

## METHADONE MAINTENANCE VS. LAAM MAINTENANCE: EFFICACY FOR TREATING OPIATE ADDICTION

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### **ABSTRACT AND INTRODUCTION**

One pharmacological treatment for opiate addiction is maintenance on opioid agonists (McKim, 2007). Maintenance drugs alleviate withdrawal symptoms, reduce craving, and block some of the effects of heroin, thereby decreasing the likelihood of relapse and drug-associated criminal behavior (McKim, 2007). Methadone is an orally-administered mu-opioid agonist, which was approved for maintenance therapy in the U.S. during the 1960s (Julien, Advokat, & Comaty, 2011). This drug has been rigorously tested and has been called the “most effective treatment for opiate addiction” by the Center for Disease Control (2002, p. 1). Despite this praise, methadone maintenance may not be the most preferred pharmacotherapy because of its short duration of action. Methadone is only effective for about 24 hours; consequently, patients are often required to return to the treatment facility each day to receive a new dose, which can be impractical, or are given take-home doses, which have abuse liability (McKim, 2007). Furthermore, methadone may not hold for a number of patients, such that they continue to experience withdrawal symptoms and craving despite receiving an adequate dose of the drug (Dyer & White, 1997). Levo-alpha acetylmethadol (LAAM) is an alternative agonist that may mitigate these issues because it has a longer duration of action than methadone and thus, is administered only three times per week (Julien et al., 2011). The purpose of this paper is to review the literature comparing the efficacy of methadone maintenance to LAAM maintenance for treating opiate addiction, and to assess LAAM’s viability as an alternative treatment. Several outcome variables are discussed, including retention in treatment, reduction in opiate use, involvement in criminal activity, effects on health, and patient preferences.

### **LITERATURE REVIEW**

#### **Meta-Analyses**

Two major meta-analyses have compared LAAM maintenance to methadone maintenance. These studies summarize about 40 years of clinical research on the topic and provide the basis for the interpretation of future results. Glanz, Klawansky, McAullife, and Chalmers (1997) performed the first study, which consists of all randomized, controlled trials in the Medline database from 1966-1996. The authors found that there was a non-significant trend for heroin use to be lower in the LAAM groups. Additionally, they reported that LAAM patients were more likely to drop out due to side effects (not specified), causing the LAAM groups to have lower retention rates. The authors noted several limitations to this latter finding. First, retention was assessed as an “all-or-none” phenomenon: participants either remained in treatment through the entirety of the study or were considered to be dropouts. As a result, the number days in treatment was not taken into account. Second, many studies allowed individuals to switch from LAAM to methadone, but rarely were participants allowed to stop methadone and switch to LAAM. Third, there was an anti-LAAM sentiment in the U.S. during the period of some of the studies as researchers and patients considered it an experimental drug and were suspicious of its effectiveness. Thus, differences in retention rates may have been caused by methodological faults and social pressures.

The second meta-analysis, performed by Clark et al. (2002), yielded similar results. They gathered all randomized control trials, controlled clinical trials, and controlled perspective studies from 1972-2002. Fifteen studies were included in their final analyses. There were two main findings: First, LAAM treatment resulted in less heroin use and greater abstinence; and second, individuals were more likely to cease LAAM treatment, such that methadone maintenance programs had higher retention rates. Differences in retention rates were found to be due in part to the side effects (although the side effects

were not described) of LAAM, although the authors noted complications with interpretation of this finding similar to those enumerated by Glanz et al. (1997). Clark et al. (2002) also reported on additional outcomes that Glanz et al. (1997) did not include in their analyses. First, participants more often reported a preference for LAAM because it more effectively prevented cravings and symptoms of withdrawal. Second, there were no significant differences in mortality rates associated with the two treatments, providing evidence that they are similarly safe.

### **Studies That Clearly Favored LAAM**

Several trials comparing LAAM to methadone have been performed since the publication of the above meta-analyses. Two of these publications clearly favored LAAM maintenance over methadone maintenance; that is, LAAM was superior to methadone on all outcome variables measured. For example, White et al. (2001) compared patient preferences for LAAM and methadone in a sample of 62 Australian methadone-maintained individuals. Half of the participants were randomly assigned to methadone maintenance for three months, followed by LAAM maintenance for three months. The other half received LAAM first, followed by methadone. Participants gave hair samples, which were tested for the presence of heroin metabolites, and were interviewed at three and six months. LAAM proved more effective than methadone on three measures: heroin use, rate of abstinence, and hair concentration of morphine, a heroin metabolite. After six months, the participants could choose to continue either LAAM or methadone maintenance. Significantly more patients chose LAAM ( $n = 27$ ) than methadone ( $n = 12$ ). Those who chose LAAM used heroin less often and had better overall health outcomes. These results are consistent with the meta-analyses of heroin use data performed by Clark et al. (2002), and further suggest that patients' preference for LAAM is beneficial for health.

The second study that favored LAAM maintenance to methadone maintenance was performed by Anglin, Conner, Annon, and Longshore (2007). These researchers randomly assigned 315 treatment-seeking opiate users to either LAAM maintenance or methadone maintenance therapy. Participants were monitored for retention and given weekly urine tests until their 52-week follow-up had been completed. In addition, individuals in the LAAM group were subjected to monthly electrocardiograms (ECGs). The researchers found a higher one-year retention rate (57.4%) for participants assigned to LAAM than for participants assigned to methadone (46.2%). These results are inconsistent with those of Glanz et al. (1997) and Clark et al. (2002), who found methadone to result in greater retention compared with LAAM. Furthermore, LAAM patients in Anglin et al.'s (2007) study were more likely to report at least 12 weeks of abstinence and were less likely to give opiate-positive urine samples during treatment than were methadone patients. Finally, after one year, only 50.4% of LAAM participants tested positive for heroin, whereas 62.5% of methadone participants tested positive. These heroin use outcomes are comparable with the findings of White et al. (2001) and Clark et al. (2002), which favored LAAM. Finally, no serious adverse events (SAEs), or health complications that are life threatening, require hospitalization, result in permanent or enduring damage, or are deemed by medical investigators to be significantly hazardous (National Institute of Health, 2011), were observed with LAAM administration. Taken together, the results of Anglin et al. suggest that LAAM is superior to methadone on treatment retention and heroin use, and that LAAM does not result in serious side effects.

### **Studies That Demonstrated Limited Support for LAAM**

In contrast to these studies, which favored LAAM over methadone on all outcome variables, one only found LAAM to be superior in only certain respects. This publication, by Longshore, Annon, Anglin, and Rawson (2005), was a precursor to Anglin et al.'s 2007 study. The authors used the same sample and procedures, but limited their observations to a six-month period. Longshore et al. (2005) found no differences in treatment retention among the experimental groups, contrary to Glanz et al. (1997), White et al. (2001), Anglin et al. (2007), and Clark et al. (2002), who reported significant differences. In addition, Longshore et al. (2005) found that fewer LAAM patients (40%) than methadone patients (60%) tested positive for opiate use during treatment. Similarly, fewer LAAM patients (39.8%) than methadone patients (60%) tested positive at 26-week follow-up. These results, obtained from heroin-dependent users, parallel those of White et al. (2001), Anglin et al. (2007), and Clark et al. (2002), who found LAAM to result in less heroin use than methadone. Finally, no SAEs were observed in the LAAM group.

### **Studies That Favored Methadone**

Two studies diverged from these others because they generated results favoring methadone over LAAM. In the first experiment, performed by Ritter et al. (2003), 93 methadone-maintained individuals were randomly assigned to either LAAM maintenance or methadone maintenance therapy. Treatment retention, self-reported heroin use, and SAEs were measured at baseline, 3-month, 6-month, and 12-month follow up periods. Ritter et al. (2003) found no significant differences in treatment retention or self-reported use among groups. The results on treatment retention parallel those of Longshore et al. (2005), who reported no differences between LAAM and methadone. In contrast, the results from heroin-dependent users are inconsistent with those from any of the previously discussed publications. Finally, Ritter et al. (2003) was the first study to report that participants receiving LAAM experienced SAEs significantly more frequently compared with those receiving methadone.

The second study that favored methadone was published by Wieneke et al. (2009). These authors performed ECGs on 53 participants who had been randomly assigned to methadone or LAAM maintenance. Readings were taken at baseline and at a 24-week follow-up point. The purpose of the ECGs was to detect QT prolongation, or an extension of the time between the beginning of the Q wave and the end of the T wave in the heart's electrical cycle. QT prolongation is an electrocardiological indicator of the presence of potentially dangerous cardiac arrhythmias. Although no serious cardiac problems were observed in either group, LAAM patients showed significant increases their QT intervals, whereas methadone patients did not. In addition, LAAM patients were more likely to exhibit dangerously long QT intervals than were methadone patients. The results of Wieneke et al. suggest that LAAM may be associated with greater cardiovascular risks than methadone, but additional research is necessary to replicate these findings.

### **Studies That Found LAAM and Methadone to Be Similar**

Two studies reported no differences between LAAM and methadone on health-related outcomes. The first, published by Digiusto, Shakeshaft, Ritter, O'Brien, and Mattick (2004), assessed differences in the number of SAEs associated with the pharmacotherapies for opiate dependence. The study was based on data gathered from 12 national Australian trials, consisting of 1244 total participants. The authors reported no overdoses or deaths during LAAM or methadone treatment; however, one individual was admitted for detoxification in a methadone-maintenance program. Several other SAEs were observed during both types of treatments, although these occurrences were seldom fatal, and were often due to events like car accidents, general illnesses, and psychiatric problems, which may or may not have been related to the drug treatment. The results indicated that LAAM and methadone are similarly safe for use in the treatment of opiate dependence. These findings regarding the health effects of LAAM and methadone are consistent with all the discussed studies, except for Ritter et al. (2003), who found that LAAM was associated with a larger number of SAEs than methadone.

The second study that found comparable results on health-related outcomes for methadone and LAAM was completed by Wedam, Bigelow, Johnson, Nuzzo, and Haigney (2007). They looked for evidence of QT prolongation in a sample of 165 opiate addicted individuals, who were randomly assigned to LAAM, methadone, or buprenorphine maintenance. The researchers administered ECGs to all participants at baseline and every 4-weeks over a 17-week trial. They found that participants in the LAAM and methadone groups were equally likely to exhibit dangerously long QT interval readings. They also displayed similar dangerous increases in their QT intervals over time. These findings contradict those of Wieneke et al. (2009), who found LAAM to result in greater QT prolongation and more dangerous QT interval readings than methadone.

### **Studies with Mixed Results**

The final category of publications comparing LAAM maintenance to methadone consists of three studies that reported mixed results. For instance, Digiusto et al. (2006) examined whether the different pharmacotherapies for opiate dependence affected criminal behavior and expenditure on illicit drugs. The researchers examined data from 13 Australian pharmacotherapy trials for opiate dependence in a procedure analogous to the one used by Digiusto et al. (2004). At a 3-month follow-up, participants

answered questions about their involvement in criminal activities and their expenditure on drugs over the last month. Digiusto et al. (2004) reported two separate findings regarding treatment retention. First, among participants not previously stabilized on methadone, retention in therapy was statistically similar for individuals in methadone maintenance (71%) and LAAM maintenance (62%) programs. This result is consistent with the finding of Longshore et al. (2005), who reported no differences in treatment retention in a sample of people who had not been maintained on methadone; however, this finding conflicts with the results of Anglin et al. (2007), who found that LAAM resulted in better treatment retention in a sample of individuals who had not received maintenance therapy. The second finding on treatment retention reported by Digiusto et al. (2004) was that among patients already stabilized on methadone, methadone yielded better retention rates (90%) than LAAM (72%). These results conflict with reports of treatment retention by Ritter et al. (2003), who found no differences in treatment retention in a sample of methadone-maintained individuals. The other major finding of Digiusto et al. (2004) was that participation in criminal behavior was similar across treatment types, although LAAM participants reported lower expenditures on heroin than methadone participants. This study suggests that both maintenance therapies have beneficial effects on criminal involvement. Furthermore, it adds complexity to the understanding of differences in treatment retention between LAAM and methadone programs. Specifically, it suggests that patients who have been exposed to methadone maintenance in the past may have more success with methadone maintenance, whereas individuals who are new to maintenance therapy may find LAAM maintenance more effective.

The second study to report mixed results was performed by Wolstein et al. (2009). Their experiment consisted of a sample of 84 European, methadone-maintained individuals who were randomly assigned to either methadone maintenance or LAAM maintenance. Outcome measures included urine analysis and retention rate, as well as subjective measures of craving, withdrawal, and self-reported substance use. Both groups exhibited similar retention rates and levels of opiate use (as measured by both objective and subjective means), as well as similar ratings of withdrawal symptoms and craving. A slightly greater number of adverse events (i.e., minor side effects) occurred in the LAAM group, although SAEs were similar among groups. The main findings parallel those of Ritter et al. (2003), who found no significant differences in treatment retention or heroin use between groups. The secondary findings report on previously unstudied variables, and indicate that LAAM maintenance is largely similar to methadone maintenance, except that it may result in a greater number of minor negative side effects.

The final study with equivocal findings was performed by Anglin, Conner, Annon, and Longshore (2009). These researchers extended the work of Longshore et al. (2005) and Anglin et al. (2007), reporting on additional outcome variables at baseline, 6, 12, and 18 months. They found that of the individuals still in treatment, participants in the LAAM group were less likely to report receiving illegal income at 6-month follow-up, were more likely to be employed at 6- and 12-month follow-ups, and were less likely to test positive for heroin at 6-month follow-up. In contrast, methadone participants were more likely to own a residence at 6-month follow up only. In the final analysis at 18 months, treatment differences attenuated on all outcome variables, including retention in treatment, heroin use, employment status, arrest rate, conviction rate, incarceration rate, reception of illegal income, level of HIV risk, and residential status. The short-term results are consistent with studies reporting LAAM's greater efficacy, while the long-term results parallel studies suggesting similar efficacy for the two pharmacotherapies. Thus, LAAM may be superior to methadone initially, but similarly effective to methadone over longer periods of time.

## **CONCLUSIONS**

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### **Treatment Retention**

Retention in treatment is critical during maintenance therapy because individuals who remain in treatment have continued access to counseling and social services and generally fare better than those who leave treatment (Anglin et al., 2009). Seven studies reported on treatment retention. The two meta-analyses found methadone to result in greater retention rates than LAAM. Studies performed after the two meta-analyses have been conflicting, with one study favoring LAAM, three finding no differences among groups, and one reporting mixed results. This discrepancy between the meta-analyses and the

later studies could be explained by changing perceptions of LAAM. As Glanz et al. (1997) and Clark et al. (2002) acknowledged, there was an anti-LAAM sentiment, consisting of suspicion of the pharmacotherapy's effectiveness, during the time period of the studies analyzed for the meta-analyses. It may be that this negative bias dissipated by the time the newer studies were conducted, resulting in greater confidence in LAAM and higher retention rates. Treatment retention may also depend on the sample of addicts selected: in their analysis of national Australian data, Digiusto et al. (2006) found that in samples of addicts that had never undergone previous maintenance therapy, retention rates were similar for the methadone and LAAM groups, whereas in samples of addicts already maintained on methadone, the methadone groups exhibited greater retention.

Taken as a whole, the reviewed studies indicate that while methadone maintenance was once a better pharmacotherapy for keeping people in treatment, LAAM may now be similarly effective. More research is needed to determine definitively whether or not there are differences in retention between the two approaches to treatment, especially because the results of methodologically sound studies conflict with each other. Even if methadone maintenance remains the more effective therapy for treatment retention, LAAM is an important alternative because it can be used to convert non-holders on methadone maintenance into holders on LAAM maintenance (Newcombe, Bochner, White, & Somogyi 2004).

### **Heroin Use**

Another main goal of maintenance therapy is preventing heroin use because it is associated with several harms, such as increased mortality and degraded social functioning (McKim, 2007). The studies reporting data on heroin use and abstinence from heroin overwhelmingly favor LAAM maintenance over methadone maintenance. Five studies, including the two meta-analyses, suggest that patients receiving LAAM are less likely to give heroin-positive biological samples during treatment and are more likely to remain abstinent for extended periods. One study, by Wolstein et al. (2009), reported no difference in heroin use between LAAM and methadone groups; however, unlike the other researchers, who used objective measures to detect heroin use, Wolstein et al. (2009) relied on self-report, which is subject to dishonesty and recall bias. Thus, the preponderance of evidence suggests that LAAM maintenance is more effective at reducing heroin use, though this effect may attenuate over extended periods of time (Longshore et al., 2009).

### **Involvement in Criminal Activity**

Heroin use often results in drug-associated criminal behavior (McKim, 2007). Thus, an important goal of maintenance therapy is a reduction in criminal involvement for patients (McKim, 2007). The studies reporting on criminal involvement during maintenance treatment found that methadone and LAAM patients generally had similar numbers of legal problems and similar levels of involvement in crime. However, there was some support for the superiority of LAAM, since LAAM patients spent less on heroin (Digiusto et al., 2006) and were less likely to report receiving illegal income at 6-month follow up (Anglin et al., 2009). Further research is necessary to confirm possible treatment differences on criminal involvement. Nonetheless, these findings demonstrate the comparable efficacy of LAAM to methadone in preventing drug-related criminal activity.

### **Health Effects**

Another major indicator of the success of maintenance therapies is their effect on health (McKim, 2007). Eight studies reported on a variety of health outcomes. Three studies, including the two meta-analyses, analyzed the prevalence of negative side effects during LAAM and methadone treatment. The studies revealed that LAAM resulted in a greater number of minor negative side effects than methadone.

One particular side effect, QT prolongation, was the focus of two publications. Weineke et al. (2009) found LAAM to result in longer QT intervals than methadone, whereas Wedam et al. (2007) found the two maintenance therapies to result in similar QT prolongations. These differences may be related to the time of measurement because Wedam et al. (2007) took ECG readings over a 17-week period, whereas Weineke et al. (2009) only took ECG readings at baseline and 24-week follow up. Thus, it could be that LAAM is more dangerous to heart health over longer periods of time. Sampling or environmental

differences also may have played a role. Thus, more research is necessary to determine whether LAAM and methadone produce differential effects on cardiovascular health.

In addition to these analyses of specific side effects, five studies recorded the more general measure of SAE occurrence with opioid-agonist administration. Two publications limited their observations of SAEs to the participants in the LAAM group, and reported none (Anglin et al., 2009; Longshore et al., 2005). One paper found LAAM to result in more SAEs (Ritter et al., 2003), while two found similar rates of SAEs for methadone and LAAM (Digiusto et al., 2004; Wolstein et al., 2009). Although these results appear to be conflicting, there is substantial evidence that the two maintenance treatments are equally safe because three experimentally-controlled studies and one national study consisting of 1244 participants all concluded that LAAM was about as safe as methadone.

Four other studies analyzed different health outcomes. Longshore et al. (2009), White et al. (2001), and Clark et al. (2002) found methadone and LAAM to result in similar HIV risk, self-reported health, and mortality, respectively. Thus, LAAM and methadone are similar on a variety of other health related variables.

Overall, the research seems to suggest that LAAM is fairly similar to methadone in terms of health effects. LAAM may result in a greater number of minor health complications than methadone, but appears similarly safe for widespread use, as indicated by the findings on SAEs. These findings support efforts to make LAAM concurrently available with methadone so that patients can choose their preferred treatment, though continued research and vigilance is needed to monitor for potential cardiac complications.

#### **Patient Preference**

Along with these main outcome variables, it is important to consider a patient's perceptions of different pharmacotherapies for opiate addiction. Certainly, doctors often take into account patient preferences when prescribing treatments to improve health outcomes (Say & Thomson, 2003). Two studies, by Clark et al. (2002) and White et al. (2001), analyzed patient preferences for LAAM versus methadone. They revealed that more people preferred LAAM to methadone. The participants stated that LAAM warded off withdrawal symptoms more effectively, required fewer visits to pick up the drug, and decreased cravings for opiates. These conclusions are limited because very few studies in the meta-analysis asked about patient preference, and only the one newer study used it as an experimental outcome. As a result, further research is needed on this topic, though the current evidence suggests that more patients may prefer LAAM and that it would be received positively as a second option to methadone.

#### **SUMMARY**

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Although LAAM has been studied extensively, LAAM is not currently available as a maintenance therapy in the United States because of concerns about possible negative effects on cardiovascular health (Julien et al., 2011). However, evidence on the cardiac effects of LAAM and methadone is conflicting, and the bulk of research findings on SAEs indicate that LAAM is as safe as methadone for widespread use. Furthermore, LAAM has exhibited similar treatment retention rates as methadone in recent studies, and is more effective than methadone at reducing heroin use. Finally, LAAM is equally effective at decreasing criminal involvement and may be preferred by a larger percentage of patients. Thus, the literature supports using LAAM as an alternative to methadone for maintenance therapy.

It is likely that making these two highly effective drugs concurrently available would greatly improve outcomes for opiate addicts. Indeed, there are differential predictors of success in methadone and LAAM therapy, such as gender (Marsch et al., 2005); consequently, alternative maintenance therapies can be tailored based upon individual differences to improve outcomes. Research on programs in which LAAM and methadone are made concurrently available could address the effectiveness of this strategy. If improvements can be made to the current treatment program for opiate addicts, then it is the responsibility of researchers to test these possibilities.

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