Recommendations from the EXTRIP workgroup on extracorporeal treatment for baclofen poisoning

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Baclofen toxicity results from intentional self-poisoning (acute baclofen poisoning) or accumulation of therapeutic dose in the setting of impaired kidney function. Standard care includes baclofen discontinuation, respiratory support and seizure treatment. Use of extracorporeal treatments (ECTRs) is controversial. To clarify this, a comprehensive review of the literature on the effect of ECTRs in baclofen toxicity was performed and recommendations following EXTRIP methods were formulated based on 43 studies (1 comparative cohort, 1 aggregate results cohort, 1 pharmacokinetic modeling, and 40 patient reports or series). Toxicokinetic data were available for 20 patients. Baclofen's dialyzability is limited by a high endogenous clearance and a short half-life in patients with normal kidney function. The workgroup assessed baclofen as "Moderately dialyzable" by intermittent hemodialysis for patients with normal kidney function (quality of evidence C) and "Dialyzable" for patients with impaired kidney function (quality of evidence C). Clinical data were available for 25 patients with acute baclofen poisoning and 46 patients with toxicity from therapeutic baclofen in kidney impairment. No deaths or sequelae were reported. Mortality in historical controls was rare. No benefit of ECTR was identified in patients with acute baclofen poisoning. Indirect evidence suggests a benefit of ECTR in reducing the duration of toxic encephalopathy from therapeutic baclofen in kidney impairment. These potential benefits were balanced against added costs and harms related to the insertion of a catheter, the procedure itself, and the potential of baclofen withdrawal. Thus, the EXTRIP workgroup suggests *against* performing ECTR in addition to standard care for acute baclofen poisoning and suggests performing ECTR in toxicity from therapeutic baclofen in kidney impairment, especially in the presence of coma requiring mechanical ventilation.

Kidney International (2021) **100,** 720–736; https://doi.org/10.1016/j.kint.2021.07.014

KEYWORDS: baclofen; hemodialysis; overdose; pharmacokinetics; poisoning; toxicity

Over recent decades, the use of baclofen for prescribed conditions and recreational use has increased, leading in both cases to a greater number of patients with toxicity.[1–6] In 2018, there were 5341 baclofen exposures reported to American poison centers, 2316 of which were single poison exposures, including 341 with a major outcome, and 2 fatalities.[1] Treatment consists of nonspecific supportive interventions, as there is no antidote. Debate is ongoing about the role of extracorporeal treatments (ECTRs) in baclofen toxicity cases, especially in patients with normal kidney function.[7–9]

The EXtracorporeal TReatments In Poisoning (EXTRIP) workgroup is composed of international experts representing diverse specialties and professional societies (Supplementary Table S1). Its mission is to provide recommendations on the use of ECTRs in poisoning (http://www.extrip-workgroup.org).[10,11] We present EXTRIP's comprehensive review and recommendations for the use of ECTR in patients with baclofen poisoning.

Clinical pharmacology and toxicokinetics

Baclofen acts primarily as a γ-aminobutyric acid $(GABA)_B$ receptor agonist. Baclofen was approved in Europe in 1975 and in the US in 1977 for treatment of conditions causing spasticity or rigidity. Baclofen is also increasingly prescribed off-label in alcohol use disorder. The pharmacokinetics of baclofen are summarized in Table 1.[12–43] It is rapidly absorbed from the gastrointestinal tract, is largely unbound to plasma proteins, and exhibits a small volume of distribution. In animal models, baclofen enters the central nervous system quickly after absorption but diffuses out of that compartment much more slowly.[21] Baclofen is partially deaminated to β-(*p*-chlorophenyl)-γ-hydroxybutyric acid, but is mostly filtered unchanged in urine[12] with some evidence of active tubular secretion.[13,14,44] The elimination half-life of baclofen is short, but as kidney function declines, the half-life is prolonged.[15,16] Baclofen exhibits interindividual variability in its pharmacokinetics, which are potentially influenced by dose and indication.[22,45] In overdose, the apparent half-life of baclofen is similar to that observed with therapeutic use.[29,30] However, there are reports of prolonged apparent elimination half-lives, suspected to reflect saturable absorption and/or biotransformation kinetics, or clinical conditions such as pharmacobezoar formation or ileus.[31–33,46–48]

Overview of toxicity

Although the clinical presentations often overlap, there are 2 major clinically recognized patterns of baclofen toxicity: (i) acute overdose from intentional self-harm, recreational use, or misuse (herein called "acute baclofen poisoning"); and (ii) unintentional accumulation of baclofen from therapeutic dosing in patients with acute or chronic kidney impairment (herein called "toxicity from therapeutic baclofen in kidney impairment"). The workgroup decided *a priori* not to evaluate a third clinical pattern of toxicity, poisoning from intrathecal baclofen (from pump malfunction, for example), because this was outside EXTRIP's stated scope of removing poison from the blood.

Acute baclofen poisoning

Mild symptoms of acute poisoning include lethargy, nausea, and headaches, which can progress to myoclonus and hypotonia. In more severe cases, autonomic instability (bradycardia, hypothermia), respiratory depression, seizures, and coma develop.[49–53] Following large ingestions, brainstem reflexes may be lost, thereby mimicking brain death.[54,55] Approximately one-third to one-half of patients described in historical cohorts require ventilatory support,[4,6,30,49,53,56,57] and up to one-quarter of patients develop aspiration pneumonia, likely from deep coma and loss of their gag reflex.[6,9,30,57,58] Fatalities from acute poisoning are exceedingly rare with access to ventilatory support.[4,42,49,51,52,59] Likewise, long-term sequelae are extremely uncommon.

A dose–response relationship for neurologic toxicity is described[2,4,50,53,57,59]; acute

Table 1 | Physicochemical properties and pharmacokinetics of baclofen

Characteristic	Result	References
Molecular weight, g/mol	213.7	
pKa	3.87	
Protein binding	30%–35% (unknown if changes in overdose and kidney impairment)	12,13
Time to peak concentration, h	1–4	12,14–20
Volume of distribution, l/kg[a]	Normal GFR: 0.8–1.0 (up to 2 in children) CKD and ESKD: 0.4–0.8	13,15,16,19,21–28
Oral bioavailability	60%–90%	17,21,24,29
Endogenous half-life, h[b]	Normal GFR: 3–6 Overdose (normal GFR): 3–10 Stage 2: 6–8 Stage 3: 9–12 Stages 4 and 5: 20–80	13–42
Endogenous clearance, ml/min[a,b]	Normal GFR: 150–250 Stage 2: 70–100 Stage 3: 50–70 Stage 4: 10–50	12,15,16,19,22,24–28
Renal clearance (normal GFR), ml/min	100–150	13,14,26
Serum therapeutic range (antispastic), mg/l	0.08–0.4	21,34,43

CKD, chronic kidney disease; CL/F, clearance after oral administration; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; V/F, volume of distribution after oral administration.
[a]Values adjusted for bioavailability (F) of 75% when given as V/F or CL/F.
[b]CKD stages are per Kidney Disease: Improving Global Outcomes (KDIGO) classification.

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Received 21 January 2021; revised 4 June 2021; accepted 8 July 2021; published online 4 August 2021

ingestions greater than 200–400 mg are associated with a greater likelihood of coma, seizures, intubation, or intensive care unit admission.[4,9,49–53,59,60] This dose–response relationship is unclear in patients on long-term baclofen therapy due to tolerance. For example, doses associated with coma in overdose are similar to those taken therapeutically in patients with alcohol use disorder.[61–63] However, these higher therapeutic doses are carefully titrated for tolerability and are not ingested acutely. A concentration–response relationship also seems to exist with the duration of mechanical ventilation.[4,30,42]

Toxicity from therapeutic baclofen in kidney impairment

Baclofen accumulates quickly in the body when kidney function is impaired, leading to toxicity.[15,16,64–66] There are reports of encephalopathy with single doses as little as 5 mg.[66–69] The relative risk of encephalopathy in baclofen-treated patients with chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] <60 ml/min per 1.73 m^2) and end-stage kidney disease, compared to a similar population who were not prescribed baclofen, is 10 and 78, respectively.[64,65] The 30-day risk of hospitalization of patients prescribed baclofen is inversely related to the eGFR—that is, 0.4% if the eGFR is 45–59 ml/min per 1.73 m^2, 1.1% if the eGFR is 30–44 ml/min per 1.73 m^2, 2.3% if the eGFR is <30 ml/min per 1.73 m^2, and 7.2% in patients receiving chronic hemodialysis.[64,65]

Patients with CKD can develop toxicity within 3 days of baclofen initiation.[64,66,70,71] Compared to patients with acute poisoning, these patients have more indolent symptoms, mainly consisting of a progressive debilitating encephalopathy. The incidences of seizures, bradycardia, hypotension, respiratory failure, and coma are lower, ranging between 5% and 20%.[66] As in acute poisoning, there are also dose–response and concentration–response relationships in this type of chronic poisoning, although with more variability.[16,66,71–74]

Management

Management of baclofen toxicity includes assuring the stability of the patient's airway and ventilation, with endotracheal intubation and mechanical ventilation, treatment of hypotension with fluids or vasopressors, discontinuation of baclofen, and administration of $GABA_A$ receptor agonists (e.g., benzodiazepines, propofol, barbiturates) for seizures. Gastrointestinal decontamination is reasonable in patients with suspected residual baclofen in the gastrointestinal tract.[75,76]

Withdrawal

Baclofen withdrawal occurs after abrupt discontinuation of baclofen therapy in patients who have developed tolerance to baclofen during maintenance therapy. Symptoms of withdrawal can be confused with those of baclofen poisoning and include muscle spasm, progression to seizures, and occasionally death.[24,77,78] There are no clear data on the minimum duration of baclofen therapy required before sudden cessation produces clinical withdrawal: this period is reported as being as short as 2 weeks in animals,[79] although it is considered unusual in humans if the duration of baclofen use is less than 1 month.[78,80,81] Treatment includes reintroduction of baclofen and adjunctive therapy such as $GABA_A$ receptor agonists.

METHODS

The workgroup reviewed the literature and developed recommendations on the use of ECTR following the EXTRIP methodology previously published,[11] with modifications, updates, and clarifications. The methodology is presented in the Supplementary Methods.

RESULTS

Results of the literature search (first performed on March 1, 2019, and last updated October 23, 2020) are presented in Figure 1.[5,29,33,47,48,66,68,70–74,82–103]

Summary of evidence

Dialyzability. Baclofen possesses many physicochemical and toxicokinetic properties that suggest it would be amenable to extracorporeal elimination (Table 1). These theoretical considerations are confirmed in toxicokinetic publications of baclofen-poisoned patients undergoing ECTR. Unfortunately, no pharmacokinetic data were found in dialysis-dependent patients receiving therapeutic baclofen dosing. Toxicokinetic data were available for 20 patients. As shown in Table 2,[12–20,22–42,44,71–74,90,94,97,98,104] the half-life of baclofen in patients with normal kidney function is reduced by the use of ECTR, although this finding did not reach statistical significance in one cohort study that compared 6 patients receiving intermittent hemodialysis (median, 3.1 hours [range, 2.2–4.8 hours]) to 19 patients who did not (median, 3.4 hours

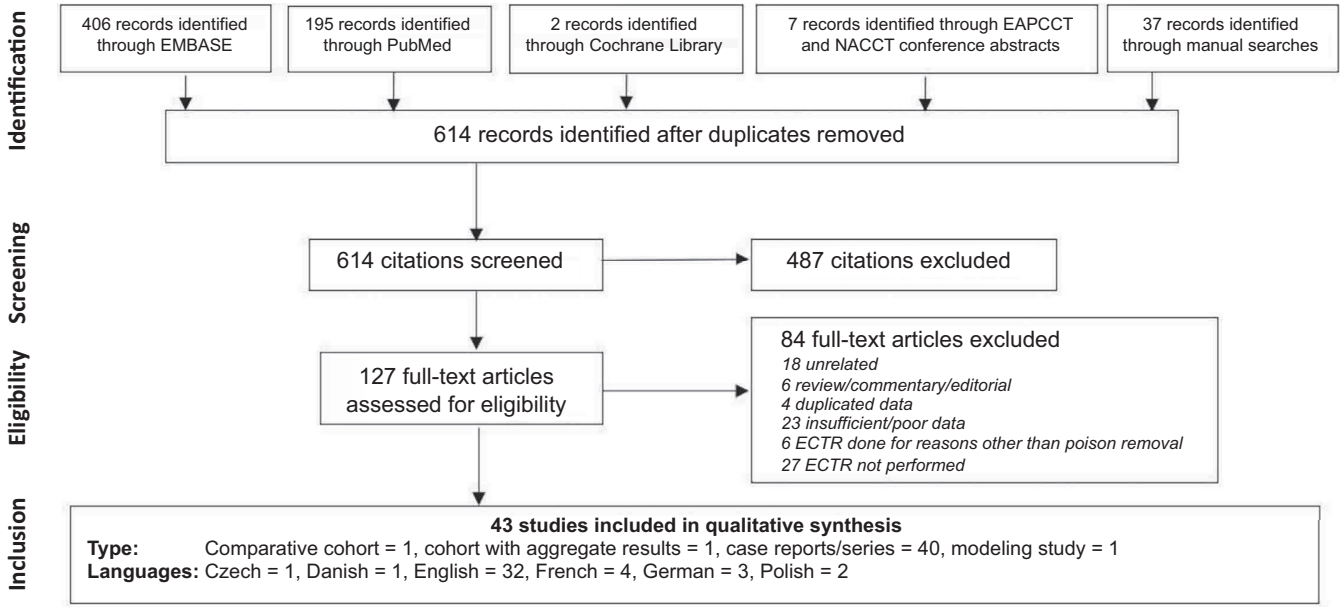

Figure 1 | Study selection flow diagram. A total of 614 articles were identified after the removal of duplicates. In the final analysis, 43 studies were included for qualitative analysis, including 1 cohort study with aggregate data,[66] 1 comparative cohort study,[29] 40 case reports or case series,[5,47,68,70–74,82–102] and 1 pharmacokinetic modeling publication[48] based on a case report published elsewhere.[33,103] A total of 23 articles were excluded because of lack of precision regarding extracorporeal treatment (ECTR) and/or outcomes. EAPCCT, European Association of Poison Centres and Clinical Toxicologists; NACCT, North American Congress of Clinical Toxicology.

[range, 1.4–5.5 hours], $P = 0.53$).[29] However, ECTR can enhance the clearance of baclofen and reduce its half-life dramatically in patients with impaired kidney function, especially those with an eGFR of <30 ml/min. This effect can be illustrated graphically with assumptions (Figure 2[15,16,41,44]): Intermittent hemodialysis would contribute 88% to the total baclofen clearance in a patient with stage 4 CKD compared to only 38% in a patient with normal kidney function. The contribution of continuous kidney replacement therapy to endogenous clearance would be less than that of hemodialysis. The effect of peritoneal dialysis would be insignificant regardless of underlying kidney function (33% in stage 4 CKD and 4% in normal kidney function). The toxicokinetic data and the above example contradict the result of one report, presented in abstract form only, that utilized pharmacokinetic modeling to describe the concentration-time profile of a single case.[48] The authors concluded that intermittent hemodialysis would contribute only 1% of total body clearance when activated charcoal is used, or 5% of total clearance in a baclofen-poisoned patient with normal kidney function. However, gastrointestinal absorption appeared to be ongoing for at least 8 days in the original report,[33,48,103] which is a very atypical result, compared to other published data.

Baclofen removal was quantified in 3 cases: charcoal hemoperfusion removed 29.2 mg (total body content ≈ 61–76 mg) in 6 hours[104]; intermittent hemodialysis removed 13.5 mg (total body content ≈ 36–45 mg) in 4 hours in 1 study,[90] and 3.1 mg in 3 hours (ingestion = 1200 mg) in another.[44] In this latter publication, intermittent hemodialysis was performed more than 24 hours after

Table 2 | Toxicokinetic summary of baclofen-poisoned patients undergoing ECTRs

	Toxicokinetics						
	$T_{1/2}$ during ECTR, h			ECTR clearance, ml/min			
Clearance modality	Median	Number of patients	Range	Median	Number of patients	Range	References
Endogenous		4–6 (therapeutic) 3–10 (overdose) 6–80 (kidney impairment)			150–250 (normal kidney function) 20–100 (kidney impairment)		12–20,22–42,90,97
CKRT	4.2	2	3.6–4.8	40[a]	1		39,41
IHD	3.1	17	1.4–6.9	150[a]	2	128–171	29,32,33,44,71–74,90,94,97,98,
Charcoal HP	2.2	1		73[a]	1		104

CKRT, continuous kidney replacement therapy; ECTR, extracorporeal treatment; HP, hemoperfusion; IHD, intermittent hemodialysis.
[a]Extracorporeal clearance.

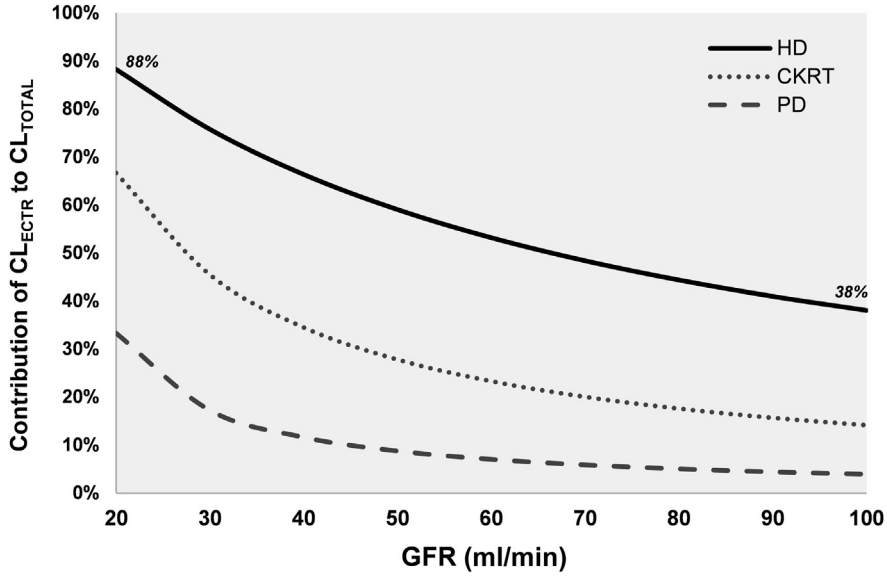

Figure 2 | Impact of extracorporeal baclofen clearance (CL_{ECTR}) on total clearance of baclofen (hemodialysis + endogenous; CL_{TOTAL}), relative to kidney function. Assumptions: (i) endogenous baclofen clearance = 250 ml/min in patients with normal glomerular filtration rate (GFR); (ii) endogenous baclofen clearance = 20 ml/min in patients with stage 4 chronic kidney disease[15,16]; (iii) CL_{ECTR} = 150 ml/min by intermittent hemodialysis[44]; (iv) CL_{ECTR} = 40 ml/min by continuous kidney replacement therapy (CKRT)[41]; and (v) CL_{ECTR} = 10 ml/min by peritoneal dialysis (based on achievable solute clearance). HD, hemodialysis; PD, peritoneal dialysis.

ingestion, when the body burden of baclofen had already decreased considerably, thereby reducing the apparent effect of hemodialysis.

Intermittent hemodialysis is more efficient than continuous kidney replacement therapy at removing baclofen, due to its higher blood and effluent flow.[105,106] Charcoal hemoperfusion offers no advantage over intermittent hemodialysis, because of baclofen's low level of protein binding and because of rapid saturation of charcoal cartridges.[104] No toxicokinetic data were available for peritoneal dialysis, exchange transfusion, liver support devices, or therapeutic plasma exchange, but baclofen clearance is anticipated to be significantly lower with these techniques, compared to that achieved with intermittent hemodialysis, given the well-described differences in operational parameters.[105]

Kidney function impacts the grading of dialyzability because the contribution of extracorporeal clearance to total clearance increases as kidney function declines (Figure 2). For this reason, baclofen is considered "moderately dialyzable" by intermittent hemodialysis in patients with normal kidney function versus "dialyzable" for patients with impaired kidney function (Supplementary Table S7). The panel acknowledged the low number of supporting publications and assessed the level of evidence for dialyzability as "low" or "very low" for all studied ECTRs.

Rebound was assessed in only a minority of publications. It was absent in 3 publications and present in 3 others.[33,44,97] In 1 case, there was a massive rebound after ECTR.[33,103] Based on a red blood cell/plasma baclofen concentration ratio ≈1 in overdose patients not receiving hemodialysis, and a relatively small volume of distribution, the authors assessed that this rebound was more likely caused by ongoing absorption than redistribution.[48] These arguments do not exclude a contribution of redistribution. For example, it is presumed that the red blood cell/plasma baclofen concentration ratio would exceed 1 immediately after hemodialysis, which may promote baclofen redistribution to the plasma.

Clinical data. The available evidence of a clinical effect for ECTR in baclofen toxicity consists of 1 comparative cohort study of acute baclofen poisoning (6 cases treated with ECTR and 19 controls), 1 cohort study with aggregate results (28 patients with toxicity from therapeutic baclofen in kidney impairment, 54% of whom were treated with ECTR), and 40 case reports (65 cases described, 19 with acute poisoning, 46 with toxicity from therapeutic baclofen in kidney impairment). Among case reports and case series, the panel acknowledged variability in the methodological quality and a considerable lack of reporting of critical information.[107] The demographics, clinical findings,

Table 3 | Summary of clinical findings of patients receiving ECTR for baclofen removal

		Acute baclofen poisoning, $n = 25$[a]	Toxicity from therapeutic baclofen in kidney impairment, $n = 46$
Patient characteristics	Age, yr	31 [25, 42]	61 [49, 70]
	Female	42	35
	ESKD	0	72
Poisoning info	Self-poisoning (%) and suspected dose, mg	100, 1000 [510, 1485]	0
	Patients on prior maintenance therapy (%), length of exposure, d	78, 1175 [660, 1690]	100, 2 [1.3, 4]
	Co-ingestants	76	NA
	Peak baclofen concentration, μg/l	2304 [1665, 5400]	620 [495, 1025]
	Time between ingestion and admission, h	4.8 [2, 8]	NA
Signs/symptoms	Coma	100	36.4
	Altered consciousness	100	100
	Bradycardia	71	3
	Seizures	53	8
	Hypotension	33	10
	Acute kidney injury	0	9
	Respiratory failure	96	27
Other treatments	Gastric lavage	79	0
	Activated charcoal	50	0
	Vasopressors/inotropes	22	2
	Mechanical ventilation	95	13
	Benzodiazepines/propofol	69	3
ECTR	Time from ingestion to ECTR, h	14.5 [7.8, 22]	NA
	Intermittent hemodialysis (%), median number of sessions	64, 1	88, 2
	Continuous kidney replacement therapy	24	2
	Peritoneal dialysis	0	10
	Hemodialysis–hemoperfusion in series	8	0
	Charcoal hemoperfusion	4	0
Outcome	Survival	100[b]	100
	Mechanical ventilation time, h	48 [33, 72]	72 [48, 96]
	Hospital length of stay, d	12 [6.5, 17]	3 [2, 4.5]
	Intensive care unit length of stay, d	4 [1.5, 5]	4 [2.2, 5]
	Mechanical ventilation time after ECTR completed, h	15 [10, 24]	No data

ECTR, extracorporeal treatment; ESKD, end-stage kidney disease; NA, not applicable.
[a]Includes data from the comparative cohort study.[29]
[b]One patient expired from unrelated causes prior to discharge.
Values are %, or medians and quartiles, unless otherwise indicated.

management, and outcomes of cases receiving ECTR are listed in Table 3.[29] No deaths or permanent sequelae were reported.

Acute baclofen poisoning

One cohort of patients with acute baclofen poisoning compared the effect of ECTR and standard care to that of standard care alone in populations with normal kidney function from the same poison care center.[29] There was no difference in the median duration of mechanical ventilation in 6 patients receiving intermittent hemodialysis (72 hours [interquartile range, 48–72 hours]) compared to 19 patients not receiving hemodialysis (72 hours [interquartile range, 24–96 hours]; $P = 0.38$). This comparative cohort study was judged to be at high risk of bias, that is, unadjusted for confounders (high incidence of coingestants) and the presence of confounding-by-indication (higher initial baclofen concentration in the ECTR group). The analysis is also likely underpowered due to the small sample size.

Approximately three-quarters of included patients from case reports were on maintenance baclofen therapy prior to acute poisoning (Table 3). One hemodialysis session was usually enough to attain expected clinical endpoints (extubation or recovery from coma). Although rapid clinical improvement in the level of consciousness was noted in most cases, a minimal effect was reported in others,[89,108,109] likely due to the impact of coingestants or slower removal techniques. In one case, there was a recurrence of coma after ECTR, coinciding with a rebound of the baclofen concentration.[33,103] In another report, the resolution of encephalopathy occurred only after the baclofen concentration became undetectable, which suggests either an alternative diagnosis, withdrawal, or a persistent central nervous system baclofen burden.[41] Agitation and psychosis were described in 6 patients following ECTR,[108–110] lasting up to several days. Although suggestive of baclofen withdrawal, this clinical assessment may be clouded

Table 4 | ECTRs plus standard care, compared with standard care alone, in patients severely poisoned with baclofen (evidence profile table)

Type of baclofen toxicity	Quality assessment						Summary of findings				
	Study design and no. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECTR + standard care	Standard care (controls)	Effect	Quality	Importance
Mortality											
Acute poisoning[a]	Observational studies ($n = 6$)[b]	Very serious[c]	Not serious	Serious[d]	Serious[e]	Publication bias strongly suspected[f]	0 of 20 = **0%**	**Overall, 0 of 100 = 0%**[g] 0 of 13[49] 0 of 28[52] 0 of 18[51] 0 of 27[59] 0 of 14[42]	**Comparable mortality** between the 2 groups (risk difference = 0 per 1000 patients)	⊕◯◯◯ VERY LOW	CRITICAL
TTBKI	Observational studies ($n = 12$)[h]	Very serious[c]	Not serious	Serious[d]	Serious[e]	Publication bias strongly suspected[f]	0 of 39 = **0%**	**Overall, 0 of 11 = 0%**[70,72,111–119]	**Comparable mortality** between the 2 groups (risk difference = 0 per 1000 patients)	⊕◯◯◯ VERY LOW	CRITICAL
Duration of mechanical ventilation											
Acute poisoning	Observational studies ($n = 1$)[i]	Serious[j]	Not serious	Not serious	Serious[k]	Not serious	Median, **72 h [48, 72 h];** 6 pts[29]	Median, **72 h [24, 96 h];** 19 pts[29]	**Comparable duration of mechanical ventilation** between the 2 groups	⊕◯◯◯ VERY LOW	CRITICAL
	Observational studies ($n = 6$)[b]	Very serious[c]	Not serious	Serious[d]	Serious[l]	Publication bias strongly suspected[f]	Median, **48 h [33, 72 h];** 23 pts	Median, **[32, 72 h];** 32 pts[29,49,h] Mean, **42.7 h;** 59 pts[42,51,59]	No formal statistical comparison possible due to reporting of aggregate data with various summary statistics but reported median **duration of mechanical ventilation seems comparable** in the 2 groups		
TTBKI	Observational studies ($n = 1$)[m]						Median, **72 h;** 5 pts	No data (no patient required intubation)	No comparison possible due to lack of data in control group	⊕◯◯◯ VERY LOW	CRITICAL
Length of hospital stay											
Acute poisoning	Observational studies ($n = 4$)[n]	Very serious[c]	Not serious	Serious[d]	Serious[l]	Publication bias strongly suspected[f]	Median, **12.0 d [6.5, 17.0 d];** 11 pts	Median, **[1.8, 12.0 d];** 41 pts[49,52] Mean, **4.9 d;** 57 pts[6,59]	No formal statistical comparison possible due to reporting of aggregate data with various summary statistics	⊕◯◯◯ VERY LOW	IMPORTANT

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Table 4 | (Continued) **ECTRs plus standard care, compared with standard care alone, in patients severely poisoned with baclofen (evidence profile table)**

Type of baclofen toxicity	Quality assessment						Summary of findings				
	Study design and no. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECTR + standard care	Standard care (controls)	Effect	Quality	Importance
TTBKI	Observational studies ($n = 5$)[o]	Very serious[c]	Not serious	Serious[d]	Serious[k]	Publication bias strongly suspected[f]	Median, **3.0 d [2, 4.5 d];** 19 pts	Median, **8.0 d [6.7, 11.3 d]**; 4 pts[111,112,115,119]	**Trend toward a shorter duration of length of hospital stay of 5 days** in the ECTR group as compared to controls, but not statistically significant	⊕◯◯◯ VERY LOW	IMPORTANT
Length of ICU stay											
Acute poisoning	Observational studies ($n = 3$)[p]	Very serious[c]	Not serious	Serious[d]	Serious[l]	Publication bias strongly suspected[f]	Median, **4.0 d [1.6, 5.0 d];** 5 pts	Median, **[4.0, 5.4 d];** 95 pts[4,57,q]	No formal statistical comparison possible due to reporting of aggregate data, but medians **of length of ICU stay seem comparable** in the 2 groups	⊕◯◯◯ VERY LOW	IMPORTANT
TTBKI	Observational studies ($n = 1$)[m]						Median, **4.0 d [2.0, 4.5 d];** 19 pts	No data	No comparison possible due to lack of data in control group		IMPORTANT
Duration of mental status alteration											
TTBKI	Observational studies ($n = 9$)[r]	Very serious[c]	Not serious	Serious[d]	Serious[k]	Publication bias strongly suspected[f]	Median, **2.0 d [1.5, 3.0 d];** 43 pts	Median, **3.0 d [2.8, 3.3 d];** 8 pts[70,72,111–113,115,116,119]	**Trend toward a shorter duration of mental status alteration of 1 day** in the ECTR group vs. controls, but not statistically significant	⊕◯◯◯ VERY LOW	IMPORTANT
Development of baclofen withdrawal[s]											
Acute poisoning	Observational studies ($n = 1$)[m]					Publication bias strongly suspected[f]	1–6 of 13 = **8%–46%** in pts on long-term baclofen therapy	No data	No comparison possible due to lack of data in control group		CRITICAL
TTBKI	Observational studies ($n = 2$)[t]	Very serious[c]	Not serious	Serious[d]	Serious[e]	Publication bias strongly suspected[f]	1 of 4 = **25%** in pts on long-term baclofen therapy	1 of 5 = **20%** in patients on long-term baclofen therapy[111]	**Comparable incidence of baclofen withdrawal** in both groups	⊕◯◯◯ VERY LOW	CRITICAL

(*Continued on following page*)

Table 4 | (Continued) **ECTRs plus standard care, compared with standard care alone, in patients severely poisoned with baclofen (evidence profile table)**

Type of baclofen toxicity	Quality assessment						Summary of findings				
	Study design and no. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECTR + standard care	Standard care (controls)	Effect	Quality	Importance
Serious complications of catheter insertion[u]											
NA	Observational studies ($n = 5$)[v]	Not serious	Not serious[w]	Not serious[x]	Not serious[y]	Strong association[z]	Rate of serious complications of catheter insertion varies from **0.1% to 2.1%**	≈ 0	Absolute effect is estimated to be varying from **1 to 21 more serious complications per 1000 patients** in the ECTR group	⊕⊕⊕○ MODERATE	CRITICAL
Serious complications of ECTR[aa]											
NA	Observational studies ($n = 6$)[bb]	Not serious	Not serious	Not serious	Not serious	Strong association[cc]	Rate of serious complications of ECTR varies according to the type of ECTR performed from **0.005%** (IHD and CKRT), and up to **1.9%** (HP)	≈ 0	Absolute effect is estimated to vary from **>0 to 19 more serious complications per 1000 patients** in the ECTR group depending on the type of ECTR performed	⊕⊕⊕○ MODERATE	CRITICAL

CI, confidence interval; CKRT, continuous kidney replacement therapy; ECTR, extracorporeal treatment; ICU, intensive care unit; IHD, intermittent hemodialysis; HP, charcoal hemoperfusion; NA, not applicable; pts, patients; TTBKI, toxicity from therapeutic baclofen in kidney impairment.

[a]Only control cohorts with populations resembling those receiving ECTR were included.[42,49,51,52,59] Cohorts with ECTR-treated patients,[4,9,50] with nonacute poisonings,[30] and with few patients requiring intubation[2,3,53,56,57,60] were excluded because they did not represent adequate controls.

[b]Includes our comprehensive review of the literature on ECTR, and 5 case series/cohorts on standard care alone.

[c]Case reports published on effect of ECTR. Uncontrolled and unadjusted for confounders such as severity of poisoning, co-ingestions, supportive and standard care, and co-interventions. Confounding-by-indication is inevitable as ECTR was usually attempted when other therapies failed.

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

[e]Few events in a small sample size; optimal information size criteria not met. The 95% CI includes the potential for both appreciable benefit and appreciable harm (i.e., cross the null value).

[f]Publication bias is strongly suspected due to the study design (case reports published in toxicology report very severe poisoning with/without impressive recovery with treatments attempted).

[g]One large cohort with 111 patients was excluded because it contained 12 patients who received dialysis, possibly skewing data.

[h]Includes our comprehensive review of the literature on ECTR and 11 case reports on standard care alone.

[i]Includes 1 cohort study directly comparing ECTR to standard care.[29]

[j]Uncontrolled and unadjusted for confounders such as severity of poisoning, co-ingestions, supportive and standard care, and co-interventions. Confounding-by-indication is inevitable since ECTR was usually attempted when other therapies failed.

[k]Small sample size; optimal information size criteria not met. The 95% CI includes the potential for both appreciable benefit and appreciable harm (i.e., cross the null value).

[l]Small sample size; optimal information size criteria not met.

[m]Includes our comprehensive review of the literature on ECTR.

[n]Includes our comprehensive review of the literature on ECTR and 3 cohorts on standard care alone.

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

[p]Includes our comprehensive review of the literature on ECTR and 2 cohorts on standard care alone.

[q]These cohorts are not considered to be reliable controls as they included some patients treated with ECTR,[4] or a cohort with fewer patients needed mechanical ventilation[57] but they were included because these were the best data available.

[r]Includes our comprehensive review of the literature on ECTR and 8 case reports on standard care alone

[s]Withdrawal is rarely confirmed and may be misdiagnosed for alcohol withdrawal or other causes of delirium.

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

[u]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 to be not serious and, therefore, were excluded from this composite outcome. Deep vein thrombosis and infection complications were not included, considering the short duration of catheter use.

by the possibility of concomitant ethanol withdrawal or other causes of delirium.

The evidence table (Table 4[2–4,6,9,29,30,42,49,50–53,56,57,59,60,70,72,111–128]) presents the cases of patients with acute baclofen poisoning treated with ECTR from our comprehensive review, compared to historical controls deemed closest in terms of severity, as well as cases from the aforementioned comparative cohort study.[29] Although the importance of the evidence supporting the comparison of interest is very unclear, no benefit could be observed with regard to mortality, duration of mechanical ventilation, or intensive care unit length of stay.

Toxicity from therapeutic baclofen in kidney impairment

As expected, these patients had fewer features of severity, compared with patients with acute poisoning—that is, lower incidence of coma, respiratory failure, and seizures (Table 3). Most articles reported improvement during or soon after ECTR,[47,73,84,92,100] although more than one session was usually required before a full recovery was achieved, in contrast to results for patients with acute baclofen poisoning.

Historical controls receiving only standard care without ECTR are rarely reported in the literature, as end-stage kidney disease patients (those most at risk for baclofen toxicity) already receive chronic dialysis for treatment of uremia. One cohort study described 28 patients with varying levels of kidney impairment, 54% of whom received intermittent hemodialysis[66]; unfortunately, no data were presented comparing outcomes of patients who did not receive ECTR to those who did. Eleven patients with CKD or acute kidney injury who did not get ECTR were reported.[70,72,111–119] Compared to cases receiving ECTR, patients who did not receive ECTR tended to have an apparent longer median duration of altered consciousness and median length of hospital stay (Table 4). The magnitude of this difference would likely have been greater had there been controls with end-stage kidney disease. Signs and symptoms compatible with baclofen withdrawal occurred in 1 patient.[82]

Complications

Four patients developed hypotension and/or bradycardia during hemodialysis, although whether this was caused by the toxic effects of baclofen or the ECTR itself is difficult to ascertain.[39,108,109] One patient developed epistaxis during hemodialysis, requiring nasal tamponade.[108]

[v]Based on 5 single-arm observational studies: 2 meta-analyses comparing serious mechanical complications associated with catheterization using or not using an ultrasound, which included 6 randomized controlled trials in subclavian veins[120] and 11 in internal jugular veins[121]; 2 randomized controlled trials comparing major mechanical complications of different sites of catheterization[122,123]; and 1 large multicenter cohort study reporting all mechanical complications associated with catheterization.[124] Rare events were reported from case series and case reports.
[w]Not given a lower rating 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.
[x]Not given a lower rating for indirectness, because cannulation and catheter insertion were judged to be similar to the procedure for other indications.
[y]Not given a lower rating for imprecision, because the wide range reported is explained by inconsistency.
[z]The events in the control group are assumed to be zero (as no catheter is installed for ECTR); 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% CIs, which included the null value, and all observed complications occurred within a very short timeframe (i.e., a few hours).
[aa]For IHD and CKRT, serious complications (air emboli, shock, and death) are exceedingly rare, especially if there is no net ultrafiltration. Minor bleeding from heparin, transient hypotension, and electrolyte imbalance were judged to be not serious. For HP, serious complications include severe thrombocytopenia, major bleeding, and hemolysis. Transient hypotension, hypoglycemia, hypocalcemia, and thrombocytopenia were judged to be not serious. All nonserious complications were excluded from this composite outcome.
[bb]IHD/CKRT: based on 2 single-arm studies describing severe adverse events per 1000 treatments in large cohorts of patients.[125,126] HP: based on 2 small single-arm studies in poisoned patients.[127,128] Rare events were reported in case series and case reports.
[cc]Assuming that patients in the control group would not receive any form of ECTR, the events in the control group would be zero; 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% CIs, which included the null value, and all observed complications occurred within a very short timeframe (i.e., a few hours).
Data representing results of interest are bold for emphasis. Data are presented as medians and quartiles, unless otherwise indicated.

Summary of results

Direct and indirect evidence does not suggest a benefit for ECTR in patients with acute baclofen poisoning. In patients with toxicity from therapeutic baclofen in kidney impairment, although the comparators consist of a low number of case reports, there appears to be an indirect benefit from ECTR with regard to duration of altered consciousness and length of stay, which is supported by the toxicokinetic evidence. The quality of the evidence for all reported patient-important outcomes assessing the potential benefits of ECTR in addition to standard care was graded as "very low."

RECOMMENDATIONS

1. General statement

- In severe acute baclofen poisoning, ***we suggest against performing*** ECTR in addition to providing standard care, but rather support providing standard care alone (weak recommendation, very low quality of evidence).
- In severe toxicity from therapeutic baclofen in kidney impairment, ***we suggest performing*** ECTR in addition to providing standard care, rather than providing standard care alone (weak recommendation, very low quality of evidence).

2. Indications

In patients presenting with toxicity from therapeutic baclofen in kidney impairment, ***we suggest performing*** ECTR in the presence of an associated coma requiring mechanical ventilation (weak recommendation, very low quality of evidence).

3. Type of ECTR

In patients requiring ECTR, ***we recommend performing*** intermittent hemodialysis, rather than any other type of ECTR (strong recommendation, very low quality of evidence).

4. Cessation of ECTR

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

1. General statement

- In severe acute baclofen poisoning, ***we suggest against performing*** ECTR in addition to providing standard care, but rather support providing standard care alone (weak recommendation, very low quality of evidence).

Rationale. Acute baclofen poisoning results in severe symptoms, including seizures, autonomic dysfunction, profound coma, and even absent brainstem reflexes. However, the panel suggested against performing ECTR in addition to providing standard care (result of votes: median, 3.0; upper quartile, 5.0; disagreement index, 0.75), despite dialyzability of baclofen, for several reasons. First, mortality and other serious long-term sequelae are exceedingly rare in patients with baclofen mono-ingestions who are receiving appropriate standard care. ECTR would, therefore, not likely affect those outcomes positively. Second, acute baclofen poisoning is expected to be of limited duration, owing to its short elimination half-life, even if rare cases of prolonged poisoning due to ongoing absorption are reported.[33,103] Third, there is no direct or indirect evidence that ECTR shortens duration of mechanical ventilation, although it is possible that this lack of difference is due to heterogeneous extubation algorithms in various intensive-care units (e.g., patients extubated mostly in the morning) or to the delay from ingestion to ECTR. Fourth, given that baclofen is rapidly absorbed, it is unlikely that ECTR could ever be performed quickly enough to prevent intubation in a patient who is not yet symptomatic. Fifth, serious risks of ECTR and catheter insertion are rare but not nil. Finally, there are realistic concerns that ECTR may precipitate withdrawal in those patients who overdose after being on long-term baclofen therapy (this occurred in the majority of cases reported; Table 3), the likelihood of which is unknown and probably varies on a case-by-case basis. Baclofen withdrawal may be particularly challenging to manage[60] and may require extended mechanical ventilation for proper sedation, thereby negating the benefits of ECTR.

Some panel members noted that there may be mitigating factors for considering ECTR in acute baclofen poisoning, such as preexisting lung disease, extremes of age, massive overdose, absent brainstem reflexes, refractory seizures, and the patient being baclofen-naive (who is unlikely to experience withdrawal). In a patient presenting with acute poisoning and concomitant kidney impairment, the benefits of ECTR are expected to largely outweigh the risks. If the overdose was massive and the duration of mechanical ventilation is expected to exceed several days, there would also be increased support for ECTR. The panel also mentioned

that if symptoms suggestive of baclofen overdose persist over 3–4 days in a patient with normal kidney function (assuming no baclofen assay is available), then an alternate diagnosis should be sought, and ECTR is unlikely to be of benefit.

Research gap. More data are needed on the toxicokinetics of baclofen overdose in patients with normal kidney function. The cost–benefit ratio of ECTR in special populations presenting with acute poisoning (baclofen-naive, extremes of age, modest kidney impairment, massive overdose) remains unclear. Study designs evaluating the clinical benefit of ECTR in acute baclofen poisoning should include outcomes such as the incidence of withdrawal and the duration of mechanical ventilation, with extubation performed when it is clinically indicated rather than per institutional practice.

- In severe toxicity from therapeutic baclofen in kidney impairment, ***we suggest performing*** ECTR in addition to providing standard care, rather than providing standard care alone (weak recommendation, very low quality of evidence).

Rationale. The half-life of baclofen in patients with impaired kidney function (especially those with stage 4 or 5 CKD or with severe acute kidney injury) is several-fold greater than that in patients with normal kidney function. Although toxicity from acute baclofen poisoning is more severe, symptoms from therapeutic baclofen in kidney impairment are debilitating and last longer. Further, of the cases identified in this comprehensive review (Table 3), the likelihood of baclofen withdrawal is reduced in these patients because the duration of baclofen exposure is short before toxic symptoms are noted,[64,66,70,71] except in patients with long-term baclofen therapy who develop acute kidney injury. Patients who already have a functional vascular access for chronic dialysis have no added risk of adverse effects from catheter insertion. Pharmacokinetic data (drastic reduction in baclofen half-life with ECTR), and indirect clinical data suggesting a benefit in patient-important outcomes (Table 4), both support this suggestion. This recommendation was considered conditional, as the panel recognized that ECTR would not reduce overall mortality, but instead would reduce the duration of encephalopathy and its associated morbidity (result of votes: median, 7.0; lower quartile, 6.0; disagreement index, 0.22).

Research gap. Comparative studies of baclofen toxicity in patients with moderate kidney impairment (non–end-stage kidney disease) in which ECTR is compared to standard care are lacking. Baclofen toxicokinetics and concentration–response relationships of patients with severe kidney impairment are also lacking.

2. Indications

In patients with toxicity from therapeutic baclofen in kidney impairment, ***we suggest performing*** ECTR in the presence of a coma requiring mechanical ventilation (weak recommendation, very low quality of evidence).

Rationale. A requirement of mechanical ventilation was considered to be the most important indication for ECTR to shorten time on a ventilator and reduce its related risks. Symptoms such as seizures and autonomic instability alone would be considered unlikely without a coma. In patients on chronic hemodialysis and presenting with milder symptoms (confusion, encephalopathy), a scheduled dialysis session could be moved ahead in time and repeated daily until satisfactory improvement is achieved. The majority of the panel also expressed their support for ECTR in addition to standard care in patients with kidney impairment (but without a preexisting vascular access) if altered consciousness was present without a coma, with the objective of reducing both length of stay and nosocomial complications.

Only 4 of the 38 members had access to baclofen assays in their clinical settings, although never within 6 hours of admission. The panel assessed that serum baclofen concentration, even if available in a short turnaround time, is not a reliable criterion for ECTR initiation. Although there is evidence of a concentration–response relationship, this applies more specifically to patients with acute poisoning, especially in those who are baclofen-naive. Patients on long-term baclofen therapy (as noted in most of the published cases of acute poisoning; Table 3) may have considerable tolerance and exhibit few symptoms at a concentration that would cause coma in naive patients. Further, patients with kidney impairment may have toxic symptoms at modest baclofen concentrations. It is unlikely that a patient with an extremely high baclofen concentration would be asymptomatic, and, therefore, the panel preferred clinical indicators for ECTR, rather than any numerical baclofen concentration. However, baclofen assays can support or refute a diagnosis of baclofen overdose.

3. Type of ECTR

In patients requiring ECTR, ***we recommend performing*** intermittent hemodialysis rather than any other type of ECTR (strong recommendation, very low quality of evidence).

Rationale. Intermittent hemodialysis is the most efficient ECTR at eliminating baclofen (Table 2 and Supplementary Table S7) and is the ECTR most likely to be used in dialysis-dependent patients. Intermittent hemodialysis is also less costly, most available, and quickest to institute compared to other ECTRs.[129] For these reasons, the panel overwhelmingly preferred intermittent hemodialysis over all other ECTRs, when ECTR is indicated. In the uncommon instance in which ECTR is indicated and intermittent hemodialysis is unavailable, continuous kidney replacement therapy (with settings to optimize clearance), intermittent hemofiltration, sustained low-efficiency dialysis (SLED), prolonged intermittent renal replacement therapy (PIRRT), or even charcoal hemoperfusion, can be considered. Some authors have proposed that peritoneal dialysis would be as efficient as intermittent hemodialysis to reduce the length of altered consciousness.[88] However, an underpowered subanalysis of our comprehensive review suggests that the median duration of encephalopathy was shorter in patients receiving hemodialysis (2 days) compared to those receiving peritoneal dialysis (3 days). The panel also considered it questionable that peritoneal dialysis would provide comparable efficacy, considering the respective solute clearances offered by these procedures.

4. Cessation of ECTR

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

Rationale. The EXTRIP panel recommended clinical parameters for termination of ECTR, specifically improvement of a coma, permitting extubation. As soon as this is accomplished, there is little justification to pursue ECTR. If ECTR is initiated for a patient with kidney impairment and marked encephalopathy (but not needing mechanical ventilation), more than 1 ECTR session may be needed before clinical normalization, as baclofen exits the central nervous system slowly. If no improvement is noted, again, alternative diagnoses should be considered, including withdrawal. The panel did not support the use of a fixed duration or a target baclofen concentration for cessation; a 6-hour session, for example, will allow decrease of the baclofen concentration by 75% (assuming a $T_{1/2} = 3$ hours), but this may not be long enough if the initial baclofen concentration is extremely high or there is ongoing absorption. A "safe" concentration is difficult to interpret in the setting of tolerance. The use of baclofen assays, if available quickly, may inform the decision as to when ECTR is no longer useful and lessen the risk of withdrawal.

5. Miscellaneous

The panel judged that it is important, if ECTR is performed, that the patient be admitted and followed closely in an appropriately monitored setting for possible signs of withdrawal, especially in patients on long-term maintenance therapy. There may be some rationale for restarting baclofen soon after ECTR in patients who are free of symptoms but are otherwise at high risk of developing withdrawal and who have no kidney impairment.

CONCLUSION

This article presents the EXTRIP workgroup's comprehensive review and recommendations of ECTR for baclofen poisoning. On the basis of our comprehensive review and analysis, the EXTRIP workgroup ***suggests against performing*** ECTR in addition to standard care, but rather supports standard care alone, in acute baclofen poisoning and ***suggests performing*** ECTR in cases of toxicity from therapeutic baclofen in kidney impairment, if there is a coma requiring intubation and mechanical ventilation.

APPENDIX

Additional members of the EXTRIP workgroup

The EXTRIP workgroup also includes Badria Alhatali, Kurt Anseeuw, Steven Bird, Josée Bouchard, Timothy E. Bunchman, Diane P. Calello, Paul K. Chin, David S. Goldfarb, Hossein Hassanian-Moghaddam, Lotte C. Hoegberg, Siba Kallab, Sofia Kebede, Jan T. Kielstein, Joshua D. King, Yi Li, Etienne M. Macedo, Rob MacLaren, Bruno Megarbane, James B. Mowry, Marlies E. Ostermann, Ai Peng, Jean-Philippe Roy, Greene Shepherd, Anitha Vijayan, Steven J. Walsh, Anselm Wong, David M. Wood, and Christopher Yates.

DISCLOSURE

TDN reports personal fees from MediBeacon, CytoSorbents, and McGraw-Hill Education, outside the submitted work. MG is a scholar of the Fonds de Recherche du Québec—Santé. DMR acknowledges

support from St. Vincent's Centre for Applied Medical Research Clinician "Buy-Out" Program. AV reports consulting functions for NxStage, Astute Medical, and Boehringer-Ingelheim and speaker fees from Sanofi-Aventis. EXTRIP received support consisting of an unrestricted grant of $60,633 Canadian from the Verdun Research Fund (the institution of MG) solely for the reimbursement of travel expenses for the in-person guideline meeting and payment to dedicated translators for retrieval and translation of non–English-language articles. All the other authors declared no competing interests.

ACKNOWLEDGMENTS

We acknowledge the valuable help of our dedicated translators, librarian, data extractors, and meeting secretary. Official translators were Alexandra Angulo, Alla Abbott, Anant Vipat, Andreas Betz, Angelina Kovaleva, Denise Gemmellaro, Ewa Brodziuk, Helen Johnson, Junzheng Peng, Marcela Covic, Nathalie Eeckhout, Rosie Finnegan, Salih Topal, and Vilma Etchard. The librarian was Elena Guadagno. Data extractors for EXTRIP-2 included Maria Rif, François Filion, Karine Mardini, Maria Rif, Tudor Botnaru, Elizabeth Koo, and Gabrielle Wilson. The meeting secretary was Brenda Gallant. We also acknowledge the participation of our patient representative (name undisclosed).

AUTHOR CONTRIBUTIONS

MG, SG, RSH, VL, TDN, and DMR designed the study; IB, MG, SG, RSH, VL, and DMR carried out extractions; IB, MG, and VL made the tables and figures; all authors drafted and revised the article; and all authors approved the final version.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary EXTRIP group composition.
Table S1. Represented societies.
Supplementary Methods. EXTRIP methodology for clinical practice guideline.
Table S2. Standard care for each poison reviewed.
Table S3. PRISMA-P 2015 checklist.
Table S4. EXTRIP criteria for assessing dialyzability.
Table S5. Quality of individual studies for toxicokinetic outcomes.
Table S6. Quality of evidence for toxicokinetic outcomes.
Figure S1. Approach to and implications of rating the quality of the evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.
Figure S2. Voting process for recommendations.
Table S7. Final dialyzability grading according to EXTRIP criteria of clinical cases reporting kinetic data.

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