inevitable because ECTR was usually attempted when other therapies failed.

[c]ECTR and standard care are not directly compared in the same cohort of patients.

[d]Few events in both groups with a very small sample size in the ECTR group, so optimal information size criteria was not met.

[e]Due to the study design (case reports published in toxicology either report very severe poisoning with/without impressive recovery with treatments attempted).

[f]Single drug exposures only.

[g]Includes our systematic review of the literature on ECTR and 6 case reports/case series on standard care alone.

[h]Few events in a very small sample size, so optimal information size criteria was not met.

[i]Includes our systematic review of the literature on ECTR and 8 cohorts on standard care alone.

[j]Includes our systematic review of the literature on ECTR and 3 case reports on standard care alone.

[k]Includes our systematic review of the literature on ECTR and 2 case reports on standard care alone.

[l]Very small sample size, so optimal information size criteria was not met.

[m]Includes our systematic review of the literature on ECTR (no data on standard care alone).

[n]Includes our systematic review of the literature on ECTR and 4 case reports on standard care alone.

[o]Includes our systematic review of the literature on ECTR and 1 case report on standard care alone.

[p]Includes our systematic review of the literature on ECTR and 5 case reports/series or cohorts on standard care alone.

[q]Includes our systematic review of the literature on ECTR and no data on standard care alone.

[r]Includes our systematic review of the literature on ECTR and 1 cohort on standard care alone.

[s]Includes 6 case reports/series on standard care alone.

[t]For venous catheter insertion: serious complications include hemothorax, pneumothorax, hemomediastinum, hydromediastinum, hydrothorax, subcutaneous emphysema retroperitoneal hemorrhage, embolism, nerve injury, arteriovenous fistula, tamponade, and death. Hematoma and arterial puncture were judged not serious and thus excluded from this composite outcome. Deep vein thrombosis and infection complications were not included considering the short duration of catheter use.

[u]Based 5 single-arm observational studies: 2 meta-analyses comparing serious mechanical complications associated with catheterization using or not an ultrasound, which included 6 randomized control trials in subclavian veins[144] and 11 in internal jugular veins[143]; 2 randomized control trials comparing major mechanical complications of different sites of catheterization[162,163]; 1 large multicenter cohort study reporting all mechanical complications associated with catheterization.[164] Rare events were reported from case series and case reports.

[v]Not rated down for inconsistency because heterogeneity was mainly explained by variation in site of insertion, use of ultrasound, experience of the operator, populations (adults and pediatric), urgency of catheter insertion, practice patterns, and methodological quality of studies.

[w]Not rated down for indirectness because cannulation and catheter insertion was judged similar to the procedure for other indications.

[x]Not rated down for imprecision because wide range reported explained by inconsistency.

[y]The events in the control group are assumed to be zero (because no catheter is installed for ECTR), so the magnitude of effect is at least expected to be large, which increases the confidence in the estimate of effect. Furthermore, none of the studies reported 95% CI which included the null value, and all observed complications occurred in a very short time frame (ie, a few hours).

[z]For IHD and CKRT: serious complications (air emboli, shock, and death) are exceedingly rare especially if no net ultrafiltration. Minor bleeding from heparin, transient hypotension, and electrolytes imbalance were judged not serious. For HP: serious complications include severe thrombocytopenia, major bleeding, and hemolysis. Transient hypotension, hypoglycemia, hypocalcemia, and thrombocytopenia were judged not serious. All nonserious complications were excluded from this composite outcome.

[A]IHD/CKRT: Based on 2 single-arm studies describing severe adverse events per 1,000 treatments in large cohorts of patients.[145,165] HP: Based on 2 small single-arm studies in poisoned patients.[166,167] Rare events were reported in case series and case reports.

[B]Assuming that patients in the control group would not receive any form of ECTR, the events in the control group would be 0; therefore, the magnitude of effect is at least expected to be large, which increases the confidence in the estimate of effect. Furthermore, none of the studies reported 95% CI which included the null value and all observed complications occurred in a very short time frame (ie, a few hours).

General Recommendations and Indications for ECTR

Recommendation 1.1

In patients severely poisoned with gabapentinoids and normal kidney function, ***we suggest against*** performing ECTR in addition to standard care rather than standard care alone (weak recommendation, very low quality of evidence).

Rationale

Gabapentinoid poisoning can occasionally result in severe symptoms such as coma, seizures, hypotension, or respiratory depression requiring mechanical ventilation. Despite the dialyzability of these drugs, the panel did not suggest ECTR for gabapentinoid poisoning in addition to standard care (result of votes: median, 2.0; upper quartile, 5.0; disagreement index, 0.75) due to the following: first, severe symptoms are infrequent, admission to a critical care unit is rarely required,[45,48,49,51,54,58,62,63] and mortality and sequelae are extremely rare with appropriate standard care in patients with isolated gabapentinoid poisoning. ECTR would therefore have little impact in improving these outcomes; second, gabapentinoid poisoning is expected to be of limited duration (<24 hours) due to its short elimination half-life in patients with normal kidney function.[45,51] ECTR does not reduce the duration of mechanical ventilation in patients with normal kidney function (Table 5). Thus, ECTR would not reduce the duration of poisoning to a clinically significant extent; however, this may not apply to sustained-release formulations for which data were nonexistent; third, there is a potential risk of withdrawal associated with abrupt dialytic removal in patients on long-term treatment with gabapentinoids. Some panel members expressed that there may be some mitigating factors in considering ECTR if there was pre-existing lung disease or a massive ingestion with a very high serum concentration. As mentioned, intentional gabapentinoid overdoses often occur with coingestants[54,146]; the decision to initiate ECTR will ultimately depend on the contribution of each coingestant to the patient's condition and their characteristics for extracorporeal removal. The panel also discussed that if symptoms suggestive of gabapentinoid overdose of an immediate release formulation persist beyond 24 hours in a patient with normal kidney function (with no possibility of serum assay confirmation), then an alternate diagnosis should be investigated.

Research Gap

Additional clinical data are needed in patients who exhibit or are at high risk of severe toxicity (seizures, need for mechanical ventilation, massive overdose), especially from sustained-release formulations for which very scant data exist. Assessment of the risk of withdrawal from ECTR is needed.

Recommendation 1.2

In patients severely poisoned with gabapentinoids and coexisting kidney impairment, ***we suggest*** performing ECTR in addition to standard care rather than standard care alone, especially in the presence of associated coma requiring mechanical ventilation (weak recommendation, very low quality of evidence).

Rationale

The half-life of gabapentinoids is significantly prolonged in patients with decreased kidney function, especially in patients with severe AKI or CKD stages 3b-5 who are not already on dialysis. There are limited clinical data with the use of ECTR in severely symptomatic patients with decreased kidney function, precluding a reliable analysis of the impact of ECTR in this subgroup. However, favorable pharmacokinetic data suggest considerable drug removal by hemodialysis. Patients who already have a functional vascular access have no added risk of adverse effects from catheter insertion. For this recommendation, the panel recognized that ECTR would not reduce mortality, but would reduce resource utilization of ICU and mechanical ventilation (result of votes: median, 7.0; lower quartile, 5.0; disagreement index, 0.52). The benefit would appear greater the more severe the CKD or AKI.

A requirement of mechanical ventilation was considered the most important indication for ECTR, to shorten ventilator time and reduce its related risks. Symptoms such as recurrent seizures and persistent hypotension, without associated coma, are unlikely to be caused by isolated gabapentinoid poisoning. In patients on maintenance hemodialysis and presenting with milder symptoms (confusion, debilitating myoclonus), it is reasonable to advance the time of the scheduled routine dialysis session and repeat sessions daily until complete disappearance of symptoms. Some panelists also expressed their support for ECTR in addition to standard care in patients with modestly decreased kidney function if altered consciousness without coma was present, with the objective of reducing length of stay and associated nosocomial complications.

Only 8 of the 38 members had access to gabapentinoid assays at their respective institutions, and only 2 with a turn-around time of ≤6 hours. The panel assessed that serum gabapentinoid concentrations, even if available rapidly, are not reliable criteria for ECTR initiation. Although there is evidence of a concentration-response relationship,[60] there is large interpatient variability[60,67-69] and tolerance in patients on maintenance therapy. Nevertheless, a serum concentration < 1 mg/L excludes a diagnosis of gabapentinoid toxicity.[147,148]

Research Gap

Studies comparing outcomes of patients with modestly decreased kidney function treated with and without ECTR are lacking, especially with regards to outcomes such as

mechanical ventilation, duration of altered mental state, and length of stay. Better understanding of toxicokinetic/toxicodynamic relationships and how they relate to outcomes is needed.

Type of ECTR

Recommendation 2.1

In patients severely poisoned with gabapentin/pregabalin requiring ECTR: when all modalities are available, ***we recommend*** using intermittent hemodialysis rather than any other type of ECTR (strong recommendation, very low quality of evidence).

Rationale

Hemodialysis is the most efficient ECTR at eliminating gabapentinoids (Tables 2 and 3) and is the most likely used ECTR in maintenance dialysis patients. Hemodialysis is also less expensive and can be initiated more rapidly than other ECTRs.[142] For these reasons, the panel clearly preferred intermittent hemodialysis over all other ECTR modalities, if indicated. If ECTR should be administered and hemodialysis is unavailable, some members of the panel mentioned that intermittent hemofiltration, CKRT, sustained low efficiency dialysis (SLED)/prolonged intermittent renal replacement therapy (PIRRT), or even hemoperfusion could be considered with settings to optimize clearance. Peritoneal dialysis would not provide significant gabapentinoid clearance.

Research Gap

Studies of gabapentinoid poisoning in symptomatic patients treated with intermittent hemodiafiltration are lacking.

Cessation of ECTR

Recommendation 3.1

In patients severely poisoned with gabapentinoids requiring ECTR, ***we recommend*** stopping ECTR based on clinical improvement (strong recommendation, very low quality of evidence).

Rationale

The panel recommended that an improvement in consciousness allowing for extubation was an appropriate criterion to stop ECTR. Due to large interpatient variability, the panel did not support a fixed duration of ECTR, or reliance on serum gabapentinoid concentrations, even if available within a clinically meaningful time frame, to determine ECTR cessation. However, if there is no clinical improvement, gabapentinoid concentrations, if available, may support consideration of alternate diagnoses. Some panel members mentioned that a single treatment of 6 hours should improve neurological status; in the absence of clinical improvement, the benefit of continuing hemodialysis is unlikely and other etiologies should be considered.

Miscellaneous

If ECTR is performed, patients should be followed closely in an appropriately monitored setting for possible signs and symptoms of withdrawal. Withdrawal was identified as a knowledge gap for future research. Studies of gabapentinoid poisoning treated with ECTR should report incidence and severity of withdrawal symptoms.

Conclusion

Based on our systematic review and analysis, the EXTRIP workgroup suggests ECTR for gabapentinoid toxicity resulting in coma and mechanical ventilation in patients with decreased kidney function, but suggests *against* ECTR in patients with normal kidney function.

Supplementary Material

Supplementary File (PDF)

Item S1: Methods.

Item S2: Glossary.

Article Information

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