
**REVIEW ARTICLE**

# Potential of Agmatine as a New Neuroprotective Molecule in Brain Disorders

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## Abstract:

Agmatine, a cationic endogenous polyamine in the central nervous system, is obtained from the decarboxylation of arginine. Agmatine exerts neuroprotective properties, according to a growing body of experimental data. This review aims to describe the present understanding of the involvement of agmatine in the central nervous system and highlight its potential as a new pharmacological therapy as a neuroprotective agent. A few molecular pathways for agmatine's neuroprotective properties are also highlighted. Several studies have shown that agmatine has neuroprotective properties in a variety of neurological conditions, including stroke and traumatic brain damage. The prevention of brain edema, blood-brain barrier protection, anti-oxidation, anti-apoptosis, and anti-inflammation is some of the proposed neuroprotective mechanisms of agmatine. Agmatine is extremely effective in treating neurological diseases, as evidenced by its safety and low occurrence of side effects. However, the majority of the studies on agmatine that is now accessible were conducted using different experimental models; further, clinical trials are required before agmatine may be used extensively in clinical settings.

**Keywords:** Agmatine, Neuroprotection, Stroke, Traumatic brain injury, Mechanisms

## 1. Introduction

Agmatine, a polyamine that regulates inflammation, oxidative stress, cellular apoptosis, and brain edema, has been shown to exert neuroprotective effects in several neurological illnesses [1]. Albrecht Kossel, a Nobel Prize winner, found that it was widely generated in both bacteria and plants [2]. It was produced by L-arginine being decarboxylated by arginine decarboxylase (ADC), whereas agmatine hydrolyzed it to form putrescine and urea [3]. Li G *et al* discovered ADC and agmatine in the mammalian brain in 1994 [4]. Practically all rodent organs have been studied for agmatine,

and in fact, the brain agmatine concentration is substantially lower than that of other organs, primarily the stomach, aorta, and small intestine, where agmatine is very high [5]. The cellular and regional distribution of agmatine has been mapped immunohistochemically using highly specific antibodies in the central nervous system (CNS) of mammals. Agmatine immunoreactivity at the cellular level was discovered to be largely neuronal, but it was also detected chemically and immunocytochemically in cultured astrocytes and C6 glioma cells [6,7]. Recently, it was found that agmatine is synthesized in the spinal cord and brain. L-arginine enters the presynaptic terminal

through a transporter, where it is decarboxylated by the mitochondrial ADC to agmatine, which is then stored in synaptic vesicles, released by  $\text{Ca}^{2+}$ -dependent depolarization, inactivated by reuptake, and enzymatically destroyed by an enzyme called agmatinase [8]. Importantly, agmatine is found in the brain in concentrations comparable to several common neurotransmitters [5,9]. All data points to the possibility that agmatine is a novel neurotransmitter in the CNS, where it interacts with receptors and neuronal pathways to produce several biological effects [10]. A growing number of studies are examining the consequences of agmatine on the CNS in various cellular and animal models.

Agmatine has recently attracted a lot of attention due to its neuromodulatory and neuroprotective qualities. Studies investigating the consequences of exogenous agmatine administration have found a number of CNS-relevant functions of this amine that has potential therapeutic significance. For instance, preclinical studies have proven that agmatine is useful for treating hypoxic ischemia [11], nociception [12], morphine tolerance [13], drug withdrawal [14], seizures [15], depression [16,37], anxiety [17], memory [18], and Parkinson's disease [19]. The potential utility of agmatine in treating certain CNS illnesses has been further explored over the past few years. Agmatine binds with great affinity to all subclasses of  $\alpha_2$ -adrenoceptors and imidazoline binding sites, even though its own postsynaptic receptor has not yet been discovered [4]. In addition, it engages nicotinic cholinergic receptors [20], serotonin 5-HT<sub>3</sub> receptors [21], and inhibits ligand-gated cation channels, particularly the glutamate N-methyl-D-aspartate (NMDA) receptors [22]. In addition, agmatine reduces inflammation and protects against oxidative stress brought on by an increase in mitochondrial volume, a collapse in mitochondrial membrane potential, and apoptosis by scavenging free radicals [23-25]. Furthermore, agmatine activates neurotrophic and neuroprotective pathways and partially contribute to its cellular and molecular effects [26]. The pharmacological and physiological impact of agmatine on mammals was the subject of the numerous studies that followed. Agmatine has proven to exhibit protection against several organ illnesses, including cardio-, nephro-,

gastro-, neuro-, and gluco-protection [27]. Agmatine lowers blood pressure and heart rate through regulating imidazoline receptor subtypes, norepinephrine release, and nitric oxide (NO) generation. It may also improve cardiac ischemia and hemodynamic recovery, and restore blood pressure [28]. Agmatine elevates the glomerular filtration rate (GFR) by activating endothelial NO synthase (eNOS). Furthermore, agmatine improves renal disease through cytoprotective mechanisms [29].

Numerous studies have examined the probable causes of neurological disorders and the neuroprotective properties of different medications during the past few decades. However, additional clinical trials were severely restricted by the negative impact of these medications. It was interesting to discover that agmatine occurs naturally in a wide variety of foods. Agmatine-containing sulfate salt is now available on the market as a nutraceutical after being used for many years as a dietary component [30]. By taking a daily dose of oral agmatine for 4–5 years, researchers evaluated the safety of the medication over a long period of time. Over the course of the follow-up period, all measurements stayed within normal ranges, and no discomfort was noticed [31]. Moreover, since 1994, several research studies have discovered that agmatine possesses a neuroprotective effect, which was initially discovered by Gilad [32]. Numerous therapeutic benefits and a low incidence of side effects have drawn considerable interest. Agmatine has since been linked to a neuroprotective effect in research on stroke, traumatic brain injury, and other conditions. The common mechanisms behind the neuroprotective benefits include: (i) Inhibition of oxidative stress, apoptosis, and inflammation, (ii) protection of the blood-brain barrier (BBB), and (iii) inhibition of cerebral edema. The main focus of this review is on the neuroprotective properties of agmatine and their likely mechanisms in relation to neurological diseases.

## 2. Neuroprotective role of agmatine

### 2.1. Agmatine and ischemic stroke

In the world's adult population, stroke is the second-most frequent disorder to result in death and disability. Lack of blood and oxygen reaching the brain causes ischemic stroke [33]. It was found that

the incidence of stroke increased the generation of matrix metalloproteinase-2 (MMP-2) and MMP-9, which can damage the BBB structure and cause brain edema [34]. Numerous studies support the fact that agmatine is helpful in the prevention of stroke. Agmatine's neuroprotective effects were demonstrated both *in vitro* and *in vivo* [1]. The mechanism used for this was the competitive inhibition of inducible NO synthase (iNOS) and neuronal NO synthase (nNOS), which reduced NO generation. Agmatine, on the other hand, has the ability to activate eNOS, which raises the formation of NO and works as a vasodilator to enhance blood flow rate in ischemic areas [35,36]. According to the researcher, both exogenous and endogenous agmatine can show their effects on the NOS and lessen hypoxic-ischemic brain damage in newborn rats [38]. Maintaining microvascular integrity and homeostasis requires the BBB, which is crucial. Agmatine can suppress the generation of MMP-9 and MMP-2 by inducing eNOS *in vitro*. In another study, a retrovirus was used to stimulate endogenous agmatine, which revealed that endogenous agmatine lowers MMP-2 and MMP-9 activation by regulating eNOS and NO and activating transcription factor 3 (ATF3) [39,40].

Brain edema has frequently been seen to play a role in the development of cerebral ischemia and the rise in mortality following stroke attacks. According to research, brain edema is strongly correlated with the upregulation of aquaporins-1 and -9 (AQPs) and BBB disruption, both of which are significantly mitigated by agmatine treatment. In addition, other research demonstrated how agmatine inhibited the formation of AQP-4, which in turn reduced cerebral edema [41]. Overall, both *in vitro* and *in vivo* models of ischemic stroke demonstrated the neuroprotective properties of agmatine.

## 2.2. Agmatine and traumatic brain injury

A traumatic brain injury (TBI) is described as brain damage brought on by external physical trauma. TBI pathophysiological manifestations can be divided into acute and delayed events. Acute events include all manifestations that can happen minutes to hours after the initial injury, such as impaired regulation of cerebral blood flow, tissue damage, focal contusions, hematomas, diffuse swelling,

microporation of membranes, and conformational changes in proteins [42]. Delayed events usually follow acute events and can manifest hours, days, or even weeks after the trauma. Edema, inflammatory reactions, dysfunction of astrocytes and microglia, BBB disruption, excitotoxicity, oxidative stress, mitochondrial dysfunction, and hypoxia are examples of delayed events [42,43].

Agmatine's therapeutic effects in TBI have recently been confirmed by numerous investigations. Agmatine's neuroprotective properties were initially studied in mouse brain injuries [11]. Agmatine (50 mg/kg, intraperitoneal) was given to rats shortly after the onset of lateral fluid percussion injury. It decreased the TBI-induced elevation of the hippocampal lactate to pyruvate ratio, glycerol, cerebral hypoperfusion, intracranial hypertension, and cerebral infarction, as well as deficits in motor and proprioception. It also decreased the excessive buildup of NO and glutamate. Agmatine can reduce glial and neuronal apoptosis, suppress gliosis, and promote angiogenesis and neurogenesis, according to a series of studies done by researchers on the substance's neuroprotective properties [44]. Researchers also discovered that agmatine lowers brain edema by inhibiting the activation of AQP-1, -4, and -9. In addition, they discovered that agmatine prevents cellular death by preventing MAPK phosphorylation and enhancing NF- $\kappa$ B nuclear translocation following TBI. Agmatine has also been shown to have neuroprotective effects in a rat model of spinal cord injury. By reducing the NOS and NMDA receptors, it has the potential to significantly improve locomotor activity and decrease tissue damage [45].

## 3. Role of agmatine in neural injuries

### 3.1. Spinal cord injury

Agmatine also had beneficial effects in animal models of spinal cord injury. Through increasing bone morphogenetic protein 7 (BMP-7), a neuroprotective marker, and decreasing transforming growth factor-beta 2 (TGF- $\beta$ 2), a marker of collagen deposition, mice treated chronically (4 weeks) with agmatine demonstrated improved recovery of medullar tissue transection (as shown by the reduced collagen scar) [46]. According to the study, it was found that continuous

agmatine treatment (35 days) decreased the deficits brought on by spinal cord compression. Improved motor and bladder function, a reduction in demyelinated cells, neuronal loss, and glial buildup near the injury were all protective benefits of this amine [46-47].

### 3.2. Neurotoxicity caused by glutamate

Studies examining the influence of agmatine on cellular models of glutamatergic neurotoxicity showed that the drug produced neuroprotective action on hippocampal neurons in culture, cerebellar granule cells, and PC12 cells, a line generated from a pheochromocytoma of the rat adrenal medulla [48-50]. These protective effects of agmatine in neuronal cultures were not seen in spermine and spermidine's metabolites [49]. In a glutamatergic model of epilepsy, the use of agmatine exhibited protective effects as well. These results indicate that NMDA receptor antagonistic activity is a key neuroprotective mechanism through which agmatine exerts its positive benefits.

### 3.3. Retinal injury

Agmatine exerts neuroprotective benefits against the hydrogen peroxide-induced damage of cultured retinal cells; this amine's antioxidant property is another significant feature that may be helpful in the neuroprotective property of this compound [51]. For neurons to operate perfectly, mitochondrial activities are necessary. In this context, a few facets of agmatine's participation in the mitochondrial process were assessed. Agmatine treatment preserved mitochondrial activity and reduced cell death processes such as apoptosis, necrosis, DNA fragmentation, and chromatin condensation. Agmatine also exhibited scavenger capabilities as it reduced oxidative stress, B-cell lymphoma 2 (Bcl 2) and caspase-3 expression, along with apoptosis induced by camptothecin and 5-fluorouracil [52] (Table 1).

## 4. The molecular basis for agmatine's neuroprotective effects

Agmatine has been well studied for its neuroprotective properties, and the mechanisms governing such effects include anti-oxidation, anti-inflammation, anti-apoptosis, BBB protection, and the protection of brain edema.

### 4.1. Anti-oxidant effects

Oxidative stress has a significant role in the etiology of many diseases. It is primarily caused by an imbalance in the cell's pro-oxidant and anti-oxidant systems. It has been demonstrated that agmatine and other substances can decrease oxidative stress and protect cells from damage. According to several findings, agmatine protects retinal ganglion cells (RGCs) from H<sub>2</sub>O<sub>2</sub>-induced damage by activating the  $\alpha$ 2 adrenergic receptor signaling pathway [62,74]. Agmatine can exert its anti-oxidative impact by preserving the antioxidant defense system and reviving the antioxidant capacity of liver tissue. In addition, many studies have demonstrated that agmatine has an anti-oxidative impact in the context of neurological illnesses. The oxidative stress evoked by lipopolysaccharide (LPS) in the prefrontal cortex and hippocampus can be reduced by agmatine [63]. This effect may be attained by preventing lipid peroxidation and controlling the activities of superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione reductase (GR). In addition, it was found that agmatine reduces the generation of free radicals and reactive oxygen species (ROS), which have been shown to exert anti-oxidative stress in stroke and TBI [27].

### 4.2. Anti-inflammatory effects

An intricate immunological reaction of the injured organisms is inflammation. In normal circumstances, inflammation may aid in scavenging dead cells or tissues and the beginning of the tissue repair process. Although overactive immune responses can injure organisms and result in injury, agmatine's anti-inflammatory effects manifested themselves in numerous ways. Agmatine decreases the symptoms of arthritis in living organisms by lowering the levels of inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor (TNF- $\alpha$ ). In an *in vitro* study, agmatine was also proven to be able to minimize cell mortality and block the formation of pro-inflammatory cytokines, including IL-6, TNF- $\alpha$ , and CCL2 [64,73]. Agmatine could lessen sub-chronic stress by lowering the levels of pro-inflammatory cytokines and the gene expression of the nod-like receptor protein-3 (NLRP3) and its inflammasome components (NLRP3, NF-kappaB,

**Table 1.** The neuroprotective properties of agmatine in various forms of neural injury

S. No.	Injury types	Agmatine concentration	Observations	References
<b>Neurotoxicity caused by glutamate</b>				
1.	Excitotoxic; glutamate (10 mM), NMDA (100 mM), staurosporine (100 nM), or calcimycin (100 nM), for 10 min	10, 100, or 1000 $\mu$ M for 24 h.	(1) Effect induced by blocking NMDA receptors. (2) Although staurosporine protein kinase blockade and calcimycin increase cellular calcium, they have no effect on the reduction in LDH release caused by glutamate.	[48]
2.	Excitotoxic; NMDA/ glutamate (100 or 200 $\mu$ M), 1 h	1–100 $\mu$ M, or MK801 (10 $\mu$ M), arcaine, spermine, or putrescine (100 $\mu$ M)	(1) Agmatine prevented neurotoxicity similar to arcaine, MK801. Spermine and putrescine do not show this effect. (2) Probable NMDAR channel blockage or potential anti-apoptotic property.	[49]
<b>Oxidative Stress</b>				
3.	Oxidative toxicity LPS	100 $\mu$ M	By lowering the production of Iba1, iNOS, TNF- $\alpha$ , and IL-1 $\beta$ , agmatine suppressed LPS-induced microglial injury.	[53]
4.	Oxidative toxicity LPS	1–300 $\mu$ M	(1) Agmatine decreased neuronal loss brought on by NO produced by microglia. (2) Agmatine reduced LPS-induced NO generation but had no effect on the formation of iNOS.	[54]
<b>Spinal cord injury</b>				
5.	Spinal cord injury, complete transection	100 mg/kg/day, i.p., 5 min after SCI and daily till 4 weeks	(1) Agmatine improved the surface-righting reflex. (2) Decreased formation of TGF $\beta$ -2, elevated formation of BMP-7.	[42]
6.	SCI, contusion	100 mg/kg/day, 30 min after SCI and daily till 14 days	Up to 44 days after SCI, increased locomotor function and lowered tissue injury.	[45]
7.	SCI, compression	50 or 100 mg/kg/day i.p.; 5 min after SCI, daily till 10 day	Agmatine improved functional recovery and reduced NO level.	[55]
<b>Protection of the retinal ganglion cells</b>				
8.	Hypoxic; O <sub>2</sub> 5%, 48 h	100, 500 $\mu$ M	(1) Agmatine prevented hypoxia-induced apoptotic death (2) Effects exhibited, along with the action of JNK & NF- $\kappa$ B pathways	[56]
9.	Transient ischemia-reperfusion	50 mg/kg, i.p.	Agmatine inhibited retinal thickening, lipid peroxidation, NO synthesis	[57]
10.	Phototoxicity	1–8 $\mu$ M	Agmatine prevented phototoxic effects by controlling the elevation of ROS, Ca <sup>2+</sup> , NO, TNF- $\alpha$	[58]

(Cont'd...)

**Table 1. (Continued)**

S. No.	Injury types	Agmatine concentration	Observations	References
<b>Neurotoxicity caused by glucocorticoids</b>				
11.	Neurotoxic; DXM (0.05, 0.5 or 5 mM) and/or COS 1 $\mu$ M	100 $\mu$ M (or arcaine, spermine or putrescine 100 $\mu$ M)	(1) Glucocorticoids increased LDH, caspase-3 activities TUNEL-positive cell numbers, caused morphological alterations (2) Agmatine and arcaine therapy reduced GC-induced effects, but neither spermine nor putrescine did	[59]
12.	Neurotoxic; 6 h of restraint stress daily till 21 days	50 mg/kg/day, i.p.	(1) Agmatine reduced restrain stress induced elevated ADC levels in the striatum, hippocampus, mPFC, hypothalamus (2) Exogenous agmatine prevented an elevated ADC levels (3) Agmatine attenuated the morphological alterations brought on by stress in the hippocampus and mPFC	[60]
13.	Neurotoxic; COS 1 $\mu$ M	100 $\mu$ M	(1) Morphologic alterations, increased ROS generation, and apoptosis were brought on by COS (2) Agmatine decreased the impacts of COS	[61]

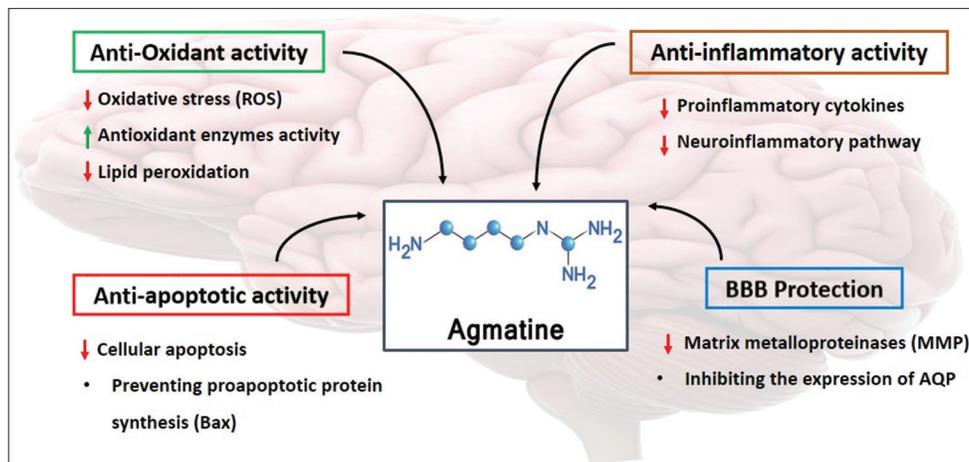
Abbreviations: ADC: Arginine decarboxylase; BMP-7: Bone morphogenetic protein 7; COS: Chitosan Oligosaccharides; DXM: Dexamethasone; GC-induced: Glucocorticoids-induced; Iba1: Ionized calcium-binding adaptor molecule 1; IL-1  $\beta$ : Interleukin 1 beta; iNOS: Inducible NO synthase; JNK: Jun N-terminal kinase; LDH: Lactate dehydrogenase; LPS: lipopolysaccharide; mPFC: Medial prefrontal cortex; NF- $\kappa$ B: Nuclear factor kappa B; NMDA: N-methyl-D-aspartate; NO: Nitric oxide; ROS: Reactive oxygen species; SCI: Spinal cord injury; TGF $\beta$ -2: Transforming growth factor beta 2; and TNF- $\alpha$ : Tumor necrosis factor.

PYCARD, caspase-1, IL-1 $\beta$ , and IL-18). In addition, agmatine has the capability to reverse the alteration of several anti-inflammatory cytokines, including IL-4 and IL-10 [65]. By controlling the activation of pro-inflammatory cytokines, agmatine also demonstrated anti-inflammatory effects in a variety of different neurological conditions, including temporary brain ischemia, depression, TBI, and micro-opioid receptor tolerance [37] (Figure 1).

### 4.3. Anti-apoptotic effects

Apoptosis is a type of programmed cell death that is essential for hemostasis by scavenging aged or damaged cells, sculpting organs, and controlling the immune system by removing

faulty and surplus cells. It is also important for appropriate physiological metabolism, growth, and development. However, unchecked apoptosis can lead to many degenerative processes in various diseases, such as cancer, Alzheimer's disease, and stroke. Agmatine could protect the rat liver from nicotine-induced harm by preventing the synthesis of the pro-apoptotic protein Bax. By lowering the activation of Bax and caspase-3 in the Ha-ras-transformed murine NIH-3T3 cell line, the anti-apoptotic actions of agmatine were discovered *in vitro* [25]. Several studies indicate that agmatine has an anti-apoptotic impact on a variety of neurological diseases. Agmatine, for instance, has been able to decrease cellular apoptosis in rat models of traumatic brain damage by suppressing MAPK phosphorylation



**Figure 1.** Molecular mechanisms of agmatine neuroprotective effect. Abbreviations: ROS: Reactive oxygen species; BBB: Blood brain barrier.

and enhancing the nuclear translocation of NF-kappaB. In addition, researchers found that lipopolysaccharide (LPS)-induced spatial memory impairment and hippocampus death could both be avoided by inhibiting caspase-3 expression with agmatine [66]. In several *invitro* investigations (SH-SY5Y), agmatine was found to protect the human-derived dopaminergic neuroblastoma cell line. By increasing the quantity of phosphorylated Akt/Akt, limiting GSK-3 activity, and inhibiting the activation of apoptotic markers such as caspase 3, Bax, and cytochrome c, agmatine exercised its anti-apoptotic actions [67,72]. Agmatine's ability to inhibit apoptosis has been well demonstrated in neurological conditions.

#### 4.4. BBB protection and brain edema

The BBB controls the mobility of numerous particles and cells, including ions, toxicants, and inflammatory cells. It is a continuous, non-fenestrated system. If the BBB were to be disrupted in any way, the severity of neurological illnesses such as stroke, TBI, and neurodegenerative diseases would worsen [68]. According to one study, agmatine significantly reduces the activation of matrix metalloproteinases [39]. Agmatine's control over matrix metalloproteinase expression may therefore be a viable strategy for protecting the blood-brain barrier and reducing vasogenic brain edema. In addition, cytotoxic brain edema is another type of brain edema that frequently happens with brain damage. Brain AQP failure is one of the most common and complex mechanisms

of cytotoxic edema. The AQPs are a group of water channel proteins that regulate the flow of water molecules across plasma membranes. The brain tissue contained abundant amounts of AQP-1, -4, and -9. According to reports, dysfunctional AQP-1 and -4 are involved in the generation of cerebrospinal fluid and may be a factor in cerebral edema [69]. Agmatine has been demonstrated in numerous investigations to reduce cytotoxic edema by reducing the expression of AQP-1, -4, and -9. The modifications were found in a variety of neurological illnesses, including TBI, stroke, and degenerative diseases [3,70,71].

#### 5. Conclusion

Agmatine demonstrated its neuroprotective properties across a range of neurological conditions, including brain ischemia and traumatic brain injury (TBI). The underlying processes such as anti-oxidation, anti-inflammation, anti-apoptosis, protection of the BBB, and avoidance of brain edema constitute these neuroprotective properties. The effectiveness of agmatine in the treatment of neurological illnesses is enormous, as evidenced by its safety and low occurrence of side effects. The amount of central agmatine before and after cerebral damage is well documented; however, preclinical results do not account for the fact that agmatine is an endogenous component of the CNS. Furthermore, there is currently no clinical evidence to confirm or verify the preclinical findings. In spite of this, agmatine has been demonstrated to have neuroprotective properties in animal models,

and more research into this molecule's CNS-related pharmacology, physiology, molecular processes, and analog creation may prove worthwhile. Clinical trials are required before agmatine may be widely used in medicine.

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### Conflict of interest

The authors declare no conflicts of interest.

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Not applicable.

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### Availability of data

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