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The Toxicity of Newer and Lesser-Known Anticonvulsant Drugs

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Abstract

Purpose of Review This review describes newer and lesser-known anticonvulsant drugs. Due to increased diagnostic accuracy of seizure disorder subtypes, as well as escalating off-label and experimental usage, these agents are becoming more commonplace. Important mechanisms of action, pharmacokinetics/pharmacodynamics, critical medication interactions, adverse reactions, toxicities, and treatment strategies are discussed.

Recent Findings Cenobamate, clobazam, eslicarbazepine, ethosuximide, everolimus, felbamate, lacosamide, perampanel, methsuximide, levetiracetam (and the related compound brivaracetam), rufinamide, stiripentol, vigabatrin, and zonisamide are reviewed. As with much in medical toxicology, data and recommendations are derived mainly from physiology bench research, case studies, and expert opinion.

Summary Anticonvulsants are a heterogeneous group of drugs, with newer and lesser-known agents increasing in prominence. These drugs have varied and unique mechanisms of action and toxicities, with which clinicians should be familiar.

Keywords Adverse medication effect · Anticonvulsant · Antiepileptic · Epilepsy · Seizure · Toxicology

Introduction

Anticonvulsants are a diverse group of drugs with varied mechanisms of action. Many are well-characterized and frequently used; however, a variety of newer and lesser-known anticonvulsants are rising in prominence. Toxicities from these drugs are neither well-established nor frequently encountered by most clinicians. A quick reference table for the information included in this review is contained in Table 1.

Supportive care including oxygenation, ventilation, and hemodynamic support with crystalloid and vasopressors is the hallmark of therapy for all xenobiotics discussed. Those caring for these patients should exclude coingestants that may be contributing to the patient's clinical condition. Most of these drugs are sedating; therefore, rhabdomyolysis, aspiration pneumonitis, and concomitant trauma should be considered. All testing discussed in this review is in addition to the minimum studies typical for a toxicology patient: an electrocardiogram, electrolyte panel, acetaminophen and salicylate concentrations, and a pregnancy test (if applicable). While concentrations of these agents are available from reference laboratories, acute management of toxicity is not guided by drug levels. Gastrointestinal decontamination has not been studied in most of these ingestions and should be used with caution. Little data or consensus exists regarding the efficacy of extracorporeal removal of these drugs. Patient care should be coordinated with a toxicologist.

Of note, these drugs' pharmacokinetics and pharmacodynamics are discussed; however, their toxicokinetics and toxicodynamics are much less-studied. Overdose introduces many variables (increased dose, uncertain time of ingestion, presence of vomiting, saturation of proteins and enzymatic processes, coingestions that alter absorption and/

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Table 1 Adverse effects associated with newer and lesser-known anticonvulsants

Drug	Common	Serious	DIHS
Cenobamate	CNS depression	CNS depression	Yes
Clobazam	CNS depression	CNS depression	Rare
Eslicarbazepine	CNS depression	QRS/QTc prolongation	Yes
Ethosuximide	CNS depression	Agranulocytosis	Yes
Everolimus	Stomatitis	Pancytopenia Anemia Thrombocytopenia Leukopenia	Rare
Felbamate	CNS depression	Aplastic anemia Hepatic failure	No
Lacosamide	CNS depression	Crystalluric renal failure QRS prolongation	No
Perampanel	CNS depression	Behavioral/psychiatric	No
Methsuximide	CNS depression	CNS depression	Yes
Levetiracetam/brivaracetam	CNS depression	Psychosis	Yes
Rufinamide	CNS depression	Leukopenia	Yes
Stiripentol	CNS depression	Thrombocytopenia Leukopenia	
Vigabatrin	CNS depression	Vision loss	No
Zonisamide	CNS depression Renal calculi Hyperchloremic metabolic acidosis	Aplastic anemia QTc prolongation	No

or gastrointestinal tract transit times, compromised organ perfusion resulting in decreased elimination, etc.) that affect kinetics and dynamics. The kinetic and dynamic information discussed herein is to be considered a starting point, rather than definitive information upon which disposition decisions are made, in the overdose situation. The authors advise against using a drug's elimination half-life in attempting to predict onset or duration of toxicity. Often, with these substances in particular, insufficient clinical experience exists to inform treatment guidelines or threshold doses for toxicity. Until we gain further experience with overdose of these xenobiotics, anticipated toxicity and suggested management are based upon theory and application of accepted strategies of toxicologic management with other (sometimes similar) substances.

The fifteen drugs discussed herein were chosen by the authors after reviewing the current literature regarding anticonvulsants and the Food and Drug Administration (FDA) prescribing information for such agents. PubMed was queried using the substance name and/or "toxicity," "overdose," and "adverse drug effect." Titles and abstracts were screened by the authors for appropriateness and included if applicable.

This review discusses current knowledge of pharmacokinetics/toxicokinetics of the chosen drugs, reports published clinical experience with toxicity, and suggests reasonable management strategies.

Cenobamate

Cenobamate is a tetrazole alkyl carbamate derivative used to treat partial-onset seizures, either as monotherapy or with other anticonvulsants. Proposed mechanisms of action include voltage-gated sodium channel inhibition and allosteric modulation of $GABA_A$ ion channels, both resulting in inhibition of neuronal signaling and decreased seizure frequency [1, 2].

Peak plasma concentrations occur within 4 h and the drug is approximately 60% protein-bound. Terminal half-life is approximately 50–60 h [1–3]. Metabolism occurs primarily by CYP2E1 and 2C19 [1–3].

Cenobamate decreases the efficacy of oral contraceptives. It decreases plasma concentrations of carbamazepine and lamotrigine, as well as increases phenytoin and phenobarbital concentrations. It competes with and possibly decreases efficacy of other 2B6 substrates such as bupropion, coumarins, cyclophosphamide, efavirenz, methadone, nevirapine, and propofol. It may increase the effects of 2C19 substrates including citalopram, escitalopram, and sertraline.

Experience with cenobamate toxicity is limited. A variety of central nervous system (CNS) effects including dizziness, ataxia, diplopia, nystagmus, and dysarthria have been described in initial efficacy studies and post-marketing surveillance. Patients have also experienced fatigue, somnolence, increased suicidality, and nausea/vomiting. Life-threatening

drug-induced hypersensitivity syndrome (DIHS, formerly termed drug reaction with eosinophilia and systemic symptoms or DRESS) has been reported [2, 4]. Limited evidence suggests liver enzyme elevation and elevation of creatinine occurring with higher dosing [1]; however, the clinical significance of such is unclear.

Treatment of toxicity is supportive; no antidote exists, and the drug's relatively high degree of protein binding makes it resistant to extracorporeal removal. An adequate airway, oxygenation, and ventilation should be ensured. DIHS mandates that the offending drug be discontinued immediately; treatment should be supportive and undertaken in conjunction with dermatology and immunology specialists. Cenobamate toxicokinetics have not been established; therefore, 24-h monitored observation of overdose patients is reasonable, particularly given its sodium channel blocking properties.

Clobazam

Clobazam is a 1,5-benzodiazepine used in the treatment of Lennox-Gastaut syndrome. As a benzodiazepine, clobazam is a $GABA_A$ antagonist that increases neuronal chloride influx and subsequent hyperpolarization.

Concentrations peak within 3 h. Clobazam is metabolized by CYP3A4 to *N*-desmethylclobazam (NDMC), with 2B6 and 2C19 playing minor roles [5–7]; the majority is renally excreted. Similar to diazepam and its active metabolite desmethyldiazepam, NDMC is an active metabolite that also acts at the GABA receptor, prolonging overall effects of the drug. Similar to diazepam and midazolam, hepatic dysfunction and resultant decreased metabolism lead to increased clobazam concentrations and may cause prolonged clinical effects. Clobazam and its metabolites are highly protein-bound [8].

Clobazam is generally well-tolerated. Overdose is characterized by CNS depression without inhibition of respiratory drive, though respiratory depression is possible when combined with other sedatives. DIHS occurs with therapeutic use, but at a much lower frequency than other implicated anticonvulsants. Benzodiazepine withdrawal is possible in patients who chronically take clobazam.

Supportive care is the hallmark of treatment. Clobazam overdose is expected to respond to flumazenil; however, this reversal agent should be used with caution, as it can precipitate difficult-to-treat seizures and other withdrawal phenomena. Extracorporeal removal is difficult. A 6-h monitored observation period is reasonable; if the patient remains asymptomatic, significant toxicity is unlikely. Similar to other benzodiazepines, clobazam withdrawal is treated with GABA agonists such as benzodiazepines and barbiturates.

Eslicarbazepine

Eslicarbazepine is a third-generation dibenzazepine related to carbamazepine and oxcarbazepine. It is used to treat temporal lobe and complex partial seizures [9]. This drug is similar to oxcarbazepine in that they are both prodrugs that exert their anticonvulsant effects after being converted to the active metabolite licarbazepine, a voltage-gated sodium channel blocker.

Peak absorption occurs within 4 h [10], the drug is approximately 30% protein-bound [11], and elimination half-life is approximately 20–40 h. Eslicarbazepine primarily undergoes renal excretion [10, 11]. Likely due to cytochrome p450 interactions, anticonvulsant effects of eslicarbazepine are decreased by carbamazepine, phenobarbital, phenytoin, and topiramate. Eslicarbazepine increases the concentration of phenytoin and decreases concentrations of carbamazepine, lamotrigine, topiramate, and valproic acid.

Experience with eslicarbazepine toxicity is limited; however, given its similarity to oxcarbazepine in producing a common metabolite, toxicity is expected to be similar. CNS and cardiovascular effects would be expected in both acute and chronic overdose. Somnolence, dizziness, nystagmus, and tremor are typical. PR and QTc interval prolongation have been reported, and QRS widening may occur due to sodium channel blockade [12]. In severe cases, respiratory depression and blood pressure fluctuations are also possible. Drug-induced liver injury is possible, similar to oxcarbazepine.

Treatment of eslicarbazepine toxicity is primarily supportive; however, sodium bicarbonate administration should be undertaken for QRS widening, as well as magnesium delivery for QTc prolongation. The sodium channel blockade from eslicarbazepine can be severe; coordination of care with a toxicologist is advised. A single case report describes improvement with hemodialysis [9]; however, the patient also underwent multiple other treatment modalities, making it difficult to assess extracorporeal removal's effectiveness. A minimum observation period of 6 h is recommended; 24 h may be prudent given eslicarbazepine's cardiotoxicity.

Ethosuximide

Ethosuximide is a succinimide used to treat absence seizures. It reduces low-voltage calcium currents in the thalamocortical neurons, thus suppressing absence seizure activity [13].

Peak concentrations are reached within 5 h and the drug is not significantly protein-bound. Elimination half-life averages 30–60 h in adults and 30–40 h in children [14]. Metabolism is mainly by CYP3A4 [14, 15].

Ethosuximide causes numerous adverse effects in both therapeutic dosage and overdose. Dose-dependent CNS symptoms range from headache and dizziness to fatigue,

somnolence, and coma. Idiosyncratic effects seen both in normal usage and overdose include serum sickness, DIHS, agranulocytosis, and pancytopenia.

Treatment of toxicity remains supportive, as no specific antidote or reversal agent exists. Hemodialysis has been posited as a treatment for overdose, but definitive data are lacking [16]. Similarly, hematologic toxicity such as agranulocytosis and leukopenia may be treated with colony-stimulating factors, but no data exist regarding their effectiveness in the overdose situation. In addition to supportive care, blood counts should be assessed and the patient should be observed for at least 6 h in a monitored setting following acute overdose. While no specific data exist regarding such, the authors suggest monitoring blood counts daily if symptoms develop, and every 3 days for 10 days after overdose in asymptomatic patients.

Everolimus

Everolimus is a mammalian target of rapamycin (mTOR) inhibitor used for seizures in patients with tuberous sclerosis. mTOR dysregulation results in dysplastic neurons and abnormal excitatory axogenesis in the brain, leading to overstimulation and seizures [17, 18].

Everolimus reaches peak serum concentrations within 2 h, and is metabolized by CYP3A4, 3A5, and 2C8. Everolimus is also a substrate for p-glycoprotein. CYP3A4 and p-glycoprotein inhibitors should be avoided or the dosage of everolimus should be decreased to prevent toxicity. Hundreds of p-glycoprotein inhibitors exist, including amiodarone, ketoconazole, diltiazem, verapamil, and proton-pump inhibitors.

Overdose is not well-described; however, toxicity in therapeutic usage includes stomatitis, oral ulcers, and increased risk of infection. Interstitial lung disease is well-described in chronic use. Other effects include fatigue, headache, convulsions, and gastrointestinal distress [18–20]. Metabolic derangements include hypertriglyceridemia, elevated transaminases, and renal insufficiency. Hematologic effects (thrombocytopenia, leukopenia, and anemia) also occur [19]. Amenorrhea and irregular menstruation are reported.

Treatment of toxicity is primarily supportive, analogous to sirolimus and other mTor inhibitors. Acute overdoses are likely to be well-tolerated, while chronic toxicity may require treatment with blood product transfusion (for anemia and/or thrombocytopenia), colony-stimulating factors to treat leukopenia, and corticosteroids for pulmonary toxicity. Given that evidence of everolimus toxicity can be delayed, a 24-h observation period and repeat laboratory assessment following overdose are reasonable.

Felbamate

Felbamate is a dicarbamate derivative used as adjunctive treatment for partial seizures in adults and Lennox-Gastaut syndrome in children. It is not considered a first-line agent due to its significant adverse effect profile and prolonged half-life. Felbamate antagonizes the strychnine-insensitive glycine-recognition site of the *N*-methyl-D-aspartate (NMDA) receptor-ionophore complex, thereby indirectly potentiating endogenous GABA effects [21].

After ingestion, felbamate reaches peak plasma concentrations in 3 to 5 h; about 25% is protein bound [22]. About 50% of the drug is excreted unchanged in the urine [23]. Hydroxylation by CYP2E1 and 3A4 and subsequent conjugation produce inactive metabolites.

Felbamate increases the steady-state concentrations of phenytoin and valproic acid and decreases carbamazepine levels. Carbamazepine and phenytoin may decrease levels of felbamate; gabapentin and valproic acid increase felbamate concentration.

Therapeutic felbamate usage has been associated with acute hepatic failure and a 100-fold increase in the risk of aplastic anemia. It is contraindicated in patients with liver dysfunction. It is prudent to monitor transaminases, coagulation parameters, and blood counts in patients taking felbamate.

While no mortality has been reported, clinical manifestations reported following felbamate overdose include sinus tachycardia and nausea/vomiting. CNS effects include drowsiness, slurred speech, and ataxia. Case reports describe needle-shaped felbamate crystalluria associated with reversible renal failure [24, 25].

Management is supportive, with no specific toxicologic recommendations for felbamate-associated liver injury. Parenteral hydration is the mainstay of therapy for felbamate-induced crystalluria [24, 25]. We recommend supportive care and monitoring patients for at least 6 h; evaluation should include a complete blood count, coagulation parameters, transaminases, bilirubin fractionation, and urinalysis with crystal analysis. If the patient remains asymptomatic and studies are normal at that time, we feel that significant acute toxicity is unlikely.

Lacosamide

Lacosamide is used as monotherapy or in combination with other anticonvulsants for partial seizures, as well as in the treatment of diabetic neuropathy [26]. Lacosamide is a functionalized amino acid that binds a collapsin response mediator protein (CRMP-2) [27], enhancing slow inactivation of voltage-gated sodium channels, therefore decreasing neuronal firing and resultant epileptiform activity [28]. This mechanism

is different to traditional sodium-channel blocking drugs, which affect the fast inactivation of the channels [29].

Maximum plasma concentration is reached within 4 h. Protein binding is less than 15%. Lacosamide is a CYP2C19 substrate. Atazanavir and saquinavir's cardiotoxicity can be potentiated by lacosamide. Lacosamide is primarily excreted in the urine, and it is not known to cause clinically significant drug interactions with other anticonvulsants.

Lacosamide overdose is characterized by CNS depression, gastrointestinal effects, QRS prolongation with resultant dysrhythmias [30–34], and hypotension. Hepatotoxicity [35] and pancreatitis [36] have also been reported in therapeutic usage.

Management is primarily supportive. Bicarbonate has been effective in treating QRS prolongation and resultant dysrhythmias. Hemodialysis results in removal of lacosamide from the blood compartment, although there are no reports of it being used in overdoses [37]. Given its sodium channel effects, we suggest a minimum of 6 h monitoring.

Perampanel

Perampanel is a noncompetitive AMPA receptor antagonist; excitatory glutamatergic AMPA receptors reside on postsynaptic neurons, and antagonism results in termination of epileptiform discharges [38].

Peak plasma concentrations are reached within 2.5 h after ingestion. It is almost completely protein-bound, and has an extremely long half-life of more than 70 h. Almost all perampanel is metabolized by CYP3A4 to inactive compounds. Its metabolism is induced by carbamazepine and phenytoin, likely via CYP2C9 and the 3A family [39].

Somnolence, stupor, and prolonged unconsciousness that require extended periods of airway protection and intensive care [40•, 41] have been reported after overdose of perampanel. Psychiatric or behavioral reactions including aggression, worsening of depression, and suicidality have been reported following both therapeutic and toxic ingestions of perampanel [42, 43].

Management of toxicity is supportive, primarily focusing upon adequate ventilation and oxygenation. We suggest a 6-h monitoring period; if symptoms do not develop in that time, significant toxicity is unlikely.

Methsuximide

Methsuximide is a succinimide that treats absence seizures. Although the exact mechanism of action is unknown, it is similar to ethosuximide as it reduces low-voltage, low-threshold T-type calcium channel currents in thalamic neurons and decreases corticothalamic activity of absence seizures.

The drug's anticonvulsant and toxic effects are likely due to its major hepatic metabolite *N*-desmethylmethsuximide (NDM), formed by CYP3A4. The half-life of methsuximide is slightly less than 3 h; NDM's half-life is 15 h, which may accumulate during repeated dosing and overdose.

Acute overdose causes nausea, vomiting, and deep/prolonged CNS depression. Toxicity follows a biphasic course, with an initial short phase of somnolence followed by transient recovery before prolonged depression of mental status occurs, likely due to the presence of both methsuximide and NDM [44]. Like other succinimides, methsuximide may cause DIHS in therapeutic usage.

Supportive management and close monitoring for delayed deterioration of mental status are required. A minimum of 24 h of monitored observation is suggested, due to the biphasic nature of toxicity. Charcoal hemoperfusion was shown to eliminate NDM and improve mental status in a case report [45]; however, this case report was complicated by coingestions.

Levetiracetam/Brivaracetam

Levetiracetam is a pyrrolidine which inhibits the membrane glycoprotein synaptic vesicle protein 2A (SV2A), which plays a key role in action potential-induced vesicular neurotransmitter release [46]. Inhibition of SV2A results in decreased neuronal activation and subsequent prevention/termination of seizure activity. Brivaracetam is a levetiracetam analogue with twenty times higher affinity for SV2A [47].

Levetiracetam reaches peak concentrations in approximately 1 h; less than 10% is protein-bound, and two-thirds of the drug is renally excreted unchanged. Metabolism is independent of CYP450 activity; this, coupled with low protein binding, makes levetiracetam less likely to interact with other medications. Brivaracetam also reaches peak concentrations quickly, and less than 20% is protein-bound. It undergoes metabolism similar to levetiracetam by enzymatic hydrolysis, although a smaller proportion is also hydroxylated by CYP2C19 [48].

Most overdoses are rather benign, with mild CNS depression, ataxia, and vertigo. Symptom onset should occur within 6 h. Massive ingestion may result in CNS depression, hypoventilation, hypoactive deep tendon reflexes, bradycardia, and hypotension [49].

Management is primarily supportive. Extracorporeal elimination has been reported to effectively eliminate levetiracetam, although no literature supports its use in overdose scenarios. Brivaracetam pharmacokinetics are not altered by hemodialysis [50].

Rufinamide

Rufinamide is a triazole derivative used as adjunctive therapy for Lennox-Gastaut syndrome. It prolongs sodium channel inactivation, preventing the generation of sustained bursts of action potentials and subsequent seizure activity.

Time to peak is 5–6 h after ingestion. Less than 35% is protein-bound. Rufinamide is hepatically metabolized and renally eliminated. Rufinamide is a weak CYP3A4 inducer [51], and may decrease plasma carbamazepine and lamotrigine levels. It may minimally increase phenobarbital and phenytoin concentrations [52].

Rufinamide causes fatigue, somnolence, dizziness, diplopia, nausea/vomiting, and leukopenia [52, 53]. Rufinamide can also shorten the QTc interval and should be avoided in those with familial short QT syndrome, due to a possibly increased risk of life-threatening dysrhythmias [54].

In overdose, we suggest 24 h of monitoring and assessment of a CBC in addition to standard supportive care.

Stiripentol

Stiripentol is an aromatic allylic alcohol introduced as adjuvant therapy for Dravet syndrome. Stiripentol's anticonvulsant activity is likely multifactorial. Its direct activity is likely due to enhancement of $GABA_A$ neurotransmission, particularly receptors containing an alpha-3 subunit. Alpha-3 subunit expression is developmentally regulated, with the highest levels of such in immature brains (which may explain the drug's greater clinical efficacy in childhood-onset seizures, including Dravet syndrome). Stiripentol also inhibits many cytochrome isozymes. This may enhance the clinical effect of other anticonvulsants such as phenytoin, carbamazepine, clobazam, phenobarbital, and valproic acid, all of which are frequently used in concert with stiripentol.

Stiripentol causes CNS effects such as somnolence and paradoxical agitation, tremor, dysarthria, ataxia, and hypotonia. Nausea/vomiting and hematologic effects include thrombocytopenia and neutropenia.

Management of toxicity is supportive. Very little literature exists regarding overdose; therefore, we suggest 24 h of monitored observation and a CBC in addition to supportive care.

Vigabatrin

Vigabatrin is a stereospecific structural analogue of GABA which irreversibly inhibits GABA transaminase (hence the name "viGABA-Trin"), the enzyme responsible for GABA catabolism. This inhibition results in increased CNS GABA concentrations and a raised seizure threshold. Vigabatrin is typically used in patients with refractory partial seizures and infantile spasms.

Peak concentrations occur within 2 h. No significant plasma protein binding is observed. Vigabatrin decreases concentrations of phenytoin and may increase carbamazepine concentrations.

Acute vigabatrin overdose causes a variety of CNS effects, ranging from somnolence and coma to agitation and acute psychosis; the reason for paradoxical CNS hyperexcitability is unknown. Chronic use is associated with dizziness, tremor, depression, and psychosis. Retinopathy with permanent visual loss, typically in peripheral visual fields, occurs in more than 40% of patients taking vigabatrin [22, 55, 56•, 57].

Management of toxicity is largely supportive. Activated charcoal does not significantly adsorb vigabatrin. Benzodiazepines should be used for CNS excitation. Although renal clearance has improved in those with chronic renal failure, extracorporeal vigabatrin removal has not been studied in overdose situations. While the risk of visual field defects is dose-dependent and cumulative, we recommend ophthalmologic consultation after overdose.

Zonisamide

The sulfonamide zonisamide is used for partial seizures. Blockade of neuronal voltage-gated sodium channels and low-voltage, low-threshold T-type calcium channels likely accounts for its anticonvulsant effect. Zonisamide inhibits carbonic anhydrase; however, this does not contribute to its anticonvulsant effect [58–60].

Absorption peaks within 5 h, but elimination half-life is long at approximately 60 h. There is approximately 40–50% binding to plasma proteins. Zonisamide is hepatically metabolized via CYP3A4; therefore, other 3A4 drugs (e.g., phenytoin, carbamazepine, and valproic acid) may affect and be affected by zonisamide [61].

CNS depression is the cardinal clinical effect [62, 63]. Hyperchloremic metabolic acidosis and renal calculi due to carbonic anhydrase inhibition are possible. QTc prolongation, hypotension, aplastic anemia, and DIHS have also been noted.

In addition to supportive care, we suggest 24 h of monitored observation and assessing blood counts in an acutely poisoned patient. There is no antidotal therapy. Zonisamide is renally cleared and a single dialysis session has been shown to reduce plasma concentrations by 50% [64]. No data suggests extracorporeal removal is recommended in acute ingestions.

Conclusion

Caring for overdose patients can be challenging due to lack of clinical experience and evidence-based guidance. Supportive care is the hallmark of therapy for all poisonings, including those due to esoteric anticonvulsants. Timely drug levels are not typically available in these situations and do not guide management. A thorough history, examination, screening studies, and coordination with a toxicologist are recommended.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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