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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR § 1.53(c)

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TITLE OF THE INVENTION

METHOD AND COMPOSITION FOR ADMINISTERING AN NMDA RECEPTOR ANTAGONIST TO A SUBJECT

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ENCLOSED APPLICATION PARTS

☒ **Specification** — Number of Pages: 20
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☐ **Other documents** (specify):

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government:
☒ No.
☐ Yes, the name of the U.S. Government agency and the Government contract number are:

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Respectfully submitted,

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METHOD AND COMPOSITION FOR ADMINISTERING AN NMDA RECEPTOR ANTAGONIST TO A SUBJECT

FIELD OF THE INVENTION

The invention relates to compositions containing N-methyl-D- Aspartate (NMDA) receptor antagonists and methods for using such compositions.

BACKGROUND OF THE INVENTION

Acute and chronic neurological and neuropsychiatric diseases are among the leading causes of death, disability, and economic expense in the world. One of the key challenges in treating these disorders is the high degree of interplay amongst the pathways that control both normal and abnormal neuronal function.

Excitatory amino acid receptors, including the N-Methyl-D-Aspartate (NMDA) receptor, are important mediators of excitatory synaptic transmissions (i.e., stimulation of neurons) in the brain, participating in wide-ranging aspects of both normal and abnormal central nervous system (CNS) function. The NMDA receptor and its associated calcium (Ca2+) permeable ion channel are activated by glutamate, a common excitatory neurotransmitter in the brain and the spinal cord, and the co-agonist glycine. NMDA receptor activity and consequent Ca2+ influx are necessary for long-term potentiation (a correlate of learning and memory).

Aberrant glutamate receptor activity has been implicated in a large number of neurodegenerative conditions including, for example, Alzheimer's disease, depression, neuropathic pain, multiple sclerosis, epilepsy, ALS (amyotrophic lateral sclerosis or Lou Gehrig's disease), and Huntington's disease. In this regard, the abnormal activation of the NMDA receptor resulting from elevated levels of glutamate, for example, may lead to sustained activity of the receptor's ion channel (often lasting for minutes rather than milliseconds), thereby allowing Ca2+ to build-up. The excessive influx of Ca2+ eventually leads to the generation of damaging free radicals, extended release of excitatory amino acids, and inappropriate stimulation of adjacent neurons. Thus, strategies that reduce glutamate-mediated excitotoxicity are needed, particularly those that inhibit the consequences of over-stimulation while preserving normal glutamate activity.

Certain NMDA receptor antagonists, such as memantine, readily cross the blood-brain barrier, achieving nearly identical concentrations in the extra cellular fluid surrounding brain tissue and systemic serum. Ideally, the NMDA receptor antagonist should be present at a concentration sufficient to reduce the symptoms of the disease in the absence of debilitating side effects. In the present dosage forms however, these drugs, which have a relatively long half-life, need to be administered frequently and require an initial dose escalation to avoid side effects associated with initial exposure. This leads to difficulty in achieving adequate patient compliance, which is further exacerbated by the complicated dosing schedules of therapeutic modalities used for neurological or neuropyschiatric disorders.

Thus, better methods are needed to treat and prevent neurological disorders.

SUMMARY OF THE INVENTION

In general, the present invention provides pharmaceutical compositions that are administered so as to deliver to a subject in a single administration, an amount of an NMDA receptor antagonist (e.g., an aminoadamantine derivative such as memantine) that is high enough to treat symptoms of an underlying disease but is low enough to avoid undesirable side effects. Also provided are methods for using such compositions.

According to this invention, at least 95%, 97%, 98%, 99% or even 100% of the NMDA receptor antagonist is provided in an extended release dosage form and upon the administration of this composition to a subject (e.g., a mammal such as a human), the NMDA receptor antagonist has a C_{max}/C_{mean} of approximately 2.5, 2, 1.5, or 1.0, approximately 1, 1.5, 2 hours to at least 6, 9, 12, 18, 21, 24 hours following such administration. When referring to an agent, the term "C" designates the blood or serum levels of such agent at any point in time. Thus, the "Cmean" of an agent refers to the mean concentration of such agent in the blood or plasma as measured by any standard method known in the art over a set period of time. The "Cmax" of an agent refers to the maximum concentration that such an agent can reach at any point in time. If desired, the release of the NMDA receptor antagonist may be monophasic or multiphasic (e.g., biphasic). Desirably, 99%, 98%, 95%, 90%, 85%, 80%, 70%, 50%, or 30% of the NMDA receptor antagonist remains in an extended release dosage form within one hour of such administration. The pharmaceutical composition may be formulated for oral, topical

transepithelial, subdermal, or inhalation delivery. Optionally, the pharmaceutical composition may be formulated as a lotion, patch, or device (e.g., a subdermally implantable delivery device or an inhalation pump).

Upon contact with a cell, the pharmaceutical compositions described herein reduce the activity of an NMDA receptor. Accordingly, such compositions may be employed to treat, prevent, or reduce conditions associated with deregulation in NMDA receptor activity or conditions that would benefit from a reduction in such activity. Exemplary conditions include Parkinson's disease, multiple sclerosis, neuropathic pain, depression, Alzheimer's disease, amyotrophic lateral sclerosis, and neuropathic pain. Accordingly, a subject (e.g., human) having or at risk of having such conditions is administered the composition described herein (e.g., once a day, every 2 days, every 3 days, every week, or every month).

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present Specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. All parts and percentages are by weight unless otherwise specified.

Other features and advantages of the invention will be apparent from the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

In general, the present invention features pharmaceutical compositions that contain an NMDA receptor antagonist formulated for extended release to provide a concentration over a desired time period that is high enough to be therapeutically effective but low enough so as to avoid adverse events associated with excessive levels of the NMDA receptor antagonist in the subject. Control of drug release is particularly desirable for reducing and delaying the peak plasma level without affecting the extent of drug availability. Therapeutic levels are therefore

achieved while minimizing debilitating side-effects that are usually associated with immediate release formulations. Furthermore, as a result of the delay in the time to obtain peak plasma level and the extended period of time at the therapeutically effective plasma level, the dosage frequency is reduced to, for example, once or twice daily dosage, thereby improving patient compliance.

Making NMDA Receptor Antagonist Controlled Release Formulations

A pharmaceutical composition according to the invention is prepared by combining a desired NMDA receptor antagonist or antagonists with one or more additional ingredients that, when administered to a subject, causes the NMDA receptor antagonist to be released at a targeted concentration range for a specified period of time. A release profile, i.e., the extent of release of the NMDA receptor antagonist over a desired time, can be conveniently determined for a given time by calculating the C_{max}/C_{mean} for a desired time range. For example, the NMDA receptor antagonist can be provided so that it is released at C_{max}/C_{mean} of approximately 2 or less for approximately 2 hours to at least 6 hours after the NMDA receptor antagonist is introduced into a subject. One of ordinary skill in the art can prepare combinations with a desired release profile using the NMDA receptor antagonists and formulation methods described below.

Selecting an NMDA Receptor Antagonist

In general, any non-toxic NMDA receptor antagonist can be used so long as it is non-toxic when used in the composition. The term "nontoxic" is used in a relative sense and is intended to designate any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to humans or, in keeping with established regulatory criteria and practice, is susceptible to approval by the FDA for administration to humans.

Many suitable NMDA receptor antagonists are known in the art. Desirably, the NMDA receptor antagonist is an aminodamantane. Suitable aminoadamantane compounds are known in the art and include, e.g., memantine (1-amino-3,5-dimethyladamantane), rimantadine (1-(1 -aminoethyl)adamantane), amantadine (1-amino-adamantane), as well as pharmaceutically acceptable salts thereof. Additional aminoadamantane compounds are described in, e.g., U.S.

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