**Abstract:** Background: Beta-lactam molecules are a family of drugs commonly used for their antibiotic properties; however, recent research has shown that several members of this group present a large number of other effects such as neuroprotective, antioxidant, analgesic or immunomodulatory capabilities. These properties have been used in both preclinical and clinical studies in different diseases such as hypoxic neuronal damage or acute and chronic pain. The present work briefly reviews the antibiotic effect of these molecules, and will then focus specially on the non-antibiotic effects of three beta-lactam subfamilies: penicillins, cephalosporins and beta lactamase inhibitors, each of which have different molecular structure and pharmacokinetics and therefore have several potential clinical applications.

**Methods:** A thorough search of bibliographic databases for peer-reviewed research was performed including only classic experiments or high quality reviews for the antibiotic mechanisms of beta-lactam molecules and only experimental research papers where included when the non-antibiotic properties of these molecules were searched. Only published articles from indexed journals were included. Quality of retrieved papers was assessed using standard tools. The characteristics of screened papers were described and findings of included studies were contextualized to either a mechanistic or a clinical framework.

**Results:** Seventy-eight papers were included in the review; the majority (56) were relative to the non-antibiotic properties of beta-lactam molecules. The non-antibiotic effects reviewed were divided accordingly to the amount of information available for each one. Twelve papers outlined the epileptogenic effects induced by beta-lactam molecules administration; these included both clinical and basic research as well as probable mechanistic explanations. Eighteen papers described a potential neuroprotective effect, mostly in basic in vitro and in vivo experiments. Analgesic properties were identified in twelve papers and basic research was described alongside with both experimental and serendipic clinical findings. Seven papers described a down-regulation effect exerted by beta-lactam molecules administration in different addiction animal models. Finally other effects such as penile erection, dopamine release facilitation and anti-neoplasic effects where described from seven papers.

**Conclusion:** The findings of this review show that beta-lactam molecules may induce several effects, which may be clinically relevant in a lot of different diseases. This paper is, to our knowledge, the first comprehensive review of the non-antibiotic effects shown by beta-lactam molecules and may help increase the interest in this field, which may result in a direct translation of this effects to a clinical context.

**Keywords:** Analgesia, beta-lactam molecules (BLMs), ceftriaxone (CFX), clavulanic acid (CA), GLT1, glutamate, neuroprotection.
1. INTRODUCTION

Beta-lactam molecules (BLMs) are a group of drugs that changed the clinical settings regarding infectious disease due to their antibiotic properties [1]. While initially a direct effect in eukaryotic cells was unknown [2] recent findings have demonstrated an actual and important interaction which results in several changes human cell’s metabolism and function. This review will summarize BLMs antibiotic and non-antibiotic effects demonstrated to date.

2. BETA-LACTAM MOLECULES AS ANTIBIOTICS

2.1. Discovery

The quintessential member of the BLMs, penicillin, was first discovered by serendipity in 1928 by Alexander Fleming. He developed the methodology that would ultimately lead to the subsequent purification of penicillin and the other beta-lactam molecules we use today [1]. Further research showed that the moiety that provided the antibiotic trait [2, 3] is produced by the fungus Penicillium; this antibiotic is characterized by the presence of an azetidinone nucleus containing a cyclic amide with the carbonyl β-lactams, also known as beta-lactam ring (a cycle of four members). However, despite the intrinsic importance of this discovery, it was not until 1940 that this molecule could be clinically used due to the fact that at the beginning only a small amount of it could be purified [1].

While initially the use of penicillin dramatically improved the prognosis of patients with infectious diseases [3], susceptible bacteria such as Staphylococcus aureus, quickly developed resistance mechanisms for BLM which mainly involved the destruction of the beta-lactam ring by an enzyme named β-lactamase, thus cancelling the antibiotic effect [4]. This event made it necessary to find an alternative for increasing the BLM antibiotic efficacy, which led to the discovery of, on one hand, a new molecule isolated from a strain of Cephalosporium acremonium named at the time cephalosporin C (now known as ceftriaxone) [5-6] and on the other, a way to avoid β-lactamase activity with a new mechanism based novel group of drugs known as β-lactamase inhibitors, of which the main member is clavulanic acid (CA) [7].

Cephalosporin C is the precursor for many beta-lactam molecules, known generically as cephalosporins, which possess a 7-aminocephalosporinic moiety in their nucleus. Several new beta-lactam molecules have been synthesized with such a nucleus as a precursor [1]. Azetidinone can be fused with a saturated or unsaturated pentacycle or hexacyle and position 1 of this ring can be occupied by a sulfur, oxygen, or carbon atom, producing: a) penicillins (Fig. 1), including penams, carbapenams, and oxopenams (penicillin and ampicillin); b) penems and carbapenems (imipenem); c) cephalosporins, including cephems, carbacephems, and oxacephems; and d) azetidinone, which by itself and not fused with another ring originates monolactams or monobactams (aztreonam) [8]. One of the most clinically used antibiotics belonging to the cephalosporin family is ceftriaxone (Fig. 1, CFX) which is a third-generation cephalosporin with a wide spectrum antibiotic effect, originally named cephalosporin N [9] upon discovery.

Fig. (1). Some Beta-lactam Molecules (BLMs). The moiety known as beta-lactam ring are showing in all structures with grey.
On the other hand, other beta-lactam molecules with clinically negligible antibiotic properties are currently being widely used to prevent lactamase-based resistance. For example, CA (Fig. 1) is a beta-lactam molecule first isolated from a *Streptomyces clavuligerus* culture [10]. Contrary to initial expectations, several different authors found its antibiotic spectrum clinically negligible [7], although it proved useful as an adjuvant for the antibiotic effect of other beta-lactam molecules when in presence of beta-lactamase molecules [10, 11], and was then co-formulated with other beta-lactam antibiotics with a wider spectrum such as amoxicillin or penicillin [12]. On the other hand, sulbactam (Fig. 1) is another BLM clinically used as an adjuvant in the treatment of certain infections; however, it does have an intrinsic antibiotic activity against *Acinetobacter* spp. or *Bacteroides fragilis* [13].

### 2.2. Antibiotic Mechanism of Action

Considering the great importance of BLMs as antibiotics and the great amount of thorough reviews that have been published on the subject [14-15] we will only give a brief review of the general antibiotic mechanism of action of this molecules.

The bacterial cell wall is formed by a peptidoglycan mesh-like layer, which is thick in gram-positive bacteria and thin in gram-negative organisms. This peptidoglycan mesh consists of a polysaccharide N-acetylglucosamine (NAG) and N-acetylmaramic acid (NAM) polymer that is cross-linked by peptide bonds, and completely surrounds the cell acting as a protective layer against internal osmotic pressure variations [16]. Peptidoglycan synthesis depends on four main steps. In the first step, the components forming the cell wall are synthesized and transported to the periplasmic space. In the second, their formation requires NAG and NAM to assemble as a penta peptide outside the cytoplasmic membrane. The third step is the conversion from a penta peptide to a tetra peptide by either an endopeptidation or a transpeptidation through the action of a group of enzymes known as Penicillin Binding Protein (PBP) (Fig. 2) [14, 17].

Although the antibiotic properties of BLMs were recognized since the beginning, their mechanism of action remained obscure for several decades [18], however through the passing of years, a consensus was achieved attributing the bactericidal trait to an interference on the third synthetic step of the bacterial cell wall [16], targeting on the PBP enzymes involved in the biosynthesis of peptidoglycan and leading to bacterial autolysis [14].

As previously mentioned, the most important resistance mechanism against BLM’s is that of β-lactamase molecules which can hydrolyze the beta-lactam ring inactivating the antibiotic effect of any BLM in contact with this enzyme [19]. Unless a PBP molecule is altered as in some *Staphylococcus aureus* strains [20], BLMs to a greater or lesser extent share an affinity towards different PBPs, a fact that allows a heterogeneous range of antibiotic spectra [17]. Additionally, there are certain BLMs with minimal or no antibacterial effect that can act as either reversible or irreversible enzyme inhibitors, thus reestablishing the clinical effect of other BLMs in otherwise resistant bacteria [21].

### 3. NON-ANTIBIOTIC PROPERTIES OF BETA-LACTAM MOLECULES

#### 3.1. Epileptogenic Properties

While at first penicillin and its derivatives where thought to be innocuous to humans, in 1947 Reuling and Cramer reported that when penicillin was administered intrathecally it could cause neurological symptoms when they observed a convulsive episode in a pregnant female which disappeared 24 hours after drug administration [22-23]. This fact was regarded as unimportant since penicillin crosses the blood-brain barrier with difficulty; although several subsequent clinical reports [22, 24] established this effect as a factor to be taken into account.

Although epilepsy encompasses several seizure disorders caused by a variety of cellular or molecular alterations, they all share an abnormal hypersynchronous electrical activity caused by an imbalance between excitation and inhibition. Epileptogenesis refers to the alteration of a normal neuronal network into a hyperexcitable system which may lead to spontaneous seizures [25].

The mechanism of this effect of penicillin has been studied by several research groups throughout the decades; for example, in 1976, a study reported...
an increase in membrane resistance after administration of penicillin G in concentrations greater than 2 mM; this was apparently due to an antagonizing effect in the inhibitory neurotransmitter gamma aminobutyric acid (GABA) activity; an increase in input resistance of the muscle and an effect on presynaptic excitatory transmission [26]. This fact was corroborated by further studies performed in 1975 in which the importance of the integrity of the beta-lactam ring was shown to be necessary for the increase in excitatory junction potential [27]. Another study showed that application of 500 IU of the antibiotic to the rabbit neocortex generated abnormal spikes in the uppermost layers and induced rhythmic paroxysmal activities in lower layers during the first minutes, involving all layers as time passed or concentration increased [28]. Furthermore, when penicillin was administered to cultured cells in the presence of iontophoretically applied GABA, there was a dose-related receptor antagonism [29]. This could mean that penicillin is a competitive GABA-specific antagonist, which would further explain its epileptogenic properties.

According to more recent studies, the neuronal effects of BLMs appear to be ambivalent, since anticonvulsant actions have also been described. For example, when CFX (200 mg/kg) was administered once daily for 6 consecutive days to mice 4 and 12 weeks old there was a significant prolongation in the latency of seizures and a decrease in mortality induced by the administration of a GABA antagonist [30]. This effect was subsequently corroborated when CFX (200 mg/kg) was administered to knock-out mice lacking glutamate transporters, a condition resembling a human pathology known as tuberous sclerosis complex. CFX administration once daily from postnatal week 3 decreased seizures and increased survival, although no significant effect was apparent when treatment was initiated at postnatal week 6.
[31]. Finally other BLMs such as tazobactam and CA had a similar effect in an invertebrate assay using either glutamate or cocaine [32]. In contrast, CA did not share these results when tested in three different murine seizure models [33].

This protective effect can be explained by a glutamate transporter up-regulation exerted by BLM’s initially described by Rothstein, Patel [34] which will be dealt with in detail in the following paragraphs.

3.2. Neuroprotective Properties

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system and is involved in several physiological processes such as memory, learning or pain [35]. Its deregulation, however, induces an aberrant effect in neuronal excitation known as excitotoxicity which is implied in many pathological conditions such as stroke, epilepsy, multiple sclerosis, Alzheimer’s disease, amyotrophic lateral sclerosis (ALS) or Parkinson’s disease among others [36]. The metabolism of this neurotransmitter depends on its removal from the synaptic cleft by astrocytes and its transformation to glutamine [37]. Even though there are several glutamate transporters in both the central and peripheral nervous systems, the most important are GLT1/EAAT2, GLAST and EAAT1 which combined are responsible for more than 95% of glutamate uptake in the adult forebrain [38-39]; and their dysfunction is implicated in several diseases [35, 39].

Given the main role of GLT1 transporters in neurotoxicity, one of the first experimental approaches in search for BLM pathology-altering effects was on glutamate-induced excitotoxicity models. The first demonstration of the neuroprotective properties of BLM’s was published in 2005; the authors showed that ceftriaxone prevented cell death in cultured neurons deprived of oxygen and glucose and prevented cellular hypergliosis and loss of muscular strength in a knock-out mouse model [34]. In this study, nearly 15 beta-lactam antibiotics, including penicillin and its derivates, as well as cephalosporin, were highly active as stimulators of GLT1 expression in both murine and human fetal astrocytes [34]. This proved to prevent motor neuron loss and reduced cellular hypergliosis in an in vivo ALS model. This effect was not produced with other antibiotic molecules (minocycline and vancomycin), lacking a beta-lactam ring. These results suggest that the neuroprotective effect induced by beta-lactam antibiotics is due to their capacity to stimulate GLT1 expression and thus regulate the concentration of glutamate in the synaptic cleft. GLT1 is a glutamate transporter inducing its reuptake by astrocytes preventing excessive glutamate concentration in the synaptic cleft [40] (Fig. 3).

Following this conclusion, other experiments were conducted in search for more specific effects; for example, pretreatment for 7 days with CFX (200 mg/kg daily) ameliorated both the neurotoxicity and motor deficit induced by a lesion with 6-hydroxydopamine. In addition, CFX brain concentrations ranging from 16 to 54 ng/ml prevented dopaminergic cell loss and improved motor symptoms when they were already present [41].

Other workers determined the influence of repeated CFX treatment on glutamate concentration in a mesocorticolic limbic area known as nucleus accumbens. They showed that intraperitoneal (IP) administration for 5 days of 100 and 200 mg/kg of CFX reduced glutamate concentration up to 50% for 20 days after discontinuation of treatment. They also found that this effect was prevented by inhibition of GLT1 suggesting that the reduction in glutamatergic transmission induced by ceftriaxone is mediated by this transporter [42].

Studies focusing on the up regulating effect of CFX showed that the antibiotic promoted nuclear translocation of p65 and activation of NF-κB transcriptional factor and that this effect was specific for the GLT1 transporter as its administration did not induce either GLAST or EAAT1 receptor expression [43]. Further work showed that up regulation of the GLT1 induced by CFX involved modulation via the PI3K/Akt/NF-κB signaling pathway [44]. This pathway begins with activation of a PI3K, which phosphorylates the Akt protein kinase. Meanwhile, activated Akt phosphorylates IKKα that in turn promotes nuclear translocation of p65 in cell survival signal pathways [44].

It was subsequently shown that the neuroprotective effect of BLMs was due not only to glutamate down regulation, but also to a diminished glutamate-induced intracellular Ca²⁺ concentration and an increased uptake of glutamate [40]. These
changes also occurred when a hypoxic-ischemic procedure was induced on neonatal rats treated with CFX 5 days previously [45]. Protection was persistent and did not depend on brain maturation.

Another probable mechanism of neuroprotection induced by BLMs is down-regulation of oxidative stress and modulation of apoptotic pathways shown in rat spinal cord when CFX was administered for 7 days prior to induction of constrictive neuropathy. This effect was apparently mediated by both a reduction in proapoptotic proteins Bax, and an increment in the antiapoptotic protein Bcl2 [46].

Although most research has been focused on the effects of CFX, other BLMs have also shown neuroprotective capacity. CA, on one hand, improves motor function in a neurotoxin 1-methyl-4-phenylpiridium induced damage model, which mimics Parkinson’s disease. Damage induced in this model is a consequence of generation of reactive oxygen species and CA appears to inhibit their production [47-48]. CA also decreased levels of Bax and reduced activation of caspase induced by neurotoxin, contributing to the prevention of cellular apoptosis [47]. On the other hand, sulbactam showed similar effects when it unregulated GLT1 and prevented delayed neuronal death after 8 minutes of ischemia in a murine model [49]. Finally, a 5-day ampicillin pretreatment has also shown to attenuate neuronal damage in a transient global forebrain ischemia model. These effects were apparently related not only to a GLT1 up-regulation but also to an attenuation of the immunoreactivity induced by the hypoxic event. [50].
CFX may induce neuroprotection by other mechanisms besides GLT1 overexpression. Yamada and Jinno [51] reported that the antibiotic reversed axotomy-induced up regulation of GFAP, a neuronal damage marker, and increased neuronal survival; apparently not only through glutamatergic regulation, but also by direct reduction of glial hypereactivity. Supplementary to this is the finding of an attenuation of microglial activation-induced IL-1β expression in an ischemic injury model when CFX was administered as a pretreatment [52]. This result may indicate a direct action on glial cells since partial reduction of astrocytes and microglia was observed.

This novel effect has been confirmed in several pathology specific models such as traumatic brain injury [53], subarachnoid hemorrhage [44], or chronic nervous constriction injury [46].

3.3. Analgesic Properties

Interestingly, despite the widespread clinical use of BLMs, some of their known non-antibiotic effects have been either disregarded or misinterpreted as resulting from bacterial microbiome regulation. For example, Caperton, Heim-Duthoy [54] hypothesized that chronic inflammatory arthritis could have a bacterial component and that therefore the clinical course of a patient could be affected by administration of CFX. They found that patients improved both subjectively and objectively after a 14-day course of daily intravenous administration of 2 grams of CFX. This observation may be compared with that of a more recent study in which a course of amoxicillin and CA thrice daily for 90 days was administered to a group of patients previously diagnosed with chronic back pain and who had shown resonance changes attributed to bone edema [55]. Similar to Caperton’s findings, this study revealed a significant improvement in all outcome measures such as number of days with pain, disease-specific dysfunction and globally perceived effect.

The first non-clinical demonstration of the analgesic properties of BLMs was that of Hu, Li [56], of an antiallodynic and antihyperalgesic effect of a 7-day course of 200 mg/kg IP of CFX as a pretreatment in a chronic neuropathic pain model. This effect was statistically significant in both therapeutic and preventive approaches in mechanical and thermic pain. The mechanism proposed by the authors as responsible for the observed analgesic effects was GLT1 up regulation and the consequent decrease of glutamate concentrations in the synaptic cleft, since there were several reports of glutamate-elicited hyperalgesia via the direct excitation of peripheral afferent fiber terminals [57]; however, others claimed that such up regulation might not be the only explanation.

For example, it was shown that acute administration of CFX (10-200 mg/kg) produces a significant dose-dependent antihyperalgesia in a somatic inflammatory pain model and increases the antinociception induced by some nonsteroidal analgesics such as ibuprofen, celecoxib and acetaminofen [58]. However, in this case, the effect induced by CFX does not seem to correspond with GLT1-transporter up regulation since the time needed for CFX to activate the transcriptional process is longer [34]. These authors suggested that CFX could attenuate the release of proinflammatory cytokines involved in nociception in carrageenan model used [58].

Although at one time neglected, the astroglial system is of fundamental importance in both normal and pathological pain processing. This neuron-astroglia interrelation is responsible for the regulation of physiologic pain, suppressing several inputs to maintain homeostasis. Nevertheless, a nervous system lesion, or even an important peripheral inflammatory process, initiates a change in glial cells in which a series of pro-inflammatory cytokines (IL1β, TNF-α) are released from glia (Fig. 3), activating in turn several transcription cascades leading to chronic pathologic pain [57]. All three NSAIDs described earlier elicit neuroprotection by either attenuating oxidative damage [59-60] or down regulating glial reaction to peripheral proinflammatory cytokines [57]. In addition, antiapoptotic [46], antioxidant [47] and antiligiotic [51, 61] effects have been shown for BLMs. Some have peripheral anti-inflammatory properties [62] and can influence the release of several neurotransmitters involved in pain modulation such as dopamine [63] or serotonin [64] (Fig. 3).

Both the anti-inflammatory and neuromodulating effects exerted by BLMs either peripherally or centrally may be related to their analgesic properties in some pathologies that are difficult to treat such
as the complex regional pain syndrome [65] or to the analgesic effect of a single preoperative dose of CFX in a clinical protocol [66].

3.4. BLMs and Addiction

The mesocorticolimbic dopaminergic system (MDS) is part of the brain circuitry dealing with reward and plays a crucial role for reward and reinforcement processing, motivation and goal-directed behavior [67-68]. Disregulation of this area is implicated in affective disorders such as anhedonia, dysphoria or depression [68] as well as addiction. In an addictive process, such dysregulation involves synaptic modifications in different components of the MDS, such as the ventral tegmental area (VTA), nucleus accumbens (NAcc) and prefrontal cortex (PFC). These changes include a glutamate increase, due in part to the decrease in GLT1 expression in those areas, this being implied in almost every aspect of addiction [67].

Considering the above, the GLT1 modulating effect induced by CFX was tested in a cocaine-seeking behavioral model by Sari, Smith [69]. They found a significant blocking effect on cocaine self-administration when CFX was administered for 5 days after extinction of the drug. This was correlated with an increase in GLT1 expression in both PFC and NAcc, which suggested a direct implication of CFX in glutamate homeostasis and drug seeking behavior.

The same effect has also been found when CA (1 and 10 mg/kg) was also administered for 5 days [70]. CA and CFX effects were compared in a similar cocaine self-administration model and GLT1 up-regulation was also assessed. Although both drugs induced a similar self-administration and GLT1 up-regulation effect, the 100-fold lower dose difference for CA may relate to an easier translation to a clinical practice.

This addiction altering effect of CFX has been observed with other addictive agents such as alcohol. For example, CFX (100 and 200 mg/kg for 7 days) reduced ethanol intake for 7 weeks in alcohol-preferring rats with access to 15 and 30% ethanol. In the third day post treatment, animals receiving CFX showed increases in GLT1 expression levels in the PFC and NAcc. These results indicate that the reduction in ethanol intake produced by CFX could involve activation of GLT1 [71]. This would indicate that CFX affects only the pathological process induced by addiction, as it does not induce anhedonia or depression.

When tested in an opiate dependence model, both CFX [72] and CA [73] inhibited both physical dependence and withdrawal symptoms. This could mean that the effect shown by CFX is not due to its particular molecular structure, but can be reproduced by other BLMs (several BLMs effects shown on Fig. 3).

3.5. Other Effects

Since Rothstein, Patel [31] described the neuromodulator effect of BLMs, several other actions have been studied and described in different brain areas. For example, as was previously mentioned, CA has been shown to increase dopamine release [63], an effect probably related to a stabilizing influence on two different SNARE proteins, Munc 18-1 and Rab4 that act as exocytosis modulator and synaptic vesicle recycling intermediate, respectively [74]. This could mean that BLM’s may have an affinity for these particular proteins and could facilitate secretion of other neurotransmitters as well.

Moreover, CA has proven effective as an anxiolytic drug, since it was reported that this drug diminished anxiety-like conduct in both rodent and primate models [75]. It also increased sexual arousal in cotton-top tamarins, which led Chan, Kim [68] to study how a 14-day treatment with CA would affect sexual behavior as a whole. They found that CA increased the number of ejaculations and intromissions, and that this effect lasted longer than that induced by paroxetine. In agreement with this finding, it was reported that CA induces dose-dependent penile erection and yawning in rats [64]. This effect was reduced by haloperidol and mianserin; a dopamine D2 receptor antagonist and a serotonin 5HT2c receptor antagonist, respectively. It was concluded that CA induces these responses, at least in part, by increasing both central dopaminergic and serotoninergic neurotransmission. Dopamine in turn activates oxytocinergic neurotransmission and the centrally released oxytocin induces penile erection and yawning [76].
Finally, also has been reported that CFX elicit antitumor activity both in vitro and in vivo models. The kinase Aurora B was identified as the novel target involved in this action, since it is unregulated in several types of lung cancer and CFX suppressed cell growth in 3 strains of neoplastic cells of this type [77]. This new information makes the possibility of different targets for BLMs more plausible, altering current concepts and encouraging further research with these molecules.

CONCLUSION
BLMs are widely used in the clinic as antibiotics, and recent investigations have revealed their capacity to induce other effects. These results could lead, with time, to a series of new indications for this group of molecules.

More research is needed, however, to determine if the non-antibiotic effects of BLMs are due exclusively to the presence of a beta-lactam ring and if compounds sharing this moiety but lacking antibiotic effects could be developed.

LIST OF ABBREVIATIONS
5HT = 5 Hydroxytryptamine
AKT = Protein kinase B
BAX = Bcl-2-associated X protein
BCL = B cell lymphoma
BLMs = Beta-lactam molecules
CA = Clavulanic Acid
CFX = Ceftriaxone
EAAT = Excitatory amino acid transporter
GABA = Gamma amino butyric acid
GFAP = Glial fibrillary acidic protein
GLAST = Glutamate aspartate transporter
GLT = Glutamate transporter
IKK = Inhibitor of Kappa B kinase
IP = Intraperitoneal
MDS = Mesocorticolimbic dopamine system
NAcc = Nucleus Accumbens
NAG = N-acetylglucosamine
NAM = N-acetylmuramic acid
NF-kB = Nuclear factor Kappa B
NSAIDs = Non Steroidal Anti inflammatory drugs
PFC = Prefrontal Cortex
PI3K = Phosphoinositide 3 kinase
SNARE = Snap Receptor
VTA = Ventral Tegmental Area

CONFLICT OF INTEREST
The authors deny any conflict of interest related to this study.

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