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Dextromethorphan: A Review of *N*-methyl-D-aspartate Receptor Antagonist in the Management of Pain

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ABSTRACT

Dextromethorphan (DM) is a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, which is widely used as an antitussive agent. DM also prevents neuronal damage and modulates pain sensation via noncompetitive antagonism of excitatory amino acids (EAAs). DM has been found to be useful in the treatment of pain in cancer patients and in the treatment of methotrexate-induced neurotoxicity. Clinical studies with DM in cancer patients are reviewed in this article.

INTRODUCTION

Dextromethorphan (DM) is a common ingredient of more than 125 cough and cold remedies. Patented by Hoffmann-La Roche in 1954 as an antitussive agent, DM has strong safety and efficacy profiles with no sedative or addictive properties at the recommended doses (Bem and Peck 1992).

It has now been recognized that DM could also be used as an analgesic in the treatment of pain associated with cancer. Some studies have shown that DM modulates neuropathic pain and may protect from neurotoxic effects of chemotherapy in cancer patients. In addition, cancer patients with pathologic cough can benefit from the antitussive effects of DM. The antitussive effects of DM have been known for many years, while its analgesic activity at

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higher than antitussive doses has not been widely recognized. If DM is administered at higher doses (35 to 45 mg) than typically prescribed for the treatment of cough it may be useful in the management of pain in cancer patients (Price et al. 1996). The mechanism associated with DM-induced analgesia appears to be related to its potent *N*-methyl-D-aspartate (NMDA) receptor blocking effect. This review highlights the pharmacology of DM and its potential role in the treatment of pain associated with cancer.

CHEMISTRY

DM is a methyl ether of dextrorotatory (D) isomer of levorphanol, a codeine analog. Its chemical name is 3-methoxy-17-methyl-9α, 13α, 14α-morphinan. DM is used clinically in the form of salt, dextromethorphan hydrobromide. The molecular weight of the hydrobromide salt is 370.3 and an empirical formula of $C_{18}H_{25}$ $NOHBrH_2O$ (Fig. 1). Physically, it is a white crystal or crystalline powder, sparingly soluble in water and freely soluble in alcohol.

PHARMACOLOGY

DM is widely used as an antitussive; it increases the cough threshold by acting at the level of the medulla oblongata (Mansky and Jasinski 1970). At currently recommended adult doses of 10 to 30 mg orally three to six times daily, DM is a highly effective and safe antitussive agent (Bem and Peck 1992). Unlike the L-isomer of levorphanol, DM has no affinity for opioid receptors. DM has no classical addictive properties, but at doses substantially higher than recommended, DM has central nervous system (CNS) depressant properties and may have some abuse potential.

Effects at *N*-methyl-D-aspartate (NMDA) Receptors

Neuroprotective activity

The excess production of excitatory amino acids (EAAs) in the CNS results in neuronal damage and cell death: a process called excitotoxicity. Glutamate, the primary EAA, is

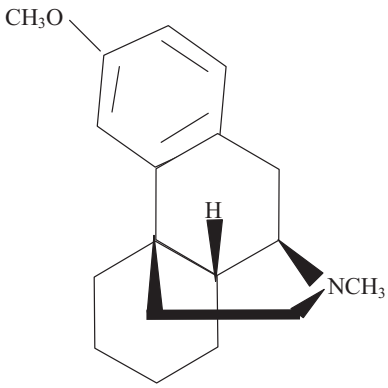

FIG. 1. Chemical structure of dextromethorphan.

located in the CNS and is primarily stored in the presynaptic vesicles. Upon membrane depolarization, glutamate targets either the metabotropic or ionotropic postsynaptic receptors.

Most metabotropic glutamate receptors are G protein–coupled receptors, activating intermediate G proteins to initiate the second messenger systems within the neuron. Ionotropic glutamate receptors are ligand-gated channels that regulate ion conductance of calcium and sodium. Ionotropic receptors are further subdivided into three classes based on the affinity of ligands: NMDA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and kainate. Excessive EAA levels lead to an increased influx of calcium into the neuron, resulting in the production of free radicals, cell damage, and ultimately cell death. Other glutamate analogs such as homocysteine and its metabolites also act to activate NMDA receptors, leading to neuronal cell damage and apoptosis.

The central site of pharmacological action of DM is not yet fully understood. In the early 1980s, *in vitro* studies suggested that DM binds to specific high- and low-affinity DM binding sites in the CNS, enabling a chemical antagonism of the EAA-induced cell death pathway (Craviso and Musacchio 1983a; Craviso and Musacchio 1983b). The studies showed that DM and its major metabolite, dextrorphan, act as low-affinity noncompetitive NMDA receptor antagonists, suppressing glutamate-induced excitotoxicity in the CNS and spinal regions. These experiments suggested a neuroprotective role of DM. This mechanism of action is especially important in the treatment of conditions, such as amyotrophic lateral sclerosis (ALS) or methotrexate neurotoxicity (Drachtman et al. 2002; Hollander et al. 1994). The methotrexate-induced neurotoxicity, seen most commonly in patients with acute lymphoblastic leukemia (ALL) or osteosarcoma (OS) where methotrexate is often a major component of therapy, is likely to be related to glutamate-induced excitotoxicity (Quinn and Kamen 1996). DM appears to be useful in the treatment of this neurotoxicity. Other studies have shown that DM or its metabolite may be used to treat seizures secondary to NMDA excess (Croucher et al. 1982; Ferkany et al. 1988).

Somatic and neuropathic pain

Besides NMDA causing neuronal excitotoxicity and cell death, it can also cause somatic and neuropathic pain. Upon tissue injury, pain transmission passes through the A-delta and C-sensory fibers to the dorsal horn neurons, causing the release of peptides and EAAs and the activation of the NMDA receptors (Aanonsen and Wilcox 1987; Battaglia and Rustioni 1988). This hyperexcitabilty event is described as the "wind-up" phenomenon, leading to longer and more severe pain sensations.

Although not widely used today as analgesics, DM and levorphanol were initially considered as pharmacological alternatives to morphine for pain management (Weinbroum et al. 2000). DM modulates pain sensation by reducing the excitatory transmission of the primary afferent pathways along the spinothalamic tract. This process occurs in the dorsal horn of the spinal cord, where DM blocks NMDA receptors, reducing the threshold for pain transmission via the A-delta and C-sensory fibers (Woolf and Chong 1993). The activation of neuronal firing by NMDA receptors leads to an increase in the intracellular calcium levels (Church et al. 1985; Mendell 1966). DM has been shown to reduce and regulate the influx of intracellular calcium through the NMDA receptor-gated channels (Church et al. 1991). This action antagonizes the effects of EAAs and reduces the release of various peptides, such as glutamate and aspartate, and ultimately may lead to an overall reduction of pain sensation (Battaglia and Rustioni 1988).

PHARMACOKINETICS

DM is rapidly absorbed in the gastrointestinal tract; its peak serum levels are reached at approximately 2 to 2.5 hours after oral administration (Hollander et al. 1994; Pender and Parks 1991). At therapeutic doses its onset of action is 15 to 30 minutes and its duration of action is 5 to 6 hours (Pender and Parks 1991). At appropriate adult doses (i.e., 30 mg orally every 4 hours for 7 days) the therapeutic blood levels of DM range from 0.002 to 0.207 mg/L (Baselt 2002; DeZeeuw and Johnkman 1988). DM is readily absorbed into the bloodstream and crosses the blood–brain barrier with measurable cerebral spinal fluid/plasma ratio of 32.8 to 80% (Hollander et al. 1994).

The biotransformation of DM occurs in the liver, where it is rapidly metabolized (Woodworth et al. 1987). DM undergoes a first-pass metabolism via hepatic portal vein and is *O*-demethylated to produce the active metabolite; it is further *N*-demethylated, and partially conjugated with glucuronic acid and sulfate ions. Cytochrome P450 in the 2D6 isoenzyme is responsible for the inactivation of DM. Poor metabolizers or those receiving medications inhibiting CYP2D6 experience accumulation of the active drug (Kupfer et al. 1986; Motassim et al. 1987). Examples of drug interactions resulting in an increase of DM levels include interactions with monoamine oxidase inhibitors (MAO-Is), fluoxetine, paroxetine, and haloperidol.

The main metabolite dextrorphan, the 3-hydroxy derivative of DM, is pharmacologically active with a half-life of 3.4 to 5.6 hours. Dextrorphan is a potent NMDA antagonist (Church et al. 1991). Inactive metabolites include (+)-3-hydroxy-*N*-methylmorphinan, which is metabolized by CYP3As and CYP2D6 and (+)-3-morphinan that is metabolized by CYPAs (Fig. 2) (Ducharme et al. 1996; Motassim et al. 1987). DM is eliminated renally unchanged or as a demethylated metabolite.

TOXICOLOGY

The adverse effects of over-the-counter (OTC) agents, such as DM, are often overlooked. Under typical circumstances, DM is safe when used at appropriate doses, but significant morbidity can occur with overdoses of DM. Acute intoxication with DM usually resolves within 24 hours (Manaboriboon and Chomchai 2005).

The majority of DM's adverse effects occur at the level of the CNS. Neurologic toxicity associated with DM includes dystonia, fatigue, drowsiness, and dizziness. Nystagmus, slurred speech, light-headedness, and fatigue were more commonly reported at higher doses of DM (10 mg/kg/day) and occurred within 1 to 2 hours of administration (Hollander et al. 1994). Binding of DM to D_2 receptors can lead to psychoses, visual hallucinations, or manic symptoms (such as restlessness, insomnia, irritability, and racing thoughts) (Achamallah 1992; Bostwick 1996; Drachtman et al. 2002). Patients with these psychiatric symptoms are often receiving other drugs to treat their underlying psychiatric disorders so it is difficult to identify side effects as those of DM. Other non-CNS-related effects, such as dermatologic and metabolic, have also been reported. Dermatologic adverse effects, such as a specific drug eruption, can occur after therapeutic doses of DM (Stubb and Reitamo 1990). Uncommon side effects associated with DM also include hyperpyrexia, hyperglycemia, and anaphylaxis (Knowles and Weber 1998; Konrad et al. 2000; Rivers and Horner 1970).

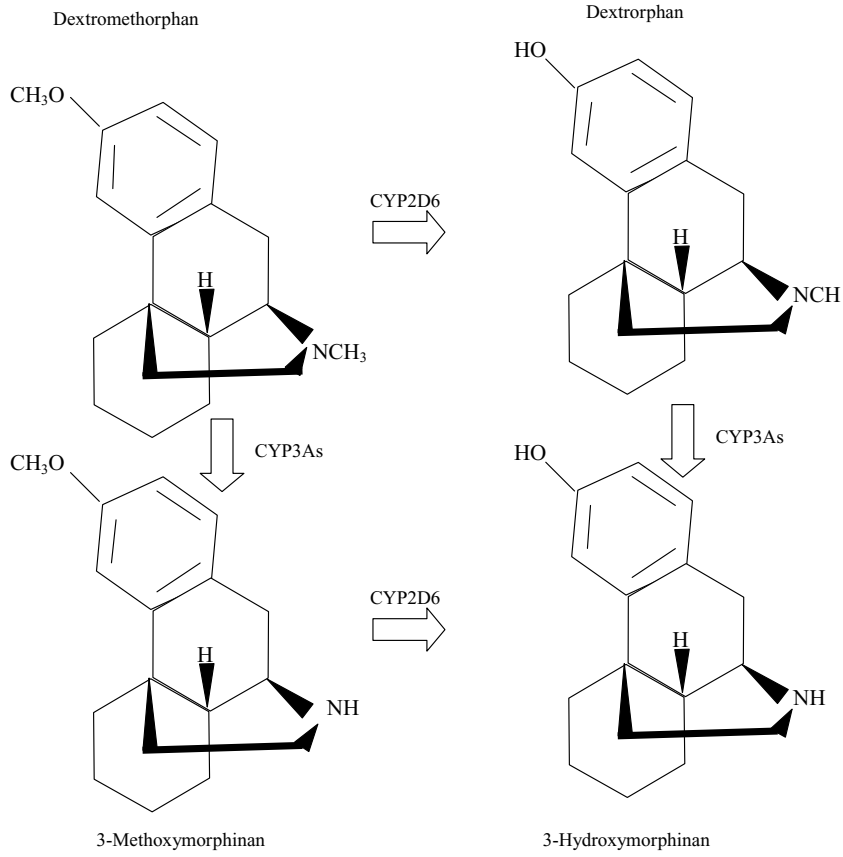

FIG. 2. Structure of dextromethorphan and metabolites.

Warden and colleagues were the first to report extrapyramidal symptoms (EPS) following ingestion of toxic doses of DM (Warden et al. 1997). A 30-month-old female child accidentally ingested 38 mg/kg of DM. The normal pediatric dosage of DM in this age group is 2.5 to 5 mg, orally every 4 hours or 7.5 mg every 6 to 8 hours (Product Information: Pertussin Children's Strength(R) dextromethorphan hydrobromide 1999). The patient presented to the emergency department with clinical manifestations of opisthotonus, ataxia, and bidirectional nystagmus. The child failed to respond to naloxone administration; however, the opisthotonus resolved with diphenhydramine. The authors concluded that the mechanism associated with this dystonic reaction may be due to DM's ability to block dopamine receptors.

CLINICAL STUDIES

Cancer Pain

Although the cure rate for cancer has dramatically increased over the last few decades, the side effects of cancer treatment have become more obvious as considerations of supportive

care and quality of life have moved to the frontlines of cancer care. Pain management is an essential part of cancer management, encompassing both acute and chronic pain, which may occur either as a result of the actual tumor or secondary to complications of the treatment and management of cancer. Pain management in these patients relies primarily on opioid drugs, the use of which is complicated by addiction, potential for respiratory depression, severe constipation, and the possibility for undertreatment as a result of the societal stigma associated with opioid use. Adequate pain care remains challenging. DM has some potential use as an adjunctive therapy for pain in cancer patients.

NMDA receptors are ubiquitous throughout the central nervous system. Excitatory amino acids may play a role in the sensation of pain via the ascending pathways of the spinal cord. Following acute injury, the excitatory amino acids stimulate the NMDA receptors located within the synapses, stimulating the synaptic neurons to transmit sensations of pain. This mechanism leads to a state of hyperexcitabilty and may cause such pain syndromes as allodynia and hyperpathia. As alluded to earlier, "wind-up" is a phenomenon whereby the C-fiber mediated activity of dorsal horn nociceptive neurons is enhanced and prolonged as a result of activation of the NMDA receptors. The "wind-up" phenomenon may lead to reduced sensitivity to opioids (Dickenson 1994). It is conceivable that DM could reduce central sensitization and be an effective analgesic agent (Price et al. 1996; Weinbroum et al. 2000).

DM was initially shown to be effective as an adjunct pain medication in patients undergoing tonsillectomy. In this group of patients, premedication with DM, post-tonsillectomy pain was reduced. The dose was similar to that used for the antitussive effect (3 to 45 mg, orally). More pertinent to cancer patients is the reported reduction in meperidine requirement by DM in postsurgical patients after radical mastectomy (Kawamata et al. 1998; Wong et al. 1999). Other clinical trials regarding pain management with DM were reported in a previously published review article (Weinbroum et al. 2000). Although the use of DM in the maintenance of pain appears to be promising, it is still difficult to assess the contribution of DM to the control of pain because of the use of other preoperative medications. The postoperative intervention has also not been properly controlled in many of the studies cited. There is, however, a number of more recent double-blind placebo-controlled trials that include the use of DM in phantom pain after resection of a bone malignancy as well as for postoperative pain in orthopedic oncology patients (Abraham et al. 2002; Weinbroum et al. 2002; Weinbroum et al. 2003; Weinbroum et al. 2004). These studies suggest that DM could reduce pain intensity, sedation, and analgesic requirements in some cancer patients, particularly those who are postoperative, without changing the incidence of side effects, ambulation, or time to discharge. The potential use for treating phantom pain is particularly intriguing for oncologists, as this pain persists beyond the immediate postoperative period, and while phantom pain is not unique to cancer patients, it is a type of pain commonly seen in centers that specialize in bone tumors.

The use of DM in chronic pain has also been evaluated, albeit with less encouraging results. Many of these studies are summarized in a prior review (Weinbroum et al. 2000). Few studies have specifically addressed chronic pain as a result of cancer. Mercadante et al. (1998) reported an open-label study in a home palliative setting designed to examine the effects of combining DM with nonsteroidal anti-inflammatory agents, dextropropoxyphene, or morphine in the treatment of cancer patients with chronic pain. In this trial, a highly significant reduction of pain was observed with conventional treatment, but no additional effects were found when DM was combined with standard care. The addition of morphine

sulfate to DM in a preparation called Morphidex (containing a 1:1 ratio of morphine sulfate to DM) was studied by Katz in patients with cancer pain. (Katz 2000). In this double-blind multiple-dose trial, the interval between doses was longer in the study group, and lower doses of morphine were necessary to achieve analgesia. There was no difference in the number of adverse events.

Further studies are necessary to determine the role, if any, of DM in the routine treatment of pain in cancer patients. The availability of DM makes this an attractive agent to study further. One major factor limiting the use of DM is its potential abuse, as it is now recognized that at higher than recommended doses DM may produce a euphoric effect (Darboe et al. 1993). It is possible that the use of DM for effective pain management would require doses that would cause side effects similar to those produced by narcotics. Supporting this is the finding of Steinberg et al. (1996) where they showed that DM produces side effects when used at higher doses as a neuroprotective agent. The reported side effects were feeling "drunk," dizziness, ataxia, distorted vision, and nystagmus as well as nausea and vomiting. Physical withdrawal symptoms included intermittent vomiting, night sweats, muscle aches, diarrhea, restlessness, insomnia, and anxiety. The documented dependence and physical withdrawal may be secondary to serotonergic and sigma-1 opioidergic properties of the drug (Miller 2005).

Future trials need to be standardized taking into account all medications and other ancillary pain management that patients are receiving. Since most published reports on the use of DM in cancer pain involved postoperative pain, studies with DM in nonsurgical cancer patients should be considered in settings more unique to cancer patients. In particular, the use of DM in patients with phantom limb pain should be evaluated further.

Antitussive Effects

Cough can be a symptom and a sign of cancer. The inability to control coughing can be quite debilitating to the average patient even though this is not typically considered a major cause of suffering in patients with cancer. The pathophysiology of cough in this setting is multifocal and extremely variable due to the involvement of mechanical stimulation and inflammatory processes.

Treatment of pathologic cough is dependent on the cause of the cough in any individual patient. When the actual cancer is the cause of cough, treatment of the underlying disease is most appropriate. It is also important to rule out more common causes of cough that are present in the general population, including asthma, cigarette smoke, and postnasal drip.

There are many antitussive agents available. They fall into two primary groups: those that act peripherally to inhibit cough stimuli or cough receptors, and those that act centrally to depress the central nervous system cough control center (Hagen 1991).

DM is a centrally acting drug that increases the cough threshold. It has been available for this indication in the United States since 1954. DM and similar centrally acting antitussives work via non-opioid receptors. Consistent with this is the fact that naloxone does not reverse DM activity and codeine does not have significant activity at high-affinity DM binding sites (Craviso and Musacchio 1983b).

A potential advantage of DM is the lack of gastrointestinal side effects such as constipation and less CNS depression than seen with opioids when used as antitussives in usual doses. However, extremely high doses of DM can cause CNS depression, occasionally prompting

its abuse. There is also a potential synergy of DM and an opioid analgesic, although this has not been studied and clinical investigation would be warranted prior to making any recommendations of this sort.

An additional side effect of some concern is histamine release, another side effect shared with opioid drugs. There is at least one report of bullous mastocytosis in an infant with urticaria pigmentosa treated with DM as a cough suppressant (Cook et al. 1996). This, however, is not an issue in the typical patient treated with DM as an antitussive, although it would be prudent not to prescribe DM to a patient with urticaria pigmentosa.

Methotrexate Toxicity

Methotrexate is a core component of many treatment regimens for acute lymphoblastic leukemia and lymphoblastic lymphoma. High-dose methotrexate is also commonly used to treat osteogenic sarcoma, a malignancy most commonly diagnosed in the adolescent population. In addition, methotrexate is used for nonmalignant conditions such as psoriasis, rheumatoid arthritis, and systemic lupus erythematosus. Methotrexate neurotoxicity is a frequent complication of methotrexate therapy both for malignant and nonmalignant diseases. It occurs with low, intermediate, and high doses of methotrexate. Neurotoxicity secondary to methotrexate is not typically a life-threatening problem; however, the frequency of methotrexate neurotoxicity is probably underestimated and the presence of underlying methotrexate neurotoxicity may contribute to noncompliance. The severity of methotrexate neurotoxicity can range from affective disorders, malaise ("methotrexate blahs") and headaches to somnolence, transient focal neurologic deficits, and seizures. Leukoencephalopathy manifested by disturbances of higher cognitive function can occur weeks to months after initiation of the methotrexate therapy (Kishi et al. 2000).

Although the pathogenesis of methotrexate neurotoxicity is not completely understood and is likely to be multifactorial, DM has been used as an antidote in the affected patients. This is because the likely mechanism of methotrexate-induced neuropathy is related to the folate-dependent remethylation of homocysteine. Methotrexate therapy increases the blood and cerebrospinal fluid concentrations of homocysteine and its metabolites. Although the toxic effect of homocysteine on vascular endothelium is well documented, its neurotoxicity is not as well appreciated.

Metabolites of homocysteine are excitatory agonists at the NMDA receptors. The use of NMDA antagonists as anticonvulsant agents has been studied, exploiting this mechanism. One of the metabolites of homocysteine is S-adenosylhomocysteine, an inhibitor of S-adenosylmethionine-dependent reactions, including serotonin and dopamine synthesis and the transmethylation of proteins required for myelination. Increased cerebrospinal fluid levels of homocysteine have been reported in patients with clinical evidence of methotrexate neurotoxicity (Drachtman et al. 2002). This has led to the use of DM as a treatment for methotrexate neurotoxicity. In a similar setting, DM has also been shown to potentially protect against methamphetamine-induced neurotoxicity by blocking microglial activation.

DM is a noncompetitive NMDA receptor antagonist that has been successfully used in the treatment of methotrexate neurotoxicity in patients with rheumatoid arthritis or cancer (Bettachi et al. 1999). The use of DM is not typically associated with the sedative effects at recommended dosages, although the potential for abuse exists when DM is taken at

higher than recommended doses. Patients under treatment with methotrexate for rheumatoid arthritis have reported significant improvement or resolution of neurologic complications such as memory impairment, malaise, headache, insomnia, numbness, feeling "zoned out," sexual dysfunction and confusion with DM. Patients on chemotherapeutic regimens with methotrexate at significantly higher than recommended doses and have developed dysarthria and hemiplegia have been successfully treated with DM, 1 to 2 mg/kg.

The role of DM needs to be addressed in larger studies of patients receiving methotrexate both with cancer and nonmalignant diseases. While the use of DM is established in acute methotrexate-induced CNS toxicity, its role in the treatment of more insidious neurocognitive toxicity needs to be studied further.

CONCLUSIONS

DM is a methyl ether of the D-isomer of levorphanol acting as an antitussive in the medulla oblongata to increase cough threshold. The drug also possesses noncompetitive NMDA blocking effects. These effects led to the discovery of additional neuropharmacologic indications for this agent. It has been proposed that DM has neuroprotective effects and may prevent somatic and neuropathic pain. Activation of NMDA receptors promotes excitotoxicity of EAAs in the neuronal cells as well as excitatory pain transmission in the CNS. As an NMDA-receptor antagonist, DM prevents excitotoxicity caused by methotrexate and reduces pain sensation.

Although the role of DM as an NMDA-receptor antagonist appears attractive, its clinical use in the treatment of pain in cancer patients led to controversial results. Four studies showed a reduction in pain intensity. Its effects in the chronic pain management were, however, less promising (Abraham et al. 2002; Katz 2000; Weinbroum et al. 2002; Weinbroum et al. 2003; Weinbroum et al. 2004). The antitussive properties of DM are well documented and may be useful in the treatment of chronic cough in cancer patients. Although only limited research is available, DM has shown encouraging results in the prevention of methotrexate-induced neurotoxicity (Drachtman et al. 2002).

DM is a widely known ingredient in cough syrups and is commercially available over the counter in various formulations (i.e., syrups or lozenges). Combination products are also available with antihistamines and other agents. Further and larger studies are needed to explore potential indications for DM as a therapeutic agent in cancer pain and methotrexate-induced neurotoxicity.

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