# ACMT Position Statement: Determining Brain Death in Adults and Children After Drug Overdose

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The position of the American College of Medical Toxicology, endorsed by the American Academy of Clinical Toxicology and affirmed by the Neurocritical Care Society, is as follows:

We agree with the American Academy of Neurology (AAN) recommendation that the clinical determination of brain death should only be made in the absence of drug intoxication or poisoning. However, drug screening and clearance calculation using five drug half-lives ($T_{1/2}$) are not sufficient to exclude intoxication in all cases. Drug screens are not sufficiently comprehensive to detect all drugs that may cause mental status depression. Even when the specific drugs are quantitatively identified, the use of kinetic data to determine clinical effects is limited because drugs often have prolonged half-lives in overdose. For certain drugs and toxins, the duration of effect may extend beyond their detected presence in the vascular space. We recommend identification of drugs or toxins by careful history and targeted testing. An observation period of longer than five half-lives is necessary when there is a possibility of a large drug overdose, delayed drug absorption, delayed elimination, or interaction with another agent. In cases where brain death is considered but intoxication is unclear, consultation with a medical toxicologist or clinical toxicologist is recommended to guide decision-making regarding the timing or appropriateness of clinical testing, as clinical brain death determination cannot take place until intoxication is excluded.

While individual practitioners may differ, these are the positions of the ACMT at the time written, after a review of the issue and scientific literature.

The American Academy of Neurology (AAN), American Academy of Pediatrics (AAP), Child Neurology Society (CNS), and Society of Critical Care Medicine (SCCM) offer guidance for the diagnosis of brain death/death by neurologic criteria (BD/DNC). BD/DNC is diagnosed clinically when a permanent and proximate cause of brain injury is identified and no brain function is present upon clinical assessment [1]. “The process of this determination always begins with the presumption that the patient does *not* meet brain death/death by neurologic criteria (BD/DNC), a presumption that must then be disproved [1].” A prerequisite for clinical testing is ensuring that “intoxication and medications that depress the CNS are excluded . . . or eliminated” prior to BD/DNC clinical evaluation [1]. The only evidence available regarding brain death determination in the setting of intoxication derives from case reports. In our previous

position statement, we conducted a review of the literature, and only ten case reports of brain death mimicry were found (baclofen, snake envenomation, valproic acid, amitriptyline, mixed diazepam + ethylene glycol, bupropion, and organic phosphorous compound) [cite previous position statement]. In addition to these, a 2021 review also named tricyclic antidepressants, alcohols, antiseizure medications, barbiturates, and antidysrhythmics as categories of drugs responsible for brain death mimics, in addition to magnesium, succinylcholine, tetrodotoxin, and zolpidem as individual agents [2].

The "Pediatric and Adult Brain Death/Death by Neurologic Criteria Consensus Guideline" recommends that the clinician should exclude the presence of a central nervous system (CNS)-depressant drug effect by history, toxicology screen (if indicated), and "allow[ing] at least 5 half-lives for all CNS-depressing medications or intoxicants (Recommendation Statement 12a)." [1] However, there are limitations to this approach in the overdose patient. The specific drug responsible for intoxication may not be identified by history or drug screening. Drug screening in the clinical setting is not comprehensive, so a negative drug screen does not exclude intoxication. Urine immunoassays are screening tools to identify recent exposure to only those drugs included in the testing panel, so a negative screen does not exclude drug intoxication. Moreover, the detection interval of drug screens is longer than the duration of action of drugs, so a positive screen does not establish acute drug intoxication or even the presence of any effects at all. For example, a typical opiate screen does not reliably identify oxycodone and hydrocodone and does not identify synthetic opioids such as fentanyl or buprenorphine, and a typical benzodiazepine screen does not reliably identify clonazepam. Many novel psychoactive substances are not included in traditional drug screens. In contrast, a "positive" urine drug screen by itself is not confirmatory, but in the setting of an appropriate history, clinical presentation and physical examination can support intoxication.

Although most hospital laboratories can readily measure serum concentrations of some common drugs in overdose, including lithium, digoxin, phenobarbital, phenytoin, and valproic acid, there are many drugs that cannot be measured in a clinically relevant time frame. When drug concentrations are available, the distribution of the drug into tissues may complicate the relationship between concentration and clinical effect.

In cases in which drug concentrations are not available but a specific drug is suspected, experts recommend waiting five half-lives prior to clinical determination of brain death [1]. This figure is likely derived from the mathematical observation that $0.5^5$ (50% elimination, five times) equals 0.03125, suggesting that only 3% of a drug remains following five half-lives. This strategy is appropriate for drugs given therapeutically after presentation. However, this approach may not be appropriate in every case. If a patient was exposed to an exceedingly large quantity of drug or toxin, 3% of the original dose could potentially still have clinical effects. In addition, the pharmacokinetics of many drugs will be altered in patients with organ failure [3, 4].

Furthermore, the pharmacokinetics of absorption and elimination of a drug in large doses may be different than published pharmacokinetic data suggest, which are typically obtained following therapeutic dosing, generally in healthy subjects without co-exposures [5]. Moreover, published data is primarily obtained from healthy adult volunteers and may not apply to children, given their known differences in absorption, distribution, metabolism, and excretion.

The reasons for prolonged half-lives in overdose are numerous. Delays in gastric emptying and gut hypomotility may result from fasting status, overdose itself, or co-ingestion of opioids or anticholinergic drugs, and controlled-release drugs have a prolonged absorption phase [6, 7]. Hypoperfusion of the gastrointestinal tract secondary to hypotension and/or splanchnic vasoconstriction can slow absorption [8]. Hypothermia may slow drug metabolism [9]. Enterohepatic recirculation may play a role in elimination of certain drugs. Mechanisms of metabolism may be saturated in overdose [5]. As an example of prolonged half-life in overdose, many references indicate the half-life of baclofen is approximately 2–4 h, but in overdose, the duration of effect far exceeds the recommended five half-life calculation [10]. Reported cases of coma mimicking brain death secondary to baclofen overdose have described a duration of coma of up to 7 days [10, 11]. Furthermore, pharmacokinetic elimination (i.e., "normal" or negative serum concentration) does not equate to pharmacodynamic duration of effect (i.e., drug remaining at the target organ receptor). Finally, published pharmacokinetic data may not account for pharmacodynamic or pharmacokinetic interactions [12]. It is for these reasons that the 2023 guideline recommends waiting longer "if there is renal or hepatic dysfunction or the patient is obese or was hypothermic (Recommendation Statement 12a)." [1] We would also recommend waiting longer for patients with overdose prior to presentation, in both adults and children. The duration of waiting can be directed by toxicology consultation.

Ancillary testing to assess cerebral blood flow, including cerebral angiography, transcranial Doppler, and radionuclide cerebral blood flow scan, has been recommended to assist in the determination of death when the examination or apnea test cannot be completed or findings cannot be interpreted fully [1]. Anecdotal evidence has suggested the possibility of survival after nuclear medicine study demonstrated absences of cerebral blood flow, but this has not been produced elsewhere [13]. For this reason, the 2023 guidelines recommend that "clinicians should not use ancillary tests to assist in the diagnosis of BD/DNC in the setting of . . . high levels of sedating medications (Recommendation Statement 27c)." [1]

The requirement to identify "a catastrophic, permanent brain injury caused by an identified mechanism that is known to lead to BD/DNC" (Recommendation Statement 7a) [1] of brain injury ***should*** prevent clinical brain death determination in overdose patients. Extreme caution should be employed in declaring BD/DNC in overdose patients when the neuroimaging is normal and there is no history of cardiac arrest [5]. We recommend identification of drugs or toxins by careful history and targeted testing. Five drug half-lives should be considered an

absolute minimum period to ensure clearance. A longer period is necessary when there is a possibility of a large drug or toxin exposure, likelihood of delayed drug absorption, likelihood of delayed elimination (from relevant organ failure or extremes of age [14, 15]), pharmacokinetic or pharmacodynamic interactions, saturable elimination kinetics, or interactions with another agent. In cases where brain death is considered but the possibility of persistent intoxication is possible or unclear, a medical toxicologist or clinical toxicologist can be consulted to guide decision-making regarding clinical testing, as clinical brain death determination cannot begin until intoxication is excluded. In the absence of an on-site toxicologist, one can be consulted via a local poison center at 1-800-222-1222.

Source of Funding for the Project
None.

Conflicts of Interest
None.

Footnotes
This is an update of the 2017 ACMT Position Statement: Determining Brain Death in Adults After Drug Overdose. The intent of this position statement is to reduce the likelihood of erroneous declaration of brain death in the setting of drug- or toxin-induced coma.

New References

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