Journal of Experimental Pharmacology

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REVIEW

Montelukast: The New Therapeutic Option for the Treatment of Epilepsy

This article was published in the following Dove Press journal:
Journal of Experimental Pharmacology

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Abstract: Currently, there is no definitive cure for epilepsy. The available medications relieve symptoms and reduce seizure attacks. The major challenge with the available antiepileptic medication is safety and affordability. The repurposing of montelukast for epilepsy can be an alternative medication with a better safety profile. Montelukast is a leukotriene receptor antagonist that binds to the cysteinyl leukotrienes (*CysLT*) receptors used in the treatment of bronchial asthma and seasonal allergies. Emerging evidence suggests that montelukast's anti-inflammatory effect can help to maintain BBB integrity. The drug has also neuroprotective and anti-oxidative activities to reduce seizure incidence and epilepsy. The present review summarizes the neuropharmacological actions of montelukast in epilepsy with an emphasis on the recent findings associated with *CysLT* and cell-specific effects.

Keywords: repurposing, seizure, inflammation, cysteinyl leukotriene receptors

Introduction

Epilepsy is one of the most common chronic brain diseases and it affects over 70 million people worldwide.[1] Epilepsy is life-altering, in part, because it is unpredictable, and as such it curtails daily activities like driving, attending school, and working.[2] Available anti-epilepsy treatment options include medications, keto diets, vagal nerve stimulation, and surgery.[3] However, the currently available anti-epileptic medications do not bring a definitive cure.[4] More than one-third of the epileptic patients who take the currently available drugs do not get the required benefit. These drugs also have serious side effects.[5] Particularly, pregnant women, children, the elderly, and patients with chronic comorbidities such as chronic kidney or liver disease are at higher risk of toxicity from those drugs.[6,7] Developing a new anti-epileptic medication could be expensive and time consuming. Repurposing available medications could reduce the cost and time required for the discovery of new anti-epileptic drug.

Montelukast is a cysteine leukotriene receptors (*CysLT*R) antagonist which is currently being used for the treatment of bronchial asthma and seasonal allergies.[8,9] In recent years, montelukast has been reported to have beneficial pharmacological effects in the nervous,[10] cardiovascular,[8] and cerebrovascular systems.[11] Epidemiologic studies have shown that montelukast reduces the incidence and severity of seizures.[12,13] These results indicate that montelukast could be developed into a disease-modifying drug for epilepsy. This review summarizes the current findings on the role of montelukast to control seizures.

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http://doi.org/10.2147/JEP.S277720

Epilepsy Pathophysiology and Cysteine Leukotrienes

Leukotrienes (LTs) are one of the major constituents of biologically active eicosanoids.[14] LTs are secreted during inflammation by mast cells, eosinophil, and leukocytes.[15] They possess a wide range of biological activities including leukocyte chemotaxis, vascular leakage, endothelial cell migration, smooth muscle cells and astrocyte proliferation.[15]

In the human body, LTs are derived de novo from arachidonic acid (AA).[16] AA is released from membrane phospholipids through the action of phospholipase A2.[17] The biosynthesis of LTs from AA is dependent on the action of the enzyme 5-lipoxygenase and its activating protein, 5-lipoxygenase activating protein (FLAP).[8] There are five types of LTs: leukotriene A4 (LTA4), leukotriene B4 (LTB4), leukotriene C4 (LTC4), leukotriene D4 (LTD4), and leukotriene E4 (LTE4).[16] LTA4 and LTB4 are non-cysteinyl leukotrienes as they lack the cysteine moiety[18] which is present in the Cys-LTs (LTC4, LTD4, and LTE4)[15] (Figure 1).

Cysteinyl leukotrienes exhibit several biological activities in nanomolar concentrations through at least two specific G-protein coupled receptor subtypes named

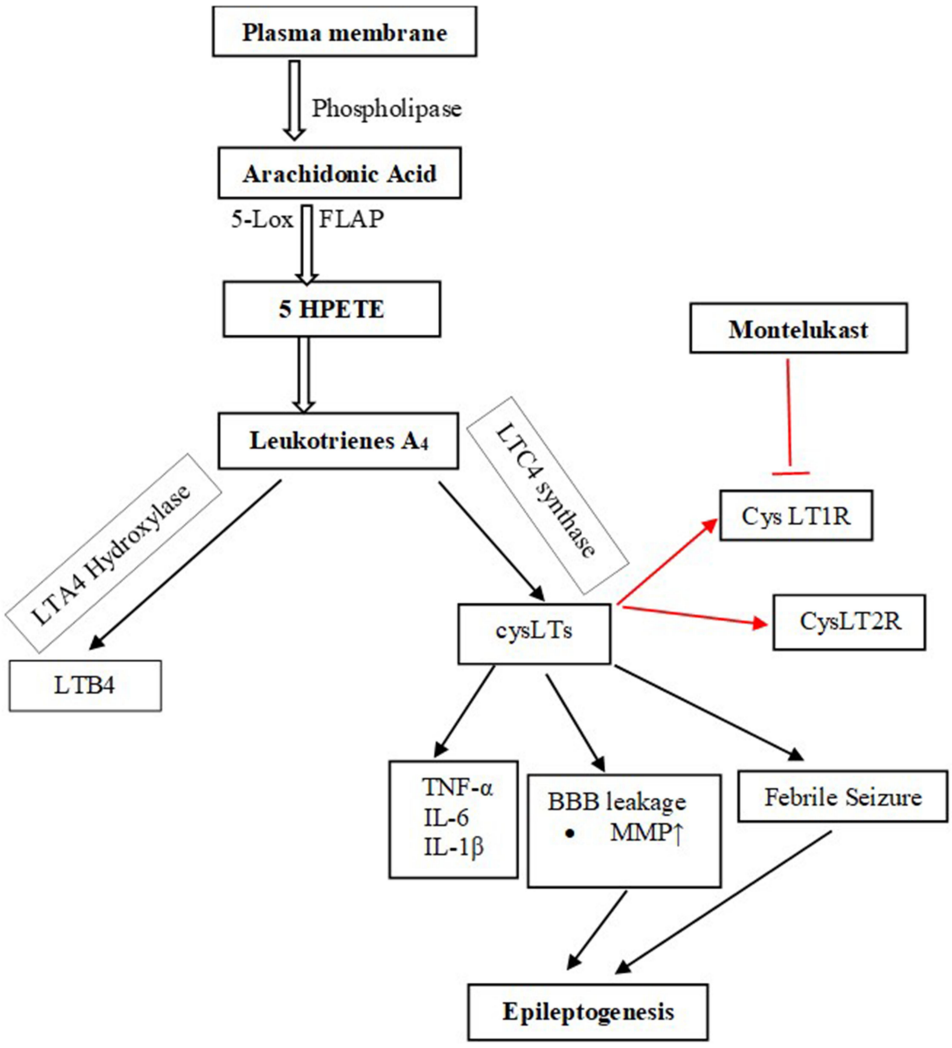

Figure 1 Biosynthesis pathway of the Cys-LT and their receptors. Biosynthesis of CysLTs starts with the release of arachidonic acid from plasma membrane by the action of phospholipase. Arachidonic acid is metabolized to leukotriene A_4 that in turn is metabolized to both non-cysteine leukotriene, LTB4, and cysteine leukotrienes. The CysLTs act on the receptors, CysLT1R and CysLT2R. Montelukast competitively block the effects of CysLTs on these receptors. The red color of the arrows show the site where montelukast acts.

Abbreviations: 5-Lox, 5-lipoxygenase; FLAP, 5-lipoxygenase activating protein; 5HPETE, 5-hydroperoxyeicosatetraenoic acid; LTB4, leukotriene B4; CysLTs, cysteinyl leukotrienes; CysLT1Rs, cysteinyl leukotrienes 1 receptor; CysLT2Rs, cysteinyl leukotrienes 1 receptor; TNF-α, tumour necrosis factor alpha; IL-6, interleukin-6; IL-1β, interleukin 1 beta; MMP, matrix metallopeptidases.

*CysLT*R-1 and *CysLT*R-2 which show 38% homolog.[19] Different studies have demonstrated that binding of LTD4 to the *CysLT*1 receptor leads to G-protein activation and the release of secondary intracellular messengers including diacylglycerol, inositol phosphates, and Ca2þ. This is followed by the activation of protein kinase C and accompanied by the mobilization of Ca2þ derived from both intracellular and extracellular stores.[20,21] Furthermore, *CysLT*1 receptor activation by LTD4 has been reported to be associated with a transduction system based on the activation of phosphoinositide-3-kinase, extracellular-receptor kinase, mitogen-activated protein kinase, nuclear factor-kB (NF-kB), tumor necrosis factor, and matrix metalloproteinases-9 pathway.[22]

Cys-LTs also induce the release of Matrix metallopeptidases (MMPs), including MMP-2 and MMP-9, inflammatory cytokines such as interleukins (ILs), NF-kB, and tumor necrosis factor- α (TNF-α) from macrophages through the cys-LT1 receptor.[23,24] The release of these inflammatory mediators was highly associated with Amyloid beta1-42 (Ab1–42) induced cytotoxicity.[10]

LTs and 5-lipoxygenase metabolite overexpression cause severe tissue damage. Relative to airway inflammation, many mediators, such as orupeptides and substance P, play a role in many of these interactions with LTs.[25] During inflammatory activation, LTs are synthesized and become functional. *CysLT*s induce smooth muscle contraction, vascular leakage,[26] eosinophil recruitment, mucus production and chemotaxis. LTB4 induces leukocyte chemoattraction, particularly of granulocytes and T cells, rapid invasion and recruitment of these cells to the plasma membrane of endothelial cells and production of reactive oxygen species.[18] *CysLT*s bind to their two receptors, *CysLT*1R and *CysLT*2R. These receptors are therapeutic targets for drug development to cure asthma and other immune diseases.[27] *CysLT*1 receptors also mediate astrocyte proliferation, which is the basis of post-ischaemic astrocytosis and glial scar formation.[28] *CysLT*1 receptor antagonists can inhibit ischaemia-like injury-induced astrocytosis, thereby inhibiting glial scar formation.[29]

The role of inflammation in central nervous system disease pathogenesis has already been widely investigated, and elevated serum inflammatory mediators have been found in many neurological disorders.[30] Experimental and clinical studies have shown that seizures induce brain inflammation and recurrent seizures perpetuate chronic inflammation.[31] In a healthy brain, the expression of the *CysLT*Rs is weak, but it was reported to increase during several pathological conditions.[19] Earlier studies have associated *CysLT*s and their receptors with several neurodegenerative disorders like, multiple sclerosis, parkinson's disease, Huntington's disease, epilepsy, traumatic brain injury[32,33] and alzheimer's disease.[18]

Emerging evidence indicates that inflammatory mediators including LTD4 play a relevant role in the pathophysiology of epilepsy.[19] However, only a few studies have investigated the role of LOX- derived arachidonic acid metabolites in epilepsy. Leukotriene levels were found to increase in a time-dependent manner in the brain during kainate-induced seizures in rats. Besides, LTD4 Intracerebroventricular (ICV) injection facilitated pentylenetetrazol (PTZ) induced seizures and increased Blood Brain Barrier (BBB) permeability in mice.[34] This effect could be relevant since magnetic resonance imaging studies in patients with post-traumatic epilepsy demonstrated that the site of increased BBB permeability colocalized with the presumed epileptic focus and animal studies found a positive correlation between the extent of BBB opening and the number of seizures.[35]

Chemically induced seizures in rodents are associated with an early upregulation of hippocampal 5-lipoxygenase enzyme and resultant accumulation of leukotrienes.[21] Spontaneously epileptic gerbils have demonstrated higher levels of cysteinyl-leukotriene formation in their brain tissue than their normal counterparts.[36] Leukotrienes level increased in the brain during kainate-induced seizures.[34]

In addition, kainic acid-induced seizures are associated with increased brain levels of leukotrienes and PGF2a in the cortex, hippocampus, and hypothalamus of rats.[37] The effects of pharmacological treatment, kindling, and challenge with PTZ on *CysLT*1 and *CysLT*2 receptor immunoreactivity in the cerebral cortex of mice were examined. It was found that epilepsy is associated with increased levels of inflammatory mediators in the brain, including leukotrienes, which are produced by neurons, glia, and endothelial cells in the BBB.[12] Neutrophils that have breached the BBB can lead to the immediate synthesis of *CysLT*s.[38] Farias et al demonstrated that *cysLT*s significantly increase after fluid percussion-induced brain injury, being detected as early as 10 min after injury and continuing to rise over an hour.[39] A pharmacological data provided by Lenz et al also indicated that *CysLT*1R antagonism maintains BBB integrity.[34] In accordance, Palmer et al demonstrated that LTD4 increases the firing rate of Purkinje cells in vivo,

suggesting an excitatory role for this lipid mediator.[40] Glutamate released during seizures acts on capillary NMDA receptors to cause blood-brain barrier disruption through cPLA2, COX-2 and 5-LOX leading to increased MMP expression, degradation of Tight Junction Proteins (TJs) and increased barrier leakage which increases the likelihood of further seizures.[41,42]

Pharmacological modulation of 5-lipooxygenase, an enzyme required for the biosynthesis of leukotrienes, has been shown to potentiate the protective effect of a COX-2 inhibitor on kainic acid induced seizures in rodents.[21] Inhibition of LOX using dual inhibitors of LOX/COX pathway like phenidone and BW755C has led to decreased production of *CysLT*s and attenuated seizure activity, respectively.[43] Similarly, zileuton, a LOX inhibitor, was shown to decrease spike-wave discharges in pilocarpine-induced epileptic rats, strongly suggesting that leukotrienes play a role in epilepsy.[19] Montelukast, a *CysLT*1 receptor inverse agonist and 1,2,3,4-tetrahydroisoquinoline, regarded as a LTD4 synthetic pathway inhibitor, dose-dependently suppress the development of kindled seizures, as well as pilocarpine-induced spontaneous recurrent seizures.[21] Interestingly, it has been shown that while LTD4 facilitates, montelukast, pranlukast and Bay-u9773 (a dual *CysLT*1/*CysLT*2 antagonist) decrease PTZ-induced seizures and BBB permeability disruption. Pranlukast, zafirlukast and montelukast are *cysLT*-1 antagonists that are available in the market.[44]

Repurposing of Montelukast as an Antiepileptic Drug

Montelukast, 1-((1(R)-(3-(2-(7-chloro-2-quinolinyl)-(E)-ethenyl)phenyl)-3-[(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thiol]-methyl)] cyclopropane acetate, is a selective *CysLT*1 receptor antagonist[45] possessing anti-inflammatory effects and has been widely used for the treatment of inflammatory diseases such as asthma and allergic rhinitis.[46] Montelukast was approved for use in the United States in 1998 and is widely used with more than 20 million prescriptions being filled yearly.[47] Montelukast is the most prescribed *CysLT*1 receptor antagonist in Europe and the USA.[48]

Montelukast showed a neuroprotective effect through antioxidant, anti-inflammatory, and antiapoptotic mechanisms.[49] It is reported to have a neuroprotective activity in several neuronal disorders such as alzheimer's disease, cerebral ischemia, multiple sclerosis and seizures.[13,50] Other studies also displayed that it possesses a wide spectrum of anti-inflammatory properties in several chronic diseases.[8] The evidences of the antiepileptic activities of montelukast from animal studies are summarized below (Table 1).

Montelukast protected hippocampal tissue by reducing oxidative stress, inflammatory and apoptotic markers.[11] Furthermore, it reduced glutamate and lactate dehydrogenase activity as well as infarct size elevated by ischemia/reperfusion.[49] Montelukast markedly reduced ox-LDL-induced adhesion of monocytes to endothelial cells.[8] An in vitro study has recently shown that montelukast suppressed phagocytosis induced by rotenone and decreased the subsequent proinflammatory cytokine release.[36]

Montelukast Suppresses inflammatory mediators induced by TNF-a.[23] It induces M2 macrophages[51] polarization which is important in the removal of cellular debris, embryonic development, and tissue repair.[52] It also suppresses the activity of MMP-2 and MMP-9.[53] Montelukast, MK571, and zafirlukast (inverse agonists of *CysLT*1R) increased cell surface receptor expression in COS-7 cells while LTD4 (a *CysLT*1 receptor agonist) did the opposite.[12] Several forms of brain injuries trigger leukotriene production, including ischemia, trauma, stroke, and seizures, which are associated with increased BBB permeability.[54] Epilepsy-related BBB disruption is mediated by Cys-LT and modulation of Cys-LT by montelukast suppresses the development and frequency of seizures in vivo.[34] Montelukast and LTD4, respectively, reduced and increased the BBB disruption induced by PTZ.[12] Montelukast prevented PTZ-induced BBB disruption by inhibiting paracellular diffusion and leukocyte infiltration and slowing the onset of PTZ-induced seizures.[34] Obermeier et al's finding indicated that the maintenance of BBB integrity may underlie the currently reported anticonvulsant effect of *CysLT*1R antagonists.[55] Intracerebroventricular injection of montelukast prevented seizures and maintained the BBB integrity at the same range of doses and increased latency to seizures correlated with low BBB permeability scores.[34]

Moreover, the ICV injection of LTD4 facilitates the convulsant effect of PTZ and reverts the anticonvulsant action of montelukast which constitutes converging pharmacological evidence for the involvement of *CysLT* receptors in seizures.[12,19] The two other *CysLT* receptor antagonists (pranlukast and Bay-u9973) also decreased PTZ-induced seizures which indicated that *CysLT* receptors' role in seizures.[45,56] Montelukast suppressed the

Table 1 Preclinical Studies Done on the Antiepileptic Effect of Montelukast

Experimental Approaches	Study Subjects	Interventions	Major Outcome(s)	References
PTZ-induced seizures	Male Swiss mice weighed between 25–28 g and aged 42 days	Three groups of PTZ kindled mice: phenobarbital treated group, montelukast treated group, and normal saline treated group	Both montelukast and phenobarbital improved the latency period to generalized seizures.	[12]
Montelukast against PTZ induced acute seizure	112 adult Swiss albino male mice weighing 15–35g and aged 8 weeks were used	Two animal study models were used. The first was an acute PTZ model where mice were divided into five groups and treated with single IP dose; saline, PTZ, valproate, montelukast, and both montelukast and valproate. The second was a kindling model where mice were divided into five groups and treated daily for 17 days IP with; saline, PTZ, valproate, montelukast, both montelukast, and valproate.	Montelukast, alone or in combination with valproate blocked *CysLT*Rs and protected the mice's brain against PTZ induced seizures. Montelukast, alone or in combination with valproate also reduced oxidative stress and inflammatory cascades. The authors reported a significantly increased level of GSH and significantly reduced levels of MDA, IL1β, TNFα, and LTD4 as compared to PTZ treated control groups.	[69]
PTZ-induced seizure: electroencephalography (EEG), Racine's Convulsion Scale (RCS), onset times of first myoclonic jerk (FMJ), Malondialdehyde (MDA) and superoxide dismutase (SOD) levels were determined	48 male Sprague-Dawley rats were used (weighed between 200–250 g)	Rats were grouped into two as group "A" to study EEG and "B" for behavioral studies. Group "A" were further divided into A1, A2, A3, and A4 and treated with IP; normal saline and 25, 50, and 100 mg/kg of montelukast. Animals in Group "B" were similarly divided as B_1 B_2, B_3, and B_4 and treated with IP normal saline and 25, 50, and 100 mg/kg of montelukast.	Montelukast showed significant anticonvulsant and anti-oxidant action. Rats administered with 50 or 100 mg/kg of montelukast significantly lowered RCS and significantly elevated FMJ onset time compared to the controls. A significantly lower MDA and higher SOD levels were also found in the animals treated with 25, 50, or 100 mg/kg ($p<0.001$) of montelukast as compared to the saline treated group.	[13]
Isobolographic analysis of the synergistic activity of montelukast and phenobarbital on PTZ induced seizures	A total of 134 adult female Swiss mice (25 ± 3 g) were used:	Five different groups of animals were treated with montelukast, phenobarbital, montelukast plus phenobarbital, montelukast plus LTD4, and vehicle respectively.	The combination of montelukast and phenobarbital was found to have a synergistic effect. The group of animals treated with the combination showed an increased latency period to PTZ-induced tonic–colonic seizures. The ED50 of phenobarbital for anti-seizure activity was also significantly lowered by montelukast.	[70]
Effect of CYSLT receptor antagonists on PTZ induced seizure and BBB integrity	Male albino Swiss mice weighing 25 ±3.5gm were used	Mice were divided into five groups and treated with the antagonists (montelukast, pranlukast, Bay u-9773), agonist (LTD_4), and a solvent respectively. This was followed by an injection with PTZ after 30 minutes.	All three antagonists prolonged the latency period to generalized seizures. They also decreased mean EEG amplitudes during seizure episodes. Montelukast also stopped PTZ induced BBB leakages.	[34]

(*Continued*)

Table 1 (Continued).

Experimental Approaches	Study Subjects	Interventions	Major Outcome(s)	References
Effect of montelukast and 1,2,3,4, tetrahydroisoquinoline on PTZ induced seizures and pilocarpine induced status epilepticus	Male albino mice weighed 25±2g were used	Animals categorized into 8 groups as Group I - Group VIII were treated with vehicle only, PTZ only, low dose montelukast plus PTZ, medium dose montelukast plus PTZ, high dose montelukast plus PTZ, low dose 1,2,3,4 tetrahydroisoquinoline plus PTZ, medium dose 1,2,3,4 tetrahydroisoquinoline plus PTZ, and high dose 1,2,3,4 tetrahydroisoquinoline plus PTZ respectively.	Both montelukast and 1,2,3,4, tetrahydroisoquinoline halted the development of PTZ kindled seizure and pilocarpine-induced status epilepticus significantly and in a dose-dependent manner.	[21]

development of kindled seizures, as well as pilocarpine-induced spontaneous recurrent seizures in mice. Clinical evidence highlights the efficacy of cysLT receptor antagonists such as pranlukast in patients with intractable partial epilepsy.[57] Pranlukast reduced seizure frequencies probably normalizing MMP-9 in serum, reducing leakage of proinflammatory cytokines into CNS, and inhibiting extravasation of leucocytes from brain capillaries.[19,57] Inflammatory cytokines and matrix metalloproteinases that cause degradation of the extracellular matrix IL-1 and TNF-α receptors are rapidly upregulated in neurons during seizures, suggesting that they mediate the effects of cytokines on neuronal excitability.[58] Cytokine receptors in the CNS are expressed by neurons, microglia,[59] and astrocytes.[60] Evidence exists for cell type–specific IL-1β signaling in the CNS through the IL-1 type 1 receptor: IL-1β activates the p38 mitogen-activated protein kinase pathway in neurons, leading to induction of cyclic adenosine monophosphate response element–binding protein, whereas NF-κB is activated predominantly in astrocytes, suggesting that this cytokine may have distinct functional effects on neurons and glia.[61]

Ab1–42-induced *CysLT*1R expression results in neurotoxicity, inflammatory and apoptotic responses in cultured primary neurons.[62,63] Ab1-42 is involved in the pathologic mechanisms of axon damage, axon growth, and network reorganization observed in refractory epilepsy[64] and late onset epilepsy of unknown origin mediated by D1 receptor.[65] This is because of Ab1–42 activated nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling by selectively inducing the nuclear translocation of p65 and p50 subunits, and promoting expression of genes such as proinflammatory or apoptotic profile.[66] Treatment with montelukast was able to decrease this increment of nuclear p65 subunit which indicates that montelukast may block Ab1–42-activated NF-κB signaling in primary neurons.[10,67] Moreover, blockade of *CysLT*1R with montelukast reversed Ab1–42-mediated increase of *CysLT*1R expression, and concomitant changes of the pro-inflammatory factors and the apoptosis-related proteins which result in Ab1–42-associated late onset of epilepsy.[68]

Conclusion

Overexpression of *cysLT* in the brain causes the tissue damage, which is responsible for the pathogenesis of many neurological disorders including epilepsy. Various experimental studies indicated that montelukast which is a potent *cysLT* receptor antagonist blocked CNS inflammation resulting in neuro-protection, treating febrile seizures, potentiate the action of the old antiepileptic drugs, and maintained BBB integrity from dysfunction. It is also relatively safe drug as it has been used for the treatment of asthma for more than two decades. Therefore, montelukast has the potential to be an alternative treatment for epilepsy. However, further studies of both preclinical and clinical studies are required before considering montelukast for a prescription to treat epilepsy.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation,

or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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