ORIGINAL ARTICLE

Induction With Levomethadyl Acetate

Safety and Efficacy

Hendrée E. Jones, PhD; Eric C. Strain, MD; George E. Bigelow, PhD; Sharon L. Walsh, PhD; Maxine L. Stitzer, PhD; Thomas Eissenberg, PhD; Rolley E. Johnson, PharmD

Background: Levomethadyl acetate hydrochloride (known as LAAM) is a μ-opioid agonist approved for the treatment of opioid dependence. Clinical trials comparing LAAM and methadone have reported lower patient retention rates during LAAM induction; however, this may reflect dose and schedule differences. Few studies have systematically examined LAAM dose induction. This study compared induction with 3 different LAAM dosage levels.

Methods: In a randomized, double-blind trial, male and female opioid-dependent patients (N = 180) were assigned to 1 of 3 LAAM doses. The low-dose (25 mg) induction was constant from the onset of treatment, the medium-dose (50 mg) induction lasted 7 days, and the high-dose (100 mg) induction lasted 17 days. Safety and efficacy were assessed on retention, urinalysis and self-reported drug use, symptoms, and patient ratings of medication adequacy.

Results: The high-dose group had significantly fewer illicit opioid–positive urine samples in weeks 3 and 4 as compared with the low-dose group. The high-dose group had significantly lower self-reported heroin craving in weeks 2 and 3. All groups demonstrated significant decreases in illicit drug use, withdrawal symptoms, and depression. There were no between-group differences in retention; however, there was a trend ($P = .08$) for lower retention and a greater number of agonist adverse effects were observed in the high-dose group. Overall, LAAM doses were well tolerated by most patients.

Conclusion: Induction with low and medium LAAM doses can be safely and effectively achieved within 7 days. Induction with higher LAAM doses can be safely achieved within 17 days, but may result in greater rates of patient dropout and opioid agonist adverse effects. Therefore, higher doses should be approached more slowly.

Arch Gen Psychiatry. 1998;55:729-736

From the Behavioral Pharmacology Research Unit, Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, Md. Dr Eissenberg is now with the Department of Psychology and Center for Drug and Alcohol Studies, Virginia Commonwealth University, Richmond. For activities unrelated to this study, Dr Johnson is a consultant for the manufacturer of LAAM, Roxane Laboratories Inc, Columbus, Ohio.

LEVOMETHADYL ACETATE hydrochloride (known as LAAM) was approved in 1993 by the US Food and Drug Administration for the treatment of opioid dependence. In early 1998, approximately 3000 patients were being treated with LAAM (oral communication, J. Sincich, Roxane Laboratories Inc, Columbus, Ohio, 1998). Levomethadyl acetate is similar to methadone; it is a μ-opioid agonist with good oral bioavailability and produces opioid blockade. Levomethadyl acetate is reported to be less potent than its active metabolites, nor-LAAM and dinor-LAAM.[1] Compared with methadone, LAAM has a longer half-life,[2-4] reducing dosing frequency to 3 times a week.[5] Levomethadyl acetate is as safe and effective as methadone,[6,7] although patient retention may be lower with LAAM than methadone during induction.[7-9] Although LAAM has been approved for maintenance treatment, uncertainties remain about the early treatment adequacy and patient acceptability of LAAM.[10-12]

Induction is a critical time in agonist substitution treatment. The goal is to transfer the patient to the treatment opioid with minimal complications of opioid withdrawal and adverse effects. A LAAM dose-induction study reaching 50 to 75 mg compared rapid (within 5 dosing days) vs slow (within 13 dosing days) induction schedules. Results indicated that rapid induction was safe and the rate of induction did not influence illicit opioid use.[13] However, this 20-year-old study was open-label and 95% of patients were men.

The purpose of this study was to examine the safety and efficacy of LAAM induction in a contemporary male and female opioid-dependent population and provide detailed characterization of the efficacy of different LAAM doses during induction and the time course of behavior changes associated with treatment initiation.

RESULTS

SUBJECTS

Table 1 summarizes the demographic characteristics for completers vs noncompleters and for completers by dose condition. Noncompleters had significantly

©1998 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 09/03/2014

SUBJECTS AND METHODS

SUBJECTS

Opioid-dependent patients were recruited by word of mouth and referrals from local treatment programs between May 1994 and November 1995. Eligibility criteria included age 21 to 55 years, a preadmission opioid-positive urine specimen, a negative pregnancy test, *DSM-III-R*[14] diagnosis of opioid dependence, and absence of significant psychiatric or medical illness.[15] Nonenrollees, dropouts, and study completers were assisted in seeking alternative treatment. Of 207 patients screened, 180 (110 men, 70 women) were enrolled (**Table 1**).

GENERAL METHODS

The local Institutional Review Board approved the study and informed consent was obtained. The Structured Clinical Interview for the *DSM-III-R* (SCID)[16] was used to diagnose opioid dependence and antisocial personality disorder. Eligible patients were stratified on 4 variables associated with treatment outcome[17-20]: sex, race, cocaine use, and antisocial personality disorder diagnosis, and then randomly assigned to 1 of 3 induction conditions, administered under double-blind conditions. After dose induction, patients were maintained on Monday/Wednesday/Friday doses of 25/25/35 mg (low-dose regimen; n = 62), 50/50/70 mg (medium-dose regimen, n = 59), and 100/100/140 mg (high-dose regimen, n = 59). Levomethadyl acetate doses were selected as equivalent to methadone doses of 20, 40, and 80 mg[21,22] based on a methadone:LAAM relative potency estimate of 1:1.2.[23] Friday doses were increased 40% to compensate for the 72-hour interdose interval.[23] Outcomes during the first 28 days (4 weeks) are presented. Outcomes during the maintenance phase (weeks 5-17) have been presented elsewhere.[15]

DRUG ADMINISTRATION AND CLINIC ATTENDANCE

All patients received 25 mg on their admission day. For the next 13 days, patients attended the clinic daily for medication and active LAAM doses were alternated with placebo (vehicle only). Starting on day 15 patients attended the clinic thrice weekly for medication.

Patients in the low-dose group received 25 mg of LAAM on alternate days throughout the first 14 days. Patients in the medium-dose group received 30, 40, and 50 mg of LAAM on their second, third, and fourth active dosing days, respectively. Patients in the high-dose group received 30 mg of LAAM on their second active dosing day and the dose was then increased 10 mg every other day, with the target maintenance dose being reached on the ninth active dosing day (study day 17).

DRUG PREPARATION

Levomethadyl acetate hydrochloride (10 mg/mL) was obtained from Roxane Laboratories Inc and the National Institute on Drug Abuse, Rockville, Md. Doses were prepared in a volume of 40 mL using a sugar-free sweetened vehicle (Ora-Sweet SF, Paddock Laboratories Inc, Minneapolis, Minn) and water (1:4) containing 12 ng/mL of denatonium benzoate (Bitrex, Macfarlan Smith Ltd, Edinburgh, Scotland) as an additional flavor mask.[15]

CLINICAL TREATMENT

During their first treatment week, patients were assigned to counselors who developed an individualized treatment plan. Patients were expected to meet weekly with their counselor and attend weekly group therapy.

OUTCOME MEASURES

Treatment Retention and Compliance

Retention was calculated as the cumulative number of days in treatment from first dose until completion of 28 days, the blind dose code was broken, or the last day prior to missing medication for 7 days. Compliance was calculated as the number of days the patient was medicated divided by the number of days the patient could be medicated.

Table 1. Demographic Characteristics of Completers vs Noncompleters Randomly Assigned to 1 of 3 Double-blind, Thrice-Weekly LAAM Dose Conditions*

				Completers' LAAM Dose Condition†			
Characteristic	Noncompleters (n = 31)	Completers (n = 149)	Significance	Low (n = 54)	Medium (n = 51)	High (n = 44)	Significance
Mean (SD) age, y	33.2 (5.3)	35.3 (6.8)	F = 2.3, *P* = .1	36.2 (7.2)	35.1 (6.3)	34.5 (6.7)	F = 1.2, *P* = .3
Female, %	38.7	38.9	χ^2 = 0.03, *P* = .9	38.9	35.3	43.2	χ^2 = 0.6, *P* = .7
Nonwhite, %	45.2	46.4	χ^2 = 0.8, *P* = .4	50.0	58.8	52.3	χ^2 = 0.9, *P* = .7
APD, %	35.5	38.3	χ^2 = 0.1, *P* = .8	42.6	33.3	38.6	χ^2 = 1.3, *P* = .5
Legal problems, %	45.2	23.5	χ^2 = 7.0, *P* = .01	27.8	21.6	20.5	χ^2 = 0.9, *P* = .6
Married, %	12.9	20.8	χ^2 = 0.2, *P* = .7	18.5	21.6	22.7	χ^2 = 0.3, *P* = .9
Employed, %	9.9	30.2	χ^2 = 4.4, *P* = .04	35.2	31.4	22.7	χ^2 = 1.8, *P* = .4
Mean (SD) years of education	10.9 (1.8)	11.0 (1.7)	F = 0.1, *P* = .8	11.2 (1.9)	11.0 (1.7)	10.8 (1.6)	F = 0.7, *P* = .5
Mean (SD) past 30-day drug use, d							
Cocaine	12.0 (11.9)	9.6 (11.3)	F = 1.6, *P* = .2	10.3 (11.7)	10.9 (11.9)	7.4 (9.9)	F = 1.5, *P* = .2
Heroin	28.8 (5.4)	29.5 (2.7)	F = 0.9, *P* = .3	29.6 (1.9)	29.9 (0.4)	29.0 (4.4)	F = 0.2, *P* = .8
Mean (SD) lifetime drug use, y							
Cocaine	3.4 (4.4)	2.7 (4.2)	F = 0.8, *P* = .4	2.4 (3.7)	3.3 (5.3)	2.5 (3.4)	F = 1.0, *P* = .4
Heroin	7.3 (5.4)	8.2 (6.7)	F = 0.8, *P* = .4	6.8 (6.3)	8.8 (6.5)	9.2 (7.5)	F = 2.4, *P* = .09
Mean (SD) previous treatment episodes	1.6 (1.6)	1.3 (1.7)	F = 0.5, *P* = .4	1.3 (1.7)	1.3 (1.8)	1.4 (1.7)	F = 0.0, *P* = .9

*LAAM indicates levomethadyl acetate hydrochloride; APD, antisocial personality disorder.
†Dose conditions refer to Monday/Wednesday/Friday doses that were low, 25/25/35 mg; medium, 50/50/70 mg; or high, 100/100/140 mg.

©1998 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 09/03/2014

Safety Assessments

Safety assessment data were obtained from a termination report completed by staff within 14 days of each patient's last LAAM dose.

Urine Testing

Patients provided supervised urine samples for toxicology screening on Mondays, Wednesdays, and Fridays. Samples were tested on-site for the presence of opiates, methadone, cocaine, and benzodiazepines using the enzyme-multiplied immunoassay technique (Syva Corp, Palo Alto, Calif). A specimen was deemed positive if drug metabolite concentration was 300 ng/mL or higher. For quality assurance, urine specimens were sent to an independent laboratory for thin-layer chromatography assay. During the 28-day study period, correlations between the 2 methods for methadone (n = 178), other opiates (n = 179), cocaine (n = 179), and benzodiazepines (n = 179) were 0.81, 0.87, 0.91, and 0.82, respectively.

Counseling Contacts

Using a structured questionnaire, counselors recorded the number and duration of patient contacts per week.

Self-reports

Patients completed 5 self-report questionnaires. (1) The Dose Adequacy Questionnaire measures Holding, Hooked, Liking, Heroin Craving, and Cocaine Craving using a 10-cm visual analog scale anchored on the left by "not at all" (0) and on the right by "a lot" (10). Patients responded by placing a vertical mark on the line. (2) The 20-item Withdrawal Symptom Questionnaire assesses typical opioid withdrawal symptoms (eg, muscle cramps, runny nose). The 10 graded response alternatives for each item ranged from "not at all" (0) to "severe" (9); total scores could range from 0 to 180. (3) The 21-item Beck Depression Inventory assesses typical depressive symptoms.[24] Patients select 1 of 4 answers graded for severity; higher scores reflect greater depressive symptoms and are correlated with depression diagnoses.[24] (4) The 8-item Intravenous (IV) Drug Use questionnaire queried about the number of times in the past week various IV drugs were used. (5) The 10-item Non-IV Drug Use questionnaire asked how many days out of the past 7 days various drugs were used by smoking, snorting, or drinking.

DATA ANALYSIS

For demographic data, first, a single-factor (survivor condition) between-subjects analysis of variance (ANOVA) was used to compare noncompleters with completers. Second, the survivors' demographic data were examined using a single-factor (treatment condition) between-subjects ANOVA. χ^2 Tests were used for categorical variables.

Analyses for outcome measures included a consideration of sex effects, because sex has been shown to influence treatment outcome.[25] Treatment retention was analyzed using the Cox regression model. Main effects and the interaction of treatment and sex were modeled on days in treatment before dropout.

For urine test results, first, the percentage of opioid-positive urine samples and the percentage of cocaine-positive urine samples were calculated for each patient through the end of 28 days to generate means for each group. Second, urinalysis results for all patients who completed 28 days were analyzed using a 3-factor ANOVA. Group factors were treatment condition and sex; treatment week was a within-subject factor. The percentages of opioid-positive urine specimens (opiates and/or methadone) were calculated for each patient based on all available specimens in each week.

Self-report questionnaires for completers were analyzed using a 3-factor ANOVA. Group factors were treatment condition and sex; treatment week was a within-subject factor.

Significance levels of repeated ANOVAs were adjusted for violations of sphericity assumption using the Huynh-Feldt correction. The Tukey honestly significant difference, a 1-step procedure not requiring a significant F test,[26] was used for pairwise comparisons. For group means, SD and 95% confidence interval (CI) were determined.[27] Comparisons for which $P<.05$ are reported as significant.

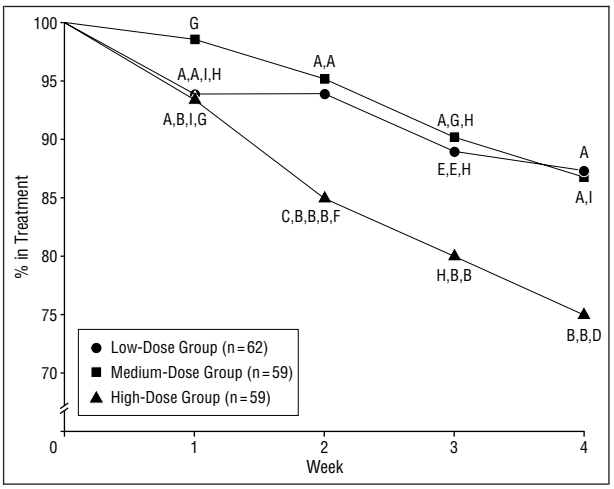
greater frequencies of unemployment and legal problems compared with completers. For completers, there were no significant differences between dose conditions on demographic variables.

TREATMENT RETENTION, COMPLIANCE

Neither drug condition ($\chi^2 = 4.31$; $df = 2$; $P = .11$), sex ($\chi^2 = 0.43$; $df = 1$; $P = .81$), nor their interaction ($\chi^2 = 4.50$; $df = 5$; $P = .48$) were significantly related to treatment survival (**Figure**). There was a trend ($\chi^2 = 3.03$; $df = 1$; $P = .08$) toward a difference between dose conditions with a lower retention rate in the high-dose group. Overall, 83% of the patients completed 28 days.

SAFETY ASSESSMENTS

The Figure shows the number of patients in each group who dropped out and the reason for their early termination. Fifty percent of early terminations were due to failure to attend the clinic for 7 consecutive days (ie, missed 3 consecutive active dosing days) or medication



Percentage of patients in each levomethadyl acetate hydrochloride (LAAM) dose group remaining in treatment at the end of each week. Letter codes correspond to categories and represent an individual patient and his or her reason for termination. Letter codes are as follows: A, missed 7 days; B, agonist adverse effects; C, dislike LAAM; D, LAAM not "holding"; E, medical (not related to study drug); F, death; G, incarceration; H, employment; and I, other.

©1998 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 09/03/2014

Table 2. Time Course and Overall Urinalysis Results*

	LAAM Dose Condition							
	Low, 25 mg (n = 54)				Medium, 50 mg (n = 51)			
	Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4
Opioids								
Overall % (95% CI)	81.6 (86.2-77.0)				77.5 (72.3-83.7)			
Weekly %	89.8	79.3	80.3	77.2	94.1	77.1	70.6	67.9
(95% CI)	(79.7-99.8)	(73.4-85.2)	(70.2-90.4)	(66.2-87.2)	(90.1-98.1)	(66.4-87.6)	(59.4-81.8)	(61.3-74.5)
Cocaine								
Overall % (95% CI)	61.4 (55.4-67.4)				61.1 (54.9-67.3)			
Weekly %	67.6	61.1	57.7	59.3	65.03	60.8	58.2	60.4
(95% CI)	(55.9-79.3)	(49.1-73.1)	(45.5-69.9)	(46.8-71.8)	(54.03-76.03)	(47.6-73.9)	(45.4-71.0)	(47.5-73.3)

*LAAM indicates levomethadyl acetate hydrochloride; CI, confidence interval.
†High dose condition is significantly different from the low dose, P<.05.

Table 3. Self-report Questionnaire Results for Visual Analog Scale Ratings From the Dose Adequacy Questionnaire*

	LAAM Dose Condition							
	Low, 25 mg (n = 54)				Medium, 50 mg (n = 51)			
Dose Adequacy† Questionnaire	Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4
Hooked								
Weekly means	15.9	11.5	15.5	15.4	16.5	20.3	19.8	24.3
(95% CI)	(10.1-21.4)	(7.2-15.8)	(10.0-21.0)	(9.9-20.7)	(10.9-22.1)	(15.2-25.4)	(14.4-25.06)	(18.5-30.1)
Craved heroin								
Weekly means	51.7	48.7	43.1	44.1	42.1	39.9	37.3	31.0‡
(95% CI)	(47.2-56.3)	(39.8-57.6)	(33.6-51.9)	(35.3-52.9)	(33.2-51.0)	(31.4-48.4)	(28.6-46.0)	(23.2-38.8)
Craved cocaine								
Weekly means	25.0	20.6	17.9	19.0	26.3	22.8	27.6	28.7
(95% CI)	(17.0-33.0)	(12.9-28.3)	(10.9-24.9)	(12.0-26.0)	(18.6-34.0)	(15.8-29.8)	(20.0-35.2)	(21.0-36.4)
Holding								
Weekly means	22.2	24.9	24.8	25.4	27.4	31.6	31.4	33.3
(95% CI)	(16.7-27.7)	(19.4-30.4)	(18.4-31.2)	(19.4-31.4)	(21.7-33.1)	(26.1-37.2)	(24.9-37.9)	(26.6-40.0)
Liking								
Weekly means	35.8	36.5	31.7	35.1	39.0	41.1	42.1	45.1
(95% CI)	(28.3-43.3)	(28.9-44.2)	(24.4-39.0)	(27.7-42.5)	(31.0-46.9)	(34.4-47.7)	(34.6-49.6)	(37.9-45.1)

*LAAM indicates levomethadyl acetate hydrochloride; CI, confidence interval.
†For the Dose Adequacy Questionnaire, Hooked refers to the question, "For the past week (last 7 days), how much have you felt hooked by the medication?" Craved Heroin, "How much have you craved heroin for the past week (last 7 days)?" Craved Cocaine, "How much have you craved cocaine for the past week (last 7 days)?" Holding, "How well has this dose of medicine been holding you for the last week (past 7 days)?" Liking, "For the past week (last 7 days), how much have you liked the medicine?"
‡Significantly different from low-dose condition at that week, P<.05.

adverse effects. Failure to attend was the reason for early termination of 3 patients, 4 patients, and 1 patient in the low-, medium-, and high-dose groups, respectively. Thus, fewer patients dropped out of the high-dose group owing to attendance failure. All patients who dropped out because of LAAM-related adverse effects were in the high-dose group (5 women and 3 men). The adverse effects reported were primarily agonist-related including anorexia, feeling overmedicated, sedated/drowsy, nausea, and vomiting. Overall, the 31 patients who dropped out averaged 14 days in treatment and had a mean dose of 53 mg. One female patient assigned to the high dose died during her second week in treatment. Although no specific cause of death was determined, toxicological analysis revealed the presence of multiple drugs and LAAM, nor-LAAM, and dinor-LAAM levels were within expected ranges.[16]

URINE TESTING

The overall percentage of opiate-positive urine samples did not differ significantly among groups (**Table 2**). Within each condition, rates of opiate-positive urine samples decreased over time. Later in treatment (weeks 3 and 4), there were significantly lower rates of illicit opioid-positive urine samples for the high-dose compared with the low-dose group. Groups did not differ in rates of cocaine-positive urine samples either globally or over time. Opiate-positive ($F_{1,143} = 1.43$; $P = .23$) and cocaine-positive ($F_{1,143} = 2.45$; $P = .12$) urine results were independent of sex.

COUNSELING CONTACT

There were no differences between groups for the total number of counseling contacts or total time counsel-

©1998 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 09/03/2014

High, 100 mg (n = 44)				Significance					
				Treatment		Time		Interaction	
Week 1	Week 2	Week 3	Week 4	Test	*P*	Test	*P*	Test	*P*
71.1 (65.1-77.1)				$F_{2,146} = 1.66$	.91	$F_{3,438} = 30.47$	.00	$F_{6,438} = 2.78$	.01
90.1 (83.5-96.7)	76.1 (64.5-87.7)	61.0† (49.0-73.0)	56.4† (42.9-70.0)						
60.4 (53.6-67.2)				$F_{2,146} = 0.01$	.99	$F_{3,438} = 1.56$	.32	$F_{6,438} = 1.32$	.26
64.4 (51.0-77.8)	69.3 (56.3-82.3)	54.5 (40.6-68.4)	53.4 (39.2-67.6)						

High, 100 mg (n = 44)				Significance					
				Treatment		Time		Interaction	
Week 1	Week 2	Week 3	Week 4	Test	*P*	Test	*P*	Test	*P*
12.36 (6.8-18.0)	17.41 (11.5-23.3)	19.81 (14.1-25.5)	23.76 (15.9-31.5)	$F_{2,146} = 1.68$	.19	$F_{3,438} = 5.27$	.00	$F_{6,438} = 2.02$	.07
51.4 (41.7-61.1)	36.0‡ (27.5-44.5)	30.0‡ (21.3-38.7)	32.2 (22.7-41.7)	$F_{2,146} = 1.14$	.12	$F_{3,438} = 14.50$	.00	$F_{6,438} = 2.20$	.04
22.7 (15.3-30.1)	16.8 (10.8-22.8)	20.9 (13.3-28.5)	22.7 (15.2-30.2)	$F_{2,146} = 1.12$	.33	$F_{3,438} = 2.53$	.06	$F_{6,438} = 1.58$	.16
22.8 (17.9-27.7)	29.8 (23.6-36.0)	36.9 (30.1-43.7)	30.5 (22.9-38.0)	$F_{2,146} = 2.05$	.13	$F_{3,438} = 7.85$	.00	$F_{6,438} = 2.01$	.07
45.1 (36.4-53.8)	42.5 (34.2-50.8)	47.1 (37.8-56.4)	44.9 (36.0-53.9)	$F_{2,146} = 2.42$	.09	$F_{3,438} = 0.15$	.91	$F_{6,438} = 1.19$	.31

ors spent with patients. Each group averaged 1 contact per week. Each contact averaged 21, 21, and 19 minutes for low-, medium- and high-dose groups, respectively.

SELF-REPORTS

Dose Adequacy Questionnaire

Table 3 presents the results from the Dose Adequacy Questionnaire. For the measure of Hooked, there was a main effect of time. Patients on the highest LAAM dose felt more hooked in week 4 than week 1.

For Heroin Craving, there was a significant main effect for time and treatment × time interaction. Compared with the low-dose group, the high-dose group reported less heroin craving for weeks 2 and 3 and the medium-dose group reported less craving in week 4.

There were no main effects or interactions for Cocaine Craving. For the measure of Holding, there was a main effect of time with patients reporting increased ratings of the medication holding. Neither group nor time were significant for Liking of the medication.

Withdrawal Symptom Questionnaire

There were significant main effects for sex and time on Withdrawal Symptom Questionnaire scores (**Table 4**). At baseline, women reported higher Withdrawal Symptom Questionnaire scores than men. There was a significant decrease over time in Withdrawal Symptom Questionnaire scores during the study for both sexes at all LAAM doses.

Beck Depression Inventory

There were no significant differences between treatment groups on Beck Depression Inventory scores, although there were significant main effects for time ($F_{3,429} = 69.87$; $P < .001$) and sex ($F_{1,143} = 10.1$; $P = .002$). Beck Depression Inventory scores for all groups significantly decreased in weeks 2, 3, and 4 relative to week 1. Women reported higher Beck Depression Inventory scores than men throughout the study.

©1998 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 09/03/2014

Table 4. Self-report Questionnaire Results for Total Scores on the Withdrawal Symptom Questionnaire

Withdrawal Symptom Questionnaire	LAAM* Dose Condition									
	Low, 25 mg (n = 54)					Medium, 50 mg (n = 51)				
	Week 0	Week 1	Week 2	Week 3	Week 4	Week 0	Week 1	Week 2	Week 3	Week 4
Women†										
Means	95.4	61.6	54.0	50.1	52.8	107.9	54.4	47.0	50.0	41.8
(95% CI)	(78.2-112.6)	(45.2-78.0)	(40.0-68.0)	(34.9-65.3)	(34.0-71.6)	(97.1-118.7)	(40.2-68.6)	(33.0-61.0)	(35.0-65.0)	(25.8-57.8)
Men										
Means	60.3	32.5	26.4	22.7	22.8	72.2	35.3	34.9	29.5	29.4
(95% CI)	(47.1-73.5)	(24.7-40.3)	(19.8-33.0)	(16.1-29.3)	(16.4-29.2)	(58.6-85.8)	(25.9-44.7)	(24.1-45.7)	(20.1-38.9)	(19.8-39.0)

*LAAM indicates levomethadyl acetate hydrochloride; CI, confidence interval.
†There was a main effect for sex ($F_{1,146}$) = 14.3, P = .00.

Table 5. Self-reports of Illicit Opioid and Cocaine Use*

Daily IV Drug Use Questionnaire	Low, 25 mg (n = 54)					Medium, 50 mg (n = 51)				
	Week 0	Week 1	Week 2	Week 3	Week 4	Week 0	Week 1	Week 2	Week 3	Week 4
IV opioid use†										
Means	28.0	10.0	8.7	5.7	5.1	34.4	13.8	11.5	9.5	6.2
(95% CI)	(20.6-35.4)	(6.5-13.5)	(4.4-13.0)	(3.2-8.2)	(2.6-7.7)	(23.7-44.6)	(8.6-19.0)	(5.4-17.6)	(4.0-14.9)	(2.5-9.9)
IV cocaine use‡										
Means	11.0	3.2	3.3	2.4	1.8	12.6	7.3	6.9	7.3	7.6
(95% CI)	(5.5-16.5)	(1.2-5.2)	(1.2-5.4)	(0.8-4.0)	(0.6-2.9)	(7.7-17.5)	(3.4-11.0)	(2.6-11.2)	(3.3-11.3)	(2.9-12.3)

*IV indicates intravenous; CI, confidence interval.
†Includes heroin, other opioids, and heroin-cocaine combinations ("speedball").
‡Includes cocaine and heroin-cocaine combinations ("speedball").

IV Drug Use Questionnaire

There were no significant group differences or group × time interactions, but there were significant decreases over time in response to many questions. Self-reported IV drug use did not differ between sexes. Completers reported IV opioid use an average of 34 times in the 7 days before entering treatment (95% CI, 30.0-37.6) vs an average of 6.2 times (95% CI, 4.9-7.5) in the last 7 days of the study (approximately an 80% decrease). Compared with baseline, self-reported IV opioid use was significantly less in weeks 1 through 4 (**Table 5**).

No between-group differences or changes over time were seen in IV cocaine use, though reported rates did decline to half of pretreatment rates (Table 5).

Non-IV Drug Use Questionnaire

Self-reported non-IV drug use decreased significantly with time in all groups relative to baseline (data not shown).

COMMENT

This is the first randomized double-blind clinical trial assessing safety and efficacy of induction with several LAAM doses in a contemporary opiate-abusing population. More than 80% of enrollees were retained and they attended more than 90% of scheduled clinic visits. These high retention and compliance rates suggest induction onto LAAM via 10 mg increases every other day is well tolerated.

Although the overall retention rate was not different between groups, the pattern of dropout and drug use differed. For instance, although 100 mg of LAAM was most effective in reducing opioid use and craving, it was associated with a greater incidence of agonist adverse effects and highest dropout percentage (25% vs 13% and 14% for medium- and low-dose groups, respectively). Unlike the other groups, only 1 high-dose group patient dropped out because of missing 7 days. All patients who dropped out because of agonist adverse effects were in the high-dose group and the average LAAM dose received before dropping out was 73 mg, suggesting that the present dose escalation procedure may be appropriate only up to 70 to 80 mg.[23] A slower rate of dose increase after achieving a 50-mg dose should decrease dropouts caused by agonist adverse effects. This limitation is likely due to the gradual accumulation of active LAAM metabolites.

A majority (5/7) of high-dose noncompleters reporting excessive opioid agonist effects were women. Perhaps these women received higher milligram per kilogram doses compared with men, resulting in overmedication.[15] Sex differences observed on other outcome measures including depression and withdrawal severity also suggest that women may differ in treatment needs.

©1998 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 09/03/2014

High, 100 mg (n = 44)					Significance					
					Treatment		Time		Interaction	
Week 0	Week 1	Week 2	Week 3	Week 4	Test	*P*	Test	*P*	Test	*P*
83.8 (66.0-101.6)	43.2 (26.6-59.8)	42.0 (27.2-56.8)	33.2 (20.6-45.8)	33.0 (19.8-46.2)	$F_{2,146} = 0.39$	.66	$F_{3,438} = 98.3$	.00	$F_{6,438} = 0.54$	.6
72.2 (56.2-88.2)	41.3 (29.9-52.7)	30.6 (21.0-40.2)	27.9 (21.0-40.2)	31.3 (19.7-42.9)	$F_{2,146} = 0.08$	.93	$F_{3,438} = 59.18$	.00		

High, 100 mg (n = 44)					Significance					
					Treatment		Time		Interaction	
Week 0	Week 1	Week 2	Week 3	Week 4	Test	*P*	Test	*P*	Test	*P*
37.4 (23.7-51.1)	12.6 (9.6-15.6)	9.9 (4.4-15.4)	5.5 (3.3-7.7)	10.3 (2.8-17.8)	$F_{2,146} = 0.08$	.93	$F_{3,438} = 59.18$	.00	$F_{6,438} = 0.54$	.6
11.0 (5.5-16.5)	5.4 (1.2-9.6)	5.2 (1.8-8.6)	3.5 (0.4-6.6)	6.6 (0.0-13.2)	$F_{2,146} = 2.08$	.13	$F_{3,438} = 1.01$	.37	$F_{6,438} = 1.63$	.2

High-dose LAAM decreased subjective reports of opioid craving and withdrawal while objective urinalysis results showed that high-dose LAAM decreased illicit opioid use by 30% within 28 days. Taken together, these data may suggest that factors other than drug craving and withdrawal result in drug use. The difference observed in subjective self-report and objective urinalysis is not incongruent because urinalysis is an insensitive index of drug use (ie, reducing use from 8 doses per day to 2 doses per day is undetected by urinalysis; both rates result in 100% positive urine specimens). Therefore, self-reports and objective toxicology are both important and are complementary outcome indices.

Results from the Dose Adequacy Questionnaire and Withdrawal Symptom Questionnaire suggest that LAAM is acceptable to most patients and suppresses withdrawal symptoms. The present Holding and withdrawal symptoms scores are similar to scores observed in patients maintained on comparable doses of methadone.[28] Thus, these data help remove uncertainty over patient acceptability of LAAM.

Significant harm reduction occurred for patients in all LAAM groups. Self-reported weekly IV drug use revealed large and rapid reductions in IV opiate and other drug use. Reports of non-IV drug use also decreased with time, though less dramatically. However, one question asked how many times patients used IV drugs, whereas the other asked how many days they used non-IV drugs; occasions of use may be a more sensitive index than days of use. This is also consistent with the difference observed in urinalysis and self-reported opiate use.

Several limitations should be considered when evaluating these results. First, the randomized-dose assignment did not allow for flexible individualized dosing; superior results may be obtained by titrating the dose to clinical response. Second, the lack of a placebo group does not permit a complete evaluation of efficacy; however, the 3 dose regimens do characterize relative efficacy. Finally, because the present induction period culminated in different maintenance doses, other induction methods remain to be studied to find the optimal clinical strategy.

In summary, these results show that induction with low and medium LAAM doses can be safely and effectively achieved within 7 days. Induction with a high LAAM dose within 17 days decreases opiate use and craving but is associated with increased dropout owing to opioid agonist adverse effects. Clinical judgment based on subjective agonist and objective drug use indices should be used when increasing the dose. Our study contradicts the perceptions that LAAM is less acceptable to patients, that induction must be accomplished over several weeks, and that there are few early opioid agonist effects. This and other reports on LAAM's use in treating opiate dependency should provide important data to guide the optimal prescribing of LAAM pharmacotherapy.

©1998 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 09/03/2014

Accepted for publication April 9, 1998.

This research was supported by grants P50 DA05273, K05 DA00050, K20 DA00166, and T32 DA 07209 from the US Public Health Service, Washington, DC.

Preliminary results were presented at the annual meeting of the College on Problems of Drug Dependence, San Juan, Puerto Rico, June 27, 1996.

We thank Tim Mudric for data management, John Yingling for technical services, Mike DiMarino for statistical analyses, and the pharmacy, recruiting, dispensary-nursing, counseling, toxicology, and clinical computer center support staffs for their excellent services.

Reprints: Rolley E. Johnson, PharmD, The Johns Hopkins University School of Medicine, Department of Psychiatry and Behavioral Sciences, Behavioral Pharmacology Research Unit, 5510 Nathan Shock Dr, Baltimore, MD 21224-6823.

REFERENCES

1. Ling W, Rawson RA, Compton MA. Substitution pharmacotherapies for opioid addiction: from methadone to LAAM and buprenorphine. *J Psychoactive Drugs*. 1994;26:119-128.
2. Fraser HG, Isbell H. Actions and addiction liabilities of alpha-acetyl-methadol in man. *J Pharmacol Exp Ther*. 1952;105:458-465.
3. Henderson GL. Pharmacodynamics of LAAM in man: plasma levels of LAAM and its metabolites following acute and chronic administration in man (fourth- and sixth-quarter progress reports), 1974-1975. In: Blaine JD, Renault P, eds. *Rx: 3x/Week LAAM-Alternative to Methadone: NIDA Research Monograph 8*. Rockville, Md: National Institute on Drug Abuse; 1976:64-65.
4. Billings RE, McMahon RE, Blake DA. ι-Acetylmethadol (LAM) treatment of opiate dependence: plasma and urine levels of two pharmacologically active metabolites. *Life Sci*. 1974;14:1437-1446.
5. Ling W, Charuvastra VC, Klett CJ. Current status of the evaluation of LAAM as a maintenance drug for heroin addicts. *Am J Drug Alcohol Abuse*. 1975;2:307-315.
6. Ling W, Charuvastra C, Kaim S, Klett J. Methadyl acetate and methadone as maintenance treatments for heroin addicts. *Arch Gen Psychiatry*. 1976;33:709-720.
7. Ling W, Klett JC, Gillis RD. A cooperative clinical study of methadyl acetate, I: three times-a-week regimen. *Arch Gen Psychiatry*. 1978;35:345-353.
8. Senay EC, Dorus W, Renault RF. Methadyl acetate and methadone: an open comparison. *JAMA*. 1977;237:138-142.
9. Savage C, Karp EG, Curran SF, Hanlon TE, McCabe LO. Methadone/LAAM maintenance: a comparison study. *Comp Psychiatry*. 1976;17:415-424.
10. Zangwell BC, McGahan P, Dorozynsky L, McLellan AT. How effective is LAAM treatment? clinical comparison with methadone. In: Harris LS, ed. *Problems of Drug Dependence, 1985: NIDA Research Monograph 67*. Rockville, Md: National Institute on Drug Abuse; 1985.
11. Swan N. States slow to approve LAAM. *NIDA Notes*. 1994;9:12-13.
12. Prendergast ML, Grella C, Perry SM, Anglin MD. Levo-alpha-acetylmethadol (LAAM): clinical, research and policy issues of a new pharmacotherapy for opioid addiction. *J Psychoactive Drugs*. 1995;27:239-247.
13. Judson BA, Goldstein A. Levo-alpha-acetylmethadol (LAAM) in the treatment of heroin addicts, I: dosage schedule for induction and stabilization. *Drug Alcohol Depend*. 1979;4:461-466.
14. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*. Washington, DC: American Psychiatric Association; 1987.
15. Eissenberg T, Bigelow GE, Strain EC, Walsh SL, Brooner RK, Stitzer ML, Johnson RE. Dose-related efficacy of levomethadyl acetate for treatment of opioid dependence: a randomized clinical trial. *JAMA*. 1997;277:1945-1951.
16. Spitzer RL, Williams JBW, Gibbon M. *Instruction Manual for the Structured Clinical Interview for* DSM-III-R. New York, NY: New York State Psychiatric Institute; 1987.
17. McLellan AT, Luborsky LK, Woody GE, O'Brien CP, Druley KA. Predicting response to alcohol and drug abuse treatments. *Arch Gen Psychiatry*. 1983;40:620-625.
18. Woody GC, McLellan AT, Luborsky L, O'Brien CP. Sociopathy and psychotherapy outcome. *Arch Gen Psychiatry*. 1985;42:1081-1086.
19. Hartel DM, Schoenbaum EE, Selwyn PA, Kline J, Davenny K, Klein RS, Friedland GH. Heroin use during methadone maintenance treatment: the importance of methadone dose and cocaine use. *Am J Public Health*. 1995;85:83-88.
20. Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Useful predictors of outcome in methadone-treated patients: results from a controlled clinical trial with three doses of methadone. *J Maintenance Addict*. In press.
21. D'Aunno T, Vaughn TE. *Methadone Maintainence: Some Treatment Programs Are not Effective, Greater Federal Oversight Needed*. Washington, DC: US General Accounting Office; 1990.
22. D'Aunno T, Vaughn TE. Variations in methadone treatment practices: results from a national study. *JAMA*. 1992;267:253-258.
23. Medical Economics Data. *Physicians Desk Reference*. Montvale, NJ: Medical Economics Data Production Co; 1997.
24. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4:53-63.
25. Weiss RD, Martinez-Raga J, Griffin ML, Greenfield SF, Hufford C. Gender differences in cocaine dependent patients: a six-month follow-up study. *Drug Alcohol Depend*. 1997;44:35-40.
26. Hochberg Y, Tamhane AC. *Multiple Comparison Procedures*. New York, NY: John Wiley & Sons; 1987.
27. Pocock SG. *Clinical Trials: A Practical Approach*. New York, NY: John Wiley & Sons; 1983.
28. Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Buprenorphine versus methadone in the treatment of opioid dependence: self-reports, urinalysis and Addiction Severity Index. *J Clin Psychopharm*. 1996;16:58-67.

©1998 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 09/03/2014