

Dextromethorphan Mitigates Phantom Pain in Cancer Amputees

Ron Ben Abraham, MD, Nissim Marouani, MD, and Avi A. Weinbroum, MD

Background: Hyperexcitability of *N*-methyl-D-aspartate (NMDA) receptors may play a role in the persistence of phantom pain. Dextromethorphan (DM) blocks NMDA receptors.

Methods: Eight cancer and two noncancer amputees with established, disabling phantom pain received oral DM 60 or 90 mg twice daily (BID) in a three-period double-blind crossover placebo-controlled trial. This followed an open-phase trial in which either dose was given three times daily if pain relief during the double-blind phase was <50% of pretreatment intensity. Patients then underwent a 3-month phase of treatment with the best regimen and a subsequent 1-month posttreatment follow-up.

Results: All patients reported a >50% decrease in pain intensity, better mood, and lower sedation in each treatment phase. Four individuals reported this level of pain relief with the 60-mg and one with the 90-mg BID regimen during the double-blind phase, whereas two amputees benefited from the 60-mg and three from the 90-mg thrice-daily regimen in the open-phase trial. One reported exacerbation of pain with the 90-mg BID regimen, and three reported pain rebound at the 1-month posttreatment follow-up phase. Three patients stopped all previous analgesic use during the study.

Conclusions: Persistent phantom pain probably involves NMDA receptor hyperexcitability because DM 120 to 270 mg/day mitigated the pain satisfactorily.

Key Words: Pain—Phantom—NMDA receptor—Antagonist—Dextromethorphan.

Phantom pain is considered an abnormal sensation because it is perceived as coming from anatomical locations that no longer exist.¹ Although it was originally described as occurring after the amputation of a limb, it is also present after the amputation of other parts of the body, such as the breast.² It is reported to occur in up to two thirds of affected patients within the first 6 months after the amputation.³ In 5% to 10% of these patients, the pain is described as being severe, persistent, and disabling, as well as resistant to conventional therapy, such as paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), propoxyphene, or even morphine.² Various means for the attenuation of phantom pain have been attempted, among them different anesthetic approaches,

surgical ablative therapies, or intrathecal stimulatory delivery systems, but they have often failed to provide satisfactory pain relief.^{4,5}

The underlying pathophysiology of this unique chronic pain syndrome remains obscure, with both peripheral and central neural mechanisms having been implicated.⁶ There is some evidence that excitability of the dorsal horn neurons⁷ is partly mediated by excitatory amino acids acting at the *N*-methyl-D-aspartate (NMDA) receptor sites, which, if antagonized, may block this central excitability and its clinical manifestations.⁸ This is because spinal NMDA receptors cause amplification and facilitation of pain transmission toward higher centers,⁹ and their blockade was shown to have alleviated the sensations of somatic and neuropathic pain in both animal and human models.^{9,10} Ketamine, a highly competitive NMDA-receptor antagonist, was reported to reduce spontaneous pain in phantom pain,¹¹ but it has not gained much clinical popularity because of its only parenteral route of administration and frequent dissociative side effects. Recent studies with other NMDA receptor antagonists also failed to demonstrate their having effectiveness in chronic pain syndromes.^{12,13}

Received August 7, 2002; accepted October 28, 2002.

From the Post-Anesthesia Care Unit and Acute Pain Service, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

Address correspondence and reprint requests to: Avi A. Weinbroum, MD, Post-Anesthesia Care Unit, Tel-Aviv Sourasky Medical Center, 6 Weizman Street, Tel Aviv 64239, Israel; Fax: 972-3-692-5749; E-mail: draviv@tasmc.health.gov.il.

Published by Lippincott Williams & Wilkins © 2003 The Society of Surgical Oncology, Inc.

Dextromethorphan (DM), a noncompetitive NMDA receptor antagonist, was recently shown to be capable of attenuating and even inhibiting nociceptive stimuli.¹⁴ Its application for the relief of phantom pain has not been previously reported. This investigation was conducted under the hypothesis that if phantom pain involves a central mechanism of activity, then oral DM might affect it by blocking NMDA receptors.

PATIENTS AND METHODS

Patient Selection

Adult patients with postamputation phantom limb pain were recruited from the Tel Aviv Sourasky Medical Center's Acute Pain Service (APS) between January and June 2001. Because of the highly subjective nature of pain and to control for confounding elements, the exclusion criteria for this study were especially stringent: they included a history of psychiatric or severe pulmonary, cardiovascular, or renal disease; metastatic cancer; brain tumor; and phantom sensations other than pain. The candidates were also evaluated psychologically, neurologically, and metabolically in addition to undergoing a thorough physical examination and imaging evaluations to rule out any possible treatable physical or metabolic causes of pain. Inclusion criteria were severe or disabling phantom pain that persisted for at least 1 month despite extensive antinociceptive therapy (Table 1) that, because most individuals were postcancer patients, adhered to the World Health Organization three-step analgesic ladder: NSAIDs (including the new cyclo-oxygenase 2 inhibitors), mild opioids (codeine, buprenorphine, or tramadol), and opioids for severe pain (controlled-release mor-

phine, immediate-release morphine, fentanyl patch, or oxycodone). Adjuvants (e.g., antidepressants or anti-convulsants) or regional blocks were added whenever suitable. The candidates who fulfilled the entry criteria signed an informed consent that, together with the study format, had been approved by the Institutional Helsinki Committee.

Drug Treatment

The study consisted of a three-phase study: a double-blind phase, an open-design phase, and a 3-month treatment phase. The first phase had a three-period double-blind crossover design with placebo as the control medication, followed or not by the second open phase (see below). A physician who was not involved in the study prepared the batches of medication and their order of administration. The three double-blind regimens consisted of sucrose-based placebo or identical capsules of DM 60 or 90 mg administered twice daily. Following the design of a previous study,¹⁵ each of the three regimens was prescribed for 10 days when the patients returned to the APS for physical examination and submitted their written daily reports. At the end of the 30 days, the patient's best drug regimen according to the self-evaluated pain intensity score (see below) was recorded. When neither of the double-blind DM regimens decreased pain intensity by >50% (as judged by the patients' self-rated scores), the patient's regimen was changed to an open phase in which DM 60 mg and then 90 mg three times daily (TID) were prescribed for 10 days each. A negative result during this phase would have excluded the patient from further DM treatment. Effectiveness of one of the

TABLE 1. Prestudy analgesic treatment

Patient No.	Sex/age (y)	Analgesics and duration of treatment (oral administration unless otherwise indicated)
1	M/31	Paracetamol, dipyrrone, diclofenac (PR), oxycodone, MIR, MCR, fentanyl patch, amitriptyline, clonazepam, regional block (2 mo)
2	F/41	MO-IV PCA, MCR, MIR (days 1-7 after surgery No. 2), ketamine + MO-IV PCA, oxycodone (days 8-10 after the second operation), NSAIDs, MCR, MIR, tramadol, perphenazine, propranolol, gabapentin (day 11 after surgery onward)
3	M/74	Paracetamol + codeine + dipyrrone, rofecoxib, oxycodone + aspirin, buprenorphine (IV), fentanyl patch, propranolol, gabapentin, acupuncture, repeated psoas blocks (6 wk after second surgical procedure)
4	M/33	Dipyrrone, NSAIDs, MO-IV PCA, meperidine (IM), MIR, MCR (40 d)
5	F/52	Dipyrrone, NSAIDs, MIR, benzodiazepines, amitriptyline, clonazepam, sodium valproate, carbamazepine, clomipramine, mexiletine, hypnosis, gabapentin, oxycodone, anticyclo-oxygenase 2 (3 mo)
6	F/62	Paracetamol, dipyrrone, NSAIDs, MO-IV PCA, clonazepam, sodium valproate, carbamazepine (45 d)
7	M/38	Paracetamol, dipyrrone, NSAIDs, MCR, MIR, clonazepam, amitriptyline, sodium valproate (6 mo)
8	F/64	Dipyrrone, paracetamol, NSAIDs, MIR, MCR, fentanyl patch, amitriptyline, clonazepam, gabapentin, anticyclo-oxygenase 2, sodium valproate, carbamazepine, acupuncture, hypnosis (10 mo)
9	M/53	Dipyrrone, NSAIDs, MIR, benzodiazepines, amitriptyline, clonazepam, carbamazepine (2 mo)
10	F/48	Dipyrrone, paracetamol, NSAIDs, MIR, MCR, fentanyl patch, amitriptyline, gabapentin, continuous epidural block (1 mo)

MIR, morphine immediate release; MCR, morphine controlled release; MO, morphine; PR, rectally; IV, intravenous; PCA, patient-controlled analgesia; NSAIDs, nonsteroidal anti-inflammatory drugs; IM, intramuscularly.

DM regimens in one of the study phases determined what the patient's regimen would be for the next 3 months of treatment; all patients were under 1-month follow-up after drug administration was terminated.

The DM 60- and 90-mg doses were similar to those that had been used in other clinical studies.¹⁴⁻¹⁶ Because DM at a single dose >100 mg was reported to be associated with a >50% increase in the incidence of side effects and had caused patients to withdraw from the studies,¹⁵ this study protocol imposed an ethical constraint to use DM <100 mg per dose. Also, for ethical reasons, no drugs that the patients had been taking previously were stopped unless they felt well enough to taper their use on their own initiative.

Pain and Other Subjective Measures

Each patient compiled a report during each phase of the investigation; the report was based on a visual analog scale at the time of compiling it. The primary outcome measure was the subjective pain intensity score at the time of compiling the report; it ranged from 0 (no pain) to 100 (unbearable pain). The subjectively scored sedation level ranged from 0 (none) to 100 (overwhelming tiredness), whereas the state of well-being ranged from 0 (sad) to 100 (content).

In addition, patients were asked to record any adverse effects that they had not experienced before entering the study. The patients' pre-experimental mean scores (rated 3 times a day) were an average of 10 consecutive evaluations of pain, feeling, and sedation. The scores rated during each of the 10-day treatment periods (during either the double-blind or the open study phases) are the average of those recorded over days 2 to 10. The evaluations performed on the first day were omitted to exclude any possible effect of the previous treatment or that

of transition from one drug regimen to another. The 3-month treatment scores, as well as those rated during the 1-month follow-up, were rated by the patients once daily and were then averaged.

Statistics

The analyses were performed with SPSS for Windows, version 9 (SPSS Inc., Chicago, IL). The background characteristics of the study groups were compared by using the unpaired *t*-test. The paired *t*-test was used to evaluate differences and changes in the crossover data among the patients. Comparisons of the patients' self-reported scores used the one-way analysis of variance with repeated measures. All values are expressed as mean \pm SD, with significance defined as $P < .05$.

RESULTS

Of the 45 patients who were referred by the APS to participate in this study, 10 (mean age \pm SD, 50 \pm 14 years) fulfilled entry criteria; all but 2 (patients 3 and 4) had undergone limb amputation because of cancer. Tables 1 and 2 list their relevant data, medical history, and previous medications. Phantom pain appeared only after a minor surgical intervention but not after the amputations themselves in six of our amputees (patients 1-4, 6, and 10). Two patients (patients 1 and 3) reported experiencing stump hyperalgesia triggered by slight pressure or scratching in addition to the persistent phantom pain.

The patients' self-evaluations during the double-blind phase of the study are reported in Fig. 1, whereas data pertaining to the open and 3-month phases are reported in Table 3. All the patients were able to return to ordinary simple activities of daily living during the 3-month best-

TABLE 2. Patients' physical and medical data

Patient No.	Diagnosis: amputation pattern	Phantom pain characteristics	Amputation-to-pain interval	Pain-to-study interval
1	Scapular and humerus osteosarcoma: FQA	Burning sensation in fingers; stump hyperalgesia	1.5 y	2 mo
2	Humerus schwannoma: FQA; 14 mo later, lung biopsy	Pain of arm and burning sensation of elbow	14 mo	1 mo
3	Buenger's disease: AKA; 7 y later, wound plastic repair	Burning and itching pain at knee and toes; stump hyperalgesia	7 y	18 mo
4	Crush injury of tibia and fibula: BKA	Ankle pain	1 mo	40 d
5	Femur osteosarcoma: AKA	Knee pain	13 mo	3 mo
6	Humerus osteosarcoma: FQA	Forearm pain	3 y	45 d
7	Humerus osteosarcoma: FQA	Burning sensation of digits	2 y	6 mo
8	Humerus osteosarcoma: FQA	Burning sensation of humerus	1.5 y	1 y
9	Femur single meta (hypernephroma): disarticulation	Knee pain	9 mo	2 mo
10	Femur osteosarcoma: AKA	Knee pain	2 mo	1 mo

FQA, forequarter amputation; AKA, above-knee amputation; BKA, below-knee amputation.

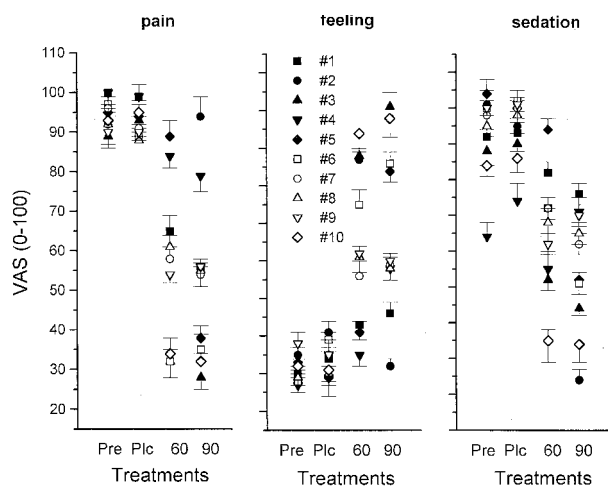


FIG. 1. Patients' self-rated subjective evaluation. The data represent the means \pm SD of the self-reported visual analog scale (VAS) of each patient during each of the three double-blind treatment regimens and prestudy period. The patients' pre-experimental values (Pre) are the average of 10 consecutive evaluations of pain, feeling, and sedation. The data during each treatment regimen (Plc, placebo; 60 and 90, 60 and 90 mg of dextromethorphan twice daily) are the average of those recorded over days 2 to 10 of the double-blind phase. The evaluations performed on the first day were omitted to exclude any possible effect of the previous treatment or that of transition from one drug regimen to another.

regimen treatment phase, and patients 4 and 10 were even capable of participating in a rehabilitation program.

Double-Blind and Open Study Phases

Pain Score

Overall, all the patients reported a $>50\%$ pain reduction from the use of DM. In the double-blind phase of the study (Fig. 1, left column), four patients (patients 2, 3, 6, and 10) achieved their best pain reduction with the 60-mg regimen, and one patient (patient 5) required 90 mg to achieve this level ($P = .01$ compared with the pretreatment or placebo scores). Patient 2 showed a paradoxical dose-response relationship (i.e., intensification of pain) with the DM 90-mg double-blind regimen.

Five patients reverted to the open phase study: two (patients 8 and 9) reported satisfactory benefit from 60 mg TID, and three patients (patients 1, 4, and 7) reported satisfactory benefit from 90 mg TID ($P < .05$ compared with double-blind phase values). All patients concluded their 3-month treatment with the best DM regimen. Three patients (patients 1, 5, and 10) were even able to stop completely their previous daily analgesics while under this phase of study; another four individuals reduced their use partially. Inclusive data analyses indicated no correlation between the best dose regimen in

each of the treated patients and the cause of pain; with the time interval between surgery and pain appearance; or with the time that had elapsed between the first pain appearance and the time DM was first administered.

Sedation Score

Sedation was reported as being significantly ($P = .01$) lower under both DM regimens compared with placebo or the levels before treatment (Fig. 1, right column). The lower sedation score in patient 2 (when DM 90 mg TID was administered) was presumably due to the 90-mg-induced pain exacerbation noted previously. The scores in the patients who reverted to the open study (Table 3) were better than the ones obtained during the double-blind phase ($P < .05$).

Feeling of Well-Being Score

Treatment by DM yielded significantly ($P = .025$) better scores in the double-blind phase compared with placebo or the pretreatment period in all patients (Fig. 1, middle column). The five patients (patients 1, 4, and 7-9) who reverted to the open study, although they reported low feelings of well-being (<40) during the double-blind study (Fig. 1), self-rated their well-being >70 ($P < .05$) during the open-phase study (Table 3). The low scores (21 ± 3) of patient 2's feeling of well-being during the double-blind phase reflected her pain perception (see previously); these represented the only untoward side effect reported by the patients during either study phase.

The 3-Month Treatment Phase and the Poststudy Follow-Up Data

None of the patients withdrew from the study, and all continued treatment with the identified best drug regimen for 3 months, noting satisfaction with it on their self-rated reports (Table 3). Pain intensity, sedation, and subjective well-being scores at the end of the 1-month time that followed the cessation of DM treatments were slightly lower but did not reach statistical significance compared with those rated during the time pain was satisfactorily controlled (either during the double-blind or open-study phase) in seven of the patients (Table 3). Three patients (patients 1, 3, and 8) reported intensification in pain sensation ($P < .05$), although it was still significantly ($P < .05$) below pretreatment scores; at this time, patients 1 and 8 resumed the use of NSAIDs. No side effects were recorded for any of the patients throughout drug treatment and during the 1-month follow-up.

TABLE 3. Patients' self-rated visual analog scale scores during the open and the 3-month treatment study phases and during the 1-month follow-up (mean \pm SD)

Patient No.	Open study phase			3-mo treatment phase			1-mo follow-up		
	Pain	Feeling	Sedation	Pain	Feeling	Sedation	Pain	Feeling	Sedation
1	32 \pm 3	70 \pm 5	52 \pm 5	37 \pm 4	68 \pm 5	50 \pm 6	79 \pm 6	49 \pm 5	52 \pm 5
2				41 \pm 3	70 \pm 4	36 \pm 4	42 \pm 4	61 \pm 5	42 \pm 4
3				34 \pm 5	74 \pm 3	41 \pm 4	71 \pm 5	59 \pm 3	45 \pm 4
4	36 \pm 4	70 \pm 2	51 \pm 3	33 \pm 4	66 \pm 3	55 \pm 6	44 \pm 5	48 \pm 4	51 \pm 5
5				42 \pm 4	75 \pm 5	39 \pm 5	46 \pm 5	66 \pm 5	47 \pm 4
6				39 \pm 3	80 \pm 6	34 \pm 6	43 \pm 3	75 \pm 4	41 \pm 4
7	40 \pm 2	79 \pm 5	48 \pm 2	42 \pm 5	76 \pm 5	53 \pm 5	48 \pm 6	61 \pm 4	49 \pm 6
8	41 \pm 3	80 \pm 4	49 \pm 3	44 \pm 5	76 \pm 4	46 \pm 4	78 \pm 5	67 \pm 5	41 \pm 5
9	39 \pm 3	78 \pm 3	41 \pm 4	37 \pm 5	79 \pm 5	44 \pm 5	47 \pm 4	66 \pm 4	48 \pm 4
10				37 \pm 3	84 \pm 6	31 \pm 4	41 \pm 3	75 \pm 5	39 \pm 5

The data during each phase were calculated as were the data in Fig. 1.

DISCUSSION

This study investigated the usefulness of oral DM, an NMDA antagonist, in reducing phantom pain associated with limb amputation. This sometimes severe and debilitating pain syndrome, which is known to resist conventional (and nonconventional) pain treatment, did respond favorably to DM, even to the point of enabling 3 of the 10 study patients to stop completely the use of their previous medications during the time they received DM. Oral DM at daily doses of 120, 180, or 270 mg was subjectively effective in relieving pain without adverse side effects and in maintaining good levels of wakefulness and status of well-being for almost 4 months. Post-treatment pain recurred in one third of the study group, albeit at a lower intensity than before the study.

It was originally reported that phantom pain appears immediately after amputation,³ but a later study showed that there is usually a short period of latency from the time of amputation.¹ Although our patients had experienced preoperative pain and some were understandably anxious because they had been diagnosed as having cancer, we could not conclude whether the level of pain was related to the degree of perioperative psychological distress, as suggested previously,^{3,17} because of the small number of patients involved.

Six of the study patients had first complained of phantom pain after they had undergone a minor surgical procedure, with the limb amputation having been performed months to years earlier; one of them also experienced local hyperalgesia (Table 1). It is possible that the second and minor surgical procedure that preceded the advent of this painful syndrome reignited a silent state of hyperexcitability and wind-up conditions within the central nervous system that had been established but not activated by the amputation in our four patients. Pain sensations that followed the later operation could have

transformed the latent hyperexcitability state into an active state in response to peripheral sensory nerve stimulation that had not heretofore evoked overt hyperactivity within the spinal cord. Once silent synapses had been activated by tissue or nerve injury, they would remain functionally active and continue to send messages to the brain even when there was no actual anatomical structure that could be receiving a painful stimulus. Glutamate is one of the excitatory amino acids involved in the activation of NMDA receptors, which further supports the effectiveness of DM in attenuating pain within the present clinically acceptable dose range. DM thus reduced the central hyperexcitability and the subsequent secondary wind-up phenomenon by means of its antagonistic activity at the NMDA receptor sites of activity.

DM does not always lead to satisfactory results¹⁸: several studies on chronic pain described partial or total ineffectiveness after the use of DM in a wide range of doses. McQuay et al.¹⁵ compared the analgesic effect of DM (40–80 mg/day) with that of placebo and found no difference in chronic neuropathic pain perception over two phases of 10-day periods of surveillance. Mercadante et al.,¹⁹ in an open study—the only previous one performed on patients with cancer-related pain, also found no benefit from a dose of DM 30 mg TID combined with either dextropropoxyphene or morphine and added to a previous multidrug therapy. Because these doses might be considered too low, our protocol called for higher doses of DM and combined both a double-blind phase, in which dose responsiveness can be reliably tested, and an open phase, to enable individually adjustable dosing. Regimens <100 mg per dose were also chosen because DM at higher doses (e.g., 125 mg per dose for 7–14 days) in postherpetic patients alleviated pain in only some of them but evoked disturbing untoward effects.^{16,20,21} Moreover, much higher incremental

dose regimens (up to 381 mg/day) in 14 patients with diabetic neuropathy decreased the level of pain in only 24% of the patients²⁰ but had no beneficial effect in patients with postherpetic neuralgia. This raised the possibility that NMDA antagonists could prevent the neural arousal that accompanies chronic ongoing noxious tissue damage (e.g., in diabetic neuropathy) but not of fixed painful lesions (e.g., in postherpetic neuralgia). It is not yet clear to which of these two major types of chronic pain phantom pain best relates: its characteristics indicate that it is similar to the fixed-pain type, but its not starting until sometime after the amputation and its variable response to DM might indicate a possible fit (at least in some of the cases) into chronic ongoing tissue-damage syndromes.

This latter categorization and the above-mentioned contention of an ongoing process of central hyperexcitability could explain patients' experiencing intolerable pain or the onset of new pain.^{15,19–21} The rare phenomenon of pain exacerbation was previously reported in patients with chronic pain syndromes: DM was added to a pre-existing analgesic treatment, and increased pain was suggested as being the result of DM sensitizing the central neurons or exacerbating the spinal interneurons' state of excitation instead of inhibiting pain response, as had been shown in rats.^{22,23} Despite the small number of patients enrolled in this study, those who reported secondary hyperalgesia before the study also reported pain intensification when they were interviewed 1 month after the test drug was discontinued. This could have occurred because of a state of neural pain transmission system sensitization that existed even before the study; as soon as the NMDA receptors' sensitizing activity was no longer antagonized (as during the 1 month after DM was stopped), hyperexcitability returned to its "high-voltage" activity, i.e., the pain sensation rebounded.

Although the overall self-rated sedation level did not change to a similar magnitude as was observed for pain, it was significantly lower as compared with the placebo and with the pretreatment levels of sedation. This result is interesting because it reiterates our previous findings of DM being safe in the herein-used dose ranges²⁴ compared with higher doses used in patients with neuropathic pain.^{16,20} Higher doses could contribute to deeper levels of sedation by affecting the central NMDA receptors that were shown to regulate vigilance²¹ and behavior. This central effect could modulate feelings of well-being that, in association with the better physical feeling, contributed to such subjective judgment. Finally, it is possible that patients' reducing the dosages of their previous analgesics could also contribute to their rating the level of sedation lower than before.

Limitations of DM treatment are dose dependent and are not associated with the duration of the administration.²⁵ Indeed, except for one patient, who exhibited accentuated pain sensation when first given the 90-mg (but not the 60-mg) dose, none of the individuals experienced any untoward event even after approximately 4 months of DM. Doses of DM >100 mg per dose were reported to accentuate pain and to induce hallucinations and drowsiness in acute or chronic neuropathic pain patients.^{15,16,21,26,27} Although these events sometimes followed DM that was concomitantly administered with high doses of other analgesics, it is also noteworthy that the neural plasticity and response to DM that accompany neuropathic pain are probably different from the present pain (see previously),^{1,2} so it cannot be excluded that the herein-used dosages are indeed below the minimally effective antagonism dose of the central NMDA receptors.

In conclusion, oral DM 120 to 270 mg/day was effective in reducing phantom pain by >50% and did so with no side effects. Further clinical trials are still necessary to refine our understanding of the mechanisms involved and to delineate the best therapeutic regimen of DM that would provide consistent and predictable phantom pain attenuation.

ACKNOWLEDGMENTS

The acknowledgments are available online at www.annalsurgicaloncology.org.

REFERENCES

1. Devor M. The pathophysiology of damaged peripheral nerves. In: Wall PD, Melzack R, eds. *Textbook of Pain*. 3rd ed. London: Churchill Livingstone, 1994:79–100.
2. Melzack R. Phantom limb pain. *Anesthesiology* 1971;35:409–19.
3. Bach S, Noreng MF, Tjelliden NU. Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. *Pain* 1988;33:297–301.
4. Danshaw CB. An anesthetic approach to amputation and pain syndromes. *Phys Med Rehabil Clin North Am* 2000;11:553–7.
5. Nikolajsen L, Jensen TS. Phantom limb pain. *Curr Rev Pain* 2000;4:166–170.
6. Jensen TS, Krebs B, Nielsen J, Rasmussen P. Immediate and long-term phantom limb pain in amputees: incidence, clinical characteristics and relationship to pre-amputation pain. *Pain* 1985; 21:267–78.
7. Woolf CJ, Wall PD. The relative effectiveness of C primary afferent fibres of different origins in evoking a prolonged facilitation of the flexor reflex in the rat. *J Neurosci* 1986;6:1433–43.
8. Ren K, Hylden JL, Williams GM, et al. The effects of a non-competitive NMDA receptor antagonist, MK801, on behavioral hyperalgesia and dorsal horn neuronal activity in rats with unilateral inflammation. *Pain* 1992;50:331–44.
9. Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation: implications for the treatment of post-injury pain hypersensitivity states. *Pain* 1991;44:293–9.

10. Eisenberg E, Pud D. Can patients with chronic neuropathic pain be cured of dextromethorphan in pain control. *Pain* 1998;74:337-9.
11. Nikolajsen L, Hansen CL, Nielsen J, et al. The effect of ketamine on phantom pain: a central neuropathic disorder maintained by peripheral input. *Pain* 1996;67:69-77.
12. Nikolajsen L, Gottrup H, Kristensen AG, Jensen TS. Memantine (a N-methyl-D-aspartate receptor antagonist) in the treatment of neuropathic pain after amputation or surgery: a randomized, double-blinded, cross-over study. *Anesth Analg* 2000;91:960-6.
13. Gottschalk A, Schroeder F, Ufer M, Oncu A, Buerkle H, Standl T. Amantadine, a N-methyl-D-aspartate receptor antagonist, does not enhance postoperative analgesia in women undergoing abdominal hysterectomy. *Anesth Analg* 2001;93:192-6.
14. Weinbroum AA, Gorodezky A, Niv D, et al. Dextromethorphan attenuation of postoperative pain and primary and secondary thermal hyperalgesia. *Can J Anaesth* 2001;48:167-74.
15. McQuay HJ, Carroll D, Jadad AR, et al. Dextromethorphan for the treatment of neuropathic pain: a double-blind randomized controlled crossover trial with integral n-of-1 design. *Pain* 1994;59:127-33.
16. Ilkjaer S, Dirks J, Brennum M, Dahl JB. Effect of systemic N-methyl-D-aspartate receptor antagonist (dextromethorphan) on primary and secondary hyperalgesia in humans. *Br J Anaesth* 1997;79:600-5.
17. Angrilli A, Koster U. Psychophysiological stress responses in amputees with and without phantom limb pain. *Physiol Behav* 2000;68:699-706.
18. Ben-Abraham R, Weinbroum AA. Dextromethorphan in chronic pain: a disappointing update. *Isr Med Assoc J* 2000;2:708-10.
19. Mercadante S, Casuccio A, Genovese G. Ineffectiveness of dextromethorphan in cancer pain. *J Pain Symptom Manage* 1998;16:317-22.
20. Nelson KA, Park KM, Robinovitz E, Tsigos C, Max MB. High dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. *Neurology* 1997;48:1212-8.
21. Kauppila T, Gronroos M, Pertovaara A. An attempt to attenuate experimental pain in humans by dextromethorphan, an NMDA receptor antagonist. *Pharmacol Biochem Behav* 1995;52:641-4.
22. Tal M, Bennet G. Dextrophan relieves neuropathic heat-evoked hyperalgesia in the rat. *Neurosci Lett* 1993;151:107-10.
23. Sugimoto T, Bennett G, Kajander K. Transsynaptic degeneration in the superficial dorsal horn after sciatic nerve injury: effects of chronic constriction injury, transection, and strychnine. *Pain* 1990;42:205-13.
24. Weinbroum AA. Dextromethorphan reduces immediate and late postoperative analgesic requirements and improves patients' subjective scorings after epidural lidocaine and general anesthesia. *Anesth Analg* 2002;94:1547-52.
25. Weinbroum AA, Rudick V, Paret G, Ben-Abraham R. The role of dextromethorphan in pain control. *Can J Anaesth* 2000;47:585-96.
26. Henderson DJ, Withington BS, Wilson JA, Morrison LM. Perioperative dextromethorphan reduces postoperative pain after hysterectomy. *Anesth Analg* 1999;89:399-402.
27. Suzuki T, Kato J, Saeki S, Ogawa S, Suzuki H. Analgesic effect of dextromethorphan for postherpetic neuralgia (in Japanese). *Masui* 1996;45:629-33.