

# Effects of LAAM and Methadone Utilization in an Opiate Agonist Treatment Program

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## Abstract

The development and approval of levo-alpha-acetylmethadol (LAAM) as a pharmacotherapeutic agent in opioid agonist therapy provided an alternative to methadone. Clinicians recognized the potential benefits that LAAM, a synthetic mu agonist with pharmacological properties which differ from those of methadone, could have in the treatment management of addicts in opioid agonist therapy. We report our experience utilizing LAAM from 1995 to 1999 at the Hines VA opioid agonist therapy clinic. The addition of LAAM to the clinic's treatment armamentarium has resulted in management options that have improved the areas of patient recruitment, patient retention, patient traffic, take-home medication, detoxification, and treatment outcomes.

**Key Words:** LAAM, methadone, opiate addiction, opioid replacement therapy.

## Introduction

SINCE ITS INTRODUCTION, opioid agonist therapy has been shown to be effective in the treatment of opiate addiction. (1). The synthetic mu agonist methadone has been the primary agent used for this treatment modality. Its 24–36 hour half-life and oral administration made it an ideal agent when compared to the shorter half-life opiates. Numerous subsequent studies have shown treatment with methadone to be a cost-effective manner of decreasing illicit opiate use (2, 3), improving social functioning (4, 5), decreasing associated criminality (2, 6, 7), and improving public health (8–11).

In the past 35 years since methadone was first used in opioid agonist therapy, long-term, high-dose methadone maintenance therapy has been shown to be most beneficial to the chronic opiate addict. As a result of such obstacles as regulatory pressures, stigma associated with methadone treatment, methadone diversion fears, and initial daily clinic attendance requirements, only 20% of the opiate addicts who need treatment actually access the opioid substitution clinics (3), despite their proven efficacy. These factors, along with the fact that methadone fails to stop illicit opiate use in approximately 45% of patients, have fueled the search for additional pharmacotherapeutic replacement agents.

Levo-alpha-acetylmethadol (LAAM) has been shown to be an effective opioid agonist pharmacotherapeutic agent, comparable to methadone, for decreasing illicit opiate use, improving social functioning, decreasing criminality and improving public health (12–15). Most recently, results of a meta-analysis of randomized controlled trials comparing LAAM to methadone in treating heroin addiction showed no difference in the level of illicit drug use. There was, however, a small but statistically significantly greater patient retention rate in the methadone group, and discontinuation of treatment because of side effects of LAAM also favored methadone (16). The authors noted that the differences in retention rates might not be due entirely to the pharmacological properties of the replacement agents. Staff and patient factors, as well as the novelty of LAAM coupled with the familiarity of methadone, influence retention rates. In many of the clinical trials, LAAM patients could return to methadone, if they no longer wished to take LAAM. Meta-analysis supports LAAM as an effective alternative to methadone in the treatment of heroin addiction.

LAAM was approved for use as an opioid agonist medication by the Food and Drug Administration (FDA) in 1993. In 1995, the Center for Substance Abuse Treatment (CSAT) of the Substance Abuse and Mental Health Services Administration (SAMSHA) issued Treatment Improvement Protocol (TIP) #22, summarizing the clinical and basic research on LAAM, with guidelines for patient selection, induction of patients on the medication, dosing, stabilization, and ongoing maintenance.

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Initial recommendations for dosing and administration schedules for LAAM were proposed following research trials involving more than 4,000 patients (12–18). Dose-related efficacy for LAAM has been demonstrated, by Eisenberg et al. (19), who showed higher treatment retention rates and lower illicit opioid use relative to pre-treatment levels when LAAM dosing regimens of 100/100/140 mg (high-dose group) were compared to those of 50/50/70 mg (medium-dose group) and 25/25/35 mg (low-dose group).

The primary pharmacological differences between LAAM and methadone that make LAAM a positive addition to opioid agonist therapy include the production of active metabolites during liver metabolism and half-lives for the active compounds ranging from 2–4 days. These properties result in adequate levels of active narcotic compounds to suppress the dependence syndrome and maintain a “blockade” of the opiate receptors despite fewer doses per week than with methadone. The reader is referred to more extensive papers of the pharmacological properties of the agents currently in use for opioid replacement therapy (20–22). The main purpose of this paper is to relate the effects of LAAM utilization in everyday clinical practice. The ability of the long half-life mu agonists (LAAM and methadone) to develop “quality tolerance,” as compared to the short half-life mu agonists (heroin, morphine, etc.), and its importance in opioid replacement treatment is also discussed.

### Quality Tolerance

The concept of what we have termed “quality tolerance” has provided us with a theoretical framework for understanding the effects, benefits, and disadvantages of methadone, LAAM, and the short-acting narcotics in opioid substitution. Although partly speculative, it is meant not only to provide a theoretical framework, but also to promote further work in the concept.

Tolerance can be defined as loss of or diminished effect, of a given amount of drug in an individual. It is an adaptation of the target site of action to the continuous presence of a foreign substance, such as an opioid. The adaptation probably occurs at the receptor level, mediated by receptor-opioid interactions. The opiate receptor and opioid pharmacokinetic and pharmacodynamic properties determine the level and quality of adaptation (tolerance).

The half-life of the agent is an important factor determining the tolerance produced; the longer the half-life, the better the “quality tolerance.”

“Quality tolerance” allows the opioid agonist patient to function. Opioid agonist benefits would not be possible without the ability of methadone and LAAM to produce “quality tolerance.” The short half-life agents produce little if any clinically significant “quality tolerance.” The difference in the ability to produce “quality tolerance” between methadone, LAAM and the short half-life opiates results in the following: (a) limited benefit of short half-life agents in opioid agonist treatment, (b) the need to induce a patient onto methadone or LAAM despite years of abusing the short-half life opiates, (c) a more normal feeling with LAAM maintenance than with methadone maintenance.

LAAM and its two active metabolites, nor-LAAM and dinor-LAAM, produce an equilibrium state at the receptor level, characterized by prolonged occupation of the mu receptors. Methadone also produces such an equilibrium, but to a slightly lesser extent than LAAM. Short half-life agents would not produce such an equilibrium. Their use actually sets up a disequilibrium state, as the addict fluctuates from a peak to a rapidly decreasing level of opiate with each use. This disequilibrium seems to fuel the addictive process, as clinically manifested in the compulsion and craving that a heroin addict exhibits. LAAM and methadone, on the other hand, decrease the compulsion and craving as a result of the equilibrium they establish and the “quality tolerance” that then develops. The decrease in compulsion and craving is likely to be the clinical reflection of the neuronal system responsible for the addictive process, i.e., re-stabilizing. This re-stabilization leads to a successful treatment outcome, i.e., stopping or reducing the use of illicit opiates. The establishment of an equilibrium in opioid agonist treatment arrests the addictive disorder, much like the abstinent equilibrium of the abstinent treatment approach.

We will refer to the concept of “quality tolerance” and the theoretical framework outlined above at various points during presentation of our experience utilizing LAAM.

### Induction

We have placed patients on LAAM in one of two ways:

- 1) An established methadone maintenance patient can be converted directly to LAAM. The 48-hr dose of LAAM is obtained by multiplying the daily methadone dose by 1.2. The fact that the “quality tolerance” produced

by methadone is near the level of that produced by LAAM allows conversion from methadone to LAAM and vice versa without any need for re-stabilization. The conversion is clinically equivalent.

In patients with rapid liver metabolism maintained on methadone doses greater than 100 mg per day, the first dose of LAAM should not exceed 120 mg/48 hr. This rule is needed since liver metabolism of methadone results in inactive metabolites whereas liver metabolism of LAAM results in active compounds. Converting such a patient to LAAM using the 1.2 conversion would result in too high a LAAM dose. Our experience has been that this patient may require an increase or decrease in the range of 10–15 mg from their initial dose of 120 mg/48 hr. The production of active metabolites has made LAAM our preferred method of managing a rapid metabolizer that cannot be stabilized despite doses of methadone well beyond 100 mg per day. Conversion of such a patient to LAAM will allow stabilization and bring the dose of agent to normal ranges.

The equivalency of the conversion is an important fact since it has provided us with the ability to dose a patient for 24 hrs, 48 hrs, or 72 hrs, whether they are on methadone or LAAM. The only thing that cannot be done is to give LAAM on sequential days; all other combinations of LAAM and methadone are possible. The benefits of combining LAAM and methadone are most apparent in the management of take-home doses of methadone. This is discussed in more detail later in this article.

- 2) A patient can also be placed directly on LAAM from illicit street opiates. In this case, an induction is necessary, since the illicit short half-life opiates do not produce any significant amount of “quality tolerance.” This is our preferred method of inducing a patient. We do not utilize the technique of inducing a patient onto methadone first, reaching an adequate dose of methadone, and then converting to LAAM. We found that this method is unnecessary, cumbersome, and without significant advantages over direct rapid induction onto LAAM.

We begin with a 30 mg/48 hr dose of LAAM. We then increase the dose by 5–10 mg incre-

ments each time the patient comes to dose, with the minimal target dose being 75 mg/48 hrs. If sedation occurs in an individual patient, using smaller incremental increases in the dose or increasing the interval between increases can slow induction. Our experience has been that the majority of patients tolerate the rapid induction technique. Furthermore, the rapid induction method is important in alleviating patients’ withdrawal symptoms, increasing retention and improving outcome.

We prefer to have at least three 48-hr LAAM doses before giving a patient being induced a 72-hr dose of LAAM. This prevents any significant sedation with the larger 72-hr dose (quality tolerance better developed), and assures better coverage for the 72-hr period. We use the 72-hr dose since we are a 6-day per week clinic. LAAM 48-hr doses and equivalent methadone doses can be used to shift the patient’s dosing schedule to a desired day of the week prior to using a 72-hr dose.

An example of what we have termed “phase shifting” is the case of a patient who is admitted on Monday in moderate withdrawal. The decision is made to place the patient on a Monday/Wednesday/Friday schedule of LAAM (a Tuesday/Thursday/Saturday schedule is also possible), but we want to give him more than two 48-hr LAAM doses (Monday and Wednesday) prior to the 72-hr dose (Friday). We would give this patient a 30-mg dose of methadone on the Monday he was admitted — first shift — then he would get LAAM 30 mg/48 hr on Tuesday, 40 mg/48 hr on Thursday, 50 mg/48 hr on Saturday — second shift — 60 mg/48 hr on Monday, 70 mg/48 hr on Wednesday, and 112 mg/72 hr on Friday. This Monday/Wednesday/Friday dosing schedule would be maintained for at least a month in order to reach steady state. During this interval, we would have the opportunity to counsel the patient, and determine if illicit opiate use ceases. We increase the dose if illicit opiate use continues. Similar examples of “phase shifting” can be generated for patients admitted on different days of the week and/or placed on a Tuesday/Thursday/Friday dosing schedule, the goal being at least three 48-hr LAAM doses prior to a 72-hr dose.

### Maintenance

We have found that, as a group, patients maintained on doses below 95 mg/48 hrs have greater rates of opiate-positive urine toxicologies

as compared to patients maintained on doses above 95 mg/48 hrs. This is consistent with Eisenberg's randomized clinical trial (19). It has been uncommon in our clinic for patients to require 48-hr LAAM doses above 140 mg.

### Dosing Regimens and the 72-hr Dose

LAAM can be dosed every 48 hrs or three times per week. The latter method requires two 48-hr doses and one 72-hr dose. We have used the three times per week dosing regimen exclusively, and have not found it necessary to supplement this regimen with a methadone take-home dose. We are aware that some clinics use a three time per week dosing schedule that gives a patient two 48-hr doses of LAAM with coverage for the 72-hr period carried out with a 48-hr dose of LAAM and a take-home dose of methadone for the third day. The latter method is unnecessary if the increase in LAAM dose for the 72-hr period is calculated correctly.

We give an additional 40% amount of LAAM for the 72-hr period as compared to the 48-hr period. A patient on a 48-hr LAAM dose of 100 mg will get a 72-hr LAAM dose of 140 mg. This results in adequate coverage for the 72-hr period for the large majority of patients (95%). The other 5% of patients in our clinic have noted that the increase for the 72-hr period made them feel "heavy" on the first day. These patients can be given a lower increase the next time a 72-hr dose is calculated (30%, rather than 40%). If a clinic calculates the 72-hr dose using less than 40%, a proportional number of patients will complain of "not being held" on the third day, and implementation of LAAM utilization will be compromised. Opioid replacement patients tend to reject an agent that does not provide adequate coverage from the beginning, and they are less likely to accept the argument that all that may be needed is an increase in dose. We strongly recommend that an increase of 40% be used initially for calculating the 72-hr dose of LAAM.

The advantages that our clinic has seen as a result of the three times per week LAAM dosing have been:

- 1) Avoids need for methadone take-home doses for LAAM patients.
- 2) Increases our clinic patient capacity since we are able to: (a) decrease the number of weekly doses per patient on maintenance, (b) decrease patient traffic since we can have M/W/F and T/Th/Sat LAAM patients, and (c)

relieve counselor workload by having a part of their patient caseload come to the clinic only three times per week.

Our clinic was able to double its census without an increase in drug dispensing or counselor resources in part because of these advantages.

The advantages of the three times per week dosing makes it the preferred method, even in 7-day-per-week clinics. Dosing days for a given patient remain the same and do not change each week as they would with a regimen that uses 48-hr doses only.

### Patient Selection

We have used LAAM for the following patients:

1. Those desiring less frequent visits to the clinic from the beginning of treatment.
2. Those who had not done well on methadone maintenance despite doses of methadone above 60 mg per day. We converted 37 patients that continued using illicit opiates to LAAM. The average methadone dose in this group of patients was 66 mg. The LAAM dose was obtained by using the conversion factor of 1.2. No dose increases of LAAM were made following the conversion. At 6 months, 87% of the patients were still in treatment, and 83% of these patients had stopped using illicit opiates. LAAM should be tried with those patients who have not done well on methadone.
3. Those suspected of diversion. Diversion is prevented, daily clinic attendance is avoided, and patient retention is increased.
4. Those desiring confidentiality regarding their participation in substitution treatment, since LAAM is not routinely tested for in commonly used toxicology screens. In our clinic, this has helped us retain patients who contemplated leaving treatment because they did not want their employers to know they were on methadone for fear of either losing their job or not getting desired jobs. In the past, these patients would have detoxified and, more often than not, would have relapsed to illicit opiate use.
5. Those experiencing too much sedation with methadone maintenance, due to LAAM's

greater "quality tolerance" and more normal feeling. This has been helpful in managing patients who have jobs operating machinery and who experience significant sedation after dosing with methadone.

6. Those with absenteeism problems, with a drug that is dosed less frequently.
7. Those who are medically and/or cognitively compromised. This avoids daily visits to the clinic and reduces the need for take-home medication for which they may not be completely responsible.
8. Those who are "rapid metabolizers," as previously mentioned.

The expanded patient selection options have been particularly helpful in improving our retention rates, access to treatment, and ultimately our clinic census. These options are among the factors that have allowed us to increase and maintain our census at twice the level of that prior to the utilization of LAAM.

#### **Improved Take-Home Dose Management**

We have combined the use of LAAM and methadone to improve management of methadone for methadone-maintained patients who report from Monday to Saturday.

In our clinic, patients who are maintained on daily methadone from Monday to Friday, since they have not qualified for methadone take-home doses, are given an equivalent 48-hr dose of LAAM on Saturday. They are given their regular dose of methadone when they return to the clinic on Monday. This avoids the previously routine Sunday take-home doses of methadone. We have done this for nearly two years and have had no major problems. A comparison between the period of time covered with methadone and the period of time covered with LAAM shows no significant differences in withdrawal symptoms, drug craving, and drug use history (23). Past attempts to use this technique by other investigators did not succeed primarily because of low dose of LAAM given (24).

The above technique could allow a clinic which must remain open 7 days per week because of regulations preventing Sunday take-home doses, to close on Sunday without the need to give a take-home dose of methadone.

One- or two-day coverage during the week can be provided to a methadone-maintained

patient by converting to an equivalent 48-hr or 72-hr LAAM dose, respectively. This has been helpful in our clinic as an alternative to methadone take-home doses for short-term personal and/or medical hardship requests by patients who have not qualified for take-home privileges.

#### **Improved Overall Clinic Treatment Outcome**

Utilization of methadone and LAAM improved the rate at which our patients succeeded in achieving opiate-free status. This success was defined as negative urinalysis for illicit opiates for the previous three months following at least six months of treatment. Prior to introducing LAAM to our clinic at the end of 1995, we had 125 patients in methadone maintenance, and our rate of heroin-free status was 55%. Two years after the introduction of LAAM, our census was 250 patients, 2/3 on methadone and 1/3 on LAAM. The rate of heroin-free status had improved by 12% to 67%. The methadone-maintained group had a heroin-free rate of 60%, while the LAAM-maintained group had a heroin-free rate of 80%.(25). These statistics suggest that improved treatment-patient matching might have resulted from the availability of two opioid agonist agents. The 12% improvement supports the utilization of available agents for opioid agonist treatment.

#### **Detoxification**

The 2–4 day half-lives of LAAM and its active metabolites, nor-LAAM and dinor-LAAM, suggests that the intensity of withdrawal symptoms after discontinuation would be less intense for LAAM than for methadone, which has a half-life of 24 hrs. The slower clearance rates of LAAM and its active metabolites attenuate withdrawal symptoms. A double-blind comparison of gradual and abrupt withdrawal from LAAM (25) suggested that intensity of withdrawal symptoms due to discontinuation of LAAM might be helpful in detoxification.

LAAM-maintenance patients in our clinic detoxify from LAAM by decreasing their 48-hr dose by 4 mg each time they are dosed. When a 40 mg/48 hr dose is reached, we slow the detoxification to a 3-mg decrease each time they are dosed. When a 20 mg/48 hr dose is reached, we complete the detoxification by 2-mg decreases each time they are dosed. More important, if we have a patient who has failed detoxification from methadone maintenance as a result of symptom intensity, when lower doses are reached, we like

to convert them to LAAM if and when they ask to detoxify from methadone. Some of these patients have been able to complete the detoxification. LAAM should be evaluated further for use in detoxification from opiates.

### Side Effects

We have found the side effect profile of LAAM to be similar to that of methadone. This is not surprising since they are both mu agonists. The most common and lasting side effect of LAAM in our clinic has been constipation. Sexual dysfunction, nervousness, and sweating have occurred at rates and intensity similar to those for methadone.

We have used LAAM without complications in patients with hepatitis C and alcoholic hepatitis. Our clinical experience suggests that if a patient can be given methadone, LAAM can also be tolerated. Further work is needed on the use of opioid replacement agents in special populations.

We have not found that LAAM poses any greater danger than does methadone for a patient who abuses other illicit drugs. Unfortunately, we have not noticed any significant difference in the use of cocaine or benzodiazepines between patients on LAAM and those on methadone maintenance.

### Conclusion

The utilization of LAAM and methadone in our clinic has increased the options available to us for the management of our patient population. Access to treatment, patient retention in treatment, and positive treatment outcome have consequently increased. Our clinic experience supports the expansion of LAAM utilization in opioid agonist therapy.

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