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Effects on Opioid-Induced Rate Reductions by Doxepin and Bupropion

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MACENSKI, M. J., J. CLEARY AND T. THOMPSON. *Effects on opioid-induced rate reductions by doxepin and bupropion.* PHARMACOL BIOCHEM BEHAV 37(2) 247–252, 1990.—Twelve pigeons key-pecked under a multiple variable interval 15-second, variable interval 150-second schedule of food reinforcement. Effects of two opioid drugs, buprenorphine and methadone, were determined alone and in combination with chronic daily administration of the antidepressants doxepin or bupropion. Methadone initially produced dose-dependent key-pecking rate reductions when administered acutely, prior to the session, while buprenorphine produced key-pecking rates that reached a plateau at 50–80% of baseline rate and were not reduced further by higher doses. Neither doxepin nor bupropion, given alone, had lasting effects on key-pecking rates. Chronic daily doxepin administration significantly attenuated methadone-induced response rate reductions. Bupropion reduced the effect of the highest methadone dose, but this effect was mitigated by the development of opioid tolerance. Unlike bupropion, doxepin interfered with the development of opioid tolerance. Neither antidepressant systematically altered effects of buprenorphine on key-pecking.

Antidepressant Opioid Buprenorphine Bupropion Doxepin Methadone Pigeons

SIGNIFICANT and beneficial interactions between opioids and antidepressants have been reported in areas as diverse as analgesia, drug dependence, and operant behavior. As an adjunct to methadone maintenance for chronic opioid users, antidepressant therapy has been shown to reduce or alleviate depressive symptoms and psychomotor retardation (28,30). Explanations for the beneficial effects of adjunct antidepressant treatment with opiate addicts often focus on improvement of the underlying depression (28) or other psychological distress (15,30).

In addition to depression-related explanations for beneficial effects of the antidepressant-opioid combination, research in other areas suggests a direct pharmacological interaction that may alter the effects of the opioid. For example, antidepressants are known to be effective antinociceptive agents when given alone [e.g., (29)] and to enhance opioid analgesia in laboratory animals (1, 13, 24) and humans (18). A recent study by Hwang and Wilcox (13) suggests that norepinephrine reuptake blockers, which include several antidepressant drugs, consistently increase the antinociceptive properties of opioids. Amelioration of opioid-induced behavioral suppression by a tricyclic antidepressant was examined by Cleary, Nader and Thompson (4). In that study, chronic daily imipramine lessened the suppressive effects of methadone on pigeons' key-pecking rates. Increases in rate of response were seen under relatively high doses of methadone (3.0 mg/kg), and were more evident under a schedule producing a higher density of reinforcement. Further pharmacological interaction is suggested by nonhuman studies showing tricyclic antidepressants increase opioid withdrawal effects (14) and increase amounts of methadone present in brain tissue (19).

The present study employs two antidepressants with markedly different neurochemical mechanisms of action, doxepin and bupropion, in combination with two different opioids, methadone and buprenorphine. Doxepin appears to exert its main effect by blocking norepinephrine (NE) reuptake (3, 11, 16), whereas bupropion's neurochemical action appears to be blockade of dopamine (DA) reuptake, and to some extent, attenuation of the NE depletion caused by increased DA (6, 8, 23, 25). Behaviorally, doxepin and bupropion have dissimilar general effects. Acute doxepin administration causes a dose-dependent decrease in positively maintained operant behavior and shock avoidance (22). Bupropion has been shown to produce a dose-dependent increase in locomotor behavior (6, 23, 31).

The two opioids are also neurochemically and behaviorally distinct. Methadone, a μ-receptor agonist, produces typical opioid effects such as analgesia, euphoria, respiratory depression and sedation (20). Like other μ-receptor agonists, methadone also reduces the rates of operant responding maintained by positive reinforcement (4, 26, 27). Buprenorphine is a partial μ-receptor agonist that shares many of the agonist properties with methadone, but acts as an antagonist at higher doses and has a higher affinity for the receptor (12,19). Buprenorphine increases response rates under fixed interval schedules (17), but has little or no effect on response rates under other schedules of reinforcement (5,17). Buprenorphine also has a duration of behavioral action that may extend up to 48 hours after administration and it has been suggested as a substitute for methadone in the treatment of opioid dependence (10, 17, 21).

METHOD

Subjects

Twelve adult female White Carneau pigeons (Palmetto Pigeon

Plant, Sumter, SC) were used as subjects. Pigeons were experimentally naive at the start of the study and maintained at 80% of their free-feeding weights (400–600 g) throughout the study. Birds were housed in individual cages in a colony room maintained at 24 degrees Celsius under constant illumination. Water and grit were freely available.

Apparatus

Experimental sessions were conducted in eight commercially available small animal operant chambers (BRS/LVE, Laurel, MD). The chambers were enclosed within sound-attenuating compartments and masking noise was present at all times. Each chamber was equipped with an overhead house light and a solenoid-operated feeder. A feeder light was illuminated during operation of the solenoid. The front wall of each chamber was equipped with three keys that could be transilluminated. In the present experiment only the center key was used. Execution of the experimental program and data recording were accomplished using two Apple II Plus computers (Apple Computers, Inc., Cupertino, CA) located in adjacent rooms.

Procedure

Initially, bird's pecks were autoshaped to the center key (white), then exposed to a continuous reinforcement schedule (CRF) with the center key illuminated red. Following each key-peck, birds were allowed 4 seconds access to mixed grain. When a consistent key-pecking rate was achieved under the CRF schedule, contingencies were slowly changed to those of a variable interval 15-second (VI 15″) schedule (9). Under this schedule, reinforcement was presented immediately following the first key-peck occurring after varying intervals, with the average interval being 15 seconds. Finally, the illumination of the center key was changed from red to green every 10 minutes. When the key was illuminated green, the first peck occurring after an average interval of 150 seconds (VI 150″) produced food. Conditions under red illumination remained the same (i.e., VI 15″). The terminal schedule for all birds was a multiple VI 15″ VI 150″ (*mult* VI 15″ VI 150″).

Under the terminal schedule, sessions started with house light illumination, and four seconds access to mixed grain, after which the *mult* VI 15″ VI 150″ schedule conditions were started. Ten-minute components alternated, starting with the VI 15″ component, until each component had been presented twice. Each component change was preceded by 10 seconds of darkness, during which key-pecks had no scheduled consequences. The total session time during which reinforcement was available under one of the schedules was 40 minutes.

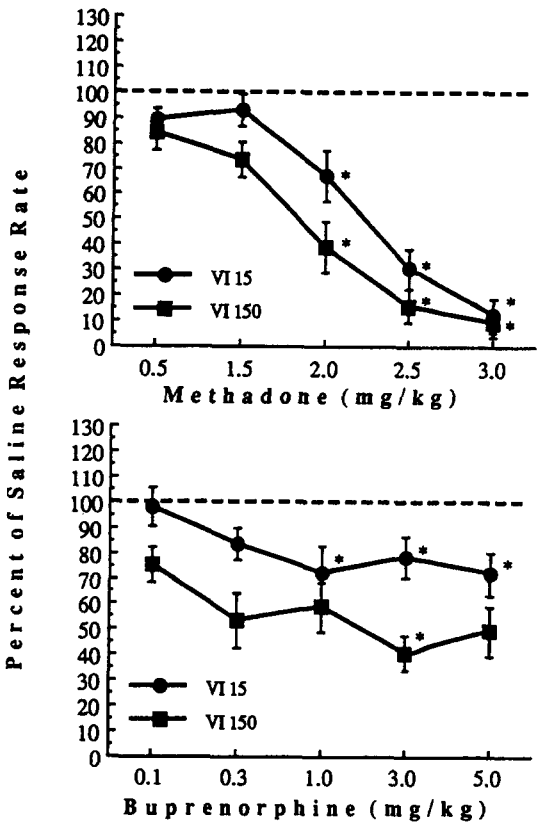

FIG. 1. Effects of acute methadone and buprenorphine on key-peck rates as a percentage of baseline rates under saline. Vertical bars under drug conditions encompass plus and minus 1 standard error of the mean (SEM). SEM under saline ranged from 0.83 to 1.39 percent. Asterisks indicate significant differences from saline baseline (*t* LSD, $p<0.01$).

Drug Preparation and Administration

Methadone hydrochloride (Eli Lilly, Chicago, IL) was dissolved in isotonic saline (0.9%) and buprenorphine hydrochloride

TABLE 1

RESPONDING AS PERCENT BASELINE UNDER ACUTE BUPRENORPHINE

	VI 15″ Dose of Buprenorphine in mg/kg					VI 150″ Dose of Buprenorphine in mg/kg				
Treatment	0.1	0.3	1.0	3.0	5.0	0.1	0.3	1.0	3.0	5.0
None (first)	111.44	88.92	92.48	76.58	74.92	76.92	48.75	53.04	40.42	50.05
Doxepin	95.92	102.73	55.06	102.06	95.29	73.85	64.57	56.56	63.04	60.89
None (final)	96.85	91.05	79.43	98.34	96.68	59.36	62.97	66.18	70.18	67.12
None (first)	77.88	67.29	58.90	67.08	59.34	72.71	33.08	54.80	27.82	35.37
Bupropion	63.94	77.25	78.63	78.74	75.23	51.46	65.93	71.92	55.81	57.94
None (final)	100.17	72.47	77.49	69.81	68.90	84.91	57.83	57.44	59.33	58.23

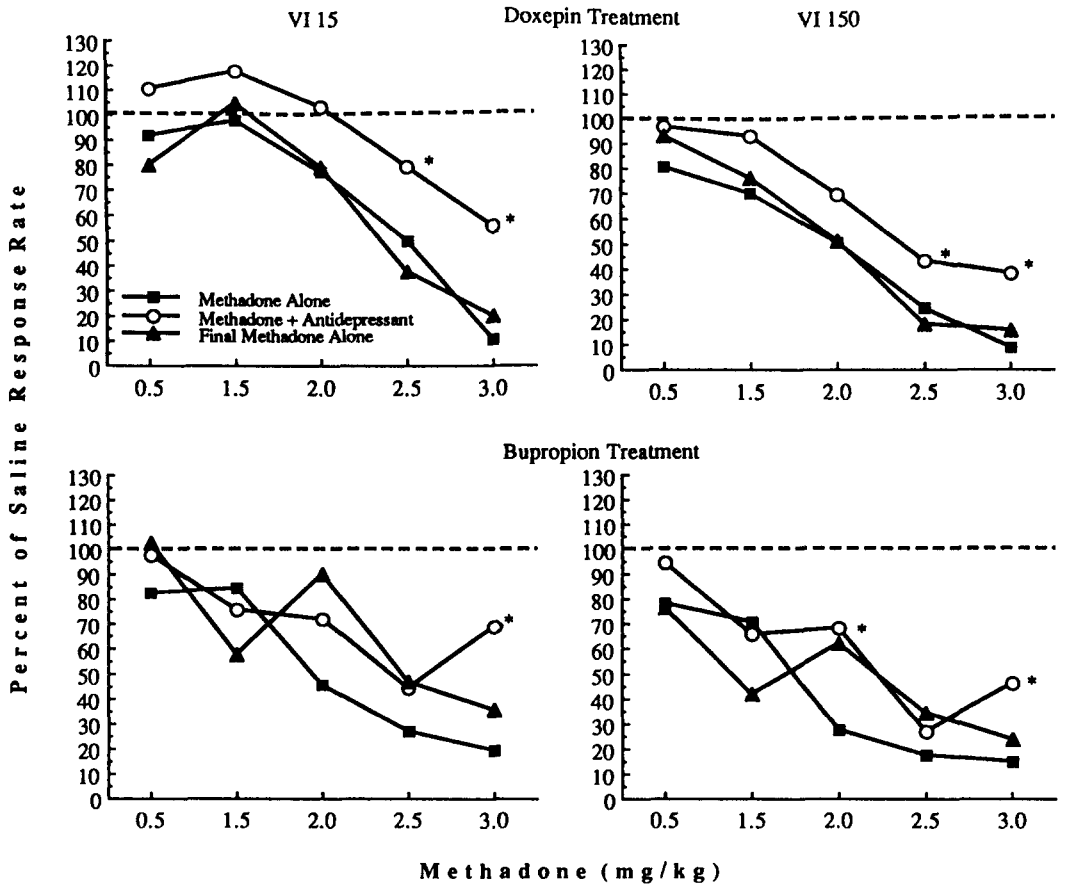

FIG. 2. Effects of acute methadone on key-peck rates before, during, and after chronic daily antidepressant treatment for the VI 15″ schedule (left panel) and the VI 150″ schedule (right panel). Response rates are presented as a percentage of the rate under saline administration during each individual phase. Standard errors of the mean for the saline baselines ranged from 1.54 to a maximum of 4.05 percent. Asterisks indicate significant differences from first determination (t LSD, $p<0.05$).

(Burroughs Wellcome, Research Triangle Park, NC) was dissolved in distilled water. Methadone (0.5, 1.0, 2.0, 2.5, and 3.0 mg/kg) and buprenorphine (0.1, 0.3, 1.0, 3.0, and 5.0 mg/kg) doses are expressed in terms of total salts. Injections were given intramuscularly, thirty minutes prior to sessions. Dose order was randomly selected for each bird, with at least one week between each drug injection. A saline control injection was given on one of the three days preceding drug injection. Injection volume was kept constant at 1.0 ml/kg.

Acute dose-effect relationships were first determined for each drug. Following this phase, chronic daily injections of saline or one of two antidepressants drugs began. During this phase, each bird received either 2.0 mg/kg/day of doxepin hydrochloride (Pfizer Laboratories, Hoffman Estates, IL), 5.0 mg/kg/day of bupropion (Burroughs Wellcome, Research Triangle Park, NC), or 1.0 ml/kg isotonic saline (0.9%). Antidepressants were dissolved in 0.9% saline, with doses expressed in terms of the total salts. To maintain a more constant antidepressant blood level, one-half the total daily antidepressant dose was administered twice daily, immediately following the session and twelve hours later. The twice-daily antidepressant or saline injections were continued for two weeks prior to reestablishing the methadone and buprenorphine dose-effect curves. Following reestablishment of the opioid dose-effect relationships, antidepressant and saline treatment was discontinued and all birds were drug free for three weeks. Finally, the dose-effect relationship for the opioid drugs was again established with all doses of methadone and buprenorphine randomly assigned to each individual bird.

RESULTS

Effects of acute administration of methadone and buprenorphine on key-pecking rates are shown in Fig. 1. Key-pecking rates were higher in the presence of the VI 15″ schedule (mean = 74.0 responses/minute) than the VI 150″ schedule (mean = 26.7 responses/minute). Methadone reduced key-pecking in a dose dependent fashion under both schedules [RMANOVA, $F(11,21) = 42.3$, $p<0.001$]. Response rates at the three highest methadone doses were significantly different from saline under both schedules (t LSD, $p<0.01$). Methadone produced a greater percent reduction in key pecking under the VI 150″ schedule than under the VI 15″ schedule. Buprenorphine also reduced key-peck rates at the higher doses. Multiple comparison tests revealed VI 15″ key-peck rates under buprenorphine doses of 1.0, 3.0, and 5.0 mg/kg, and VI 150″ rates at doses of 0.3, 1.0, 3.0, and 5.0 mg/kg, to be significantly different from those under saline (t LSD, $p<0.01$). Again, responding under the VI 150″ showed a greater percent reduction than responding under the VI 15″ schedule.

The effects of methadone during chronic daily doxepin or bupropion administration are shown in Fig. 2. The methadone

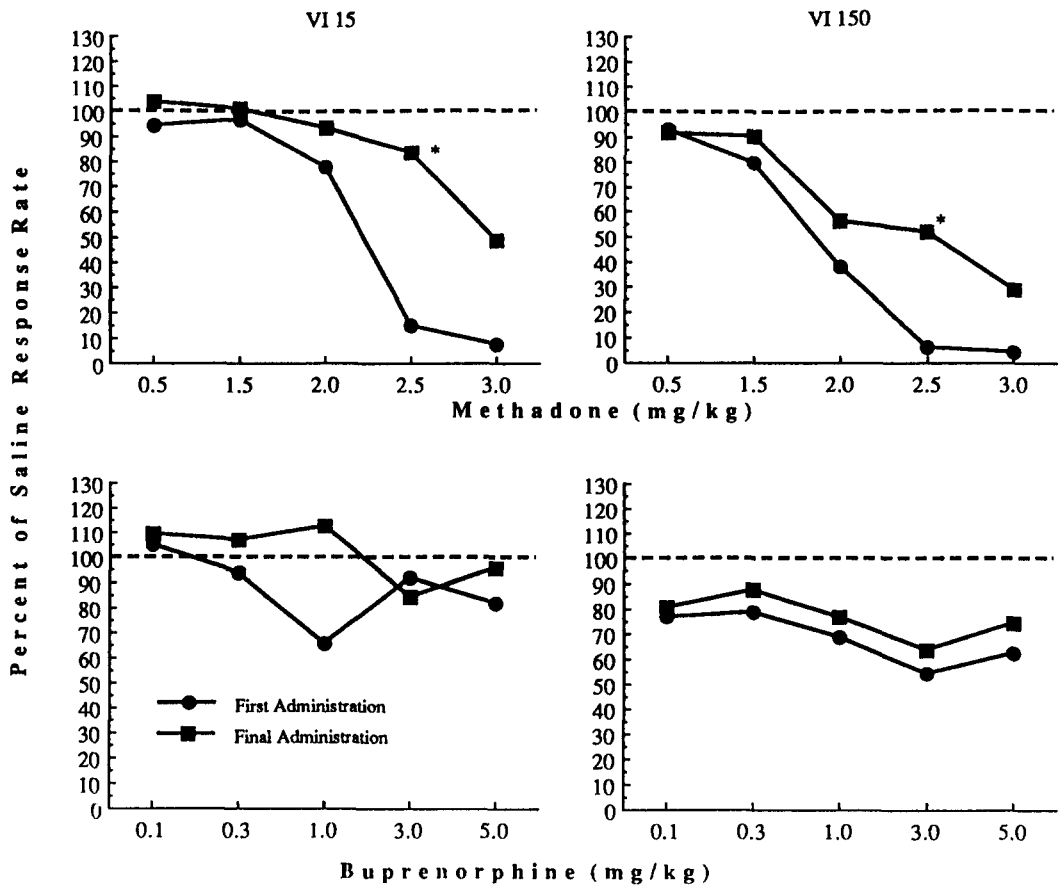

FIG. 3. Effects of repeated acute opioid administration on key-peck rates for the chronic daily saline treatment group under the VI 15″ schedule (left panel) and the VI 150″ (right panel). Asterisks indicate significant differences from first determination (*t* LSD, $p<0.01$).

dose-effect curve was shifted to the right during chronic doxepin under both VI parameters (top panels). No tolerance to methadone was apparent when the dose-effect relationship was reestablished following discontinuation of doxepin. For this group, attenuation of methadone-induced key-peck rate reductions was greater under the schedule producing the higher reinforcement density (VI 15″). Although bupropion did reduce methadone's effects at the higher doses, this effect is not easily interpreted because of the substantial opioid tolerance evident during the final methadone administration phase (lower panels). Bupropion did appear to ameliorate the rate reducing effects at the highest methadone dose (3.0 mg/kg; see Fig. 2).

Key-pecking following buprenorphine administration during chronic daily injections of the antidepressants (or saline) showed no systematic changes. These results are presented in Table 1. Key-peck rates were reduced from 20 to 50 percent by low doses of buprenorphine, with higher doses producing no further reductions. This was the case regardless of antidepressant treatment (see Table 1). Between-subject variability under buprenorphine was high, with the standard error of the mean percent baseline for individual doses ranging from 1.1 to 20.8. To assess whether changes in opioid dose-effect curves were the result of antidepressant administration or the consequence of repeated administration of the opioid (i.e., tolerance) a third dose-effect relationship was determined following withdrawal of the antidepressant. Figure 3 shows the effect of repeated administrations of methadone and buprenorphine on key-peck rates under both schedules in the saline treatment group. Key-peck rates following the final series of methadone administrations in this group showed typical right shifted dose-effect curves under both schedule parameters. Repeated buprenorphine administration engendered some recovery of baseline rate under both schedules, in spite of the relatively small initial decrement in key-pecking seen during the first dose regimen.

DISCUSSION

Methadone produced characteristic dose-dependent decreases in rates of operant performance maintained by positive reinforcement. The key-pecking rate reductions were greater (by percent) under the VI 150″ reinforcement schedule, which engendered lower rates and a lower reinforcement density, than those under the VI 15″ schedule. Methadone has previously been shown to be less effective at suppressing behavior when reinforcement frequency is not directly dependent upon the rate of response (26). In the present experiment, even if responding is infrequent, the probability that a key-peck was reinforced increased with passage of time. Zeiler (32) suggests that this property of time-based schedules of reinforcement regenerates weakened performance by reinforcing a single response after a long pause. The greater regenerative capacity of the VI 15″ schedule, in comparison to the VI 150″ schedule, may account for the proportionately higher rates

of responding following methadone administration.

The relationship between reinforcement frequency and response rate may also help explain the disproportionate effects of methadone under the two schedules. As rates decrease, reinforcement frequency is more severely affected under the VI 15″ schedule. In contrast, key-pecking rates can decrease substantially without affecting reinforcement density under the VI 150″ schedule. Thus, response rate decreases due to methadone are "costly" under the VI 15″ schedule, in terms of reinforcement frequency, but may actually be viewed as more efficient under the VI 150″. Just as increased response cost (2) or reduction in reinforcement density (7) accelerate tolerance, a similar cost/efficiency mechanism could account for smaller decrements in key-pecking rates following methadone administration under the VI 15″ schedule in the present study.

Unlike methadone, buprenorphine produced only a modest reduction of key-pecking rates and a relatively flat dose-effect relationship. Again, greater reductions in key-pecking rates were seen in the VI 150″ component than in the VI 15″ component. Similar buprenorphine-induced response decrements for pigeons responding under a repeated acquisition of behavior chains procedure has been previously reported (5). These rate reductions following buprenorphine administration are in contrast to earlier reports (17) of buprenorphine's effect on pigeons' behavior. In that study, pigeons receiving doses of buprenorphine as high as 40 mg/kg showed no decrements in key-pecking rates under fixed ratio schedules and rates actually increased under fixed interval schedules. However, this study differed from the others in that a short 10-minute injection-session interval was used.

The primary focus of the present experiment was to determine whether these antidepressants altered the key-pecking reductions typically seen following opioid administration. Response rates following buprenorphine injections were reduced from 20 to 50 percent of saline baseline values regardless of experimental phase, chronic antidepressant administration, or schedule parameter. There were no systematic effects due to any of the chronic injection regimens. In contrast, methadone reduced key-pecking substantially less when pigeons were concurrently treated with doxepin. For this group, doxepin produced a right shifted methadone dose-effect curve under the VI 15″ and VI 150″ schedule parameters. This attenuation of the rate-reducing effects of methadone cannot be accounted for by opioid tolerance, in fact, tolerance to methadone is diminished following doxepin treatment (see Figs. 2 and 3). These results are in agreement with the earlier report of attenuation of rate-reducing effects of methadone by the prototypic tricyclic antidepressant imipramine (4). Bupropion's effects on methadone-induced response rate decrements are obscured by tolerance to the opioid and did not show the unambiguous right shifted methadone dose-effect seen during chronic doxepin administration. However, bupropion did appear to consistently reduce key-peck rate decrements under the highest methadone dose.

The difference in doxepin's and bupropion's abilities to attenuate the effects of methadone may be related to their different neurochemical mechanisms of action. Tricyclic antidepressants are thought to exert their main effects by blocking biogenic amine reuptake (11). The two antidepressants showing efficacy in reducing methadone's effects, doxepin and imipramine, have substantial ability to block NE reuptake. Both drugs are approximately 60 times more potent at blocking NE reuptake than is bupropion (25). In contrast, bupropion's main neurochemical mechanism of action appears to be inhibition of DA uptake (23). None of these drugs substantially affect 5-HT reuptake. The adrenergic system is further implicated in the manifestation of opioid effects by evidence from related areas and clinical practice. For example, opioid analgesia is potentiated by concurrent tricyclic therapy, and clonidine, a NE agonist, reduces many of the symptoms associated with opioid withdrawal (18).

Clinical interpretation and application of antidepressant-opioid interactions is complex. Tricyclic antidepressants used to treat opioid dependence may alleviate depressive symptoms in the methadone maintained patient, but may also interact pharmacologically even in the absence of depression. The present data suggest this interaction will be greatest for behavior maintained under a high density of reinforcement. Although tricyclics appear to reduce some of methadone's effects under these circumstances, they do not antagonize all opioid effects. In fact, laboratory data and at least one human trial indicate they actually enhance opioid analgesia. Antidepressant enhancement of opioid analgesia would allow lower doses to be used for equivalent pain relief. The current data and those in a previous study by Cleary, Nader and Thompson (4) suggest further benefit of the combination may be realized through increased activity and lessened sedation. This holds promise for patients with chronic pain, tolerant to opioids, and whose opioid side-effects are directly related to opioid dose.

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