**Table 1.** Primary endpoints used to determine efficacy in randomized clinical trials of medications for opioid use disorder (studies in Table identified from (Biondi et al., 2020; Dennis et al., 2020))

*Note.* This table is from a review and conceptual analysis of Urine Opioid Screen (UOS)-based primary endpoints used to establish effectiveness for trials in opioid use disorder by Brandt, Odom, Balise, Bouzoubaa, and Luo (manuscript in preparation).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Primary Endpoint** | **Reference** | **Definition/Assessment of Outcome** | **Frequency of UOS** | **Missing UOS coded as** |
| ***Abstinence from non-study opioids*** | | | | |
| **Continuous abstinence** | Ling et al., 1998 | % of participants who maintained 13 consecutive negative UOS | 3x/week | Missing/not imputed |
|  | (Kosten et al., 1993) | % of participants attaining at least 3 weeks of consecutive negative UOS | weekly | Missing/not imputed |
| **Length of Initial Abstinence** | Schottenfeld, Chawarski, & Mazlan, 2008 | Days to 1st positive UOS after randomization | 3x/week | Positive |
|  | Shufman et al., 1994 | Weeks between 1st day of NTX administration and 1st positive UOS | weekly | Missing1 |
|  | Mokri, Chawarski, Taherinakhost, & Schottenfeld, 2016 | Days to 1st positive UOS | 2x/week | Positive |
| **Longest period of abstinence** | Schottenfeld et al., 2008 | Longest period of negative UOS | 3x/week | Positive |
|  | Schottenfeld et al., 2005 | Max. number of consecutive weeks of negative UOS | 3x/week | Missing |
| **Complete Abstinence** | Krupitsky et al., 2011 | Confirmed opioid abstinence during weeks 5‐24 based on UOS | weekly | Positive |
|  | Rosenthal et al., 2016 | No evidence of opioid use based on UOS | 1×/month + 4 random UOS | Imputed2 |
|  | Lofwall et al., 2018 | No evidence of opioid use based on UOS | weeks 1‐12, 16, 20, and 24 + 3 random UOS during weeks 12‐24 | Positive |
| **Abstinence weeks** | Fiellin et al., 2006; Krupitsky et al., 2011 | Weeks of confirmed opioid abstinence | weekly | Positive |
| **Abstinence period** | *CTN-0030* | Negative UOS during the last week AND for at least 2 of the previous 3 weeks of the third month of BUP/NX treatment | weekly | Positive |
| ***Relapse to non-study opioids*** | | | | |
| **Time to opioid use/relapse** | Schottenfeld et al., 2008 | Days to relapse (3 consecutive positive UOS) | 3x/week | Positive |
|  | Lee et al., 2016 | Weeks to relapse (≥10 days of opioid use in a 28‐day period [a positive UOS was computed as 5 days of opioid use]) | biweekly | Positive |
|  | Lee et al., 2018 *CTN-0051* | Weeks to relapse (starting at day 21 post-randomization: 4 consecutive weeks with positive UOS) | weekly | Positive |
| **Relapse/failure rate** | Krupitsky et al., 2004, 2006 | Relapse rate (3 consecutive positive UOS) | biweekly | Not defined |
|  | Johnson, Jaffe, & Fudala, 1992 | Failure rate: 2 consecutive positive UOS following 4 weeks of treatment | 3x/week (only Monday sample was considered for this endpoint) | Positive |
| ***Reduction of regular opioid use*** | | | | |
| **Opioid use rate** | Sees et al., 2000 | Monthly proportion of positive UOS | monthly | Missing/not imputed |
|  | Soyka, Zingg, Koller, & Kuefner, 2008 | Monthly rates of positive UOS | weekly | Missing/not imputed |
|  | Schwartz et al., 2006 | Number of positive UOS at 120-day follow-up | BL and 120-day follow-up | Missing/not imputed |
|  | Strain, Stitzer, Liebson, & Bigelow, 1996 | Percentage of positive UOS – Overall *AND* summarized in consecutive 2-week blocks | 3x/week | Missing/not imputed |
|  | Ling, Charuvastra, Kaim, & Klett, 1976 | Index of illicit morphine use | weekly | Positive3 |
|  | Woody et al., 2008 | Percentage of positive UOS at weeks 4, 8, and 12 | weeks 4, 8, 12 | Imputed4 |
|  | Eissenberg et al., 1997 | Weekly percentage of positive UOS for patients who remained in treatment through week 17 | 3x/week | Imputed5 |
|  | Strain, Stitzer, Liebson, & Bigelow, 1993 | Rate of positive UOS through the end of the stable dosing period | 3x/week | Not defined |
|  | Zaks, Fink, & Freedman, 1972 | Number of positive UOS | 2x/week | Not defined |
|  | Strain, Bigelow, Liebson, & Stitzer, 1999 | 1) Intent-to-treat analysis: Overall rate of positive UOS; 2) Retained sample: Three-weekly rate of positive UOS for patients who remained in treatment to the end of the stable dosing phase | 2x/week | Missing/not imputed |
|  | Petitjean et al., 2001 | Weekly proportion of positive UOS (intent-to-treat and completer analysis) | weekly | Positive |
|  | Shufman et al., 1994 | Percentage of positive UOS | Weekly | Missing1 |
|  | Krupitsky et al., 2004 | Number of positive UOS among retained sample at each time point | biweekly | Not defined |
|  | Strain, Stitzer, Liebson, & Bigelow, 1994 | Overall rate of positive UOS | 3x/week | Missing/not imputed |
|  | Fischer et al., 1999 | Percent positive UOS in 8 successive 3-week intervals | weekly; twice weekly in the first 3 weeks of the study | Positive |
| **Rate of negative UOS** | Strang et al., 2010 | ≥50% negative UOS during weeks 14-26 | weekly | Positive6 |
|  | (Kosten et al., 1993) | ≥70% negative UOS during the 24-week trial period | weekly | Missing/not imputed |
|  | Ling et al., 2010 | Percentage of negative UOS during weeks 1-16 of the trial | 3×/week | Positive |
|  | Mattick et al., 2003 | “Percentage of clean urines (PCU)”: Rate of negative UOS for the time that the patient remained in the study *AND* “treatment effectiveness percentage (TEP)”: Rate of negative UOS for the full 13‐week study (ITT) | biweekly | Missing/not imputed |
|  | Fiellin et al., 2006 | Percentage of negative UOS | weekly | Positive |
|  | Tanum et al., 2017 | Rate of negative UOS: Number of negative UOS divided by the total number of attended tests (group proportion) | weekly | Positive |
|  | Haight et al., 2019 | Percentage of negative UOS from week 5 to week 24 | weekly | Positive |
|  | Lofwall et al., 2018 | Mean percentage of negative UOS for weeks 1 to 24 | weeks 1‐12, 16, 20, and 24; plus 3 random visits during weeks 12‐24 | Positive |
|  | Strang et al., 2019 | Proportion of negative UOS at the end of the 12‐week post-randomization time point | 3x/week | Positive7 |
|  | Comer et al., 2006 | Percentage of negative UOS during 8 weeks of treatment | 2x/week | Positive |
|  | Kamien, Branstetter, & Amass, 2008 | Percentage of negative UOS per week | 3x/week | Positive |
|  | Wolstein et al., 2009 | Number of negative UOS per number of weeks of study participation | weekly | *No access to full text* |
|  | Kosten, Schottenfeld, Ziedonis, & Falcioni, 1993 | Weekly percentage of negative UOS (ITT, completer, and efficacy [patients remaining for at least 1 week of the medication dosage] analysis) | weekly | Missing/not imputed |
|  | Ling et al., 1998 | Mean percentage negative UOS *AND* mean no. of negative UOS (“treatment effectiveness score”) | 3x/week | Missing/not imputed |
|  | Pani, Maremmani, Pirastu, Tagliamonte, & Gessa, 2000 | PCC: Percentage ratio of negative UOS and the total number of UOS carried out for each patient during the period of treatment *AND* TEC: Percentage ratio between the number of negative UOS and the number of UOS as per protocol | weekly | Positive |
|  | Preston, Umbricht, & Epstein, 2000 | “Mean intervention percent negative”: Percentage of negative UOS in the treatment phase | 3x/week | Positive |
|  | Schottenfeld et al., 2005 | Proportion of negative UOS | 3x/week | Missing |
|  | Fudala et al., 2003 | Percentage of negative UOS | 3x/week | Missing |
|  | Jaffe et al., 1972 | Percentage of treatment weeks characterized by negative UOS for patients who completed ≥8 weeks of the study | 3x/week | Imputed8 |
|  | Johnson et al., 1992 | Average percentage of negative UOS | 3x/week | Positive |

ITT: Intention to Treat; UOS: Urine Opioid Screen

1For the assessment of urine tests, patients were divided into four subgroups, each providing a similar number of urine tests (1-3, 4-5, 6-7, above 8 analyses).

2Missing urine test data were imputed by randomly generated binary outcome (positive or negative for opioid use) using a 20% relative penalty against the buprenorphine implant group based on urine test results from each group.

3A missing urine test result is handled in exactly the same manner as a positive urine test except that it is not weighted as heavily. A positive urine test in the last eight weeks would be weighted 5 1 = 5; a missing value would be weighted 5 x 0.22 = 1.1.

4A pattern-mixture model was used to assess the impact of missing data on urine test results.

5The percentages of opioid-positive urine specimens were calculated for each patient based on all available specimens in each week. Where urinalysis data were missing for an entire week the average of that patient's results from the 2 weeks surrounding the missing week was substituted for the missing value.

6Missing data were handled with multiple imputation for cases in which urine samples were missing because of hospital admission, imprisonment, agreed absence (holiday), safety reasons, or clinical omission or error (e.g., leakage, no label, failure to ask patient for sample, sample not sent for analysis). Urine samples that were not provided because of non-compliance (refusal to provide or unplanned failure to attend) were presumed to be positive.

7It was proposed that urine samples be recorded as positive if patients did not attend (or refused) clinic visits or refused to give urine samples. It was planned to impute missing values for the urine samples, provided there was a reasonable assumption that the missing data mechanism was ignorable (i.e. at least ‘missing at random’).

8Estimates were calculated by averaging all of a patient's available scores for the day (e.g., Mondays) which correspond to the missing day.

**References**

Biondi, B. E., Zheng, X., Frank, C. A., Petrakis, I., & Springer, S. A. (2020). A Literature Review Examining Primary Outcomes of Medication Treatment Studies for Opioid Use Disorder: What Outcome Should Be Used to Measure Opioid Treatment Success? *The American Journal on Addictions*, *29*(4), 249–267. https://doi.org/10.1111/ajad.13051

Comer, S. D., Sullivan, M. A., Yu, E., Rothenberg, J. L., Kleber, H. D., Kampman, K., Dackis, C., & O’Brien, C. P. (2006). Injectable, Sustained-Release Naltrexone for the Treatment of Opioid Dependence. *Archives of General Psychiatry*, *63*(2), 210. https://doi.org/10.1001/archpsyc.63.2.210

Dennis, B. B., Sanger, N., Bawor, M., Naji, L., Plater, C., Worster, A., Woo, J., Bhalerao, A., Baptist-Mohseni, N., Hillmer, A., Rice, D., Corace, K., Hutton, B., Tugwell, P., Thabane, L., & Samaan, Z. (2020). A call for consensus in defining efficacy in clinical trials for opioid addiction: combined results from a systematic review and qualitative study in patients receiving pharmacological assisted therapy for opioid use disorder. *Trials*, *21*(1), 30. https://doi.org/10.1186/s13063-019-3995-y

Eissenberg, T., Bigelow, G. E., Strain, E. C., Walsh, S. L., Brooner, R. K., Stitzer, M. L., & Johnson, R. E. (1997). Dose-related efficacy of levomethadyl acetate for treatment of opioid dependence: A randomized clinical trial. *Journal of the American Medical Association*. https://doi.org/10.1001/jama.277.24.1945

Fiellin, D. A., Pantalon, M. V., Chawarski, M. C., Moore, B. A., Sullivan, L. E., O’Connor, P. G., & Schottenfeld, R. S. (2006). Counseling plus Buprenorphine–Naloxone Maintenance Therapy for Opioid Dependence. *New England Journal of Medicine*. https://doi.org/10.1056/nejmoa055255

Fischer, G., Gombas, W., Eder, H., Jagsch, R., Peternell, A., Stühlinger, G., Pezawas, L., Aschauer, H. N., & Kasper, S. (1999). Buprenorphine versus methadone maintenance for the treatment of opioid dependence. *Addiction*. https://doi.org/10.1046/j.1360-0443.1999.94913376.x

Fudala, P. J., Bridge, T. P., Herbert, S., Williford, W. O., Chiang, C. N., Jones, K., Collins, J., Raisch, D., Casadonte, P., Goldsmith, R. J., Ling, W., Malkerneker, U., McNicholas, L., Renner, J., Stine, S., & Tusel, D. (2003). Office-Based Treatment of Opiate Addiction with a Sublingual-Tablet Formulation of Buprenorphine and Naloxone. *New England Journal of Medicine*. https://doi.org/10.1056/nejmoa022164

Haight, B. R., Learned, S. M., Laffont, C. M., Fudala, P. J., Zhao, Y., Garofalo, A. S., Greenwald, M. K., Nadipelli, V. R., Ling, W., Heidbreder, C., Andersen, J. L., Bailey, G. L., Bartley, S. R., Biunno, M. J., Boyett, B., Carr, J. M., Cifuentes, E., Duarte-Sckell, S. D., Dueno, O. R., … Wiest, K. L. (2019). Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*. https://doi.org/10.1016/S0140-6736(18)32259-1

Jaffe, J. H., Senay, E. C., Schuster, C. R., Renault, P. R., Smith, B., & Dimenza, S. (1972). Methadyl Acetate vs Methadone: A Double-Blind Study in Heroin Users. *JAMA: The Journal of the American Medical Association*. https://doi.org/10.1001/jama.1972.03210040013004

Johnson, R. E., Jaffe, J. H., & Fudala, P. J. (1992). A Controlled Trial of Buprenorphine Treatment for Opioid Dependence. *JAMA: The Journal of the American Medical Association*. https://doi.org/10.1001/jama.1992.03480200058024

Kamien, J. B., Branstetter, S. A., & Amass, L. (2008). Buprenorphine-naloxone versus methadone maintenance therapy: A randomised double-blind trial with opioid-dependent patients. *Heroin Addiction and Related Clinical Problems*, *10*(4), 5–18.

Kosten, T. R., Schottenfeld, R., Ziedonis, D., & Falcioni, J. (1993). Buprenorphine versus methadone maintenance for opioid dependence. *Journal of Nervous and Mental Disease*. https://doi.org/10.1097/00005053-199306000-00004

Krupitsky, E. M., Zvartau, E. E., Masalov, D. V., Tsoi, M. V., Burakov, A. M., Egorova, V. Y., Didenko, T. Y., Romanova, T. N., Ivanova, E. B., Bespalov, A. Y., Verbitskaya, E. V., Neznanov, N. G., Grinenko, A. Y., O’Brien, C. P., & Woody, G. E. (2004). Naltrexone for heroin dependence treatment in St. Petersburg, Russia. *Journal of Substance Abuse Treatment*. https://doi.org/10.1016/j.jsat.2004.02.002

Krupitsky, E. M., Zvartau, E. E., Masalov, D. V., Tsoy, M. V., Burakov, A. M., Egorova, V. Y., Didenko, T. Y., Romanova, T. N., Ivanova, E. B., Bespalov, A. Y., Verbitskaya, E. V., Neznanov, N. G., Grinenko, A. Y., O’Brien, C. P., & Woody, G. E. (2006). Naltrexone with or without fluoxetine for preventing relapse to heroin addiction in St. Petersburg, Russia. *Journal of Substance Abuse Treatment*. https://doi.org/10.1016/j.jsat.2006.05.005

Krupitsky, E., Nunes, E. V., Ling, W., Illeperuma, A., Gastfriend, D. R., & Silverman, B. L. (2011). Injectable extended-release naltrexone for opioid dependence: A double-blind, placebo-controlled, multicentre randomised trial. *The Lancet*. https://doi.org/10.1016/S0140-6736(11)60358-9

Lee, J. D., Friedmann, P. D., Kinlock, T. W., Nunes, E. V., Boney, T. Y., Hoskinson, R. A., Wilson, D., McDonald, R., Rotrosen, J., Gourevitch, M. N., Gordon, M., Fishman, M., Chen, D. T., Bonnie, R. J., Cornish, J. W., Murphy, S. M., & O’Brien, C. P. (2016). Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders. *New England Journal of Medicine*. https://doi.org/10.1056/nejmoa1505409

Lee, J. D., Nunes, E. V, Novo, P., Bachrach, K., Bailey, G. L., Bhatt, S., Farkas, S., Fishman, M., Gauthier, P., Hodgkins, C. C., King, J., Lindblad, R., Liu, D., Matthews, A. G., May, J., Peavy, K. M., Ross, S., Salazar, D., Schkolnik, P., … Rotrosen, J. (2018). Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *The Lancet*, *391*(10118), 309–318. https://doi.org/10.1016/S0140-6736(17)32812-X

Ling, W., Casadonte, P., Bigelow, G., Kampman, K. M., Patkar, A., Bailey, G. L., Rosenthal, R. N., & Beebe, K. L. (2010). Buprenorphine implants for treatment of opioid dependence: A randomized controlled trial. *JAMA - Journal of the American Medical Association*. https://doi.org/10.1001/jama.2010.1427

Ling, W., Charuvastra, C., Collins, J. F., Batki, S., Brown, L. S., Kintaudi, P., Wesson, D. R., Mcnicholas, L., Tusel, D. J., Malkerneker, U., Renner, J. A., Santos, E., Casadonte, P., Fye, C., Stine, S., Wang, R. I. H., & Segal, D. (1998). Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction*, *93*(4), 475–486. https://doi.org/10.1046/j.1360-0443.1998.9344753.x

Ling, W., Charuvastra, V. C., Kaim, S. C., & Klett, C. J. (1976). Methadyl Acetate and Methadone as Maintenance Treatments for Heroin Addicts: A Veterans Administration Cooperative Study. *Archives of General Psychiatry*. https://doi.org/10.1001/archpsyc.1976.01770060043007

Lofwall, M. R., Walsh, S. L., Nunes, E. V., Bailey, G. L., Sigmon, S. C., Kampman, K. M., Frost, M., Tiberg, F., Linden, M., Sheldon, B., Oosman, S., Peterson, S., Chen, M., & Kim, S. (2018). Weekly and monthly subcutaneous buprenorphine depot formulations vs daily sublingual buprenorphine with naloxone for treatment of opioid use disorder a randomized clinical trial. *JAMA Internal Medicine*. https://doi.org/10.1001/jamainternmed.2018.1052

Mattick, R. P., Ali, R., White, J. M., O’Brien, S., Wolk, S., & Danz, C. (2003). Buprenorphine versus methadone maintenance therapy: A randomized double-blind trial with 405 opioid-dependent patients. *Addiction*. https://doi.org/10.1046/j.1360-0443.2003.00335.x

Mokri, A., Chawarski, M. C., Taherinakhost, H., & Schottenfeld, R. S. (2016). Medical treatments for opioid use disorder in Iran: A randomized, double-blind placebo-controlled comparison of buprenorphine/naloxone and naltrexone maintenance treatment. *Addiction*. https://doi.org/10.1111/add.13259

Pani, P., Maremmani, I., Pirastu, R., Tagliamonte, A., & Gessa, G. (2000). Buprenorphine: a controlled clinical trial in the treatment of opioid dependence. *Drug and Alcohol Dependence*. https://doi.org/10.1016/s0376-8716(99)00140-4

Petitjean, S., Stohler, R., Déglon, J. J., Livoti, S., Waldvogel, D., Uehlinger, C., & Ladewig, D. (2001). Double-blind randomized trial of buprenorphine and methadone in opiate dependence. *Drug and Alcohol Dependence*. https://doi.org/10.1016/S0376-8716(00)00163-0

Preston, K. L., Umbricht, A., & Epstein, D. H. (2000). Methadone Dose Increase and Abstinence Reinforcement for Treatment of Continued Heroin Use During Methadone Maintenance. *Archives of General Psychiatry*, *57*(4), 395. https://doi.org/10.1001/archpsyc.57.4.395

Rosenthal, R. N., Lofwall, M. R., Kim, S., Chen, M., Beebe, K. L., & Vocci, F. J. (2016). Effect of buprenorphine implants on illicit opioid use among abstinent adults with opioid dependence treated with sublingual buprenorphine a randomized clinical trial. *JAMA - Journal of the American Medical Association*. https://doi.org/10.1001/jama.2016.9382

Schottenfeld, R. S., Chawarski, M. C., & Mazlan, M. (2008). Maintenance treatment with buprenorphine and naltrexone for heroin dependence in Malaysia: a randomised, double-blind, placebo-controlled trial. *The Lancet*, *371*(9631), 2192–2200. https://doi.org/10.1016/S0140-6736(08)60954-X

Schottenfeld, R. S., Chawarski, M. C., Pakes, J. R., Pantalon, M. V., Carroll, K. M., & Kosten, T. R. (2005). Methadone versus buprenorphine with contingency management or performance feedback for cocaine and opioid dependence. *American Journal of Psychiatry*. https://doi.org/10.1176/appi.ajp.162.2.340

Schwartz, R. P., Highfield, D. A., Jaffe, J. H., Brady, J. V., Butler, C. B., Rouse, C. O., Callaman, J. M., O’Grady, K. E., & Battjes, R. J. (2006). A randomized controlled trial of interim methadone maintenance. *Archives of General Psychiatry*. https://doi.org/10.1001/archpsyc.63.1.102

Sees, K. L., Delucchi, K. L., Masson, C., Rosen, A., Clark, H. W., Robillard, H., Banys, P., & Hall, S. M. (2000). Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence: A randomized controlled trial. *Journal of the American Medical Association*. https://doi.org/10.1001/jama.283.10.1303

Shufman, E. N., Porat, S., Witztum, E., Gandacu, D., Bar-Hamburger, R., & Ginath, Y. (1994). The efficacy of naltrexone in preventing reabuse of heroin after detoxification. *Biological Psychiatry*. https://doi.org/10.1016/0006-3223(94)91240-8

Soyka, M., Zingg, C., Koller, G., & Kuefner, H. (2008). Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: Results from a randomized study. *International Journal of Neuropsychopharmacology*. https://doi.org/10.1017/S146114570700836X

Strain, E. C., Stitzer, M. L., Liebson, I. A., & Bigelow, G. E. (1993). Dose-response effects of methadone in the treatment of opioid dependence. *Annals of Internal Medicine*. https://doi.org/10.7326/0003-4819-119-1-199307010-00004

Strain, Eric C., Bigelow, G. E., Liebson, I. A., & Stitzer, M. L. (1999). Moderate- vs high-dose methadone in the treatment of opioid dependence: A randomized trial. *Journal of the American Medical Association*. https://doi.org/10.1001/jama.281.11.1000

Strain, Eric C., Stitzer, M. L., Liebson, I. A., & Bigelow, G. E. (1994). Comparison of buprenorphine and methadone in the treatment of opioid dependence. *American Journal of Psychiatry*. https://doi.org/10.1176/ajp.151.7.1025

Strain, Eric C., Stitzer, M. L., Liebson, I. A., & Bigelow, G. E. (1996). Buprenorphine Versus Methadone in the Treatment of Opioid Dependence: Self-Reports, Urinalysis and Addiction Severity Index. *Journal of Clinical Psychopharmacology*. https://doi.org/10.1097/00004714-199602000-00010

Strang, J., Kelleher, M., Mayet, S., Day, E., Hellier, J., Byford, S., Murphy, C., McLennan, B., Shearer, J., Ryan, E., & Marsden, J. (2019). Extended-release naltrexone versus standard oral naltrexone versus placebo for opioid use disorder: The NEAT three-arm RCT. *Health Technology Assessment*. https://doi.org/10.3310/hta23030

Strang, J., Metrebian, N., Lintzeris, N., Potts, L., Carnwath, T., Mayet, S., Williams, H., Zador, D., Evers, R., Groshkova, T., Charles, V., Martin, A., & Forzisi, L. (2010). Supervised injectable heroin or injectable methadone versus optimised oral methadone as treatment for chronic heroin addicts in England after persistent failure in orthodox treatment (RIOTT): a randomised trial. *The Lancet*. https://doi.org/10.1016/S0140-6736(10)60349-2

Tanum, L., Solli, K. K., Latif, Z. E. H., Benth, J. Š., Opheim, A., Sharma-Haase, K., Krajci, P., & Kunøe, N. (2017). Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: A randomized clinical noninferiority trial. *JAMA Psychiatry*. https://doi.org/10.1001/jamapsychiatry.2017.3206

Wolstein, J., Gastpar, M., Finkbeiner, T., Heinrich, C., Heitkamp, R., Poehlke, T., & Scherbaum, N. (2009). A randomized, open-label trial comparing methadone and Levo-Alpha- Acetylmethadol (LAAM) in maintenance treatment of opioid addiction. *Pharmacopsychiatry*. https://doi.org/10.1055/s-0028-1083818

Woody, G. E., Poole, S. A., Subramaniam, G., Dugosh, K., Bogenschutz, M., Abbott, P., Patkar, A., Publicker, M., McCain, K., Potter, J. S., Forman, R., Vetter, V., McNicholas, L., Blaine, J., Lynch, K. G., & Fudala, P. (2008). Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth A randomized trial. *JAMA - Journal of the American Medical Association*. https://doi.org/10.1001/jama.2008.574

Zaks, A., Fink, M., & Freedman, A. M. (1972). Levomethadyl in Maintenance Treatment of Opiate Dependence. *JAMA: The Journal of the American Medical Association*. https://doi.org/10.1001/jama.1972.03200060039005