CLAIMS

1. A pharmaceutical composition comprising a metal channel activator and an NMDA receptor antagonist.

2. The pharmaceutical composition of Claim 1, wherein the metal channel activator is a potassium channel activator.

3. The pharmaceutical composition of Claim 2, wherein the potassium channel activator is a Kv7 channel activator.

4. The pharmaceutical composition of Claim 3, wherein the Kv7 channel activator is a Kv7.1 channel activator, a Kv7.2 channel activator, a Kv7.3 channel activator, a Kv7.4 channel activator, a Kv7.5 channel activator, or any combination thereof.

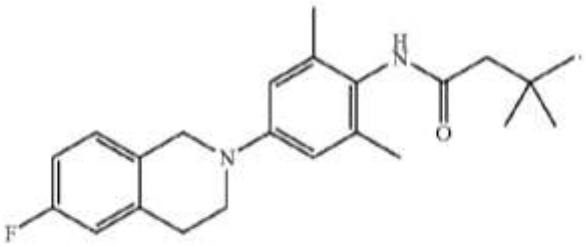
5. The pharmaceutical composition of Claim 3 or 4, wherein the Kv7 channel activator is a Kv7.2/7.3 channel activator.

6. The pharmaceutical composition of any one of claims 1 to 5, wherein the metal channel activator is selected from one or more compounds according to any one or more of formulas 1 to 171.

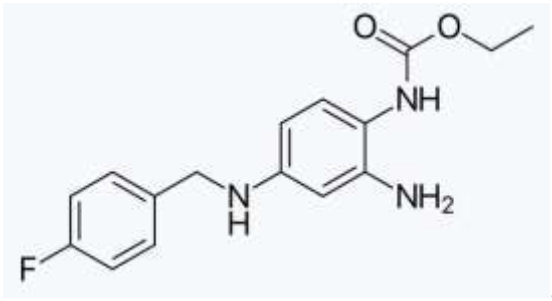
7. The pharmaceutical composition of any one of claims 1 to 6, wherein the NMDA receptor antagonist is selected from one or more compounds according to any one or more of formulas 200 to 260.

8. The pharmaceutical composition of any one of claims 1 to 5, wherein the NMDA receptor antagonist is selected from one or more compounds according to any one or more of formulas 200 to 260, and wherein the metal channel activator is selected from one or more of the disclosed compounds according to any one or more of formulas 1 to 171.

9. The pharmaceutical composition of any one of claims 1 to 8, wherein the metal channel activator is



10. The pharmaceutical composition of any one of claims 1 to 8, wherein the metal channel activator is



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11. The pharmaceutical composition of any one of claims 1 to 10, wherein the NMDA receptor antagonist is ketamine, lanicemine, dextromethorphan (DXM), phencyclidine (PCP), methoxetamine (MXE), or a pharmaceutically acceptable salt thereof.

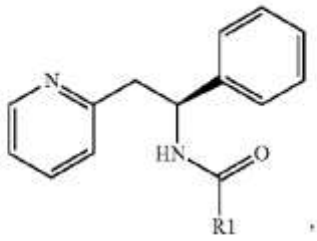
12. The pharmaceutical composition of any one of claims 1 to 11, wherein the NMDA receptor antagonist or a pharmaceutically acceptable salt thereof is in a form of a prodrug.

13. The pharmaceutical composition of any one of claims 1 to 12, wherein the NMDA receptor antagonist is lanicemine or a pharmaceutically acceptable salt thereof.

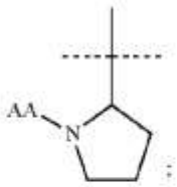
14. The pharmaceutical composition of Claim 13, wherein the lanicemine or a pharmaceutically acceptable salt thereof is in a form of a prodrug.

15. The pharmaceutical composition of Claim 14, wherein the prodrug of lanicemine has the following structure:

(I)

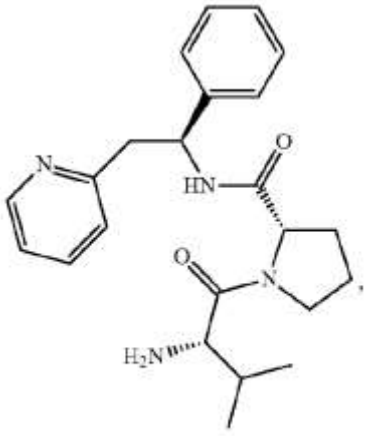


wherein R1 is C_{1-6} alkylC(O)O(C_{1-6}alkoxy), or



AA is a peptide bond-linked natural amino acid;
or a pharmaceutically acceptable salt thereof.

16. The pharmaceutical composition of Claim 14 or 15, wherein the prodrug of lanicemine has the following structure:



or a pharmaceutically acceptable salt thereof.

17. Use of the pharmaceutical composition of any one of Claims 1-16 in the manufacture of a medicament for treating a depressive disorder.

18. The use of Claim 16, wherein the depressive disorder is major depressive disorder (MDD), disruptive mood dysregulation disorder, persistent depressive disorder, bipolar spectrum disorder, postpartum depression, premenstrual dysphoric disorder (PMDD), seasonal affective disorder (SAD), atypical depression, treatment-resistant depression (TRD), depression associated with agitation or anxiety, adjustment disorder with depressed mood, prolonged depressive reaction, or a combination thereof.

19. Use of the pharmaceutical composition of any one of Claims 1-16 in the manufacture of a medicament for treating a neurological or neurodegenerative disorder.

20. The use of Claim 19, wherein neurological or neurodegenerative disorder is amyotrophic lateral sclerosis, bipolar disorder, treatment resistant and major depression, general anxiety disorder, panic disorder, social anxiety, mood disorders, cognitive disorders, dementia, agitation, apathy, psychoses, post-traumatic stress disorders, irritability, disinhibition, learning disorders, memory loss, personality disorders, bipolar disorders, Rett syndrome, eating disorders, conduct disorder, neurodegenerative disorders, pain disorders, supranuclear palsy, frontotemporal dementia, frontotemporal lobar degeneration, delirium, Alzheimer's disease, mild cognitive impairment, mild cognitive impairment due to Alzheimer’s disease, drug addiction, tinnitus, mental retardation, obsessive-compulsive disorder, spinal muscular atrophy, radiation therapy, multiple sclerosis, chronic cerebellar ataxia, cervical spondylotic myelopathy, spinal cord injury, hereditary cerebellar ataxia, Tourette syndrome, autism spectrum disorder, schizophrenia, fragile X syndrome, Parkinson's Disease, Huntington’s disease, or any combination thereof.

21. Use of the pharmaceutical composition of any one of Claims 1-16 in the manufacture of a medicament for treating a pain disorder.

22. The use of Claim 21, wherein the pain disorder is acute pain, chronic pain, neuropathic pain, nociceptive pain, and/or radicular pain.

23. The use of Claim 21, wherein the pain disorder is migraine, inflammatory pain, persistent pain, cancer pain, and/or postoperative pain.

24. A kit for treating a patient afflicted with a disorders in which a metal channel activator is clinically relevant, said kit including:

(a) the metal channel activator; and

(b) instructions for administering said metal channel activator in combination with an NMDA receptor antagonist by one of the use of Claims 17-23.

25. A kit for treating a patient afflicted with a disorder in which an NMDA receptor antagonist is clinically relevant, said kit including:

(a) the NMDA receptor antagonist; and

(b) instructions for administering said NMDA receptor antagonist with a metal channel activator by one of the use of Claims 17-23.