REVIEW ARTICLE

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Topiramate and other kainate receptor antagonists for depression: A systematic review of randomized controlled trials

Ahmad Shamabadi[1,2] 🆔

[1]School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[2]Psychiatric Research Center, Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, Tehran, Iran

Correspondence
Ahmad Shamabadi, MD, Psychiatric Research Center, Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, South Kargar Street, Tehran, Iran.
Email: a-shamabadi@alumnus.tums.ac.ir

Abstract

Background: Depression is a common disorder that affects patients' quality of life and incurs health system costs. Due to the resistance to treat depression, better understanding of neurophysiology was considered; one of the implications is the glutamatergic system. This study aims to systematically review clinical trials investigating the antidepressant effects of kainate receptor antagonists.

Methods: The study protocol was registered in PROSPERO (CRD42021213912). Scopus, ISI, Embase, PubMed, Cochrane Library, Google Scholar, and two trial registries were searched for randomized controlled trials on the effectiveness of topiramate, phenobarbital, and other ten barbiturates in depression. The difference with control groups in terms of changing depressive symptoms was the primary outcome.

Results: Nine trials were identified, in which 784 patients were studied. The efficacy of thiopental was comparable to that of imipramine, with fewer side effects. When administered with electroconvulsive therapy, it had fewer to similar effects and fewer side effects than ketamine. Both monotherapy and adjunctive therapy with topiramate were effective and tolerable in treating depressed patients. Phenobarbital had therapeutic effects compared to imipramine and amitriptyline with fewer side effects.

Conclusion: Regarding the glutamatergic hypothesis of depression and obtained promising results, further studies of kainate receptor antagonists in high-quality trials are recommended. Given the high prevalence of depression in epileptic patients, more problems with its treatment, and the fact that the studied agents were anticonvulsants, it is recommended that future studies prioritize depressed-epileptic patients.

KEYWORDS
barbiturates, depression, epilepsy, glutamate receptors, topiramate

1 | INTRODUCTION

Depression is a common mental and psychological disorder that affects approximately 280 million people worldwide.[1,2] Its lifetime prevalence is reported to be from 2 to 21% in different countries.[3]

Depression is one of the main contributors to the global disability-adjusted life years (DALY), which alarmingly is predicted to be the leading cause by 2030.[2] The psychosocial function of patients is limited, and their quality of life decreases due to the disorder.[4] Moreover, patients with depression have a higher risk of suicide.[5] The economic

costs of depression and its complications imposed on the US health system are estimated at more than $200 billion annually.[6]

Pharmacotherapy is one of the treatments for depression commonly used by clinicians.[6] Late onset of efficacy, moderate efficacy, a response rate of only 50% at the first trial for treatment, and the persistence of subsyndrome symptoms after the treatment in some patients are some of the disadvantages of pharmacotherapy with current agents.[7]

Researchers have considered drug repositioning, drug discovery, complementary and traditional medicine, and therapies other than pharmacotherapy to overcome these problems.[7–9] Conducting studies to understand the unknown parts of the pathogenesis of depression and scrutinizing and applying the known features could lead to overcome these resistances to treatment.[10] The glutamatergic system is a known area of depression neurobiology that has received special attention from scientists.[11] Numerous receptors and proteins are involved in the glutamatergic system; so far, the most attention in this system regarding treating the depression was focused on agents interacting with N-methyl-D-aspartate (NMDA) receptor. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors are also glutamate receptors and have roles in the glutamatergic system but have been studied less than the NMDA receptor.[11,12] The kainate receptor is a voltage-dependent and fast-acting ionotropic glutamate receptor.[11] Medicines with an approved antagonist action on this receptor include topiramate, phenobarbital, and ten other barbiturates.[13] This study aims to systematically review clinical trials investigating the effectiveness of kainate receptor antagonists – as a part of the glutamatergic system – in treating depression. The rationale for separating and selecting this part of the glutamatergic system is that these drugs are all known anticonvulsants, so if their efficacy is proven, they could be prescribed for both treatments of depression and maintenance therapy of epilepsy in depressed-epileptic patients – which will be addressed below.

2 | METHODS

2.1 | Search strategy

The study protocol was registered in the International prospective register of systematic reviews (PROSPERO) with the number CRD42021213912. To obtain the information for the systematic review, Scopus, ISI Web of Science Core Collection, Embase, PubMed, Cochrane Library, and Google Scholar (the first 200 citations) databases were searched on September 25, 2020, without limitations on timespan, document type, language, and publication status. The study aimed to evaluate the effectiveness of kainate receptor antagonists in treating depression. Thus, the searched terms were selected based on the keywords, including effectiveness and treatment (#1), kainate receptor antagonists (#2), and depression (#3), as follows. The names of drugs approved with kainate receptor target and the antagonist action on the receptor were compiled by searching DrugBank online database.[13]

#1. effect* OR efficacy OR impact OR therapy OR treat*.

#2. amobarbital OR butabarbital OR butobarbital OR butalbital OR methylphenobarbital OR pentobarbital OR phenobarbital OR primidone OR secobarbital OR talbutal OR thiopental OR topiramate OR "kainate receptor" OR "kainic acid receptor".

#3. depress*.

The last search in all databases was obtained by combining the above searches: #1 AND #2 AND #3.

ClinicalTrials.gov, European Union Clinical Trials Registry, and included articles references were also manually searched to obtain articles with mentioned characteristics.

2.2 | Selection criteria

Regarding the PICOS process, randomized controlled trials (RCTs) with participants diagnosed with depression, by a group receiving a kainate receptor antagonist as the intervention and a control group with placebo or known antidepressant, and examining the symptoms of depressive disorder as the outcome were included in this systematic review. It was not necessary to diagnose depression using the Diagnostic and Statistical Manual of Mental Disorders (DSM) and evaluate it using validated scoring systems such as the Hamilton Depression Rating Scale (HDRS). Intervention and control groups could be added to the same conventional treatment, such as electroconvulsive therapy (ECT). Therefore, the effectiveness of the drug prescribed in the intervention group should be discussable alone, not in combination – after eliminating similar treatments in groups. The setting was not a limitation for inclusion.

Book chapters, case reports, editorials, reviews, and nonrandomized studies of intervention (NRSIs) were excluded. In-vitro and animal studies were excluded. Studies on patients with bipolar disorder were not of interest. No age, gender, or ethnicity restrictions were considered for patients. There was no language limitation for included studies.

The authors of included studies were contacted for additional data whenever necessary.

2.3 | Data extraction

EndNote X9 and Microsoft Excel 2016 spreadsheets were used to remove duplicate results and record the extracted data, respectively.

Setting to conduct each trial, the study design, the number of patients who participated, type of depression diagnosed, criteria for diagnosing, treatment groups, the dose of prescribed drugs, the duration of treatment, how to measure outcomes, the significance of effectiveness alone compared to the control group, and side effects were assessed in each study. An agent with a statistically significant difference with placebo and/or no statistically significant difference with a known antidepressant in changing depressive symptoms was considered effective as the primary outcome. Side effects were the secondary outcome.

The methodological qualities of included RCTs were evaluated using the Cochrane Risk of Bias II Tool and the modified Jadad scale. The bias risk of each RCT was assessed by the Cochrane Risk of Bias Tool II through random sequence generation, allocation concealment, selective reporting, other sources of bias, blinding (participants and personnel), detection bias blinding (outcome assessment), and incomplete outcome data domains.[14] The modified Jadad scale has the highest validity and reliability in assessing the methodological quality of clinical trials.[15] Describing randomized design (Yes: +1, No: 0), randomization method appropriateness (Yes: +1, No: −1, Not described: 0), blindness (Double: +1, Single: +0.5, No: 0), blinding method appropriateness (Yes: +1, No: −1, Not described: 0), mentioning withdrawals and dropouts (Yes: +1, No: 0), description of inclusion and exclusion criteria (Yes: +1, No: 0), side effects assessment (Yes: +1, No: 0), and description of statistical analyses made (Yes: +1, No: 0) are the items of this scoring system. Total scores of 4 and 5 signify moderate quality, and scores lower and higher indicate low-quality and high-quality trials, respectively.[16,17]

3 | RESULTS

3.1 | Search results

Figure 1 shows the process of selecting studies from searched results according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline. A total of 40 related results were found. Among these studies, 12 were noninterventional studies, nine of which examined the prevalence or incidence of depression in epileptic patients. One study was excluded because it was retrospective. Another study evaluated the effectiveness of an herbal agent, for which the mechanism of interest in this study was not mentioned. Another study was excluded because it included patients with bipolar depression. Then, seven trials were excluded because they did not evaluate the antidepressant effect of the drugs. Control groups were not placebo or known antidepressants in the other five trials. Moreover, the other three trials did not measure the effects of drugs alone, which were excluded – they prescribed them in a combination. One NRSI was also excluded. At last, nine RCTs were included in this systematic review. The characteristics of these trials are listed in Table 1.

3.2 | Quality of included studies

The risk of bias and quality score of each trial is judged by the Cochrane Risk of Bias II Tool and the modified Jadad scale, given in Table 1. One study conducted by Kuşçu et al had borderline scores of 5.5, which is marked as high quality in Table 1 due to the specified range.[18] Double-blind was written in the title of one of the trials, and single-blind was written in its methods section, and since no explanation was given about it, the single blind score was considered.[19]

3.3 | Thiopental

Five controlled trials evaluated the effectiveness of thiopental on depressive disorders, with 359 patients participating in these studies. The studies were performed on hospitalized patients, and thiopental was intravenously administered in all five. Only one study in 1963 clinically diagnosed depression[20] and other studies used DSM, Fourth Edition (DSM-IV).[18,19,21,22]

In the nonblinded study conducted by Fahy et al in 1963, patients were trichotomized due to outcome: recovery, improvement, and no change/worse. Out of 17 patients receiving anesthetic doses of thiopental and 16 patients receiving 100 mg of imipramine daily, a total of eight and ten recovered and improved patients were reported, respectively, with no significant difference. It appears that all patients in this study thought they received active treatment, while 17 underwent only thiopental anesthesia and 17 underwent electroconvulsive therapy (ECT).[20]

In four other studies, all patients underwent ECT. In Yoosefi et al trial, both ketamine and thiopental significantly reduced HDRS compared to baselines, and by comparing two groups, ECT and ketamine significantly decreased HDRS more, just before the second ECT session.[22] In the study by Salehi et al, both agents significantly reduced HDRS, a significant difference was observed between the two groups only in the eighth session, and recovery time from anesthesia was faster in the ketamine group. Headache, nausea, and fear of the illusion of awakenings were significantly higher in ketamine-receiving patients.[19] In the study by Kuşçu et al,[18] there was no difference among three groups of thiopental, ketamine, and the combination of the two due to HDRS reduction. However, the anxiety scores of patients increased in the ketamine group. Jagtiani et al designed a trial with a Jadad score of 8 to examine which groups of thiopental and ketamine have a more rapid recovery, and they followed these patients for six weeks after their last ECT sessions. HDRS and Beck Depression Inventory (BDI) were more decreased in the ketamine group at weeks one and two. HDRS was lower in the ketamine group at the last session, BDI was similar between the groups, and HDRS and BDI were similar in follow-ups. Emergence reactions, secretions, nausea/vomiting, delirium, blood pressure rising, and heart rate rising were more prevalent in the ketamine group, and headache rate was higher in the thiopental group, for which no p-value was reported.[21] In two studies, the seizure duration was significantly longer in ketamine groups.[21,22]

3.4 | Topiramate

Two controlled trials with 117 patients evaluated topiramate effectiveness. In a placebo-controlled trial in which all patients were female, Nickel et al reported topiramate monotherapy effects on the recurrent major depression diagnosed based on DSM-IV. The effect of topiramate on HDRS was initially gradual, with HDRS decreasing more rapidly at approximately six to seven weeks of treatment. Topiramate was associated with significant weight loss
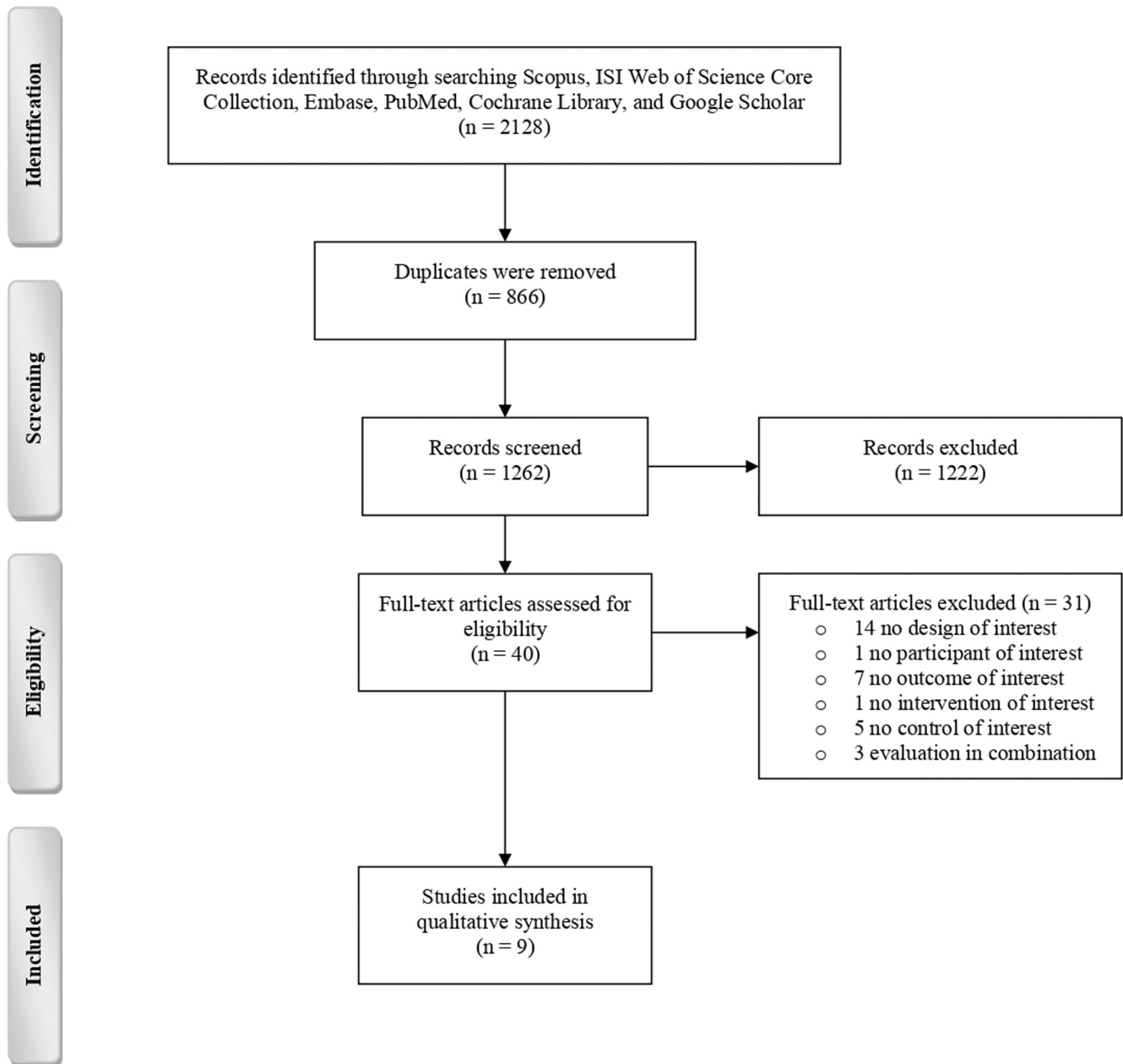
FIGURE 1 Processing the selection of trials

and had no severe side effects.[23] In a trial with a Jadad score of 8, Mowla and Kardeh reported the effectiveness of eight-week treatment with adjunctive topiramate on reducing HDRS in patients with resistant major depressive disorder diagnosed based on DSM-IV. In this study, depressed mood, suicidality, insomnia, agitation, and anxiety symptoms were significantly lower in topiramate recipients.[24]

3.5 | Phenobarbital

The effect of phenobarbital on depression was investigated in two controlled trials with 308 patients. Wheatley, by comparing one to two phenobarbital 20 mg t.i.d. and one to two imipramine 25 mg t.i.d.,

reported that phenobarbital was more effective than imipramine at the end of the second week in reducing the symptoms of neurotic depression. Except for the second week, in other evaluations, they did not differ in reducing depression. Furthermore, due to adverse events, phenobarbital was better in the first two weeks and had fewer side effects. Drowsiness was the only complication that was significantly more in the phenobarbital group – at week eight – than in the imipramine group. Dry mouth – at week two – and feelings of tenseness and irritability – at weeks two and four – were more in the imipramine group.[25] In a double-blind and randomized trial by Rickels et al, phenobarbital 120 mg daily, diazepam 20 mg daily, and amitriptyline 100 mg daily were not different in improving depression. In this study, phenobarbital was more effective in patients with low education levels and high family stress. Sedation-related side

TABLE 1 Characteristics of the included studies

Author, year	Modified Jadad scale	Cochrane bias risk II	Patients	Setting[a]	Diagnosis	Intervention group	Dose	Weeks or sessions	Control group(s)	Outcome measure	Difference (p-value<0.05)
Fahy et al, 1963	Moderate	High risk	50	In	Psychotic depression	Thiopental	Anesthetic dose	3 w	Imipramine ECT	Trichotomized	No
Wheatley, 1969	Moderate	High risk	170	Out	Neurotic depression	Phenobarbital	20 mg, 1 to 2 t.i.d.	8 w	Imipramine	A five-item rating scale	Yes (early)
Rickels et al, 1973	High	Some concerns	138	Out	Nonpsychotic depression	Phenobarbital	120 mg, daily	4–6 w	Amitriptyline Diazepam	HDRS	No
Nickel et al, 2005	High	Some concerns	64	Out	Recurrent major depression	Topiramate	50–200 mg, daily	10 w	Placebo	HDRS	Yes
Mowla and Kardeh, 2011	High	Low risk	53	Out	Resistant major depression	Topiramate	100–200 mg, daily	8 w	Placebo	HDRS	Yes
Yoosefi et al, 2014	High	Some concerns	31	In	Major depression	Thiopental	2–3 mg/kg	6 s	Ketamine	HDRS	Yes (only before 2nd s, ketamine was more effective)
Salehi et al, 2015	Moderate	High risk	160	In	Resistant major depression	Thiopental	1–1.5 mg/kg	8 s	Ketamine	HDRS	Yes (ketamine was more effective)
Kuşçu et al, 2015	High	High risk	58	In	Resistant major depression	Thiopental	4 mg/kg	8 s	Ketamine Thiopental+ ketamine	HDRS	No
Jagtiani et al, 2019	High	Low risk	60	In	Major depression	Thiopental	2.5 mg/kg	8.33 vs. 5.57 s	Ketamine	HDRS BDI	Yes (ketamine was more rapid)

Note: t.i.d. three times a day. w weeks. s sessions. HDRS Hamilton Depression Rating Scale. BDI Beck Depression Inventory.

[a] Inpatient or Outpatient.

effects such as drowsiness and dizziness were more common in diazepam recipients, and autonomic nervous system side effects such as dry mouth, syncope, tachycardia, nasal congestion, and blurred vision were more common in amitriptyline recipients.[26] In both studies, phenobarbital was not found to be more effective in anxious-depressed patients – there was no difference between depression and anxiety-associated depression.[25,26]

4 | DISCUSSION

Regarding the glutamatergic hypothesis for treating depression, this study systematically reviewed trials investigating the effectiveness of kainate receptor antagonists in the treatment of depression. In total, nine trials of thiopental, topiramate, and phenobarbital, including 784 patients, were found through the search. Despite obtaining promising effectiveness and tolerability, it is still early to conclude the clinical presentation.

4.1 | Glutamatergic system in depression

Alongside the monoaminergic system, which was the focus of studies on depression for years, the role of the glutamatergic system in depression has recently been highlighted.[27] The main reasons for turning to novel agents acting on the glutamatergic system have been the resistance to typical therapies and the reported effectiveness of novel agents for resistant depression.[11] Ketamine, a noncompetitive NMDA receptor antagonist, has been the representative of glutamate receptor modulator agents, which was the subject of numerous studies to evaluate its effectiveness in depression.[12,13] A review investigating the effectiveness of ketamine has shown that it has a rapid antidepressant effect – up to 1 week.[12,28] However, studies on ketamine for depression have had significant limitations, and further studies are needed to determine suicidality, cognition, quality of life, and long-term effects. Moreover, studies on agents other than ketamine are limited.[12,29]

4.2 | Limitations of included studies

Five RCTs were cited regarding the effectiveness of thiopental in treating depression. Fahy et al conducted the first one in 1963 and examined a relatively small number of patients. Only 17 patients receiving thiopental were compared with 16 patients who received imipramine.[20] Another limitation of the RCTs investigating the effectiveness of thiopental for depression is that thiopental was always used in combination with ECT.[18-22] In this regard, it seems difficult to gauge the actual effects of thiopental as ECT is itself an effective method of treating depression.

The studies of intervention of topiramate suggest an improvement of depressive symptoms with topiramate mono- or combination therapy.[23,24,30] Actually, the conducted studies are too small

to confirm an antidepressant effect. It is known that topiramate itself can cause depression as a side effect. The fact is that the agent is not approved for depression or bipolar depression, and to prescribe it would be "off label".[13] Although there are studies in favor of its efficacy. In another study by McIntyre et al, 36 patients meeting DSM-IV criteria for bipolar I/II depression received topiramate – 50 mg daily, increasing every 2 weeks – or bupropion SR. Both groups, without differences, had significant decreases in HDRS compared to the baseline values. The only significant different adverse event observed between the groups was sleep difficulty, which was higher in the bupropion SR group.[30] Epileptologists use the drug only to tailor the treatment, which means using it in obese patients or epileptic patients with migraine but not in epilepsy and depression.[13,31,32] In epilepsy patients with depression as comorbidity, epileptologists tailor the treatment with lamotrigine or pregabalin since both have a positive psychotropic effect.[33]

Only two studies of phenobarbital were found.[25,26] The first was conducted in 1967 and carried out in general practice. In addition, its design was not double-blind and placebo-controlled.[25]

4.3 | Clinical implications of agents

Kainate receptor antagonists include topiramate and eleven barbiturates, which are used for managing different types of seizures.[13] The development of barbiturates, which are sedative-hypnotic agents, was a significant step in managing epilepsy. In particular, phenobarbital is a class of barbiturates, due to its efficacy and cost-effectiveness, was used to manage status epilepticus and all types of seizure disorders.[34] Thiopental is a rapid-onset short-acting barbiturate indicated in the treatment of refractory generalized convulsive status epilepticus and the control of convulsive states during or after inhalation or local anesthesia.[13,35] Besides, topiramate is indicated in treating Partial-Onset or Primary Generalized Tonic–Clonic Seizures and Lennox–Gastaut syndrome and is suggested to manage some other types like juvenile myoclonic epilepsy.[36]

As mentioned earlier, these agents are administrated with specific indications for managing and treating epilepsy. However, both the disease itself, which is chronic, and possibly the prescribed drugs may cause depression in patients.[37,38] Pharmacotherapy of depression becomes even more difficult in patients with epilepsy for several reasons. First, depression is a side effect of several medications prescribed to patients with epilepsy.[37] Second, antidepressants may also cause seizure aggravation in epileptic patients.[39] Third, there is no credible evidence of the effectiveness of antidepressants in epileptic patients with depressive symptoms.[40] Fourth, typical antidepressants do not appear to be effective in children, while a significant percentage of patients with epilepsy are children.[41,42] Fifth, antidepressants and anticonvulsants have significant pharmacokinetic interactions.[43] In an open, multicentered, and uncontrolled trial, Specchio et al investigated the effect of citalopram at a daily dose of 20 mg in treating

depression in patients with epilepsy who were also on antiepileptic drugs. They concluded that four months of citalopram treatment improved depressive symptoms and reduced the frequency of seizures,[44] but there are many cases of adverse effects and resistance to treatment.[37,44]

4.4 | The epilepsy depression connection

Depression can occur subsequent to chronic and debilitating illnesses as comorbidity or a natural reaction to living with the illness in patients.[39,45] Epilepsy is a chronic neurological disorder, with an estimated 50 million people affected worldwide, and it is the most significant contributor to global DALY among neurological diseases.[39] Depression is reported in up to 62% of people with epilepsy.[37] Due to occurring depression before the onset of seizures as usual and also the lower rate of seizure recovery after epilepsy surgery in depressed patients, hypotheses were formed about the biological relationship between the two.[46]

As mentioned, the studied agents are used in epilepsy, secondary to which depression is common and burdensome. Given the high prevalence of depression in epileptic patients and more problems with its treatment, it is recommended that future studies on these agents prioritize depressed-epileptic patients as their depression sample.

4.5 | Conflicting results in other studies

In this study, nine RCTs with the results were generally favoring the antidepressant effects of thiopental, topiramate, and phenobarbital were documented. However, conflicting results were reported in some studies and some of the agents were themselves considered to promote depression. In a study by Vajda et al on 2039 pregnant women with epilepsy, who were followed during pregnancy to one year after its end, carbamazepine recipients were found to have lower rates of patient-recognized depression than those receiving topiramate.[47] Furthermore, the depressogenic effect of phenobarbital compared to carbamazepine was reported in children receiving it. In this cohort study, which was performed on 15 patients treated with phenobarbital and 24 patients treated with carbamazepine, the observed difference was only in patients with a history of a major affective disorder among first-degree relatives.[48] Another drug in this category is primidone, which has been linked to depression in epileptic patients. In a six-month cross-sectional study of 241 epileptic patients in an outpatient setting, primidone use was associated with depression.[49] In contrast, Zhang et al, in a nonrandomized study, whose primary purpose was to investigate the effect of topiramate on smoking cessation, examined the effects of adjunctive topiramate on 99 depressed smokers under antidepressant therapy and cognitive-behavioral intervention. The daily dose of topiramate in the first four weeks was 200 mg daily, which was gradually

discontinued in the next four weeks.[50] Although the studies with results in favor of antidepressant effects are more and of higher quality, the studies with results of depressogenic effects cannot be ignored; hence, they should be considered in future studies. To date, regarding systematic search, no RCTs of kainate receptor antagonists in patients diagnosed with simultaneous epilepsy and depression were published. However, since these agents are indicated in the treatment of epilepsy – not all types – and there are the glutamatergic hypothesis and several interventional studies in favor of their antidepressant effects, they seem logical for examination in trials. It is recommended to conduct a controlled trial of a kainate receptor antagonist adjunct to citalopram on a sufficient number of depressed-epileptic patients – not a large-scale one.

5 | CONCLUSION

The study reviewed nine clinical trials, all of which found results favoring the effectiveness of a kainate receptor antagonist in treating depression. Thiopental alone was not different from imipramine regarding the effectiveness and had fewer side effects. When used with ECT, it had fewer to similar effects and fewer side effects than ketamine with ECT. In both monotherapy and adjunctive therapy, topiramate had significant antidepressant effects, which may be more rapid after about six weeks of treatment. Phenobarbital was also effective in treating depression in two studies controlled with imipramine and amitriptyline, and its side effects were less than those of imipramine and amitriptyline.

One of the limitations that should be mentioned is the number of obtained trials evaluating each agent. Second, not all trials have diagnosed depression following DSM. Third, the study results cannot evaluate the effectiveness in the clinic and can only address the statistical differences between the drug and the control group – this is also the case with typical antidepressants.[51] Fourth, none of the studies compared the effectiveness of a kainate receptor antagonists with selective serotonin reuptake inhibitors (SSRIs), which are now considered the first choice for depression and the medication of choice for the treatment of comorbid depression in epileptic patients since they do not lower the seizure threshold in sufficient doses. Although the obtained results are crude and insufficient for the recommendation of therapeutic use, due to the resistance to treatment in about one-third of depressed patients and more problems of treating depression in depressed-epileptic patients, further high-quality trials are recommended to evaluate the effects of kainate receptor antagonists in the treatment of depressed patients – with or without underlying diseases.

CONFLICT OF INTEREST

The author has no conflict of interest.

DATA AVAILABILITY STATEMENT

Data availability does not apply to this article as no new data were created or analyzed in this study.

ANIMAL STUDIES

Not applicable.

ETHICAL STATEMENT

Not applicable.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

Not applicable.

INFORMED CONSENT

Not applicable.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY

The study protocol was registered in PROSPERO (CRD42021213912).

ORCID

Ahmad Shamabadi 🔟 https://orcid.org/0000-0002-5211-2827

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