



Research Article

Neuronal Potassium Channel Openers Flupirtine (SNEPCO) in the Treatment of the Alcohol Withdrawal without Psychiatric Comorbidity Randomized, Double-Blind, Placebo-Controlled Study

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Abstract

Objective

Alcohol withdrawal is highly prevalent in population. However, the effect of flupirtine on patients with alcohol withdrawal without psychiatric comorbidity has not been studied.

Method

Hundred patients (all men) were washed out from all medications. Each patient was randomized either to receive flupirtine (50 patients) for 2 weeks or matched on placebo (50 patients) in a double-blind manner. Eligible participants, in addition to meeting the criteria for alcohol withdrawal from *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)*, were required to be between 18 and 50 years. Response was defined Alcohol Withdrawal Scale (AWS). Response effects with flupirtine and placebo were compared by using analysis of variance and χ^2 tests. Ten patients did not return for at least 1 subsequent assessment, and 90 patients dropped out (45 taking flupirtine and 45 taking placebo) in the valuable study group.

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Results

Of the 45 flupirtine-treated participants, all responded by 2 weeks versus 6 of the 45 placebo-treated participants ($P > 0.001$). The most common and problematic adverse effect in the flupirtine group was not. The results of our study showed high efficiency flupirtine in the treatment of alcohol withdrawal syndrome. The biochemical mechanism of action of flupirtine is similar to that of ritagabine (chlorzoxazone).

Conclusion: The authors believe this to be the first double-blind placebo-controlled randomization study to test the efficacy of flupirtine in the management of alcohol withdrawal. These need to be replicated in a larger study group.

Keywords: Alcohol withdrawal; Flupirtine; Treatment

Introduction

According DSM-5 prevalence of the alcohol withdrawal approximately 50% of middle-class, highly functional individuals with alcohol use disorder have ever experienced a full alcohol withdrawal syndrome. Among individuals with alcohol use disorder who are hospitalized or homeless, the rate of alcohol withdrawal may be greater than 80%. Fewer than 10% of individuals who develop alcohol withdrawal will ever develop dramatic symptoms (e.g., severe autonomic hyperactivity, tremors, alcohol withdrawal delirium). Tonic-clonic seizures occur in fewer than 3% of individuals. It is known that symptoms of withdrawal may serve to perpetuate drinking behaviors and contribute to relapse, resulting in persistently impaired social and occupational functioning. The symptoms required urgently medically intervention. Alcohol withdrawal is associated with greater functional, social impairment and poor prognosis. The basis for the use of Flupirtine in the treatment of alcohol withdrawal syndrome was literature data suggesting that this drug reduce heavy alcohol drinking. Retigabine a drug with the same mechanism of action is also tested in this area [1-5].

The aim of our study was to evaluate the effect of flupirtine in alcohol withdrawal is highly prevalent in population. However, possibility of using flupirtine (cadadolone) - SNEPCO (Selective Neuronal Potassium Channel Opener) - in the therapy alcohol withdrawal was not study. The work was carried away with in a double-blind placebo-controlled design. This is a report on a randomized, double-blind, placebo-controlled trial of neuronal potassium channel openers flupirtine (cadadolone).

Materials and Methods of Research

In accordance with the Helsinki Declaration of the World Medical Association "Recommendations for doctors engaged in biomedical research involving people", adopted by the 18th World Medical Assembly (Finland, 1964, revised in Japan in 1975, Italy - 1983, Hong Kong - 1989, the South African Republic - 1996, Edinburgh - 2000); The Constitution of the Republic of Azerbaijan, the Law "On Psychiatric Assistance" (adopted on 12.06.2001, with amendments and additions - 11.11.2011, Decisions of the Cabinet of Ministers of the Republic of Azerbaijan No. 83, dated April 30, 2010 "On Approval of the Rules for Conducting Scientific, Preclinical and Clinical studies of medicines" are established:

- The conditions of the conducted researches corresponded to the generally accepted norms of morality, the requirements of ethical and legal norms, as well as the rights, interests and personal dignity of the participants of the studies were observed
- Conducted research is adequate to the topic of research work
- There is no risk for the subject of research
- Participants in the study were informed about the goals, methods, expected benefits of the study and associated with risk and inconvenience in the study
- The subject's informed consent about participation in the research was received

The decision of the Ethical Committee at the Azerbaijan Psychiatric Association on the article of NA. Aliyev, Z.N. Aliyev "Selective Neuronal Potassium Channel Opener flupirtine (SNEPCO) in treatment-resistant epilepsy in adults" submitted for publication in psychiatric journals: in connection with compliance with its legislative requirements and regulatory documents is to approve the article by N.A. Aliyev, Z.N. Aliyev "Selective Neuronal Potassium Channel Opener flupirtine (SNEPCO) in treatment of alcohol withdrawal". We examined 100 patients with (FI0.239). Patients were observed at the Mental Health Center of the Ministry of Health of the Republic of Azerbaijan.

According DSN-5 [6] the essential feature of alcohol withdrawal is the presence of a characteristic withdrawal syndrome that develops within several hours to a few days after the cessation of (or reduction in) heavy and prolonged alcohol use (Criteria A and B). The withdrawal syndrome includes two or more of the symptoms reflecting autonomic hyperactivity and anxiety listed in Criterion B, along with gastrointestinal symptoms. Withdrawal symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning (Criterion C). The symptoms must not be attributable to another medical condition and are not better explained by another mental disorder (e.g., generalized anxiety disorder), including intoxication or withdrawal from another substance (e.g., sedative, hypnotic, or anxiolytic withdrawal) (Criterion D). Symptoms can be relieved by administering alcohol or benzodiazepines (e.g., diazepam). The withdrawal symptoms typically begin when blood concentrations of alcohol decline sharply (i.e., within 4-12 hours) after alcohol use has been stopped or reduced. Reflecting the relatively fast metabolism of alcohol, symptoms of alcohol withdrawal usually peak in intensity during the second day of abstinence and are likely to improve markedly by the fourth or fifth day.

It is known that (CIWA-Ar) score divided to three stages:

- < 8 Mild withdrawal;
- < 8-25 Moderate to severe withdrawal and
- 25 Very severe withdrawals [Drug & Alcohol Services Council 2001: Revised 2003] our patients correspond to the moderate to severe alcohol withdrawal

Hundred patients (all men) were washed out from all medications. Each patient was randomized either to receive flupirtine (50 patients) for 2 weeks or matched on placebo (50 patients) in a doubleblind manner. Eligible participants were required to be between 18 and 65 years. Ten patients did not return for at least 1 subsequent assessment, leaving 90 patients (45 taking flupirtine and 45 taking placebo) in the

valuable study group. There were premature dropouts, in each group 5 because of noncompliance with the visits. Flupirtine and placebo were dispensed in identical appearing capsules; patients randomized to the placebo group took the same number of capsules as those assigned to the flupirtine group.

In our studies we used Flupirtine forte (flupirtinum) was prescribed the first 7 days of 200 mg 3 times a day, then 400 mg 3 times in day, in capsules for 14 days (Produced by Pliva Krakow, Pharmaceutical Plant AO). This dose was maintained until the end of the trial at week 2. Starting on week 0, patients received study medication. Capsules were supplied in numbered bottles containing study medication as determined by a random number sequence. The randomization list was held by the senior investigator outside the treatment team. No communication regarding the status of patients under study was permitted the unblinded investigator and the other investigators, save that the unblinded investigator was informed if patients complained of any adverse effects from the study medication. Hospital staff with no clinical responsibilities and knowledge of the patients oversaw the assignment procedure and assigned medication in sequential order, strictly following the randomized list. The treating psychiatrist did not have access to the list. Both the patient and the treating psychiatrist were not aware of the antipsychotic being prescribed. Patients were excluded if they displayed an acute systemic medical disorder or a medical disorder requiring frequent changes in medication and if they displayed a history of seizures, cardio-vascular disease, structural brain damage from trauma, focal neurological signs on examination, or evidence of any progressive neurological disorder, and substance dependence (except tobacco). Contraindications in our patients were following: patients with history of hypersensitivity to flupirtine, hepatic encephalopathy, cholestasis, myasthenia gravis, chronic alcoholism, primary biliary cirrhosis, and liver disease. Patients underwent physical examination, electrocardiography (if > 40 years), and laboratory analyses, including hematological measures, partial thromboplastin time, and urinalysis. All patients were evaluated on weeks 0 and 2 weeks of the study by different psychiatrists. The adverse effects were recorded by spontaneous reports. Patients attended 4 visits: initial screening (randomization (week 0)), and 2 times further visits at weeks 2. Data for clinical assessments were collected at weeks 0 and 2. Data for adverse events were spontaneous complaints at each visit. Patients were also requested to report immediately at any onset of possible rash or other skin reactions.

The patients did not receive any antidepressant or anticonvulsant drugs for a period of 2 weeks before the study. All of the patients provided with the written informed consent after a full explanation of the protocol design that had been approved by the local ethics committee (Azerbaijan Psychiatric Association approved this study). Patients who were not able to give reliable informed consent were excluded from the study. Patients were recruited from January 2016, and follow up was completed by January 2017. Dropout rates and reasons for dropping out were also recorded.

Comparison between the groups at baseline was performed using the Mann-Whitney test. Analysis of response refers to the last observation carried forward for all patients who had valuable efficacy at baseline and with treatment. The responder analysis was conducted by using the χ^2 and Analysis of Variance (ANOVA) according to Glantz [7].

Results

Characteristics of the patients randomly assigned to the 2 treatment groups are also shown in table 1.

Indicators	Treatment Groups				Statistics P
	Flupirtine Group n=50		Placebo Group n=50		
Age, mean (SD), y	38.0	(00.2)	37.4	(9.8)	NS
Duration of illness, Mean (SD), y	16.5	(13.0)	18.5	(12.2)	NS
Age at onset, Mean (SD), y	15.0	(7.0)	15.5	(7.6)	NS
Education, n (%)					
Primary school	28	(70)	30	(75)	NS
Secondary school	12	(30)	10	(25)	NS
Marital status, n (%)					
Never married	10	(25)	10	(25)	NS
Married	20	(50)	18	(45)	NS
Divorced or separated	10	(25)	12	(30)	NS
Employment status, n (%)					
Unemployed	40	(100)	40	(100)	NS

Table 1: Demographic and Clinical Characteristics of the Study Sample (N = 100).

Indicators Treatment groups Statistics P.

As shown in table 1, in the baseline Mann-Whitney U test, there were no significant differences between 2 groups. Statistical differences between the 2 groups are not significant.

Hundred patients (all men) completed the study and were included in the analyses of efficacy (Table 2). As shown in table 2, patients did not return for at least 1 subsequent assessment, leaving 90 patients (45 taking Flupirtine and 45 taking placebo) in the valuable study group. There were 5 premature dropouts, in the first group and 5 in the second (placebo) group. In both groups on 5 because of noncompliance with the visits. Hence, 45 in the first group and 45 in the second group completed the analysis. Mean total scores on the CIWA-Ar scale during treatment of alcohol withdrawal are shown in table 2. Mean total scores on the CIWA-Ar for 2 weeks were significantly different between the 2 groups. At the end of 2 weeks of therapy significantly decreased the rating in the CIWA-Ar.

Intention to Treat	Treatment Groups		Statistics P
	Flupirtine Group n=50	Placebo Group n=50	
Completers analysis means =90	45	45	NS
(CIWA-Ar) score at start of the study (wk 0)	17.5 ± 1.5	17.5 ± 1.5	NS
(CIWA-Ar) score at end of the study (wk 2)	2.0 ± 0.1	20.0 ± 1.7	P > 0.001

Table 2: Mean CIWA-Ar score scale during treatment.

Mann-Whitney U test, significant difference between the flupirtine and the placebo groups Results of the Treatment (Observed and expected number from W2 analysis) shown in the table 3.

Treatment Groups	Improvement	No Improvement	Total
Flupirtine	35 (15.60)	10 (20.43)	45
Placebo group	6 (16.43)	39 (22.68)	45
Total	41	49	90

Table 3: Results of the Treatment (Observed and expected number from the W2 Analysis).

Expected numbers indication in the brackets, W2 = 22.68, df = 1. P < 0.001

Adverse effects reported by patients who received Flupirtine and placebo. Adverse Effect Flupirtine Group (n = 45), n (%) Placebo Group (n = 45), n (%) P*

Adverse Effect	Flupirtine Group (n = 45), n (%)	Placebo Group (n = 45), n (%)	P*
Dizziness	6 (14)	35 (78)	> 0.001
Headache	2 (4)	16 (35)	>0.001
Fatigue	3 (7)	40 (89)	>0.001
Perspiration	5 (11)	35 (78)	>0.001
Sedation	5 (11)	3 (7)	NS
Nausea	1 (2)	20 (44)	>0.001
Blurred vision	4 (9)	14 (31)	>0.001
Sleepiness	1 (2)	38 (84)	>0.001
Vomiting	8 (18)	25 (55)	>0.001

Table 4: Adverse effects reported by patients who received Flupirtine and placebo.

Analysis of statistical significance was carried out with criteria of the alternative changes.

NS - not significant

Table 3 shows the results of the treatment on the W2 analysis. As shown in table 3, a statistically significant difference in improvement was observed in the first group (Flupirtine) compared with that in the second group (placebo). It is necessary to indicate that, in patients from the first group, compared with those in the second group, statistically significant adverse effects were observed (Table 4). Headache in the first group of patients was significantly lower than that in the second group of patients.

The data obtained by us in connection with a small number of patients and a short period of observation (2 wk) should be considered preliminary. The next stage of the work will be carried out on a large number of patients and longer duration of observation, with a placebo-controlled, doubleblind method.

Discussion

Flupirtine was administered as an alternative analgesic for opioids and NSAIDs. Subsequently, several other actions have been identified, such as muscle relaxation and neuroprotective activity. Flupirtine acts indirectly as an N-Methyl-D-Aspartate (NMDA) receptor antagonist by activating K⁺ channels [8].

Flupirtine causes a dose-dependent decrease in NMDA-induced glutamate induced by an increase in the intracellular Ca⁺⁺ concentration [9]. It binds and activates the G-protein bound to the K⁺ channels directed inwards. Activation of this channel leads to hyperpolarization of the neuronal membrane, and the neuron becomes less excitable; thus, stabilization of the resting neuron membrane is observed [10]. Drugs that activate this channel are called Selective Neuronal

Potassium Channel Openers (SNEPCO), and flupirtine is a prototype [8]. Experimental evidence suggests that flupirtine can inhibit channel opening by acting as an oxidant in the redox site of the NMDA receptor [11]. This action inhibits the transfer of nociceptive impulses when neurons are excited. The central effect of flupirtine is based on 4 main effects [12].

Analgesic action

Flupirtine was introduced as an alternative analgesic to opioids and NSAIDs. Subsequently, multiple other actions such as muscle relaxation and neuroprotective activity were identified. Flupirtine acts indirectly as N-Methyl-D-Aspartate (NMDA) receptor antagonist by activation of K⁺ channels [13]. Flupirtine causes a dose-dependent reduction of NMDA receptor mediated glutamate induced rise in intracellular Ca⁺⁺ concentration [9]. It binds to and activates G- protein coupled inwardly rectifying K⁺ channels. Activation of this channel leads to hyperpolarization of neuronal membrane and the neuron becomes less excitable; thus, there is stabilization of resting neuronal membrane [14]. The drugs activating this channel are called as Selective Neuronal Potassium Channel Openers (SNEPCO) and flupirtine is the prototype [8]. Experimental evidence suggests that flupirtine might suppress channel opening by acting as an oxidizing agent at the redox site of the NMDA receptor [11]. This action inhibits the transmission of nociceptive impulses during neuronal excitation.

Muscle relaxant action

The muscle relaxation is due to inhibition of both mono- and polysynaptic reflexes. The spinal polysynaptic flexor reflex, mediated by NMDA receptors, was depressed by flupirtine, whereas the monosynaptic Hoffmann reflex (H-reflex), mediated by non-NMDA receptors, was not influenced. Healthy human subjects responded with a significant reduction of both the early phase of the electrically elicited polysynaptic flexor reflex of pretibial muscles and the medium latency response of the toe-up paradigm after 2 h of 200 mg of flupirtine. Flupirtine possesses analgesic as well as muscle-relaxing effect in same dose ranges; thus, it can be used in the treatment of painful diseases of the motor system presenting with spasticity and chronic musculoskeletal pain [15].

Neuroprotective action

Apoptosis, a programmed cell death, is caused by increased intracellular Ca⁺⁺ levels, mitochondrial dysfunction, cell membrane disruption, and finally nucleolysis. *In vitro* studies with primary cortical neurons from rat embryos have shown that lead acetate; prions like PrPsc, HIV coat protein gp120, and β amyloid peptide will cause apoptotic cell death. But if preincubated with flupirtine, it completely protects apoptotic cell death caused by above agents in the neurons [16]. It has been found that flupirtine also antagonizes both glutamate and NMDA induced increase in intracellular levels of Ca⁺⁺, as observed *in vitro* cultures of cortical and hippocampal neurons [16,17]. The expression of Bcl-2, an antiapoptotic agent, and glutathione, a scavenger of reactive oxygen, are reduced during glutamate or NMDA-induced apoptosis in cells. Flupirtine is found to increase the levels of Bcl-2 and glutathione in glutamate or NMDA-induced apoptosis of human Ntera/D1 (hNT) neurons as well as cultured retinal pigment cells [11]. Flupirtine reduced the expression of oncogenes and formation of reactive oxygen radicals in experimental models which explains its action of preventing ischemia induced apoptosis. This explains the role of flupirtine in future for treatment of

neuroinfections such as Immune Deficiency Syndrome (AIDS), prion diseases, and neurodegenerative disease such as Alzheimer's [8].

Antiparkinsonian action

Flupirtine has an NMDA receptor antagonistic action and hence it was studied for its Antiparkinsonian effect as an adjuvant to L-3, 4-Dihydroxyphenylalanine (L-DOPA). Akinesia and muscular rigidity were produced in rats by giving reserpine and α methyl p-tyrosine. Flupirtine was given alone and in combination with L-DOPA, it strongly reduced muscle rigidity and increased the ability of L-DOPA to reverse Akinesia [18]. In haloperidol-induced catalepsy, which is considered as a model of Parkinson's disease, flupirtine alone and in combination with L-DOPA exerted a potent and cataleptic effect [14,17]. However, human studies are not available till date to support this evidence. If studies are done to prove effectiveness in Parkinson's disease, it can be combined with L-DOPA.

Special group

Safety Flupirtine in pregnant women, lactating women and children less than 6 years is not established. If indicated in lactating women, breastfeeding should be discontinued. Flupirtine dose should be reduced to 50% in elderly patients and patients with renal and hepatic insufficiency [18].

Contraindications

Flupirtine avoids patients with hypersensitivity to flupirtine, hepatic encephalopathy, cholestasis, myasthenia gravis, chronic alcoholism, primary biliary cirrhosis and liver diseases.

Benefits

Musculoskeletal pain: Flupirtine was compared with placebo and standard analgesics to determine the efficacy and tolerability of analgesics. Post-marketing surveillance for flupirtine 200-300 mg/day for 1 week, as assessed by visual analog pain scale. It was noted that the response rates were 94%, 89.4% and 85.9% for patients with acute, sub acute and chronic pain, respectively [18,19].

Headache: Patients who had an inadequate response to conventional analgesics for chronic headache showed a better response to flupirtine [19]. The results in our study indicate that Flupirtine is more effective in treating alcohol withdrawal than placebo. Analysis of statistical significance was carried out with criteria of the alternative changes. Indicates significant this has led us to investigate other potential pharmacotherapies, in particular the anticonvulsant Flupirtine [20]. Flupirtine acts at the presynaptic membrane to reduce the release of glutamate, and it has been shown to reverse depersonalization-related phenomena induced by the NMDA receptor antagonist ketamine in a healthy individual. The mechanisms of Flupirtine may be connected with the influence of neuronal activity and glutamate and GABA transmission.

In one hand Flupirtine mechanism of action similar; as a retigabine, and in other hand, given that retigabine is an FDA-approved drug, its use in a clinical trial on alcohol use disorder is theoretically feasible [3]. Because retigabine is also tested in this area. Thus our data correlated with some literature data [1-3, 21-24]. These data that indicated that the potassium channel may be as targets for therapeutic intervention and novel therapeutic strategies for alcohol and drug addiction retigabine is also tested in this area. We suggest that the Flupirtine mechanism of action on alcohol is same as a retigabine.

The data of Lavreskaya EF [25] shown that an increase in the membrane conductivity for K^+ ions (i.e., activation-opening of the potassium channels) causes neuronal hyperpolarization and, in most cases, reduces the frequency of neuronal excitation, exerting a strong inhibitory effect on the excitability of neurons. Potassium channels control the membrane potential of rest and, therefore, play an important role in regulating the excitability of neurons. These data served the basis for the present study. She wrote: "It is necessary to emphasize several important points relating to those functions in which a special role belongs to the potassium channels

1. The main function of potassium channels is the catalysis of the transfer of potassium ions through the membrane, which ensures the existence of a difference in electrical potentials between the inner and outer sides of the membrane in all living cells. The fulfillment of this functional role is ensured by the high conductivity and high selectivity of these channels.
2. In addition to this potential-forming role, potassium channels participate in the process of depolarization of the membrane of electro excitable cells, accelerating repolarization and as if returning the potential to a resting level. In rare cases, membrane depolarization can occur due to a decrease in potassium permeability.
3. All the mentioned above determines the special role played by the change in the potassium permeability of the membrane providing many physiological processes, in particular, excitation in nerve and muscle cells, the creation of rhythms in neuronal and cardiac pacemakers, the secretion of hormones by glandular cells and mediators by nerve endings, certain types of reception (For example, light), memory processes and many others, not fully clarified yet.
4. The multiplicity of the channels regulating the potassium conductivity of the membrane indicates a special plasticity of this membrane function. The variety of potassium channels is reflected in various sensitivity to pharmacological agents, blockers. This opens important prospects for the selective impact on various components of potassium conductivity and, thus, on the processes in which they participate".

In such a way the available up-to-date literature data indicate an increase in the membrane conductivity for K^+ ions (i.e., activation-opening of the potassium channels) cause neuronal hyperpolarization and, in most cases, reduces the frequency of neuronal excitation, exerting a strong inhibitory effect on the excitability of neurons. Potassium channels control the membrane potential of rest and, therefore, play an important role in regulating the excitability of neurons. Four limitations should be noted. First was our small study group and we recommending that these results be replicated in a larger group so that effect sizes can be more precisely estimated. Second, it is necessary to conduct this study for the possible generalizability of these data on a sample of women with alcohol withdrawal. Third, the absence of systemic side effects indeed to future investigations. Fourth, it is necessarily study, side effects of the CNS. The fifth, further research is needed to establish the optimal dosage. Notwithstanding these limitations, this study suggests that Flupirtine is efficacious and well tolerated in the treatment of alcohol withdrawal. In any event, pending a further understanding of Flupirtine's mechanisms of action, the present data suggest that this drug is a useful new agent for the treatment of alcohol withdrawal, in patients who have failed to respond to other traditional drugs. It will be important to explore further effects of Flupirtine in other disorders treated with Flupirtine.

However, our results show certain limited duration of the trial. Nevertheless, these findings provide evidence that Flupirtine treatment is well tolerated and may be proposed as an effective therapeutic strategy to improve outcome in treatment of alcohol withdrawal. Some authors established, that chlorzoxazone, reduce NAcb SK channel function with chronic ethanol intake enhances NAcb excitability and ethanol intake, and the FDA-approved SK activator chlorzoxazone reduces excessive ethanol intake [24,26]. Other authors indicated that small conductance calcium-activated potassium type 2 channels regulate alcohol-associated plasticity of glutamatergic synapses [25].

Conclusion

The results of our study showed high efficiency flupirtine in the treatment of alcohol withdrawal syndrome. The biochemical mechanism of action of flupirtine is similar to that of ritagabine (chlorzoxazone). Despite the tremendous progress that has been made recently in elucidating the neurobiological basis of addiction, the expected subsequent therapeutic improvements have not been realized. Channel blockers represent a new goal that can be translated into research clinical studies in the near future, especially with the use of drugs already approved for other indications. The novelty of the work is the first application of the neuronal potassium channel openers in the treatment of alcohol withdrawal syndrome.

Author Disclosure Information

The authors declare that the article is submitted on behalf of all authors. None of the material in the article has been published previously in any form and none of the material is currently under consideration for publication elsewhere other than noted in the cover letter to the editor. Authors declare no financial and personal relationship with other people or organizations that could inappropriately influence this work. All authors contributed to and have approved the final article.

The authors declare no conflicts of interest

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