

Efficacy of Buspirone in the Treatment of Opioid Withdrawal

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Abstract: In an attempt to develop a new opiate detoxification approach, the authors assessed the efficacy of buspirone in the treatment of acute heroin withdrawal. Buspirone, a drug interacting with the serotonergic system, was selected because there is evidence that a decrease in serotonergic neurotransmission may be involved in opiate withdrawal symptoms.

Twenty-nine hospitalized heroin addicts were randomized to 4 groups: (1) placebo; (2) methadone; (3) buspirone 30 mg daily; (4) buspirone 45 mg daily. The double-blind trial started in all patients with a 5-day methadone stabilization period ending with a 30-mg dose. This was followed from days 6 through 12 by placebo in group 1 and by a methadone taper in group 2. Because of its delayed action, buspirone was started on day 1 in groups 3 and 4 and was continued, after methadone discontinuation, through day 12. On day 13, drugs and placebo were discontinued and patients were observed through day 14. Withdrawal symptoms were assessed with the "Subjective Opiate Withdrawal Scale" (SOWS) and the "Objective Opiate Withdrawal Scale" (OOWS).

The SOWS and OOWS scores were significantly higher in the placebo group than in the methadone, buspirone 30 mg, and buspirone 45 mg groups. There were no significant differences in SOWS or OOWS scores when the methadone group was compared with each of the two buspirone groups or when the two buspirone groups were compared with one another.

In conclusion, buspirone, a nonopiate drug with no abuse potential, a safe side effect profile and no withdrawal symptoms, at doses of 30 and 45 mg, was as effective as a methadone taper in alleviating the withdrawal symptoms of heroin addicts stabilized for 5 days with, and then withdrawn from, methadone. The use of buspirone could be particularly helpful in outpatient settings where the duration of the methadone taper recommended for detoxification can be lengthy.

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Dependence on opioids is a major public health problem because of its association with criminality and law en-

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forcement costs, as well as increased mortality and health-care costs resulting in part from the transmission of HIV and hepatitis C. Managed withdrawal is a required first step for long-term drug-free treatment and should be a part of any comprehensive treatment program.

For many years, methadone and clonidine have been the mainstay of treatment for the relief of withdrawal symptoms that become manifest upon cessation of opiate use. Methadone is effective in alleviating withdrawal symptoms but its use has been limited by government restrictions. The discovery of the capacity of the α_2 -adrenergic agonist, clonidine, to alleviate some of the withdrawal symptoms led to its widespread use. Clonidine is not an opioid drug but it has disadvantages. It is not effective in the alleviation of muscle aches, insomnia, or drug craving.^{1,2} It also produces sedation and hypotension, limiting its use to normotensive individuals. Problems associated with methadone and clonidine use led to the exploration of other approaches that have included rapid and ultra rapid detoxification techniques or the use of the partial opioid agonist buprenorphine. None of these approaches has been thoroughly evaluated, none has been deemed to be problem-free, and none has gained wide acceptance yet. In a recent review of the use of buprenorphine for the management of opioid withdrawal for example, Gowing et al³ concluded that many aspects of treatment protocol and relative effectiveness of this drug need to be investigated further. The search for alternative approaches should thus continue.

It has been suggested that the serotonergic system may be involved in opiate withdrawal symptoms.⁴⁻⁶ A variety of evidence indicates that the hyperactivity of locus coeruleus neurons is an important substrate of opiate withdrawal. Some studies indicate that this hyperactivity is primarily mediated through an increased excitatory amino acid input to these cells⁷ and that 5-HT attenuates this excitatory amino acid-induced hyperactivity.⁸ This led Akaoka and Aston-Jones⁶ to study the efficacy of 5-HT agents in the attenuation of locus coeruleus hyperactivity during naloxone-precipitated withdrawal in rats chronically exposed to morphine. They observed a significant reduction in the firing rates of individual locus coeruleus neurons in animals treated with the 5-HT releaser/reuptake inhibitor D-fenfluramine, and with the 5-HT

blockers fluoxetine and sertraline. An increase in 5-HT function might be particularly indicated during withdrawal from opiates because there is preclinical evidence both from analyses of brain tissue levels⁹ and from microdialysis of the dorsal raphe nucleus of freely behaving rats¹⁰ that morphine discontinuation is accompanied by a decrease in 5-HT.

Buspirone, an azipirone, is used primarily as an anxiolytic agent. It interacts with a multiplicity of receptors but is believed to exert most of its clinical effects by enhancing serotonergic activity after a few days of use and receptor adaptation.¹¹ There is recent evidence from a study performed in rhesus monkeys maximally dependent on morphine that buspirone attenuates, in a dose-dependent manner, the withdrawal symptoms resulting from the interruption of morphine administration.¹²

In a pilot study, we evaluated the efficacy of buspirone in the alleviation of the withdrawal symptoms experienced by heroin addicts and methadone maintained patients following cessation of heroin or methadone use.¹³ In this pilot study, patients received for 5 days methadone doses that were decreased to 30 mg. They were maintained on this dose for 3 additional days. Following this stabilization period, methadone was discontinued and patients randomly assigned to buspirone (30 mg daily) or placebo treatment for 9 days. Buspirone was found to be more effective than placebo in attenuating the objective and subjective symptoms that follow cessation of opiate use, but it took a few days for its antiwithdrawal efficacy to become manifest.

In the present study, buspirone efficacy was compared with that of tapering doses of an established opioid antiwithdrawal agent, methadone, as well as to that of a placebo. Instead of 1 dose, 2 daily doses of buspirone were studied, the 30-mg dose used in the pilot study and a 45-mg dose. In addition, buspirone was started at the beginning of the methadone stabilization period to maximize its effects after methadone discontinuation when withdrawal symptoms reach their peak in untreated patients.

MATERIALS AND METHODS

Subjects

Participating patients were hospitalized male chronic opiate users. To be enrolled in the study, patients were required to have: (1) fulfilled DSM-IV diagnostic criteria for opioid dependence; (2) used heroin daily for at least the prior 6 months with claimed heroin use of at least 2.5 g/wk; (3) physical dependence on opiates as determined by history and observation; (4) admission urine samples demonstrating heroin use; and (5) expressed willingness to participate in a randomized, double-blind, placebo-controlled study for 14 days.

Exclusionary criteria included the following: (1) current or past Axis I psychiatric disorder other than opioid

dependence; (2) evidence of significant neurologic, gastrointestinal, hepatic, cardiovascular, renal, endocrine, or hematologic disease; and (3) seropositive status for the human immunodeficiency virus.

Written informed consent was obtained after complete description of the study.

Study Design

Upon entry into the study, subjects were randomly assigned to double-blind treatment in one of the following groups: *group 1*, placebo; *group 2*, methadone taper; *group 3*, daily buspirone dose of 30 mg; *group 4*, daily buspirone dose of 45 mg.

Methadone was dispensed in liquid form and a liquid placebo was given to subjects who did not undergo the methadone taper. Buspirone was given in opaque capsules. Identically looking placebo capsules were given to subjects who did not receive buspirone.

A pictorial of the medication design is displayed in Figure 1. The trial lasted 12 days and started in all patients with a 5-day methadone stabilization period. On the last 3 stabilization days, the methadone dose was 30 mg. The medication schedule for the 4 groups differed in the following ways:

- Group 1: Treatment was limited to the methadone stabilization period. From day 6 through day 12, patients received a liquid placebo. Placebo capsules were given from day 1 through day 12. Treatment was stopped on day 13.
- Group 2: Following the 5-day methadone stabilization period, methadone was decreased to 20 mg from day 6 through day 8 and to 10 mg from day 9 through day 12. It was discontinued on day 13. Placebo capsules were given from day 1 through day 12.
- Group 3: Methadone was discontinued on day 6 and a liquid placebo was given from day 6 through day 12. Buspirone was started on the first day of methadone administration. Subjects received 15 mg on day 1, 30 mg from day 2 through day 11, and 15 mg on day 12. Treatment was stopped on day 13.
- Group 4: Methadone was discontinued on day 6 and a liquid placebo was given from day 6 through day 12. Buspirone was started on the first day of methadone administration. Subjects received 15 mg on day 1, 30 mg on days 2, 3, and 4, 45 mg from day 5 through day 10, 30 mg on day 11, and 15 mg on day 12. Treatment was stopped on day 13.

After drugs and placebo were discontinued, all patients underwent a period of observation on days 13 and 14.

Clinical Assessments

The severity of withdrawal symptoms was measured daily at 1:00 PM. Measurements were made on experimental

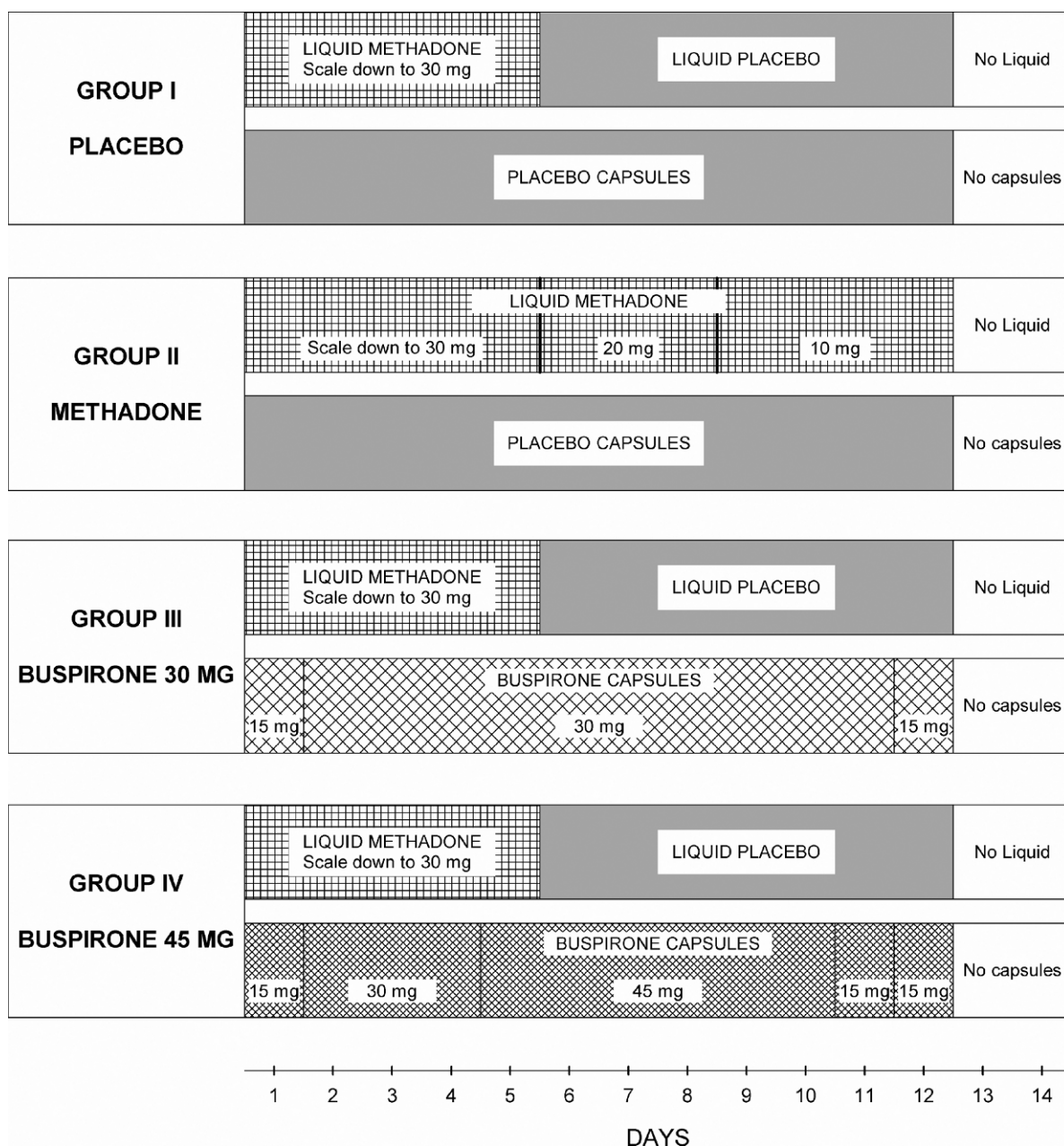


FIGURE 1. Pictorial of experimental design.

day 5 (baseline), the last methadone stabilization day, on the following 7 days (days 6 through 12) and on days 13 and 14 (following discontinuation of drugs and placebo).

Withdrawal symptoms severity was measured using the following rating scales:

1. The *Subjective Opiate Withdrawal Scale* (SOWS),¹⁴ a self-rating scale which has been shown to be a reliable and valid measure of the opiate withdrawal syndrome. This scale contains 16 symptoms whose intensity the patient

rates on a 5-point scale of (0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely). The symptoms rated are as follows: “I feel anxious,” “I feel like yawning,” “I’m perspiring,” “My eyes are tearing,” “My nose is running,” “I have goose flesh,” “I am shaking,” “I have hot flashes,” “I have cold flashes,” “My bones and muscles ache,” “I feel restless,” “I feel nauseous,” “I feel like vomiting,” “My muscles twitch,” “I have cramps in my stomach,” “I feel like shooting up now.”

2. The *Objective Opiate Withdrawal Scale* (OOWS),¹⁴ which contains 13 observable physical signs, rated on a 2-point (0 = not present, 1 = present) or a 3-point scale (0 = not present, 1 = mild, 2 = moderate/severe), based on a timed period of observation of the patient by the rater. The signs rated are as follows: yawning, rhinorrhea, goose flesh, perspiration, lacrimation, mydriasis, tremors of the hands, hot and cold flashes, restlessness, vomiting, muscle twitches, abdominal cramps, anxiety.

Data Analysis

In the analyses, the following questions were addressed: (1) Did the 2 bupirone doses decrease withdrawal symptoms when compared with a placebo? (2) Were the 2 bupirone doses as effective as a methadone taper in decreasing withdrawal symptoms? (3) Was the 45-mg bupirone dose more effective than the 30-mg dose?

Overall differences of the 4 patient groups' SOWS and OOWS response curves following the stabilization period were assessed with repeated-measures analyses of variance (ANOVA). Values used in these analyses were baseline corrected. Baseline values were those recorded on the last stabilization day. In cases of overall differences between the 4 groups, repeated-measures ANOVA were used to compare groups taken two at a time (placebo vs. each of the other 3 groups, methadone taper vs. each of the two bupirone groups, and bupirone 30 mg vs. bupirone 45 mg). The same analyses were used in comparisons of individual SOWS and OOWS symptoms. Day 5 through day 12 baseline-corrected values were also summarized as areas under the curve for the SOWS and the OOWS total scores.

RESULTS

Subjects

Thirty-one patients participated in the study. They had all come to the Medical Center seeking heroin detoxification. Eight patients were assigned to the placebo group, 8 to the methadone taper group, 8 to the bupirone 30-mg group, and 7 to the bupirone 45-mg group. Two patients assigned to the placebo group requested to discontinue the study following the methadone stabilization period. In these patients, the methadone taper was resumed. Data presented below are those obtained in the remaining 29 subjects.

These 29 patients were 48.3 ± 8.9 years old. Twelve patients were Afro-American, 10 were Caucasian, and 7 were Hispanic. They had started using heroin on a regular basis at the age of 24.6 ± 9.9 and had thus used it for 23.7 ± 13.4 years prior to the current admission. Fifteen patients had used heroin intravenously and 14 had been snorting it. Daily heroin doses during the month preceding hospitalization were 0.62 ± 0.40 g for those who used it intravenously and 0.68 ± 0.40 g for those who used it intranasally. Fourteen

patients had participated in methadone maintenance programs in the past but for brief periods only.

Assessment of Withdrawal Symptoms

Subjective Opiate Withdrawal Scale

Figure 2 illustrates the SOWS baseline-corrected response curves for the 4 patient groups following the 5-day methadone stabilization period. Baseline scores were recorded on the last stabilization day. The overall comparison of the 4 curves revealed a significant group effect [$F(3,25) = 5.54, P = 0.005$]. Comparisons between the placebo group and the 3 other groups revealed that the placebo group scores were significantly higher than those of the methadone group [$F(1,12) = 7.04, P = 0.021$], than those of the bupirone 30-mg group [$F(1,12) = 6.75, P = 0.023$] and than those of the bupirone 45-mg group [$F(1,11) = 8.79, P = 0.013$]. Comparisons of the methadone group to each of the two bupirone groups did not show significant differences. The two bupirone groups' curves did not differ significantly either. Areas under the curve values (mean \pm SD) for the 4 groups were as follows: placebo = 102.09 ± 89.71 ; methadone taper = 13.44 ± 31.12 ; bupirone 30 mg = 10.06 ± 36.89 ; bupirone 45 mg = -23.50 ± 60.70 . The lowest value was thus obtained in the patients who had received the higher bupirone dose.

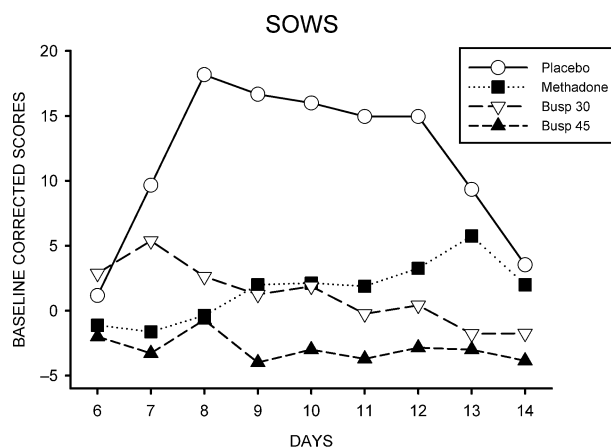


FIGURE 2. SOWS scores following a 5-day stabilization period on methadone. On day 6, methadone was gradually decreased in the methadone group and was discontinued in the placebo, Busp30 (bupirone 30 mg/d), and Busp45 (bupirone 45 mg/d) groups. Treatment was discontinued on day 13. The overall difference between the 4 groups, assessed by repeated-measures ANOVA, was significant ($P = 0.005$). Repeated-measures ANOVAs, comparing group pairs, revealed that the withdrawal symptoms of patients who received placebo were significantly more pronounced than those of patients undergoing a methadone taper or receiving 30 or 45 mg of bupirone ($P = 0.021, P = 0.023, \text{ and } P = 0.013$, respectively). There were no significant differences when the methadone taper was compared with the 2 bupirone doses.

For each individual SOWS symptom, F values and levels of significance of comparisons between the placebo group and each of the 3 other groups are shown in Table 1. Methadone was significantly more effective than placebo in decreasing the severity of symptoms 1, 2, 5, 6, 14, and 16. When compared with placebo, the lower dose of bupirone was significantly more effective in decreasing the severity of symptoms 14 and 15, whereas the higher bupirone dose produced a significant reduction in symptoms 1, 2, 5, 6, 9, 10, 11, 14, 15, and 16.

Objective Opiate Withdrawal Scale

Figure 3 illustrates the OOWS baseline-corrected scores for the 4 patient groups following the 5-day methadone stabilization period. The overall comparison of the 4 patient groups' curves showed a significant group effect [$F(3,25) = 4.16$, $P = 0.016$]. Comparisons between the placebo group and the 3 other groups revealed that the placebo group scores were significantly higher than those of the methadone group [$F(1,12) = 5.61$, $P = 0.035$], than those of the bupirone 30-mg group [$F(1,12) = 5.59$, $P = 0.036$] and than those of the bupirone 45-mg group [$F(1,12) = 13.78$, $P = 0.003$]. There

TABLE 1. Individual SOWS Symptoms: Comparisons of Placebo Group Versus Methadone Taper, Bupirone 30 mg, and Bupirone 45 mg Groups

	Placebo vs.					
	Methadone Taper		Bupirone 30 mg		Bupirone 45 mg	
	F(1,12)	P	F(1,12)	P	F(1,11)	P
1. I feel anxious.	6.18	0.029	3.07	NS	8.13	0.016
2. I feel like yawning.	5.87	0.032	2.46	NS	6.29	0.029
3. I'm perspiring.	0.45	NS	2.73	NS	0.84	NS
4. My eyes are tearing.	2.14	NS	1.42	NS	3.58	NS
5. My nose is running.	7.02	0.021	1.11	NS	5.32	0.042
6. I have goose flesh.	7.47	0.018	3.64	NS	10.64	0.008
7. I am shaking.	1.06	NS	0.37	NS	2.34	NS
8. I have hot flashes.	0.80	NS	1.53	NS	2.03	NS
9. I have cold flashes.	2.77	NS	2.30	NS	6.11	0.031
10. My bones and muscles ache.	3.12	NS	2.61	NS	6.60	0.026
11. I feel restless.	1.90	NS	1.25	NS	7.07	0.022
12. I feel nauseous.	1.94	NS	1.78	NS	3.82	NS
13. I feel like vomiting.	1.79	NS	1.20	NS	2.37	NS
14. My muscles twitch.	5.29	0.040	4.72	0.050	6.36	0.028
15. I have cramps in my stomach.	2.30	NS	4.94	0.046	6.31	0.029
16. I feel like shooting up now.	5.35	0.039	1.95	NS	5.43	0.040

Repeated-measures ANOVAs were used to assess the significance of the comparisons.

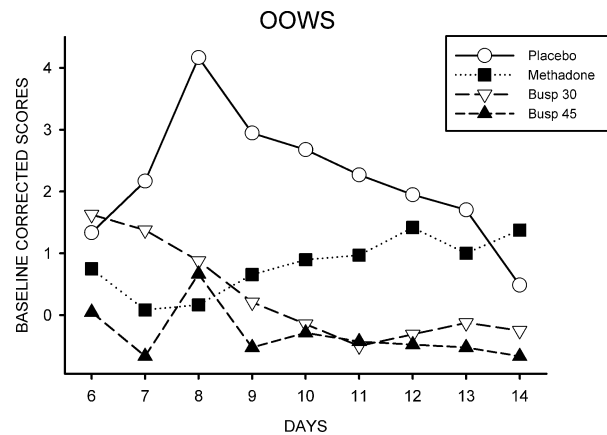


FIGURE 3. OOWS scores following a 5-day stabilization period on methadone. On day 6, methadone was gradually decreased in the methadone group and was discontinued in the placebo, Bup30 (bupirone 30 mg/d), and Bup45 (bupirone 45 mg/d) groups. Treatment was discontinued on day 13. The overall difference between the 4 groups, assessed by repeated-measures ANOVA, was significant ($P = 0.016$). Repeated-measures ANOVAs, comparing group pairs, revealed that the withdrawal symptoms of patients who received placebo were significantly more pronounced than those of patients undergoing a methadone taper or receiving 30 or 45 mg of bupirone ($P = 0.035$, $P = 0.036$, and $P = 0.003$, respectively). There were no significant differences when the methadone taper was compared with the 2 bupirone doses.

were no significant differences when the methadone group was compared with each of the two bupirone groups or when the two bupirone groups were compared with each other. Areas under the curve values (mean \pm SD) for the 4 groups were as follows: placebo = 18.79 ± 10.75 ; methadone taper = 6.25 ± 7.86 ; bupirone 30 mg = 1.31 ± 13.72 ; bupirone 45 mg = -2.55 ± 10.43 . The lowest value was thus obtained in the patients who had received the higher bupirone dose. None of the comparisons of OOWS individual symptoms revealed a significant difference.

DISCUSSION

In this study of heroin addicts stabilized for 5 days on methadone and then withdrawn from this drug, daily bupirone doses of 30 and 45 mg were found to be significantly more effective than a placebo. Global scales assessing subjective and objective withdrawal symptoms failed to show significant differences between a methadone taper and the 2 doses of bupirone. This could be interpreted as indicating that bupirone was at least as effective as the methadone taper in alleviating withdrawal symptoms.

Comparisons of SOWS individual symptoms revealed that there was a significant decrease in 10 of 16 symptoms in patients treated with the higher bupirone dose than in those who had received a placebo. This was true for only 2 symptoms in patients given the lower bupirone dose. The 45-mg

dose appeared more effective in attenuating some symptoms such as anxiety, cold flashes, bone and muscle aches, restlessness, and stomach cramps. Both buspirone doses were well tolerated by patients. If faced with a choice between the two, one might thus consider using the higher dose. The absence of significant differences between the two buspirone doses when compared with one another and not to a placebo could be attributed to the relatively small number of participants in this study, which decreased the power of the analyses.

In the present study, the mean daily dose of intravenous heroin used by patients was 0.62 ± 0.40 g and the mean daily intranasal dose was 0.68 ± 0.40 g. Some patients use larger heroin amounts. The protocol outlined in this study might have to be adapted in these individuals who might need a longer duration of buspirone treatment prior to methadone discontinuation for example.

The exact mode of action of buspirone has not yet been totally elucidated. It interacts with a multiplicity of receptors but is believed to exert most of its clinical effects by interacting with the 5-HT system.¹⁵ Acutely, it activates the 5-HT_{1A} presynaptic receptors localized on the cell bodies and dendrites of the dorsal raphe 5-HT neurons. This results in an inhibition of both cell firing and 5-HT synthesis.^{16,17} However, it has been suggested that repeated administration of buspirone desensitizes 5-HT_{1A} receptors, resulting in an increased release of 5-HT after a few days. Postsynaptically, buspirone acts as a partial 5-HT_{1A} agonist.¹¹ The activation of postsynaptic 5-HT_{1A} receptors mimics the effects of serotonin.¹⁸ Evidence suggests that buspirone has antianxiety and antidepressant activity. It has been postulated that this drug can function as a modulator of 5-HT transmission and restores homeostasis when 5-HT neurotransmission is enhanced (anxiety states) or diminished (depressive disorders).^{19,20} According to New,²¹ "the functional pharmacologic expression of buspirone... may depend on the neurophysiology of the malfunctioning 5-HT synapse." The dose of buspirone administered, baseline concentrations of extracellular 5-HT, individual differences in the distribution and density of the 5-HT_{1A} receptors or other factors could influence buspirone effects.²² Buspirone interacts also with 5-HT₂ receptors¹⁶ and has selective dopamine antagonist properties with possible clinical importance at the inhibitory dopamine D₂ autoreceptor.²³ The major metabolite of buspirone, 1-pyrimidinyl piperazine, interacts with α_2 -adrenergic receptors. Its effect remains controversial with studies showing that it may have anxiolytic properties. Although the interplay between all these receptors is not yet totally understood, the anxiolytic and mild antidepressant effects of buspirone have been established and suggestions for additional clinical applications have been made. If buspirone antiwithdrawal properties are due mostly to its actions on serotonergic pathways, it could be hypothesized that other

drugs enhancing serotonergic neurotransmission might contribute to the attenuation of withdrawal symptoms. However, the possibility that buspirone acts through the interplay of different types of receptors creating unique pharmacologic mechanisms cannot be excluded.

Buspirone has a gradual onset of clinical effects. It has been postulated that its use over a period of days and sometimes weeks is necessary to produce receptor adaptation and result in therapeutic effects. In a pilot study, as well as in this study, buspirone antiwithdrawal effects became manifest after 5 days of daily use.¹¹ For this reason, if opiate detoxification with buspirone is being contemplated on an inpatient unit, another antiwithdrawal agent, such as methadone, should be administered along with it for the first 5 days of treatment. Methadone could then be discontinued and buspirone continued for a few days and then tapered. This could limit hospitalization to 5 days. After methadone is discontinued, patients could be discharged to regular clinics instead of clinics licensed for methadone treatment or to the care of their private physician.

The use of buspirone as an adjunct to a detoxification regimen could be particularly helpful in outpatient settings where the duration of the methadone taper recommended for the detoxification of heroin addicts or methadone maintained patients can be lengthy and has to be carried out in licensed clinics. Different scenarios could be envisaged. For example, buspirone could be given in conjunction with methadone in the course of a methadone taper. When the methadone dose reaches 30 mg, it could be discontinued, thereby shortening the detoxification process. The patient could then be maintained on buspirone for a few days. It is also possible that the simultaneous administration of methadone and buspirone would allow a more rapid methadone taper, with larger and more frequent methadone decrements. Additional trials will be needed to test this hypothesis.

Buspirone has many advantages. It is a nonopioid alternative for the management of withdrawal. It is not sedating, has no abuse potential,^{24,25} has no withdrawal symptoms,²⁶ has a safe side effects profile,^{27,28} spares patients undesirable effects on psychomotor function,^{29,30} and does not potentiate the effects of central nervous system depressants.³¹

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