High-impact Papers Regarding Substance Use Disorder Treatment

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Alcohol use disorder

Article	Authors, Date, Journal	Key Points
Naltrexone in the treatment of alcohol dependence	Volpicelli et al, 1992 *Arch Gen Psych*	• Objective: To assess the effectiveness and safety of naltrexone hydrochloride as an adjunctive treatment in reducing alcohol craving, decreasing alcohol consumption, and preventing relapse in alcohol-dependent patients. • Design: 70 male alcohol-dependent patients participated in a 12-week double-blind placebo-controlled trial of adjunctive naltrexone (50mg/day) treatment following inpatient managed withdrawal. • Outcome: Nineteen (95%) of the 20 placebo-treated patients relapsed after they sampled alcohol, while only eight (50%) of 16 naltrexone-treated patients exposed to alcohol relapsed. • Conclusion: Naltrexone hydrochloride is a safe and effective adjunct to treatment for alcohol-dependent individuals, particularly in reducing alcohol craving, decreasing consumption, and preventing relapse.

Individualized treatment for alcohol withdrawal. A randomized double-blind controlled trial	Saitz et al, 1994 *JAMA*	• Objective: To assess the effect of an individualized treatment regimen on the intensity and duration of medication treatment for alcohol withdrawal.
		• Design: 101 patients enrolled in an RCT at the VA received either chlordiazepoxide 4x daily with additional medications as needed (fixed-schedule therapy) or chlordiazepoxide in response to development of signs and symptoms of alcohol withdrawal (symptom-triggered).
		• Outcome:
		  ○ Median duration of treatment in the symptom-triggered group was 9 hours compared with 68 hours in the fixed-schedule group.
		  ○ The symptom-triggered group received 100mg of chlordiazepoxide and the fixed schedule group received 425mg ($P < .001$).
		• Conclusion: Symptom-triggered therapy personalizes treatment, reduces duration, benzodiazepine use, and is equally effective as fixed-schedule therapy for alcohol withdrawal.

Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline.	Mayo-Smith, 1997
	JAMA
		• Objective: To create evidence-based guidelines for managing alcohol withdrawal pharmacologically, focusing on benzodiazepines' effectiveness and individualized treatment based on withdrawal severity.
		• Design: A meta-analysis of English-language articles published before July 1, 1995, on the pharmacological management of alcohol withdrawal.
		• Outcome:
		  ○ Benzodiazepines reduced withdrawal severity, incidence of delirium (-4.9 cases per 100 patients; 95% confidence interval, -9.0 to -0.7; P=.04), and reduce seizures (-7.7 seizures per 100 patients; 95% confidence interval, -12.0 to -3.5; P=.003).
		  ○ Individualizing therapy with withdrawal scales resulted in administration of significantly less medication and shorter treatment (P<.001).
		• Conclusion: Benzodiazepines are suitable for alcohol withdrawal treatment, with individualized dosages based on withdrawal severity, comorbid conditions, and history of withdrawal seizures, while other agents like beta-blockers, clonidine, carbamazepine, and neuroleptics may serve as adjunctive therapy but not recommended as monotherapy.

Twelve-step and cognitive-behavioral treatment for substance abuse: a comparison of treatment effectiveness	Ouimette et al, 1997
	J Consult Clin Psychol
		• Objective: To compare the effectiveness of 12-step and cognitive-behavioral (C-B) models of substance abuse treatment among patients.
		• Design: Comparative effectiveness of 12-step and cognitive-behavioral models of substance abuse treatment was examined among 3,018 patients from 15 programs at the U.S. VAMC.
		• Outcome:
		  ○ Effectiveness study showing similar overall outcomes but superior 1-year alcohol abstinence for 12-step vs CBT.
		  ○ Those mandated to treatment or with co-occurring mental illness (previously thought to be signs of poor prognosis) were shown to have similar outcomes.
		• Conclusion: 12-step, cognitive-behavioral (C-B), and combined 12-Step-C-B treatment programs are equally effective in reducing substance use and improving various aspects of functioning among patients, regardless of the specific treatment program type, patient subgroups, or mandates for treatment. This supports the effectiveness of 12-step treatment approaches in substance abuse treatment.

Project MATCH secondary a priori hypotheses.	1997
	Addiction
		• Objective: To assess whether matching alcohol-dependent clients to three different treatments based on specific client attributes improves treatment outcomes, and to discuss the implications of these findings in the context of previous matching hypotheses from Project MATCH.
		• Design: Patient randomly assigned to one of three 12-week manual-guided individual treatments: CBT, MET, or TSF.
		• Outcome:
		  ○ Patients higher in anger and treated in MET had better post-treatment drinking than in CBT.
		  ○ Aftercare clients high in alcohol dependence had better post-treatment outcomes in TSF; low dependence clients did better in CBT.
		• Conclusion: While certain client attributes, such as anger and alcohol dependence, should be considered when assigning clients to specific treatments, overall, matching effects contrasting CBT, MET, and TSF are not consistently robust, suggesting the need for a more comprehensive theory of matching.

Matching Alcoholism treatments to clien heterogeneity: treatment main effects and matching effects on drinking during treatment	1998 *J Stud Alcohol.*	• Objective: To examine client drinking and psychosocial functioning during alcoholism treatment, specifically focusing on the effects of three Project MATCH treatments, the prognostic value of client attributes used in matching hypotheses, and the interaction effects between attributes and treatments. • Design: Outpatient (n=952) and aftercare (n=774) patients were randomized to either Cognitive Behavioral Coping Skills Therapy (CBT), Motivational Enhancement Therapy (MET) or Twelve-Step Facilitation Therapy (TSF) over 12-week treatment phase. • Outcome: Forty-one percent (41%) of CBT and TSF clients were abstinent or drank moderately without alcohol-related consequences, compared with 28% of MET clients. Tests of 10 a priori primary client-treatment matching hypotheses failed to find any interaction effects that had an impact on drinking throughout the treatment phase. • Conclusion: In the outpatient setting, CBT or TSF may temporarily outperform MET in reducing heavy drinking and alcohol-related consequences, making CBT or TSF preferable choices when rapid reduction in alcohol-related problems is needed.
Naltrexone decreases	O'Malley et al, 2002	• Objective: To investigate the mechanisms by which naltrexone, an opioid

craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamo-pituitary-adrenocortical axis	*Psychopharm*	antagonist, reduces the risk of relapse to heavy drinking in individuals with alcohol dependence, with a focus on understanding its effects on craving and endocrine responses during alcohol self-administration. ● Design: 18 alcohol-dependent non-treatment seeking volunteers randomized to 50mg naltrexone or placebo for 6 days. ● Outcome: ○ Naltrexone treatment resulted in higher cortisol levels and lower levels of craving than placebo treatment. ○ Naltrexone-treated subjects drank fewer drinks, consumed them more slowly, and reported lower levels of alcohol craving during alcohol self-administration. ● Conclusion: Naltrexone effectively reduces alcohol craving and the amount of alcohol consumed in alcohol-dependent individuals, possibly by suppressing craving for alcohol and activating the hypothalamo-pituitary-adrenocortical axis.
Oral topiramate for treatment of alcohol dependence: a randomised controlled trial	Johnson et al, 2003 *Lancet*	● Objective: To determine whether topiramate is more effective than placebo as a treatment for alcohol dependence. ● Design: 12-week double-blind randomised clinical trial comparing oral topiramate and placebo for treatment of 150 individuals with alcohol dependence. 75 were assigned topiramate (escalating dose of 25-300mg per day) and 75 with placebo as adjunct to weekly standardized medication compliance management. ● Outcome: ○ Topiramate led to 2.88 (95% CI -4.50 to -1.27) fewer drinks per day, 3.10 fewer drinks per drinking day (p=0.0009), 27.6% fewer heavy drinking days (0.0003), 26.2% more days abstinence (p=0.0003). ○ Topiramate-induced differences in craving were also significantly greater than those of placebo. ● Conclusion: Topiramate, as an adjunct to medication compliance management, is more effective than a placebo in the treatment of alcohol dependence, as it significantly reduces drinking behavior, craving, and objective measures of alcohol consumption.
Combined pharmacotherapies	Anton et al, 2004 *JAMA*	● Objective: To evaluate the efficacy of medication (naltrexone and acamprosate), behavioral therapies, and their combinations in the treatment

and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial		of alcohol dependence, along with assessing the impact of placebo effect on treatment outcomes, particularly in primary care and nonspecialty settings. ● Design: RCT conducted among 1383 recently alcohol-abstinent volunteer from 11 US academic sites. Eight groups of patients received medical management with 16 weeks of naltrexone (100mg/d) or acamprosate (3g/d), both, and/or both placebos, with or without a combined behavioral intervention. A ninth group received combined behavioral intervention (CBI) only. ● Outcome: ○ All groups showed substantial reduction in drinking, though patients receiving naltrexone plus medical management, CBI plus medical management and placebo, or both naltrexone and CBI plus medical management had higher percentage days abstinent than those receiving placebos and medical management only. ○ Naltrexone was particularly effective in reducing the risk of heavy drinking days. ● Conclusion: Naltrexone and combined behavioral intervention (CBI), either individually or in combination, are effective treatments for alcohol dependence in healthcare settings, while acamprosate did not show significant efficacy, and placebo pills with healthcare professional meetings had a positive but temporary effect on outcomes.
Topiramate for treating alcohol dependence: a randomized controlled trial	Johnson et al, 2007 *JAMA*	● Objective: To determine whether topiramate is a safe and effective treatment for alcohol dependence. ● Design: Double-blind randomized, placebo-controlled, 14-week trial of 371 men and women aged 18 to 65 years diagnosed with alcohol dependence. ● Outcome: ○ Topiramate (300mg/d, n=183) performed better than placebo (n=188) at reducing % of heavy drinking days from baseline to week 14 (mean difference, 8.44%; 95% confidence interval, 3.07%-13.80%; *P=.002*). Prespecified mixed-model analysis also showed that topiramate compared with placebo decreased the percentage of heavy drinking days. ○ Adverse events that were more common with topiramate vs placebo, respectively, included paresthesia (50.8% vs 10.6%), taste perversion (23.0% vs 4.8%), anorexia (19.7% vs 6.9%), and difficulty with

		concentration (14.8% vs 3.2%). ● Conclusion: Topiramate is a promising treatment for alcohol dependence, significantly reducing the percentage of heavy drinking days and other drinking measures.
Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful?	Maisel et al, 2012 *Addiction*	● Objective: To examine the nuanced efficacy of naltrexone and acamprosate in the treatment of alcohol use disorders by considering their relative effectiveness in promoting abstinence versus reducing heavy drinking. ● Design: A systematic review of 64 randomized, placebo-controlled English language trials completed between 1970 and 2009 focused on acamprosate or naltrexone. ● Outcome: ○ Acamprosate had a significantly larger effect size than naltrexone on the maintenance of abstinence and naltrexone had a larger effect size than acamprosate on reduction of heavy drinking and craving. ○ For naltrexone, requiring abstinence before the trial was associated with larger effect sizes for abstinence maintenance and reduced heavy drinking compared to placebo. ○ For acamprosate, detoxification before medication administration was associated with better abstinence outcomes compared to placebo. ● Conclusion: Acamprosate appears slightly more effective in promoting abstinence, while naltrexone is slightly more effective in reducing heavy drinking and craving in the treatment of alcohol use disorders, and specific implementation strategies, such as detoxification and required abstinence periods, can further enhance the efficacy of these medications.
Efficacy of Gabapentin for the Treatment of Alcohol Use Disorder in Patients with Alcohol WIthdrawal Symptoms	Anton et al, 2020 *JAMA Network Open*	● Objective: To examine whether gabapentin is a useful treatment for AUD, particularly in individuals with a history of alcohol withdrawal symptoms. ● Design: RCT comparing Gabapentin up to 1200mg/day compared to placebo. ● Outcome: ○ More gabapentin-treated individuals had no heavy drinking days (12 of 44 participants [27%]) compared with placebo (4 of 46 participants [9%]), a difference of 18.6% (95% CI, 3.1-34.1; *P* = .02; number needed to treat [NNT], 5.4). ○ More total abstinence (8 of 44 [18%]) in the gabapentin-treated individuals compared with placebo (2 of 46 [4%]), a difference of

		13.8% (95% CI, 1.0-26.7; *P* = .04; NNT, 6.2). ● Conclusion: Gabapentin may be most effective as a treatment for AUD in individuals with a history of alcohol withdrawal symptoms, showing significant benefits in reducing heavy drinking and promoting abstinence in this subgroup.

Additional resources:
ASAM Guideline for AUD
UptoDate on Management of Moderate and Severe Withdrawal Syndromes
VA DOD Substance Use Disorder Guidelines
APA Practice Guideline for the Pharmacological Treatment of Patients with Alcohol Use Disorder

Tobacco use disorder

Article	Authors, Date	Key Points
Pharmacological interventions for smoking cessation: an overview and network meta-analysis (Review)	Cahill et al, 2013 *Cochrane Database Systematic Review*	● Objective: To compare the effectiveness and safety of various smoking cessation treatments, and to assess the risks of adverse events associated with these treatments. ● Design: A systematic review of Cochrane reviews of randomized trials evaluating various smoking cessation treatments. ● Outcome: ○ NRT, bupropion, and varenicline all improve the chances of quitting, with a low risk of harm. ○ Combination use of NRT is as effective as varenicline, and more effective than single types of NRT. ○ Cytisine has potential as a safe, effective and affordable treatment. ○ Nortriptyline improves the chances of quitting, with little evidence of harmful events. ● NRT, bupropion, varenicline, and cytisine have demonstrated efficacy in improving smoking cessation rates, with combination NRT and varenicline being equally effective.

Trends in Smoking Among Adults With Mental Illness and Association Between Mental Health Treatment and Smoking Cessation	Benjamin Lê Cook et al, 2014 *JAMA*	• Objective: To study the relationship between mental health treatment and smoking cessation. • Design: Target population consisted of individuals with mental illness, known for higher tobacco use rates and nicotine dependence. Surveys were employed to compare smoking trends between adults with and without mental illness across various disorders. Additionally, the study assessed smoking cessation rates among adults with mental illness who had or had not received mental health treatment. • Outcome: Individuals with mental illness who received mental health treatment within the previous year were more likely to have quit smoking. Adjusted smoking rates declined significantly among individuals without mental illness ($P < .001$). • Conclusion: Between 2004 and 2011, smoking declined less among individuals with mental illness compared to those without, highlighting the need for more effective tobacco control policies and cessation interventions targeting this population, while those receiving mental health treatment showed greater quit rates.
Sleep changes in smokers before, during and 3 months after nicotine withdrawal	Jaehne et al, 2014 *Addiction Biology*	• Objective: To evaluate the relationship between sleep (via PSG) smoking, withdrawal, and after a period of abstinence. • Design: The study included 33 smokers and used polysomnography to monitor their sleep patterns during three phases: active smoking, nicotine withdrawal (24-36 hours after smoking), and 3 months after quitting. The goal was to investigate how sleep disturbances during nicotine withdrawal could affect smoking cessation. • Outcome: Smokers with a higher degree of dependence were characterized by less REM, a longer REM latency, and subjective sleep impairments. • Conclusion: Sleep disturbances during nicotine withdrawal may contribute to earlier relapse into smoking behaviors, particularly in individuals with more severe nicotine dependence.
ADHD, Altered Dopamine Neurotransmission, and Disrupted	Kollins et al, 2014 *Neuropsychopharmacol Biol Psychiatry*	• Objective: To investigate the relationship between ADHD, smoking, and dopamine neurotransmission to inform the development of improved prevention and treatment strategies for smoking in individuals with ADHD. • Design: A review of existing research on the relationship between ADHD,

Reinforcement Processes: Implications for Smoking and Nicotine Dependence		smoking, and dopamine neurotransmission. ● Outcome: ○ ADHD is an independent risk factor for smoking. ○ Dopamine-mediated disruptions may play a role in smoking behavior among individuals with ADHD. ○ One study reported that levels of self-reported ADHD symptoms in the presence of **DRD2 and Monoamine Oxidase A (MAO-A) genes** predicted risk of lifetime regular smoking.
Smoking-attributable medical expenditures by age, sex, and smoking status estimated using a relative risk approach	Maciosek et al, 2015 *Prev Med*	● Objective: Evaluate the smoking-attributable expenditures by age, gender, and cigarette smoking status. ● Design: ● Outcome: ○ Within each age group (35 yo - 75 yo +), the expenditures of former smokers are about 70% lower than current smokers. ○ Sex- and age-group-specific smoking expenditures reflect observed disease risk differences between current and former cigarette smokers. ● Conclusion: Approximately 70% of current smokers' medical care costs are preventable by quitting.
Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial	Anthenelli et al, 2016 *Lancet*	● Objective: Compare the relative neuropsychiatric safety risk and efficacy of varenicline and bupropion with nicotine patch and placebo in smokers with and without psychiatric disorders. ● Design: Randomized, double-blind, triple-dummy, placebo-controlled and active-controlled (nicotine patch; 21 mg per day with taper) trial of varenicline (1 mg twice a day) and bupropion (150 mg twice a day) for 12 weeks with 12-week non treatment follow up done at 140 centers. ● Outcome: ○ There was not a significant increase in neuropsychiatric adverse events attributable to varenicline or bupropion relative to nicotine patch or placebo. ○ Varenicline was superior to placebo, nicotine patch, and bupropion. ○ Bupropion and nicotine patch were only superior to placebo. ● Conclusion: Varenicline and bupropion did not significantly increase the risk of neuropsychiatric adverse events when compared to nicotine patch or placebo.

The Effects of the Nicotine Patch vs. Varenicline vs. Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Controlled Trial	Baker et al, 2016
	JAMA
		• Objective: To compare the efficacies of varenicline, combination nicotine replacement therapy (c-NRT), and the nicotine patch for 26-week quit rates.
		• Design - 1086 participants were randomized to 1 of 3 12 week smoking cessation pharmacotherapy groups (Nicotine patch, Varenicline, and c-NRT) with intention to treat trials. Six counseling sessions were offered as well.
		• Regimen for each treatment:
		  ○ Varenicline
		  ■ Pre-Quit: 0.5 mg pill 1/day x 3 days, 0.5 mg pill bid x 4 days, and 1 mg pill bid x 3 day.
		  ■ On Quit date: participants took 1 mg bid x 11 weeks.
		  ○ Nicotine Patch
		  ■ 8 weeks of 21mg, then 2 weeks of 14 mg, then 2 weeks of 7 mg
		  ■ If participants smoked 5-10 cigarettes per day: 14 mg x 10 weeks, then 7mg x 2 weeks.
		  ○ c-NRT
		  ■ As mentioned above under nicotine patch + 2mg OR 4mg based on morning smoking latency.
		  ■ Asked to use at least 5 lozenges per day x 12 weeks
		• Outcome: No significant differences in confirmed rates of smoking abstinence at 26 weeks.
		• Conclusion: This study raises questions about the relative effectiveness of smoking pharmacotherapies such as c-NRT.

Pharmacogenetics of smoking cessation	Chenoweth et al, 2017
	Trends Pharmacol Sci
		• Objective: Improve understanding of genetic variation in the pharmacological targets of nicotine and smoking cessation medications.
		• Design: A review of the literature.
		• Outcome:
		  ○ CYP2A6 is responsible for approximately 90% of nicotine's inactivation to cotinine.
		  ○ Individuals with slow rates of bupropion metabolism via *CYP2B6* genetics, may require a higher dose of bupropion.
		  ○ Individuals with genetically slow nicotine metabolism have higher cessation success with counseling and NRT compared to individuals with fast metabolism.

Tobacco and	2020	• Objective: To highlight the significant perinatal risks associated with tobacco

Nicotine Cessation During Pregnancy	*ACOG Committee Opinion*	use during pregnancy, emphasize the benefits of smoking cessation at any point during gestation, and provide guidance on counseling and interventions for pregnant women who continue to use tobacco products. ● Key points: ○ Perinatal risk associated with tobacco use during pregnancy include orofacial clefts, fetal growth restriction, placenta previa, placental abruption, preterm prelabor rupture of membranes, low birth weight, increased perinatal mortality, ectopic pregnancy, and decreased maternal thyroid function. ○ Nicotine crosses the placenta and intake in any form: cigarettes, e-cigarettes, cigars, hookah, vaping products, etc. ○ Patients may not equate alternative forms of nicotine (ie, e-cigarettes, and vaping products) with tobacco use. ○ 5 A's of Tobacco and Nicotine cessation - Ask, Advise, Assess, Assist, Arrange. ○ Pharmacotherapy ■ Chantix - Several small studies have not shown teratogenicity but, overall, data are limited. ■ Bupropion - Limited data on its use in pregnancy, but there is no known risk of fetal anomalies or adverse pregnancy effects with its use. ■ NRT
Measuring cotinine to monitor tobacco use and smoking cessation	Stubbs et al, 2021 *Current Psychiatry*	● Objective: To monitor tobacco use. ● Biomarker of choice: Cotinine. ● Unlike carbon monoxide in expired air, optimal cut-off points for cotinine are relatively uninfluenced by the prevalence of smoking in the population. ● Cotinine is a general metabolite found with the use of all nicotine products (tobacco use and nicotine replacement products) ○ Measuring nicotine-derived nitrosamine ketone (NNK) and its metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) can be helpful in making this distinction between tobacco use and NRT. ● No specific guidelines on how or when cotinine should be used. ● Clinical recommendations for obtaining a cotinine level ○ Routine screening can be helpful in detecting potential drug interactions between tobacco and psychotropics.

		○ Cotinine can be used for validating self report and/or severity.
Electronic Cigarettes for Smoking Cessation (Review)	Hartmann-Boyce et al, 2022 *Cochrane Database of Systematic Reviews*	● Objective: To examine the effectiveness, tolerability, and safety of using electronic cigarettes (ECs) to help people who smoke tobacco achieve long-term smoking abstinence. ● Design: A systematic review of randomized controlled trials (RCTs) and randomized cross-over trials, as well as uncontrolled intervention studies. ● Outcomes: ○ Nicotine e-cigarettes can help individuals to stop smoking for at least six months. ○ E-cigarettes were found to be more helpful than nicotine replacement therapy, and probably better than e-cigarettes without nicotine. ● Conclusion: ECs with nicotine increase quit rates compared to nicotine replacement therapy (NRT) and ECs without nicotine, with no evidence of serious harm, although further research is needed to confirm the effect size and safety.
Treatment of Tobacco Smoking A Review	Rigotti et al, 2022 *JAMA*	● Objective: This review summarizes current evidence regarding management of tobacco smoking in clinical practice. ● Design: A comprehensive review and synthesis of existing research, including meta-analyses and clinical trials. ● Key findings: ○ FDA treatments for smoking cessation: bupropion, varenicline, and 5 nicotine replacement products (patch, gum, lozenge, oral inhaler, and nasal spray). ○ Combining a nicotine patch with other NRT products is more effective than using a single NRT product. ○ Combining drugs with different mechanisms of action, such as varenicline and NRT, is more effective than using a single product. ○ Table 2 includes FDA approved medications, dosing recommendations, advantages and disadvantages. ○ Brief tobacco cessation intervention model for clinical practice provided in figure. ● Conclusion: Combining pharmacotherapy and behavioral support, with a preference for varenicline or combination nicotine replacement therapy (NRT),

		is recommended as the first-line approach.

Additional resources:
ASAM guidelines for tobacco cessation
NIDA Research report
Smoking and Mental Illness Among Adults in the United States
Black Box warning update on Chantix

Opioid use disorder

Article	Authors, Date	Key Points

Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence: a randomized controlled trial	Sees et al, 2000 *JAMA*	• Objective: To compare outcomes of patients with opioid dependence treated with Methadone Maintenance Treatment (MMT) vs an alternative treatment, psychosocially enriched 180-day methadone-assisted detoxification.
		• Design: A randomized controlled trial.
		• Outcome:
		  ○ MMT resulted in greater treatment retention (median, 438.5 vs 174.0 days) and lower heroin use rates than did detoxification.
		  ○ Cocaine use was more closely related to study dropout in detoxification than in MMT.
		• Conclusion: MMT is more effective in reducing heroin use and HIV risk behaviors compared to a psychosocially enriched 180-day methadone-assisted detoxification.

Comparative Effectiveness of Different Treatment Pathways for Opioid Use Disorder	Wakeman et al, 2000 *JAMA network open*	• Objective: To compare the real world effectiveness of various OUD treatment pathways utilizing overdose and opioid-related acute care use as proxies for OUD recurrence. • Design: Retrospective comparative effectiveness study. Compared 6 mutually exclusive treatment pathways, including (1) no treatment, (2) inpatient detoxification or residential services, (3) intensive behavioral health, (4)

		buprenorphine or methadone, (5) naltrexone, and (6) nonintensive behavioral health. ● Outcome: Only treatment with buprenorphine or methadone was associated with a reduced risk of overdose during 3-month (adjusted hazard ratio [AHR], 0.24; 95% CI, 0.14-0.41) and 12-month (AHR, 0.41; 95% CI, 0.31-0.55) follow-up as well as reduction in serious opioid-related acute care use during 3-month (AHR, 0.68; 95% CI, 0.47-0.99) and 12-month (AHR, 0.74; 95% CI, 0.58-0.95) follow-up. ● Conclusion: Treatment with buprenorphine or methadone is associated with reductions in overdose and serious opioid-related acute care use compared with other treatments for OUD.
Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone	Fudala et al, 2003 *The New England journal of medicine*	● Objective: To evaluate the safety and efficacy of a sublingual-tablet formulation of buprenorphine and naloxone combination and buprenorphine alone in an office-based setting. ● Design: A multicenter, randomized, placebo-controlled trial involving 326 opiate-addicted persons. ● Outcome: ○ Rates of adverse events were similar in the active-treatment and placebo groups. Hence, Buprenorphine and naloxone in combination and buprenorphine alone are safe and well tolerated. ○ Buprenorphine and naloxone in combination and buprenorphine alone reduce the use of opiates and the craving for opiates. ● Conclusion: Buprenorphine and naloxone in combination and buprenorphine alone are safe and effective in reducing opiate use and craving among opiate-addicted individuals in an office-based setting.
Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial	Comer et al, 2006 *Archives of general psychiatry*	● Objective: To evaluate the safety and efficacy of a sustained-release depot formulation of naltrexone in treating opioid dependence. ● Design: Randomized, double-blind, placebo-controlled. ● Outcome: ○ Retention in treatment and time to dropout were related to the dose of injectable naltrexone. ○ Adverse effects were minimal and generally mild.

		• Conclusion: The study provided new evidence of the feasibility, efficacy, and tolerability of long-lasting antagonist treatments for opioid dependence.
Methadone Maintenance vs. Methadone Taper During Pregnancy: Maternal and Neonatal Outcomes	Jones et al, 2008 *The American journal on addictions*	• Objective: To compare the effectiveness of different treatment approaches in opioid-dependent pregnant women. • Design: 5 intervention groups included: three-day methadone-assisted withdrawal [MAW] alone, three-day MAW followed by methadone maintenance [MM], seven-day MAW alone, seven-day MAW followed by MM, and continuous MM. • Outcome: ○ Patients in the three MM groups remained in treatment longer, attended more obstetrical visits, more often delivered at the program hospital compared to the two MAW alone groups. • Conclusion: Poor maternal outcomes were observed in the MAW alone groups, suggesting that methadone maintenance should be considered as the primary treatment approach for opioid-dependent pregnant women.

Neonatal Abstinence Syndrome after Methadone or Buprenorphine Exposure	Jones et al, 2010 *The New England journal of medicine*	• Objective: Buprenorphine and methadone were compared for use in the comprehensive care of 175 pregnant women with opioid dependency to assess the primary outcomes of neonates requiring treatment for neonatal abstinence syndrome (NAS), peak NAS score, total amount of morphine needed to treat NAS, length of hospital stay for neonates, and neonatal head circumference.
		• Design: A double-blind, double-dummy, flexible-dosing, randomized, controlled study at eight international sites.
		• Outcome:
		  ○ Neonates exposed to buprenorphine required significantly less morphine, had shorter hospital stays, and shorter duration of treatment for NAS compared to neonates exposed to methadone.
		  ○ No significant differences were observed between groups in other primary or secondary outcomes or in rates of maternal or neonatal adverse events.
		• Conclusion: Results support the use of buprenorphine as an acceptable treatment for opioid dependence in pregnant women.

Adjunctive counseling during	Weiss et al, 2011 *Archives of general*	• Objective: To evaluate the effectiveness of brief and extended buprenorphine-naloxone treatment, with different counseling intensities, for patients dependent

brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial	*psychiatry*	on prescription opioids, in reducing opioid use and informing clinical practice. ● Design: A randomized clinical trial that used a 2-phase adaptive treatment research design. Included a total of 653 patients at 10 US sites. ● Outcome: ○ Extended buprenorphine-naloxone treatment during phase 2 resulted in higher success rates (49.2%) compared to phase 1 (6.6%), with no difference between counseling conditions. ○ However, success rates dropped to 8.6% at week 24 after completing the buprenorphine-naloxone taper. Successful outcomes were more common while taking buprenorphine-naloxone than after tapering. ○ Chronic pain did not significantly affect outcomes, but a history of ever using heroin was associated with lower success rates during buprenorphine-naloxone treatment. ● Conclusion: Patients dependent on prescription opioids are more likely to reduce opioid use during buprenorphine-naloxone treatment. However, if tapered off buprenorphine-naloxone, even after 12 weeks of treatment, the likelihood of an unsuccessful outcome is high, even with counseling.
Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial	Krupitsky et al, 2011 *Lancet*	● Objective: To assess the efficacy, safety, and patient-reported outcomes of an injectable, once monthly extended-release formulation of the opioid antagonist naltrexone (XR-NTX) for treatment of patients with opioid dependence after detoxification. ● Design: A double-blind, placebo-controlled, randomised trial. ● Outcome: ○ XR-NTX group had significantly higher rates of confirmed abstinence, self-reported opioid-free days, lower craving scores, longer retention, and fewer cases of relapse compared to the placebo group. ○ XR-NTX was also well tolerated, with no severe adverse events reported. ● Conclusion: The study suggests that XR-NTX, in combination with psychosocial treatment, could be a promising new treatment option for opioid dependence.
Buprenorphine maintenance versus placebo or	Mattick et al, 2014 *The Cochrane database of*	● Objective: To compare buprenorphine maintenance to placebo and to methadone maintenance in the management of opioid dependence. ● Design: Included 31 RCTs of buprenorphine maintenance treatment versus

methadone maintenance for opioid dependence (Review)	*systematic reviews*	placebo or methadone in management of opioid-dependent persons. ● Outcome: ○ Buprenorphine was more effective than placebo in retaining participants in treatment at all doses, but only high doses were effective in suppressing illicit opioid use measured by urinalysis. ○ Methadone was found to be more effective than flexible-dose buprenorphine in retaining participants, but there was no difference in suppressing opioid use. Methadone was also more likely to retain participants than low-dose buprenorphine in fixed-dose studies, but there was no difference at medium and high doses. ○ Adverse events were similar between methadone and buprenorphine, except for a higher incidence of sedation with methadone. ● Conclusion: Buprenorphine is an effective medication for the maintenance treatment of heroin dependence, particularly at doses above 2 mg, but compared to methadone, it retains fewer people in treatment when doses are flexibly delivered and at low fixed doses. Methadone is superior to buprenorphine in retaining people in treatment, with no significant difference in suppressing illicit opioid use.
Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence A Randomized Clinical Trial	D'Onofrio et al, 2015 *JAMA*	● Objective: To test the efficacy of 3 interventions for opioid dependence: (1) screening and referral to treatment (referral); (2) screening, brief intervention, and facilitated referral to community-based treatment services (brief intervention); and (3) screening, brief intervention, ED-initiated treatment with buprenorphine/naloxone, and referral to primary care for 10-week follow-up (buprenorphine). ● Design: A randomized clinical trial involving 329 opioid-dependent patients. ● Outcome: ○ ED-initiated buprenorphine treatment led to a substantial increase in addiction treatment engagement, with 78% of patients involved in treatment 30 days after randomization, compared to 37% in the referral group and 45% in the brief intervention group. ○ It also notably reduced self-reported illicit opioid use from 5.4 days per week to 0.9 days, in contrast to reductions to 2.3 days in the referral group and 2.4 days in the brief intervention group. ○ However, it did not significantly change the rates of opioid-negative urine samples, with 57.6% in the buprenorphine group, 53.8% in the

		referral group, and 42.9% in the brief intervention group. ○ Furthermore, there were no substantial differences in HIV risk across the groups. ● Conclusion: ED-initiated buprenorphine treatment for opioid-dependent patients increased addiction treatment engagement, reduced illicit opioid use, and decreased inpatient addiction treatment use compared to referral and brief intervention, but it didn't significantly affect opioid-positive urine samples or HIV risk. Further replication is needed before widespread adoption.
Long-term outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study	Weiss et al, 2015 Drug and Alcohol Dependence	● Objective: To examine long-term treatment response and outcomes in individuals with prescription opioid dependence. ● Design: A longitudinal follow up study involving 365 out of 653 participants from the original Prescription Opioid Addiction Treatment Study (POATS). ● Outcome: ○ The results at the 42-month mark showed significant improvements. Approximately 31.7% of participants were abstinent from opioids and not on agonist therapy, 29.4% were receiving opioid agonist therapy without meeting symptom criteria for current opioid dependence, 7.5% were using illicit opioids while on agonist therapy, and the remaining 31.4% were using opioids without agonist therapy. ○ Participants who reported a history of heroin use at baseline were more likely to meet DSM-IV criteria for opioid dependence at the 42-month follow-up. ● Conclusion: ○ Engagement in agonist therapy was associated with a higher likelihood of abstaining from illicit opioids. ○ A minority of participants showed a worsening trajectory, marked by the initiation of heroin use and injection opioid use.
The Prescription Opioid Addiction Treatment Study: What have we learned	Weiss et al, 2016 *Drug and Alcohol Dependence*	● Objective: To assess the effectiveness of different treatment approaches for prescription opioid dependence and evaluate long-term outcomes. ● Design: A randomized clinical trial involving 653 patients. ● Outcome: ○ The addition of drug counseling to buprenorphine-naloxone and medical management did not show an overall benefit in the main trial analysis.

		○ During a 4-week taper and 8-week follow-up, only 7% of patients achieved a successful outcome (abstinence or near-abstinence from opioids). In comparison, 49% of patients achieved success when subsequently stabilized on buprenorphine-naloxone. ● Conclusion: Combining buprenorphine-naloxone with drug counseling did not provide an overall benefit in the short term but showed more encouraging results in the long term, influencing future treatment guidelines and research in prescription opioid dependence.
Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders	Lee et al, 2016 *The New England journal of medicine*	● Objective: To evaluate the effectiveness of extended-release naltrexone compared to usual treatment in preventing opioid relapse among adult criminal justice offenders in the United States. ● Design: Open label randomized trial. ● Outcome: ○ During the 24-week treatment phase, those assigned to extended-release naltrexone had a longer median time to relapse, a lower rate of relapse, and a higher rate of opioid-negative urine samples. However, at week 78, rates of opioid-negative urine samples were equal in both groups, and the rates of other secondary outcomes were not significantly different between the two groups. ○ There were no overdose events in the extended-release naltrexone group, compared to seven in the usual-treatment group. ● Conclusion: The study concludes that extended-release naltrexone was associated with a lower rate of opioid relapse, but its effects waned after treatment discontinuation.
Long-Acting Injectable Naltrexone Induction: A Randomized Trial of Outpatient Opioid Detoxification With Naltrexone Versus Buprenorphine	Sullivan et al, 2017 *The American journal of psychiatry*	● Objective: To compare the efficacy of two outpatient detoxification regimens, naltrexone-assisted detoxification and buprenorphine-assisted detoxification, for transitioning opioid-dependent adults to extended-release injection naltrexone while preventing relapse. ● Design: A randomized controlled trial. ● Outcome: ○ Participants assigned to naltrexone-assisted detoxification were significantly more likely to be successfully inducted to extended-release injection naltrexone (56.1%) compared to those in the buprenorphine-assisted detoxification condition (32.7%).

		○ Participants in the naltrexone-assisted detoxification group were more likely to receive the second injection at week 5 (50.0%) compared to the buprenorphine-assisted detoxification group (26.9%). ● Conclusion: A detoxification approach involving low-dose naltrexone, single-day buprenorphine dosing, and adjunctive medications is safe and effective for transitioning opioid-dependent adults to extended-release injection naltrexone, offering an alternative to high rates of attrition and relapse with agonist tapers.
Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Noninferiority Trial	Tanum et al, 2017 *JAMA*	● Objective: To determine whether treatment with extended-release naltrexone hydrochloride would be as effective as daily buprenorphine hydrochloride with naloxone hydrochloride in maintaining abstinence from heroin and other illicit substances in newly detoxified individuals. ● Design: A 12-week, multicenter, outpatient, open-label randomized clinical trial conducted at 5 urban addiction clinics. ● Outcome: The results of the study showed that extended-release naltrexone hydrochloride was as effective as daily buprenorphine hydrochloride with naloxone hydrochloride in maintaining short-term abstinence from heroin and other illicit substances in newly detoxified individuals. ● Conclusion: Extended-release naltrexone can be considered as a treatment option for opioid-dependent individuals in maintaining short-term abstinence from heroin and other illicit substances.
Medication for Opioid Use Disorder After Nonfatal Opioid Overdose and Association With Mortality: A Cohort Study	Larochelle et al, 2018 *Annals of internal medicine*	● Objective: To identify MOUD use after opioid overdose and its association with all-cause and opioid-related mortality. ● Design: A retrospective cohort study with more than 17000 persons who had a nonfatal opioid overdose between 2012 and 2014. ● Outcome: ○ All-cause mortality at 12 months was 4.7 deaths per 100 person-years, and opioid-related mortality was 2.1 deaths per 100 person-years. ○ Buprenorphine and Methadone Maintenance Treatment were associated with reductions in all-cause and opioid-related mortality. ○ No associations between naltrexone and all-cause mortality or opioid-related mortality were identified. (The few patients who remained on naltrexone experienced very low risk of overdose deaths but numbers were too small to obtain significance). ● Conclusion: A minority of opioid overdose survivors received medications for

		opioid use disorder (MOUD), but both buprenorphine and methadone maintenance treatment (MMT) were associated with reduced all-cause and opioid-related mortality, while naltrexone showed no significant associations with mortality outcomes.

Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial	Lee et al, 2018 *Lancet*	• Objectives: The study aimed to estimate the difference in opioid relapse-free survival between XR-NTX and sublingual buprenorphine-naloxone (BUP-NX) in individuals with opioid use disorder who had used non-prescribed opioids in the past 30 days.
		• Design: A 24-week, open-label, randomized controlled trial conducted at eight community-based inpatient services in the United States.
		• Outcome:
		  ○ XR-NTX had a harder time initiating patients (72%) compared to BUP-NX (94%).
		  ○ Overall, 65% on XR-NTX and 57% on BUP-NX relapsed within 24 weeks.
		  ○ BUP-NX showed more favorable results in opioid-negative urine samples and opioid-abstinent days.
		  ○ Self-reported opioid craving initially favored XR-NTX but converged with BUP-NX by week 24.
		  ○ Adverse events, including overdose, were similar between groups, with five fatal overdoses (two in XR-NTX and three in BUP-NX).
		• Conclusion: XR-NTX and BUP-NX had similar safety and effectiveness once successfully initiated, but fewer participants successfully initiated XR-NTX, negatively impacting overall relapse rates.

Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine With Naloxone for Treatment of Opioid Use Disorder: A Randomized Clinical	Lofwall et al, 2018 *JAMA internal medicine*	• Objective: To determine whether treatment involving novel weekly and monthly subcutaneous (SC) buprenorphine depot formulations is noninferior to a daily sublingual (SL) combination of buprenorphine hydrochloride and naloxone hydrochloride in the treatment of opioid use disorder. • Design: An outpatient, double-blind, double-dummy randomized clinical trial conducted at 35 sites in the United States. • Outcome: The study found that depot buprenorphine was not inferior to daily sublingual (SL) buprenorphine in terms of response rate and urine samples negative for opioids. Depot buprenorphine also showed superior results on the cumulative distribution function (CDF) of no illicit opioid use.

Trial		• Conclusion: Depot buprenorphine may be an effective treatment option for opioid use disorder and may have advantages over SL buprenorphine.

Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial	Haight et al, 2019 *Lancet*	• Objective: To investigate the efficacy of different dosing regimens of monthly subcutaneously injected buprenorphine treatment (BUP-XR).
		• Design: A randomized, double-blind, placebo-controlled, phase 3 trial.
		• Outcomes:
		  ○ The study found that BUP-XR was effective in reducing opioid use and was well-tolerated. Both BUP-XR groups showed significantly higher rates of abstinence than the placebo group, and no compensatory non-opioid drug use was observed during BUP-XR treatment.
		  ○ The most common adverse events were headache, constipation, nausea, and injection-site pruritis.
		• Conclusion: In individuals with opioid use disorder, monthly BUP-XR treatment regimens significantly increased abstinence from opioids and were well-tolerated, offering a promising advance in opioid addiction treatment.

Opioid agonist treatment and risk of mortality during opioid overdose public health emergency: population based retrospective cohort study	Pearce et al, 2020 *BMJ*	• Objective: To compare the risk of mortality between individuals with opioid use disorder who were on opioid agonist treatment (OAT) and those who were not, in a region where the illicit drug supply is highly contaminated with fentanyl and other synthetic opioids. • Design: Population based retrospective cohort study. • Outcome: Opioid agonist treatment (OAT) was associated with a substantial reduction in the risk of mortality for people with opioid use disorder. The risk of mortality off OAT was 2.1 times higher than on OAT before the introduction of fentanyl. The protective effect of OAT on mortality increased as fentanyl and other synthetic opioids became common in the illicit drug supply. • Conclusion: The study highlights the importance of interventions that improve retention on OAT and prevent recipients from stopping treatment as fentanyl becomes more widespread globally.
High-Dose Buprenorphine Induction in the Emergency Department for	Herring et al, 2021 *JAMA network open*	• Objective: To evaluate the safety and tolerability of a high-dose buprenorphine induction strategy for the treatment of opioid use disorder in patients presenting to the emergency department. The study aimed to assess the effectiveness of this approach in addressing the challenges posed by the increasing potency of the illicit opioid drug supply and delays in follow-up care.

Treatment of Opioid Use Disorder		• High-dose buprenorphine in this study consisted of a minimum of 12 mg for induction, upto a maximum of 32 mg.
		• Design: A case series.
		• Outcome:
		  ○ The study found that high-dose buprenorphine induction for patients with opioid use disorder (OUD) in an emergency department (ED) was safe and well-tolerated, with no reported cases of respiratory depression or sedation.
		  ○ Precipitated withdrawal occurred in 0.8% of cases and was not associated with dose, and nausea or vomiting was rare. The median length of stay was 2.4 hours.
		• Conclusion: High-dose buprenorphine induction in the emergency department for patients with untreated opioid use disorder was found to be safe and well-tolerated, with no reported cases of respiratory depression or sedation.

Additional resources:
ASAM Guidelines for OUD
VA DOD Substance Use Disorder Guidelines