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Journal

Addiction, 100(8)

ISSN

0965-2140

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Publication Date

2005-08-01

Peer reviewed

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Levo-alpha-acetylmethadol (LAAM) versus methadone: treatment retention and opiate use

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Submitted 2 December 2003;
initial review completed 26 February 2004;
final version accepted 15 February 2005

ABSTRACT

Aims To compare the effects of levo-alpha-acetylmethadol (LAAM) and methadone maintenance (MM) on treatment retention and abstinence from opiate use.

Design A two-group experimental design with patients randomly assigned (2 : 1 LAAM : MM) to receive LAAM (three doses per week) or methadone (daily dosing).

Setting A community clinic in Los Angeles, California.

Participants A total of 315 patients seeking LAAM or methadone maintenance.

Intervention LAAM or methadone maintenance, plus ancillary services available to all patients. LAAM and methadone dose levels varied according to clinical judgement. Electrocardiograms were administered to LAAM patients monthly.

Measurements Treatment status at 26-week follow-up and number of days retained in treatment, weekly clinical urine tests and 26-week research urine test.

Findings LAAM and methadone patients did not differ on treatment retention. LAAM patients were less likely to test positive for opiate use during treatment (40% versus 60%) and at 26-week follow up (39.8% versus 60.2%). Benefits of LAAM were confined to patients ($n = 204$) still in treatment at 26 weeks (33% positive in patients receiving LAAM and 61% in patients receiving methadone). No adverse events, cardiological or otherwise, were observed with LAAM administration.

Conclusions LAAM is an effective medication for the treatment of opiate dependence with clinical advantages due not only to the reduction of opiate use but also to the alternate-day dosing schedule. LAAM may be more effective than methadone in promoting abstinence from opiate use among patients for whom LAAM is an acceptable alternative to methadone.

KEYWORDS LAAM treatment, moderator effects, outcomes, retention.

INTRODUCTION

Opiate agonist treatment of opiate dependence has relied almost exclusively on methadone (MM) since the mid-1960s, generally in a maintenance regimen requiring daily dosing. As methadone maintenance programs proliferated, clinicians and researchers observed practical deficiencies of methadone as prescribed under federal regulations. Deficiencies included variation in the drug's effects among patients, the inconvenience of daily dosing and the potential for diversion of methadone to illicit use [1–7]. These deficiencies, along with the need to accommodate greater numbers of opiate addicts seeking treatment during the 1970s, spurred consideration of alternative medications for treating opiate dependence. One such alternative is levo-alpha-acetylmethadol

© 2005 Society for the Study of Addiction doi:10.1111/j.1360-0443.2005.01122.x

(LAAM), first proposed and tested by Jaffe *et al.* [8] in a pilot study conducted at the University of Chicago and reported in the literature in 1970. Despite promising findings, LAAM remained an investigational new drug until approved by the Food and Drug Administration (FDA) in 1993, nearly 25 years later. Like methadone, LAAM in a maintenance regimen suppresses withdrawal symptoms and blocks intoxication effects of illicit opiates. The chief clinical advantage of LAAM over methadone is the duration of stable effect. Lasting 48–72 hours instead of 24 hours typical of methadone, LAAM can be taken three times per week instead of daily. There is also limited clinical evidence suggesting that some patients respond better to LAAM than to methadone, in part because of its longer interdosing duration and stability of effect.

Although clinical trials and community-based treatment evaluations have shown LAAM to be safe for most patients and generally equivalent in efficacy to methadone [8–12], LAAM was not embraced widely by treatment providers, despite major educational efforts by its maker, Roxane Laboratories, Ridgefield, CT, USA and the National Institute on Drug Abuse. Three years after FDA approval, only 810 patients were maintained on LAAM in 62 of 750 licensed clinics in the United States [13]. One hindrance to the use of LAAM in community-based treatment is concern about LAAM's potential side-effects. Recent reports of adverse events among some LAAM patients [14] indicate a possibility of cardiac arrhythmia. While a direct comparison of LAAM and methadone found few differences in cardiac measures [15], the well-established benefits of methadone appear to have outweighed the importance of systematic and close examination of the risk of side effects associated with methadone. For these reasons, Roxane Laboratories has discontinued the sale and distribution of LAAM, a decision that may take this medication out of play indefinitely regardless of its benefits for many patients [16].

Despite these cumulative hindrances, it is important to maintain full documentation of LAAM's effects, both in general community practice and in clinical trials. During trials cited above, doses of methadone and LAAM were relatively low and held constant for all patients. In contrast, standard community practice is to vary the dose in accord with clinical signs assessed at the outset of treatment and periodically thereafter. LAAM and methadone should therefore be compared under a flexible dosing protocol, i.e. when the dose is allowed to vary within patients (over time) and across patients according to clinical judgement. In a flexible dosing study using urine-based measures, Johnson *et al.* [17] found a lower rate of opiate use in patients assigned randomly to LAAM than in patients assigned to either of two methadone conditions (low- and high-dose), but this finding was based only on patients retained in the treatment to which they had been assigned (51% of the sample overall). Ritter *et al.* [18] compared the efficacy of LAAM and methadone in flexible-dosing treatment regimens. Patients were randomized to receive either LAAM or methadone. There were no significant differences between LAAM and methadone in treatment retention. LAAM patients had lower opiate use rates on some, but not all, indicators. The authors concluded that 'the next challenge is to resolve outstanding safety concerns with LAAM' [18, p. 1615]. This study, however, had a relatively small sample of patients ($n = 93$) randomized to the two conditions.

Important for community program or primary care practice, acceptability of LAAM appears to differ among patients [13,14,16,19]. Many express a strong preference for LAAM over methadone because the former has a milder, more consistent pharmacological effect and does not require daily dosing. They feel 'more normal' and 'less like an addict' [20] on LAAM. Other patients, however, report side effects or inadequate relief from withdrawal symptoms at the doses prescribed. Fixed-dose studies have generally found longer retention for methadone than for LAAM, [2,3,21] but the flexible-dose study by Ritter *et al.* [18] found equal retention.

Our study, funded by the National Institute on Drug Abuse, compared the effectiveness of LAAM maintenance (LAAM) and methadone maintenance (MM) in promoting abstinence from opiate use among patients attending a community-based clinic (Matrix) in Los Angeles, California. Here we report treatment retention, opiate use and other illicit drug use during treatment and at a follow-up occurring 26 weeks after treatment entry. Our primary measure of retention was treatment status (still enrolled or not) at the 26-week follow-up; our primary measure of opiate use was based on test results from urine specimens collected weekly by the treatment program and a research urine specimen collected at the follow-up interview. To check for a possible side effect of the use of cocaine or other illicit drugs we compared LAAM and MM patients on such use, detected by urine testing, during treatment and at follow-up. Finally, because LAAM's effect on opiate use may be most apparent among patients who remain in treatment long enough to be stabilized at a clinically optimal dose, we tested the interaction of condition (LAAM versus MM) and treatment retention (status at 26 weeks) to determine whether LAAM's effect on opiate use was contingent on retention.

METHOD

Subjects

People seeking maintenance treatment for opiate dependence were recruited between February 1997 and

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January 1999 through outreach to local agencies (e.g. social service organizations and medical clinics) and through patient and street word-of-mouth. Prospective subjects were informed by trained, research-experienced clinic staff that the study objective was to compare the effectiveness of LAAM maintenance and methadone maintenance and that they would be paid $35 for completion of each follow-up ($25 for the interview and $10 for a urine specimen provided voluntarily).

A total of 340 patients completed informed consent and were randomized to LAAM or MM conditions. Twenty-five of these patients did not return for their first dosing or, if dosed, did not return to complete intake procedures within 2 weeks required for our medication induction schedule (see below). These 25 were distributed across the LAAM and MM conditions in a 2 : 1 ratio, reflecting the experimental design (17 LAAM, eight MM). Because these patients did not differ on any of the background characteristics examined (see below), had minimal or no exposure to either treatment, and were not lost differentially from the sample or from treatment condition, we dropped them from the study. Our resulting design was a 'modified' intent-to-treat paradigm with 315 patients. At the 6-month follow-up, 19 patients (13 LAAM, six MM) could not be located, yielding an analytical sample of 296. Study retention at 26 weeks was equal in both conditions (94%), and the patients lost to follow-up did not differ from the retained sample on patient background characteristics.

Table 1 shows self-reported characteristics of patients in the analytical sample. LAAM and MM patients were similar on all characteristics except race/ethnicity. For example, one-third of patients in each condition were (non-pregnant) women. Their median age was 45 years, about 20% were employed at intake, and the mean duration of regular opiate use was over 20 years. Despite random assignment, patients in the two conditions differed by race/ethnicity ($P = 0.03$). African Americans comprised 42% of patients in the LAAM condition and only 33% in the MM condition, whereas non-Hispanic white patients were 16% of the LAAM condition and 24% of the MM condition. Accordingly, analyses included race/ethnic indicator variables as covariates. For additional information on sample characteristics, see Table 1.

Table 1 Sample characteristics.

	LAAM	*MM*
Sex (% women)	27	35
Age (mean, SD)	44.8 (7.5)	45.4 (7.5)
High school completion (% yes)	20	27
Race/ethnicity (%)*		
African Americans	42	33
Hispanics	38	33
Non-Hispanic whites	16	24
Other	4	10
Employed (% yes)	23	20
Ever arrested (% yes)	95	98
Ever incarcerated (% yes)	78	82
Ever used opiates by injection (% yes)	96	98
Ever used cocaine with opiates by injection (% yes)	79	74
Ever used crack cocaine (% yes)	77	77
Ever in drug treatment (% yes)	96	99
Daily opiate use in past 30 days (% yes)	68	60
Years of regular opiate use (mean, SD)	21 (9.9)	22 (9.5)

*$P = 0.03$. All measures were self-reported. All differences except race/ethnicity were non-significant.

Study design and protocol

We followed clinical procedures suggested for careful and prudent induction of clients onto methadone and LAAM and subsequent maintenance on either medication. To check for possible adverse cardiological events, medical staff at the clinic administered electrocardiograms to LAAM patients on a monthly basis.

Design

The project used a two-group experimental design. On the basis of a computer-generated random numbers table, patients were randomly assigned at a 2 : 1 ratio to either LAAM or MM for subsidized care, including standard clinic services (described below). The 2 : 1 ratio was chosen to ensure sufficient power to detect any clinically meaningful difference between the LAAM and MM conditions while also maximizing power for analyses of differential effectiveness within the LAAM condition. Among 315 patients in the intake sample, 209 were assigned to the LAAM condition and 106 to the MM condition.

Methadone treatment

Both conditions began with a 2-week induction to methadone maintenance treatment. Patients received an initial methadone dose of 20, 30 or 40 mg. (The 30- and 40-mg doses were split into half-doses, administered 20–30 minutes apart. Split dosing allowed observation of any signs or symptoms of adverse reaction.) Patients were considered to have stabilized on methadone when dose levels were both high enough to suppress craving for opiates, withdrawal symptoms or drug-seeking behavior and low enough to avoid sedation from the medication. If medication increases were deemed necessary to achieve stabilization, dosing was increased 1–10 mg per day until

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adverse signs were suppressed. Dose increases generally occurred within 24 hours of patients' requests.

LAAM treatment

As in Marion *et al.* [22] induction onto methadone before cross-over to LAAM allowed clinicians to observe patients initially on a daily basis. After the first 2 weeks of MM cross-over occurred if patients had achieved stabilization on methadone, with an additional week for those for whom stabilization had not yet occurred. LAAM patients received education on treatment with LAAM (provided as ORLAAM™, levomethadyl acetate hydrochloride oral solution, by Roxane Laboratories) and were cautioned regarding LAAM's effects (e.g. time between dosing and onset of effect). For most patients, the recommended initial dose of LAAM was 1.2 times their daily dose of methadone, not to exceed 120 mg. Patients randomized to the LAAM condition went through a further stabilization period for up to 2 weeks to achieve optimal LAAM dosing. Adjustments after the initial dose level were usually made in 5–10 mg increments added at every second or third dose, inasmuch as increasing the dose too rapidly can result in oversedation.

Dose variation

The initial dose of LAAM and methadone varied in relation to the patient's drug use history and medical evaluation. The dose could be adjusted at any time following stabilization, according to clinical judgement. Dosing did in fact vary within patient over time and among patients. The mean maximum dose for the MM group was 67.4 mg, and variability around this mean was substantial (SD = 17.3). The mean maximum dose for the LAAM group was 77.5 mg, and variability was again substantial (SD = 17.4). After stabilization, further dose adjustments were common; 77% of LAAM patients and 85% of MM patients had dose adjustments after stabilization. Finally, Friday doses were increased, typically by 5–10 mg, for LAAM patients on a Monday–Wednesday–Friday schedule, and LAAM patients experiencing discomfort on Sundays were able to come into the clinic for a small methadone dose, typically 20 mg. (The increase in Friday dosing is reflected in mean dosing data above.)

Ancillary services

In addition to medication visits (7 and 3 days per week for MM and LAAM patients, respectively), services available to patients included HIV education, testing and counseling; medical, psychiatric and psychosocial services; and a cocaine users group, which met twice weekly and followed a 16-week curriculum known as the Matrix model [23]. Female patients were offered transportation to a nearby health clinic for free breast and cervical cancer screening.

Treatment termination

Patients could be terminated by the clinic for any of the following reasons: clinic attendance less than 50% during any period of 30 consecutive days; disciplinary problems such as threats to other patients; or any ongoing serious adverse reactions to either medication that were not reversible by adjustments in dose as determined by the clinic's medical director. In the analysis sample of 296 patients for whom complete 26-week data were available, five were terminated by the clinic: one because of disciplinary reasons, and four (two in LAAM and two in MM) because of health problems unrelated to medication. These patients were retained in the analysis.

Data collection

Intake interview

All patients completed an intake interview to assess their personal background and drug use and treatment histories, criminal behavior and criminal justice involvement, social and family relationships, HIV risk behavior and HIV-related perceptions, education and employment history, motivation for treatment and mental health status. This interview required 90–180 minutes and was conducted by trained research staff. Subjects were not paid for intake interviews as they were receiving free treatment.

Follow-up interviews

At 26 weeks after intake, staff re-interviewed patients for 90–120 minutes to update information on drug use, other status measures, treatment services received and utilization of health services outside the clinic. A urine specimen was obtained to assess recent drug use. A payment of $25 was given for each interview, and an additional $10 for the provision of a voluntary urine specimen (research as opposed to a clinical specimen).

Measures

Retention

Treatment status at 26 weeks (left treatment or still enrolled) and number of days retained in treatment in this 26-week period were extracted from clinic records.

Drug use

To detect use of opiates, codeine, cocaine, barbiturates, amphetamine, methamphetamine and phencylidine we

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sent urine specimens provided voluntarily at the 26-week follow-up to a NIDA-certified testing laboratory (PharmChem, Menlo Park, CA, USA). Testing typically detects any use of these drugs within the past 2 or 3 days. Analyses were based on all patients who supplied a urine specimen voluntarily at 26 weeks ($n = 269$). There was no significant difference between the LAAM and MM conditions in percentage of patients providing urine specimens (92% and 88%, respectively). Weekly in-treatment urine samples taken by clinic staff were processed similarly.

Statistical analyses

Analyses were performed on a 'modified' intent-to-treat basis after the exclusion of the 25 patients who left treatment in the induction period. That is, all patients with intake and follow-up data required for this analysis were included, regardless of whether they entered or subsequently left the assigned treatment, how much of that treatment they received, how much of any other treatment they received or whether they were still in treatment at the 26-week follow-up.

Cross-tabulation and χ^2 statistics were used to compare treatment status at 26 weeks for patients in the LAAM and MM conditions. A difference-of-means test was used to compare number of days retained in treatment in the two conditions. Cross-tabulation and χ^2 statistics were also used in bivariate (unadjusted) analyses of drug use. Finding no difference between LAAM and MM patients on any measure of drug use other than opiates, we conducted no analyses of those drugs beyond the bivariate level. LAAM and MM patients differed on opiate use in bivariate analyses. Because racial/ethnic composition differed between the LAAM and MM groups, as noted above, we used multivariate logistic regression analysis to test the effect of LAAM on opiate use after adjustment for race/ethnicity. Predictors in multivariate analyses included treatment condition and three race/ethnicity indicator variables (African American, Hispanic and other).

In a final step, multivariate logistic regression analysis was used to determine whether the effect of LAAM on opiate use was contingent upon remaining in treatment. Predictors in these analyses included treatment condition, the race/ethnicity covariates, retention (treatment status at 26 weeks) and the cross-product of condition by retention.

RESULTS

Retention

There was no statistically significant difference between the LAAM group ($n = 196$) and the MM group ($n = 100$) on either retention measure. The percentage of patients still enrolled in treatment at 26 weeks was virtually the same in both groups (75.5% for LAAM patients and 77.0% for MM patients). The mean number of treatment days was 164.3 (SD = 37.0) for LAAM patients and 167.9 (SD = 36.3) for MM patients.

Opiate and other drug use: bivariate results

During treatment

During the 26-week observation period, weekly urine tests were obtained from clients for clinical reasons. On average, LAAM subjects accrued 19 tests and MM subjects 20, a non-significant difference. When converted to percentages (number of positives divided by number of tests) for the entire period, LAAM subjects had a 46% positive rate for opiates compared to 60% for MM subjects ($P < 0.000$).

To determine whether a time in treatment effect could be discerned from the opiate positive tests, we arrayed the weekly percentage positives for each group over the 26-week period. The results indicated that the two groups, as would be expected, did not differ during the induction period (see Fig. 1). However, the LAAM group had significantly lower opiate positive rates than the MM group for weeks 4–7. Beginning with week 9, the LAAM group had stabilized to an average of about 40% opiate positive tests per week, compared to a stable pattern of 60% positive by the MM group. These rates were significantly different ($P < 0.01$) between conditions in a generalized estimating equations (GEE) repeated-measures model.

Follow-up at 26 weeks

Analyses of drug use at follow-up were based on the urine sample independently collected by research staff for all subjects who could be located. As with the in-treatment results, opiate use at follow-up was significantly less common among LAAM patients than among MM patients (39.8% and 60.2%, respectively, $P < 0.002$). Other drug use detected at the 26-week follow-up was negligible (under 2%) except for cocaine and codeine (each about 15%) and did not differ between conditions.

Opiate use: multivariate results

In a multivariate model predicting opiate use, the standardized beta coefficient for condition was negative and statistically significant ($\beta = -0.18$, $P = 0.004$; see Model I in Table 2), indicating that the effect of LAAM on opiate use persisted after adjustment for race/ethnicity. To determine whether LAAM's effect on opiate use was contingent on treatment retention, we ran an additional model

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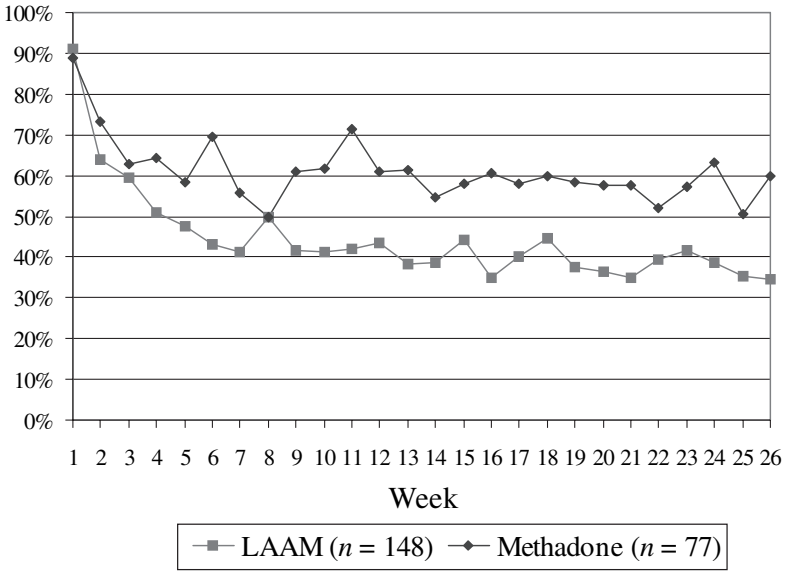

Figure 1 Opiate use over 26 weeks in treatment

Table 2 Multivariate logistic regression for opiate use at 26 weeks.

	Model I		*Model II*	
Predictor	*Standardized coefficient* (β)	*T*	*Standardized coefficient* (β)	*T*
Group (LAAM = 1)	–0.18	–2.90**	0.12	0.41
African American	–0.04	–0.45	–0.01	–0.17
Hispanic	0.08	0.96	0.09	1.10
Other	0.10	1.45	0.12	1.77
Retention (treatment status)	–	0.31	1.34	
Group × retention	–	–0.60	–2.30*	
	Adjusted $R^2 = 0.04$		Adjusted $R^2 = 0.09$	

*$P \leq 0.05$ **$P \leq 0.005$.

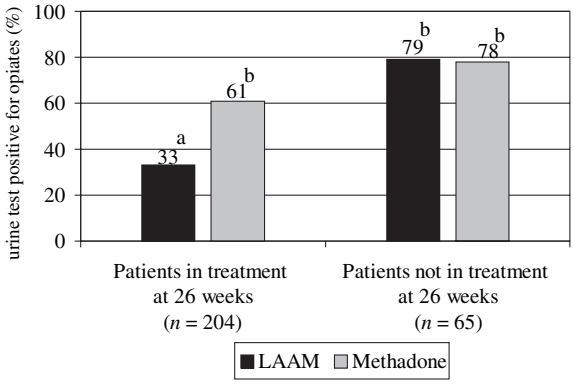

Figure 2 Contingent effect of LAAM on opiate use. Note that differing superscripts indicate statistically significant differences in percentage positive, $P \leq 0.01$

in which opiate use was regressed on study condition, treatment status at follow-up, the cross-product of condition and treatment status and the race/ethnicity covariates. With the cross-product of condition and retention in the model, the beta coefficient for condition alone dropped to non-significance, while the coefficient for the cross-product was negative and significant ($\beta = -0.60$, $P = 0.02$; see Model II in Table 2). Thus LAAM was outperforming methadone in suppression of opiate use specifically among patients still in treatment at 26 weeks.

To verify the contingent effect of LAAM on opiate use, we examined the percentage of patients testing positive for opiates in four groups: LAAM patients and MM patients still in treatment, and LAAM patients and MM patients not still in treatment, at 26 weeks (see Fig. 2). The percentage testing positive for opiate use was almost twice as high among MM patients still in treatment (61%) as among LAAM patients (33%).

As a supplement to the biological measure, we asked patients to report the number of days on which they used opiates during the 26-week period. Patients who reported abstinence throughout the period were coded 0; those who reported any use were coded 1. The LAAM effect indicated by this self-report measure ($\beta = -0.15$, $P = 0.01$) was very similar to the effect indicated by the biological measure.

DISCUSSION

LAAM and methadone have been compared primarily in efficacy trials in which doses were held constant and in many cases were relatively low. To compare the two

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medications on the basis of clinical effectiveness, we randomized patients attending a community-based program either to LAAM or to methadone maintenance treatment and allowed dosing to vary both during treatment induction and thereafter in accord with clinical judgement. Equivalent rates of retention for LAAM patients compared with MM patients (94%) indicate the suitability of LAAM as a useful medication for opiate addiction in community settings. Furthermore, the mean number of treatment days in each condition exceeded 160 days, or more than 90% of the 26-week period under study. Thus, retention was both comparable between conditions and excellent in each. These findings may be due in part to our induction procedure, in which LAAM patients were first stabilized on methadone before crossing over to LAAM [22]. Notwithstanding the comparability of LAAM and methadone from a retention perspective, use of LAAM as the medication agent in a maintenance regimen has advantages from the perspective of clinic operations. These include reduced clinic traffic and reduced staff workload. In addition, many patients find the thrice-weekly dosing schedule preferable to the daily dosing required by methadone.

In numerous controlled clinical trials, the efficacy of LAAM in reducing opiate use has been found similar or superior to that of methadone [24–26], but most of the previous literature has not compared LAAM and methadone on the basis of effectiveness among addicts treated under circumstances common in 'real world' clinical settings. Because LAAM requires thrice-weekly rather than daily clinic attendance, the stabilizing effect of LAAM on opiate use might have been less robust in a community-based treatment setting than the effect gained through methadone, requiring daily clinic contact, in that same setting. In fact, we found evidence for superior effectiveness on LAAM in reducing opiate use, measured both during treatment and at the follow-up interview. We also found that LAAM patients were no more (or less) likely than MM patients to turn to cocaine or other drugs as a substitute for opiates. Further analysis revealed that the differential effect of LAAM was contingent on remaining in treatment; relapse to opiate use occurred at similarly high rates among LAAM and methadone patients no longer in treatment at 26 weeks. Such results, along with previous research in which LAAM outperformed methadone, suggest that agency officials, treatment providers and patients may consider LAAM to be at least as effective as methadone, and frequently more effective, in reducing opiate use in community-based clinical settings—if patients are able to stabilize on LAAM. Furthermore, in previous studies that held the LAAM dose constant for all patients, inadequate dose levels may have contributed to patient complaints that LAAM did not hold them. Allowing dose to vary according to clinical judgement, as would be the practice in 'real world' clinics, may make it easier for patients to stabilize on LAAM and remain in treatment long enough to see benefit.

The contingent effect of LAAM conforms with previous research. It has been reported widely that LAAM patients do well if they stay on LAAM long enough. In a study by Johnson *et al.* [17], retention during the early weeks of treatment was higher for methadone patients than for LAAM patients. However, the retention trendlines crossed at 8 weeks, and retention remained much higher for LAAM patients throughout the final 2 months of the study, at which point 20% of methadone patients and almost 60% of LAAM patients were still enrolled. Similarly, Senay *et al*. [10] found that LAAM patients were less likely to remain in treatment than methadone patients during the first 7 weeks of treatment, but the opposite was observed during the second 7 weeks. Finally, White *et al*. [19, p. 295] found greater abstinence from opiate use among patients who chose LAAM after initial trial periods of methadone and LAAM (3 months each) and concluded that 'preference for LAAM is associated with treatment outcomes as good [as] or better than those on methadone'.

In addition to use as an alternative to methadone, LAAM may be a valuable complement to methadone in some cases. Recent research has shown the advantages of including LAAM in a methadone maintenance regimen. Valdivia & Khattak [27] reported their success in treating opiate addiction with both methadone and LAAM. Specifically, they used longer-acting LAAM as the dose provided on Saturday to MM patients who were on a Tuesday–Saturday cycle, and patients reported no adverse events during 2 years of this protocol. Where take-home privileges are prohibited or when patients have not yet earned them, the provision of LAAM to extend opiate agonist effects is a sensible course although, to ensure safety, the patient must be informed about aspects of LAAM that could pose a risk (e.g. the slower onset of anticraving effects and the potential for serious consequences resulting from LAAM interaction with illicit opiates). In contrast, LAAM patients who missed a Friday dose in our study were permitted to come to the clinic for a Saturday dose of methadone to carry them through the weekend until their regular Monday dose of LAAM. Accordingly, the feasibility and effectiveness of the combination of LAAM in a methadone maintenance regimen should be explored further.

Electrocardiograms were administered to LAAM patients on a monthly basis, and no adverse events, cardiological or other, occurred during the study period. We can offer no additional evidence on possible prolongation of the QTc interval among LAAM patients in general or among those who continued to use illicit drugs. However, safety issues surrounding LAAM have been examined

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carefully in other studies [3,9,10,28,29]. Despite the scarcity of cardiac-related adverse events in LAAM patients, in April 2001 the US Food and Drug Administration (FDA) called for removal of LAAM as front-line therapy for opiate addiction and recommended LAAM only for patients unsuccessful on methadone maintenance or other therapies. Based on our experience with administering LAAM to several thousand patients in clinical trials and in community-based treatment clinics, we maintain that LAAM is a safe and useful drug when clinicians conduct the LAAM induction process properly in compliance with FDA and manufacturer guidelines. Adherence to best practices and proper oversight by physicians greatly reduce the chance of potential side-effects, including those noted recently by clinicians who have encountered isolated incidents of cardiac-related adverse events. Federal and state agencies responsible for funding and oversight of LAAM studies and clinical practice have, in the aggregate, spent tens of millions of dollars to bring LAAM under FDA approval, only to have failed to ensure its proper induction and administration. This situation should be remedied.

Notably, and in light of recent findings suggesting that LAAM's potency may be greater than previously estimated [30], we emphasize the need for careful monitoring of patients during the induction period to ensure satisfactory levels of opiate-craving suppression while avoiding overmedication that could lead to adverse effects or patient withdrawal from treatment. Recent studies have confirmed that low-dose LAAM (35 mg) is not as effective as high-dose (75 mg) in suppressing craving [18,31,32], and future work is needed to determine optimum effective dose levels for LAAM maintenance. More generally, in view of the superior performance of LAAM patients with regard to opiate use and drug injection, we believe that the status of LAAM should be reconsidered and more data collected to calibrate the level of risk associated with LAAM in direct comparison with methadone. The substantial investment that has gone into LAAM development, along with clear evidence of its clinical advantages, combine to indicate a need for further research on its potential risks and benefits.

Acknowledgements

Data collection and analysis were supported by grant R01 DA10422 from the National Institute on Drug Abuse. Dr Anglin is supported by a Senior Research Scientist Award from NIDA (K05 DA00146). We wish to acknowledge editorial and research support from Brian Perrochet and Kris Langabeer.

References

1. Anglin, M. D. & McGlothlin, W. H. (1985) Methadone maintenance in California: a decade's experience. In: Brill, L. & Winick, C., eds. *The Yearbook of Substance Use and Abuse*, vol. III, pp. 219–280. New York: Humana Sciences Press.
2. Ling, W., Charuvastra, V. C., Kaim, S. C. & Klett, C. J. (1976) Methadyl acetate and methadone as maintenance treatments for opiate addicts. *Archives of General Psychiatry*, **33**, 709–720.
3. Ling, W., Klett, C. J. & Gillis, R. D. (1978) A cooperative clinical study of methadyl acetate. *Archives of General Psychiatry*, **35**, 345–353.
4. McGlothlin, W. H. & Anglin, M. D. (1981) Long-term follow-up of clients of high- and low-dose methadone programs. *Archives of General Psychiatry*, **38**, 1055–1063.
5. Powers, K. I. & Anglin, M. D. (1998) A differential assessment of the cumulative versus stabilizing effect of methadone maintenance treatment. *Evaluation Review*, **22**, 175–206.
6. Tennant, F. S., Rawson, R. A., Pumphrey, E. & Seecof, R. (1986) Clinical experiences with 959 opioid-dependent patients treated with levo-alpha-acetylmethadol (LAAM). *JAMA*, **3**, 195–202.
7. Trueblood, B., Judson, B. A. & Goldstein, A. (1978) Acceptability of methadyl acetate (LAAM) as compared with methadone in a treatment program for opiate addicts. *Drug and Alcohol Dependence*, **3**, 125–132.
8. Jaffe, J. H., Schuster, C. R., Smith, B. B. & Blachley, P. H. (1970) Comparison of acetylmethadol and methadone in the treatment of long-term heroin users. *JAMA*, **211**, 1834–1836.
9. Jaffe, J. H., Senay, E. C., Schuster, C. R. & Renault, P. R. (1972) Methadyl acetate versus methadone: a double-blind study in opiate users. *JAMA*, **222**, 437–442.
10. Senay, E. C., Dorus, W. & Renault, P. F. (1977) Methadyl acetate and methadone: an open comparison. *JAMA*, **237**, 138–142.
11. Ling, W., Rawson, R. A. & Compton, M. A. (1994) Substitution pharmacotherapies for opioid addiction: from methadone to LAAM and buprenorphine. *Journal of Psychoactive Drugs*, **26**, 119–128.
12. Prendergast, M. L., Grella, C. E., Perry, S. M. & Anglin, M. D. (1995) Levo-alpha-acetylmethadol (LAAM): clinical, research, and policy issues of a new pharmacotherapy for opioid addiction. *Journal of Psychoactive Drugs*, **27**, 239–247.
13. Rawson, R. A., Hasson, A. L., Huber, A. M., McCann, M. J. & Ling, W. (1998) A 3-year progress report on the implementation of LAAM in the United States. *Addiction*, **93**, 533–540.
14. US Food and Drug Administration (FDA) (2001) Talk paper T01–15. FDA announces labeling changes following cardiac adverse events with addiction drug (April 20, 2001). Available at: http://www.fda.gov/bbs/topics/ans01076.html.
15. Huber, A., Ling, W., Fradis, J. & Charuvastra, V. C. (2001) Comparison of the effects of methadone and LAAM on the electrocardiogram. *Drug and Alcohol Dependence*, **63**, S70.
16. US Food and Drug Administration (2003) Product discontinuation notice NDC 0054–3649–63 (August 23, 2003). Available at: http://www.fda.gov/cder/drug/shortages/orlaam.htm.
17. Johnson, R. E., Chutuape, M. A., Strain, E. C., Walsh, S. L., Stitzer, M. L. & Bigelow, G. E. (2000) A comparison of LAAM, buprenorphine, and methadone for opioid dependence. *New England Journal of Medicine*, **343**, 1290–1297.

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18. Ritter, A., Lintzeris, N., Clark, N., Kutin, J., Bammer, G. & Panjari, M. (2003) A randomized trial comparing levo-alphaacetylmethadol with methadone maintenance for patients in primary care settings in Australia. *Addiction*, **98**, 1605–1613.
19. White, J. M., Danz, C., Kneebone, J., La Vincente, S. F., Newcombe, D. A. L. & Ali, R. L. (2002) Relationship between LAAM-methadone preference and treatment outcomes. *Drug and Alcohol Dependence*, **66**, 295–301.
20. Karp-Gelerntner, E., Wurmser, L. & Savage, C. (1976) Therapeutic effects of methadone and 1-a-acetylmethadol. *American Journal of Psychiatry*, **133**, 955–557.
21. Glanz, M., Klawansky, S., McAullife, W. & Chalmers, T. (1997) Methadone versus 1-alpha-acetylmethadol (LAAM) in the treatment of opiate addiction: a meta-analysis of the randomized, controlled trials. *American Journal on Addictions*, **6**, 339–349.
22. Marion, I. J. (1995) *LAAM In the Treatment of Opiate Addiction*. Treatment Improvement Protocol (TIP) Series 22. Rockville, MD: Center for Substance Abuse Treatment.
23. Rawson, R. A., Shoptaw, S. J., Obert, J. L., McCann, M. J., Hasson, A. L., Marinelli-Casey, P. *et al.* (1995) An intensive outpatient approach for cocaine abuse treatment. The Matrix model. *Journal of Substance Abuse Treatment*, **12**, 117–127.
24. Freedman, R. R. & Czertko, G. (1981) A comparison of thrice weekly LAAM and daily methadone in employed opiate addicts. *Drug and Alcohol Dependence*, **8**, 215–222.
25. Whysner, J. A., Thomas, D. B., Ling, W. & Charuvastra, C. (1979) *On The Relative Efficacy of LAAM and Methadone*, pp. 429–434. Research Monograph 27. Rockville, MD: National Institute on Drug Abuse.
26. Zangwell, B. C., McGahan, P., Dorozynsky, L. & McLellan, A. T. (1986) *How Effective Is LAAM Treatment? Clinical Comparison with Methadone*, pp. 249–255. Research Monograph 67. Rockville, MD: National Institute on Drug Abuse. National Institute on Drug Abuse.
27. Valdivia, J. F. & Khattak, S. (2000) Effects of LAAM and methadone utilization in an opiate agonist treatment program. *Mount Sinai Journal of Medicine*, **67**, 398–403.
28. Jones, H. E., Strain, E. C., Bigelow, G. E., Walsh, S. L., Stitzer, M. L., Eissenberg, T. *et al.* (1998) Induction with levomethadyl acetate: safety and efficacy. *Archives of General Psychiatry*, **55**, 729–736.
29. Levine, J. W., Zaks, A., Fink, M. & Freedman, A. M. (1973) Levomethadyl acetate: prolonged duration of opioid effects, including cross-tolerance to heroin, in man. *JAMA*, **226**, 316–318.
30. Eissenberg, T., Stitzer, M. L., Bigelow, G. E., Buchhalter, A. R. & Walsh, S. L. (1999) Relative potency of levo-acetylmethadol and methadone in humans under acute dosing conditions. *Journal of Pharmacology and Experimental Therapeutics*, **289**, 936–945.
31. Houtsmuller, E. J., Walsh, S. L., Schuh, K. J., Johnson, R. E., Stitzer, M. L. & Bigelow, G. E. (1998) Dose–response analysis of opioid cross-tolerance and withdrawal suppression during LAAM maintenance. *Journal of Pharmacology and Experimental Therapeutics*, **285**, 387–396.
32. Oliveto, A. H., Farren, C. & Kosten, T. R. (1998) Effect of LAAM dose on opiate use in opioid-dependent patients: a pilot study. *American Journal on Addictions*, **7**, 272–282.

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