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# Beta-blocker and calcium-channel blocker toxicity: current evidence on evaluation and management

**Charlotte E. Goldfine [1,2]*, Andrew Troger[2,3], Timothy B. Erickson[1,2,4], and Peter R. Chai [1,2,5,6,7]**

[1]Division of Medical Toxicology, Department of Emergency Medicine, Mass General Brigham Boston, 75 Francis St, Boson, MA 02115, USA; [2]Harvard Medical School, 25 Shattuck St, Boson, MA 02115, USA; [3]Division of Emergency Medicine, Boston Children's Hospital, Boston, MA, USA; [4]Department of Global Health and Population, Harvard Humanitarian Institute, Harvard T.H. Chan School of Public Health, Cambridge, USA; [5]Department of Psychosocial Oncology and Palliative Care, Dana Farber Cancer Institute, Boston, USA; [6]The Koch Institute for Integrated Cancer Research, Massachusetts Institute of Technology, Cambridge, USA; and [7]The Fenway Institute, Boston, USA

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Beta-blocker and calcium-channel blocker overdoses are associated with severe morbidity and mortality; therefore, it is important to recognize and appropriately treat individuals with toxicity. The most common clinical findings in toxicity are bradycardia and hypotension. In addition to supportive care and cardiac monitoring, specific treatment includes administration of calcium salts, vasopressors, and high-dose insulin euglycaemia treatment. Other advanced treatments (e.g. ECMO) may be indicated depending on the severity of toxicity and specific agents involved.

**Keywords** Beta-blocker • Calcium-channel blocker • Overdose • Toxicity • Cardiovascular drug toxicity

## Introduction

Cardiovascular drug poisonings are one of the most common causes of severe toxicity. In the USA, cardiovascular drug poisonings were the 6th most common reason for calls to the poison centre and the 3rd most common cause of fatal poisoning according to the 2020 National Poison Center Data System.[1] Most of the reported fatalities were a result of calcium-channel blocker (CCB) toxicity.[2] Beta-adrenergic antagonists, more commonly called beta-blockers (BBs), were the 7th leading overall cause of poisoning deaths.[1] Given the severity of the associated morbidity and mortality, it is important to recognize and understand the management of CCB and BB toxicity.

A 2020 systematic review of treatments for BB toxicity found the evidence for all therapeutics to be low grade with a high risk for bias.[3] A review for CCB toxicity had similar findings of low-grade evidence of therapeutic interventions with a high risk of bias; however, a workgroup of critical care, toxicology, and emergency medicine associations across North America and Europe established expert consensus guidelines on the management of CCB toxicity.[4,5] In this paper, we will review the evidence and current recommendations for the evaluation and management of BB and CCB toxicity.

## Beta-blocker pathophysiology and clinical presentation

Beta-blockers are antagonists at the beta-adrenergic receptors (*Figure 1*). This antagonism blunts the effects of catecholamines at the beta receptor resulting in decreased chronotropy and decreased inotropy. They additionally cause decreased conduction through the sinoatrial (SA) and atrioventricular (AV) nodes and inhibit ectopic cardiac pacemaker cells. Peripherally, BBs can cause hyperkalemia from decreased uptake in skeletal muscles. Rarely, hypoglycaemia can occur due to decreased glycogenolysis and gluconeogenesis; however, BBs can mask the clinical symptoms commonly associated with hypoglycaemia (e.g. tachycardia, diaphoresis).

Beta-blockers are classified as selective or non-selective based on the type of beta-adrenergic receptor the drug antagonizes (*Table 1*). However, in overdose, the selectivity is often blunted.[6] They can further be categorized by lipid solubility, sympathomimetic activity, alpha antagonism, and vasodilatory effects. Non-selective BBs include nadolol, pindolol, propranolol. Selective beta-1 (B1) antagonists include acebutolol, atenolol, bisoprolol, esmolol, metoprolol.

Acebutolol, carvedilol, and propranolol additionally inhibit sodium channels which can manifest as QRS prolongation. Propranolol is highly lipid soluble and therefore has increased central nervous system penetration which can result in seizures. Acetabulol and sotalol also block potassium channels that can result in QTc prolongation and arrhythmias such as torsades de pointes. Intrinsic sympathomimetic activity has been noted in BBs such as acebutolol, carteolol, oxprenolol, penbutolol, and pindolol due to beta-adrenergic receptor agonism. Several BBs are also vasodilators. The mechanism of vasodilation varies and includes nitric oxide release (celiprolol and carteolol), alpha-adrenergic antagonism (labetalol and carvedilol), beta-2 adrenergic agonism (bucindolol, carteolol, and celiprolol), and calcium-channel antagonism (betaxolol and carvedilol).

* Corresponding author. Tel: +1 617 732 5640, Email: cgoldfine@bwh.harvard.edu

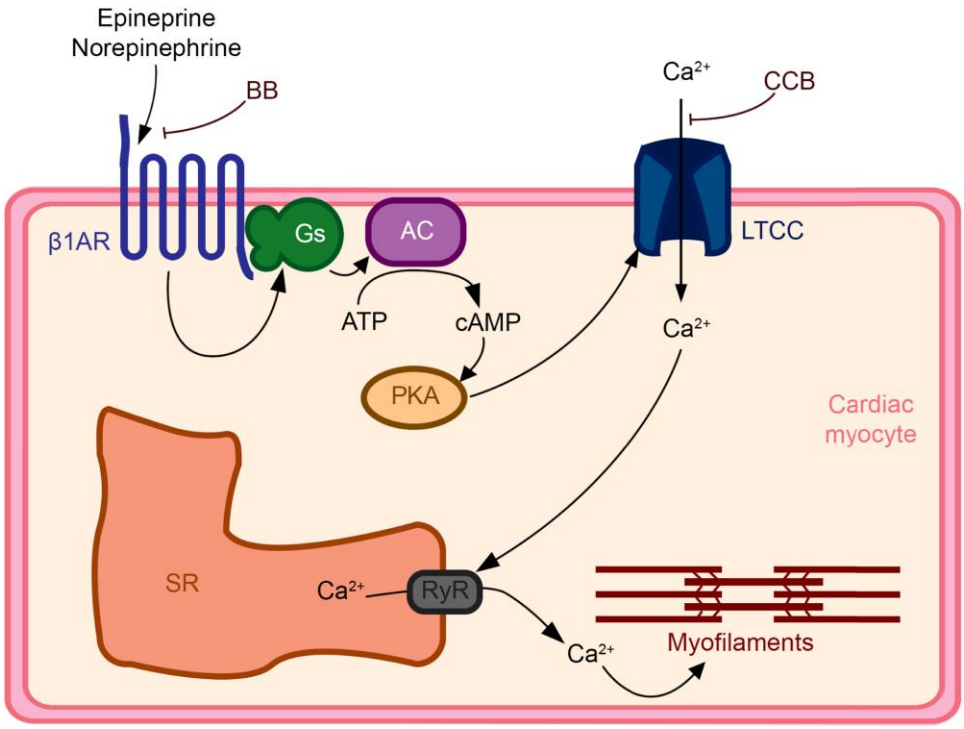


**Figure 1** Representation of the mechanism of action of beta-blocker and calcium-channel blocker on a cardiac myocyte.

Symptoms of BB toxicity include bradycardia and hypotension. Those most at risk for severe toxicity include those with underlying cardiac conditions or co-ingestion of other cardiovascular drugs.[7] Arrhythmias can include sinus bradycardia, sinus pause, or sinus arrest. Delirium, seizures (most common with propranolol toxicity), and coma can also occur, often in the setting of hypotension.

## Calcium-channel blocker pathophysiology and clinical presentation

Calcium-channel blockers are divided into dihydropyridines (e.g. amlodipine) and non-dihydropyridines (e.g. diltiazem, verapamil) (*Table 1*).[8] Dihydropyridines act peripherally on the vascular smooth muscle cells to induce vasodilation. However, in toxicity, they often lose selectivity and can also antagonize the cardiac calcium channels, resulting in decreased influx of calcium into the cardiac myocyte and decreased cardiac contractility. Non-dihydropyridines primarily act on the cardiac L-type calcium channels resulting in inhibition of the SA and AV nodes (*Figure 1*).

The resulting vasodilation and decreased cardiac contractility in toxicity leads to bradycardia and hypotension. Dihydropyridine toxicity may initially present with reflex tachycardia due to the initial vasodilation but as selectivity is lost, bradycardia will occur (*Table 2*). The blockade at the SA and AV nodes cause conduction abnormalities such as idioventricular rhythms, complete heart block, and junctional rhythms. CCB toxicity also causes blockade of the calcium channels that are present in the pancreas. This leads to decreased insulin release, insulin resistance, and hyperglycaemia. The degree of hyperglycaemia can correlate with severity of the overdose in non-dihydropyridine toxicity.[9]

In addition to pulmonary oedema secondary to cardiogenic shock, non-cardiogenic pulmonary oedema has also been described as a consequence of CCB overdose. Although the overall incidence of this phenomenon is not well described, one prospective cohort study of 19 amlodipine overdoses requiring inotrope or vasopressor support demonstrated a rate of 47%.[10] Non-cardiogenic pulmonary oedema has also been described in verapamil overdose.[11] Mechanistically, this is felt to be secondary to the direct dilatory effects on pulmonary capillary beds.[12]

## Evaluation

There are several key points in the evaluation of a patient that can help lead to a diagnosis of CCB or BB toxicity. First, any patient with bradycardia and hypotension should prompt evaluation for BB or CCB toxicity. All patients should have a 12-lead electrocardiogram and continuous cardiorespiratory monitoring. A point-of-care glucose should be obtained to evaluate for hyperglycaemia (from CCB toxicity). Serum drug levels of BBs or CCBs are not of clinical utility as they are not readily available to impact clinical management. Other lab testing such as serum electrolytes, renal function, and thyroid function tests may be indicated if the aetiology of bradycardia is undifferentiated.

## Management

As with any critical care patient, the initial management should include supportive care and cardiopulmonary monitoring. Asymptomatic patients should be observed for the onset of signs or symptoms of toxicity. In regular release preparations, the onset of symptoms should occur within 6–8 h.[13] This may be delayed in extended-release preparations or in large overdoses for up to 24 h post-ingestion. Sotalol is also

**Table 1 Classes and mechanisms of BB and CCB**

| Class | Agent | Activity |
|---|---|---|
| Dihydropyridine CCB | | |
| | Amlodipine | Vascular calcium channels |
| | Nifedipine | |
| | Nimodipine | |
| | Nicardipine | |
| Non-dihydropyridine CCB | | |
| Phenylalkylamine | Verapamil | Cardiac and vascular calcium channels |
| Benzothiazepine | Diltiazem | Cardiac calcium channels |
| Non-selective BB | | |
| | Nadolol | $\beta_1$, β2 blockade |
| | Pindolol | $\beta_1$, $\beta_2$ blockade, partial beta-agonism |
| | Propranolol | $\beta_1$, $\beta_2$ blockade, sodium channel blockade |
| | Sotalol | $\beta_1$, $\beta_2$ blockade, potassium channel blockade |
| | Carvedilol | $\alpha_1$, $\beta_1$, $\beta_2$ blockade, sodium channel blockade, vasodilation ($\alpha_1$ blockade, CCB) |
| | Labetalol | $\alpha_1$, $\beta_1$, $\beta_2$ blockade, partial $\beta_2$ agonism, vasodilation ($\alpha_1$ blockade, $\beta_2$ agonism) |
| Selective B1 blocker | | |
| | Acebutolol | $\beta_1$ blockade, partial beta-agonism, sodium channel blockade, potassium channel blockade |
| | Atenolol | $\beta_1$ blockade |
| | Betaxolol | $\beta_1$ blockade, sodium channel blockade, vasodilation (CCB) |
| | Bisoprolol | $\beta_1$ blockade |
| | Esmolol | $\beta_1$ blockade |
| | Metoprolol | $\beta_1$ blockade |

BB, beta-blocker; CCB, calcium-channel blocker.

**Table 2 BB and CCB toxidrome**

| | Heart rate | Blood pressure | Mental status | Blood glucose |
|---|---|---|---|---|
| Calcium-channel blocker | Decreased | Decreased | Normal | Hyperglycaemia |
| Beta-blocker | Decreased | Decreased | Depressed, altered | Hypoglycaemia |

BB, beta-blocker; CCB, calcium-channel blocker.

known for delayed onset of toxicity. For mild hypotension, start intravenous (IV) fluids to maintain euvolemia and proper hydration. Care should be taken to avoid excessive fluid administration as many patients have congestive heart failure. Additionally, vasodilation from CCB and BB toxicity can lead to pulmonary oedema. Atropine can also be used as a temporizing measure for bradycardia. Further pharmacotherapeutic choices should focus on improving or maintaining cardiovascular output or peripheral vascular tone. An echocardiogram can be especially useful for determining adequacy of cardiac output and to help guide the selection of additional treatment modalities (*Figure 2*).

## GI decontamination

Activated charcoal use may be efficacious depending on timing of ingestion and formulation of the product.[3] In patients who are alert and cooperative and have ingested a potentially toxic amount of a BB or CCB up to 1 h prior to presentation, administer 50–100 g of activated charcoal.[3,5] Nausea and vomiting may preclude the ability to give activated charcoal. Additional risks of activated charcoal include aspiration and therefore should be avoided in patients with respiratory depression, central nervous system depression, seizures, or inability to protect their airway. Whole-bowel irrigation with high molecular weight polyethylene glycol solution can also be considered in individuals who have ingested potentially toxic amounts of sustained-release products who are normotensive with adequate bowel perfusion.[14]

## Calcium salts

Calcium is recommended for the initial treatment of mild to moderate toxicity with BB or CCB. Dosing with calcium salts will increase the extracellular calcium gradient, which will maximize entry of calcium into the blocked cells. This leads to increased cardiac output and increased vascular tone.[14] In animal studies, IV calcium has been shown to increase cardiac output and blood pressure, with little effect on the heart rate. Human case series have also shown an improvement in blood pressure and cardiac contractility, and calcium has been useful as a temporizing inotropic agent. Furthermore, the risk of adverse effects is rare. Dosing for a patient with central access should include calcium chloride 10% 0.2 mL/kilogram (kg) bolus (4 times more elemental calcium per dose than calcium gluconate). If the patient does not have central access, administer calcium

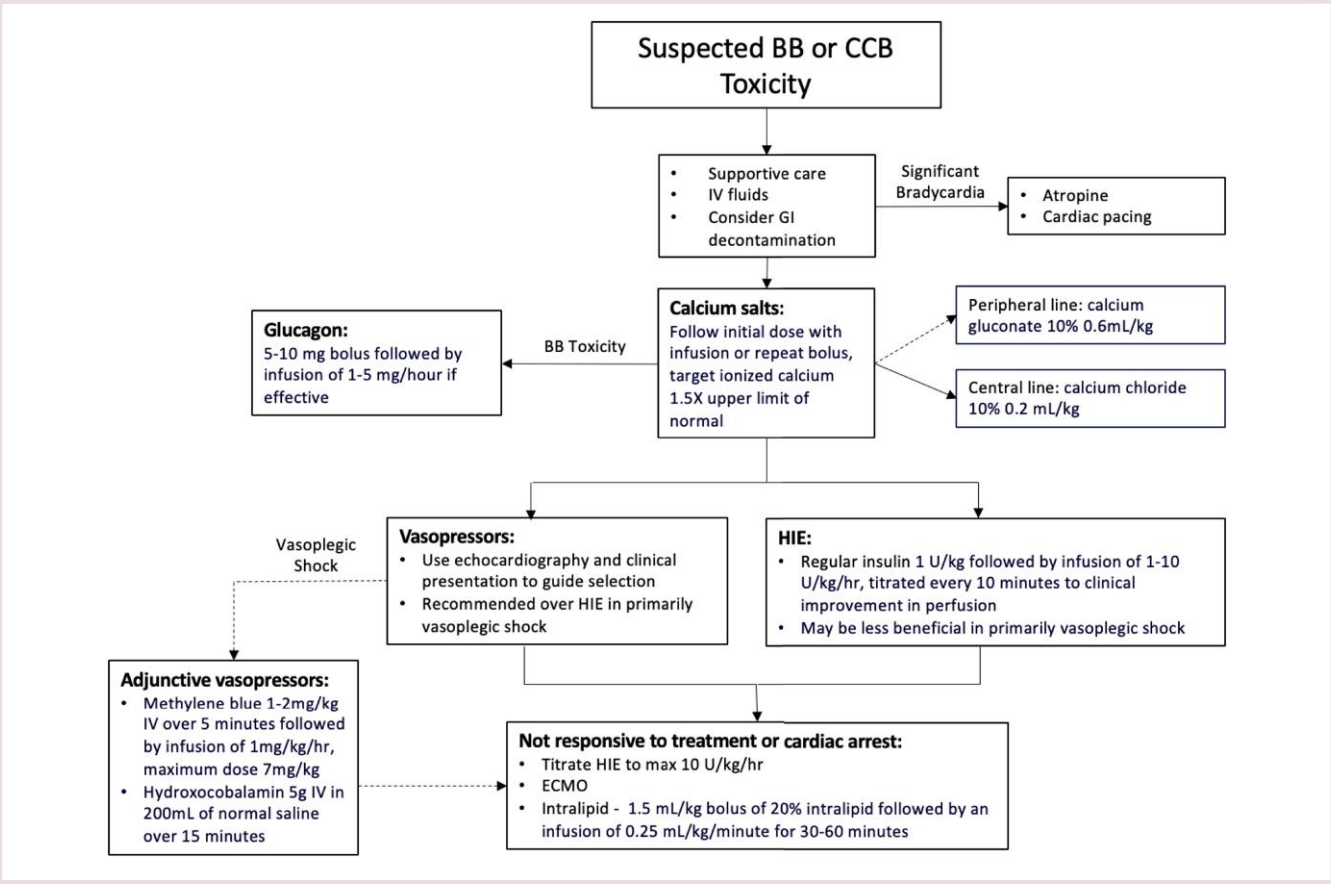


**Figure 2** Recommended treatment for BB and CCB toxicity. BB, beta-blocker; CCB, calcium-channel blocker.

gluconate 10% 0.6 mL/kg. This can be followed by an infusion of 0.2–0.5 mL/kg/h or repeated boluses. Longitudinal titration of calcium salt administration can be achieved by measuring serum ionized calcium concentrations every 1–2 h with a suggested target of 1.5 times the upper limit of the local laboratory's reference range.

## Glucagon

Glucagon is an endogenous polypeptide that in normal physiology helps to regulate plasma glucose levels. It was also found to increase cyclic adenosine monophosphate independent of alpha and beta receptors resulting in increased inotropic and chronotropic effects when used in high doses.[14] In animal studies, glucagon improved heart rate and cardiac output in BB and CCB toxicity.[15] Despite the haemodynamic improvement, glucagon did not improve animal survival in CCB toxicity. Human studies are limited to case reports and case series demonstrating haemodynamic improvement but are confounded by the concurrent use of vasopressors.[3] The main adverse effect from glucagon is nausea and vomiting most often secondary to rapid IV infusion. Glucagon should be given as a slow 5–10 mg bolus followed by an infusion of 1–5 mg/h. However, the ability to administer glucagon at appropriate doses may be limited by hospital supply. Given the limitations of the evidence, glucagon is not recommended in cases of CCB toxicity. It can be given early in BB toxicity as a bridging therapy to more effective treatment modalities.

## Vasopressors

Shock associated with CCB and BB toxicity is often characterized by profound vasodilation, bradycardia, and negative inotropy. While these physiologic parameters are therapeutically modulated by vasoactive and inotropic medications, the utilization of these medications in CCB and BB overdose can be challenging. In the setting of overwhelming beta-adrenergic blockade or downstream inhibition of L-type calcium channels, the effects of exogenous catecholamines may be attenuated, and animal studies suggest that disproportionate peripheral vasoconstriction in this setting may counterproductively reduce cardiac output.[16] A systematic review of the case literature suggested that, in humans, vasopressors may be ineffective though not overtly harmful.[17] Conversely, retrospective case data of an inpatient toxicology service covering 25 years and 48 diltiazem or verapamil overdoses demonstrated positive outcomes and low complication rate using vasopressors as the predominant treatment modality without the addition of adjunctive therapies such as high-dose insulin euglycaemic (HIE) treatment.[18] Despite a lack of clear consensus, vasopressors remain widely used in the treatment of shock associated with CCB or BB toxicity. There are no data to suggest a comparative efficacy benefit of one agent over another and choice of initial vasopressors is based upon the clinical judgment of the treating provider and the clinical presentation of the patient.[14,19] Norepinephrine or epinephrine may be beneficial if a patient has decreased cardiac contractility or decreased peripheral vascular resistance.[20] In a patient with a normal heart rate and hypotension, consider using phenylephrine or norepinephrine. Dobutamine can be used if there is confirmed myocardial dysfunction.[5]

## High-dose insulin euglycaemia treatment

High-dose insulin euglycaemic therapy has been utilized as an adjunctive therapy for shock associated with BB and CCB toxicity. Maintenance of a hyperinsulinemic, euglycaemic state has been

demonstrated in animal models to facilitate carbohydrate metabolism in myocytes, to provide inotropy independent of sugar transport, and to cause a reduction in systemic vascular resistance.[21–23] In porcine models of propranolol toxicity, the administration of high-dose insulin demonstrated a statistically significant improvement in mortality vs. placebo.[24] In the same model, vasopressors demonstrated reduced survival as compared to placebo.[16] These data suggest that high-dose insulin therapy may offer a mechanistically unique intervention for patients in refractory shock related to calcium channel or beta-adrenergic blockade.

Despite promising data in animal models, the specific role of HIE therapy remains a subject of debate in humans. Complications such as hypoglycaemia and hypokalemia are common, and safe implementation requires frequent electrolyte and glucose monitoring.[25,26] The availability of super-concentrated insulin and dextrose can be limited, and prolonged high-dose insulin therapy can require infusion of significant fluid volumes after which complications such as acute respiratory distress syndrome (ARDS) have been reported.[27] Furthermore, insulin-mediated vasodilation may be counterproductive in cases where profound vasoplegia is the primary driver of a shock state—a condition that is more common in cases of dihydropyridine as compared to non-dihydropyridine CCB toxicity.[2] As previously discussed, single-centre retrospective data has also demonstrated favourable outcomes with limited complications using a vasopressor-only approach without high-dose insulin therapy.[18]

While further investigation is necessary to more clearly elucidate the appropriate role of high-dose euglycaemic insulin therapy in CCB and BB toxicity, it does appear to have a prominent and efficacious role in the management of refractory shock associated with these conditions. In particular, patients with decreased cardiac function demonstrated by clinical findings of cardiogenic shock, systolic dysfunction on echocardiography, or inappropriately normal heart rate and left ventricular ejection fraction in the setting of significant vasoplegia may benefit from the addition of HIE therapy. The dosing regimen should include a bolus of regular insulin 1 unit/kg followed by an infusion of 1 unit/kg/h.[5] The infusion can be titrated to adequate tissue perfusion by 1–2 units/kg/h every 10 min, up to a maximum of 10 units/kg/h. Because insulin's concomitant positive inotropic and vasodilatory effects can confound titration based on blood pressure alone, we suggest titration to adequate perfusion by physical exam unless invasive monitoring is in place. Dextrose infusions are also administered at rates to maintain euglycaemia.

## Intravenous lipid emulsion

The current evidence on the utility of intravenous lipid emulsion (ILE) for CCB and BB toxicity is limited; however, it may be efficacious in specific cases of toxicity. Drugs that are more lipophilic, such as propranolol, are likely to have more benefit from ILE. In animal studies, there has been a variable response to ILE therapy. Case reports and case series have shown benefit with ILE in both BB and CCB toxicity. Although the exact mechanism is unknown, ILE is hypothesized to work by decreasing free serum drug concentrations. Intravenous lipid emulsion potentially separates the lipophilic drugs from target tissue by creating a lipid-rich compartment in the plasma. Another theory is that ILE provides energy to myocardium with high-dose free fatty acids activating the voltage-gated calcium channels in the myocytes.[28] Adverse effects include interference with laboratory testing, pancreatitis, and interference with dialysis and older extracorporeal membrane oxygenator (ECMO) circuits.[29] Intravenous lipid emulsion is not recommended as a first-line treatment, but can be considered in refractory shock or in cardiac arrest. There are no data regarding the optimal dosing. A common dosing regimen is a 1.5 mL/kg bolus of 20% intralipid followed by an infusion of 0.25 mL/kg/min for 30–60 min.[30] The bolus can be repeated if needed for haemodynamic instability.

## Extracorporeal membrane oxygenator circuits

In severe toxicity refractory to advanced treatment options, additional support with ECMO circuit may be indicated. Extracorporeal membrane oxygenator is effective in poisoned patients as it provides haemodynamic and oxygen exchange during the time needed to metabolize the xenobiotic in patients with cardiogenic or mixed shock. A review comparing outcomes of patients with cardiovascular poisoning who received timely extracorporeal life support showed improvement in survival and several case reports have also demonstrated benefit.[3,31] The main limitation is availability is often only at large tertiary care centrer. Adverse effects include bleeding, limb ischaemia, and coagulopathy.[5] Although most cases of BB or CCB toxicity require veno-arterial ECMO to augment cardiac output, veno-venous ECMO can be utilized in cases of severe non-cardiogenic pulmonary oedema or ARDS secondary to excessive volume resuscitation.

## Adjunctive treatments

In patients who are refractory to traditional resuscitative measures as well as HIE therapy where appropriate—particularly those in whom shock is primarily due to profound and refractory vasoplegia—adjunctive vasopressors such as methylene blue and hydroxocobalamin have been utilized. Methylene blue is an inhibitor of nitric oxide and cyclic guanosine phosphate-mediated vasodilation, and may provide therapeutic benefit in a non-catecholamine-dependent manner.[32] Dosing for vasodilatory shock is typically 1–2 mg/kg over 5 min followed by a continuous infusion of 1 mg/kg/h. Its utility is limited by maximum safe dosing recommendations (7 mg/kg), as it can cause pro-serotonergic toxicity and, of specific concern in patients with impaired oxygen delivery due to a shock state, induce methaemoglobinemia.[33] Hydroxocobalamin (the antidote for cyanide poisoning) is another option, originally investigated as a catecholamine-sparing agent for the management of cardiac bypass-induced vasoplegia. While the optimal dose is unknown, doses of 5 g IV in 200 mL normal saline over 15 min have been utilized.[34] Multiple mechanisms have been proposed for this therapy, including increased nitric oxide scavenging and modification of endogenously produced hydrogen sulphide.[34] Ultimately, the utility of methylene blue and hydroxocobalamin as adjunctive vasopressors for the treatment of CCB and BB toxicity is supported only by anecdotal evidence, and should be considered only in cases refractory to other treatments, or as temporizing measures to bridge to mechanical circulatory support. Methylene blue and hydroxocobolamin should be reserved for patients with refractory vasoplegia unresponsive to typical vasopressor therapy, but need not be reserved for peri-arrest situations when one would typically administer ILE. In any patient where these adjunctive therapies become necessary, consultation with a specialist to discuss the utility of ECMO cannulation is indicated.

In severe bradycardia or heart block, cardiac pacing may be an option. There have been case reports of improvement with pacemaker insertion. However, capture is commonly unable to be obtained. Therefore, in severe toxicity not responsive to other therapies, it is reasonable to trial a transcutaneous approach to see if capture can be obtained prior to more invasive methods.[5]

## Extracorporeal removal

Haemodialysis has a limited role in BB and CCB toxicity except in very specific agents. Most BBs are unable to be dialyzed due to their lipophilicity and large volumes of distribution. Calcium-channel blockers are highly protein-bound and have large volumes of distribution and therefore are also unable to be dialyzed. The Extracorporeal Treatments in Poisoning workgroup, a group of experts in medical toxicology and nephrologists, have provided consensus recommendations for the indications for dialysis in these cases.[35,36] They recommend against

extracorporeal treatment (ECTR) in patients severely poisoned with CCBs amlodipine, verapamil, or diltiazem. In patients with severe BB toxicity from atenolol or sotalol and decreased renal function, they recommend ECTR when refractory bradycardia and hypotension, or recurrent torsades de pointes are present. Extracorporeal treatment is not recommended for severe propranolol toxicity.

## Special considerations for individual agents

While the above recommendations on the approach to the evaluation and management of BB and CCB toxicity can be used for most of the drugs in the class, there are a few specific drugs that have unique presentations and management considerations. In addition to the cardiovascular effects, propranolol can also cause seizures which can be treated with benzodiazepines. Sotalol can cause QTc prolongation and can lead to dysrhythmias such as torsades de pointes. Hypokalemia and hypomagnesemia should be corrected as these can increase the risk of associated arrhythmias. If torsades de pointes occurs, both magnesium infusions and overdrive pacing may be effective.[37,38] A unique patient population that is often prescribed BBs and CCBs are individuals with permanent pacemakers or left ventricular assist devices. In these patients, the device does not preclude the development of toxicity and may fail to function.[39] Treatment should follow the same management depending on the clinical symptoms that develop.

# Gaps in knowledge and future directions

As reviewed in this article, the current evidence for the treatment recommendations is largely limited to animal studies, case reports, case series, or expert consensus. Further studies are needed to refine the appropriate treatment and management recommendations. As experience continues to grow with severe CCB and BB toxicity, it will be important to continue to review the safety and efficacy of the recommended treatments. Given the associated morbidity and mortality, there additionally should be on-going efforts to identify evidence-based effective treatments.

# Conclusions

Calcium-channel blocker and BB toxicity can cause severe and refractory bradycardia, hypotension, and shock that often requires multiple pharmacotherapeutic and haemodynamic supportive agents. Given the associated morbidity and mortality it is important to be familiar with the current recommendations for treatment. Additionally, given the limitations of the current evidence, continued evaluation of effective treatment is important for improving the care and survival of patients with CCB and BB toxicity.

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## Data availability

No new data were generated or analysed in support of this research.

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