ADITUM Journal of Clinical Psychology and Mental Health Care

Open Access Research Article

Alternative Treatment of Anxiety Disorders During Covid-19 Pandemic Which Snepco

Nadir A Aliyev[1]*, Zafar N Aliyev[2]

[1]Azerbaijan State Advanced Training Institute for Doctors named by A. Aliyev department of psychiatry and drug addiction, Baku, Azerbaijan Republic

[2]Azerbaijan Medical State University, Department of Psychiatry Baku City, Azerbaijan Republic

Article Info

Received: March 05, 2021
Accepted: March 19, 2021
Published: March 24, 2021

***Corresponding author:** Nadir A Aliyev, Professor, Department of Psychiatry and Addiction Azerbaijan State Advanced Training Institute for Doctors named by A. Aliyev, department of psychiatry and addiction, Baku, Azerbaijan; Baku City, U. Chagibekov Street, 46/50, F. 1. Baku P.O. AZ0010 Azerbaijan Republic.

Citation: Nadir A Aliyev, Zafar N Aliyev. "Alternative Treatment Of Anxiety Disorders During Covid-19 Pandemic Which Snepco". Clinical Psychology and Mental Health Care, 2(4); DOI: http;//doi.org/03.2021/1.10022.

Abstract

Objective. The pharmacological drugs used (Antidepressants SSRIs Tricyclic, MAO Benzodiazepines) for anxiety disorders in the context of the COVID-19 pandemic were not effective for several reasons. Time calls for finding new drugs to treat anxiety disorders in the COVID-19 pandemic.

Method. Hundred patients (all men) were washout from the all medications. Each patient was randomized to receive either Selective neuronal potassium channel opener (SNEPCO) - flupirtine (50 patients) for 6 weeks or matched placebo (50 patients) in a double-blind manner. Eligible participants, in addition to meeting the DSM-5 criteria for anxiety disorders and having a minimum score of 25 and more on the Hamilton Anxiety Scale, were required to be between 18 and 65 years Response was defined as a 50% reduction in the Hamilton anxiety scale score. Response and side effects with flupirtine and placebo were compared by using analysis of variance (ANOVA) and chi-square tests.

Results. Fifty i.e all patients of the flupirtine - treated responded by 6 weeks, versus four of the placebo-treated participants ($p < 0.001$).

Conclusions. The authors believe this to be the first double-blind placebo-controlled randomization study to test the efficacy of a flupirtine in the management of anxiety disorders. They need to be replicated in a larger study group.

Keywords: Anxiety disorders; COVID-19 Pandemic; Flupirtine; Treatment

Introduction:

Anxiety statistics worldwide show that anxiety disorders are common across the globe. According to the World Health Organization, 3.6 percent — or about 264 million individuals worldwide — have an anxiety disorder. Additionally, 4.6 percent of females and 2.6 percent of males globally are affected by anxiety. In the United States adult population, the prevalence of anxiety disorders is 19.1 percent within the past year, meaning that during a 12-month period, 19.1 percent of adults had an anxiety disorder. Lifetime rates are even higher at 31.1 percent, according to the National Institute of Mental Health (NIMH). The NIMH reports that the incidence of anxiety disorders varies by age. Anxiety disorders in adults are seen in 22.3 percent of those aged 18–29 and 22.7 percent of people ages 30–44. The prevalence of anxiety disorders drops to 20.6 percent for individuals ages 45–59. Anxiety in older adults is less common, affecting only 9 percent of people 60 years or older. **[1] (https://www.therecoveryvillage.com/mental-health/anxiety/related/anxiety-disorder-statistics/).** The anxiety disorders make up one of the most common groups of psychiatric disorders. The National Comorbidity Study reported that one of four persons met the diagnostic criteria for at least one anxiety disorder and that there is a 12-month prevalence rate o 17.7 percent. Women (30.5 percent lifetime prevalence) are more likely to have an anxiety disorder than are men (19.2 percent lifetime prevalence). The prevalence of anxiety disorders decreases with higher socioeconomic status. The 12-month prevalence of separation anxiety disorder among adults in the United States is 0.9%-1.9%. In children, 6- to 12-month prevalence is estimated to be approximately 4%. In adolescents in the United States, the 12-month prevalence is

1.6%. Separation anxiety disorder decreases in prevalence from childhood through adolescence and adulthood and is the most prevalent anxiety disorder in children younger than 12 years. In clinical samples of children, the disorder is equally common in males and females. In the community, the disorder is more frequent in females. In the United States, the 12-month community prevalence estimate for specific phobia is approximately 7%-9%. Prevalence rates in European countries are largely similar to those in the United States (e.g., about 6%), but rates are generally lower in Asian, African, and Latin American countries (2%-4%). Prevalence rates are approximately 5% in children and are approximately 16% in 13- to 17-year-olds. Prevalence rates are lower in older individuals (about 3%-5%), possibly reflecting diminishing severity to subclinical levels. Females are more frequently affected than males, at a rate of approximately 2:1, although rates vary across different phobic stimuli. That is, animal, natural environment, and situational specific phobias are predominantly experienced by females, whereas blood-injection-injury phobia is experienced nearly equally by both genders [2, 3].

Anxiety disorders, including panic disorder with or without agoraphobia, generalized anxiety disorder, social anxiety disorder, specific phobias and separation anxiety disorder, are the most common mental disorders and are associated with high health care costs and a high burden of disease. According to large population surveys, up to 33.7% of the population suffer from anxiety disorder during their lifetime. Significant misunderstanding and inadequate treatment of these disorders has been demonstrated. There is no evidence that prevalence rates for anxiety disorders have changed in recent years. In cross-cultural comparisons, prevalence rates vary widely. This heterogeneity is more likely due to differences in methodology than cultural influences. Anxiety disorders are chronic; however, with age, there is a natural decline in prevalence rates. Anxiety disorders are often accompanied by other anxiety disorders and other mental disorders [4].

Thus, Anxiety disorder is widely prevalence throughout the world. However, the pharmacological drugs used (Antidepressants SSRIs Tricyclic, MAO Benzodiazepines) for anxiety disorders in the context of the COVID-19 pandemic were not effective for several reasons.
The aim of this study was to develop a new treatment for anxiety disorders in the COVID-19 pandemic.

Materials and methods

In a previously published study, we found that anxiety disorders are the most common mental disorder. [5]. Currently, for the treatment of anxiety disorders, they are mainly used benzodiazepine, antidepressants SSRIs, tricyclic, tetracyclic and MAO for anxiety disorders in the context of the COVID-19 pandemic were not effective for several reasons. As the world shudders with COVID-19, the US Food and Drug Administration have made harsh admissions regarding hazardous benzodiazepine drugs. At first the FDA has recognized that patients can become "physically dependent" on them after taking them for just "a few days." Taking benzodiazepines for more than 3 or 4 weeks can put someone at risk of becoming addicted or physically dependent without developing dependence. The FDA warns that while benzodiazepines can be a beneficial treatment, stopping them suddenly or reducing the dose too quickly can lead to withdrawal symptoms that can be life-threatening. The agency recommends that patients speak with their healthcare providers to develop a plan to safely and slowly taper their benzodiazepine dose. [6]. Secondly, antidepressants SSRIs Secondly, they can cause serotonin syndrome. Thirdly, tricyclic, tetracyclic antidepressants have numerous adverse effect effects and toxic properties. Therefore, we have developed alternative Treatment of Anxiety disorders during COVID-19 Pandemic which SNEPCO **(**flupirtine)
This was a double-blind, placebo-controlled trial for patients diagnosed with DSM-5 for rapid cycle bipolar disorder. The patients gave their informed, written consent to participate.
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.

a) Conducted research is adequate to the topic of research work.
b) There is no risk for the subject of research.
c) Participants in the study were informed about the goals, methods, expected benefits of the study and associated with risk and inconvenience in the study.
d) 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. Aliev, Z.N. Aliev "**Alternative Treatment of Anxiety disorders during COVID-19 Pandemic which SNEPCO** " 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. Aliev "**Alternative Treatment of Anxiety disorders during COVID-19 Pandemic which SNEPCO** ". Patients were observed at the Mental Health Center of the Ministry of Health of the Republic of Azerbaijan. The study was conducted from January 01, 2020 to 01 of the January 2021 years.
We excluded sexually active subjects with active or unstable epilepsy, other genetic syndromes or congenital infections associated with autistic-like syndromes, prematurity; subjects who have been treated within the previous 30 days by any medication known to have a clearly defined potential for toxicity or with any psychotropic drugs; subjects with clinically significant abnormalities in laboratory tests or physical examination; subjects with a history of hypersensitivity or serious side effects associated with the use any drugs A detailed clinical

interview with parents by a clinical expert, accompanied by physical examination and blood analysis, was used to ensure that subjects did not meet any exclusion criteria. A structured clinical interview, for DSM-5 Axis I Disorder, Patient Edition, was used to diagnose anxiety disorders DSM-5 [2] and in addition having a minimum score of 25 and more on the Hamilton Anxiety Scale [7]. Hundred patients all men whom we studied were under observation in Mental Health Center of the Ministry of Health of the Republic of Azerbaijan. The length of the washout was 2 weeks. Patients were washout from the all medications. Eligible participants were required to be between 18 and 65 years of age. We excluded serious medical conditions including with other psychiatric disorders (e.g. bipolar disorder II tipi, schizophrenia, patients judged to be at serious suicidal or homicidal risk, dependence of psychoactive drugs, somatic, neurological illness etc).

Patients clinically significant of abnormal laboratory or EEG findings were ineligible. Patients before the study had not used antidepressants, antipsychotics, anxiolytics, benzodiazepines, SSRI and. Washout of all medicines was two weeks.

Eligible participants were required to be between 18 and 65 years of age.

The patients were evaluated by Hamilton Anxiety Scale at 4 and 6 weeks. Classification of symptoms: 0 — absent; 1 — mild; 2 — moderate; 3 — severe; 4 — incapacitating. Criteria: (1) Mild Anxiety: 18; (2) Moderate Anxiety: 25; and (3) Severe Anxiety: 30.

The primary efficacy variable, as defined by the protocol, was the reduction from baseline of the Hamilton Anxiety Scale total score after 6 weeks of therapy. Response defined, a priori, as at least a 50% improvement from baseline to end point and recovery as a score of no greater than 18 at the end point in the Hamilton Anxiety Scale total score, respectively. The side-effects were recorded by spontaneous reports.

Analysis of response refers to the last observation carried forward for all subjects who had valuables efficacy at baseline and with treatment. The responder analysis was conducted by using the chi-square (x^2) and analysis of variance (ANOVA) according to Glantz [8].

In our studies we used flupirtinum (cadadolone forte) was prescribed the 200 mg 3 times a day, in capsules for 6 weeks (Produced by Pliva Krakow, Pharma- ceutical Plant AO). This dose was maintained until the end of the trial at week 6. 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 unblended investigator and the other investigators, save that the unblended investigator was informed if patients complained of any adverse effects from the study medication. Medically staff with no clinical responsibilities and knowledge of the patients oversaw the 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. 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 6 weeks of the study by different psychiatrists. The adverse effects were recorded by spontaneous reports. Patients attended 4 visits: initial screening (randomization (week 0), further visits at weeks 4 and 6. Data for clinical assessments were collected at weeks 0 and 6. 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. Adverse effects reported by patients who received katadolone and placebo not observed

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 valuables efficacy at baseline and with treatment. The responder analysis was conduct- ed by using the x2 and Analysis of Variance (ANOVA) according to Glantz **[8].**

Results

Characteristic	Katadolone n =50	Placebo n =
Age (Mean SD) years	38.0 ± 10.2	37.4 ± 9.8
Education:		
— primary school	10	11
— secondary school	20	21
— high school	20	18
Marital status:		
— never married	10	9
— married	30	31
— divorced	10	10
or separated		
Employment status		
— unemployed	18	20
— employed	32	30

Table1. Characteristics of study patients

Note: differences between groups are not significant.

According to the instructions for the medical use of the katadolone (flupirtine), it refers to the clinical and pharmacological group - the non-opioid analgesic of the central action.

Mean scores on the Hamilton Anxiety Scale during treatment	Treatment groups n=50	Placebo n=50	P
Completers analysis means Hamilton Anxiety Score at Start	31.0 ±3.41	30.0 ± 3.32	p >0.10
Hamilton Anxiety Score at Week 4 of the Study	24.0 ±3.0	29.0 ± 2.0	p <0.001
Hamilton Anxiety Score at end of the Study (Week 6)	20.0 ± 4.2	27.0 ± 3.5	p < 0.001

Katadolone was superior to placebo in the ratings on Hamilton Anxiety Scale (**Table 2**).

Katadolone separated statically from placebo at the 4-week time point and beyond at the 6-week. By study end (6-week) the mean change in the total score on the Hamilton Anxiety scale was also superior for katadolone than for placebo. The difference between

groups was statistically significantly.
The responder was conducted by x^2 also demonstrated superior for katadolone than for placebo (Table 3). Katadolone was generally well tolerated by the patients in the study.

The results of the square analysis)	observed number	expected number	the chi- x2
Treatment Groups	Yes improvement	Not improvement	Total
Placebo	4 (15.43)	46 (21.57)	50
Katadolone	50 (15.56)	-------	50
Total	54	46	100

Table3. The results of the Hamilton Anxiety Scale during treatment (observed and expected number from the chi square analysis).

Note: observed and expected numbers indication in the brackets. chi- x2= 22.68, df = 1, p< 0.001.
We suggest that one of the reasons of reduction of the anxiety symptoms in our patients may be consequence of sedative and other effect of katadolone.

4. Discussion

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 place- bo-controlled, doubleblind method.

Discussion

The classification of clinical and pharmacological groups is based on the therapeutic effect. Pharmacological action: Selective Neuronal Potassium Channel Opener. By its pharmacological effects, the drug is a non-opioid analgesic of central action that does not cause addiction and habituation, in addition, it has a miorelaxing and neuroprotective effect. The action of flupirtine is based on the activation of potential- independent potassium channels, which leads to the stabilization of the membrane potential of the neuron. The effect on the current of potassium ions is mediated by the effect of the drug on the regulatory G protein system. In therapeutic concentrations, flupirtine does not link to α1, α2-adrenoreceptors, serotonin 5HT1, 5HT2 receptors, dopamine, benzodiazepine, opioid, central m-and n-cholinergic receptors.
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 [9].
Flupirtine causes a dose-dependent decrease in NMDA-induced glutamate induced by an increase in the intracellular Ca^{++} concentration **[10].** It binds and activates the G-protein bound to the K^+ channels directed inwards. Activation of this channel leads to hyperpolariza- tion 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 **[9].**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 in- tracellular 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 be- comes less excitable; thus, there is stabilization of resting neuronal membrane [14]. The drugs activating this channel are called as Selec- tive Neuronal Potassium Channel Openers (SNEPCO) and flupirtine is the prototype *[9]*. 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 poly-synaptic 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 musculo- skeletal 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 gluta- thione, 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 on-cogenes and formation of reactive oxygen radicals in experimental models which explains its action of preventing ischemia induced apoptosis.

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 reserving and α methyl p-tyro- sine. 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 Flupirtina 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]. 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.

The role of GABA in anxiety disorders is most strongly supported by the undisputed efficacy of benzodiazepines, which increase the activity of GABA at the GABA A (GABA) receptor, in the treatment of certain types of anxiety disorders. Although low potency benzodiazepines are most effective for the symptoms of generalized anxiety disorder, high potency benzodiazepines such as alprazolam (xanax) and clonazepam are effective in treating panic disorder. Studies in primates have shown that autonomic anxiety symptoms are induced by the administration of a benzodiazepine inverse agonist, β-carboline-3-carboxylic acid. β-carboline-3-carboxylic acid is also of concern in healthy control volunteers. The benzodiazepine antagonist flumazenil (romazicone) causes frequent severe panic attacks in patients with panic disorder. These findings have led researchers to speculate that some patients with anxiety disorders have abnormal functioning of their GABA receptors, although this link has not been directly shown [3].

Thus our date indicated that the potassium channel may be as targets for therapeutic intervention and novel therapeutic strategies for anxiety disorders.

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 hyper- polarization 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 anxiety disorders. Third, the absence of systemic side effects indeed to future investigations. Fourth, it is necessarily study, side effects of the CNS. The fifth, fur ther research is needed to establish the optimal dosage. Not withstand ing these limitations, this study suggests that Flupirtine is efficacious and well tolerated in the treatment of anxiety disorders. 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 anxiety disorders, 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.

Conclusion

The results of our study showed high efficiency flupirtine in the treatment of anxiety disorders. The biochemical mechanism of action of flupirtine is similar to that of ritagabiline (chlorzoxazone). Despite the tremendous progress that has been made recently in elucidating the neurobiological basis of anxiety disorders, 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 anxiety disorders.

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

No sponsor provided funding for this study. Mental Health Center of the Ministry of Health of the Republic of Azerbaijan provided the outpatient unit, the material for clinical and neuropsychological assessments, and electronic resources.

Acknowledgments

The authors would like to thank staff of the Mental Health Center of the Ministry of Health of the Republic of Azerbaijan.

References

1. Anxiety Disorders Facts and Statistics. By The Recovery Village. Editor Megan Hull About our Editorial Team. Medically Reviewed By Jenni Jacobsen, LCSW, LMFT. Updated on 11/03/20.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington 2013.
3. Sedoks Kaplan 2015 Sadock BJ, Sadock VA, Ruiz P, eds. Synopsis of psychiatry. Eleventh edition. Lippincott Williams & Wilkins; 2015:1472 pages.
4. Bandelow B., Michaelis S. Epidemiology of anxiety disorders in the 21st century. Dialogues in Clinical Neuroscience, 01 Sep 2015, 17(3):327-335; PMID: 26487813 PMCID: PMC4610617.
5. Aliyev NA, Aliyev ZN (2020) A Mental Disorders Caused by the COVID-19 Pandemic. Ann Psychiatry Ment Health 8(2): 1151.
6. U.S. Food & Drug Administration. FDA Requiring Labeling Changes for Benzodiazepines. Fda.gov. .
7. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50-5 [Medline]
8. Glantz AS (2011) Primer of Biostatistics (7thedn). McGraw Hill Profes- sional, New York, USA. Pg no: 1-320.
9. Kornhuber J, Maler M, Wiltfang J, Bleich S, Degner D, et al. (1999) [Neuronal potassium channel opening with flupirtine]. Fortschr Neurol Psychiatr 67: 466-475.
10. Rupalla K, Cao W, Krieglstein J (1995) Flupirtine protects neurons against excitotoxic or ischemic damage and inhibits the increase in cyto- solic Ca^{2+} concentration. Eur J Pharmacol 294: 469-473.
11. Osborne NN, Cazevieille C, Wood JP, Nash MS, Pergande G, et al. (1998) Flupirtine, a nonopioid centrally acting analgesic, acts as an NMDA antagonist. Gen Pharmacol 30: 255-263.
12. Harish S, Bhuvana K, Bengalorkar GM, Kumar TN (2012) Flupirtine: Clinical pharmacology. J Anaesthesiol Clin Pharmacol 28: 172-177.
13. Schmidt WJ, Schuster G, Wacker E, Pergande G (1997) Antiparkinso- nian and other motor effects of flupirtine alone and in combination with dopaminergic drugs. Eur J Pharmacol 327: 1-9.
14. Schuster G, Schwarz M, Block F, Pergande G, Schmidt WJ (1998) Flupirtine: A review of its neuroprotective and behavioral properties. CNS Drug Rev 4: 149-164.
15. Zimmer G, Balakirev M, Hofmann M, Woodcock BG, Pergande G (1998) Evidence that the cytoprotective action of the triaminopyridine flupirtine involves increases in Ca2+ uptake and ATP synthesis in mito- chondria. Br J Pharmacol 123: 1154-1158.
16. Schwarz M, Nolden-Koch M, Purr J, Pergande G, Block F (1996) An- tiparkinsonian effect of flupirtine in monoamine-depleted rats. J Neural Transm (Vienna) 103: 581-590.
17. Devulder J (2010) Flupirtine in pain management: pharmacological properties and clinical use. CNS Drugs 24: 867-881.
18. Friedel HA, Fitton A (1993) Flupirtine: A review of its pharmacological properties, and therapeutic efficacy in pain states. Drugs 45: 548-569.
19. Mueller-Schwefe G (2003) [Flupirtine in acute and chronic pain associated with muscle tenseness. Results of a postmarket surveillance study]. Fortschr Med Orig 121: 11-18.