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A pilot study of dextromethorphan in naloxone-precipitated opiate withdrawal

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Abstract

Dextromethorphan and its metabolite dextrorphan antagonize *N*-methyl-D-aspartate (NMDA)-mediated activity in pre-clinical studies. We examined dextromethorphan's effects on naloxone-precipitated opiate withdrawal in opiate-dependent subjects stabilized on 25 mg of methadone. Subjects received challenges on three different days with 0.4 mg of intramuscular naloxone. Pretreatment 1 h before naloxone was with dextromethorphan in a double-blind, balanced, randomized design with either placebo, dextromethorphan 60 mg, or dextromethorphan 120 mg for six subjects; and placebo, dextromethorphan 120 mg, or dextromethorphan 240 mg for five subjects. There was considerable inter-individual variability in the response to dextromethorphan, but no net attenuation by dextromethorphan on any withdrawal measure assessed. Two of three subjects detoxified from methadone with dextromethorphan 60 mg orally every 4 h demonstrated considerable withdrawal.

Keywords: Dextromethorphan; Opiate; Withdrawal; Naloxone; Excitatory amino acid

1. Introduction

Excitatory amino acid receptor antagonists can block the development of opiate dependence and tolerance (Trujillo and Akil, 1991). Glutamatergic pathways are involved in the expression of withdrawal (Rasmussen and Aghajanian, 1989), and glutamate levels are increased after opiate antagonist administration to morphine-treated rats (Aghajanian et al., 1994). Several excitatory amino acid receptor antagonists, after single doses, attenuate naloxone-precipitated opiate withdrawal including, MK-801 (Higgins et al., 1992), kynurenic acid (Rasmussen et al., 1991), and ketamine (Koyuncouglu et al., 1990). Single doses of the over-the-counter anti-tussive dextromethorphan dose dependently suppressed naloxone-precipitated opiate withdrawal in rats, with near elimination of withdrawal at the higher dose (Koyuncouglu et al., 1990).

In vitro, dextromethorphan decreases activity thought to be mediated by excitatory amino acids: epileptiform activity (Apland and Braitman, 1990), *N*-methyl-D-aspartate (NMDA)-induced convulsions (Ferkany et al., 1988), ischemic neuronal cell death (Steinberg et al., 1991) and NMDA bath-induced neuronal cell death (Choi et al., 1987). Inhibition of excitatory amino acid activity by dextromethorphan might reflect an effect at a non-NMDA receptor. Non-opioid anti-tussives bind to specific high affinity central binding sites (Musacchio et al., 1988) which appear to be related to σ receptors structurally (Klein and Musacchio, 1989) and functionally (Kamei et al., 1993). The anticonvulsant effects of other agents acting at these binding sites do not appear to be directly NMDA-mediated (Apland and Braitman, 1990). These binding sites might mediate dextromethorphan's reported inhibition of glutamate release from rat hippocampal slices (Annels et al., 1991).

Dextromethorphan undergoes hepatic *O*-demethylation to dextrorphan. Unlike dextromethorphan, dextrorphan's pharmacological activity appears to be primarily at the NMDA receptor. Dextrorphan inhibits NMDA receptor-mediated activity in several in vitro models at least as potently as dextromethorphan does (Choi et al., 1987; Ferkany et al., 1988; Aram et al., 1989), but dextrorphan does not bind to the high-affinity dextromethorphan binding site which is thought to mediate dextromethorphan's pre-synaptic effect (Tortella et al., 1989). Dextromethorphan binds to NMDA binding sites labeled by dextrorphan

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with 10-fold lower affinity than dextrorphan (Franklin and Murray, 1992).

Dextromethorphan has shown promise in a randomized clinical trial of 48 heroin addicts undergoing detoxification (Koyuncouglu and Saydam, 1990). Dextromethorphan (360 mg/day in divided doses) with adjunctive diazepam had considerably greater retention and efficacy than a chlorpromazine and diazepam combination. However, this study was confounded by a high dropout rate, use of several psychoactive medications, and other methodological difficulties. In contrast to the Koyuncouglu and Saydam (1990) study, Isbell and Fraser (1953) found no attenuation by two 90 mg doses of either oral or subcutaneous dextromethorphan on the abstinence syndrome after the abrupt withdrawal of maintenance morphine (120–300 mg per day). Five other subjects stabilized on 60 mg of morphine four times a day showed the same total-withdrawal severity when dextromethorphan (75–100 mg subcutaneously) was substituted for morphine as when no substitution was made. The 120 mg morphine maintenance dose is equivalent to at least 60 mg of methadone daily (Jasinski et al., 1977). It is possible an attenuation of withdrawal would be *measurable* if subjects were withdrawn from lesser levels of opioid dependence than in the Isbell and Fraser (1953) study, or that an effect on specific withdrawal signs would be observed that was not reported in their study.

We examined the effects of dextromethorphan on specific signs of naloxone-precipitated opiate withdrawal in subjects stabilized on 25 mg of methadone. Six subjects were assigned in a balanced randomized design to double-blind pretreatment 1 h before intramuscular naloxone 0.4 mg with either placebo, dextromethorphan 60 mg, or dextromethorphan 120 mg. An additional five subjects were subsequently randomized to placebo, dextromethorphan 120 mg, or dextromethorphan 240 mg. The 1 h dextromethorphan-naloxone interval was based on dextromethorphan's rapid oral absorption, and anti-tussive effect within 15–30 min after oral administration (McEvoy, 1990).

2. Materials and methods

2.1. Subjects

Eleven subjects gave written informed consent and were paid to participate in this inpatient study. Age ranged from 28 to 43 years and seven were male. Seven were Caucasian, and four were Black. Subjects were told that the purpose of the study was to determine the effects of dextromethorphan on the response to naloxone in opiate-dependent individuals. Prior to enrollment, subjects had a screening physical examination and laboratory testing, including complete blood count with differential, thyroid function tests, liver function tests, serum pregnancy test when appropriate, electrocardiography, urinalysis, urine toxicology testing (Enzyme Multiplied Immunoassay Technique), and serum glucose, electrolyte, blood urea nitrogen, and creatinine levels. Three HIV seropositive subjects were enrolled. Subjects B and F were not on any adjunctive medication; subject E was in the middle of a ten day course of Penicillin for a dental infection at the time of the challenges, and was maintained on azathioprine 100 mg, four times daily. The subjects' absolute CD4 + counts (/μl) were 513 (E), 912 (B), and 1076 (F). Subjects E and F were each in the process of detoxification from methadone maintenance and had been stabilized at 25 mg daily prior to study participation (F for 17 + days). Other subjects had no evidence of serious medical, neurological, or psychiatric illness.

All non-methadone maintenance subjects had positive urine toxicologies (Enzyme Multiplied Immunoassay Technique) for opioids upon admission and met DSM-III-R criteria for Opiate Dependence. Duration of heroin use ranged from 1.5 to 24 years. Two subjects used intranasal heroin and nine were intravenous users. Concurrent drugs of abuse reported by subjects during the 30 days prior to admission were cocaine ($n = 10$), cannabinoids ($n = 1$), benzodiazepine ($n = 1$), and amphetamine ($n = 1$).

Subjects were stabilized on methadone 25 mg orally each morning and clonidine and oxazepam as needed for residual withdrawal symptoms. Naloxone challenges began after subjects denied any subjective withdrawal for at least one day without oxazepam or clonidine. Methadone stabilization ranged from four to 14 days.

2.2. Experimental procedure

Dextromethorphan powder (Spectrum; Gardenia, CA, USA) was dissolved in wild cherry syrup and ethyl alcohol to a solution of 4.1% alcohol and either 30 mg or 60 mg per 5 ml solution. Subjects fasted after midnight prior to challenges. Sixty minutes prior to naloxone, subjects received placebo, dextromethorphan low dose, or dextromethorphan high dose. An intramuscular injection of 0.4 mg of naloxone was given at approximately 10:00 a.m. Opiate withdrawal was rated by dextromethorphan condition-blind raters on a 15-item observer-rated scale derived from the Wang scale (Wang et al., 1974). Items were rated on a scale of 1 (none), 2 (mild), 3 (moderate), 4 (severe), or 5 (extremely severe). For eight items, observers asked questions of the subjects regarding restlessness, anxiety, muscle aches, anorexia, abdominal cramps, nausea, hot/cold feelings, and craving. Seven items were based solely on observation: rhinorrhea, perspiration, yawning, goose flesh, tremors, vomiting, and tearing. Blood pressure and pulse were measured automatically (Dinamapp) and respirations were counted by observation. Subjects received their regular morning methadone dose after 30 min. The above data was collected immediately prior to dextromethorphan administration, immediately prior to naloxone administration, and every five min after naloxone

administration. Data collection continued until +30 min in the first seven subjects, and until +60 min in four of the Pla-120-240 subjects. The Profile of Mood States (POMS) (McNair et al., 1971; Fischman et al., 1990) was completed before the dextromethorphan was given, and immediately before the naloxone challenge test.

At the conclusion of the challenges, six subjects were abruptly discontinued from methadone and enrolled in a double-blind randomization to detoxification with active or placebo dextromethorphan 60 mg orally every 4 h. Withdrawal was measured twice daily by the 40-item, observer-rated Ribicoff Abstinence Rating Scale (Goodman et al., 1986), and by vital signs. Adjunctive medications included chloral hydrate 1.0 g nightly as requested, and clonidine and oxazepam for subjects judged by the prescribing physician to demonstrate moderate withdrawal.

2.3. Data analysis

The six subjects randomized to Pla-60-120 of dextromethorphan and the five subjects randomized to Pla-120-240 of dextromethorphan were analyzed in separate analyses of variance (ANOVAs). The results for five subjects in the Pla-120-240 group were analyzed and are reported out to 30 min; an analysis out to 60 min for the four subjects with complete data did not show any additional significant results. Individual withdrawal signs and symptoms were the dependent measures. Values at −60 and −2 min, including POMS subscales, were compared within each dextromethorphan condition in a one-factor (pre-dextromethorphan vs. post-dextromethorphan) repeated measures ANOVA. Measures were then summarized by calculating the mean of the change from baseline (−60) of all the post-naloxone time points. These mean-change values were analyzed in a one-factor (dextromethorphan dose) repeated measures ANOVA with planned comparisons at each active dextromethorphan dose to placebo. Univariate analyses and the Huynh-Feldt correction for departures from sphericity were used. In order to avoid a Type II error in this small sample study, all F ratios with P values less than 0.10 (two-tailed) were noted as significant. Variability around mean values is indicated in the text by means ± S.E.M. Felch et al. (1994) reviewed alternative methods of analyzing a combined data set from several sequential naloxone challenge test studies. They found that for most dependent measures, area-under-the-curve analysis yielded equivalent effect sizes as peak and time-course analyses.

3. Results

3.1. Effects of dextromethorphan alone

There were no significant differences between the values at −60 and −2 min for any dependent withdrawal measure. The only significant effects of active dextromethorphan were a decrease in mean arousal from 8.4 ± 3.5 to 5.8 ± 5.4 [$F(1,4) = 5.3$, $P < 0.09$]; and an increase in mean elation from 7.4 ± 2.8 to 9.6 ± 2.9 ($P < 0.04$) after dextromethorphan 240 mg and less confusion after dextromethorphan 120 mg [$F(1,5) = 4.4$, $P < 0.10$].

3.2. Effects of dextromethorphan by condition over time

Fig. 1 shows the effects of dextromethorphan by condition over time. There is no attenuation of withdrawal by dextromethorphan in the Pla-60-120 group, or in the Pla-120-240 group. The results by individual subjects are shown in Fig. 2. There is considerable variation in the response to dextromethorphan. Subject B who was HIV seropositive, showed considerably worsened withdrawal with dextromethorphan pre-treatment.

Table 1 shows the response to dextromethorphan by symptom and dose. The only significant effect of dextromethorphan was to decrease the mean-change for pulse at the 120 mg dose compared to the placebo dose [$F(1,5) = 8.32$, $P < 0.01$] in the Pla-60-120 group. However, this is probably not an effect of dextromethorphan, as it is primarily accounted for by the higher pulse (hence, lower mean-change) prior to dextromethorphan on the 120 mg days (70.7 ± 4.8) than the placebo (65 ± 2.6) days. In the Pla-120-240 group, there were significant main effects of dextromethorphan on restlessness [$F(1,4) = 3.58$, $P =$

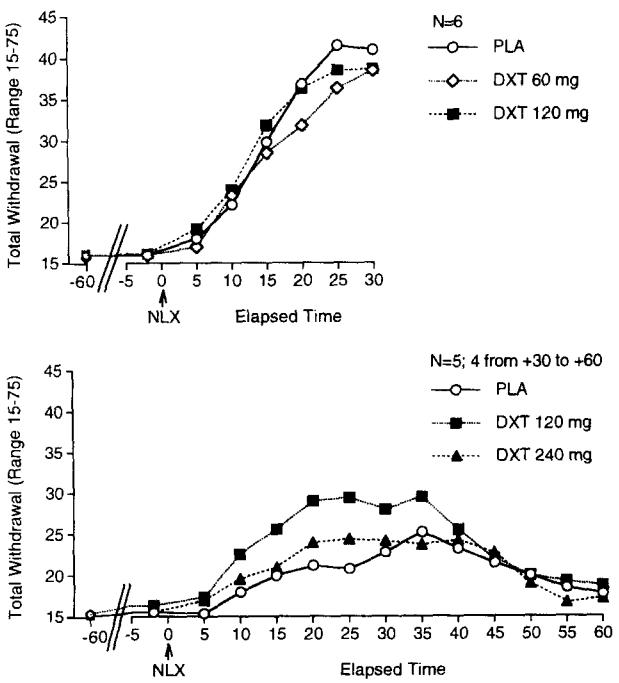

Fig. 1. Mean observer-rated withdrawal severity by dextromethorphan pre-treatment condition. Dextromethorphan (0, 60 mg, or 120 mg) administered p.o. at −60 min, followed by naloxone 0.4 mg intramuscularly administered at 0 min to subjects stabilized on methadone 25 mg p.o. daily.

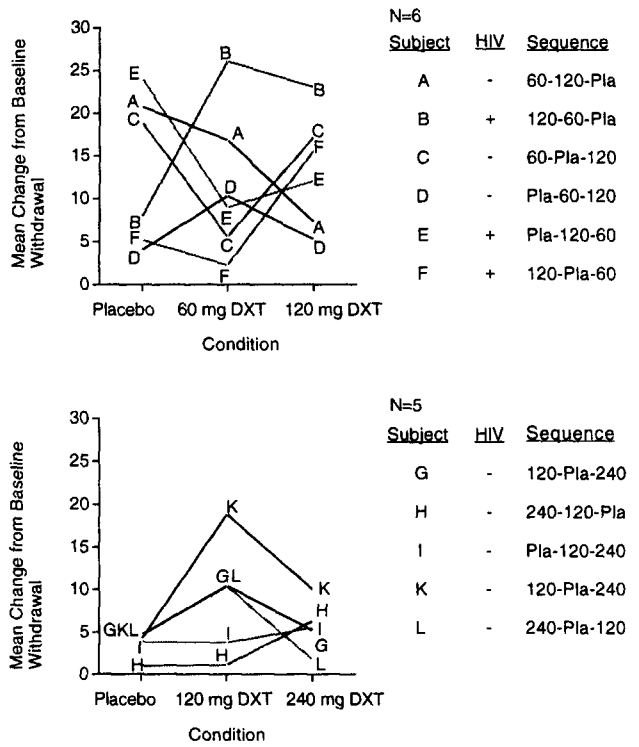

Fig. 2. Mean change from baseline in observer-rated withdrawal severity by subject and dextromethorphan pre-treatment condition.

0.09] and anxiety [$F = 6.08$, $P = 0.06$]. After the dextromethorphan 120 mg dose and prior to naloxone, subject K reported intense anxiety and 'LSD-like' feeling of floating out or her body.

3.3. Results of detoxification from methadone

Upon visual inspection of the data, there did not appear to be any less withdrawal in three control subjects receiving placebo dextromethorphan during detoxification from methadone. The three subjects who received *active* dextromethorphan are reported below. Prior studies using the 40-item observer-rated Abstinence Rating Scale (Krystal et al., 1992) and our observations suggest that ratings above 75 represent severe withdrawal.

Subject D: this 32 year old Black man was switched from heroin to methadone for a total of 13 days prior to methadone discontinuation. After five days of mild withdrawal, he had intense goose flesh, lacrimation, and muscle twitching on day six with an Abstinence Rating Scale rating of 85. He received chloral hydrate 1000 mg nightly on days 1–6, clonidine 0.2 mg on day five and 0.5 mg on day six, and serax 90 mg on day six.

Subject F: this 27 year old HIV seropositive Black man was on methadone maintenance for nine months prior to admission, and was maintained on a stable dose of 25 mg for 20 days prior to detoxification. He required clonidine doses from 0.5 mg to 0.8 mg daily on post-methadone days 1–6, and his Abstinence Rating Scale withdrawal rating was between 71 and 85 on days 2–6. He had visible sweating, rhinorrhea, and goose flesh. He described his discomfort as 'severe'.

Subject C: this 43 year old white man's intravenous heroin habit was methadone-stabilized for 11 days prior to detoxification. He received chloral hydrate 1000 mg nightly on post-methadone days 4–6. His Abstinence Rating Scale

Table 1
Mean naloxone-induced change from baseline by dextromethorphan (DXT) condition

Symptom	Pla	DXT		Drug effect	Pla	DXT		Drug effect
		60 mg	120 mg	(Y/N)		120 mg	240 mg	(Y/N)
Withdrawal total	13.5	11.7	13.4	N	3.7	8.9	5.8	N
Restlessness	1.1	0.9	1.1	N	0.2	**1.0**	0.5	**Y**
Anxiety	0.7	0.5	0.8	N	0.1	**0.8**	0.2	**Y**
Muscle ache	0.4	0.5	0.5	N	0.1	0.5	0.2	N
Anorexia	1.3	0.9	1.3	N	0.7	1.2	0.9	N
Abdominal cramps	1.0	0.8	0.9	N	0.3	0.6	0.6	N
Nausea	0.7	0.8	0.8	N	0.0	0.3	0.1	N
Hot/cold	1.0	1.1	1.4	N	0.6	0.8	0.7	N
Craving	0.9	0.6	0.9	N	0.5	1.0	0.7	N
Rhinorrhea	1.2	1.0	1.1	N	0.2	0.4	0.3	N
Perspiration	0.7	0.6	0.9	N	0.1	0.3	0.4	N
Yawning	1.4	1.2	1.1	N	0.5	0.9	0.6	N
Goose flesh	1.3	1.1	1.1	N	0.1	0.2	0.2	N
Tremor	0.4	0.2	0.2	N	0.0	0.2	0.1	N
Vomiting	0.2	0.3	0.0	N	0.0	0.0	0.0	N
Tearing	1.4	1.3	1.1	N	0.5	0.6	0.5	N
SBP (mm Hg)	2.1	5.9	12.9	N	2.3	5.9	4.6	N
DBP (mm Hg)	9.7	5.7	5.7	N	5.7	8.2	4.2	N
Pulse (beats/min)	11.6	11.0	**3.4**	**Y**	−2.9	1.1	1.8	N
Resp. (/min)	0.3	0.6	0.3	N	0.0	−0.1	0.1	N

Drug effect indicates significant ($P < 0.10$) main effect of dextromethorphan. **Bold** values indicate significant difference from placebo dextromethorphan condition.

withdrawal ratings peaked at 58 on day two post-methadone. He described a transient sensation of a visual halo around objects on day two only.

4. Discussion

This study failed to demonstrate any attenuation of naloxone-precipitated opiate withdrawal by dextromethorphan. The doses tested are considerably higher than the maximum daily recommended clinical dose of 120 mg/day, and there were some side effects noted – transient visual halos in a detoxifying subject at 60 mg every 4 h, intense anxiety and depersonalization in one subject at 120 mg but not at 240 mg, and POMS changes of significantly decreased arousal and increased elation at the dextromethorphan 240 mg dose. Our results are consistent with other reports of similar side effects at comparable doses: altered sensorium after 300–1500 mg (Degwitz, 1964), and toxic psychosis after 20 (Romilar) tablets (Dodds and Reval, 1967). Our finding of a mean increase in the elation score of the POMS of 2.2 units is comparable to the level of increased elation reported with administration of 16 mg intravenous cocaine (Foltin and Fischman, 1992). Euphoria after snorting 250 mg of dextromethorphan powder has been reported (Fleming, 1986). A controlled study (Jasinski et al., 1971) found that oral dextromethorphan, at doses of up to 240 mg, was not euphorigenic in healthy volunteers, but was associated with increases in the LSD (psychotomimetic) and PCAG (sedative) scales of the Addiction Research Center Inventory. Taken together, the reports of dextromethorphan side effects at high doses suggest that its clinical use at these doses is problematic, especially in the treatment of addicts who may find dextromethorphan to be euphorigenic.

Two caveats accompany the finding of a failure to find an effect of dextromethorphan on opiate withdrawal. One is that the small sample size limits the power to eliminate a Type II error. A sample size of six in this design is sufficient to detect a large effect size of 0.70 at a significance level of 0.10 (two-tailed) with a power of 0.80 (Cohen, 1988). Another caveat is that insufficient withdrawal may have been measured in some subjects to demonstrate attenuation by dextromethorphan. Only three of the eleven subjects (subjects A, C, and E in Fig. 2) had total withdrawal scores over ten with placebo pre-treatment. These three subjects' withdrawal was lowered in each challenge with active dextromethorphan pre-treatment. In contrast, the eight subjects whose total withdrawal with placebo pre-treatment was less than ten did not show consistent attenuation with active dextromethorphan pre-treatment.

Our findings are at odds with the report of decreased withdrawal when dextromethorphan was added to diazepam in detoxifying heroin addicts (Koyuncouglu and Saydam, 1990). Our study and the detoxification study utilize different medication regimens; the detoxification study employed dextromethorphan as an adjunct to diazepam, instead of alone, and compared dextromethorphan (plus diazepam) to chlorpromazine (plus diazepam), instead of comparing dextromethorphan to placebo. An additional confound to the detoxification study was the finding that dextromethorphan was associated with better retention in the detoxification protocol than chlorpromazine; the dropout of 15 of the 21 chlorpromazine-treated addicts in the Koyuncouglu and Saydam (1990) study may have resulted in a selected group of placebo-treated subjects willing to tolerate (and rate) severe withdrawal.

Visual inspection of the data on Fig. 2 shows considerable variability between and within individuals in the response to dextromethorphan. There may be inter-individual variability in the metabolism of dextromethorphan, and thus in the relative proportions of dextromethorphan and dextrorphan to which a subject is exposed. The metabolism of dextromethorphan can be affected by a genotypic impairment of *O*-demethylation (seen in approximately 10% of studied subjects; Hildebrand et al., 1989), severe liver disease (Larrey et al., 1989), and concomitant methadone administration (Wu et al., 1993). This variability is important because of the hypothesized toxicity and side effects of dextrorphan, and not dextromethorphan (Tortella et al., 1994). This variability may also represent a lack of reliability of this naloxone challenge paradigm. Using a modification of this paradigm, we have demonstrated a high degree of reliability (intraclass correlation coefficients $>$ 0.66) of the behavioral and physiological responses to repeated naloxone challenges in methadone-stabilized subjects (Rosen et al., 1995).

Clinically tolerated doses of dextromethorphan may be more effective in decreasing the *development* of opioid dependence than in attenuating the acute expression of opiate withdrawal; the excitatory amino acid receptor antagonist MK-801 attenuates the development of opioid dependence at considerably lower doses than the large single doses required to attenuate the expression of opiate withdrawal (Trujillo and Akil, 1995). Another potential role for dextromethorphan is in reversing existing opioid dependence. However, the reversal of existing opioid analgesic tolerance occurs only after several days of treatment with either the competitive NMDA receptor antagonist LY274614 (Tiseo and Inturrisi, 1993), a nitric oxide sythase inhibitor (Kolesnikov et al., 1993), or an agonist on the glycine site of the NMDA receptor (Kolesnikov et al., 1994). Elliott et al. (1994) have used three days of extremely high doses (30 mg/kg s.c.) of dextromethorphan to reverse tolerance to morphine analgesia in mice. The mechanism by which the NMDA receptor antagonists attenuate analgesic tolerance development or reverse existing tolerance is unclear. Tiseo et al. (1994) did not find any effect of LY274614, at doses which alter morphine analgesia tolerance, on μ-, δ- or κ-opioid receptor densities. The authors hypothesized that excitatory amino acids

may block μ-opioid-induced, NMDA-mediated increases in intracellular calcium which are related to the development of opioid tolerance.

Future studies of excitatory amino acid receptor antagonists may show more efficacy in attenuating the development of opiate dependence than in attenuating opiate withdrawal with acute administration. Dextromethorphan dosing in such studies should involve repeated dosing over time, measurement of plasma dextromethorphan and metabolite levels, and possibly dosage adjustment based on inter-individual differences in sensitivity to dextromethorphan. Another direction for future research is to administer medications which are thought to act at dextromethorphan receptors without direct NMDA receptor effects. Candidates are other non-opioid anti-tussives such as caramiphen or carbetapentane.

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