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REVIEW ARTICLE

Toxicologic Confounders of Brain Death Determination: A Narrative Review

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Abstract

The aim of this narrative review is to describe the toxicologic confounders of brain death currently reported in the literature to offer guidance for physicians assessing brain death after a toxic exposure. We established an a priori definition of a "brain death mimic" as an unresponsive, intubated patient missing some, but not all brainstem reflexes. We completed a review of the literature utilizing MEDLINE and EMBASE to find case reports of patients of all ages in English, French, and Spanish meeting the criteria and hand searched the references of the results. We recorded xenobiotic dose, duration of physical exam suggesting brain death, and how the cases failed to meet full brain death criteria, when available. Fifty-six cases representing 19 different substances met the a priori definition of brain death mimic. Xenobiotic toxicities included: snake envenomation (13), baclofen (11), tricyclic antidepressants (8), bupropion (7), alcohols (4), antiepileptic agents (3), barbiturates (2), antidysrhythmics (2), organophosphates (2), and one case each of magnesium, succinylcholine, tetrodotoxin, and zolpidem. All patients except one survived to discharge and the majority at their baseline physical health. The most common means by which the cases failed brain death examination prerequisites was via normal neuroimaging. The xenobiotics in this review should be considered in cases of poisoning resulting in loss of brainstem reflexes and addressed before brain death determination. Brain death diagnosis should not be pursued in the setting of normal cerebral imaging or incomplete evaluation of brain death prerequisites.

Keywords: Brain death, Drug overdose, Drug toxicity, Coma, Abnormal reflex

Introduction

Brain death in the USA is defined as the death of an individual due to irreversible loss of all functions of the entire brain, including the brainstem [1, 2]. It is a clinical diagnosis that is based on a prerequisite assessment that eliminates the potential for confounding factors, followed by a physical exam, and concluded with apnea testing [2]. This procedure, when interpreted and followed correctly, excludes the possibility for a brain death "mimic" or a "reversible" brain death state. A brain death mimic may be suggested, however, when the clinical exam of a patient exhibits absent brainstem reflexes but in whom confounders have not yet been addressed or eliminated. While many xenobiotics may cause coma in overdose, relatively few are known to cause respiratory failure and even fewer the loss of cranial nerve reflexes. The American Academy of Neurology (AAN), American College of Medical Toxicology (ACMT), American Academy of Clinical Toxicology (AACT) and Society of Critical Care Medicine (SCCM) agree on the importance of assuring absence of drug-intoxication or poisoning as a pre-requisite for diagnosis of brain death [3]. Intoxication has been identified as one of the most frequent confounders during brain death determination [4]. Though two recent reviews identify eleven substances that are recognized to cause a reversible loss of brainstem reflexes, there is no consensus on which xenobiotics are relevant to diagnosis of brain death [3, 4]. The aim of this review is to identify and describe all toxicologic brain death mimics currently

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reported in the literature. In addition, it will examine manners by which these cases fail other brain death prerequisites to enhance recognition of these toxicities and provide support for the accurate and timely identification of brain death.

Methods

We aimed to capture a clinical scenario that would cause a provider to consider the development of brain death, but in which full brain death prerequisites or total loss of brainstem reflexes was incomplete. We created an a priori definition of a "toxicologic brain death mimic" consisting of the following criteria: (1) intoxication by a xenobiotic, (2) intubation and mechanical ventilation, (3) loss of pupillary light reflex, (4) loss of corneal reflex, (5) loss of two or more of the following on the neurologic examination: oculocephalic reflex, oculovestibular reflex, gag reflex, cough reflex, facial muscle movement to noxious stimuli, deep tendon reflexes or motor response to noxious stimuli, and (6) patient recovers cranial nerve reflexes and purposeful responses. We developed an algorithm using the Ovid search engine and performed a review of the literature using MEDLINE and EMBASE electronic databases. We did not impose a date restriction nor patient age restriction, and we accepted articles in English, French, and Spanish languages. We identified additional cases by hand searching the references of all cases that met criteria, as well as all summary and review articles involving any aspect on the topic of brain death. A second investigator duplicated the search. If the two primary reviewers could not agree on whether a case fit the a priori definition, a third investigator independently reviewed the case for final decision. Once the cases were collected, we tabulated information on the number of cases for each substance, the age and sex of the patient, dose of xenobiotic, neurologic exam, duration of time without brainstem reflexes, failed brain death prerequisites, imaging and electroencephalogram (EEG) findings, drug concentration of the offending agent, and patient outcome, when available. If an article stated that a patient lost all brainstem reflexes, then we presumed it met criteria.

Results

The search algorithm produced 961 manuscripts; 86 were reviews or discussions on the topic of brain death and 26 contained cases that fulfilled criteria, including one duplicated case [5, 6]. A hand search of the references of all relevant papers resulted in an additional 27 manuscripts with cases that met criteria. In total, the review produced 56 patient cases, 13 different classes of substances, and ultimately 19 separate xenobiotics that met the a priori definition of brain death mimic. We grouped substances with greater than five cases into separate descriptive tables. Snake envenomation (Table 1) [7–16] was the most frequent cause of a brain death mimic, followed by baclofen (Table 2) [17–27], tricyclic antidepressants (TCA) (Table 3) [28–34] and bupropion (Table 4) [5, 6, 35–40]. We grouped all cases with three or fewer cases into Table 5 [41–57].

Snake envenomation was the largest contributor to cases. Authors suspected a neurotoxic snake in the Elapidae family (which includes the cobra and the krait) in all cases save one, in which a viper was suspected [10]. All cases occurred in India. The duration of paralysis and loss of brainstem reflexes was much longer than the majority of the other xenobiotics in this review, typically lasting 2–4 days with an average of 56.2 h. The most common means by which these patients failed to meet brain death criteria was via normal neuroimaging, but just over half of the cases described imaging. The majority of cases did not provide data regarding vital signs or laboratory results at the time of the initial physical exam that demonstrated lack of brainstem reflexes. Eleven of the cases reported clinical apnea and the remaining two were not specified. However, only two patients underwent an apnea test for determination of brain death [9, 14]—both survived and were discharged from the hospital. One of these was diagnosed with brain death after a positive apnea test but before neuroimaging had taken place [14]. Overall 46% of the cases recovered to their baseline health, including a 4-year-old girl who was manually ventilated for 5 days and mechanically ventilated for an additional 8 days [11]. Thirty-eight percent did not specify outcome and 15% (two patients) had residual weakness.

Baclofen was the second most frequent agent identified in this review. Loss of brainstem reflexes occurred at a dose as little as 450 mg [17], but was typically 1 g or more. The duration of symptoms that mimicked brain death lasted anywhere from several hours to a maximum of 4 days with a mean of 30 h. One patient underwent apnea testing for brain death but failed due to intact respiration [26]. Neuroimaging would have prevented an inaccurate diagnosis of brain death in five of the 11 cases, though seven patients had other signs preventing diagnosis of brain death such as spontaneous respirations, hypothermia, or acidosis. Two cases obtained baclofen concentrations and the results were three to eight times the upper therapeutic range of the drug. Fifty-five percent recovered to their baseline health and the remaining 45% did not specify outcome.

The eight cases of TCA poisoning included six cases of amitriptyline [30–34] and one case each of doxepin [28] and amoxapine [29]. The duration of loss of brainstem reflexes ranged from 2 to 72 h and the average was approximately 29 h. A greater percentage of the TCA

Table 1 Case reports of snake envenomation resembling brain death (13)

Source	Age*/sex	Duration of loss of brainstem reflexes	Neurologic exam	Failed brain death prerequisites	Neuroimaging	EEG	Outcome
[7]	45/M	12 h	Absent pupillary, corneal, gag, and oculocephalic reflex. No DTR or plantar reflex. No response to painful stimulation. External and internal ophthalmoplegia. Absent motor responses. Negative cold caloric testing	NR	NR	NR	Discharge at 72 h Recovery to baseline health
[8]	6/F	36 h	Absent pupillary, corneal, gag, oculocephalic, DTR, and plantar reflexes. Flaccid extremities, no response to painful stimulation	NR	NR	NR	Pupils mid-dilated, sluggish to light, truncal muscle weakness, 4/5 strength lower limbs
[9]	12/M	~ 24 h	Absent pupillary, corneal and oculocephalic reflex. "Areflexic". "Apnea test was negative"	NR	NR	NR	Extubated at 72 h Discharged day 5
[10]	12/M	3 days	Absent pupillary reflex. Complete ptosis and external and internal ophthalmoplegia. Absent DTR, plantar reflex, or movement to noxious stimulation. Comatose	Systolic BP < 100 mmHg	NR	NR	Extubated day 5 Recovery to baseline health
[11]	4/F	48 h	Absent pupillary, oculocephalic, superficial and DTR, Bilateral ptosis. Paralysis of limbs and facial muscles. Flaccid extremities	NR	NR	NR	Extubated day 13 Recovery to baseline health
[12]	10/M	4 days	Absent pupillary, corneal, oculocephalic, DTR, plantar reflex. Generalized hypotonia. No response to painful stimuli	Neuroimaging; pH 7.125	Normal CT	NR	Hospital day 12: 5/5 strength Day 14 weaned from ventilator Discharged home
[13]	35/M	5 days	Absent pupillary, corneal, cough, vestibulo-ocular reflexes. Complete ophthalmoplegia. "Completely paralyzed". Negative cold caloric testing	Neuroimaging	Normal MRI	Suggestive of diffuse encephalopathy	Extubated day 12 Discharged day 19 Able to walk unaided
[14]	18/M	8 h	"Areflexia"; pupils fixed and dilated, absent oculocephalic, no respiratory effort	Neuroimaging	Normal CT	NR	On transfer to ward: 4/5 strength of extremities, truncal muscle weakness noted. Pupils mid-dilated and sluggishly reactive.
[14]	38/M	~ 24 h	"Areflexia"; pupils fixed and dilated, no respiratory effort	Neuroimaging	Normal CT Normal MRI	NR	Extubated day 4 Transferred to ward day 5

Table 1 (continued)

Source	Age*/sex	Duration of loss of brainstem reflexes	Neurologic exam	Failed brain death prerequisites	Neuroimaging	EEG	Outcome
[14]	30/M	5 days	"No brain stem reflexes". No motor response. Neurologist performed brain death exam and patient was apneic; diagnosed with brain death. Cold calorics and MRI after exam were normal	Neuroimaging; caloric testing	Normal MRI	NR	Extubated day 15 Discharged day 29
[15]	38/M	4 days	Absent pupillary, corneal, oculocephalic, gag, DTR and plantar reflex	Neuroimaging	Normal CT	NR	Extubated day 8 Recovery to baseline health
[15]	27/F	26 h	Absent pupillary, corneal, oculocephalic, cough, gag. Generalized hypotonia. Depressed DTR. Extensor plantar response	Neuroimaging	Normal CT Normal MRI Normal MRA	Diffuse background slowing, no epileptiform changes	Extubated at 36 h Discharged day 6 Recovery to baseline health
[16]	26/M	48 h	"Areflexia". Absent pupillary, corneal, and oculocephalic reflexes. Atony	NR	NR	NR	Recovery to baseline health at 4-week follow up

*Age in years; *BP* blood pressure, *CT* computerized tomography, *DTR* deep tendon reflexes, *EEG* electroencephalogram, *F* female, *M* male, *MRI* magnetic resonance imaging, *MRA* magnetic resonance angiogram, *NR* not reported

Table 2 Case reports of baclofen intoxication resembling brain death (11)

Source	Age*/sex	Dose	Duration of loss of brainstem reflexes	Neurologic exam	Failed brain death prerequisites	Neuroimaging	EEG	Drug concentrations	Outcome
[17]	37/F	450 mg	~ 24 h	"Hypotonic and all reflexes absent"	Respirations present	NR	NR	[Baclofen] 0.197 mg/L when reflexes had returned *(no therapeutic range specified)*	Extubated "Fully conscious"
[18]	19/F	Estimated 875–1125 mg	~ 24 h	"All standard reflexes were absent"	Respirations present; pH 7.32	NR	NR	NR	Extubated at 24 h, "fully awake after 48 h"; transferred to psychiatry
[19]	28/F	900 mg	~ 24 h	Absent pupillary, corneal, oculocephalic, gag, and oculovestibular reflex. No DTR. No response to painful stimulation. Flaccid extremities	Temperature 35.5˚C; Potassium 2.8 mEq/L, Phosphorous 1.3 mg/dL, Magnesium 1.3 mEq/L	NR	NR	NR	Discharged day 17 Recovery to baseline health
[20]	57/F	> 2 g	~ 48 h	Pupils 2–3 mm and unresponsive to light. Absent corneal and oculocephalic reflex. Absent DTR. Unresponsive to pain	Temperature 34.2˚C	NR	NR	[Baclofen] 3.3 mg/L *(therapeutic: 0.08–0.40 mg/L)* [Amitriptyline]: 253ug/L *(therapeutic)* Absent nortriptyline	Extubated day 3 "Awake and alert" day 5; Transferred to psychiatric unit
[21]	25/M	2000µg/day intrathecal infusion	"several hours"	"Flaccid quadriplegia and absence of all reflexes"	NR	NR	NR	NR	NR
[22]	40/F	500 mg	~ 24 h	Small pupils unresponsive to light. Absent corneal reflex and DTR. No response to pain. Flaccid muscle tone. Plantar reflex present	Neuroimaging; pH 7.55	Normal CT	Burst suppression pattern	[Baclofen] Serum: 1.2 mg/L *(therapeutic: 0.2–0.4 mg/L)* Urine: 413 mg/L *(reference < 26 mg/L)*	Recovery to baseline health

Table 2 (continued)

Source	Age*/sex	Dose	Duration of loss of brainstem reflexes	Neurologic exam	Failed brain death prerequisites	Neuroimaging	EEG	Drug concentrations	Outcome
[23]	59/M	1870 mg over 11 days	12 h	Fixed 3 mm pupils, absent corneal, oculocephalic, cough, and gag reflex. Absent DTR in legs but 1/4 in both arms. No plantar response. No spontaneous movement or response to pain	Respirations present; Neuroimaging; pH 7.30	Normal CT Normal MRI	Burst suppression pattern without reactivity to stimulation	NR	Recovery to baseline health
[24]	18/M	3 g	12 h	Mid-range unreactive pupils. Absent corneal, oculocephalic, cough and gag reflex. No response to painful stimulation. Flaccid tone	Neuroimaging	Normal CT	Generalized slowing without reactivity to stimulation	NR	Extubated at 48 h; Recovery to baseline health
[25]	41/M	> 600 mg	10 h	Fixed 2 mm pupils. Absent corneal, oculocephalic, cough, and gag reflex. No spontaneous movements or DTR. No response to cold caloric testing. Train of four testing normal	Neuroimaging	Normal CT Normal CTA head/neck	NR	NR	Recovery to baseline health
[26]	40/F	Unknown	4 days	Pupils fixed and dilated. Absent corneal, and ocular reflex. Flaccid extremities. No response to caloric testing. Spontaneous respiration during apnea test	Neuroimaging; spontaneous respirations during apnea test	Normal CT	Burst-suppression pattern with occasional sharp waves on a flat background	NR	"Discharged to psychiatry on hospital day 15"

Table 2 (continued)

Source	Age*/sex	Dose	Duration of loss of brainstem reflexes	Neurologic exam	Failed brain death prerequisites	Neuroimaging	EEG	Drug concentrations	Outcome
[27]	15/F	Unknown	~24 h	Pupils fixed and dilated. Absent corneal and ocular reflexes. No response to painful stimulation	NR	NIRS cerebral region O_2 sat 88–94%	Cerebral bioelectric activity and ground amplitudes significantly lower than normal	NR	Discharged day 3 Recovery to baseline health

*Age in years; *CT* computerized tomography, *CTA* computerized tomography angiography, *DTR* deep tendon reflexes, *EEG* electroencephalogram, *F* female, *M* male, *MRI* magnetic resonance imaging, *NIRS* near infrared spectroscopy, *NR* not reported

cases failed brain death criteria prerequisites due to causes other than normal neuroimaging compared to the other xenobiotics. This included intact respiratory drive, hypotension, electrolyte abnormalities, acidosis, or occasional posturing movements. Drug concentrations, obtained in all the amitriptyline cases, were two to nine times the typical therapeutic ranges of 50–300 ng/mL [58]. Of the five cases (62.5%) that specified patient outcome, all recovered to their baseline health.

All seven bupropion cases exhibited seizures, several also exhibited status epilepticus, and three of the patients experienced a cardiac arrest. The duration of time patients lost brainstem reflexes ranged from 24 to 48 h and the mean was 26.4 h. Neuroimaging precluded brain death diagnosis in five out of the seven of cases, and two patients were also hypotensive at the time of the exam. Three cases reported bupropion concentrations and the results were 14–58 times the expected therapeutic range. Despite significant toxicity, the six surviving patients had a full recovery to their neurologic baseline.

Considering all cases, ethylene glycol caused the longest duration of loss of brainstem reflexes, lasting 2 months in two of the cases [42, 44]. The shortest duration of the physical exam suggesting brain death was ethanol at 40 min [41]. The neurologic exam described by the cases varied widely in detail and extent, and often did not include every finding pertinent to the brain death exam. Only three of the 56 patients underwent apnea testing for the purpose of diagnosing brain death, two for snake envenomation and one for baclofen [9, 14, 26]. All patients who underwent apnea testing survived to hospital discharge. Neuroimaging, when completed, was the most frequent manner by which a patient would fail requirements for brain death diagnosis. However, it was common that essential brain death exam prerequisites such as vital signs and laboratory findings were not fully described. Only 23 (41.1%) of the 56 cases reported drug concentrations or other confirmatory laboratory studies. Regarding outcome, 35 (62.5%) patients recovered to their baseline health, 15 (26.8%) were not specified, and five (8.9%) had residual deficits. One patient died after recovering purposeful movement and reflexes [37].

Supplementing the 11 substances and 18 cases already recognized to mimic brain death [3, 4], we identified 10 additional cases of snake envenomation, eight of baclofen toxicity, five of bupropion, five of amitriptyline, and one additional case of valproic acid, pentobarbital and organophosphorous toxicity. We identified seven new substances that were associated with reversible loss of brainstem reflexes in overdose: doxepin [28], amoxapine [29], ethanol [41], bretylium [50], magnesium [54], tetrodotoxin [56], and zolpidem [57]. Snake envenomation [59–62], baclofen [34, 63–65], TCA [28, 66–71],

Table 3 Case reports of tricyclic antidepressant intoxication resembling brain death (8)

Source	Age*/sex	Drug; dose	Duration of loss of brainstem reflexes	Neurologic exam	Failed brain death prerequisites	Neuro-imaging	EEG	Drug concentrations	Outcome
[28]	24/M	Doxepin; unknown	2–4 h	Pupils fixed, pinpoint. Absent corneal, oculocephalic, reflex and DTR. Internuclear ophthalmoplegia. Extensor plantar reflex. Flaccid extremities and no response to painful stimulation	Neuroimaging	Normal CT	NR	NR	Recovered brainstem reflexes; conscious; spontaneous respirations
[29]	40/F	Amoxapine; unknown	24 h	Pupils fixed at 4 mm. Absent corneal, oculocephalic, and ciliospinal reflex. No DTR. Decerebrate posturing of upper limbs to painful stimulation. Absent cold caloric response	Posturing to painful stimulation; Sodium 151 mmol/L; Potassium 5.9 mmol/L	NR	Burst suppression	NR	Recovery to baseline health
[30]	46/F	Amitriptyline; 9 g	24 h	Absent pupillary, corneal and oculocephalic reflex. No DTR. Flaccid extremities. No response to painful stimulation	Acidosis; Systolic BP < 100 mmHg	NR	NR	[Amitriptyline] 2350 ng/mL *(therapeutic 75–225 ng/mL)* [Phenobarbital] 3ug/mL *(therapeutic 15–35 ug/ml)*	Recovery to baseline health
[31]	39/F	Amitriptyline; unknown	48–72 h	Pupils 3 mm and unreactive. Absent corneal, oculocephalic, and gag reflex. Flaccid extremities	Neuroimaging	Normal CT	"Absence of well-developed alpha rhythm and low voltage beta activity"	[Amitriptyline] 1310 ng/mL [Nortriptyline] 39 ng/mL [Desmethylvenlafaxine] 140 ng/ml	Recovery to baseline health
[32]	52/M	Amitriptyline; 500 mg	24 h	"No detectable brainstem reflexes"	Neuroimaging	Normal CT	NR	[Amitriptyline] 2800 ng/mL *(therapeutic 75–225 ng/mL)* [Nortriptyline] 630 ng/mL [Nitrazepam] 0.62mcg/mL	Recovery to baseline health

Table 3 (continued)

Source	Age*/sex	Drug; dose	Duration of loss of brainstem reflexes	Neurologic exam	Failed brain death prerequisites	Neuro-imaging	EEG	Drug concentrations	Outcome
[33]	18/M	Amitriptyline; 6 g	~48 h	"No brainstem reflexes were present"	Neuroimaging	Normal CT Normal CTA Normal MRI	Rhythmic activity at alpha frequency bilaterally, no response to painful stimulation, no seizure activity.	36 h after admission: [Amitriptyline] 1125 ng/mL [Nortriptyline] 568 ng/mL *(no therapeutic range specified)*	Recovery to baseline health
[34]	67/F	Amitriptyline; unknown	24 h	Absent Pupillary, corneal, oculocephalic and plantar reflex	Spontaneous respirations; Systolic BP < 100mgHg; Neuroimaging	Normal CT Normal CTA	NR	[Amitriptyline] > 730 ng/mL *(therapeutic 100–300 ng/mL; toxic > 400 ng/mL);* [Nortriptyline] 400 ng/mL	Extubated day 3, Transfer to floor on day 4 with confusion
[34]	28/M	Amitriptyline; unknown	"Several hours"	Absent Pupillary, corneal, oculocephalic and plantar reflex. No muscular tone	Spontaneous respirations; Neuroimaging	Normal CT Normal CTA	"Did not show any signs of epileptiform activity or encephalopathy"	Sample collected hospital day 3: [Amitriptyline] 330 ng/mL *(therapeutic 100–300 ng/mL; toxic > 400 ng/mL)* Bromazepam: 507 ng/mL *(therapeutic 80–170 ng/mL; toxic > 250 ng/mL);*	Extubated and transferred to ward on day 3

*Age in years; *BP* blood pressure, *CT* computerized tomography, *CTA* computerized tomography angiography, *DTR* deep tendon reflexes, *EEG* electroencephalogram, *F* female, *M* male, *MRI* magnetic resonance imaging, *NR* not reported

Table 4 Case reports of bupropion intoxication resembling brain death (7)

Source	Age*/sex	Dose	Duration of loss of brainstem reflexes	Neurologic exam	Failed brain death prereq-uisites	Neuroimaging	EEG	Drug concentration: [Bupropion] reference 50–100 ng/mL; [Hydroxybupropion] reference 600–2000 ng/mL	Outcome
[35]	29/F	Unk	~ 24 h	Fixed and dilated pupils. Absent corneal, oculocephalic, gag, and plantar reflex. DTR present and diminished. No spontaneous move-ment. No response to stimulation	Neuroimaging	Normal CT x2	Burst Suppression; dif-fuse slowing	[Bupropion] 1441 ng/mL; [hydroxybupro-pion] 3342 ng/mL	Recovery to baseline health
[36]	13/F	Unk	~ 24 h	"Flaccid paralysis and absent brainstem reflexes"	Neuroimaging	Normal CT Normal MRI	Slowing; focal seizures; full recovery	[Bupropion] 4321 ng/mL; [Hydroxybupro-pion] 1903.8 ng/mL	Recovery to baseline health
[37]	13/F	21 g	24 h	Fixed and dilated pupils. Absent corneal, oculocephalic, cough, and gag reflex. No response to stimuli.	Neuroimaging	Normal CT x3 –arrival –24-h –40-h CT at 48 h: diffuse edema	6-h: Burst suppression; 18-h: generalized slowing with faster frequencies; 24-h: generalized slowing; 48-h: electrical silence	NR	Died; CT after cardiac arrest displayed edema, EEG silent
[38]	32/M	27 g	~ 24 h	Fixed and dilated pupils. Absent corneal, oculocephalic, and gag reflex	NR	NR	NR	[Bupropion] 5898.8 ng/mL; [Hydroxybupro-pion] 3521.8 ng/mL	"Discharged without appreciable motor or cognitive deficits"
[5] [6]	47/F	Unk	24–36 h	Pupils fixed and dilated. "She lacked all brain-stem reflexes"	Neuroimaging	Normal CT	Burst suppression	NR	Tracheostomy; full neuro-logic recovery
[39]	18/F	27 g	24–120 h	Fixed and dilated pupils. Absent corneal and oculocephalic reflex. No DTR. Flaccid limbs. Periodic myoclonic jerks	Myoclonic jerks	NR	Burst suppression	NR	Recovery to baseline health
[40]	24/M	19.5 g	NR	Fixed and dilated pupils. Absent corneal, vestibulo-ocular, and gag reflex	Neuroimaging	Normal CT	Interictal epileptiform discharges	NR	"Mental status returned to normal"

*Age in years; *CT* computerized tomography, *DTR* deep tendon reflexes, *EEG* electroencephalogram, *F* female, *M* male, *MRI* magnetic resonance imaging, *NR* not reported, *Unk* unknown

Table 5 Miscellaneous intoxications resembling brain death (19)

Class	Agent [reference]	Age* (range)	Duration of loss of brainstem reflexes (range)	Failed brain death prerequisites (#)	Neuroimaging (#)	EEG (#)	Outcomes (#); Drug concentration (range)**
Alcohols	Ethanol [41]	41	40 min	Neuroimaging; Spontaneous respirations; Decerebrate posturing of arms	Normal CT	NR	Transferred from ICU to the ward after 24 h; [Ethanol] 700 mg/dL
Toxic alcohols	Ethylene glycol [42–44]	21–24	2 days–2 months	Neuroimaging (2) EEG (1) NR (1)	Normal CT (2) Normal MRI (1) CT head with diffuse cerebral edema (1)	Normal (1) Day 20: Diffuse theta/delta slowing with super-imposed beta activity (1) NR (1)	Permanently deaf (2) Peritoneal dialysis (1) Ambulates with crutches (1) Ambulates unassisted (2) Full recovery to baseline (1)
Antiepileptics	Carbamazepine [45], Valproate [46, 47]	19–54	Several hours-5 days	Neuroimaging (1) Hyperammonemia (1) NR(2)	CT: cerebral edema (2) Normal CT (1)	Burst suppression (1) NR (2)	Recovery to baseline (2) Discharge from ICU (1); [Carbamazepine] 57ug/ml; [Valproate] 1792–2346 mg/L *(therapeutic 50–120 mg/L)*
Barbiturates	Pentobarbital [48, 49]	40–45	1–5 days	Neuroimaging (1) NR (1)	Normal CT/CTA (1) NR (1)	Day 2: No electrical activity (1) NR (1)	Recovery to baseline health (2); [Pentobarbital] 57 mg/L–116 mg/dL *(therapeutic 1–5 mg/L)*
Antidysrhythmics	Bretylium [50], Lidocaine [51]	7 days–60 years	5–24 h	Right bicep tendon reflex (1) NR(1)	US: Normal cerebral artery pulsations, normal sized ventricles, no hemorrhage (1) NR (1)	Mildly attenuated activity with isolated sharp waves (1) NR (1)	Normal growth and development at 1 year (1) Mild cognitive impairment with no focal deficits (1); [Bretylium] 17ug/mL; [Lidocaine]11.2 mcg/ml
Organophosphates	Phorate [52], Thiacloprid [53]	28–72	24–120 h	Neuroimaging (2) Hemiballistic movements (1)	Normal CT (2) MRI: minor cortical diffusion restriction in postcentral gyrus (1)	Global suppression of cortical activity (1) Alpha-theta waves; minimal variability (1)	Recovery to baseline health (2)
Electrolytes	Magnesium [54]	27	2 h	Neuroimaging; pH 7.27; Oculocephalic reflex abnormal	Normal CT	NR	Recovery to baseline health; [Magnesium] 9.85 mmol/L
Paralytics	Succinylcholine [55], Tetrodotoxin [56]	39–80	6–20 h	EEG (2); Train-of four (1); Electrolyte abnormalities (1) Neuroimaging (1)	CTA head with old infarct, no acute findings (1)	Moderate voltage waves. Stage 1 and 2 sleep with sleep spindles (1) Background rhythm 6–7 Hz, reactive to eye opening (1)	Recovery to baseline health (2)

Table 5 (continued)

Class	Agent [reference]	Age* (range)	Duration of loss of brainstem reflexes (range)	Failed brain death prerequisites (#)	Neuroimaging (#)	EEG (#)	Outcomes (#); Drug concentration (range)**
Hypnotic Sedative	Zolpidem [57]	40	24 h	Neuroimaging; Spontaneous respirations	Normal CT	Diffuse, nonspecific slow-wave abnormality with no epileptiform activity	Recovery to baseline health

*Age in years; (#) = number of patients with the finding, **when available; *CT* computerized tomography, *CTA* computerized tomography angiogram, *EEG* electroencephalogram, *ICU* intensive care unit, *MRI* magnetic resonance imaging, *NR* not reported, *US* ultrasound

bupropion [72–75], barbiturate [76, 77], and bretylium [78] poisoning associated with reversible loss of cranial nerve reflexes may be more common than currently recognized given the many additional cases discovered in this review that did not meet the specific a priori definition of brain death mimic used in the study.

Discussion

This review identifies 53 articles and 56 patients with poisoning that have physical exam characteristics that may lead a provider to consider the development of brain death. Normal neuroimaging, intact respiratory drive and incomplete evaluation of brain death prerequisites, however, should preclude testing for brain death. While loss of brainstem reflexes is an essential component of brain death, it is also seen to occur with neuronal dysfunction from drug toxicity, which is one reason why establishing brain death in a patient with a known overdose poses a challenge. While overdose and poisoning may indeed result in death, there is a concern that xenobiotics with properties altering nerve conduction, causing apnea, or causing central nervous system (CNS) depression may mask intact brain function and render the physical exam unreliable. Furthermore, overdose represents a peculiar instance in which a patient with profound critical illness may recover without permanent sequelae. The verification of a presumed overdose can be quite challenging. The history of the substances, dose, or timing of ingested products is frequently unclear. Even when intoxication is suspected, xenobiotic drug concentrations may take hours or days to obtain, and toxicity often does not correlate with drug concentration in the blood compartment – an obstacle recognized over 40 years ago that is still true today [79]. Summarizing cases and characteristics of xenobiotic poisoning that cause reversible loss of brainstem reflexes provides a reference for providers when pursuing brain death diagnosis in these complicated patients.

Snake Envenomation

Neurotoxic snake envenomation essentially represents the unanticipated administration of a paralytic agent. Snake venom is a complex mixture of enzymes, non-enzymatic proteins, lipids, carbohydrates and metal ions. Neurotoxic snake venom produces paralysis either by pre-synaptic blockade of acetylcholine release or post-synaptic blockade of acetylcholine receptors, depending on the species of snake [15, 58]. Though all snake envenomation cases in this review occurred in India, paralysis secondary to envenomation should be suspected in any region where neurotoxic snakes are endemic. Poisoning is generally suggested by history alone such as visualization of the snake executing the bite or evidence of typical

fang markings on physical exam [58]. Diagnosis of neurotoxic snake envenomation can be difficult as bites can be painless (as in seven of the cases) and there is currently no available confirmatory laboratory assay for most snake venom. Even among the cases in this review, eight were only diagnosed by fang marks found on a thorough physical exam. In four cases there was no sign of a bite or history of envenomation at all, but the patient recovered after receiving antivenom empirically in a region where snakes with neuroparalytic venom are endemic [14, 15]. Determining brain death in a victim of snake envenomation is challenging as loss of brainstem reflexes may occur both from the toxicity of the venom but also hypoxic-ischemic brain injury from respiratory weakness occurring before presentation to health care. Train of four testing, while not always available, is helpful in determining the presence of paralytic toxicities and may be a useful adjunct for the diagnosis of brain death in appropriate geographic regions. The cases in this review suggest a good prognosis for patients who are appropriately identified, treated with antivenom, and supported through their paralysis.

Baclofen

Baclofen is well-known to depress brainstem reflexes and is more frequently recognized as a brain death mimic [58]. It was the second most frequent cause of a brain death mimic in this review [17–27] (Table 3). The ability to interfere with reflexes is attributed to its mechanism as a γ-aminobutyric acid (GABA) type B receptor agonist, inhibiting calcium influx and preventing release of the excitatory neurotransmitters, glutamate and aspartate [27, 58]. While therapeutic dosing produces an effect chiefly at the spinal cord, higher doses result in penetration of the blood brain barrier and CNS depression [23, 27, 58]. Diagnosis is typically through history alone, as there are no readily accessible rapid laboratory tests for identification. Despite the profound sedation seen in overdose, patients often make full recovery without permanent sequelae given appropriate supportive care and if no hypoxic-ischemic cerebral injury has occurred [25, 58].

TCA

Unlike baclofen, TCA are not generally regarded as sedatives and in fact have GABA antagonist activity. Sedation in overdose is most likely attributable to its central and peripheral postsynaptic histamine antagonism or muscarinic acetylcholine receptor antagonism. There is no clear mechanism for the interference with brainstem reflexes, but it may involve anticholinergic activity [33, 67, 68] or disruption of nerve conduction due to loss of selectivity of the cardiac voltage-gated fast sodium channel blockade in overdose. While amitriptyline has previously been recognized to depress brainstem reflexes [3, 4], the cases of doxepin and amoxapine producing a similar presentation suggest that TCA as a class, rather than amitriptyline alone, may cause the profound neurotoxicity witnessed in overdose. Diagnosis is typically via history of ingestion and a characteristic toxidrome of electrocardiogram changes, altered mental status, hypotension, seizures, and cardiac dysrhythmias. As the TCA cases that lost brainstem reflexes were more likely to fail multiple brain death prerequisites, it is far less likely for a provider to mistake a patient with TCA overdose with an incorrect diagnosis of brain death. Treatment of TCA overdose is with sodium bicarbonate infusion, urine alkalinization and supportive care. Similar to baclofen overdose, if a patient survives the initial profound toxicity of TCA overdose, they are generally expected to make a full recovery to baseline health.

Bupropion

Bupropion has no known direct inhibitory action in the CNS nor sodium channel blockade. Rather, it functions by means of reuptake inhibition of dopamine and norepinephrine, a mechanism shared by cocaine and amphetamines. It is thus surprising that there were seven cases associated with loss of brainstem reflexes. There is currently no clear mechanism explaining interference with brainstem reflexes or cerebral nerve conduction, though disrupted cardiac conduction is secondary to inhibition of gap junctions between myocytes [80]. Similar to baclofen, there is no readily available laboratory assay that can be used to aid rapid diagnosis aside from history alone. Bupropion is, however, associated with false-positive amphetamine result on urine drug screen (UDS) [81, 82]. The five patients who survived showed remarkable recovery to baseline despite experiencing complications such as status epilepticus and cardiac arrest from their toxicity. One patient died [37]. In this case the patient had absent brainstem reflexes for 24 h and three head computed tomography (CT) scans that were within normal limits. She regained purposeful movements, and her EEG improved. The following day she sustained a ventricular fibrillation arrest, she once again lost all movements and reflexes, her CT showed diffuse edema, her EEG displayed electrical silence, and her exam was consistent with brain death.

Ethylene Glycol

Though ethylene glycol is known to produce a clinical syndrome that mimics brain death when in combination with benzodiazepines [43], the two cases without co-ingestants suggest that ethylene glycol toxicity acts independently to produce deep sedation and loss of reflexes.

None of the ethylene glycol cases reported confirmatory laboratory values. One case lost brainstem reflexes concurrently with acute inebriation, acidosis, and renal failure [43], while the remaining two cases exhibited neurotoxicity insidiously after developing renal failure and after the patients had recovered from the acute intoxicated state [42, 44]. It remains unclear if ethylene glycol or its metabolites are responsible for the CNS toxicity displayed in these cases. Renal injury is caused by the oxalic acid metabolite of ethylene glycol and not the parent compound. Because two of the cases demonstrated nerve injury later in their course, it may be more accurate to theorize that one of the metabolites of ethylene glycol causes direct injury to conduction pathways. Both cases reported nerve conduction studies displaying severe axonal polyneuropathy [42, 44], and a sural nerve biopsy demonstrated oxalate crystal deposition in one case [42]. This would also explain why the case that received dialysis promptly had the shortest duration of a clinical brain death mimic, as dialysis removes both the parent alcohol and its metabolites.

Presumed Toxicologic Confounders

Existing guidelines on brain death often cite "CNS-depressing drugs", sedative hypnotics, paralytics, and ethanol as the pertinent substances that must be ruled out before proceeding with a brain death exam [2, 30, 83, 84]. Cases involving traditional CNS depressants such as opioids, benzodiazepines, barbiturates and ethanol composed the minority of cases in this review, which may be secondary to a publication bias as these are known confounders. Opioids infrequently confound brain death determination. This is likely secondary to pervasive recognition as opioids as a reversible cause of coma as well as the presence of readily available rapid urine testing for common opioid and opiate agents. Furthermore, opioids typically result in miosis, an easily identifiable finding on physical exam that helps distinguish this intoxication from brain death. Lastly, the widespread availability of the rapid reversal agent naloxone, a competitive opioid antagonist, can fully reverse intoxication in many cases and assist in establishing a reversible cause of sedation.

Benzodiazepines, on the other hand, have a less profound effect on the medullary respiratory center and require the presence of endogenous GABA to bind to the GABA type A ($GABA_A$) receptor to elicit sedation. Baseline levels of endogenous GABA, therefore, may act as a check that limits the sedating action of benzodiazepines [58]. In our review there were no cases of isolated benzodiazepine ingestion that resulted in a physical exam suggesting brain death. One case identified nordiazepam as a secondary agent to pentobarbital poisoning in the gas-chromatography mass-spectrometry results of a sample, but it was lower than a therapeutic concentration [48]. Benzodiazepines were a component of overdose in three baclofen cases [18, 23, 26] and three TCA cases [32–34], but the authors specified drug concentration in only two of these. The current limited data does not provide enough information to allow an association between isolated benzodiazepine overdose and loss of brainstem reflexes, and it is unclear whether it contributes to loss of brainstem reflexes in other cases. As opposed to benzodiazepines, barbiturates can exert their effect without the simultaneous binding of GABA, which is perhaps why they have been seen to depress brain function so profoundly as to cause loss of brainstem reflexes and an isoelectric EEG [48, 49, 76, 77].

Both benzodiazepines and barbiturates display prolonged action in overdose, lasting hours or even days for full recovery. Shorter acting sedative agents are unlikely to result in a brain death mimic, however, as the patient recovers before hospital admission or thorough evaluation is completed. This may be why the GABA type B agonist γ-hydroxybutyrate (more commonly known as GHB) was not included, despite its profoundly sedating properties in overdose, and why ethanol only surfaced in one case.

Paralytic xenobiotics are unlikely to confound a brain death exam because they are not easily administered outside of a medical setting and most are short-acting. The absence of deep tendon reflexes should alert the clinician to the possibility of a paralytic xenobiotic. Train of four testing can be used to confirm the ability of muscles to contract and verify that the paralytic will not interfere with the exam. However, as was evident in this review, less common causes of paralysis such as envenomation, tetrodotoxin or organophosphorous compound toxicity may be more likely to result in a brain death mimic if not immediately suggested by the history of the present illness. Additional less common toxicologic causes of paralysis include coniine from poison hemlock, strychnine, curare, nicotine and nicotinic alkaloids, botulism, and tetanus.

Neuroimaging and Failed Prerequisites

The presence of normal cerebral imaging in a comatose patient should consistently prompt the provider to defer brain death evaluation and evaluate, or re-evaluate, for potential confounders. Normal neuroimaging caused patients to fail brain death assessment prerequisites in 34 (60.7%) cases in this review, which highlights that neuroimaging is a key component in differentiating intoxication as a reversible cause of interrupted brainstem reflexes. Three notable cases in this review reported cerebral edema on neuroimaging: a single case of ethylene glycol [43], carbamazepine [45] and valproic acid toxicity [47].

In these instances, structural cerebral disease may have been the cause of, or contributed to, the loss of brainstem reflexes rather than the direct action of the xenobiotic. The cases did not specify, however, whether there was loss of gray-white differentiation or hypodensities on CT, both portending a poorer prognosis than cerebral edema alone. Alternatively, the finding could have been suggestive of transient global edema, as may occur from causes such as hypercapnia, or an over-call by the radiologist, as may occur with younger patients with fuller brain tissue. Two of these patients made a full recovery [43, 45] and the third was not specified, but was discharged from the intensive care unit [47]. Because of the additional cases of ethylene glycol and valproate toxicity that caused a patient to have features resembling brain death without cerebral edema, these xenobiotics may still be relevant to consider as toxicologic brain death confounders. Until further cases of carbamazepine toxicity causing loss of brainstem reflexes are identified, though, it is unclear whether it can be strongly associated with causing a toxicologic brain death mimic in overdose.

Aside from neuroimaging, 25 (44.6%) patients would have failed prerequisite brain death criteria by other means, most commonly via spontaneous respirations, acidosis, or the presence of a single brainstem reflex. Brain death diagnosis should never be suspected in a patient with intact respiratory drive. Despite the presence of meticulous guidelines, inappropriate diagnosis of brain death continues to occur [14, 85, 86]. This underscores the absolute importance of establishing a contemporaneous and irreversible cause of coma and fully addressing all prerequisites before proceeding with brain death determination.

Monitoring Period

The duration of time to monitor a patient who is experiencing critical xenobiotic toxicity before pursuing brain death examination is still debated. It takes roughly five half-lives to eliminate 97% of a drug from the body. Many brain death guidelines and reviews suggest waiting five half-lives for clearance to take place [2, 3]. However, kinetic data is largely based upon a therapeutic dose in a relatively healthy person who is intended to receive the drug [58, 84]. Unfortunately, overdose often saturates normal metabolic processes and can prolong the action of a drug for an indeterminate period. Apparent clearance may be protracted based on drug effect, such as continued absorption or elimination, individual genetic factors of the patient, or accompanying liver or renal dysfunction [3, 58]. This is illustrated well by the succinylcholine case in which the patient had an unsuspected inherited pseudocholinesterase deficiency [55]. Another notable case report describes a delay in brain death diagnosis due to prolonged elimination of vecuronium secondary to renal dysfunction—nearly 13 times the expected clearance time [87]. It is therefore difficult to make a single overarching recommendation regarding the duration of time to allow xenobiotic effect to clear when attempting to fulfill prerequisites for a brain death examination. Importantly, all of the TCA and bupropion cases recovered brainstem reflexes within five half-lives of expected drug elimination. Presuming the longest estimated half-life, the pentobarbital, carbamazepine, and valproic acid overdoses also recovered within five half-lives. Most notably, over half (seven of 11) baclofen cases, the succinylcholine case, and the zolpidem case required longer than the expected five half-lives to recover brainstem reflexes.

Testing

Appropriate screening for toxins is another matter of controversy. Prototypical toxicologic screening labs such as ethanol, serum acetaminophen and salicylate, are minimally applicable to the diagnosis of brain death. The UDS most often screens for amphetamines, benzodiazepines, opioids, barbiturates, and cocaine, but may or may not include tricyclic antidepressants, phencyclidine, specific synthetic opioids, or ethanol, depending on the institution. Detection of barbiturates and TCA would be the most beneficial for evaluation of toxicity masking intact CNS function; however, the number of false positives for TCA may render the test futile. The UDS is limited due to its use of cutoff values and the presence of false positives [3, 58, 81, 82]. It should be recognized that synthetic opioids such as fentanyl and methadone, which have become increasingly prevalent, as well as many common benzodiazepines (such as lorazepam and clonazepam) are not reliably detected by UDS and produce false negative results [58, 81, 88]. Furthermore, the presence of a substance in the urine does not necessarily indicate that the substance has a high concentration in the blood compartment, or that it is actively responsible for clinical intoxication [3, 58]. These constraints highlight the importance of ensuring a thorough and accurate history before pursuit of brain death assessment. Despite the limitations, UDS can be completed to ensure absence of the substances and interfering substances it has the power to detect. When point of care urine testing is not available, many of the xenobiotics in this review have tests that are available through reference laboratories. Tests that may be available include baclofen, tricyclic antidepressants, bupropion, ethylene glycol, barbiturates, anticonvulsants, zolpidem, and antidysrhythmics. Depending on several factors, these tests may be available within hours to days in some situations and may be helpful to rule out intoxication for the purposes of a brain death evaluation. It is

less likely that tests would be available for tetrodotoxin, organophosphate pesticides, or snake venom.

Patient Outcomes

Overall, 62.5% of patients recovered to their baseline health despite manifesting toxicity profound enough to cause loss of brainstem reflexes, as well as status epilepticus and cardiac arrest in some cases. This is an improvement in the 33% rate of full recovery seen in a recent review of brain death confounders [4]. The change is likely secondary to separating intoxication from loss of reflexes caused by polyneuritis, infectious, and autoimmune causes, as many patients with severe poisoning can make a full recovery. In regards to the five cases reporting residual deficits, two cases of snake envenomation had residual muscular weakness [8, 14], two cases of ethylene glycol poisoning had deafness and muscular weakness [42, 44], and a lidocaine case had mild cognitive impairment [51].

Limitations

The most notable limitation for this narrative review is a reporting bias, as practitioners who are well-versed in the definition and diagnosis of brain death may not publish a brain death mimic based on the knowledge that this condition does not exist. This is especially true for toxicologic confounders more commonly recognized to cause coma, and will misrepresent the frequency with which different drugs are reported. The quality of evidence is very low and subject to high risk for bias, as the review is based exclusively on case reports and case series. Importantly, a minority (43%) of these cases acquired confirmatory xenobiotic laboratory values to corroborate the suspected cause of absent brainstem reflexes. This narrative review subjectively defines a toxicologic brain death mimic in order to inclusively capture case reports of patients who have some, but not all, of the physical exam characteristics of brain death. Any change in criteria would change the number of relevant cases included. Furthermore, the definition of brain death has evolved over the decades that were included in the review, and this likely also contributed to publication bias. Additionally, certain drugs and their formulations have changed over time, which may render the older case reports irrelevant.

For the purpose of fully describing the clinical state of the patients in this review, a full neurologic exam, specific vital signs, laboratory values and the exact amount of time a patient lost brainstem reflexes or was thought to appear brain dead was not routinely reported. It is likely that such information was not described as authors were not actively pursuing the brain death determination due to recognition of a toxic exposure.

Seven of the patients in the review sustained a cardiac arrest, which highlights the severity of illness in these poisoned patients, but also presents a significant confounder to the results. Cardiac arrest occurred in three bupropion cases [5, 37, 38], and a single amitriptyline [32], pentobarbital [49], lidocaine [51], and bretylium [50] case. Three of these patients demonstrated purposeful movements and reflexes after return of spontaneous circulation (ROSC) before progressing to the brain death mimic episode [37, 50, 51]. Two of the cases underwent hypothermia protocol following ROSC but then had persistent loss of cranial reflexes for an additional 24 [32] and 120 [38] hours after rewarming before making a full recovery. The pentobarbital case was maintained on ventilation after ROSC without sedation for five days, and brain death assessment was deferred due to normal CT and CT angiogram; he ultimately made a full recovery.

Conclusion

The xenobiotics identified in this review are associated with reversible loss of brainstem reflexes and should be considered before determining the presence of brain death. Complete evaluation of the prerequisites to brain death evaluation will often prevent a diagnosis of brain death in cases of intoxication or poisoning. Normal cerebral imaging should prompt the provider to carefully evaluate for potential confounders. Train of four testing should be strongly considered in regions where snakes with neurotoxic venom are endemic. Five half-lives is often, but not always, sufficient to ensure lack of ongoing effect of xenobiotic, and practitioners should be cautious in cases of overdose with baclofen. Consultation with a medical or clinical toxicologist, or local poison center, may be considered when overdose or poisoning is suspected but history is unclear.

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Author contributions

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