

Part B: 20 Questions and Answers Regarding Methadone Maintenance Treatment Research

Question 1: Is methadone maintenance treatment effective for opioid addiction?

Answer: Yes. Research has demonstrated that methadone maintenance treatment is an effective treatment for heroin and prescription narcotic addiction when measured by

- Reduction in the use of illicit drugs
- Reduction in criminal activity
- Reduction in needle sharing
- Reduction in HIV infection rates and transmission
- Cost-effectiveness
- Reduction in commercial sex work
- Reduction in the number of reports of multiple sex partners
- Improvements in social health and productivity
- Improvements in health conditions
- Retention in addiction treatment
- Reduction in suicide
- Reduction in lethal overdose

Research Highlights

- Recent meta-analyses have supported the efficacy of methadone for the treatment of opioid dependence. These studies have demonstrated across countries and populations that methadone can be effective in improving treatment retention, criminal activity, and heroin use (Mattick, Breen, Kimber, et al., 2003; Marsch, 1998).
- An overview of 5 meta-analyses and systematic reviews, summarizing results from 52 studies and 12,075 opioid-dependent participants, found that when methadone maintenance treatment was compared with methadone detoxification treatment, no treatment, different dosages of methadone, buprenorphine maintenance treatment, heroin maintenance treatment, and L-a-acetylmethadol (LAAM) maintenance treatment, methadone maintenance treatment was more effective than detoxification, no treatment, buprenorphine, LAAM, and heroin plus methadone. High doses of methadone are more effective than medium and low doses (Amato, Davoli, Perucci, et al., 2005).
- Patients receiving methadone maintenance treatment exhibit reductions in illicit opioid use that are directly related to methadone dose, the amount of psychosocial counseling, and the period of time that patients stay in treatment. Patients receiving methadone doses of 80 to 100 mg have improved treatment retention and decreased illicit drug use compared with patients receiving 50 mg of methadone (Strain, Bigelow, Liebson, et al., 1999). Patients staying in treatment for longer periods of time showed greater improvements than those who stayed in treatment for shorter periods (Sells and Simpson, 1976; Simpson, 1993).
- A systematic review conducted on 28 studies involving 7,900 patients has demonstrated significant reductions in HIV risk behaviors in patients receiving methadone maintenance (Gowing, Farrell, Bornemann, et al., 2004). In one study that followed two separate cohorts of HIV-negative injection opioid users, HIV seroconversion occurred in 22 percent of 103 out-of-

treatment subjects compared with 3.5 percent of 152 subjects receiving methadone (Metzger, Woody, McLellan, et al., 1993).

- A randomized clinical trial in Bangkok, Thailand, included 240 heroin-dependent patients, all of whom had previously undergone at least 6 detoxification episodes. The patients were randomly assigned to methadone maintenance versus 45-day methadone detoxification. The study found that the methadone maintenance patients were more likely to complete 45 days of treatment, less likely to have used heroin during treatment, and less likely to have used heroin on the 45th day of treatment (Vanichseni, Wongsuwan, Choopanya, et al., 1991).
- In the Treatment Outcome Prospective Study (TOPS), methadone maintenance patients who remained in treatment for at least 3 months experienced dramatic improvements during treatment with regard to daily illicit opioid use, cocaine use, and predatory crime. These improvements persisted for 3 to 5 years following treatment, but at reduced levels (Hubbard, Marsden, Rachal, et al., 1989).
- In a study of 933 heroin-dependent patients in methadone maintenance treatment programs, during episodes of methadone maintenance, there were (1) decreases in narcotic use, arrests, criminality, and drug dealing; (2) increases in employment and marriage; and (3) diminished improvements in areas such as narcotic use, arrest, criminality, drug dealing, and employment for patients who relapsed (Powers and Anglin, 1993).
- In a 2.5-year followup study of 150 opioid-dependent patients, participation in methadone maintenance treatment resulted in a substantial improvement along several relatively independent dimensions, including medical, social, psychological, legal, and employment problems (Kosten, Rounsaville, and Kleber, 1987).
- A study that compared ongoing methadone maintenance with 6 months of methadone maintenance followed by detoxification demonstrated that methadone maintenance resulted in greater treatment retention (median, 438.5 vs. 174.0 days) and lower heroin use rates than did detoxification. Methadone maintenance therapy resulted in a lower rate of drug-related (mean [SD] at 12 months, 2.17 [3.88] vs. 3.73 [6.86]) but not sex-related HIV risk behaviors and a lower score in legal status (mean [SD] at 12 months, 0.05 [0.13] vs. 0.13 [0.19]) (Sees, Delucchi, Masson, et al., 2000).

Patient Status Before and After Methadone Maintenance Treatment—A study by McGlothlin and Anglin (1981) examined patients from three methadone maintenance treatment programs.

Figures 1 through 5 provide the results from all three programs, which illustrate that methadone maintenance treatment is effective in improving patients' lives in terms of time spent (1) using narcotics daily, (2) unemployed, (3) involved in crime, (4) dealing drugs, and (5) incarcerated.

The left side of each graph describes patient behavior before methadone maintenance treatment, and the right side of each graph depicts patient behavior following methadone maintenance treatment, including the behavior of patients who left treatment before the year ended.

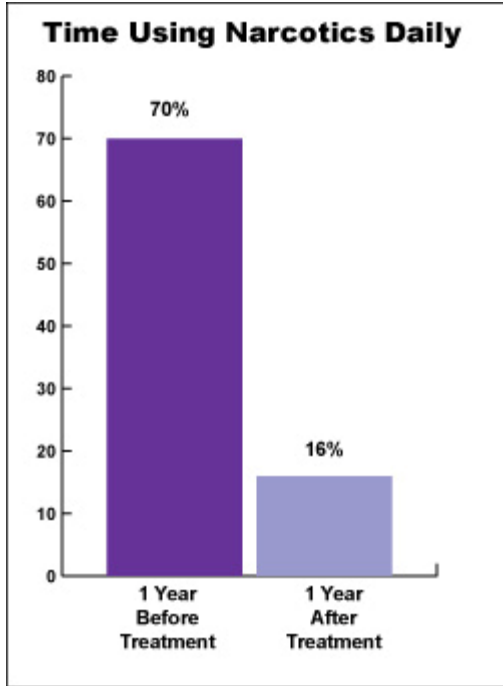


Figure 1 illustrates that the percentage of time using daily narcotics was much greater before methadone maintenance treatment than after (McGlothlin and Anglin, 1981).

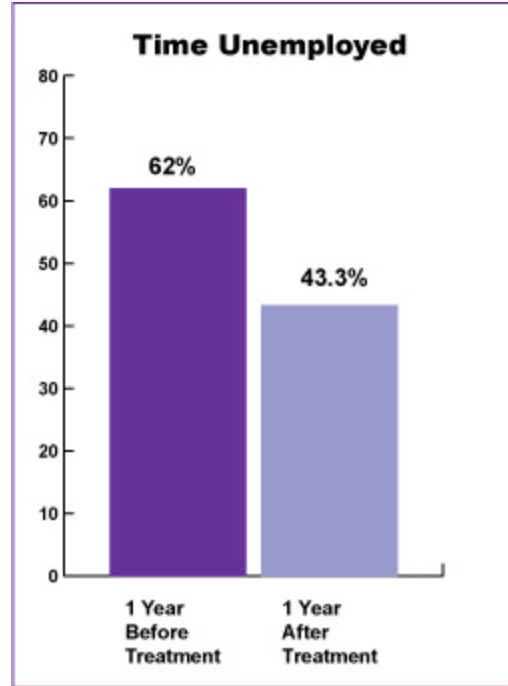


Figure 2 illustrates that the percentage of time unemployed decreased after methadone maintenance treatment (McGlothlin and Anglin, 1981).

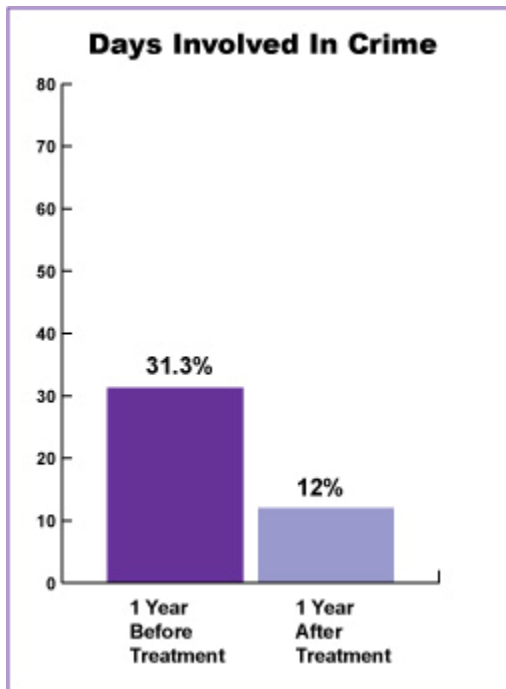


Figure 3 illustrates that the percentage of days the patient was involved in crime decreased after methadone maintenance treatment (McGlothlin and Anglin, 1981).

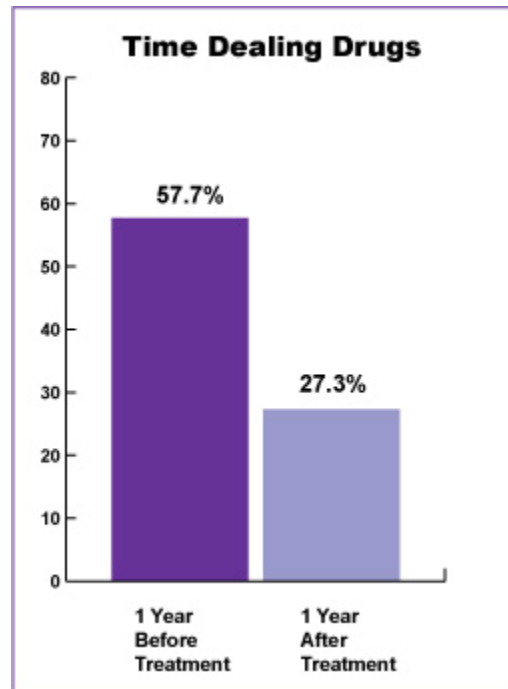


Figure 4 illustrates that the percentage of time dealing drugs decreased after methadone maintenance treatment (McGlothlin and Anglin, 1981).

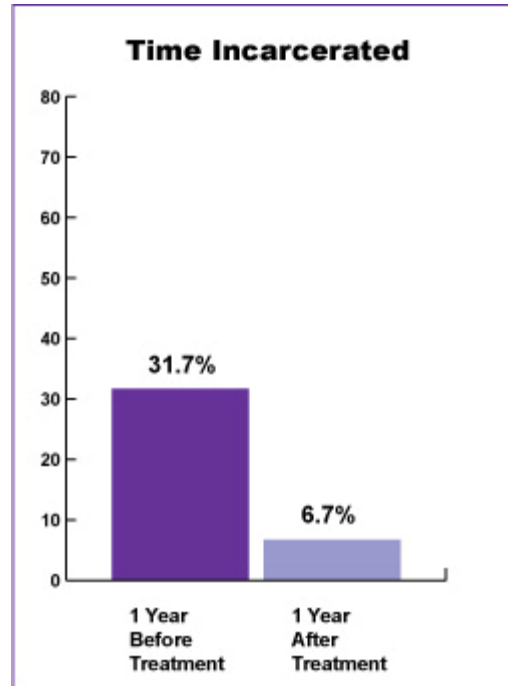


Figure 5 illustrates that the percentage of time incarcerated decreased after methadone maintenance treatment (McGlothlin and Anglin, 1981).

The Effects of Opioids (Heroin or Prescription Narcotics) and Methadone on Functional State—

Figures 6 and 7 illustrate how opioids and methadone have different effects on a patient's functional states and moods: repeated use of heroin or prescription narcotics causes multiple cycles of elevation and depression, but methadone promotes a relatively steady state.

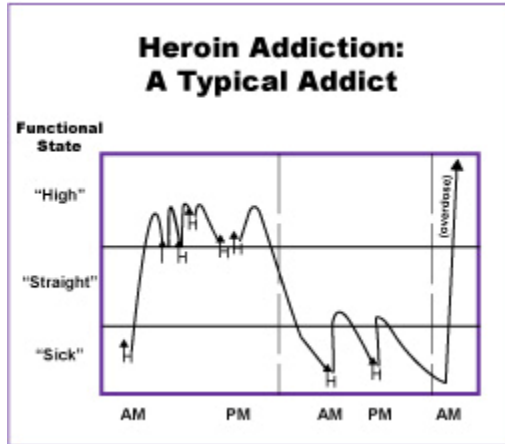
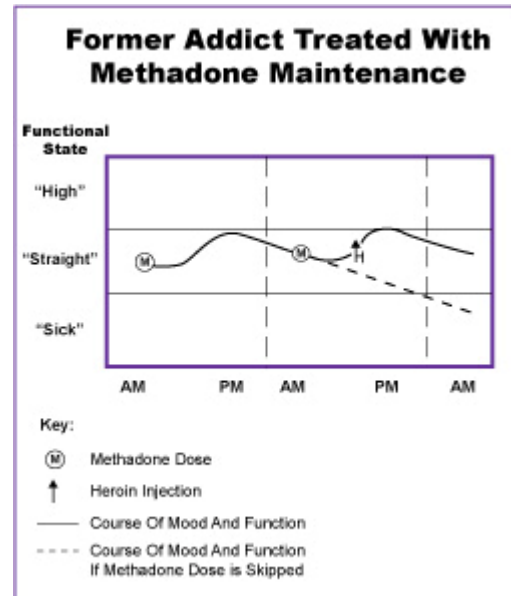


Figure 6 illustrates a typical day for a person who is opioid dependent. Note that the opioid-dependent person generally uses opioids several times each day. Each use causes an elevation in mood: the user feels “high.” This high is followed by a rapid decline in mood and functional state: the user no longer feels high and may begin to feel sick. At the end of the day, or in the morning, the user feels quite sick as the result of opioid withdrawal. Overall, a typical day includes several cycles of elevated and depressed mood and functional state. As an opioid-dependent person uses opioids for a period of time (e.g., weeks to months), that person's level of physical dependence makes it less likely that he or she will experience the high. Continued drug use results from a desire to avoid the depressions and physical symptoms associated with opioid withdrawal.



In contrast, Figure 7 illustrates that a single oral dose of methadone in the morning promotes a relatively steady state of mood and function. This graph also demonstrates that use of an opioid (e.g., injection of heroin) during methadone maintenance treatment has a less intense effect on mood and function than an injection of heroin in active users who are not in methadone treatment. The dotted line in Figure 7 predicts the course of a patient's mood and function if a dose of methadone is omitted. Dole, Nyswander, and Kreek (1966) found that the decline in mood and function is gradual, not steep.

Improvements: Drugs and Crime 1 Year After the Drug Abuse Reporting Program Study (DARP)—The DARP study (Simpson and Sells, 1982) demonstrates that methadone maintenance treatment is effective in reducing two problems associated with heroin addiction: illicit drug use and crime. The study compared reductions in illicit drug use and crime by patients who received methadone maintenance treatment and by patients who received no treatment.

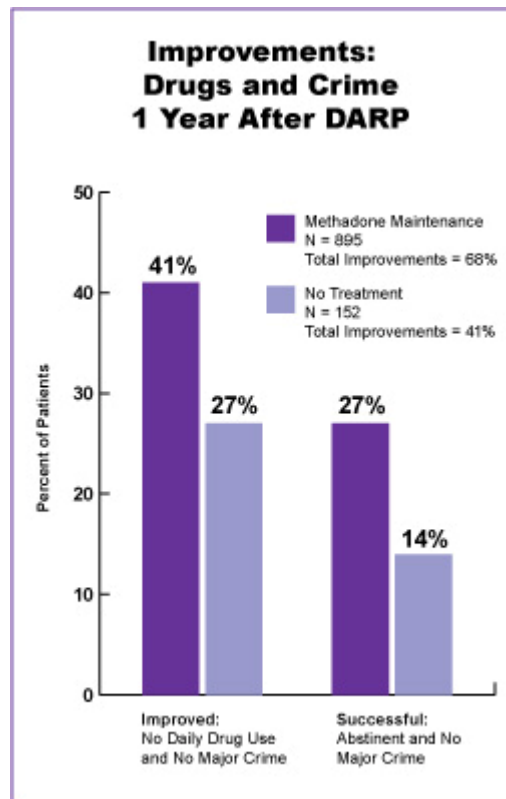


Figure 8 illustrates that, during the first year after treatment, 41 percent of methadone maintenance treatment patients were no longer addicted to illicit opioids and were not involved in major crime. In contrast, 27 percent who received no treatment were no longer addicted to illicit opioids and were not involved in major crime (Simpson and Sells, 1982).

Twenty-seven percent of methadone maintenance treatment patients had not used any illicit drugs and had no arrests or incarcerations during the year after methadone maintenance treatment. In contrast, 14 percent of those not treated reported no illicit drug use or arrests. Overall, 68 percent of methadone maintenance treatment patients experienced significant improvements regarding illicit drug use and crime in contrast to roughly 41 percent of those not treated.

The Effect of Methadone Maintenance Treatment Duration on Drug Use and Crime—The DARP study also shows that the longer patients stay in treatment, the more likely they are to remain crime free.

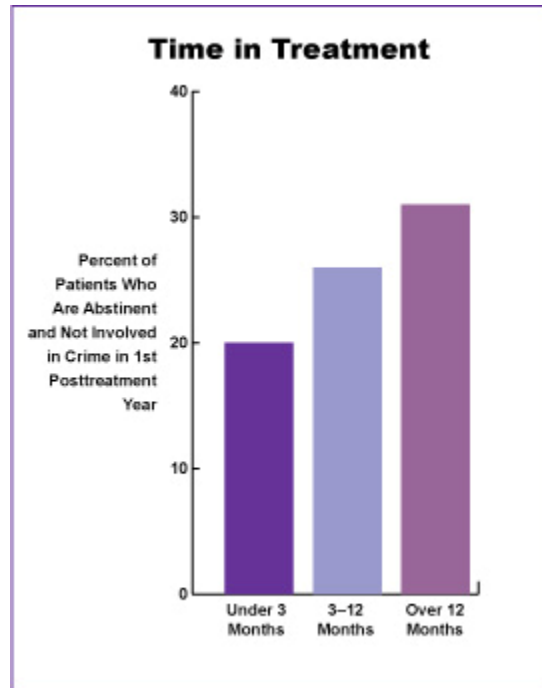


Figure 9 illustrates that there is a relationship between how long patients remain in treatment and how well they function after treatment. In this instance, the length of treatment was associated with abstinence from illicit drug use and an absence of crime. Thirty percent of patients who stayed in treatment for more than 12 months abstained from illicit drug use and criminal activity. Twenty-five percent of patients in treatment from 3 to 12 months stopped using illicit drugs and committing crimes; of those who were in treatment for under 3 months, 20 percent abstained (Simpson and Sells, 1982).

References

- Amato L, Davoli M, Perucci C, Ferri M, Faggiano F, Mattick RP. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *Journal of Substance Abuse Treatment* 2005;28(4):321-29.
- Dole VP, Nyswander ME, Kreek MJ. Narcotic blockade. *Archives of Internal Medicine* 1966;118:304-09.
- Gowing L, Farrell M, Bornemann R, Ali R. Substitution treatment of injecting opioid users for prevention of HIV infection. *The Cochrane Database of Systematic Reviews*, Issue 4, 2004.
- Hubbard RL, Marsden ME, Rachal JV, Harwood HJ, Cavanaugh ER, Ginzburg HM. *Drug Abuse Treatment: A National Study of Effectiveness*. Chapel Hill: University of North Carolina Press, 1989.
- Kosten TR, Rounsaville BJ, Kleber, HD. Multidimensionality and prediction of treatment outcome in opioid addicts: a 2.5-year follow-up. *Comprehensive Psychiatry* 1987;28:3-13.

- Marsch LA. The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behavior and criminality: a meta-analysis. *Addiction* 1998;93(4):515-32.
- Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *The Cochrane Database of Systematic Reviews*, Issue 2, 2003.
- McGlothlin WH, Anglin MD. Shutting off methadone: cost and benefits. *Archives of General Psychiatry* 1981;38:885-92.
- Metzger DS, Woody GE, McLellan AT, O'Brien CP, Druley P, Navaline H, et al. Human immunodeficiency virus seroconversion among intravenous drug users in- and out-of-treatment: an 18-month prospective follow-up. *Journal of Acquired Immune Deficiency Syndrome* 1993;6:1049-56.
- Powers KI, Anglin MD. Cumulative versus stabilizing effects of methadone maintenance. *Evaluation Review* 1993;17(3):243-70.
- Sees KL, Delucchi KL, Masson C, Rosen A, Clark HW, Robillard H, et al. Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence. A randomized controlled trial. *JAMA* 2000;283:1303-10.
- Sells SB, Simpson DD (eds.). *The Effectiveness of Drug Abuse Treatment*. Cambridge, MA: Ballinger, 1976.
- Simpson DD. Drug treatment evaluation research in the United States. *Psychology of Addictive Behaviors* 1993;7(2):120-28.
- Simpson DD, Sells SB. Effectiveness of treatment for drug abuse: an overview of the DARP research program. *Advances in Alcohol and Substance Abuse* 1982;2(1):7-29.
- Strain EC, Bigelow GE, Liebson IA, Stitzer ML. Moderate- vs high-dose methadone in the treatment of opioid dependence. A randomized trial. *JAMA* 1999;281:1000-05.
- Vanichseni S, Wongsuwan B, Choopanya K, Wongpanich K. A controlled trial of methadone maintenance in a population of intravenous drug users in Bangkok: implications for prevention of HIV. *International Journal of the Addictions* 1991;26(12):1313-20.

Question 2: Does methadone maintenance treatment reduce illicit opioid use?

Answer: Yes. Patients' illicit opioid use declines, often dramatically, during methadone maintenance treatment. However, adequate methadone dosage and basic psychosocial services are essential for treatment effectiveness.

Research Highlights

Condelli and Dunteman (1993) examined a sample of 526 patients admitted to 17 methadone maintenance treatment programs that participated in the Treatment Outcome Perspective Study (TOPS). This analysis compared the length of methadone maintenance treatment with heroin use. The average short-term treatment duration was 31 days; long-term, 233 days; and continuous, 725 days. The rate of heroin use was 100 percent before treatment, 39 percent after short-term treatment, 40 percent after long-term treatment, and 17 percent after continuous treatment. This study suggests that longer exposure to methadone maintenance treatment decreases the likelihood of heroin use.

A study of 933 heroin addicts participating in methadone maintenance treatment programs compared behavior during periods on and off methadone maintenance. The study demonstrated that during periods on methadone maintenance, illicit narcotic use decreased significantly and reduction in illicit narcotic use was the most prominent effect among nine indicators of treatment success (Powers and Anglin, 1993).

In the Drug Abuse Reporting Program (DARP) study, 44 percent of the 895 patients who entered methadone maintenance treatment reported no daily use of illicit narcotics in the first posttreatment year. This represented a 56-percent decrease from 100-percent daily use in the 2 months before admission (Simpson and Sells, 1982).

Methadone Dose

In the Ball and Ross studies (1991), patients reduced their use of injected heroin by 71 percent compared with preadmission levels. Illicit opioid use was directly related to methadone dosage: in patients on doses above 71 mg per day, no heroin use was detected, whereas patients on doses below 46 mg per day were 5.16 times more likely to use heroin than those receiving higher doses.

The impact of methadone dose has been demonstrated consistently across studies and countries. Higher (e.g., greater than 50 mg) doses of methadone are associated with better treatment retention and decreased illicit drug use (Strain, Stitzer, Liebson, et al., 1993; Strain, Bigelow, Liebson, et al., 1999; Capplehorn and Bell, 1991; Capplehorn, Bell, Kleinbaum, et al., 1993; Faggiano, Vigna-Taglianti, Versino, et al., 2003).

A meta-analysis (Faggiano et al., 2003) of 21 studies concluded that methadone dosages ranging from 60 to 100 mg per day were more effective than lower dosages in retaining patients and in reducing use of heroin and cocaine during treatment.

The following outcomes in the meta-analysis were noted:

Retention rate—randomized clinical trials: high versus low doses at short duration followup: RR = 1.36 [1.13 to 1.63], and at longer duration followup: RR = 1.62 [0.95 to 2.77]

Self-reported opioid use—randomized clinical trials: high versus low doses WMD = -2.00 [4.77 to 0.77], high versus medium doses WMD = -1.89 [-3.43 to -0.35]

Opioid abstinence by urine toxicology at greater than 3 to 4 weeks—randomized clinical trials: high versus low doses RR = 1.59 [1.16 to 2.18], high versus medium doses RR = 1.51 [0.63 to 3.61]

Cocaine abstinence by urine toxicology at greater than 3 to 4 weeks—randomized clinical trials: high versus low doses RR = 1.81 [1.15 to 2.85]

Overdose mortality—high dose versus low dose at 6 years' followup: RR = 0.29 [0.02 to 5.34]; high dose versus medium dose at 6 years' followup: RR = 0.38 [0.02 to 9.34]; medium dose versus low dose at 6 years' followup: RR = 0.57 [0.06 to 5.06]

One study noted lower rates of opioid-positive urine samples (53% vs. 62%, $p < .05$) in patients who were being treated with 80 to 100 mg of methadone compared with those who were being treated with 40 to 50 mg (Strain et al., 1999).

Counseling Services

Counseling services improve treatment outcomes over the provision of methadone alone (Amato, Minozzi, Davoli, et al., 2004). The importance of adding counseling services to methadone maintenance was demonstrated in a study that randomly assigned new patients to three levels of care: (1) methadone alone, (2) methadone plus standard counseling services, and (3) methadone plus enhanced services (counseling, medical/psychiatric, employment, and family therapy services). Patients who received the standard or enhanced services had higher treatment retention rates and less opiate use than those who received methadone alone (McLellan, Arndt, Metzger, et al., 1993). A cost-effectiveness analysis of these subjects after 1 year revealed that the standard counseling services were most cost-effective (Kraft, Rothbard, Hadley, et al., 1997).

Treatment Duration

In one study, 82 percent of 105 patients who discontinued methadone relapsed to intravenous drug use within 12 months (Ball and Ross, 1991). Concerns over high relapse rates have led authorities to advocate for maintenance treatment as long as the patient (1) continues to benefit, (2) wishes to remain, (3) is at risk of relapse, (4) suffers no significant side effects, and (5) stays in treatment as long as treatment is needed, as determined by the clinician (Payte and Khuri, 1993).

DARP studies of opioid-dependent patients 12 years following admission to treatment showed that illicit opioid use declined progressively over time until year 6, when it stabilized at about 40 percent for “any” use and 25 percent for “daily” use (Simpson, Joe, Lehman, et al., 1986).

In both the DARP and TOPS studies, long treatment duration was the strongest predictor of reduced heroin use among methadone maintenance patients.

Reductions in Illicit Opioid Use During and After Methadone Maintenance Treatment—The DARP and TOPS studies of two different groups of heroin-addicted patients were conducted several years apart. Both demonstrated about a 40-percent reduction in illicit opioid use at the end of 1 year after methadone maintenance treatment.

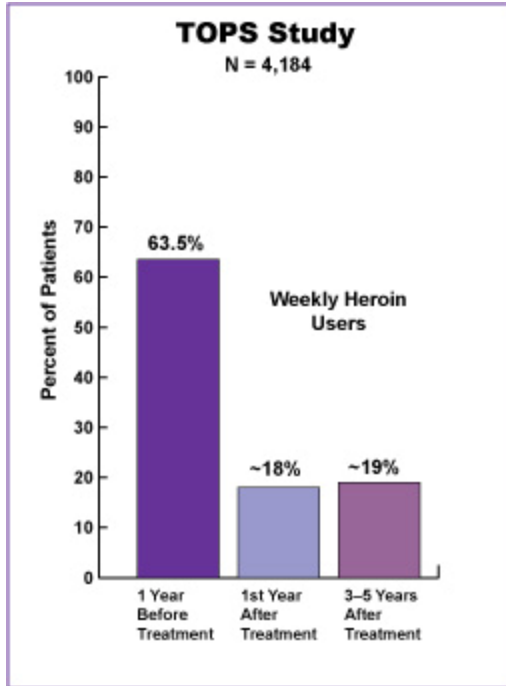


Figure 10 illustrates that, in the TOPS study, almost 64 percent of the patients used heroin at least weekly in the year before treatment; however, about 18 percent used heroin at least weekly in the year after treatment, and about 19 percent continued heroin use weekly 3 to 5 years after treatment (Hubbard, Marsden, Rachal, et al., 1989).

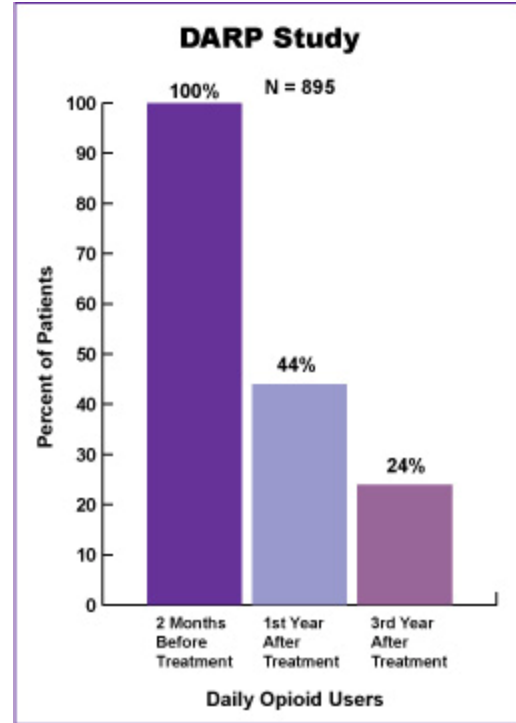


Figure 11 illustrates that in the DARP study, 44 percent of methadone maintenance treatment patients used heroin daily in the year following treatment and 24 percent used heroin daily 3 years after treatment. This represents significant reductions from the 100 percent who had used heroin daily in the 2 months before admission (Simpson and Sells, 1982). Daily illicit opioid use continued to decline steadily for the next 3 years.

DARP: Changes in Illicit Opioid Use: Pretreatment to 12-Year Followup—Among patients in the DARP studies, (1) methadone maintenance treatment resulted in a rapid decline in illicit opioid use and (2) this reduction in illicit opioid use remained steady for 12 years (Simpson and Sells, 1990).

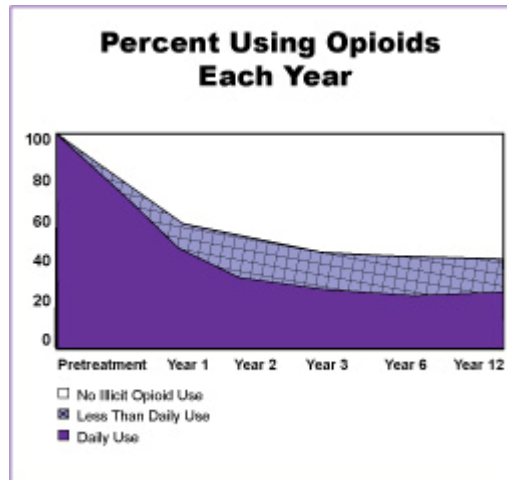


Figure 12 illustrates that improvements among patients who used no illicit opioids and who used opioids less than daily persisted into the 12th year after treatment. About one-half of those patients treated with methadone maintenance reported no illicit drug use after 12 years. The benefits associated with methadone maintenance treatment seem to improve over time. For example, at the end of 1 year, about 50 percent of the subjects reported daily illicit drug use, but by year 12, the proportion using illicit drugs on a daily basis was reduced to about 25 percent (Simpson and Sells, 1990).

Reduction of Heroin Use by Length of Stay in Methadone Maintenance Treatment—The length of stay in methadone maintenance treatment is associated with a reduction in heroin use: longer lengths of stay are associated with greater reductions in heroin use. In addition, leaving methadone maintenance treatment is associated with a return to injection drug use in 82 percent of patients within 1 year (Ball and Ross, 1991).

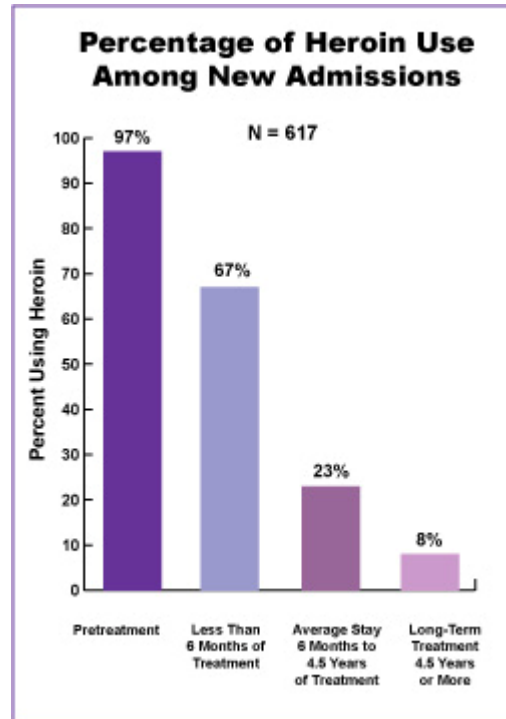


Figure 13 illustrates that heroin use among a group of 617 new admissions was nearly 100 percent. Among patients who stayed in treatment for less than 6 months, about 67 percent reported using heroin. Among patients whose average stay in methadone maintenance treatment was 6 months to 4.5 years, about 23 percent reported using heroin. Among patients who remained in treatment more than 4.5 years, about 8 percent reported using heroin (Ball and Ross, 1991).

References

- Amato L, Minozzi S, Davoli M, Vecchi S, Ferri M, Mayet S. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. *The Cochrane Database of Systematic Reviews*, Issue 4, 2004.
- Ball JC, Ross A. *The Effectiveness of Methadone Maintenance Treatment*. New York, NY: Springer-Verlag Inc., 1991.
- Caplehorn JRM, Bell J. Methadone dosage and retention of patients in maintenance treatment. *The Medical Journal of Australia* 1991;154:195-99.

Caplehorn JRM, Bell J, Kleinbaum DG, Gebiski VJ. Methadone dose and heroin use during maintenance treatment. *Addiction* 1993;88:119-24.

Condelli WS, Dunteman GH. Exposure to methadone programs and heroin use. *American Journal of Drug and Alcohol Abuse* 1993;19:65-78.

Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opioid dependence. *The Cochrane Database of Systematic Reviews*, Issue 3, 2003.

Hubbard RL, Marsden ME, Rachal JV, Harwood HJ, Cavanaugh ER, Ginzburg HM. *Drug Abuse Treatment: A National Study of Effectiveness*. Chapel Hill: University of North Carolina Press, 1989.

Kraft KM, Rothbard AB, Hadley TR, McLellan AT, Asch DA. Are supplementary services provided during methadone maintenance really cost-effective? *American Journal of Psychiatry* 1997;154:1214-19.

McLellan AT, Arndt IO, Metzger DS, Woody GE, O'Brien CP. The effects of psychosocial services in substance abuse treatment. *JAMA* 1993;269(15):1953-59.

Payte JT, Khuri ET. Treatment duration and patient retention. In: *State Methadone Treatment Guidelines*. Rockville, MD: Center for Substance Abuse Treatment, 1993.

Powers KI, Anglin MD. Cumulative versus stabilizing effects of methadone maintenance. *Evaluation Review* 1993;17(3):243-70.

Simpson DD, Joe GW, Lehman WEK, Sells SB. Addiction careers: etiology, treatment, and 12-year follow-up outcomes. *Journal of Drug Issues* 1986;16(1):107-21.

Simpson DD, Sells SB. Effectiveness of treatment for drug abuse: an overview of the DARP research program. *Advances in Alcohol and Substance Abuse* 1982;2(1):7-29.

Simpson DD, Sells SB (eds.). *Opioid Addiction and Treatment: A 12-Year Follow-Up*. Malabar, FL: Krieger Publishing Company, 1990.

Strain EC, Bigelow GE, Liebson IA, Stitzer ML. Moderate- vs high-dose methadone in the treatment of opioid dependence. A randomized trial. *JAMA* 1999;281:1000-05.

Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Dose-response effects of methadone in the treatment of opioid dependence. *Annals of Internal Medicine* 1993;119:23-37.

Question 3: Does methadone maintenance treatment reduce HIV risk behaviors and the incidence of HIV infection among opioid-dependent injection drug users?

Answer: Yes. The daily oral administration of adequate dosages of methadone reduces the need for opioid-dependent individuals to inject drugs. By decreasing injection drug use, methadone maintenance treatment helps reduce the spread of diseases transmitted through needle sharing, such as human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV), and other bloodborne infections (Sullivan, Metzger, Fudala, et al., 2005; Gowing, Farrell, Bornemann, et al., in press).

Research Highlights

A systematic review of 23 studies of 7,900 patients in diverse countries and settings reported significant decreases in the following HIV risk behaviors among patients receiving methadone maintenance treatment: (1) the proportion of opioid-dependent injection drugs, (2) the reported frequency of injection, (3) levels of sharing of injection equipment, (4) illicit opioid use, (5) reduction in the proportion of opioid-dependent injection drug users reporting multiple sex partners or exchanges of sex for drugs or money, and (6) reductions in cases of HIV infection among opioid-dependent injection drug users. However, it should be noted that methadone treatment had little or no effect on the use of condoms. The authors concluded that the provision of agonist treatment for opioid dependence should be supported in countries with emerging HIV and injection drug use problems as well as in countries with established populations of injection drug users (Gowing, Farrell, Bornemann, et al., 2004).

These results support an earlier meta-analysis of 11 studies that found a consistent, statistically significant relationship between methadone maintenance treatment and the reduction of HIV risk behaviors. This meta-analysis found that methadone maintenance treatment had a small-to-moderate effect in reducing HIV risk behaviors (Marsch, 1998).

- A study that evaluated HIV risk behavior in patients receiving ongoing methadone maintenance compared with patients receiving 6 months of methadone maintenance followed by detoxification demonstrated that those patients who received ongoing methadone maintenance treatment reported lower HIV drug (but not sex) risk behaviors after 6 and 12 months of treatment (Sees, Delucchi, Masson, et al., 2000).
- In New Haven, CT, 107 methadone-maintained injection drug users who were not in treatment were surveyed regarding their risk behaviors. The frequency of injections was found to be 50 to 65 percent ($p < .001$) higher among the out-of-treatment subjects (Meandzija, O'Connor, Fitzgerald, et al., 1994).
- In a 3-year field study of methadone maintenance treatment programs in New York, NY, Philadelphia, PA, and Baltimore, MD, treatment was found to be effective in reducing injection drug use and needle sharing by most heroin addicts. Of 388 patients who remained in treatment for 1 year or more, 71 percent had stopped injection drug use. Conversely, 82 percent of patients who left treatment relapsed rapidly to injection drug use (Ball, Lang, Meyers, et al., 1988).
- Abdul-Quader, Friedman, Des Jarlais, et al. (1987) reported that both the frequency of drug injection and the frequency of drug injection in shooting galleries were significantly reduced by the amount of time spent in methadone maintenance treatment.
- A study by Serpelloni, Carrieri, Rezza, et al. (1994) examined the effect of methadone maintenance treatment on HIV infection incidence among injection drug users. The study found that the amount of time spent in methadone maintenance treatment was the major determinant in remaining HIV-free, which confirms the effectiveness of long-term programs in reducing the risk of HIV infection. Indeed, the risk of HIV infection increased 1.5 times for every 3 months spent out of methadone treatment in the past 12 months immediately preceding seroconversion. The study noted that higher daily methadone doses were associated with a reduction in HIV infection.

- A study by Weber, Ledergerber, Opravil, et al. (1990) examined the role of methadone maintenance treatment in reducing the progression of HIV infection among 297 current and former injection drug users with asymptomatic HIV infection. The study showed that HIV infection progresses significantly more slowly in those who receive methadone maintenance treatment and those who are drug free than in active injection drug users.
- In Philadelphia, PA, a longitudinal study of HIV infection and risk behaviors among 152 injection drug users in methadone maintenance treatment and 103 out-of-treatment injection drug users found significantly lower rates of risk behavior, including needle sharing, injection frequency, shooting gallery use, and visits to crack houses among the methadone-maintained users. While 70 percent of the out-of-treatment cohort reported sharing needles during the 6 months before entry into the study, only 30 percent of those in treatment reported sharing needles during this same interval.
- At entry into this study, 18 percent of the out-of-treatment subjects and 11 percent of the methadone-maintained clients tested positive for antibodies to HIV. After 18 months of study, 33 percent of the out-of-treatment cohort were infected, whereas 15 percent of the methadone clients tested positive ($p < 0.01$). The incidence of new infection was strongly associated with the level of participation in methadone treatment. Among those who remained in methadone treatment for the entire 18-month study period, 3.5 percent became infected. Among those who remained out of treatment, 22 percent became infected with HIV (Metzger, Woody, McLellan, et al., 1993).
- Another study of HIV seroconversion followed 56 patients who were continuously enrolled in methadone maintenance and compared them with 42 patients who had intermittent methadone treatment. Subjects in continuous treatment had a seroconversion rate of 0.7 per 100 person years (95% CI = 0.1, 5.3), and those with interrupted treatment had a rate of 4.3 per 100 person years (95% CI = 2.2, 8.6) (Williams, McNelly, Williams, et al., 1992).
- A relatively short-term study of methadone maintenance versus control in a prison system in Australia found reductions in opioid use but no changes in HIV or HCV incidence (Dolan, Shearer, MacDonald, 2003).

The following two visuals—HIV Infection Rates by Methadone Maintenance Treatment Status and 18-Month HIV Seroconversion by Methadone Maintenance Treatment Retention—depict findings from this study.

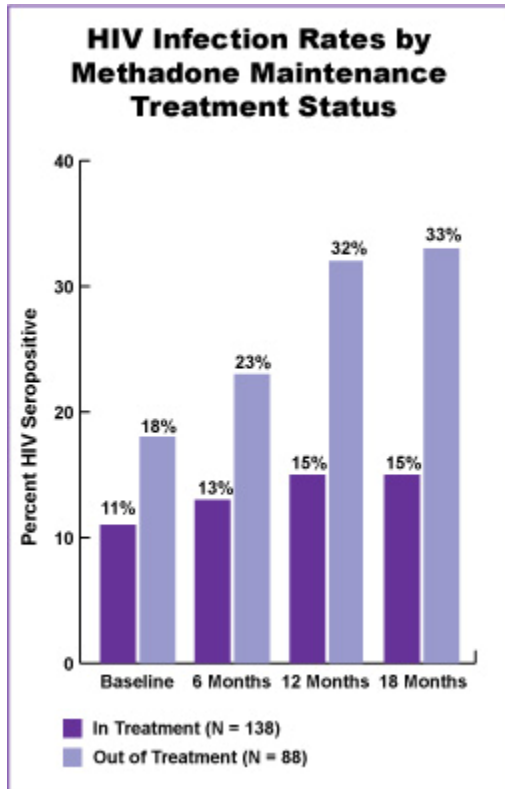


Figure 14 illustrates that at the beginning of this study, 18 percent of the out-of-treatment subjects and 11 percent of the methadone-maintained clients tested positive for antibodies to HIV. After 18 months, nearly twice as many (33 percent) of the out-of-treatment cohort were HIV-positive, whereas only 15 percent of the methadone clients tested positive ($p < .01$). The incidence of new infection was strongly associated with the level of participation in methadone treatment.

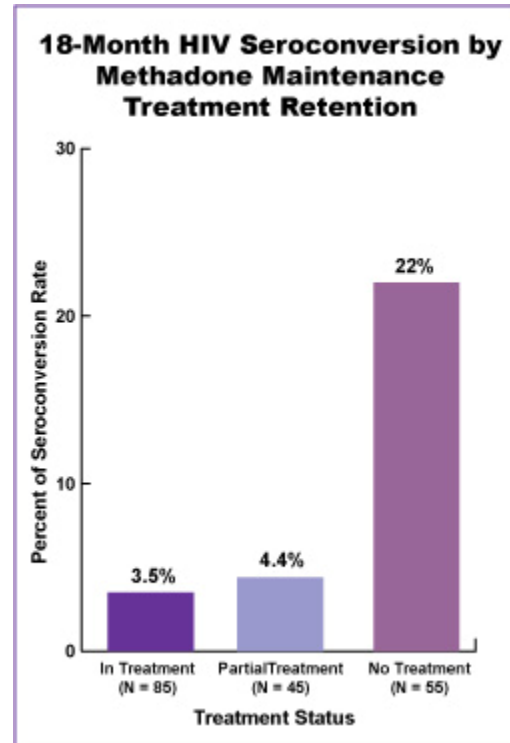


Figure 15 illustrates that among those who remained in methadone maintenance treatment for the entire 18-month study period, 3.5 percent became infected with HIV. Among those who remained out of treatment, 22 percent became infected with HIV (Metzger et al., 1993).

Rapid Return to Injection Drug Use Following Premature Termination of Methadone Maintenance Treatment—In a 3-year field study of methadone maintenance treatment programs in New York, NY, Philadelphia, PA, and Baltimore, MD, methadone maintenance treatment was found to be effective in reducing injection drug use and needle sharing by most heroin addicts. Of 388 patients who remained in treatment for 1 year or more, 71 percent had stopped injection drug use. Conversely, 82 percent of the 105 patients who left treatment relapsed rapidly to injection drug use (Ball et al., 1988).

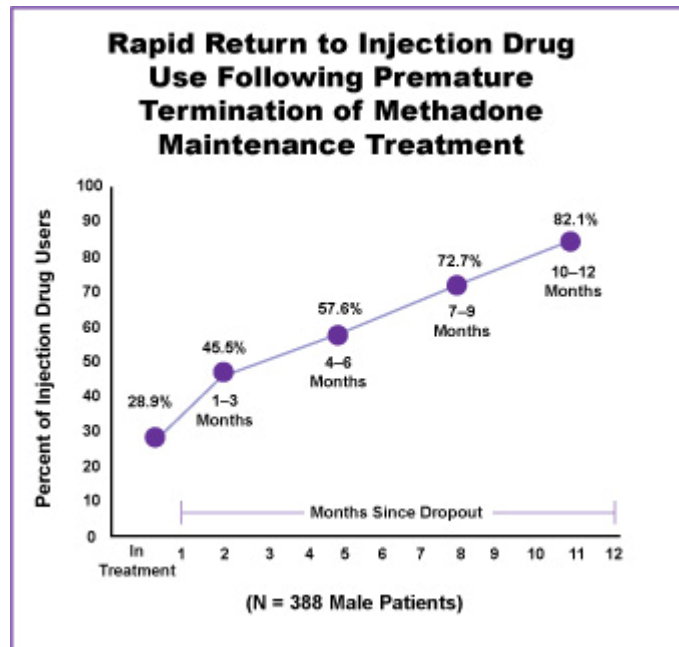


Figure 16 illustrates that methadone maintenance treatment is associated with reductions in injection drug use and the risks related to HIV infection. When drug users leave methadone maintenance treatment prematurely, they have an increased likelihood of returning to injection drug use (Ball et al., 1988).

References

- Abdul-Quader OS, Friedman SR, Des Jarlais DC, Marmor MM, Maslansky R, Bartelme S. Methadone maintenance and behavior by intravenous drug users that can transmit HIV. *Contemporary Drug Problems* 1987;14:425-33.
- Ball JC, Lange WR, Meyers CP, Friedman SR. Reducing the risk of AIDS through methadone maintenance treatment. *Journal of Health and Social Behavior* 1988;29:214-226.
- Dolan KA, Shearer J, MacDonald M, Mattick RP, Hall W, Wodak AD. A randomized controlled trial of methadone maintenance treatment versus wait list control in an Australian prison system. *Drug & Alcohol Dependence* 2003;72(1):59-65.
- Gowing L, Farrell M, Bornemann R, Ali R. Substitution treatment of injecting opioid users for prevention of HIV infection. *The Cochrane Database of Systematic Reviews*, Issue 4, 2004.
- Gowing LR, Farrell M, Bornemann R, Sullivan L, Ali, R. Methadone treatment of injecting opioid users for prevention of HIV infection. *Journal of General Internal Medicine*, in press.
- Marsch LA. The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behavior and criminality: a meta-analysis. *Addiction* 1998;93(4):515-32.
- Meandzija B, O'Connor PG, Fitzgerald B, Rounsaville BJ, Kosten TR. HIV infection and cocaine use in methadone maintained and untreated intravenous drug users. *Drug & Alcohol Dependence* 1994;36(2):109-13.
- Metzger DS, Woody GE, McLellan AT, O'Brien CP, Druley P, Navaline H, et al. Human immunodeficiency virus seroconversion among intravenous drug users in- and out-of-treatment: an 18-month prospective follow-up. *Journal of Acquired Immune Deficiency Syndrome* 1993;6:1049-56.

Sees KL, Delucchi KL, Masson C, Rosen A, Clark HW, Robillard H, et al. Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence. A randomized controlled trial. *JAMA* 2000;283:1303-10.

Serpelloni G, Carrieri MP, Rezza G, Morganti S, Gomma M, Binkin N. Methadone treatment as a determinant of HIV risk reduction among injecting drug users: a nested case-control study. *AIDS Care* 1994;6:215-20.

Sullivan LE, Metzger DS, Fudala PJ, Fiellin DA. Decreasing international HIV transmission: the role of expanding access to opioid agonist therapies for injection drug users. *Addiction* 2005;100(2):150-58.

Weber RB, Ledergerber M, Opravil M, Siegenthaler W, Luthy R. Progression of HIV infection in misusers of injected drugs who stop injecting or follow a programme of maintenance treatment with methadone. *British Medical Journal* 1990;301:1362-5.

Williams AB, McNelly EA, Williams AE, D'Aquila RT. Methadone maintenance treatment and HIV type 1 seroconversion among injecting drug users. *AIDS Care* 1992;4(1):35-41.

Question 4: Does methadone maintenance treatment reduce criminal activity?

Answer: Yes. Patients are less likely to become involved in criminal activity while in methadone maintenance treatment.

- Patients who remain in methadone maintenance treatment for long periods of time are less likely to be involved in criminal activity than patients in treatment for short periods.
- The availability of methadone maintenance treatment in a community is associated with a decrease in that community's criminal activity, particularly theft.

Research Highlights

- In a meta-analysis of 24 studies, results indicate an overall small-to-medium effect of $r = -0.25$ (unweighted) of the impact of methadone maintenance on criminal activity. A large effect size of $r = 0.70$ (unweighted) was seen in those studies that investigated the efficacy of methadone maintenance treatment in reducing drug-related criminal behaviors. A small-to-moderate effect of $r = 0.23$ (unweighted) was obtained when both drug and property-related criminal activities were evaluated. Finally, a small effect of $r = 0.17$ (unweighted) was demonstrated when drug- and nondrug-related criminal behaviors were combined (Marsch, 1998).
- In the Treatment Outcome Perspective Study (TOPS), 32 percent of the methadone maintenance patients acknowledged committing one or more predatory crimes in the year before treatment, but only 10 percent continued these activities during treatment. By 3 to 5 years after leaving treatment, only 16 percent of the patients reported predatory criminal activity—a reduction of one-half the pretreatment level (Hubbard, Marsden, Rachal, et al., 1989).
- Among the 617 patients studied by Ball and Ross (1991), there was a 70.8-percent decline in crime-days within the 4-month methadone maintenance treatment period. This decline was followed by continuing, but less dramatic, declines in mean crime-days among those in treatment for 1 to 3 years. Those in treatment for 6 or more years had the lowest rate of crime-days per year (14.5).
- The Powers and Anglin (1993) retrospective study of 933 heroin addicts demonstrated that rates of criminality, arrests, and drug dealing decreased during episodes of methadone maintenance treatment when compared with addicts not in treatment.
- In the National Treatment Outcome Research Study, acquisitive criminal behavior decreased in the majority of the 333 patients except those ($n = 88$) who were felt to have a poor treatment response. In these patients, there was no change in this type of criminal activity (Gossop, Marsden, Stewart, et al., 2000).
- The meta-analysis by Mattick, Breen, Kimber, et al. (2003) revealed that criminal activity declined in consort with reductions in heroin use, although the advantage for methadone beyond control in reducing criminal activity was not statistically significant (3 studies, 363 patients: $RR = 0.39$, 95% CI: 0.12-1.25).

The Effects of Methadone Maintenance Treatment on Crime-Days—The Ball and Ross study (1991) of 617 patients demonstrated that methadone maintenance treatment is associated with a dramatic decline in the average number of crime-days per year.

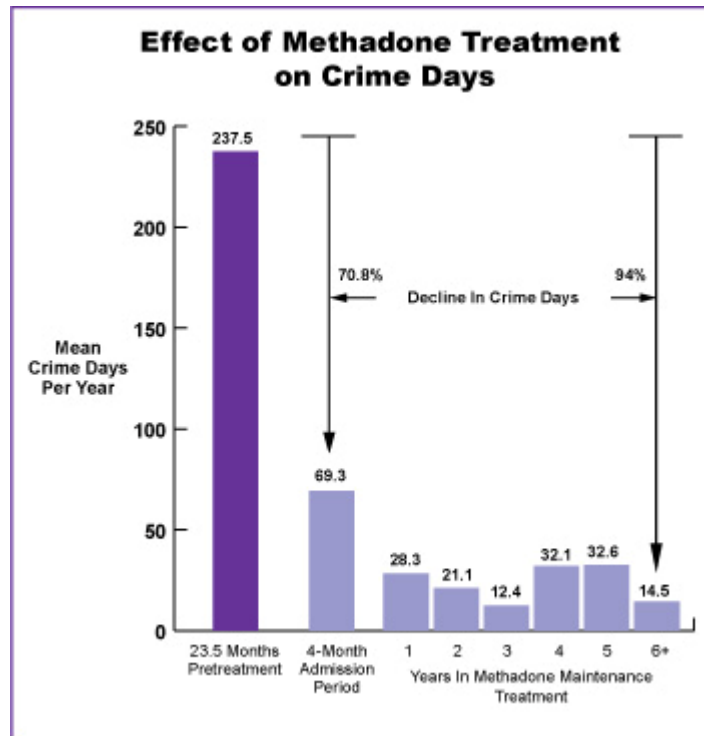


Figure 17 illustrates that the average number of crime-days per year before treatment was 237. During the 4-month initial methadone maintenance treatment, the average number of crime-days per year was 69. This represents about a 71-percent decline. This dramatic decline was followed by continuing, but less dramatic, declines in the average number of crime-days among those in methadone maintenance treatment for 1 to 3 years. Patients who remained in methadone maintenance treatment for 6 or more years reported only 14.5 crime-days per year, representing a 94-percent decline in average number of crime-days (Ball and Ross, 1991).

Crime Before and During Methadone Maintenance Treatment at Six Programs—Ball and Ross (1991) found a dramatic decline in crime when comparing pretreatment crime-days per year and the number of crime-days per year after 6 months or more in methadone maintenance treatment.

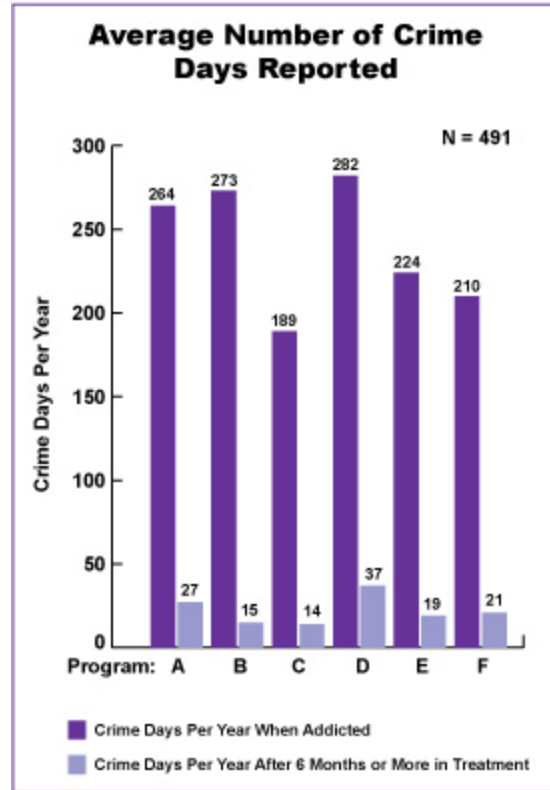


Figure 18 illustrates the average number of crime-days reported by patients in six methadone maintenance treatment programs. Although there are differences among programs, the dramatic decrease in crime-days before and during methadone maintenance treatment occurs for all six programs. Crime was reduced by approximately 90 percent in program A, 95 percent in program B, 93 percent in program C, 87 percent in program D, 92 percent in program E, and 90 percent in program F. The average reduction in crime for those in methadone maintenance treatment was just over 91 percent (Ball and Ross, 1991).

The cost benefits of methadone maintenance treatment become obvious when one compares the costs of providing treatment with the social costs that would have occurred if the crime level had continued.

References

Ball JC, Ross A. *The Effectiveness of Methadone Maintenance Treatment: Patients, Programs, Services, and Outcomes*. New York: Springer-Verlag, 1991.

Gossop M, Marsden J, Stewart D, Rolfe A. Patterns of improvement after methadone treatment: 1 year follow-up results from the National Treatment Outcome Research Study. *Drug & Alcohol Dependence* 2000;60(3):275-86.

Hubbard RL, Marsden ME, Rachal JV, Harwood HJ, Cavanaugh ER, Ginzburg HM. *Drug Abuse Treatment: A National Study of Effectiveness*. Chapel Hill: University of North Carolina Press, 1989.

Marsch LA. The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behavior and criminality: a meta-analysis. *Addiction* 1998;93(4):515-32.

Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *The Cochrane Database of Systematic Reviews*, Issue 2, 2003.

Powers KI, Anglin MD. Cumulative versus stabilizing effects of methadone maintenance. *Evaluation Review* 1993;17(3):243-70.

Question 5: Does methadone maintenance treatment improve the likelihood of obtaining and retaining employment?

Answer: Yes. The likelihood of becoming and remaining employed is increased for patients who participate in methadone maintenance treatment.

- In an early study of 100 chronic heroin users who were admitted to methadone maintenance treatment, the employment rate increased from 21 percent at admission to 65 percent 1 year later (Maddux and McDonald, 1973; Maddux and Desmond, 1979).
- A study of 92 males admitted to methadone maintenance treatment programs from 1971 through 1973 demonstrated that, following methadone maintenance treatment, employment increased about 18 percent (Harlow and Anglin, 1984).
- In a 10-year followup study, 95 chronic opioid users who spent at least 1 cumulative year in methadone maintenance treatment were compared with 77 chronic opioid users who spent less than 1 cumulative year in methadone maintenance treatment. Those who were on methadone maintenance treatment for more than 1 year had a higher average time employed (mean of 42 months) than those who were in treatment for less than 1 year (mean of 35 months) (Maddux and Desmond, 1992).
- The Powers and Anglin (1993) study of 933 heroin addicts in methadone maintenance treatment demonstrated that rates of employment (and marriage) increased during treatment.
- Methadone maintenance patients in the Treatment Outcome Perspective Studies (TOPS) had small changes in employment rates during and following treatment compared with pretreatment rates. Although 24 percent of the patients reported full-time employment in the year before admission, this rate did not increase significantly during treatment. It declined abruptly in the 3 months following discharge, improved to 29 percent by year 2, and dropped off again to less than pretreatment rates by years 3 to 5 following treatment (Hubbard, Marsden, Rachal, et al., 1989).
- In a study that compared ongoing methadone maintenance with 6 months of methadone maintenance followed by detoxification, no difference was seen in employment, although nearly 50 percent of patients were employed at entry into the study (Sees, Delucchi, Masson, et al., 2000). Similarly, a study comparing methadone maintenance with methadone-free treatment saw improvements in both groups over time but no difference in outcomes across treatment type (Abbot, Moore, Delaney, et al., 1999). The McLellan trial, which evaluated varying levels of ancillary services, provides some insight into these negative findings. Specifically, the group of patients in the McLellan trial that received enhanced psychosocial services (including employment counseling) was noted to have improvements in employment status with methadone treatment compared with patients who received no or standard services (McLellan, Arndt, Metzger, et al., 1993).

Changes in Employment During and After Methadone Maintenance Treatment—Figures 19 and 20 illustrate the effects of methadone maintenance treatment on full-time employment as demonstrated by the TOPS and DARP studies. In one study, there was little effect, but in the other, methadone maintenance treatment was associated with significant increases in full-time employment.

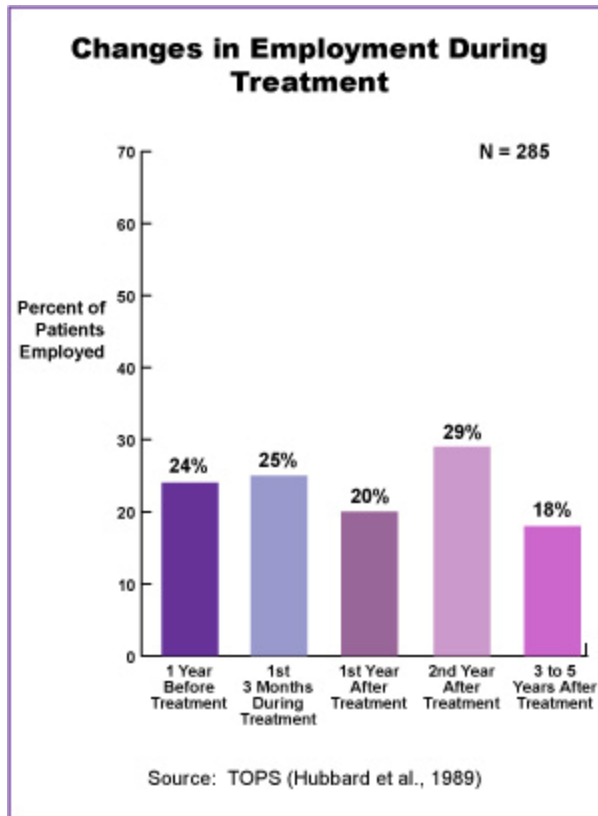
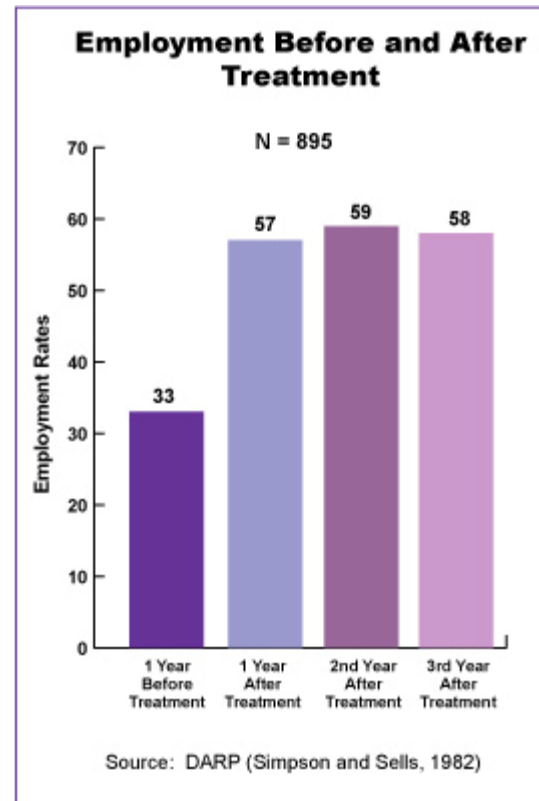


Figure 19 illustrates that patients in TOPS studies experienced small and inconsistent changes in full-time employment rates during and after treatment. Employment rates were about 24 percent 1 year before treatment, ranged from 20 to 25 percent during the first year after treatment, rose to 29 percent during the second year after treatment, and declined to 18 percent 3 to 5 years after treatment (Hubbard et al., 1989).



In contrast, Figure 20 illustrates that the DARP studies reported an abrupt increase from 33-percent full-time employment before treatment to nearly 60 percent after treatment (Simpson and Sells, 1982).

References

- Abbott PJ, Moore B, Delaney H, Weller S. Retrospective analyses of additional services for methadone maintenance patients. *Journal of Substance Abuse Treatment* 1999;17(1-2):129-37.
- Harlow LL, Anglin MD. Time series design to evaluate effectiveness of methadone maintenance intervention. *Journal of Drug Education* 1984;14(1):53-72.
- Hubbard RL, Marsden ME, Rachal JV, Harwood HJ, Cavanaugh ER, Ginzburg HM. *Drug Abuse Treatment: A National Study of Effectiveness*. Chapel Hill: University of North Carolina Press, 1989.
- Maddux JF, Desmond DP. Crime and treatment of heroin users. *The International Journal of the Addictions* 1979;14(7):891-904.
- Maddux JF, Desmond DP. Ten-year follow-up after admission to methadone maintenance. *American Journal of Drug and Alcohol Abuse* 1992;18(3):289-303.
- Maddux JF, McDonald LK. Status of 100 San Antonio addicts one year after admission to methadone maintenance. *Drug Forum* 1973;2:239-52.

McLellan AT, Arndt IO, Metzger DS, Woody GE, O'Brien CP. The effects of psychosocial services in substance abuse treatment. *JAMA* 1993;269(15):1953-59.

Powers KI, Anglin MD. Cumulative versus stabilizing effects of methadone maintenance. *Evaluation Review* 1993;17(3):243-70.

Sees KL, Delucchi KL, Masson C, Rosen A, Clark HW, Robillard H, et al. Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence. A randomized controlled trial. *JAMA* 2000;283:1303-10.

Simpson DD, Sells SB. Effectiveness of treatment for drug abuse: an overview of the DARP research program. *Advances in Alcohol and Substance Abuse* 1982;2(1):7-29.

Question 6: What effect can methadone maintenance treatment have on the use of alcohol and other drugs?

Answer: Research outcomes are mixed regarding the effect of methadone maintenance treatment on the use of illicit drugs other than opioids. That is, some research indicates that methadone maintenance treatment is associated with decreases in the use of alcohol, cocaine, and marijuana; other research indicates increases in the use of these drugs. It is important to note that the medication methadone has no direct effect and is not intended to have an effect on rates of alcohol and other drug use. Patients receiving methadone maintenance who disengage from interactions with others who are actively using drugs are less likely to engage in these behaviors. In addition, reductions in alcohol and drug use result from the counseling services included in methadone maintenance treatment. When these services are specifically designed to reduce alcohol and other drug use, such reductions are likely.

Research Highlights

- In the Drug Abuse Reporting Program (DARP) studies, there were reductions in nonopioid drug use (except marijuana) among 895 methadone maintenance patients, comparing the 2-month period before admission and the year following discharge. The reduction in nonopioid use was 13 percent—from 54 percent of patients who reported any use before admission to 41 percent at the 1-year followup point (Simpson and Sells, 1982).
- In the 12-year DARP followup study, “heavy drinking” was reported by 21 percent of the sample in the month before treatment; it rose to 31 percent during the first year afterward and then declined to 22 percent by year 12. One-half of the patients reported substituting alcohol for opioids after stopping daily illicit opioid use (Lehman, Barrett, and Simpson, 1990).
- In a study comparing buprenorphine maintenance with methadone maintenance for patients with opioid dependence and cocaine abuse, both treatments resulted in significant declines in opioid use but were indistinguishable in terms of their effect on comorbid cocaine use (Schottenfeld, Pakes, Oliveto, et al., 1997).

Methadone Maintenance Treatment and General Drug Abuse—Among three cohorts of new-admission patients in methadone maintenance treatment, Ball and Ross (1991) found that the use of all illicit drugs, except marijuana, decreased markedly in relation to time in treatment. These three cohorts had been in treatment 6 months, 4.5 years, or more than 4.5 years.

In the Treatment Outcome Perspective Study (TOPS), 90 percent of methadone maintenance treatment patients who reported drug use at intake reported a reduction in use during the first 3 months of treatment. For 80 percent, this reduction is large. In the year before treatment, less than 10 percent of methadone maintenance treatment patients were minimal drug users. During treatment, more than 50 percent of the patients were minimal drug users. During the 3 to 5 years after discharge, less than 32.5 percent were minimal drug users (Hubbard, Marsden, Rachal, et al., 1989).

In the National Treatment Outcome Research Study (NTORS), of 333 patients receiving methadone maintenance in the United Kingdom, overall declines were seen in the use of heroin, barbiturates, amphetamines, cocaine, and crack cocaine among patients receiving methadone maintenance. Alcohol use, however, did not change over time (Gossop, Marsden, Stewart, et al., 2000).

In another evaluation of 513 heroin users in methadone treatment in TOPS, a decline was observed in the use of cocaine, amphetamines, illegal methadone, tranquilizers, and marijuana, but not alcohol (Fairbank, Dunteman, and Condelli, 1993).

The Powers and Anglin study (1993) of 933 heroin addicts in methadone maintenance programs demonstrated that during episodes of methadone maintenance treatment, illicit opioid use decreased, but

alcohol and marijuana levels increased moderately. Kreek (1991) observed that by 1990, alcoholism was identified in 40 or 50 percent of new admissions to methadone maintenance treatment programs, and cocaine abuse was found in 70 to 90 percent. She also estimated that 20 to 46 percent of patients in effective methadone maintenance treatment programs continue using cocaine, and 15 to 20 percent of methadone maintenance treatment patients regularly inject cocaine.

Methadone Maintenance Treatment and Cocaine Use—Among the TOPS patients who remained in methadone maintenance treatment at least 3 months, 26.4 percent had used cocaine regularly the year before treatment. This rate fell to 10 percent during the first 3 months of treatment but returned to 16 percent by 3 to 5 years after discharge. Altogether, 40 percent of methadone maintenance treatment patients who regularly used cocaine before treatment and stayed in treatment for at least 3 months abstained from cocaine use in the year after treatment (Hubbard et al., 1989).

In the TOPS studies, although 70 percent of heroin abusers had frequently used cocaine the year before treatment, it was the primary drug of choice for only 2 percent of methadone maintenance treatment patients (Hubbard et al., 1989).

In the new admissions group of a six-program study ($n = 345$), 46.8 percent of 126 patients had used cocaine in the past 30 days. Among the average-stay group (up to 4.5 years in treatment), 27.5 percent still used cocaine; this rate dropped to 17.2 percent among the long-term group of 146 patients who had been in continuous treatment for more than 4.5 years (Ball and Ross, 1991).

A study evaluating the effect of methadone dose on treatment outcomes noted that patients receiving 50 mg of methadone, compared with those receiving 20 mg or 0 mg, had a reduced rate of opioid-positive urine samples (56.4% vs. 67.6% and 73.6%, respectively; $p < 0.05$) and cocaine-positive urine samples (52.6% vs. 62.4% and 67.1%, respectively; $p < 0.05$) (Strain, Stitzer, Liebson, et al., 1993).

A systematic review examined the impact of methadone dose on cocaine use and found three studies that addressed the question. Results from the one study in which cocaine use was based on self-reported use showed no significant excess of use of cocaine among subjects treated with higher doses compared with subjects treated with lower doses. Pooled results from the two studies that used urine analysis and looked at an abstinence period longer than 3 weeks showed that higher methadone doses increased the probability that patients would stay abstinent from cocaine, compared with lower doses (RR = 1.81 [1.15, 2.85]) (Faggiano, Vigna-Taglianti, Versino, et al., 2003).

Methadone Maintenance and Marijuana Use—Among TOPS subjects, marijuana use was common: 55 percent of methadone maintenance patients who stayed in treatment for 3 months reported regular use in the year before admission. This decreased to 47 percent during the first 3 months of treatment, continued to decline immediately posttreatment, and decreased even more to 36.4 percent in the 3- to 5-year period after discharge. However, marijuana use appeared more resistant to change than other illicit substances (Hubbard et al., 1989). It should be considered that the treatment programs likely did not clinically address marijuana or other drug use.

Ball and Ross (1991) found that marijuana continued to be used quite regularly (an average of 13 to 16 days per month) by high percentages of all patient groups in methadone maintenance treatment: 48.4 percent of the new admissions, 47.7 percent of the average-stay group, and 37.2 percent of the patients in treatment more than 4.5 years.

In one study of 132 opioid addicts participating in methadone maintenance treatment programs, it was noted that during episodes of methadone maintenance treatment, levels of alcohol and marijuana use increased modestly (Powers and Anglin, 1993).

Methadone Maintenance and the Nonmedical Use of Prescription Drugs—In the TOPS studies, the regular nonmedical use of psychoactive prescription drugs by methadone maintenance treatment patients during the first posttreatment year decreased by one-third from the pretreatment period. Although 30.3 percent of this methadone maintenance group reported regular nonmedical use of prescription drugs (i.e., barbiturates, amphetamines, tranquilizers, sedatives, and hypnotics), nonmedical prescription drug use was a primary problem for only 1.9 percent of these patients at admission (Hubbard et al., 1989).

In the NTORS study, a decline was seen in the use of benzodiazepines among patients receiving methadone maintenance (Gossop et al., 2000). In the TOPS studies, nonmedical prescription drug use declined during methadone maintenance treatment, increased immediately following discharge, and declined again to 10 percent of patients 3 to 5 years following discharge (Hubbard et al., 1989).

Ball and Ross (1991) found that although the nonmedical use of sedatives other than barbiturates was acknowledged by 31.8 percent of new admissions to methadone maintenance treatment, the percentage of sedative-using patients who had been in treatment for more than 4.5 years was less than half that of the new admission group (14.5 percent).

Methadone Maintenance Treatment and Alcohol and Other Drug Use—In the TOPS studies, improvements in the use of illicit and nonprescription drugs follow a pattern of (1) a dramatic reduction during treatment, (2) a sharp increase immediately after discharge, and (3) a leveling off at an impressively reduced rate for up to 5 years of followup contacts (Hubbard et al., 1989).

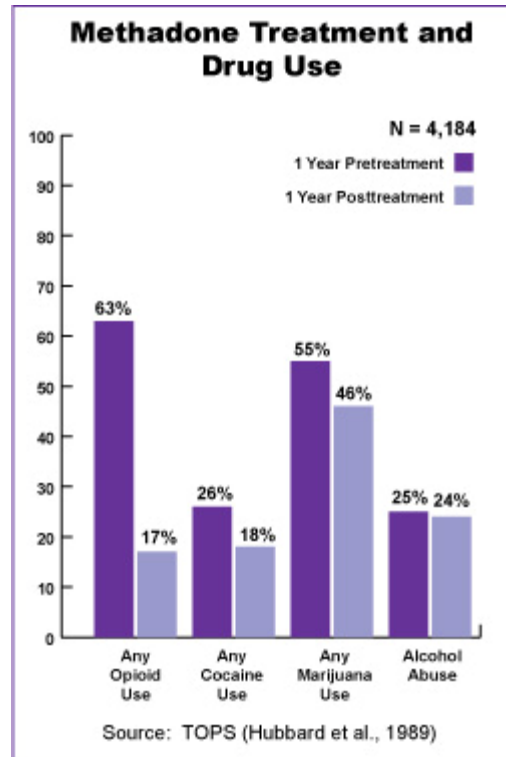


Figure 21 illustrates that as reported by the TOPS study of 4,184 patients, methadone maintenance treatment was associated with reductions in (1) any illicit opioid use, (2) any cocaine use, (3) any marijuana use, and (4) alcohol abuse (the 1-percent reduction noted here is not statistically significant) (Hubbard et al., 1989).

“Any opioid use” declined from 63 percent pretreatment to 17 percent 1 year posttreatment. This was the most dramatic decline. “Any cocaine use” declined from 26 percent to 18 percent. “Any marijuana use” declined from 55 percent pretreatment to 46 percent 1 year posttreatment. Alcohol abuse remained almost steady, declining slightly from 25 percent to 24 percent.

References

Ball JC, Ross A. *The Effectiveness of Methadone Maintenance Treatment: Patients, Programs, Services, and Outcomes*. New York: Springer-Verlag, 1991.

Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opioid dependence. *The Cochrane Database of Systematic Reviews*, Issue 3, 2003.

Fairbank JA, Duntzman GH, Condelli WS. Do methadone patients substitute other drugs for heroin? Predicting substance use at 1-year follow-up. *American Journal of Drug & Alcohol Abuse* 1993;19(4):465-74.

Gossop M, Marsden J, Stewart D, Rolfe A. Patterns of improvement after methadone treatment: 1 year follow-up results from the National Treatment Outcome Research Study. *Drug & Alcohol Dependence* 2000;60(3):275-86.

Hubbard RL, Marsden ME, Rachal JV, Harwood HJ, Cavanaugh ER, Ginzburg HM. *Drug Abuse Treatment: A National Study of Effectiveness*. Chapel Hill: University of North Carolina Press, 1989.

Kreek MJ. Using methadone effectively: achieving goals by application of laboratory, clinical, and evaluation research and by developing of innovative programs. In: Pickens RW, Leukefeld CG, Schuster CR (eds.). *Improving Drug Abuse Treatment*. NIDA Research Monograph Series 196. Rockville, MD: National Institute on Drug Abuse, 1991.

Lehman WEK, Barrett ME, Simpson DD. Alcohol use by heroin addicts 12 years after drug abuse treatment. *Journal of Studies in Alcohol* 1990;51(3):233-44.

Powers KI, Anglin MD. Cumulative versus stabilizing effects of methadone maintenance. *Evaluation Review* 1993;17(3):243-70.

Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Archives of General Psychiatry* 1997;54(8):713-20.

Simpson DD, Sells SB. Effectiveness of treatment for drug abuse: an overview of the DARP research program. *Advances in Alcohol and Substance Abuse* 1982;2(1):7-29.

Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Dose-response effects of methadone in the treatment of opioid dependence. *Annals of Internal Medicine* 1993;119:23-37.

Question 7: What components of methadone maintenance treatment account for reductions in AIDS risk behaviors?

Answer: Reductions in drug use and related AIDS risk behaviors among methadone-maintained individuals have been associated with both physiological and psychosocial factors. Recent studies have confirmed that adequate methadone dose levels are required to achieve significant reductions in opioid abuse. At the same time, research has demonstrated that methadone alone will have, at best, limited impact. Additional psychosocial support services are needed to maximize the effectiveness of methadone maintenance treatment.

Research Highlights

- A study examining the impact of psychosocial services in methadone treatment found that outcomes were significantly improved for those injection drug users who received services in addition to methadone (McLellan, Arndt, Metzger, et al., 1993). In this study, methadone patients were randomly assigned to one of three groups that received either: (1) methadone alone with no other services; (2) methadone and regular counseling; or (3) methadone with counseling and medical/psychiatric services, employment services, and family therapy. Although methadone doses were the same in each group, outcomes were significantly better in the groups that also received psychosocial services. Sixty-nine percent of the methadone-only group had to be “protectively transferred” due to unremitting use of opiates or cocaine or medical/psychiatric emergencies.
- Counseling programs specifically designed to reduce HIV risk behavior among methadone-maintained patients have been shown to be effective (Margolin, Avants, Warburton, et al., 2003).
- Patients with comorbid psychiatric disease are less likely to decrease their HIV risk behaviors during methadone maintenance treatment, compared with those without, although both groups receive benefit (King, Kidorf, Stoller, et al., 2000).
- A study of 291 patients that evaluated a high-intensity day treatment along with methadone versus enhanced methadone treatment saw decreases in drug use and HIV risk behavior in both groups; however, the study was unable to detect a significant difference in these outcomes between treatment groups (Avants, Margolin, Sindelar, et al., 1999).
- Similarly, a study that compared methadone dose (50 mg vs. 80 mg) and visit frequency (two visits per week vs. five visits per week) saw reductions in HIV risk behavior with methadone maintenance treatment but was unable to demonstrate a difference in HIV risk reduction between the four groups (Rhoades, Creson, Elk, et al., 1998).
- Hartel, Schoenbaum, Selwyn, et al. (1995) examined the drug use patterns and treatment characteristics of 652 methadone patients receiving treatment from the Montefiore Methadone Treatment Program in New York. The study found that those who were maintained on less than 70 mg per day of methadone were 2.1 times ($p < .005$) more likely to be using heroin. It is important to note that the observed effects of higher doses were found even after controlling for the length of time in treatment.
- A meta-analysis of HIV risk reduction interventions in substance abuse treatment programs found that these programs succeeded in changing knowledge, attitudes, and beliefs; sexual behavior; and injection practices. The impact of the intervention programs was negatively correlated with the presence of ethnic/minority samples and positively correlated with the number of intervention techniques used, the intensity of the intervention, interventions that were delivered within methadone treatment, and specific intervention techniques (Prendergast, Podus, Chang, et al., 2002).

References

Avants SK, Margolin A, Sindelar JL, Rounsaville BJ, Schottenfeld R, Stine S, et al. Day treatment versus enhanced standard methadone services for opioid-dependent patients: a comparison of clinical efficacy and cost. *American Journal of Psychiatry* 1999;156(1):27-33.

Hartel DM, Schoenbaum EE, Selwyn PA, Kline J, Davenny K, Klein RS, et al. Heroin use during methadone maintenance treatment: the importance of methadone dose and cocaine use. *American Journal of Public Health* 1995;85:83-88.

King VL, Kidorf MS, Stoller KB, Brooner RK. Influence of psychiatric comorbidity on HIV risk behaviors: changes during drug abuse treatment. *Journal of Addictive Diseases* 2000;19(4):65-83.

Margolin A, Avants SK, Warburton LA, Hawkins KA, Shi J. A randomized clinical trial of a manual-guided risk reduction intervention for HIV-positive injection drug users. *Health Psychology* 2003;22(2):223-28.

McLellan AT, Arndt IO, Metzger DS, Woody GE, O'Brien CP. The effects of psychosocial services in substance abuse treatment. *JAMA* 1993;269(15):1953-59.

Prendergast ML, Podus D, Chang E, Urada D. The effectiveness of drug abuse treatment: a meta-analysis of comparison group studies. *Drug & Alcohol Dependence* 2002;67(1):53-72.

Rhoades HM, Creson D, Elk R, Schmitz J, Grabowski J. Retention, HIV risk, and illicit drug use during treatment: methadone dose and visit frequency. *American Journal of Public Health* 1998;88(1):34-39.

Question 8: Do risk factors for HIV infection acquisition and transmission differ for women compared with men in methadone maintenance treatment?

Answer: Yes. Despite nearly equal HIV infection rates for men and women in drug treatment, female injection drug users differ from males in the types and contexts of their risk behaviors. While the main HIV infection risk for both male and female injection drug users is needle sharing, women frequently support themselves and their addiction habit through sex work and are more likely to have an injection drug user as a sexual partner. The most common needle-sharing context for women is with their sex partners.

In addition, women may transmit HIV infection to their infants in utero, during delivery, or through breastfeeding. Women in methadone treatment need HIV infection prevention programs that take these gender differences into account.

Research Highlights

- Patterns of needle sharing are different for males and females. Women tend to share needles in the context of a sexual relationship. This type of needle sharing may be more difficult to change than other types of injection risk behavior because the perception of risk or ability to negotiate safe needle use by women may be limited. In research conducted among 19,716 males and 6,609 females in the National AIDS Demonstration Research (NADR) project addressing street-recruited injection drug users, women were more likely than men to share needles with their sex partners. The majority of the participants injected only heroin or heroin in combination with cocaine (Brown and Weissman, 1994).

Research in other countries has shown a tendency for female injection drug users to share needles with their sex partners. For example, women in Glasgow, Scotland, were frequently injected with used needles and syringes from their partners (Barnard, 1993).

- Sexual risk behavior has been shown to be less likely to change among both male and female injection drug users than needle-sharing risk behavior. In addition, women who inject drugs are less likely than men to be in control of safer sex practices, such as condom use. Although methadone maintenance treatment may reduce drug use and prostitution or the exchange of sex for drugs, women may be at risk for HIV infection by their habitual sex partners. Female injection drug users tend to have drug users as sex partners, even after enrollment in treatment, and are not likely to practice safer sex with these partners. HIV risk reduction programs for women in methadone maintenance treatment must take into account the social and interpersonal context of sexual risk behavior in order to be effective (Finnegan, Davenny, and Hartel, 1993; Hartel, 1994).
- Women with HIV who are maintained on methadone may improve their access to medical care for HIV infection and disease and possibly reduce their chance of transmitting HIV to infants in utero. Both zidovudine (AZT) and nevirapine have been shown to reduce significantly the risk of mother-to-infant transmission of HIV infection (Connor, Sperling, Gelber, et al., 1994; Brocklehurst and Volmink, 2002).
- It is likely that some infants are infected during labor and delivery or after delivery through breastfeeding. Careful attention to factors that can place the infant at risk during birth and afterwards is needed to further reduce infant infection. In areas with a high community level of HIV infection among injection drug users, methadone programs often incorporate HIV primary health care services into the treatment program through onsite services or linkages to services nearby. These services often include obstetrical care by providers skilled in working with HIV-infected women (Finnegan et al., 1993).

Differences Between Men and Women in HIV Infection Rates and Risk Behaviors—Figure 22 illustrates that overall HIV infection rates are roughly the same for males and females entering drug abuse treatment in the United States: 5.4 percent for males and 4.4 percent for females. These rates vary greatly (0 to 48 percent) by geographic area, with the highest rates found in urban centers that have the greatest density of injection drug users (Allen, Onorato, and Green, 1992).

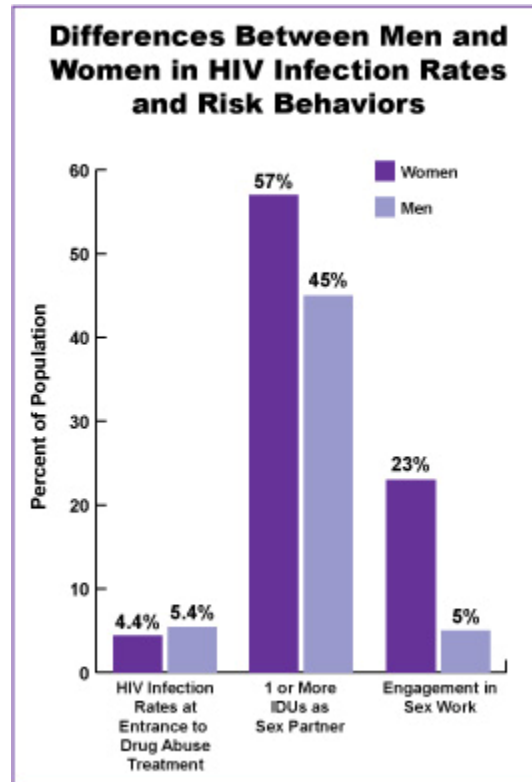


Figure 22 illustrates that overall HIV infection rates are roughly the same for men and women entering drug abuse treatment in the United States: 5.4 percent for men and 4.4 percent for women. These rates vary greatly (0 to 48 percent) by geographic area, with the highest rates found in urban centers that have the greatest density of injection drug users (Allen et al., 1992).

In research conducted in New York, NY, among 452 methadone-recruited injection drug users early in the HIV epidemic, having an injection drug user as a sex partner was associated with HIV infection status independent of or in addition to injection risk behavior. In this same study, women reported a higher level of sexual risk behavior than men: 57 percent of women compared with 45 percent of men reported one or more injection drug users as sex partners since 1978. In addition, women were more likely than men to have engaged in sex work: 23 percent of women compared with 5 percent of men (Schoenbaum, Hartel, Selwyn, et al., 1989).

References

Allen D, Onorato I, Green T. HIV infection in intravenous drug users entering drug treatment, United States, 1988 to 1989. *American Journal of Public Health* 1992;82:541-46.

Barnard, M. Needle sharing in context: patterns of sharing among men and women injectors and HIV risks. *Addiction* 1993;88:805-12.

Brocklehurst P, Volmink J. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. *The Cochrane Database of Systematic Reviews*, Issue 2, 2002.

Brown V, Weissman G. Women and men injection drug users: an updated look at gender differences and risk factors. In: Brown B, Beschner G (eds.). *Handbook on Risk of AIDS: Injection Drug Users and Sexual Partners*. Westport, CT: Greenwood Press, 1994.

Connor E, Sperling R, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *New England Journal of Medicine* 1994;331:1173-80.

Finnegan L, Davenny K, Hartel D. Drug use in HIV-infected women. In: Johnson M, Johnstone F (eds.). *HIV Infection in Women*. London: Churchill Livingstone, 1993.

Hartel D. *Context of HIV Risk Behavior Among Female Injecting Drug Users and Female Sexual Partners of Injecting Drug Users*. NIDA Research Monograph Series 143. Rockville, MD: National Institute on Drug Abuse, 1994.

Schoenbaum EE, Hartel D, Selwyn P, Klein RS, Davenny K, Rogers M, et al. Risk factors for HIV infection in intravenous drug users. *New England Journal of Medicine* 1989;321:874-79.

Question 9: Is methadone maintenance treatment effective for women?

Answer: Yes. Since the earliest methadone maintenance treatment programs in the United States, women have been treated successfully with methadone through all phases of their lives, including pregnancy. There is consensus that the major outcomes of the effectiveness of methadone maintenance treatment, especially cessation of illicit drug use and lifestyle stabilization, apply to both men and women. However, gender-specific issues, which are often related to the social status of women, are important to treatment effectiveness for female injection drug users.

Compared with men, women are more likely to

- Have total responsibility for child care
- Have lower socioeconomic status
- Encounter greater barriers to treatment entry, retention in treatment, and economic independence
- Have different psychological, counseling, and vocational training needs
- Have difficulty with transportation to treatment.

Research Highlights

- In the past, little emphasis was placed on gender-specific biopsychosocial problems in drug treatment. One reason was the predominance of drug-addicted men, estimated in the United States to be three males to every female. Although mild forms of psychoactive substance use show converging usage rates and patterns for males and females, opioid addiction and other forms of chemical dependency continue to show a male predominance (Kandel, 1992).
- Drug Abuse Reporting Program (DARP) studies showed that 19 to 28 percent of admissions to drug treatment programs from 1969 to 1973 were women. In 12 years of followup of 84 females and 91 males in methadone maintenance, there were no differences between men and women in overall reduction of opioid use. Women required more government financial assistance and had lower rates of employment than men. Compared with men, women were more likely to enter treatment for health reasons (Simpson, 1990; Marsh and Simpson, 1986).
- A study of 567 methadone-maintained patients in California found overall shorter duration of time from first entry to first discharge from treatment for women compared with men (Anglin, Hser, and Booth, 1987). Factors related to poor retention of women in treatment were likely to be a lack of child care and inadequate social and psychological support from domestic partners and other family members (Rosenbaum, 1981; Murphy and Irwin, 1992).
- A study of white, Latina, and African American women in methadone maintenance found that, in general, Latinas were more likely to report familial influences and to display evidence of low self-esteem and self-efficacy, inconsistent condom use, and high-risk injection behavior. White women reported the highest levels of regular condom use at followup; however, they were the least likely to report safer injection practices. African American women expressed the highest levels of self-esteem, yet they reported more alcohol use at intake and crack cocaine use both before and after treatment entry. African American women showed the greatest gains in adopting safer injection practices and were the least likely to report multiple sex partners after treatment entry (Grella, Annon, and Anglin, 1995).
- Drug-using women are likely to experience clinical depression, anxiety disorders, and low self-esteem to a much greater degree than their male counterparts. Women entering treatment have experienced unique gender-specific life events. In particular, female drug users often have been abused physically, sexually, and emotionally. Experiences of sexual violence, especially during childhood, have profound, lifelong psychological effects and often underlie addiction, complicating successful recovery. Methadone maintenance treatment of women requires

awareness of these issues and appropriate counseling. Confrontational styles of therapy and counseling are not effective for most women in treatment (Mondanaro, 1987; Marsh and Miller, 1985; Beschner, Reed, and Mondanaro, 1981; Hartel, 1989/1990).

Potential Treatment Issues for Women—Figure 23 delineates key treatment issues derived from the discussion above.

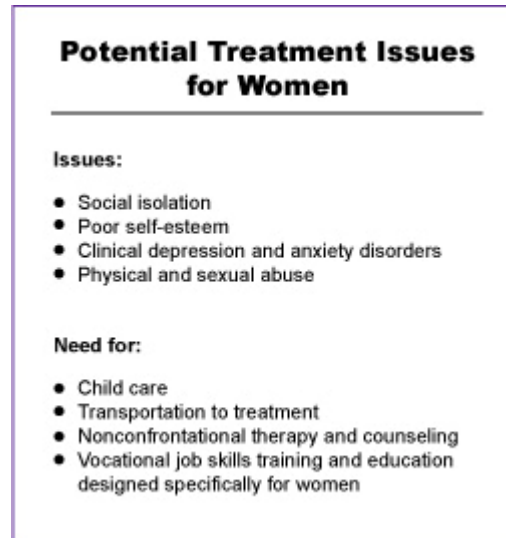


Figure 23 illustrates the potential treatment issues for women.

References

- Anglin D, Hser Y, Booth M. Sex differences in addict careers. *American Journal of Drug and Alcohol Abuse* 1987;13(3):253-80.
- Beschner G, Reed B, Mondanaro J. *Treatment Services for Drug Dependent Women*. Rockville, MD: National Institute on Drug Abuse, 1981.
- Grella CE, Annon JJ, Anglin MD. Ethnic differences in HIV risk behaviors, self-perceptions, and treatment outcomes among women in methadone maintenance treatment. *Journal of Psychoactive Drugs* 1995;27(4):421-33.
- Hartel D. Cocaine use, inadequate methadone does increase risk of AIDS for IV drug users in treatment. *NIDA Notes* 1989/1990;5(1).
- Kandel D. Epidemiological trends and implications for understanding the nature of addiction. In: O'Brien D, Jaffe J (eds.). *Addictive States*. New York: Raven Press, 1992.
- Marsh J, Miller N. Female clients in substance abuse treatment. *International Journal of the Addictions* 1985;20:995-1019.
- Marsh K, Simpson D. Sex differences in opioid addiction careers. *American Journal of Drug and Alcohol Abuse* 1986;12:309-29.
- Mondanaro J. Strategies for AIDS prevention: motivating health behavior in drug dependent women. *Journal of Psychoactive Drugs* 1987;19:143-49.
- Murphy S, Irwin J. Living with the dirty secret: problems of disclosure for methadone maintenance clients. *Journal of Psychoactive Drugs* 1992;24:257-64.

Rosenbaum M. Sex roles among deviants; the women addict. *International Journal of the Addictions* 1981;16,859-77.

Simpson DD. Longitudinal outcome patterns. In: Simpson DD, Sells SB (eds.). *Opioid Addiction and Treatment: A 12-Year Followup*. Malabar, FL: Krieger Publishing, 1990.

Question 10: Is methadone safe for pregnant women and their infants?

Answer: Yes. Since the early 1970s, methadone maintenance treatment has been used successfully with pregnant women. There is consensus that methadone can be safely administered during pregnancy with little risk to mother and infant. Maintenance on methadone is necessary to prevent relapse to illicit opioid use and thus to maintain optimal health during pregnancy.

Research Highlights

A systematic review revealed that randomized controlled studies of methadone treatment in pregnancy demonstrate an approximate threefold reduction in heroin use and a threefold increase in retention in treatment relative to nonpharmacologic treatment (Rayburn and Bogenschutz, 2004).

- All drug-using women are considered to be at higher-than-normal risk for medical and obstetrical complications. Methadone-maintained women show a far greater improvement in obstetrical health than untreated women. Hepatitis types A, B, and C and other sexually transmitted diseases; bacterial endocarditis; septicemia; and cellulites are common among active injection drug users, particularly those who share needles. Women maintained on methadone who have stopped illicit drug use and injection before pregnancy are less likely to experience these and other medical complications during pregnancy. Obstetrical complications such as spontaneous abortion, placental insufficiency, and other conditions also occur at a lower rate among methadone-maintained women than among opioid-dependent women not enrolled in treatment. When compared with opioid-addicted women not in treatment, women in methadone maintenance treatment have been observed to maintain better overall health and nutritional status during pregnancy because of stability provided through treatment. In addition, methadone clinics can provide onsite prenatal services or link patients to these services in nearby clinics, coordinating addiction treatment and prenatal care to optimize both (Finnegan, 1991; Kaltenbach, Silverman, and Wapner, 1993).
- Some women in methadone maintenance treatment are infected with HIV before pregnancy. Treatment programs that link women to appropriate medical care during pregnancy may reduce the burden of illness suffered by HIV-infected women. In a study of 191 methadone-maintained women in a New York City clinic with extensive medical linkages, medical and obstetrical complications did not differ among women with and without HIV infection. HIV infection occurred among 37 percent of women, most of whom were asymptomatic for HIV disease and AIDS before pregnancy. Adverse birth outcomes were relatively infrequent and occurred at approximately the same rates as observed in studies of methadone-maintained women before the HIV epidemic (Selwyn, Schoenbaum, Davenny, et al., 1989).
- U.S. research in the 1970s demonstrated that methadone does cross the placenta. Passive exposure to methadone in utero can result in neonatal abstinence syndrome among exposed infants. The syndrome varies considerably and depends on a number of factors, including the use of other drugs during pregnancy, anesthesia during delivery, the maturational and nutritional status of the infant, and other aspects of maternal health that affect the fetal environment. The relationship of maternal methadone dose in the last trimester of pregnancy has been explored in a number of studies, but results have not consistently delineated a dose-response relationship between maternal dose and severity of infant abstinence syndrome. For those neonates experiencing withdrawal, the length and severity of the withdrawal vary greatly; however, pharmacotherapy for neonatal methadone abstinence syndrome is simple and effective. Methadone maintenance treatment affords protection of the fetus from erratic maternal opioid levels and repeated episodes of withdrawal typically seen in users of illicit opioids (Finnegan, 1991).

- The majority of infants exposed to methadone in utero are healthy and have fewer adverse outcomes than infants exposed to heroin and other illicit drugs. Methadone maintenance treatment for pregnant women can reduce in utero growth retardation and neonatal morbidity and mortality, in comparison with women not in treatment (Finnegan, 1991). Such infants may be smaller at birth than nondrug-exposed infants, but differences tend to disappear over time. A careful review of the major studies of long-term neurobehavioral effects of methadone on exposed infants revealed no methadone-associated adverse effects (Kaltenbach and Finnegan, 1984).

A review of the literature on methadone and lactation reveals that the amount of methadone in breast milk is very small and depends on the dose of methadone that a mother is receiving. The amount of methadone received by an infant from breast milk is not enough to prevent neonatal abstinence syndrome. Therefore, even though a mother is receiving methadone, her infant may require additional opiate treatment of neonatal abstinence syndrome (Jansson, Velez, and Harrow, 2004).

Methadone Safety for Pregnant Women and Their Infants—Figure 24 outlines key points discussed in the research citations above regarding the safety of methadone maintenance treatment for pregnant women.

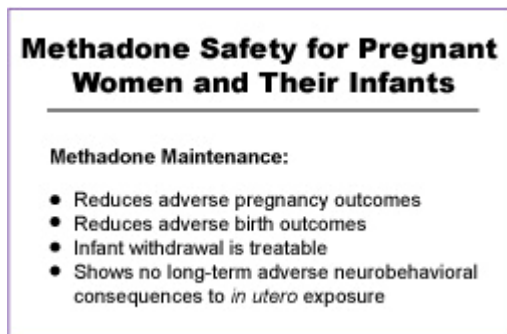


Figure 24 illustrates the safety of methadone maintenance treatment for pregnant women and their infants.

References

- Finnegan L. Treatment issues for opioid-dependent women during the perinatal period. *Journal of Psychoactive Drugs* 1991;23:191-201.
- Jansson LM, Velez M, Harrow C. Methadone maintenance and lactation: a review of the literature and current management guidelines. *Journal of Human Lactation* 2004;20(1):62-71.
- Kaltenbach K, Finnegan L. Developmental outcome of children born to methadone maintained women: a review of longitudinal studies. *Neurobehavioral Toxicology and Teratology* 1984;6:271-75.
- Kaltenbach K, Silverman N, Wapner R. Methadone maintenance during pregnancy. In: *State Methadone Treatment Guidelines*. Rockville MD: U.S. Department of Health and Human Services, 1993.
- Rayburn WF, Bogenschutz MP. Pharmacotherapy for pregnant women with addictions. *American Journal of Obstetrics & Gynecology* 2004;191(6):1885-97.
- Selwyn P, Schoenbaum E, Davenny K, Robertson VJ, Feingold AR, Shulman JF, et al. Prospective study of human immunodeficiency virus infection and pregnancy outcomes in intravenous drug users. *JAMA* 1989;261:1289-94.

Question 11: Is it necessary to reduce methadone dose or detoxify women from methadone during pregnancy to protect the fetus?

Answer: No. Women have been safely maintained on stable methadone dosage during pregnancy without adverse long-term effects on their health and the health of their infants. Withdrawal of medication during pregnancy leads to opioid abstinence syndrome, which is harmful to the pregnancy and often leads to relapse to illicit drug use. Dosage change in pregnancy must be carefully evaluated on an individual basis. Some women experience lowered blood levels of the methadone during pregnancy and may need an increase in dosage or split (e.g., twice daily) dosing. It is important to determine the relapse risk for each woman when considering a dosage change because a woman steadily maintained on methadone is more likely to have a healthy pregnancy and infant than a woman who uses alcohol and other drugs. The intermittent periods of withdrawal that typically occur with illicit opioid use and can adversely affect the fetus do not occur when methadone is individually determined and properly administered.

Research Highlights

- Optimal methadone dosage for pregnant women in methadone maintenance treatment should be based on careful consideration of risks and benefits to both mother and fetus on an individual basis. Individual dose should be evaluated, taking into account the stage of pregnancy, the relapse risk potential of the mother, pre-pregnancy methadone dose, previous experience with methadone, and history of addiction recovery. When the mother does not relapse to illicit drug use, short-term reductions in maternal dose have been effectively administered during the last stage of pregnancy. However, many women in treatment have been successfully maintained on a constant dose and, in some cases, on an increased dose to keep blood levels stable throughout pregnancy (Finnegan, 1991).
- Some women in treatment experience decreased blood levels of methadone during pregnancy, causing withdrawal symptoms. This decrease in blood levels of methadone during pregnancy can be accounted for by an increased fluid space, a large tissue reservoir that can store methadone, and drug metabolism by both the placenta and the fetus. Pregnant women in treatment with low blood levels of methadone frequently experience a high level of discomfort, withdrawal symptoms, and drug craving and anxiety and may be at high risk of relapse to opioid use and treatment dropout. Determination of methadone blood levels and possibly raising the methadone dosage to maintain sufficient blood levels may be warranted in such cases but must be carefully evaluated. Dosages should be evaluated in conjunction with ongoing medical monitoring of the pregnancy. Since the greatest risks to maternal and infant health occur when women in treatment relapse to illicit drug use, it is important to promote methadone dosage stability during and after pregnancy to optimize both maternal and child health (Kreek, Schecter, Gutjahr, et al., 1974; Pond, Kreek, Tong, et al., 1985).

Methadone Dosage Adjustment During Pregnancy—Figure 25 outlines the three main considerations regarding dosage for pregnant women in methadone maintenance treatment.

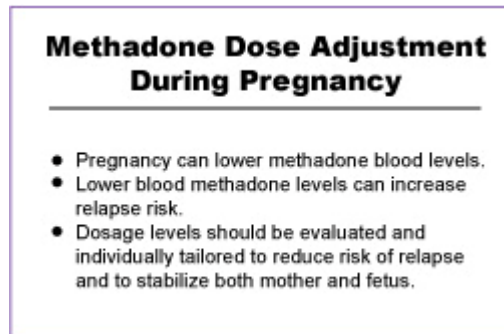


Figure 25 illustrates three main considerations regarding methadone dosage adjustment during pregnancy.

References

Finnegan L. Treatment issues for opioid-dependent women during the perinatal period. *Journal of Psychoactive Drugs* 1991;23:191-201.

Kreek M, Schecter A, Gutjahr C, Bowen D, Field F, Queenan J, et al. Analyses of methadone and other drugs in maternal and neonatal body fluids: use in evaluation of symptoms in a neonate of mother maintained on methadone. *American Journal of Drug and Alcohol Abuse* 1974;1:409.

Pond S, Kreek M, Tong T, Raghunath J, Benowitz NL. Altered methadone pharmacokinetics in methadone-maintained pregnant women. *Journal of Pharmacology and Experimental Therapeutics* 1985;233:1-6.

Question 12: Is the long-term use of methadone medically safe, and is it well tolerated by patients?

Answer: Yes. Studies of the long-term administration of methadone confirm that it is a medically safe drug. Long-term methadone maintenance treatment at doses of 80 to 120 mg per day is not toxic or dangerous to any organ system after continuous treatment for 10 to 14 years in adults and 5 to 7 years in adolescents.

Research Highlights

- Methadone has few adverse biological effects. There appear to be no dangerous or troubling psychological effects from long-term administration (Kreek, 1979; Lowinson, Marion, Joseph, et al., 1992), although one study demonstrated a delay in neuropsychological tests in patients receiving methadone compared with abstinent (not active) former heroin-dependent patients (Verdejo, Toribio, Orozco, et al., 2005).
- Methadone sometimes causes minor side effects, such as sweating, constipation, temporary skin rashes, weight gain, water retention, and changes in sleep and appetite (Jaffe and Martin, 1985; Kreek, 1979). These side effects are more likely to occur when the methadone dosages are first being established in a patient, and the side effects generally subside or diminish over time. They can be reduced or eliminated by raising or lowering the methadone dose (Lowinson et al., 1992).
- Methadone prescribed in high doses for a long period of time has no toxic effects and only minimal side effects for adult patients maintained in treatment for up to 14 years and for adolescent patients treated for up to 5 years (Hartel, 1989/1990; Kreek, 1978).
- Although early studies demonstrated no persisting abnormalities directly attributable to methadone in the functioning of five organ systems (pulmonary, cardiovascular, renal, ophthalmologic, and liver) (Kleber, Mezritz, and Slobetz, 1980), later reports have focused on the potential effect of methadone on QTc interval (Martell, Arnsten, Krantz, et al., 2005) and central sleep apnea (Wang, Teichtahl, Drummer, et al., 2005). It should be noted, however, that cardiac complications with methadone are more commonly seen in patients who are prescribed very high doses (mean doses greater than 350 mg per day) for treatment of pain and those who are receiving concomitant medications that affect methadone metabolism (Krantz, Lewkowicz, Hays, et al., 2002).
- Patients maintained on methadone have no impairment in driving and have no more frequent motor vehicle accidents than people not receiving methadone maintenance treatment (Maddux, Williams, and Ziegler, 1977; Lenne, Dietze, Rumbold, et al., 2003; Schindler, Ortner, Peternell, et al., 2004).
- The most common and enduring complaints after 6 months to 3 years of continuous methadone treatment are sweating, constipation, abnormalities in libido and sexual functioning, sleep abnormalities (insomnia and nightmares), and altered appetite (mild anorexia, weight gain) (Kreek, 1979; Jaffe and Martin, 1985). Most of these symptoms can be medically managed (Kreek, 1979). A study of 92 methadone-maintained patients found that the rate of global sexual dysfunction in methadone-treated men was similar to the general population but that orgasm dysfunction may respond to methadone dose reduction.
- Although euphoria and drowsiness, with occasional nausea and vomiting, can occur before tolerance develops, these side effects are most noticeable when doses are increased too rapidly. Conversely, if a heroin habit has been particularly heavy, initial methadone doses may be too low to prevent the onset of early withdrawal symptoms (Kreek, 1979).

- Life-threatening interactions of methadone with other drugs have not been identified. Drugs found to affect the metabolism of methadone include phenytoin (Dilantin) and rifampin. Opioid antagonists such as pentazocine (Talwin) and buprenorphine can cause withdrawal symptoms in methadone patients and should not be prescribed (Kreek, 1978).

Common Side Effects After 6 Months to 3 Years of Methadone Maintenance Treatment		
Symptoms and Signs	Intermediate Length Treatment (6 Months or More; <40 to >80 mg/d)	Long-Term, High-Dose Treatment (3 Years or More; 80 to 120 mg/d)
	Percent	Percent
Increased Sweating	47	48
Constipation	57	17
Libido Abnormalities	26	22
Orgasm Abnormalities	—	14
Sleep Abnormalities (Insomnia)	23	16
Appetite Abnormalities	19	4
Nausea	25	—
Drowsiness	23	—
Nervousness/Tension	21	—
Headaches	12	—
Body Aches and Pains	11	—
Chills	10	—

— = no data available

Figure 26 illustrates that methadone maintenance patients, in the early stages of treatment, can experience several minor side effects: sweating, constipation, orgasm abnormalities, alterations of sexual interest, alterations of sleep and appetite, nausea, drowsiness, nervousness, headaches, body aches and pains, and chills. However, the figure also shows that many of these side effects almost disappear with long-term, high-dose methadone maintenance treatment (Kreek, 1979; Jaffe and Martin, 1985; Hartel, 1989/1990).

References

- Hartel D. Cocaine use, inadequate methadone does increase risk of AIDS for IV drug users in treatment. *NIDA Notes* 1989/1990;5(1).
- Jaffe JHI, Martin WR. Opioid analgesics and antagonists. In: *Goodman & Gilman's the Pharmacological Basis of Therapeutics*. New York: Pergamon Press, 1985.
- Kleber HD, Mezritz M, Slobetz F. *Medical Evaluation of Long-Term Methadone-Maintained Clients*. Rockville, MD: National Institute on Drug Abuse, 1980.
- Krantz MJ, Lewkowicz L, Hays H, Woodroffe MA, Robertson AD, Mehler PS. Torsade de pointes associated with very-high-dose methadone. *Annals of Internal Medicine* 2002;137(6):501-04.
- Kreek MJ. Medical complications in methadone patients. *Annals of the New York Academy of Science* 1978;311(29):110-34.
- Kreek MJ. Methadone in treatment: physiological and pharmacological issues. In: DuPont RL, Goldstein A, O'Donnell J, Brown B (eds.). *Handbook on Drug Abuse*. Rockville, MD: National Institute on Drug Abuse, 1979.

Lenne MG, Dietze P, Rumbold GR, Redman JR, Triggs TJ. The effects of the opioid pharmacotherapies methadone, LAAM and buprenorphine, alone and in combination with alcohol, on simulated driving. *Drug & Alcohol Dependence* 2003;72(3):271-78.

Lowinson JH, Marion IJ, Joseph H, Dole VP. Methadone maintenance. In: Lowinson JH, Ruiz P, Millman RB (eds.). *Substance Abuse: A Comprehensive Textbook*. Second Edition. Baltimore, MD: Williams & Wilkins, 1992.

Maddux JF, Williams TR, Ziegler JA. Driving records before and during methadone maintenance. *American Journal of Drug and Alcohol Abuse* 1977;4(1):91-100.

Martell BA, Arnsten JH, Krantz MJ, Gourevitch MN. Impact of methadone treatment on cardiac repolarization and conduction in opioid users. *American Journal of Cardiology* 2005;95(7):915-18.

Schindler SD, Ortner R, Peternell A, Eder H, Opgenoorth E, Fischer G. Maintenance therapy with synthetic opioids and driving aptitude. *European Addiction Research* 2004;10(2):80-87.

Verdejo A, Toribio I, Orozco C, Puente KL, Perez-Garcia M. Neuropsychological functioning in methadone maintenance patients versus abstinent heroin abusers. *Drug & Alcohol Dependence* 2005;78(3):283-88.

Wang D, Teichtahl H, Drummer O, Goodman C, Cherry G, Cunningham D, et al. Central sleep apnea in stable methadone maintenance treatment patients. *Chest* 2005;128(3):1348-56.

Question 13: Are there program characteristics associated with the success of methadone maintenance treatment?

Answer: Yes. There are several program characteristics associated with a variety of improved treatment outcomes in patients receiving methadone maintenance. These program characteristics are as follows:

- Establishment of evidence-based dosing policies and dose ranges
- Availability of a variety of psychosocial services for those who require them
- Attention to staff training and quality
- When possible, integration of medical, counseling, and administrative services

Research Highlights

- A meta-analysis of 12 trials involving 981 people comparing varying levels of psychosocial treatment added to methadone maintenance showed additional benefit in adding any psychosocial treatment to standard methadone maintenance treatment in relation to the use of heroin during the treatment; relative risk was 0.69 (95% CI 0.53 to 0.91). However, no statistically significant additional benefit was shown in terms of retention in treatment—relative risk was 0.94 (95% CI 0.85 to 1.02)—or proportion of patients retained or abstinent at followup—relative risk was 0.90 (95% CI 0.76 to 1.07) (Amato, Minozzi, Davoli, et al., 2004).
- Ball and Ross (1991) noted wide differences among the six methadone maintenance clinics studied with respect to the reduction of injection drug use by patients. Factors that account for treatment success include (1) adequate dosing; (2) participation in programs that had high retention rates, high rates of scheduled attendance, low treatment staff turnover, and a close, consistent, and enduring relationship between staff and patients; (3) an effective treatment director; (4) combined medical, counseling, and administrative services; (5) experienced counselors providing comprehensive counseling services; and (6) staff/patient agreement about the status of patients and their treatment needs.
- In a United Kingdom study of 262 patients who were admitted to and retained in methadone treatment programs at 6 months, structural equation models were used to evaluate relationships between treatment process variables and heroin use at 1 and 6 months. Patients' perceptions of program characteristics and methadone dose were related to reduced heroin use at 1 month. In addition, early engagement with treatment services was associated with decreased heroin use at 6 months (Gossop, Stewart, and Marsden, 2003).
- Studies comparing methadone treatment in general practice or primary care with treatment in specialty treatment clinics are limited, but at least two have demonstrated similar treatment outcomes between these two locations of care (Gossop, Marsden, Stewart, et al., 1999; Fiellin, O'Connor, Chawarski, et al., 2001).
- The Treatment Outcome Perspective Study (TOPS) examined a sample of 606 methadone maintenance treatment patients from 21 different clinics to identify treatment process factors related to improved patient retention rates. Results showed higher patient retention rates for programs (1) using organized and professional staff to diagnose problems and define treatment plans, (2) meeting and satisfying the needs perceived as important by clients, and (3) using higher methadone doses (Joe, Simpson, and Hubbard, 1991).
- A 6- to 7-year followup study of 347 methadone maintenance treatment patients examined different retention policies. Two programs had a high-dose, long-retention policy in which involuntary termination was used as a last resort. A third program had a low-dose, 2-year retention policy with strict terminations for program violations. Retention rates were longer in the two less structured programs (means of 4.3 and 3.2 years) than in the more structured program (mean of 2.2 years) (McGlothlin and Anglin, 1981).

- One study randomly assigned 69 patients at admission to structured and unstructured treatment groups. Structured groups had limits on illicit drug use that, if exceeded, resulted in withdrawal from methadone. The unstructured groups had no limits on illicit drug use. At the end of 1 year, 53 percent of the patients in structured groups remained in treatment, but only 30 percent of the patients in unstructured groups remained in treatment (McCarthy and Borders, 1985).
- A nationwide U.S. telephone survey of a randomized and stratified representative sample of 172 outpatient methadone units found that relatively high methadone dosage levels and patient participation in dosage decisions are related to higher retention rates (D'Aunno and Vaughn, 1992).
- According to Kreek (1991), adequate staff numbers, training, and concern for patient needs and high staff stability (low staff turnover) are associated with improved patient outcomes (Center for Substance Abuse Treatment, 1993).

The Effects of Dosage on Methadone Maintenance Treatment—Research regarding methadone dosage levels clearly establishes that low average doses are inappropriate in methadone maintenance treatment. No single level is effective for all patients, although NIDA-supported research has suggested that the minimum effective dosage for most methadone maintenance patients is 60 mg per day. The specific dosage for a patient cannot be determined arbitrarily because patients metabolize methadone at different rates. In addition, the appropriate dosage can change over time or in response to specific situations such as pregnancy or the use of other medications. Overall, methadone dosage should be based on the patient's individual needs, goals of treatment, and progress in treatment.

In the Ball and Ross studies (1991), illicit opioid use was directly related to methadone dosage levels. In methadone maintenance patients on dosages of about 71 mg per day, no heroin use was detected, but methadone maintenance patients on dosages below 46 mg were 5.16 times more likely to use heroin than those on higher dosages.

Ball and colleagues (1988) found that 18.6 percent of 490 patients who were in methadone maintenance treatment for 6 months to 4.5 years used heroin within the last 30 days, but use correlated strongly with methadone dosage level. At doses of 75 mg per day and above, the continuing use of heroin stopped altogether. In contrast, 64 percent of patients maintained on 10 mg per day or less continued frequent heroin use. A dose of 40 mg per day seemed to be the cutoff point for a large decrease in heroin use.

Despite recent attention to the importance of adequate methadone dosages, a large-scale survey of methadone maintenance treatment programs conducted in the United States in 1992 found that 50 percent of patients nationwide receive suboptimum methadone doses (D'Aunno and Vaughn, 1992). A subsequent evaluation found that the percentage of patients receiving methadone doses less than 60 mg per day has decreased from 79.5 percent in 1988 to 35.5 percent in 2000. Programs with a greater percentage of African American patients were more likely to dispense low doses of methadone, and programs with Joint Commission on Accreditation of Healthcare Organizations accreditation were more likely to provide adequate methadone doses (D'Aunno and Pollack, 2002).

In an exhaustive review of 22 studies that compared the effects of different methadone dosages on outcomes such as patient retention, continuing illicit opioid use, and symptoms, Hargreaves (1983) concluded that daily methadone doses of 100 mg were superior to those of 50 mg during the first 5 to 10 months of methadone maintenance treatment for a sizeable subgroup (10 percent to 30 percent) of opioid addicts.

In a study of 2,400 patients enrolled in methadone maintenance over a 15-year period, those patients maintained on a daily dose of 60 mg or more had longer retention in treatment; less use of heroin and

other drugs, including cocaine; and a lower incidence of HIV infection and AIDS (Hartel, Selwyn, and Schoenbaum, 1988a and 1988b).

In a multiclinic study of 12 Veterans Administration hospitals, methadone maintenance treatment patients were assigned to two dosage levels of methadone: 50 mg and 100 mg. The percentage of patients retained for 10 months was higher in the 100-mg group (52 percent) than in the 50-mg group (42 percent), but the difference was not statistically significant (Ling, Charuvastra, Kaim, et al., 1976).

Studies that examined the relationship between methadone maintenance treatment dosage and retention suggest that, although many patients will continue in treatment on methadone doses of less than 50 mg, some patients need higher doses. In a review of five well-designed dose-retention studies, three found statistically nonsignificant trends toward increased retention with higher doses and two did not (Maddux, Vogtsberger, Desmond, et al., 1993).

In a study of 180 methadone maintenance treatment patients randomly assigned at admission to three groups that received doses of 30 mg, 50 mg, and 100 mg, the percentages retained for 53 weeks were as follows: 45 percent of the 30-mg group, 55 percent of the 50-mg group, and 35 percent of the 100-mg group. The 100-mg group had the lowest retention rate, but the differences were not statistically significant (Garbutt and Goldstein, 1972).

A study of 322 methadone maintenance treatment patients receiving an average daily dose of 30 mg demonstrated a high dropout rate. Only 17 percent of the sample remained in treatment at the end of 6 months, and only 10 percent remained by the end of a year. Moreover, patients who dropped out within the first 30 days had the same drug-using behavior as they did before treatment (Craig, 1980).

Methadone dose should not be rapidly increased or decreased—or used in contingency management—because such changes tend to disrupt the normalization of physiological function achieved by steady dose treatment. If the stabilized methadone dose/plasma levels are disrupted, drug hunger and drug-seeking behaviors are likely to reappear (Kreek, 1991; Kreek, 1992).

Need for Comprehensive Services in Methadone Maintenance Treatment—In a study of 351 daily or weekly heroin users who were admitted to 1 of 17 publicly funded methadone maintenance treatment programs, nearly all (85 percent) reported having difficulty in at least one of the following problem areas: medical or physical; mental health or emotional; family or friends; police or legal; job, work, or school; and financial or money. Nearly one-half (44 percent) reported having difficulties in more than three of these areas (Condelli, 1993).

Program Characteristics Associated With Success of Methadone Maintenance Treatment—Other program characteristics that appear to improve treatment success include having sufficient staff, low staff turnover and high staff stability, sufficient staff training, and close and enduring relationships between staff and patients.

**Program Characteristics
Associated With
Success of Methadone
Maintenance Treatment**

Successful programs have:

- Comprehensive services
- Integrated medical, counseling, and administrative services
- Individualized treatment
- Adequate dosing policies
- Sufficient and stable staff
- Sufficient staff training

Figure 27 illustrates the program characteristics, identified by numerous research studies, that contribute to methadone maintenance treatment success (McLellan, Arndt, Metzger, et al., 1993; Ball and Ross, 1991; Joe et al., 1991).

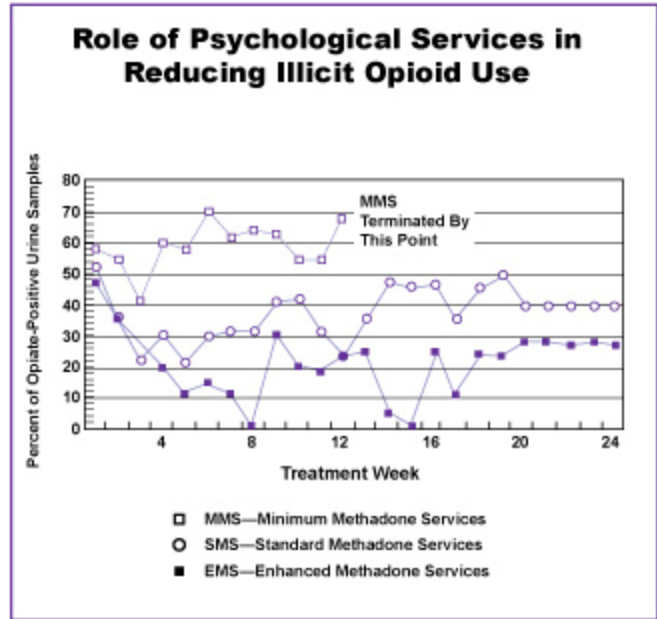


Figure 28 illustrates that in a recent study, 102 patients were divided into three groups: (1) minimum methadone maintenance treatment services (methadone alone); (2) standard methadone maintenance treatment services (methadone plus counseling); and (3) enhanced methadone maintenance treatment services (methadone, counseling, and onsite medical, psychiatric, employment, and family therapy services). At 24 weeks, methadone alone resulted in minimal improvements; methadone plus counseling resulted in significant improvements over methadone alone; and enhanced Services, including a broad range of psychosocial services plus methadone, had the best outcomes of all (McLellan et al., 1993). Patients receiving the most comprehensive array of treatment services were the most likely to have opioid-free urine tests for the 24 weeks of the study. Patients receiving minimal services were the most likely to have urine tests that were positive for illicit opioids. Note: These patients were removed from participation in the study because of drug use and psychiatric difficulties. Additional treatment services were made available.

References

- Amato L, Minozzi S, Davoli M, Vecchi S, Ferri M, Mayet S. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. *The Cochrane Database of Systematic Reviews*, Issue 4, 2004.
- Ball JC, Lange WR, Meyers CP, Friedman SR. Reducing the risk of AIDS through methadone maintenance treatment. *Journal of Health and Social Behavior* 1988;29:214-26.
- Ball JC, Ross A. *The Effectiveness of Methadone Maintenance Treatment: Patients, Programs, Services, and Outcomes*. New York: Springer-Verlag, 1991.
- Center for Substance Abuse Treatment. *State Methadone Treatment Guidelines. Treatment Improvement Protocol Series 1*. Rockville, MD: Center for Substance Abuse Treatment, 1993.
- Condelli WS. Strategies for increasing retention in methadone programs. *Journal of Psychoactive Drugs* 1993;25(2):143-47.
- Craig RJ. Effectiveness of low dose methadone maintenance for the treatment of inner city heroin addicts. *International Journal of the Addictions* 1980;15(5):701-10.
- D'Aunno T, Pollack HA. Changes in methadone treatment practices: results from a national panel study, 1988-2000. *JAMA* 2002;288(7):850-86.
- D'Aunno T, Vaughn TE. Variations in methadone treatment practices. Results from a national study. *JAMA* 1992;267(2):253-58.
- Fiellin DA, O'Connor PG, Chawarski M, Pakes JP, Pantalon MV, Schottenfeld RS. Methadone maintenance in primary care: a randomized controlled trial. *JAMA* 2001;286(14):1724-31.
- Garbutt GD, Goldstein A. Blind comparison of three methadone maintenance dosages in 180 patients. In: *Proceedings of the Fourth National Conference on Methadone Treatment*. New York: National Association for the Prevention of Addiction to Narcotics, 1972, pp. 411-14.
- Gossop M, Marsden J, Stewart D, Lehmann P, Strang J. Methadone treatment practices and outcome for opiate addicts treated in drug clinics and in general practice: results from the National Treatment Outcome Research Study. *British Journal of General Practice* 1999;49(438):31-34.
- Gossop M, Stewart D, Marsden J. Treatment process components and heroin use outcome among methadone patients. *Drug & Alcohol Dependence* 2003;71(1):93-102.
- Hargreaves WA. Methadone dose and duration for maintenance treatment. In: *Research on the Treatment of Narcotic Addiction: State of the Art*. National Institute on Drug Abuse Research Monograph Series. Rockville, MD: National Institute on Drug Abuse, 1983.
- Hartel D, Selwyn PA, Schoenbaum EE. Methadone maintenance treatment and reduced risk of AIDS and AIDS-specific mortality in intravenous drug users. Abstract No. 8546. Fourth International Conference on AIDS, Stockholm, Sweden, June 1988a.
- Hartel D, Selwyn PA, Schoenbaum EE. Temporal patterns of cocaine use and AIDS in intravenous drug users in methadone maintenance. Abstract 8526. Fourth International Conference on AIDS. Stockholm, Sweden, June 1988b.
- Joe GW, Simpson DD, Hubbard RL. Treatment predictors of tenure in methadone maintenance. *Journal of Substance Abuse* 1991;3(1):73-84.
- Kreek MJ. Rationale for maintenance pharmacotherapy of opiate dependence. In: O'Brien CP, Jaffe JH (eds.). *Addictive States*. New York: Raven Press, 1992.

Kreek MJ. Using methadone effectively: achieving goals by application of laboratory, clinical, and evaluation research and by developing of innovative programs. In: Pickens RW, Leukefeld CG, Schuster CR (eds.). *Improving Drug Abuse Treatment*. NIDA Research Monograph Series 196. Rockville, MD: National Institute on Drug Abuse, 1991.

Ling W, Charuvastra VC, Kaim SC, Klett CF. Methadyl acetate and methadone as maintenance treatments for heroin addicts. *Archives of General Psychiatry* 1976;33:709-20.

Maddux JF, Vogtsberger KN, Desmond DP, Esquivel M. Program changes and retention on methadone. *Journal of Substance Abuse Treatment* 1993;10:585-88.

McCarthy JJ, Borders OT. Limit setting on drug abuse in methadone maintenance patients. *American Journal of Psychiatry* 1985;142(12):1419-23.

McGlothlin WH, Anglin MD. Shutting off methadone: cost and benefits. *Archives of General Psychiatry* 1981;38:885-92.

McLellan AT, Arndt IO, Metzger DS, Woody GE, O'Brien CP. The effects of psychosocial services in substance abuse treatment. *JAMA* 1993;269(15):1953-59.

Question 14: Are there patient characteristics associated with the success of methadone maintenance treatment?

Answer: Yes. Patient characteristics associated with treatment success include the following:

- Age
- Age of first heroin use
- Overall drug-use history
- Severity and duration of drug use
- Emotional health
- Psychiatric health
- Social health
- Vocational stability
- Criminal history

Research Highlights

One review found the following characteristics to be associated with improved methadone outcomes: older age, absence of criminal behavior, shorter duration of opioid use, less severe psychopathology, being employed, being married, less polysubstance use, and higher expressed desire in getting help with a drug problem (Ward, Mattick, Hall, et al., 1998).

- In a review of 113 studies that attempted to evaluate the relationship of patient characteristics to retention and other outcomes (reported from 1971 to 1983), it was noted that patient characteristics probably accounted for only 25 to 45 percent of the variance in retention (McLellan, 1983).
- For methadone maintenance treatment patients in the Drug Abuse Reporting Program (DARP) studies, the most important predictors of posttreatment outcomes were (1) preadmission criminality and (2) measurements of crime, drug use, and employment during treatment. Of all the patient characteristics, chronic criminality is the strongest predictor of unfavorable posttreatment outcomes (Simpson and Sells, 1982).
- Ball and Ross's work (1991) supports the finding that a younger age at the onset of heroin use is associated with poorer treatment outcomes. Overall, however, this study noted that patient characteristics had less impact on outcomes than program variables.
- Anglin and Hser (1990) note that better psychosocial adjustment predicts superior treatment outcomes. Psychosocial adjustment was described as an intact marriage, a job, a shorter history of drug abuse, lower levels of psychiatric dysfunction, and minimal or no criminal history.
- Rounsaville, Glazer, Wilber, et al. (1983) assessed 123 opioid addicts who were followed for 6 months after admission and found that outcome was predicted by the behavior examined: greater pretreatment criminality predicts criminal activity following discharge. Conversely, pretreatment employment predicts posttreatment employment. This study found that patients who abuse alcohol, are unemployed, are dually diagnosed, manifest psychopathology, and engage in criminality have poor outcomes.

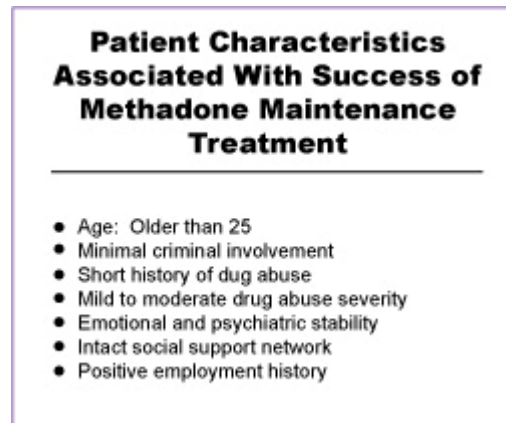


Figure 29 illustrates that, overall, patients who demonstrate emotional, psychological, and social well-being generally experience greater treatment success than patients who have emotional, psychological, and social problems. Several studies have noted that certain patient characteristics, which are listed in Figure 29, are associated with success in methadone maintenance treatment (McLellan, 1983; Simpson and Sells, 1982; Ball and Ross, 1991; Anglin and Hser, 1990).

References

- Anglin MD, Hser IY. Treatment of drug abuse. In: Tonry M, Wilson JQ (eds.). *Drugs and Crime*. Chicago: University of Chicago, 1990.
- Ball JC, Ross A. *The Effectiveness of Methadone Maintenance Treatment: Patients, Programs, Services, and Outcomes*. New York: Springer-Verlag, 1991.
- McLellan AT. Patient characteristics associated with outcome. In: Cooper JR, Altman F, Brown BS, Czechowicz D (eds.). *Research in the Treatment of Narcotic Addiction*. NIDA Treatment Research Monograph Series. Rockville, MD: National Institute on Drug Abuse, 1983.
- Rounsaville BJ, Glazer W, Wilber CH, Weissman MM, Kleber HD. Short-term interpersonal psychotherapy in methadone maintained opiate addicts. *Archives of General Psychiatry* 1983;40:629-36.
- Simpson DD, Sells SB. Effectiveness of treatment for drug abuse: an overview of the DARP research program. *Advances in Alcohol and Substance Abuse* 1982;2(1):7-29.
- Ward J, Mattick RP, Hall W. Duration of methadone maintenance treatment. In: Ward J, Mattick RP, Hall W (eds.). *Methadone Maintenance Treatment and Other Opioid Replacement Therapies*. Amsterdam: Harwood Academic Publishers, 1998, p. 571.

Question 15: Are there cost benefits to methadone maintenance treatment?

Answer: Yes. Research has demonstrated that methadone maintenance treatment is beneficial to society, cost-effective, and pays for itself in basic economic terms.

Research Highlights

A cost-effectiveness analysis reviewed five policy questions from an economic perspective: (1) whether methadone should be a healthcare benefit; (2) what level of ancillary services is optimal; (3) what methadone dose is appropriate; (4) what length of treatment is appropriate; and (5) whether contingency contracts should be employed. The analysis found that expanded access to methadone maintenance had an incremental cost-effectiveness ratio of less than \$11,000 per quality-adjusted life year (QALY). Ancillary services were shown to be an effective part of methadone maintenance therapy, especially during the beginning of a treatment episode. The cost of additional methadone was found to be low compared with the benefits of adequate doses. Short episodes of methadone maintenance were felt not likely to be cost-effective (Barnett and Hui, 2000).

A unique and timely analysis was performed that focused on the cost-effectiveness of methadone treatment based on its impact on the HIV epidemic. The analysis considered populations in which HIV prevalence among injection drug users ranged from 5 percent to 40 percent. The results demonstrated that increased methadone maintenance capacity costs \$8,200 per QALY gained in high-prevalence communities and \$10,900 per QALY gained in low-prevalence communities. Interestingly, the majority of benefits were gained by individuals who do not inject drugs (Zaric, Barnett, and Brandeau, 2000).

- A standard cost-effectiveness evaluation of methadone considered the incremental effect of methadone on the lifespan and treatment cost of a cohort of 25-year-old heroin users. The results demonstrated that providing opioid-dependent patients with methadone maintenance had an incremental cost-effectiveness ratio of \$5,915 per life-year gained. A sensitivity analysis determined that the ratio was less than \$10,000 per life-year over a range of assumptions. This cost-effectiveness ratio was lower than that of many common medical therapies and well within the \$50,000 threshold typically used in developed countries for judging cost-effectiveness (Barnett, 1999).
- A systematic review from Lithuania on studies of the cost-effectiveness of methadone noted that methadone maintenance had higher economic efficiency with daily doses of 80 to 100 mg, and daily doses lower than 40 mg were considered inefficient. In addition, short treatment episodes were not likely to be cost-effective, and ancillary services were more cost-effective at the beginning of methadone maintenance than in the later stages. Economic efficiency was found to be higher as treatment program census increased as opposed to the provision of more ancillary services (Vanagas, Padaiga, and Subata, 2004).
- The most comprehensive examination of economic benefits and costs was performed on data from the Treatment Outcome Perspective Study (TOPS). After examining the average cost of a methadone maintenance treatment day, detailed measurements of criminal activities rates, and the cost to society of various crimes, the study yielded a final benefit-to-cost ratio of 4 to 1 (Harwood, Hubbard, Collins, et al., 1988).
- Rufener, Rachal, and Cruz (1977) studied the cost-effectiveness of methadone maintenance (and other treatment modalities) and determined a benefit-to-cost ratio of 4.4 to 1.
- McGlothlin and Anglin (1981), using data from low-dose programs, compared patients who left methadone maintenance treatment when a community clinic was closed in Bakersfield, California, with patients in another community's program that remained open. For men, the ratio of crime-related economic benefits to treatment costs was 1.7 to 1 over a 2-year period. In

addition, the continuous treatment group reported significantly higher rates of employment than those who had been closed out of treatment, although the factor was not formally assessed in the study.

- Methadone maintenance treatment, when implemented at sufficient resource levels, provides individual and social benefits for at least several years that are substantially higher than the cost of delivering this treatment. The daily benefits equal the daily costs in virtually every case, even among those who continue drug use at a reduced level (Gerstein and Harwood, 1990).
- There are many more costs to society associated with active heroin use (Rufener et al., 1977). These include medical costs, law enforcement costs, judicial system costs, corrections costs, nondrug crime costs, drug traffic control, drug abuse prevention costs, reducing housing stock costs, absenteeism costs, unemployment costs, and drug-related deaths. Thus, when all costs to society are considered, methadone maintenance treatment is extremely cost-effective and beneficial to society.
- A study that randomly assigned new patients to three levels of care (methadone alone, methadone plus standard counseling services, and methadone plus enhanced services [counseling, medical/psychiatric, employment, and family therapy services]) found that methadone plus standard counseling was most cost-effective. At 12 months, the annual cost per abstinent client was \$16,485, \$9,804, and \$11,818 for the low, intermediate, and high levels of counseling, respectively (Kraft, Rothbard, Hadley, et al., 1997). A similar finding was obtained in a cost-effectiveness study of varying levels of care provided along with methadone maintenance in Spain (Puigdollers, Cots, Brugal, et al., 2003).
- In a study comparing ongoing methadone maintenance with 6 months of methadone maintenance followed by detoxification, total healthcare costs were greater for maintenance than detoxification treatment (\$7,564 vs. \$6,687; $p < 0.001$). However, detoxification patients incurred significantly higher costs for substance abuse and mental healthcare services. Methadone maintenance appeared to provide a small survival advantage compared with detoxification. The cost per life-year gained was \$16,967. Sensitivity analysis revealed a cost-effectiveness ratio of less than \$20,000 per QALY over a range of modeling assumptions (Masson, Barnett, Sees, et al., 2004).

Comparison of Treatment and Societal Costs of Active Heroin Addiction—A study of the cost benefits of methadone maintenance treatment showed that the costs to society of the criminal activities related to active heroin use can run as high as four times more than the costs for methadone maintenance treatment (Harwood et al., 1988).

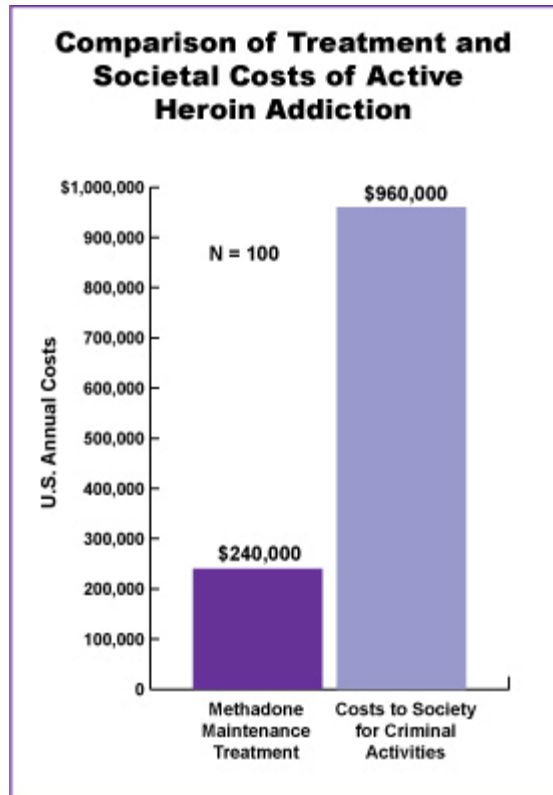


Figure 30 illustrates the cost-benefit relationship. For example, if the approximate annual cost for providing methadone maintenance treatment is \$2,400 per person, it would cost about \$240,000 to provide treatment for 100 patients for 1 year. In contrast, the annual costs to society related to the criminal activities of 100 active heroin addicts not in treatment would exceed \$960,000 (Harwood et al., 1988).

Through the New York State Department of Substance Abuse Services, NIDA researchers have estimated the yearly cost to maintain an opioid addict in New York: untreated and on the street (\$43,000), in prison (\$34,000), in a residential drug-free program (\$11,000), and in methadone maintenance treatment (\$2,400) (New York State Committee of Methadone Program Administrators, 1991).

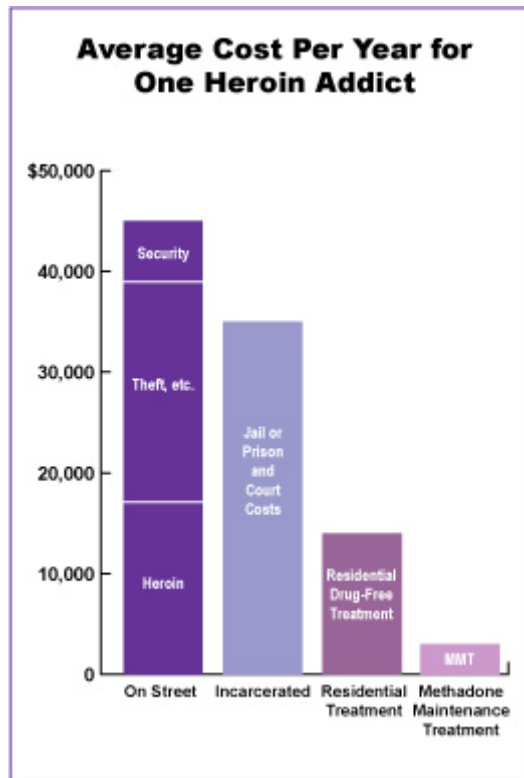


Figure 31 illustrates the cost of active heroin use for one addict for a year at about \$43,000 in 1991. This includes the cost of the heroin, the loss of property related to theft and burglary, and the costs of security measures to combat such crimes.

References

- Barnett PG, Hui SS. The cost-effectiveness of methadone maintenance. *Mount Sinai Journal of Medicine* 2000;67(5-6):365-74.
- Barnett PG. The cost-effectiveness of methadone maintenance as a health care intervention. *Addiction* 1999;94(4):479-88.
- Gerstein DR, Harwood HJ (eds.). *Treating Drug Problems*. Volume I. Washington, DC: National Academy Press, Institute of Medicine, 1990.
- Harwood HJ, Hubbard RL, Collins JJ, Rachal JV. The costs of crime and the benefits of drug abuse treatment: a cost-benefit analysis using TOPS data. In: Leukefeld CG, Time FM (eds.). *Compulsory Treatment of Drug Abuse: Research and Clinical Practice*. NIDA Research Monograph Series 86. Rockville, MD: National Institute on Drug Abuse, 1988.
- Kraft MK, Rothbard AB, Hadley TR, McLellan AT, Asch DA. Are supplementary services provided during methadone maintenance really cost-effective? *The American Journal of Psychiatry* 1997;154(9):1214-19.
- Masson CL, Barnett PG, Sees KL, Delucchi KL, Rosen A, Wong W, Hall SM. Cost and cost-effectiveness of standard methadone maintenance treatment compared to enriched 180-day methadone detoxification. *Addiction* 2004;99(6):718-26.
- McGlothlin WH, Anglin MD. Long-term follow-up of clients of high- and low-dose methadone programs. *Archives of General Psychiatry* 1981;38:1055-63.

New York State Committee of Methadone Program Administrators. COMPA's Five Year Plan for the Methadone Treatment System in New York State. New York: New York State Committee of Methadone Program Administrators, 1991.

Puigdollers E, Cots F, Brugal MT, Torralba L, Domingo-Salvany A. Methadone maintenance programs with supplementary services: a cost-effectiveness study. [Spanish] *Gaceta Sanitaria* 2003;17(2):123-30.

Rufener BL, Rachal JV, Cruz AM. *Management Effectiveness Measures for NIDA Drug Abuse Treatment Programs. Cost Benefit Analysis*. Rockville, MD: National Institute on Drug Abuse, 1977.

Vanagas G, Padaiga Z, Subata E. Economic efficiency of methadone maintenance and factors affecting it. [Lithuanian] *Medicina (Lith)* 2004;40(7):607-13.

Zaric GS, Barnett PG, Brandeau ML. HIV transmission and the cost-effectiveness of methadone maintenance. *American Journal of Public Health* 2000;90(7):1100-11.

Question 16: What are the retention rates for methadone maintenance treatment?

Answer: Retention in methadone is related to the dose of methadone but not the provision of ancillary services.

Research Highlights

- A meta-analysis of studies comparing the provision of methadone maintenance with and without ancillary services demonstrated decreased illicit heroin use with ancillary services but found no statistically significant additional benefit in terms of retention in treatment, RR 0.94 (95% CI, 0.85 to 1.02) (Amato, Davoli, Perucci, et al., 2005).
- An observational study of 351 patients in the United Kingdom receiving methadone maintenance compared with those receiving methadone dose reduction found the following retention rates: 88 percent vs. 86 percent at 1 month, 71 percent vs. 58 percent at 2 months, 62 percent vs. 50 percent at 1 year, and 42 percent vs. 30 percent at 2 years (Gossop, Marsden, Stewart, et al., 2001).
- An Italian study followed 1,503 heroin-dependent patients who received treatment in the form of methadone maintenance, a drug-free program, or naltrexone. The retention rate after 1 year was 40 percent for patients in methadone maintenance, 18 percent in naltrexone, and 15 percent in the drug-free program. Patients receiving methadone greater than or equal to 60 mg per day and 30 to 59 mg per day were respectively 70 and 50 percent more likely to remain in treatment than those receiving less than 30 mg per day. Patients receiving methadone maintenance were 30 percent more likely to remain in treatment than those not receiving methadone (D'Ippoliti, Davoli, Perucci, et al., 1998).
- Thirty-eight percent of the new patient group (total 126) in the Ball and Ross (1991) studies of six methadone maintenance treatment programs remained in treatment after a year; 63 percent of the moderate-stay group (total 345) were still in treatment a year later; and 84 percent of the long-term patients (total 146) continued their methadone maintenance treatment for another year.
- In a study of 311 admissions to three methadone maintenance treatment programs during 1990 and 1991, 24 percent dropped out within 60 days. The significant predictors of retention were social stability (being married, employed, and having few prior arrests); previous treatment experience; high dosage levels; and motivation for treatment (Simpson and Joe, 1993).

Additional Studies

- In a study of 351 daily or weekly heroin users who were admitted to 1 of 17 publicly funded methadone treatment programs, predictors of retention in methadone maintenance treatment programs included (1) positive patient evaluations of the quality of social services received during the first month after admission (e.g., family, legal, educational, employment, financial services); (2) positive patient ratings of how easily accessible the program was; and (3) participation in programs that informed patients of their methadone dosage levels (Condelli, 1993).

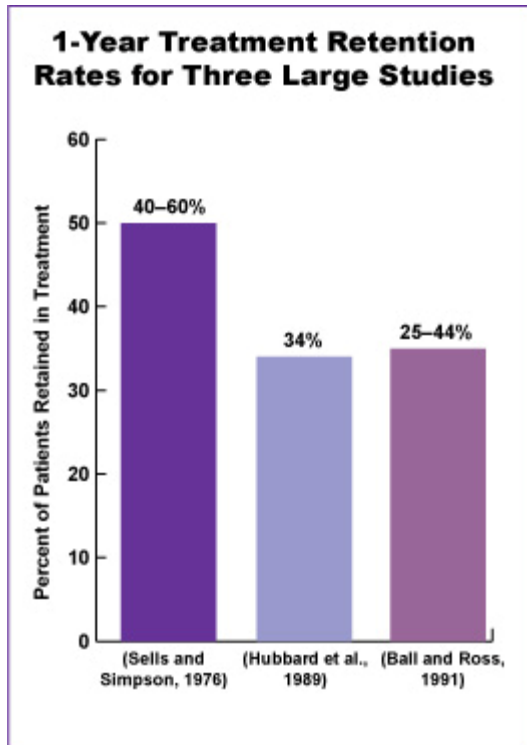


Figure 32 illustrates 1-year treatment retention rates for three large studies.

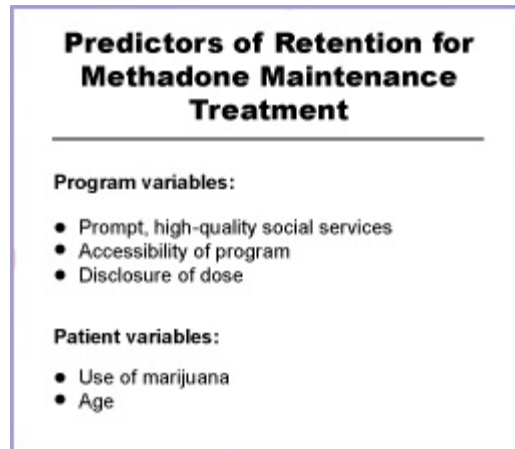


Figure 33 illustrates that in the Treatment Outcome Perspective Study (TOPS), patient self-report ratings of the quality (not the number) of social services received during the first month of methadone maintenance treatment were a strong predictor of retention (Condelli and Dunteman, 1993). The study suggests that methadone maintenance treatment programs should provide patients with high-quality social services as soon as possible after admission in order to promote retention. The study found that three program and two patient variables predicted retention. It also noted that patients who were 25 years of age or younger were more likely than older patients to drop out of methadone maintenance treatment programs, possibly because they lacked the motivation, maturity, and life goals that often characterize older patients.

Likelihood of Relapse After Leaving Methadone Treatment—Of 105 patients who were followed in the community after leaving methadone maintenance treatment after 1 month to 1 year or longer, two-thirds (67.6 percent) relapsed to injection drug use (Ball and Ross, 1991).

References

Amato L, Davoli M, Perucci C, Ferri M, Faggiano F, Mattick RP. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *Journal of Substance Abuse Treatment* 2005;28(4):321-29.

Ball JC, Ross A. *The Effectiveness of Methadone Maintenance Treatment: Patients, Programs, Services, and Outcomes*. New York: Springer-Verlag, 1991.

Condelli WS. Strategies for increasing retention in methadone programs. *Journal of Psychoactive Drugs* 1993;25(2):143-47.

Condelli WS, Dunteman GH. Exposure to methadone programs and heroin use. *American Journal of Drug and Alcohol Abuse* 1993;19:65-78.

D'Ippoliti D, Davoli M, Perucci CA, Pasqualini F, Bargagli AM. Retention in treatment of heroin users in Italy: the role of treatment type and of methadone maintenance dosage. *Drug & Alcohol Dependence* 1998;52(2):167-71.

Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opioid dependence. *The Cochrane Database of Systematic Reviews*, Issue 3, 2003.

Gossop M, Marsden J, Stewart D, Treacy S. Outcomes after methadone maintenance and methadone reduction treatments: two-year follow-up results from the National Treatment Outcome Research Study. *Drug & Alcohol Dependence* 2001;62(3):255-64.

Hubbard RL, Marsden ME, Rachal JV, Harwood HJ, Cavanaugh ER, Ginzburg HM. *Drug Abuse Treatment: A National Study of Effectiveness*. Chapel Hill: University of North Carolina Press, 1989.

Sells SB, Simpson DD (eds.). *The Effectiveness of Drug Abuse Treatment*. Cambridge, MA: Ballinger, 1976.

Simpson DD, Joe GW. Motivation as a predictor of early dropout from drug abuse treatment. *Psychotherapy* 1993;30(2):357-68.

Question 17: Is mandated methadone maintenance treatment as effective as voluntary treatment?

Answer: Yes. Mandated methadone maintenance treatment (being forced to attend treatment by the criminal justice system) is as effective as voluntary treatment.

Research Highlights

A study examined the relationship between length of stay in methadone maintenance treatment and referral by legal and nonlegal sources of 2,200 patients. It was determined that patients who are legally referred to methadone maintenance treatment stay in treatment longer than, and do at least as well as, those who seek treatment voluntarily (Collins and Allison, 1983).

A study of 121 male veterans in a 90-day Veterans Administration drug rehabilitation program compared court-referred and voluntary patients. Objective and subjective measures both indicate that the court-referred patient is potentially as responsive to methadone maintenance treatment as the voluntary patient. Sixty-two percent of the court-referred patients were judged to have a good prognosis compared with 58 percent of the voluntary patients (McLellan and Druley, 1977).

Three samples of methadone maintenance treatment admissions, who were treated during the years of 1971 to 1973, participated in a followup study 7 years later. These groups included (1) a random sample of 100 patients, (2) a sample of 136 patients who had a minimum of 30 months remaining on civil addict parole status at the time of admission, and (3) a matched sample of 136 patients not on parole. The addition of parole supervision with urine testing resulted in only marginal improvements in behavior over that attributable to methadone maintenance treatment alone; however, parole status did significantly reduce the length of intervals of daily heroin use both before and after admission (Anglin, McGlothlin, and Speckart, 1981).

Mandated Methadone Maintenance Treatment and Three Treatment Outcomes—Patients who are legally coerced into methadone maintenance treatment experience treatment success at about the same rate as patients who participate voluntarily in treatment.

A study by Anglin, Brecht, and Maddahian (1990) examined patients who were mandated to treatment and those who entered voluntarily. One group was forced to participate in methadone maintenance treatment (high coercion). A second group (not represented in Figures 34 through 36) had moderate legal pressure to participate in methadone maintenance treatment (medium coercion). A third group had mild legal pressure to participate in methadone maintenance treatment (low coercion).

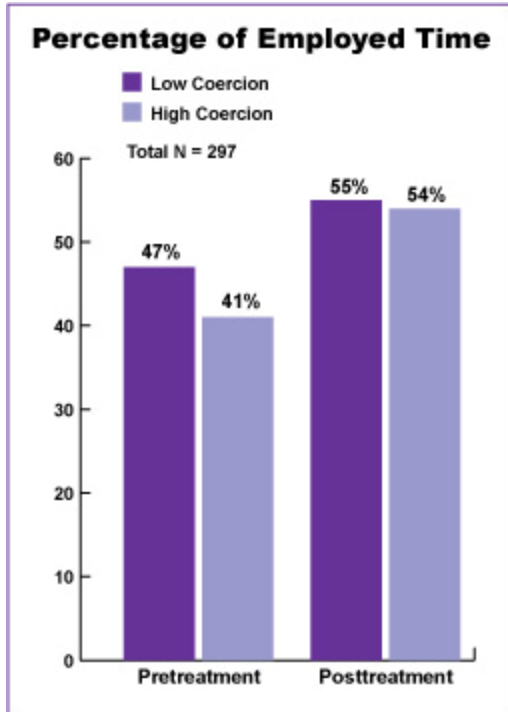


Figure 34 compares the behaviors of individuals in the high-coercion group with those of individuals in the low-coercion group for the treatment outcome of time employed. As the figure illustrates, patients who are coerced in treatment achieve this treatment outcome at about the same rate as patients who voluntarily participate in methadone maintenance treatment (Anglin et al., 1990).

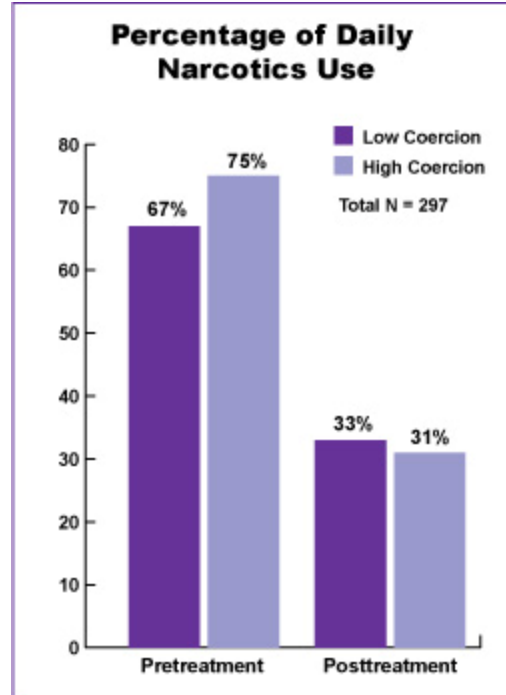


Figure 35 compares the behaviors of individuals in the high-coercion group with those of individuals in the low-coercion group for the treatment outcome of daily narcotics use. As the figure illustrates, patients who are coerced in treatment achieve this treatment outcome at about the same rate as patients who voluntarily participate in methadone maintenance treatment (Anglin et al., 1990).

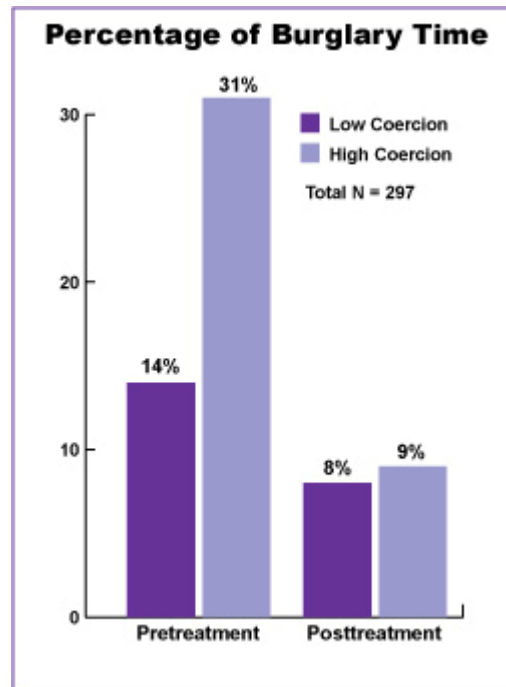


Figure 36 compares the behaviors of individuals in the high-coercion group with those of individuals in the low-coercion group for the treatment outcome of criminal involvement. As the figure illustrates, patients who are coerced in treatment achieve this treatment outcome at about the same rate as patients who voluntarily participate in methadone maintenance treatment (Anglin et al., 1990).

References

- Anglin MD, Brecht ML, Maddahian E. Pre-treatment characteristics and treatment performance of legally coerced versus voluntary methadone maintenance admissions. *Criminology* 1990;27:537-57.
- Anglin MD, McGlothlin WH, Speckart GR. The effect of parole on methadone patient behavior. *American Journal of Drug and Alcohol Abuse* 1981;8:153-70.
- Collins JJ, Allison M. Legal coercion and retention in drug abuse treatment. *Hospital and Community Psychiatry* 1983;34(12):1145-49.
- McLellan AT, Druley KA. A comparative study of response to treatment in court-referred and voluntary drug patients. *Hospital and Community Psychiatry* 1977;28:241-45.

Question 18: What is the role of L-alpha-acetyl-methadol (LAAM)?

Answer: L-alpha-acetyl-methadol (LAAM), a potent opioid with a longer duration of action than methadone, can suppress opioid withdrawal for up to 72 hours. Research on both LAAM and methadone maintenance treatment provides comparable results regarding patients' reported clinic attendance, opioid withdrawal symptoms, illicit drug use, employment status, and criminal activity. Both treatments are similar regarding overall effectiveness.

Due to concerns over reports of QT interval prolongation and episodes of Torsades de Point, LAAM was removed from the European markets and subsequently had limited use in the United States.

Question 19: How do buprenorphine and methadone compare?

Answer: Buprenorphine is approved for use in the treatment of opioid dependence in a large number of countries, including Australia, Belgium, Canada, Croatia, Germany, Iran, England, France, the United Kingdom, and the United States. Buprenorphine is a partial agonist at the opioid receptor, as opposed to a full agonist such as methadone or heroin. This means that buprenorphine has a unique pharmacologic profile leading to a lower likelihood of overdose or respiratory depression. Like methadone, buprenorphine has the ability to suppress opioid craving and withdrawal, block the effects of self-administered opioids, retain patients in treatment, and decrease illicit opioid use. Because it is a partial agonist, buprenorphine maintains patients in a milder degree of physical dependence and is associated with milder withdrawal syndrome following cessation.

Clinical trials comparing the efficacy of buprenorphine to methadone on the outcomes of retention and illicit opioid use have demonstrated similar results when compared with low doses of methadone (20 to 30 mg) (Johnson, Jaffe, and Fudala, 1992; Ling, Wesson, Charuvastra, et al., 1996). Comparisons to higher doses (35 to 90 mg) of methadone have yielded mixed results (Strain, Stitzer, Liebson, et al., 1994; Kosten, Schottenfeld, Ziedonis, et al., 1993).

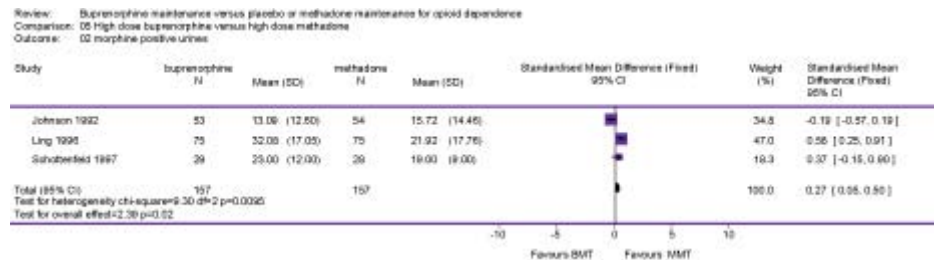


Figure 37a

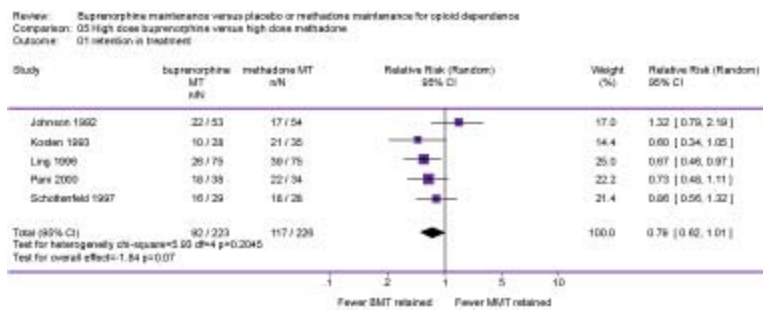


Figure 37b

Figures 37a and 37b illustrate that a meta-analysis of 13 clinical trials that compared buprenorphine maintenance with methadone maintenance had the following findings: “Buprenorphine given in flexible doses appeared statistically significantly less effective than methadone in retaining patients in treatment (RR = 0.82; 95% CI: 0.69-0.96). Low-dose buprenorphine is not superior to low-dose methadone. High-dose buprenorphine does not retain more patients than low-dose methadone, but may suppress heroin use better. There was no advantage for high-dose buprenorphine over high-dose methadone in retention (RR = 0.79; 95% CI: 0.62-1.01), and high-dose buprenorphine was inferior in suppression of heroin use. Buprenorphine was statistically significantly superior to placebo medication in retention of patients in treatment at low doses (RR = 1.24; 95% CI: 1.06-1.45), high doses (RR = 1.21; 95% CI: 1.02-1.44), and very high doses (RR = 1.52; 95% CI: 1.23-1.88). However, only high and very high dose buprenorphine suppressed heroin use significantly above placebo.” (Mattick, Kimber, Breen, et al., 2003.) (Please note, this review will be updated.)

Patients receiving buprenorphine can be either (1) discontinued without significant withdrawal, (2) maintained, or (3) transferred to opioid antagonist treatment, such as naltrexone. Patients with a higher level of physical dependence and whose needs cannot be met by buprenorphine can be transferred to an opioid agonist, such as methadone or L-alpha-acetyl-methadol (LAAM).

Research Highlights

- Mello and Mendelson showed that buprenorphine suppresses heroin self-administration by opioid-dependent primates and humans (Mello and Mendelson, 1980; Mello, Mendelson, and Kuehnle, 1982; Mello, Bree, and Mendelson, 1983).
- Findings from a subsequent dose-ranging study at the Los Angeles Addiction Treatment Research Center (LAATRC) suggest that the median doses of buprenorphine for adequate clinical stabilization may be in the 12- to 16-mg range (Compton, Ling, Charuvastra, et al., in press).
- A NIDA-sponsored, 12-site LAATRC/Veterans Administration/NIDA multicenter study compared doses of 1, 4, 8, and 16 mg of buprenorphine in 631 patients. The primary comparison between the 8-mg and the 1-mg groups shows that the 8-mg group used fewer illicit opioids and remained in treatment longer (Ling, Charuvastra, Collins, et al., 1998).

A clinical trial comparing buprenorphine, the buprenorphine/naloxone combination, and placebo was terminated early because buprenorphine and naloxone in combination and buprenorphine alone were found to have greater efficacy than placebo. Opioid-negative urine samples were found more frequently in the buprenorphine and buprenorphine/naloxone groups (17.8% and 20.7%, respectively) than in the placebo group (5.8%, $p < 0.001$ for both comparisons) (Fudala, Bridge, Herbert, et al., 2003).

Potential Benefits of Buprenorphine

Research on buprenorphine has shown that it has the potential to be a feasible alternative to methadone maintenance treatment. One potential benefit of buprenorphine compared with methadone that needs further investigation is a lower prevalence of medication interactions between buprenorphine and highly active antiretroviral treatment used to treat patients with HIV (Sullivan and Fiellin, 2005). Additional potential benefits of buprenorphine treatment are outlined in Figure 38.

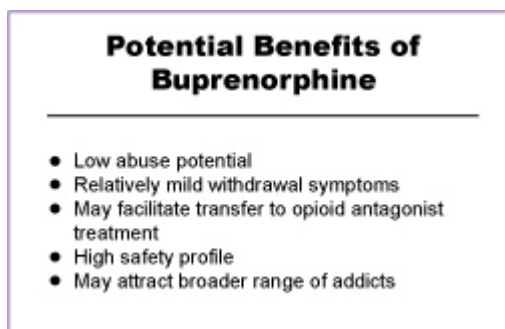


Figure 38 illustrates the potential benefits of buprenorphine.

References

- Compton P, Ling W, Charuvastra C, Wesson DR. Buprenorphine as a pharmacotherapy for opioid addiction: what dose provides a therapeutic response? *American Journal of the Addictions*, in press.
- Fudala PJ, Bridge TP, Herbert S, Williford WO, Chiang CN, Jones K, et al. Buprenorphine/Naloxone Collaborative Study Group. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *New England Journal of Medicine* 2003;349(10):949-58.
- Johnson RE, Jaffe JH, Fudala JP. A controlled trial of buprenorphine treatment for opioid dependence. *JAMA* 1992;267(20):2750-55.
- Kosten TR, Schottenfeld R, Ziedonis D, Falcioni J. Buprenorphine versus methadone maintenance for opioid dependence. *Journal of Nervous and Mental Disease* 1993;181(6):358-64.
- Ling W, Charuvastra C, Collins JF, Batki S, Brown LS, Kintaudi P, et al. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction* 1998;93(4):475-86.
- Ling W, Wesson DR, Charuvastra C, Klett CJ. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Archives of General Psychiatry* 1996;53(5):401-47.
- Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *The Cochrane Database of Systematic Reviews*, Issue 2, 2003.
- Mello NK, Bree MP, Mendelson JH. Comparison of buprenorphine and methadone effects on opioid self-administration in primates. *Journal of Pharmacological Experimental Therapy* 1983;225:378-86.
- Mello NK, Mendelson JH. Buprenorphine suppresses heroin use by heroin addicts. *Science* 1980;27:657-59.
- Mello NK, Mendelson JH, Kuehnle JC. Buprenorphine effects on human heroin self-administration: an operant analysis. *Journal of Pharmacological Experimental Therapy* 1982;223:30-39.
- Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Buprenorphine versus methadone in the treatment of opioid-dependent cocaine users. *Psychopharmacology (Berl)* 1994;116(4):401-06.
- Sullivan LE, Fiellin DA. Buprenorphine: its role in preventing HIV transmission and improving the care of HIV infected patients with opioid dependence. *Clinical Infectious Diseases* 2005;41(6):891-96.

Question 20: Can methadone and buprenorphine be abused?

Answer: Both methadone and buprenorphine can be diverted from their intended recipients. This diversion occurs in countries that provide these medications via supervised dispensing (e.g., pharmacies) and by prescription. Oftentimes, this diversion is by individuals who are seeking a therapeutic benefit (e.g., unobserved treatment). Other times, this diversion results in abuse. The extent of these two types of diversion varies, although most studies note that the benefits of providing the treatment outweigh the risks associated with diversion. For instance, the efficacy of methadone has been demonstrated over the past 40 years (O'Connor and Fiellin, 2000). The provision of methadone and buprenorphine treatment was associated with a 75-percent decrease in fatal heroin overdoses in France (Lepere, Gourarier, Sanchez, et al., 2001; Auriacombe, Fatseas, Dubernet, et al., 2004).

In studies that have compared death rates from heroin overdose among those who are untreated and those who receive methadone, deaths are higher among untreated opioid-dependent individuals (Caplehorn, Dalton, Haldar, et al., 1996; Zanis and Woody, 1998).

Research Highlights

Methadone Abuse

Methadone can be diverted for oral or intravenous use (Fiellin and Lintzeris, 2003; Green, James, Gilbert, et al., 2000). Some diverted methadone can result in fatal overdoses; however, the rate of overdose among patients enrolled in methadone maintenance is low. A meta-analysis revealed a relative risk of death of 0.25 (95% CI: 0.19-0.33) for patients receiving methadone maintenance (Caplehorn et al., 1996). A study of nearly 10,000 individuals inducted onto methadone determined that the mortality rate was 7.1 deaths per 10,000 inductions (95% CI: 1.8± 12.4). In this same study, 51 percent of methadone-related deaths occurred in people who were not registered in methadone maintenance (Zador and Sunjic, 2002).

In addition, while methadone may be detected in drug-related deaths, it is often not the causative agent. In one study in the west of Scotland, during the period 1991–2001, methadone alone was judged to be the causative agent in only 29 percent (56) of drug-related deaths (Seymour, Black, Jay, et al., 2003).

Similarly, with the increased use of methadone as a treatment for chronic pain, the majority of methadone-related deaths in Australia and the United States are believed to be associated with the use of this medication for pain treatment instead of treatment of opioid dependence (Williamson, Foreman, White, et al., 1997; Center for Substance Abuse Treatment, 2004).

Buprenorphine Abuse

As a partial agonist, buprenorphine has less potential for abuse than most full agonists. However, there is a reinforcing effect that subjects can experience with buprenorphine administration, especially via the injection route. This reinforcement is less likely if the subject has recently used a full agonist compound; in fact, buprenorphine can lead to a painful and uncomfortable precipitated withdrawal under this scenario. In addition, the development of a tablet that combines buprenorphine with naloxone, in a 4 to 1 ratio, has demonstrated decreased abuse potential and the ability to precipitate withdrawal in patients who are receiving a full opioid agonist (Mendelson, Jones, Welm, et al., 1999).

When the buprenorphine/naloxone combination tablet is taken sublingually, as prescribed, naloxone is poorly absorbed, and the patient receives a buprenorphine effect. However, if the tablet is dissolved and injected, the naloxone will antagonize the buprenorphine, resulting in a range of reactions, including blockade of opioid effects and precipitation of an immediate withdrawal. In this way, the combination gives the therapeutic benefit but greatly reduces opportunities for abuse by injection.

References

- Auriacombe M, Fatseas M, Dubernet J, Daulouede JP, Tignol J. French field experience with buprenorphine. *American Journal on Addictions* 2004;13(Suppl 1):S17-28.
- Caplehorn JR, Dalton MS, Haldar F, Petrenas AM, Nisbet, JG. Methadone maintenance and addicts' risk of fatal heroin overdose. *Substance Use and Misuse* 1996;31:177-96.
- Center for Substance Abuse Treatment. *Methadone-Associated Mortality: Report of a National Assessment, May 8-9, 2003*. CSAT Publication No. 28-03. Rockville, MD: Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, 2004.
- Fiellin DA, Lintzeris N. Methadone syrup injection in Australia: a sentinel finding? *Addiction* 2003;98:385-386.
- Green H, James RA, Gilbert JD, Harpas P, Byard RW. Methadone maintenance programs—a two-edged sword? *American Journal of Forensic Medicine & Pathology* 2000;21(4):359-61.
- Lepere B, Gourarier L, Sanchez M, Adda C, Peyret E, Nordmann F, et al. Reduction in the number of lethal heroin overdoses in France since 1994. Focus on substitution treatments. *Annales de Medecine Interne* 2001;152:5-12.
- Mendelson J, Jones RT, Welm S, Baggott M, Fernandez I, Melby AK, et al. Buprenorphine and naloxone combinations: the effects of three dose ratios in morphine-stabilized, opiate-dependent volunteers. *Psychopharmacology* 1999;141(1):37-46.
- O'Connor PG, Fiellin DA. Pharmacologic treatment of heroin-dependent patients. *Annals of Internal Medicine* 2000;133:40-54.
- Seymour A, Black M, Jay J, Cooper G, Weir C, Oliver J. The role of methadone in drug related deaths in the west of Scotland. *Addiction* 2003;98(7):995-1002.
- Williamson PA, Foreman KJ, White JM, Anderson G. Methadone-related overdose deaths in South Australia, 1984-1994. How safe is methadone prescribing? *Medical Journal of Australia* 1997;166(6):302-05.
- Zador DA, Sunjic SD. Methadone-related deaths and mortality rate during induction into methadone maintenance, New South Wales, 1996. *Drug & Alcohol Review* 2002;21(2):131-36.
- Zanis DA, Woody GE. One-year mortality rates following methadone treatment discharge. *Drug & Alcohol Dependence* 1998;52:257-60.