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Article *in* Canadian Journal of Anaesthesia · July 2000

Impact Factor: 2.53 · DOI: 10.1007/BF03018952 · Source: PubMed

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Review Article

The role of dextromethorphan in pain control

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Purpose: To review the clinical benefits of dextromethorphan (DM) in pain management, describe its neuropharmacological properties.

Source: A Medline search was made for experimental and clinical data on DM use from 1967 to date using keywords *nociception, acute and chronic pain control, N-methyl-D-aspartate, antagonists, dextromethorphan.*

Principle findings: The 930 DM citations mostly described its antitussive, metabolic and toxicological aspects, animal studies and its possible role in minimizing post-brain ischemia complications in humans. The use of DM in *acute* pain revealed eight original studies involving 443 patients, as well as two preliminary reports and our own unpublished data on 513 patients. Most of the 956 patients had general anesthesia. Eight studies (154 patients) and one case report dealt with *chronic* pain management. This N-methyl-D-aspartate (NMDA) receptor antagonist binds to receptor sites in the spinal cord and central nervous system, thereby blocking the generation of central acute and chronic pain sensations arising from peripheral nociceptive stimuli and enabling reduction in the amount of analgesics required for pain control. DM attenuated the sensation of *acute* pain at doses of 30-90 mg, without major side effects, and reduced the amount of analgesics in 73% of the postoperative DM-treated patients. Studies in secondary pain models in healthy volunteers and in various types of *chronic* pain showed DM to be associated with unsatisfactory pain relief.

Conclusion: DM attenuates *acute* pain sensation with tolerable side effects. Its availability in oral form bestow advantages over other NMDA antagonists.

Objectif : Passer en revue les bénéfices cliniques du dextrométhorphane (DM) et décrire ses propriétés neuropharmacologiques.

Source : Une recherche dans Medline a fourni des données expérimentales et cliniques sur le DM, utilisé de 1967 à aujourd'hui, à l'aide des mots-clés *nociception, soulagement de la douleur aiguë et chronique, N-méthyl-D-aspartate, antagonistes, dextrométhorphane.*

Constatations principales : Les 930 références trouvées décrivent surtout les aspects antitussifs, métaboliques et toxicologiques du DM, les études sur des animaux et le rôle possible dans la réduction des complications de l'ischémie cérébrale chez l'humain. Huit études originales auprès de 443 patients, deux rapports préliminaires et nos propres données non publiées sur 513 patients concernent le soulagement de la douleur *aiguë*. La majorité des 956 patients ont eu une anesthésie générale. Huit études (154 patients) et une observation portent sur le traitement de la douleur *chronique*. Cet antagoniste des récepteurs N-méthyl-D-aspartate (NMDA) se fixe sur les sites récepteurs dans la moelle épinière et le système nerveux central. Il empêche ainsi la propagation centrale des sensations de douleurs aiguës et chroniques provenant de stimuli nociceptifs périphériques, et contribue à la réduction de la quantité d'analgésiques nécessaires au traitement. Des doses de 30-90 mg de DM atténuent la sensation de douleur *aiguë,* sans produire d'effets secondaires importants, et permettent de réduire la quantité d'analgésiques chez 73 % des patients traités avec du DM après une intervention chirurgicale. Les études de modèles de douleurs secondaires chez des volontaires sains et de différents types de douleurs *chroniques,* ont révélé que le DM n'apporte pas de soulagement de la douleur satisfaisant.

Conclusion : Le DM atténue la sensation de douleur *aiguë* et présente des effets secondaires acceptables. Son conditionnement sous forme orale lui confère des avantages sur d'autres antagonistes de NMDA.

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This review was facilitated by aid from the "Anonymous Italian Family Foundation", Milan, Italy.

Accepted for publication March 3, 2000.

THE pharmacological management of acute postoperative pain and chronic pain syndromes has been traditionally based on various regimens of opioids and their congeners or NSAIDs. All opioids have side effects, of which the most dangerous are respiratory and cardiovascular depression associated with excessive sedation. NSAIDs may also induce side effects such as exacerbation of bleeding tendencies and impaired renal function. The search for alternative pain control strategies has focused on the N-methyl-D-aspartate (NMDA) receptors and their antagonists which were recently shown to alleviate somatic and neuropathic pain sensation in both animal and human models.[1–5] Their clinical utility stems from their ability to block the NMDA receptors located at the junction where pain generated by peripheral nociceptive stimuli is conveyed to central receptors via A_δ and C sensory fibres.[6] From a clinical standpoint, the amounts of conventional pain killers that are needed for effective pain control would be much smaller. One of these compounds is dextromethorphan (DM), a low-affinity, non-competitive NMDA receptor antagonist which has a long history of clinical safety as a cough suppressant.[7]

SEARCH STRATEGY

We conducted a Medline search of the English language literature using the following keywords: *nociception, acute and chronic pain control, N-methyl-D-aspartate, antagonists, dextromethorphan.* This review summarizes the neuropharmacological mechanism of action of DM, describes its clinical utility and limitations in different pain settings, i.e. acute, chronic, and neuropathic states, and also presents the published animal and clinical studies that had been carried out on the pain-control capabilities of this compound.

Excitatory amino acids and modulation of NMDA receptors

Considerable evidence has accumulated over the past few years on the role of excitatory amino acids (EAA), such as glutamate and aspartate, in modulating the sensation of pain via the ascending pathways along the spinal cord and central nervous system.[6] The stimulation of NMDA receptors located in the dorsal horn of the spinal cord - the area responsible for relaying, modulating and transmitting pain - by intra-spinal deposition of glutamate in experimental rat and monkey models generated an increased response to noxious stimuli and lowered the threshold of pain.[8,9] This response was successfully abolished by NMDA antagonists, such as phencyclidine,[9] suggesting that the initiation of pain can be attenuated by blocking the activity of these receptors. Investigations of chronic pain syndromes revealed that the same mechanisms are involved in the initiation and the perpetuation of secondary pain in mouse and rat models.[9,10]

In terms of neurophysiology, following acute tissue injury, transduction is accomplished by action potentials being generated at the nerve endings and transmitted along the A_δ and C fibres to the synapses of the dorsal part of the spinal cord where they induce the release of various peptides, including EAA.[8,9] The EAA activate the NMDA receptors that are located within the synapses, thus stimulating the synaptic neurones to transmit sensations of pain. This state of hyperexcitability, or "wind up" amplifies the magnitude and duration of neurogenic responses to any existing volley of nociceptive activity. Once initiated, this state of hyperexcitability can exist even after the peripheral input has ceased.[11] This phenomenon is currently thought to be responsible for various clinical pain syndromes such as allodynia, an intense sensation of pain following a relatively minor stimulus that would not ordinarily induce pain sensation or hyperpathia, a sensation of pain that persists long after the initial nociceptive stimulus has subsided.[9,10,12] The role of NMDA in the "wind up" phenomenon of pain perception was clarified in animals by intraspinal administration of NMDA-receptor antagonists.[13,14] In one human study, *iv* ketamine reduced the magnitude of both primary (immediate) and secondary hyperalgesia and the pain evoked by prolonged heat stimulation in a dose-dependent manner.[15] DM acts in a similar manner: Klepstad *et al.* published a case report of a patient who had undergone four years of satisfactory ketamine treatment for postherpetic neuralgia: experimental substitution of the ketamine by DM 125 mg in four divided doses for seven days was found to be as efficient.[2]

It is important to note that the NMDA receptors are widespread throughout the central nervous system, and as such, are associated with highly diverse neurophysiological functions as far removed from the modulation of pain as learning and memory processing.[1] It is, therefore, not surprising that their antagonists can interfere with its physiological activity, leading to sedation, motor dysfunction or altered behavior.[1,9] Antagonism of the potentially deleterious effects of an excessive release of EEA, such as that which occurs in patients with focal brain ischemia (an example of diverse NMDA activity) can lead to episodes of agitation, hallucinations, somnolence, nausea, vomiting and nystagmus.[16–18] This is why so few NMDA-receptor antagonists have been tested in humans despite their effectiveness in pain manage-

ment, and despite the extensive animal data that point to their promising beneficial effect.[19–21] To date, DM, ketamine and amantadine are the only drugs with NMDA-receptor antagonistic properties that are FDA-approved drugs for clinical use. However, due to the high affinity of ketamine to its receptors and its related dysphoric effects, together with the need to administer it intravenously, research in pain control has turned its focus to DM as the preferred NMDA antagonist for clinical use.

Dextromethorphan – basic neuropharmacology

Dextromethorphan and levorphanol were originally synthesized as pharmacological alternatives to morphine more than 40 yr ago. DM is the D-isomer of the codeine analogue, levorphanol but, in contrast to its L-isomer, it has no effect on the opioid receptors.[22] From the beginning, its clinical use was mainly that of an antitussive in syrup preparations, at adult doses of 10 to 30 mg three to six times daily.[7] The specific central sites upon which DM exerts its antitussive effect are still uncertain, but they are distinct from those of opioids, insofar as the effect is not suppressed by naloxone.[23] Also, unlike opioids, DM has an established safety record, i.e., the therapeutic cough suppressant dose (1 $mg \cdot kg^{-1} \cdot dy^{-1}$) has no major opioid-like respiratory or hemodynamic side effects, neither does it induce histamine released-complications.[7]

The binding of the antagonists to the NMDA receptors results in modifying the receptor-gated Ca^{2+} current. Changes in the Ca^{2+} current normally lead to NMDA-induced neuronal firing which, if it persists, is followed by a heightening of the intensity of the primary nociceptive stimulus, i.e., "wind up" phenomenon, and the triggering of secondary sensory pain.[24,25] In contrast to the other NMDA-receptor antagonists, DM has widespread binding sites in the central nervous system that are distinct from those of opioids and other neurotransmitters, so that its activity is not limited to the NMDA receptors alone, as was shown in pigs and rats.[26,27] Besides the ability of DM to reduce intracellular Ca^{2+} influx through the NMDA receptor-gated channels, DM also regulates voltage-gated Ca^{2+} channels which are normally activated by high concentrations of extracellular K^{+}.[27] One of the physiological consequences of these multi-channel regulation capabilities is the attenuation by DM of NMDA-mediated neuronal firing in the brain that is normally transformed into seizures, as was shown experimentally in rats and in neurone cell cultures[25,28,29] as well as in humans (see below). The neuropharmacological cascade of events that provokes the reduced intracellular accumulation of Ca^{2+} to cause changes in the activity of NMDA receptors remains to be elucidated.

In humans as in animals, DM was also capable of ameliorating discomfort associated with excitotoxicity-related neurological disorders, such as intractable seizures and Parkinson's disease when administered at doses of 30 or 60 qid,[30] 45-180 mg od[31] or 120 mg od[32] for periods of three weeks to three months. No serious untoward neurological effects were detected in these and in another study where eight healthy human volunteers in whom motor cortex excitability (as indicated by motor-evoked potentials) was reduced after a single oral high (150 mg) dose.[33] In addition, motor cortex excitability and levodopa-induced dyskinesis were reduced by DM at a dose of 100 mg in a double-blind placebo-control study in patients with Parkinson's disease,[34] with only negligible side effects in this study as well.

Dextromethorphan is rapidly metabolized in the liver[35] where it is transformed to dextrorphan, its active and more potent derivative as an NMDA antagonist.[25] It was suggested that the side effects documented in clinical studies and attributed to the oral administration of DM might be mediated by this metabolite acting at the phencyclidine receptorial site rather than DM itself.[36]

The potential of Dextromethorphan in pain control

Satisfactory pain control achieved with the least amount of opioids has always been an important goal in view of both the psychological and somatic dependence these drugs may induce and the often intolerable side effects that may follow their extensive use. The searchers for techniques of pain control that will afford full orientation, co-ordination and collaboration, and normal respiration as well as stable hemodynamics view these factors as important cornerstones in postoperative planning of pain control. This applies equally to patients who had undergone either general or regional anesthesia and to inpatients as well as outpatients. Moreover, in view of the contention that persistent NMDA receptor activation can evoke central hyperexcitability that can lead to secondary pain, proper pain control should both modulate primary pain sensation and preempt an analgesic state that would prevent *acute* pain from progressing into *chronic* pain. This concept of preemptive analgesia (i.e., reducing pain sensation in advance) is feasible via NMDA modulation, as had been demonstrated by the administration of opiates and ketamine to patients before surgery.[37,38] Importantly, this neuropharmacological receptor conditioning is also beneficial for reducing the need for additional doses of opioids postoperatively. In addition, while the neurovegetative stimulation and adrenergic overproduction that accompany the continuous neurally transmitted acute

and, to a greater extent, secondary pain are clearly detrimental to all patients, they may be particularly harmful for cardiac patients. In this regard, the preemptive approach is an especially promising and beneficial one. The use of DM may, therefore, become an established component in protocols of treating pain and of alleviating the accompanying neurovegetative phenomena. Finally, the availability of DM in the oral form (indeed, in most human studies the administration was per os, Tables I and II) makes it much more preferable to the other anti-NMDA drugs that need to be injected, such as ketamine.

As a potential morphine-sparing agent for pain, the use of DM was shown to be efficient and well tolerated[39] (Weinbroum *et al.*, unpublished data). It is noteworthy that NMDA receptor antagonists, including DM, are not in themselves anti-nociceptive[40] but rather inhibit central sensitization and, thus, the perception of primary and secondary pain[41,42] (Table I). The preemptive use of these antagonists, while blunting the development of a central sensitization of a nociceptive stimulus,[42,43] still requires the use of an analgesic for complete abolishment of pain perception.

Evaluation of Dextromethorphan efficacy

While the methodology for evaluating postoperative pro-analgesic effects of DM in controlling *acute* pain in humans shares many features with commonly employed methods of assessment, for example double-blind study with randomization, other scales were also used among the various studies we retrieved (Table I):

I ***Objective scores***
- A The total amount of postoperative analgesics consumed
  1. Opioids (morphine IV-PCA,[39,42,44,45,50] Weinbroum *et al.*, unpublished, meperidine *im*,[46,47] oral codeine[44])
  2. Non-steroidal anti-inflammatory drugs (diclofenac[5,39])
  3. Specific drugs (codydramol [paracetamol 500 mg + dihydrocodeine 10 mg][39])
- B The time to first request of analgesic[5,46,47]
- C Bed rest time[46,47]
- D Sedation (0-10 VAS),[39,42] Weinbroum *et al.*, unpublished.

II ***Patient self-evaluation***
- A Pain intensity
  1. A verbal rating scale (0=none to 3=severe)[45]
  2. Graded or analogue visual score (VAS, from 0 - no pain, to 10 or 100 – worst pain), [5,39,42,46-50] Weinbroum *et al.*, unpublished
  3. Von Frey hairs[50] Weinbroum *et al.*, unpublished
- B Pain relief
  1. Visual Analogue Scale (0-100)[42,48]
  2. The time to onset of meaningful relief[48]
- C Sedation
  1. Visual Analogue Scale (0-100) Weinbroum *et al.*, unpublished

III ***Specific modes of assessment***
- A One pediatric study[44] compared
  1. Admission *vs* discharge Children's Hospital of Eastern Ontario Pain Scale (CHEOPS)
  2. Children behavioral scale (1=asleep to 4= thrashing)
  3. Parental satisfaction rate (1-10 VAS).
- B Intraoperative DM usefulness was determined in one study based on blood pressure and heart rate[45]
- C Written questionnaire one month postoperatively.[50]

The evaluation of DM efficacy in patients with *chronic* pain is much more complicated because of ethical problems that do not allow the exclusion of a previously used analgesic, the many untoward side effects, and/or because of a possible 'placebo effect'. Most of the studies on *chronic* pain were also double blind, and cross-over methods were used to minimize intersubject variability in response to (primary or secondary) pain or the learning phenomenon in volunteers[40,51] (Table II).

I ***Patient self-evaluation***
- A Pain intensity (e.g.,)
  1. Verbal rating score[52]
  2. 0-100 VAS[2,4,40,41,52-54]
  3. Descriptive scale of eight words[52] or 13 words[55]
  4. Personal descriptive sensation (volunteers)[40]
  5. The McGill Pain Questionnaire (20 groups of 78 descriptors)[52]
- B Pain relief rating
  1. Categorical (none=0 to complete=4[52] or = 5[55])
  2. Specific pain alleviation (e.g., allodynia[54])
  3. Daily treatment (0=poor, 4=excellent)[52]
- C Personal feelings
  1. Mood (VAS, 0=worst to 100=best)[52]
  2. Sleep quality (0=poor to 4=excellent)[52]
- D Volunteer evaluation
  1. Pre- and post-drug alertness[51]
  2. Pain sensation (VAS)[4,51]

- Threshold to mechanical pressure (Von Frey hairs), puncture, electrical stimuli, heat
- Post-insult contralateral hand pain

E Cancer patients
1. Magnitude of escalation in morphine requirement[53]

II ***Objective findings***
A Pain intensity (VAS, categorical)[52]
B Pain relief (VAS, categorical)[52]
C Rate of compliance with treatment[55]
D Nature of side effects[41,51-53,55]
1. Gastrointestinal, behavioral, or new pain onset
2. Grade of tolerability or provoking withdrawal from study

Dextromethorphan in ***acute*** pain control (Table I)
The majority of the studies on the role of DM in attenuating acute postoperative pain or in reducing the consumption of analgesics compared one or two doses of oral DM premedication with placebo in patients who underwent surgery with general anesthesia (Table I). The pioneering study of Kawamata *et al.* showed that a single DM premedication of 30 or 45 mg (a dose used as a cough suppressant) administered 60 min before tonsillectomy under general anesthesia was effective in reducing post-tonsillectomy pain sensation, even upon swallowing, in adult patients.[5] This single dose of DM also reduced the pain score and diclofenac requirement for the seven days following surgery. Henderson *et al.*[39] recently confirmed the efficacy of oral DM during the first two postoperative days in patients premedicated with 40 mg the night before and three times·dy^{-1} for 48 hr after hysterectomy and with very few side effects (Table I). Two interesting studies also compared the efficacy of parenteral DM when given pre- as opposed to post-incisional.[42,46] According to the tested parameters, preincisional intravenous 5 mg DM was more efficacious than the same post-insult regimen, but the latter was accompanied by a high rate of side effects[42] (Table I). The high incidence can be explained by the expected high plasma concentrations following the *iv* or *im* drug administration compared to a much lower one because of the low bioavailability (~10%) of DM after oral administration.[35,47] Support for this explanation can be found in two preliminary reports (Table I) which showed that 60 mg of oral DM preoperatively reduced postoperative pain, while 120 mg was not more efficient but rather evoked side effects.[48,49] Wu *et al.*[46] also compared the effect of pre- *vs* postincisional 40 mg DM given intramuscularly (*im*). They found that the former produced a better postoperative pain relief and reduced meperidine *im* consumption during the 48 hr following laparoscopic cholecystectomy in adult patients, compared to the postincisional patients. However, both regimens reduced the values of the tested parameters compared to otherwise matched patients who received a placebo. These authors recently reported having given preoperatively the same dose regimen to patients who underwent radical mastectomy under general anesthesia and that it resulted in an identical postsurgical decrease of pain and meperidine requirement.[47]

These encouraging reports on the effects of oral DM on pain sensation are, however, challenged by the results of several double-blind studies on *acute* pain in which 255 patients did not benefit from DM (Table I). In one, DM at doses of 0.5 or 1.0 mg·kg^{-1} did not reduce the pain score, analgesic requirement or other subjective and objective scores in children after tonsillectomy under multi-drug general anesthesia during the 24 postoperative hr[44] (Table I). These results that are in opposition to those found by Kawamata *et al.*,[5] could be explained by the different study and drug protocols and in the age of the patients that could have accounted for their compliance with pain. Premedication with drugs that effect central function (Table I) could also have obscured DM effects and affected the interpretation of the results. In a recent study by McConaghy *et al.*, oral 27 mg DM was given twice preoperatively and three times during the 24-hr after total abdominal hysterectomy.[50] Data from this study showed no benefit as expressed by VAS, MO consumption, etc., over placebo at 24 or 48 hr after surgery or one month later. Grace *et al.*[45] had earlier demonstrated that 60 mg DM given the night before surgery to non-premedicated patients scheduled for laparotomy under general anesthesia reduced the intraoperative morphine requirement based on blood pressure and heart rate, but not the postoperative patient-controlled morphine requirement. In view of the earlier mentioned study of Kawamata *et al.*,[5] Grace *et al.*[45] suggested that, in order to reduce postoperative pain sensation and analgesic requirements, DM must be administered together with morphine, i.e., needs to be continued postoperatively. Wong *et al.*[47] suggested that the DM doses used by these latter studies were too low to produce analgesia because of the earlier described low oral bioavailability.

In a recent double-blind randomized study (Weinbroum *et al.*, unpublished data), the postoperative morphine-sparing effect (compared to placebo) was confirmed for DM 60 or 90 mg only premedicated patients undergoing medium-sized low abdominal

TABLE I Clinical studies on the use of DM in acute pain control, in chronological order.

Authors, Reference number, Year, Procedure	*Trial (Patients)*	*Dosage (mg, po) (Once Preop)**	*Additional Medication#*	*Anesthesia (O_2 included)*	*Effects; No. Pts. Effective/ DM-Treated Pts.; Duration of Follow-up*	*Side effects*
Grace *et al.*,[45] 1998 Large & small bowel resection	DB, R, PC (n = 37)	60	None	N_2O/Isoflurane /MO	Reduced *Intraoperative* IV-PCA-MO; 18/18	N/A
Kawamata *et al.*,[5] 1998 Tonsillectomy	DB, R, PC (n = 36)	30,45	MDZ, Atropine Postop: NSAIDs	N_2O/Isoflurane	Reduced postop pain, Diclofenac; 24/24; 7d	None
McConaghy *et al.*,[50] 1998 Total abdominal hysterectomy	DB (n = 53)	27 twice Preop, 27tid/24h Postop	Diazepam	N_2O/Isoflurane/ MO	None; 27/27; 24h ,48h, 1m	High incidence in DM and placebo patients¶
Caruso *et al.*,[48] 1998 Oral surgery	DB, PC (n = 250)	30, 60	Alone or combined with MO	N/A	Reduced postop pain if Combined with MO but not alone; 100/200; 8h	N/A
Minn *et al.*,[49] 1998 Oral surgery	DB, PC (n = 173)	60, 120	Combined with MO or Placebo	N/A	Reduced postop pain 86/86; 60mg effect equals 120; 6h	Dizziness, nausea, Drowsiness, vomiting
Wu *et al.*,[46] 1999 Cholecystectomy	DB, R (n = 90)	40 (IM) Pre-*vs* Post-Incision	Chlorpheniramine	Desflurane/ Fentanyl	Pre- > Post-incisional DM Reduction of postop pain, Meperidine IM; 60/60; 2h, 48h	None
Wong *et al.*,[47] 1999 Modified radical mastectomy	DB, PC (n = 60)	40 (IM) Preincisional	Chlorpheniramine	Desflurane/ Fentanyl	Reduced postop pain, meperidine IM; 30/30; 2h, 48h	None
Henderson *et al.*,[39] 1999 Hysterectomy	DB, R, PC (n = 50)	40 Preop, 40tds for 24h Postop	Temazepam	General Anesthesia†	Reduced postop pain, IV-PCA-MO, Codydramol§; 25/25; 3d	Dizziness, nausea, vomiting
Rose *et al.*,[44] 1999 Adenotonsillectomy (Children)	DB, R, PC (n = 57)	0.5 or 1/kg	MDZ, Atropine postop: MO, Codeine, AMP,	General Anesthesia‡	None; 38/38; 24h	N/A
Chia *et al.*,[42] 1999 Hysterectomy, major Intraabdominal surgery	DB (n = 60)	5/kg (IV) Pre-*vs* Postop	None	N_2O/Isoflurane/ Fentanyl	Preop superior to postop DM Reduced postop IV- PCA-MO 30/30; 2d;	Nausea (n = 11), vomiting (n = 26)
Weinbroum *et al.* (unpublished) Laparoscopic surgery	DB, R, PC (n = 30)	90	None	N_2O/Fentanyl	Reduced postop IV-PCA -MO & sedation; 15/15; 4h	None
Weinbroum *et al.* (unpublished) Lower body surgery	DB, R, DB (n = 60)	60, 90	None	Lidocaine via Epidural space	Reduced postop IV- PCA-MO Pain & sedation; 35/35; 4h	None

DB = Double Blind; R = Randomized; PC = Placebo-Controlled; *po* = Per Orally; tid = 3 times·dy^{-1}; N/A = Not Available; VAS = Visual Analogue Scale; MO = Morphine; h = Hour; d = Day; m = month; MDZ = Midazolam; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; Postop = Postoperative; AMP = Acetaminophen; IV-PCA-MO = Intravenous patient-controlled analgesia with morphine.

* Different modes of administration or dosing are specified.

Additional medications were pre-incisional unless otherwise specified.

† General anesthetics included N_2O, enflurane, fentanyl, morphine, droperidol, bupivacaine infiltration, rectal diclofenac.

¶ Reported side effects attributed to DM were found in 27 *vs* 26 placebo patients within 24 hr and in 14 *vs* 12 patients within 24-48 hr postoperatively.

§ Paracetamol 500 mg + dihydrocodeine 10 mg

‡ General anesthetics included N_2O, sevoflurane for induction of anesthesia then desflurane for maintenance, acetaminophen, morphine, dexamethasone, ondansetron.

surgery under lidocaine epidural anesthesia. We suggest that nitrous oxide, which had been shown to block central sensitisation,[56,57] could have reduced afferent pain input, leading to only a marginal additional effect of DM over placebos. Indeed, Wu *et al.*,[46] whose patients underwent general anesthesia for laparoscopic cholecystectomy, still found that providing DM afforded the possibility of reducing the amount of meperidine after having anesthetized their patients with desflurane plus fentanyl and oxygen *without* nitrous oxide. It should be borne in mind that halothane, which, like desflurane, is a halogenated agent, was shown to antagonize N_2O-induced preemptive analgesia..[56] Moreover, in the study of Wu *et al.*,[46] patients were also preoperatively given benzodiazepines and atropine, two drugs with clear central modulatory effects on perception and attitude. Thus, a better understanding of the delicate mechanisms of interaction between DM, the NMDA receptor and possibly other factors that converge positively or negatively on NMDA receptor modulation of *acute* pain still awaits further confirmation from laboratory and clinical investigations.

Dextromethorphan in ***chronic*** and ***neuropathic*** pain (Table II)

The current understanding of the neuropharmacological role of NMDA antagonists in modulating *chronic* pain is still far from complete. A number of drugs with different neuropharmacological activities, such as sodium channel blockers,[58,59] opioids,[60,61] antidepressants,[62,63] or capsaicin,[64] were used with only moderate success and caused considerable side effects. Two excellent and comprehensive articles reviewed the complicated entity of *neuropathic chronic* pain, its pathophysiology and various therapeutic approaches that had been tested over the past few years.[65,66] Indeed, drugs that appeared promising for blocking the NMDA receptors in animal models of *chronic* pain[43,67] and in clinical trials (e.g., ketamine, amantadine)[68,69] not only did not provide satisfactory results in humans but even induced untoward neurological manifestations, including dysphoria, dissociative episodes and local irritation at the infusion site.[20,21] Elliot *et al.*[70] showed the ability of DM to suppress formalin-induced nociceptive behavior in a dose-dependent manner as well as a formalin-induced increase in spinal cord c-fos mRNA transcription (which is associated with NMDA receptor channel activation) in a rat model. In another model of *chronic* pain caused by sciatic nerve ligation in the rat, the intrathecal administration of DM reduced heat-evoked hyperalgesia.[71] When compared to other NMDA receptor antagonists, such as MK-801and CGS 19755, the use of DM in the rat model of *chronic* pain after ischemic spinal injury proved to induce fewer side effects compared to the motor impairment and sedation caused by the other tested compounds.[72] The particular potential of DM in reducing the "wind up" phenomenon which transforms *acute* pain into *chronic* pain syndromes and its oral availability made DM an ostensibly attractive drug in *chronic* pain management.[2,55] In addition, DM has a higher therapeutic ratio than, for example, ketamine, endowing it with a high safety profile even in prolonged administrations.[7]

Two thirds (72/110) of the patients involved in experiments simulating *chronic* pain or individuals who were actually suffering from various *chronic* pain syndromes had no benefit from DM at various doses detailed in Table II. No experimental studies showed satisfactory effects of DM used alone on secondary pain in volunteers. A single dose of 30 or 45 of DM given to six volunteers partially attenuated the secondary temporal summation of pain induced by thermal stimuli,[42] while 100 mg given to eight healthy volunteers did not attenuate pain intensity induced by tourniquet ischemia to the hand, thermal stimuli or by topical capsaicin (a substance used for experimental induction of pain)[51] (Table II). When these latter eight volunteers were given 200 mg DM, they all suffered from substantial side effects with no beneficial analgesia, leading four of them to withdraw from the study. In another study of 10 volunteers who were given 90 mg before capsaicin was injected intradermally, DM caused severe side effects in five of them and, again, no beneficial effect in any of them.[4] In a burn injury study, when a single DM dose of 60 or 90 mg was given to 24 volunteers, it had only a slight inhibitory effect on the development of pinprick-induced hyperalgesia (Table II) but there still were some side effects.[40]

The result of the few double-blind humans studies of DM in *chronic* and in *neuropathic* pain showed it to be ineffective for the most part. Contrary to the conclusions reached by Wong *et al.*,[47] this review of the literature supports the contention that the low dose regimen is not the cause for DM ineffectiveness. Perhaps it is because of the small number of patients enrolled in most studies or, alternatively, because of the many side effects that provoked patients to withdraw. This latter issue can be related to DM given in higher than clinically applicable doses, as had been established in animal protocols (Table II). McQuay *et al.*[52] compared the analgesic effect of DM (40–80 $mg \cdot dy^{-1}$) to placebo and found no difference in *chronic neuropathic* pain perception over two phases of 10-dy^{-1} periods of surveillance.

TABLE II Clinical studies of dextromethorphan in experimental second pain and in chronic and neuropathic pain control.

Author, Reference Number, Year, Procedure	*Trial (Patients)*	*Dosage (mg, po), (Once#)/Duration*	*Coadjutant Drugs*	*Results; No. Pts. Effective/DM-Treated Pts.*	*Side Effects (Patients)*
Experimental pain					
Price *et al.*,[41] 1994 Electric shock & heat pulse	DB (Volunteers n = 6)	15,30, 45 alternate day	None	Reduced temporal summation of secondary pain; 6/6	Dizziness (n = 3), floating (n = 1)
Kauppila *et al.*,[51] 1995 Thermal stimuli + tourniquet ischemia + topical capsaicin + mechanical pressure	DB, PC, CO (Volunteers n = 8)	100 or 200 1-wk apart	none	No effect of either dose in all types of pain; 8/8	Diarrhea, dizziness, & clumsiness (n - 1), impaired alertness (n=8)*
Ilkjaer *et al.*,[40] 1997 Burn injury model	DB, R, PC, CO; (n = 24	60 *vs* 120/3d 1-wk apart	None	Reduced secondary Pinprick hyperalgesia§ only; 16/16	Dizziness, nausea, discomfort, drowsiness (frequent)
Kinnman *et al.*,[4] 1997 Capsaicin pain model	DB (n = 10 Volunteers)	90, duplicated 1-wk apart	None	No effect¶ 10/10	Dizziness (n = 4), nausea (n = 1)
Neuropathic & chronic pain					
McQuay *et al.*,[52] 1994 Neuropathic pain	DB, R, PC, CO(n = 19)	13.5 or 27tid/10d	Previous medications continued	No short- or long-term effect 12/12	Multiple (n = 9)†
Suzuki *et al.*,[54] 1996 Postherpetic neuralgia	CO (n = 25)	45 *vs* 90/14d	N/A	Reduced pain & allodynia; 9/25	Gastrointestinal (n = 8)
Klepstad *et al.*,[2] 1997 Postherpetic neuralgia	DB, CR (n = 1)	125 in 4 portions /d/7d	4y Ketamine stopped	Reduced pain 1/1	None
Nelson *et al.*,[55] 1997 Diabetic neuropathy Postherpetic neuralgia	CB, R, CO (n = 14) (n = 18)	Incremental mean doses/d 152 at wk 1 to 381 at wk 6 157 at wk 1 to 439 at wk 6	Previous analgesics continued	Reduced pain; 6/14 None; 18/18	Ataxia (n = 2), sedation (n=18), increased pain‡
Mercadante *et al.*,[53] 1998 Cancer pain	Open (n = 30)	30tid plus alternated 1 Coadjutant Drug /Group/ until deceased	Dextropropoxyphene 240/d or MO 60mg/d or 100/d. Previous therapy continued but not anti-cancer drugs	None; 30/30	Dry mouth (n = 17), drowsiness (n = 25), constipation (n = 5), confusion (n = 6), nausea/vomiting (n = 15)

DB = Double Blind Study; PC = Placebo Controlled; CO = Cross-over; R = Randomized; tds = 3 times/day; CR = Case Report; d = Day; wk = Week; y = Years; Pts. = Patients; N/A = Data Not Available.

All regimens involve the administration of a single dose unless otherwise specified.

*Side effects in the 200-mg treated patients, provoking also the withdrawal of four out of the eight subjects.

†Adverse reactions occurred in both low and high doses: drowsiness (n = 3), heartburn (n = 2), constipation (n = 2), tremor (n = 1), shakiness (n = 1), dizziness (n = 2), hot flushes (n = 2), urinary frequency (n = 1), tiredness (n = 1), rash (n = 1), increased pain (n = 5). Seven patients withdrew from study because of increased pain.

‡Withdrawal of one patient in the diabetic neuropathy group and five in the postherpetic neuropathy group because of intolerable pain.

§Dextromethorphan did not alleviate secondary hyperalgesia to stroke, primary hyperalgesia, pain during prolonged noxious heat stimulation, or heat pain detection threshold in undamaged skin.

¶Dextromethorphan resulted ineffective in unabated pain, von Frey stimuli, hypersensitivity to mechanical pressure or mechanical puncture, and/or changes in skin temperature.

Mercadante *et al.*[53] in an open study - the only one done on patients with cancer-related pain - also found no benefit from a similar dose of DM 30 mg three times a day combined with either dextropropoxyphene or morphine and added to a previous multi-drug therapy. Dextromethorphan at higher doses 45-125 mg·dy^{-1}) for 7-14 dy^{-1} in post-herpetic patients[2,54] (Table II) did alleviate pain in some of the patients, but evoked side effects. A much higher dose of DM, e.g., an incremental mean dose starting at 152 mg·dy^{-1} in the first week of treatment and reaching a dose of 381 mg·dy^{-1} at the sixth week given together with previous analgesic treatment to 14 patients with diabetic neuropathy (Table II), decreased the level of pain in only 24% of the patients.[55] A similar incremental dose trial, however, had no beneficial effect in a second group of 18 patients with postherpetic neuralgia. One patient from the first group and five from the second group were compelled to withdraw from the study because of intolerable side effects, while almost all of the other patients suffered from disturbing untoward effects (Table II). The discordant results in these two types of pathologies led the authors to suggest that NMDA antagonists could prevent neural arousal following ongoing noxious input due to ongoing damage, such as that which occurs in diabetic neuropathy, but not in the presence of "fixed" painful lesions, such as in postherpetic neuralgia. This and other explanations underline the complexity, heterogeneity and diversity of neural response in individual *chronic* pain syndromes.

Dextromethorphan and untoward effects in pain control (Tables I, II)

Dextromethorphan is considered to induce fewer side effects than other NMDA antagonists, partly because of its low affinity at its receptor site.[7] The clear picture of the incidence of side effects and their gravity is somewhat limited because six studies of the 21 retrieved and herein discussed did not recount their presence or did report the incidence.[39,40,44,45,48,49] Also, several authors attributed the occurrence of untoward side effects to DM, although identical events at similar rates were recorded for the patients who received a placebo.[50] A survey of the well-documented adverse side effects of DM in its clinical dosing (45-90 mg·dy^{-1} orally, Tables I and II) revealed that there were either no untoward effects[5,46] Weinbroum *et al.*, unpublished data, or two main types of side effects, i.e., gastrointestinal and neurological, which were, however, tolerable and characteristically infrequent at low doses.[7,41] Higher doses (Table I) were associated with a higher incidence of side effects.[39,49,50,54] For example, patients who were given 120 mg orally instead of 60 mg DM preoperatively suffered from side effects that were absent when the lower dose had been given.[49] Studies that had used DM parenterally (Table I) or DM doses >100 mg in a single dose reported a rate of side effects as high ≥50% of the participants, and they included even behavioral effects as well.[4,40,42,49,51,53] The lack of side effects in the study of Wu *et al.*[46] might be explained by the chlorpheniramine that they had administered to the patients preoperatively. However, the rate of side effects was minimal if a high dose was divided into smaller portions.[2] Of 181 neurosurgical patients at risk for cerebral injury that were given protective courses of medium-to high doses of DM (0.8 to 9.64 mg·kg^{-1}·dy^{-1}), 89 reported tolerable and reversible side effects, without severe adverse reaction.[73] In this unique and analytic study, the authors demonstrated that the incidence of side effects was related to dose (higher in patients who were given DM >5 mg·kg^{-1}), serum concentration (>400 ng·ml^{-1})l or brain concentration (>6000 ng·g^{-1}). The rate of side effects was also higher when dextrorphan, the active derivative, was found at high serum and brain concentrations. Interestingly, 55% of the patients that reported untoward effects were females compared with 45% males. Subjects in the age range of 26-40 yr had the highest rate. Importantly, a prolonged treatment and, consequently, a possible accumulative dose effect does not necessarily evoke severe side effects, as was shown after a period of two weeks where oral DM 45 or 90 mg was administered in postherpetic neuropathic patients[54] and as had been observed in patients with intractable seizures and Parkinson's disease after three weeks to three months of DM 30-180 mg·dy^{-1}.[30–32]

The rate of side effects also appears to be higher when a DM dose of only 60 mg is co-administered with drugs that can themselves cause side effects or in patients who already suffer from *chronic* pain. They can occur with considerable ferocity in a very high percentage of these patients (up to 100%) and cause patients to withdraw from participating in the studies.[52,53] In addition to nausea and vomiting, dizziness, hot flushing, drowsiness, heartburn, headache and other untoward but reversible side effects in patients with neuropathic pain, there were rare complaints of respiratory depression,[46] intolerable pain or the onset of new pain,[51–53,55] to the extent that patients withdrew from chronic pain studies. This latter rare exacerbation of pain that occurred in *chronic* pain syndromes in which DM was added to a pre-existing analgesic treatment, was suggested to be the result of DM sensitizing the central neurons or exacerbating the spinal interneurons' state of excitation instead of inhibiting pain response as was

shown in rats.[74,75] However, for obvious ethical reasons, DM cannot be used by itself while withholding daily treatment in *chronic* patients, especially in a double blind, placebo-controlled fashion.

Conclusions

Animal and clinical research indicate a beneficial role of NMDA receptor antagonists as part of multi-modal analgesic therapy, mainly for *acute* pain. For these patients, oral DM at doses of 30–90 mg appears to have an advantage over other antagonists in reducing the sensation of pain and sparing the requirement of conjointly administered analgesics, and has proven to have no or a low rate of untoward side effects. Further clinical trials, some currently now underway by the present authors, are still necessary to determine (1) the role of DM in various clinical pain-associated conditions, (2) the optimal clinical dose regimen that will considerably lower the rate of side effects, and (3) how long efficacious and safe treatment can be carried out both in *acute* and *chronic* pain syndromes.

Acknowledgment

The authors wish to thank Esther Eshkol for her editorial assistance.

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