Medications for Opioid Use Disorder: Enhancing Retention to Achieve Long-term Remission and Recovery

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Review and Commentary

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ABSTRACT

Medications for the treatment of Opioid Use Disorder (MOUD) utilizing methadone, buprenorphine, or naltrexone constitute the current “gold standard” for the medical treatment of opioid use disorders (OUDs). The effectiveness of MOUD is contingent upon treatment adherence and retention, with multiple achievements in OUD remission and recovery increasing incrementally over months and years. Yet, most MOUD patients prematurely discontinue treatment, creating increased risks of OUD recurrence, deterioration in psychosocial functioning, and increased harm to self, family, and community. The present review explores this limitation of MOUD with suggestions for elevating retention and related outcomes. The future of MOUD rests upon: 1) expanding treatment goals and choices across the dimensions of problem severity/complexity/chronicity and widely varying levels of recovery capital, 2) reconceptualizing MOUD retention within the framework of long-term addiction/treatment/recovery careers, 3) addressing MOUD retention in tandem with ten key in-treatment and post-treatment process measures, 4) promoting continual advancements in OUD medication development, related neuropsychological interventions, and adjunctive or alternative mechanisms of OUD remission and recovery, 5) identifying and matching the most potent service combinations and sequences across diverse clinical phenotypes and cultural contexts, 6) assertively addressing personal, programmatic, and community obstacles to OUD treatment adherence and retention, and 7) implementing enriched protocols for long-term remission maintenance and recovery management.

Key Words: opioid use disorder, medications for treatment of opioid use disorder, methadone, buprenorphine, naltrexone, treatment adherence, treatment retention, treatment completion, psychosocial services, peer support, recovery management.

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Introduction

Opioid use disorder (OUD) and *opioid addiction* (the most severe and complex form of OUD) exist within the larger continua of opioid use and opioid-related problems.[1] The global prevalence of nonmedical opioid use is estimated at more than 60 million individuals,[2] OUD prevalence exceeds 26 million, and worldwide opioid overdose deaths exceed 100,000 annually,[3] more than 80,000 of which occur in the United States.[4]

Opioid addiction is a chronic (remitting and relapsing), potentially lifelong condition that profoundly affects physical health, life expectancy, psychosocial functioning, quality of personal and family life, and community health and safety.[5] Though a centuries-old problem, OUD severity, complexity, and mortality have been amplified by the recent infusion of illicitly manufactured fentanyl and related analogues into international drug markets.[6] OUD is a severe and complex substance use disorder as evidenced by its related mortality risks, debilitating effects on global health and psychosocial functioning, and the average number of treatment attempts required before achievement of remission and recovery stability.[7] Long-term OUD recurrence rates are high following assisted and unassisted abstinence attempts and may be accompanied by increased alcohol and other drug use.[8] Adolescents and young adults experiencing high severity OUD are at particular risk for prolonged addiction careers and related morbidity and mortality risks.[9]

The personal resolution of OUD encompasses qualitatively different achievements commonly referred to as *remission* and *recovery*. Remission involves the elimination or reduction of OUD-related pathology below the OUD diagnostic threshold, while recovery conveys achievement of remission plus enhancement of global health, social functioning, and the potential to flourish, i.e., to get “better than well.”[10] Put simply, OUD remission is about finding a way to survive; OUD recovery is about then finding a way to thrive.[11] This nuanced distinction grew from the recognition that recovery was far more than deceleration or cessation of drug use from an otherwise unchanged life and recognition that abstinence alone was not a consistent predictor of subsequent quality of life and social functioning.[12]

People experiencing OUD are initiating and sustaining OUD remission and recovery with and without professional treatment, with and without participation in recovery mutual aid organizations, with and without medication support, and through a combination of such resources, reflecting a broad diversity in problem resolution pathways, styles, and resulting quality of life.[13]

Hoffman and colleagues in a national survey of U.S. adults found an estimated 1.18 million individuals who had resolved an opioid problem with support from a range of recovery support resources: recovery mutual aid groups (both Narcotics Anonymous and Alcoholics Anonymous), inpatient and outpatient treatment, pharmacotherapy, and support from other recovery support institutions (e.g., faith-based recovery ministries,

recovery community centers).[14] Achievement of remission beyond one year was associated with the use of a greater number of recovery support resources, suggesting additive effects of combining recovery support mechanisms.

OUD remission and recovery strategies vary across the spectrum of problem severity, ranging from achievement of complete abstinence to a sustained deceleration of drug use and reduced risk of related injury to self and others.[15] Among those seeking resolution of opioid related problems, the goal of abstinence from all non-medical opioid use is associated with greater past problem severity.[16] The abstinence style of OUD remission is also linked to greater long-term remission stability and greater improvements in quality of life.[17] For most individuals, gains in psychosocial functioning and quality of life made during abstinence quickly decline following reinitiation of opioid use.[18] Variations in style of OUD problem resolution are reflected in the self-expressed goals of patients seeking MOUD, with 70 percent expressing a goal of non-medical opioid abstinence at treatment admission and 30 percent expressing a non-abstinence goal, e.g., reduction of opioid use and related problems.[19]

The risk of substance use disorder (SUD) recurrence and related untoward outcomes declines with the duration of stable remission and recovery,[20] with remission quite fragile during the first year.[21] A lifetime remission stability/durability set point—the time at which risk of future SUD recurrence drops below 15 percent—is not reached in most SUD studies until five years of sustained remission.[22] Recognition of this set point influenced the five-year duration of monitoring and support within assistance programs designed for SUD-impaired physicians, dentists, veterinarians, nurses, pilots, lawyers, and other professionals.[23] That five-year set point has also been recommended as a benchmark for evaluating all addiction treatment outcomes.[24] However, studies suggest that such a lifetime sustainability setpoint may require sustained remission beyond that five-year standard for opioid use disorders.[25] The sustained risk of OUD recurrence suggests the need for prolonged personal vigilance, assertive recovery support measures, long-term recovery management check-ups, and if/when needed, early reintervention.[26]

The present review addresses the challenges of achieving long-term stable OUD remission and recovery, and, more specifically, the related challenges involved in adherence and retention within the pharmacotherapeutic treatment of OUD.

The Treatment of Opioid Use Disorder

The professional treatment of OUD utilizes two broad approaches with varying levels of integration: 1) psychopharmacological treatment, and 2) psychosocial treatment. These competing but potentially complementary approaches are often nested within isolated silos of care with proponents of each claiming moral, clinical, and scientific superiority. Such conflicting claims make it difficult for affected individuals, families and allied professionals to evaluate OUD treatment and recovery support options.[27] The low rate of OUD help-seeking across these modalities is influenced by cultural beliefs (e.g., OUD-linked social stigma, the perception of treatment ineffectiveness) and by self-perception of those affected (e.g., failure of problem recognition or belief that OUD can be self-managed without professional treatment or recovery mutual aid involvement).[28]

Despite the strong evidence supporting the effectiveness of medications, only a minority (25%, 2,353,000) of individuals in the United States needing OUD treatment (9,367,000) received one of the three recommended medications for OUD treatment, including less than half of those with the most severe OUDs.[29] Mainstream addiction treatment programs, despite poor treatment outcomes for OUD, have historically been adamantly opposed to using medications for OUD beyond withdrawal management. In a 2022 survey of U.S. addiction treatment facilities, 35.2% offered only psychosocial approaches to the treatment of OUD.[30] An earlier study by Huhn et al., found less than a third of residential addiction treatment programs in the U.S. provided MOUD as a treatment option,[31] and a study by Cole et al., found only 46.9% of OUD patients in residential treatment received any follow-up contact or MOUD 30 days following discharge.[32] For those who do seek addiction treatment, it is common to experience multiple types of treatment over the course of one's addiction, treatment, and recovery career.[33]

The pharmacotherapeutic treatment of OUD—variably christened Methadone Maintenance Therapy (MMT), Drug Substitution Treatment (DST), Opioid Substitution Treatment (OST), Drug Replacement Therapy (DRT), Opioid Agonist Treatment (OAT), Opioid Maintenance Therapy (OMT), Medication-Assisted Opioid Therapy (MAOT), Office-based Opioid Treatment (OBOT), Medication-assisted Treatment (MAT), Medication Assisted Recovery (MAR), buprenorphine-containing transmucosal products for the treatment of opioid dependence (BTOD), and, more recently, Medication for Opioid Use Disorders (MOUD)—is the most scientifically and clinically recognized treatment for OUD.[34]

The pharmacological treatment of OUD usually involves maintenance on methadone (a full opioid agonist), buprenorphine (a partial opioid agonist), or naltrexone (an opioid antagonist), but may also involve other less utilized and less rigorously evaluated substances (e.g., opium tincture, morphine, diacetylmorphine/heroin, and psychedelics--ibogaine, psilocybin, LSD, MDMA, ketamine, ayahuasca).[35] Herbal folk medicines (e.g., kratom, *Mitragyna speciosa),* though lacking in empirical evaluation, may also be used as an indigenous treatment to suppress opioid withdrawal, lower opioid tolerance, or aid the transition from one OUD medication to another, e.g., herbal adjuncts used in transition from methadone to buprenorphine.[36]

In certified opioid treatment programs (OTPs), methadone is administered orally each day, with stabilizing effects lasting 24 to 36 hours. Withdrawal from illicit opioids is not required prior to initial methadone administration but patients with a high or unknown level of tolerance could experience opioid withdrawal and treatment disengagement when given an inadequate medication dosage, just as higher dosages for patients with low tolerance could result in oversedation and related medical consequences. During initial induction and prior to full clinical stabilization, patients are required to make daily visits to the OTP to receive medication. For clinically stable patients, from 14 to 28 days of take-home methadone can be dispensed in tamper proof, child-resistant bottles to avoid incidents of accidental poisoning. However, the actual availability of take-home dosing varies: only half to two-thirds of OTPs report offering take-home methadone depending on patient stability, and only a minority of patients receive take-home doses.[37]

Buprenorphine for the treatment of OUD can now be prescribed by any physician, physician assistant, or nurse practitioner who has DEA authorization to prescribe controlled substances. Broadening the clearance for prescribing to non-physicians in the U.S. was undertaken as a response to high opioid mortality rates and through efforts to expand MOUD access. Buprenorphine used in the treatment of OUD has several formulations: subcutaneous extended release (Sublocade), subdermal implant (Probuphine), sublingual tablets (Subutex), and two combination buprenorphine and naloxone formulations—one film (Suboxone) and one tablet (Zubsolv)—or generic equivalents of these medications.[38] Extended release (weekly or monthly) intramuscular injection formulations are also available (Brixadi). In order to avoid precipitating withdrawal symptoms, enough time is allowed since the last use of opioids for the patient to avoid mild withdrawal symptoms. Particular care must be exercised if the patient has been using methadone or fentanyl.

Naltrexone is administered orally (Revia) with effects lasting 24-72 hours or by injection (Vivitrol) with effects from a single injection lasting 28 days. Opioid withdrawal is required prior to naltrexone initiation.

Methadone and buprenorphine at higher dosages reduce illicit opioid use by blocking the effects of illicit opioids, reducing craving and withdrawal distress and creating a window of neurological normality.[39] It is rare for all three primary OUD medications to be available within OUD treatment facilities (only 6.1% in treatment facilities in the U.S. in 2016.[40]

MOUD treatment non-adherence is variably defined but most often includes such behaviors as missed dosing appointments, failure to take medication, unprescribed split dosing, self-injection of medication, unsecure medication storage, using other substances, sharing medication with others, or failure to follow program rules.[41] Comparing rates of adherence / nonadherence is not possible due to varying definitions and cut points used to demarcate adherence from non-adherence,[42] but there is consensus that MOUD non-adherence is a major problem. Some studies note rates of non-adherence in excess of 50-60% of MOUD patients[43]—rates in excess of medication non-adherence in treatment of other complex medical conditions.[44] Subtherapeutic dosing of medication that in turn leads to withdrawal distress, drug craving, and drug-seeking is a major factor contributing to MOUD non-adherence.[45]

Non-adherence is often a precursor to MOUD discontinuation, overdose risk, and increased risk of hospitalization.[46] In one study, non-adherent MOUD patients were 3.5 times more likely to experience an opioid overdose as patients who were treatment adherent.[47] High rates of MOUD non-adherence are linked to such factors as high OUD severity, low MOUD knowledge; misconceptions about MOUD; greater obstacles to remission/recovery (e.g., younger males, homelessness, remote distance from dispensing site, low income), low recovery capital,[48] low quality of life,[49] and such programmatic factors as low-dose medication policies.[50] Increasing medication dosages in response to continued heroin use by MOUD patients has been shown to decrease illicit drug use and reduce medication discontinuation.[51] Caplehorn et al., found that the odds of methadone patients using heroin were reduced by 2% for every 1 mg increase in methadone dose.[52] However, some treatment programs respond to continued opioid use not by increasing medication dosage, but administratively discharging patients from treatment (see later discussion).

One predictor of post-treatment substance/opioid use is the status of substance use in the month prior to treatment discharge. In 2022, abstinence from any substance at treatment discharge in the U.S. was reported for 17% of opioid-related treatment episodes that included MOUD treatment versus 13% for non-MOUD treatment episodes. Abstinence from opioids at discharge was reported in 35% of MOUD treatment episodes and 29% of non-MOUD episodes.[53] For many patients in MOUD and non-MOUD treatment settings, post-treatment substance/opioid use is not a "relapse," but continuation of substance use that existed regularly or episodically throughout the treatment period.

Concurrent prescribed use of MOUD and nonmedical use of drugs is common[54] and can take diverse patterns—frequent opioid use, frequent use of other drugs (e.g., cocaine, methamphetamine, benzodiazepines, alcohol, and nicotine), frequent dual use (opioids and other drugs), sporadic use, and infrequent use.[55] Such patterns decline with MOUD continuation, but all are potential precursors to medication discontinuation, treatment dropout, and escalation of drug use. Bjørnestad and colleagues reported in a study of MOUD patients that a third achieved abstinence of illicit drug use while others continuing various patterns of drug use.[56] Raffa et al., in a study of the relationship between illicit drug use and MOUD retention, found only four of sixty MOUD patients in the study abstinent from all illicit drug use.[57] Senbanjo et al., in a study of continued illicit drug use among of methadone patients, found half the patients reporting heroin use in the two weeks preceding the survey.[58]

Theoretical underpinnings of medication-based therapies for OUD include the following propositions. OUDs are rooted in the synergy between genetic/biological, developmental, and social vulnerabilities that when combined with repeated opioid exposure induce potentially long-lasting neuroplastic alterations of brain networks (including both opioid and non-opioid receptor systems). Opioid-induced brain dysregulation incites acute and post-acute withdrawal distress, cellular craving for opioid relief, compulsive drug-seeking, and the acceleration of related personal and social harms that are at the core of the OUD experience.[59] Opioid-induced dysregulation of brain networks affecting reward, motivation, memory, stress, emotion, and decision-making can be ameliorated by sustained administration of MOUD.[60]

The conceptual foundations of psychosocial treatments for OUD are based on alternative but more variable assumptions. Compulsive drug use springs from maladaptive conditioning of rewards and punishments or constitutes a manifestation of and attempt to manage personal and family pathology—a failed effort that results in unanticipated aberrations in cognitive and emotional health, radical changes in personal identity and values, a breakdown of interpersonal relationships, and radical alterations in daily lifestyle.[61] Recovery from OUD thus requires intrapersonal psychological processes (reconstructing memory, identity, values, worldview, decision-making, and stress management) and psychosocial processes (altering reward contingencies—repairing intimate and family relationships, reconstructing daily lifestyle and social networks, and reconstructing one's relationship to community)—processes that far transcend the neurobiological dimensions of addiction and recovery.[62] Recovery from the most severe and complex SUDs is best achieved through professional guidance by those trained to facilitate such processes. Advocates of psychosocial treatment have historically criticized MOUD for continuing a pattern of drug dependence, prolonging the

addiction process, failing to address underlying causes of addiction, failing to promote global health and social functioning, and promoting long-term maintenance out of financial interests rather than the best interests of patients.[63]

The assumptions upon which MOUD and psychosocial treatment methods are based are not mutually exclusive, meaning that multiple mechanisms (push and pull factors) may interact within the processes of OUD initiation and maintenance as well as within and across the stages of remission and recovery.

Less than 25 percent of self-managed opioid withdrawal attempts are successfully completed,[64] and of those that are completed, less than half are followed by any form of recovery support.[65] Even contact with a primary care physician has been found to improve substance-related outcomes.[66] Short-term medical management of acute opioid withdrawal, formerly known as *detoxification*, provides welcome relief but does not constitute a "treatment" for OUD due to the near-universal experience of post-withdrawal recurrence of opioid use and its related consequences, including a significant elevation of mortality risks.[67] Improved effectiveness of medically managed opioid withdrawal has not resulted in parallel increases in post-withdrawal opioid abstinence rates[68] (see later discussion and Table A2).

Most OUD patients initially lack the internal and external assets (recovery capital) to sustain OUD remission and recovery in the absence of medication support.[69] Medical management of acute opioid withdrawal in the absence of broader and more sustained care and recovery support most often results in repeated cycles of treatment admission, premature discharge, OUD recurrence, readmission, further failures to complete treatment, and continued morbidity and mortality risks.[70] Sustained MOUD treatment is the only modality (compared to no treatment, inpatient detoxification, residential services, intensive behavioral health, and non-intensive behavioral health) that significantly lowers mortality risks in the year following treatment initiation.[71]

In summary, brief experiments in opioid abstinence sampling, with or without treatment involvement, do not constitute stable remission or recovery; they are as likely to be milestones within one's addiction career as a catalyst of long-term recovery initiation.[72] What is required to sustain OUD recovery is quite different than what is required to initiate brief periods of opioid abstinence. The transition from recovery initiation to stable recovery maintenance is marked by the problem of extreme ambivalence: the desire to end opioid entrapment, escape the painful consequences of opioid use, and achieve a better quality of life—all while experiencing thoughts and impulses to resume opioid use in the face of cravings, euphoric recall of drug experiences, peer invitations to use, boredom, frustration, real and symbolic losses, anger, resentment, shame, and grief. This ambivalence extends to feelings of gratitude for the benefits that MOUD has granted and simultaneous feelings of wanting to break free of medication dependence.[73] This ambivalence in popular addiction literature has been portrayed as a problem of duality between the sober self (the honest, well-meaning and health-seeking Dr. Jekyll) and the addictive self (the lying, manipulative, self-destructive, aggressive Mr. Hyde). That ambivalence can be expressed by continued illicit drug use during MOUD and other patterns of treatment nonadherence and simultaneous expressions of desire to remain and progress within treatment. What varies over time is the strength of the desire on both sides of that ambivalence and the

power of the drug versus the medication and the actions of and relationships with caregivers in tipping this balance.

MOUD Retention: Evidence to Date

Seen as a whole, evaluations of MOUD (of methadone, buprenorphine, and naltrexone) consistently report cessation or reduction in opioid use, reduced infectious disease risk, reduced mortality risk, enhancements in health, including enhanced antenatal care and prenatal outcomes, and enhanced social functioning (e.g., housing stability, employment, reduced criminality) during active treatment.[74] These same scientific investigations note several limitations of MOUD: social/professional stigma, limited attraction and availability, inaccessibility/unaffordability, inconsistency between patient and program goals, suboptimal and subtherapeutic medication dosing, ineffectiveness with co-occurring non-opioid SUDs, inadequate psychosocial support services, and the absence of post-treatment monitoring and support.[75] More common concerns involve high rates of MOUD treatment nonadherence, treatment discontinuation, post-treatment OUD recurrence, and prolonged recycling through varied treatment approaches.[76] MOUD patients also express unmet expectations related to enhancements of global health and quality of life.[77]

Treatment of OUD with evidence-supported medications (i.e., methadone, buprenorphine, naltrexone) is currently conceived internationally as corrective but not curative.[78] OUD remission rates are enhanced during the period of medication adherence. OUD medication disruption or discontinuation are often, but not universally, followed by clinical deterioration, OUD recurrence, and related consequences, including significantly increased mortality risks in the first days, weeks and months following treatment discontinuation.[79] Hser and colleagues, in a multi-site follow-up study of 795 MOUD patients, noted five trajectories of opioid use at follow-up: low use, high use, increasing use, and decreasing use, with high and increasing use associated with substantial impairments in health and social functioning.[80]

The optimum duration of MOUD treatment and the advisability and choices of MOUD cessation strategies continue to be debated at professional and public levels.[81] Clinical guidelines for MOUD either offer no definitive recommendation for MOUD duration beyond noting the import of treatment retention[82] or suggest a minimal period of methadone treatment of one year[83] to two years[84] and a minimum duration of buprenorphine or naltrexone treatment of six to twelve months.[85] The reality of the psychopharmacological treatment of OUD at the practice level, however, is quite different.[86] The median duration of U.S. opioid-related treatment episodes was between 46 and 60 days for MOUD treatment and 9 days for non-MOUD treatment in 2022[87]

Many MOUD patients view medication support as a bridge to medication-free recovery from OUD.[88] Most express conflicting intentions of continuing medication support for at least one year[89] and discontinuing medication maintenance in the near future.[90] Lenné et al., found that 70% of surveyed MOUD patients expressed interest in medication discontinuation, but only 17% were judged to have a good tapering prognosis.[91] Patients tapering off MOUD via a dosage reduction schedule have higher rates of concurrent illicit drug use and increased risk of treatment drop-out.[92] A significant portion if not the majority of patients who attempt tapering off methadone or

buprenorphine do not successfully complete the tapering process and either cease tapering and return to medication maintenance or drop out of treatment before tapering is complete.[93] The challenges of tapering, particularly rapid tapering, include sleeplessness, gnawing pain, joint achiness, excessive sweating, itchy skin, diminished appetite, nausea/vomiting/diarrhea, and emotional volatility. Even in studies reporting high rates of completion of medication withdrawal, rates of post-withdrawal opioid abstinence are low[94] and include reports of considerable physical and psychological distress during the withdrawal process as well as increased risk of opioid-related death.[95]

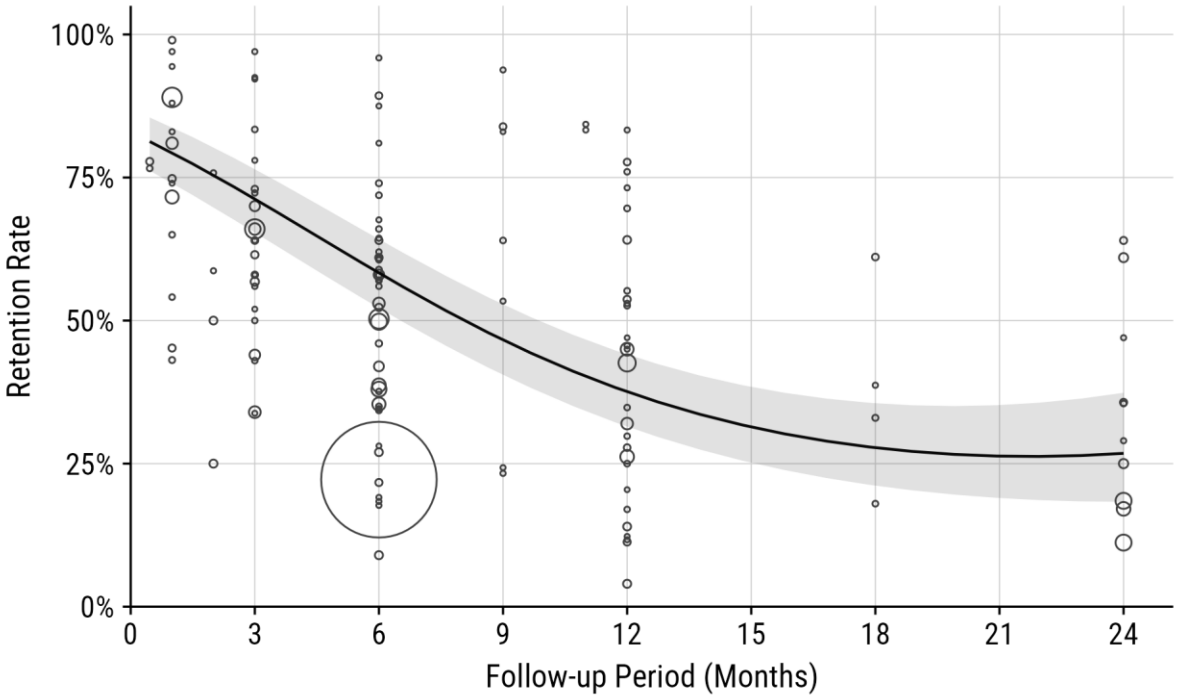
Patients who complete medication tapering as planned, presumably those with greatest chance of post-MOUD remission and recovery stability, experience a high rate (over 50% within the first month) of OUD recurrence or excessive use of other substances.[96] Some patients using MOUD employ a "chronic relapsing disease" perspective to maintain personal vigilance, justify continued medication maintenance, and embrace a refined personal definition of abstinence: not using illicit drugs, not using/misusing other psychoactive substances, and using treatment medications as prescribed.[97]

To ascertain MOUD retention rates in recent years, a convenience search using PubMed and Google Scholar was conducted using keyword combinations that included methadone, buprenorphine, naltrexone, adherence, retention, dropout, treatment completion, abstinence, remission, recovery, and quality of life. This identified 77 international studies that reported retention rates for MOUD treatment published between 2014 and 2024. The retention rates reported in these studies are displayed in Table A1 in the appendix.

We conducted an ad-hoc meta-regression analysis on these studies to summarize findings on retention in MOUD treatment, including the trajectory of retention over increasing follow-up periods. Meta-regression is a form of meta-analysis that synthesizes outcomes (in this case, retention) across studies and tests how one or more study characteristics (in this case, follow-up period) predicts variability in these outcomes. The fitted meta-regression model can then be used to predict the retention rate at various follow-up times, yielding a model-predicted retention trajectory as shown in Figure One. The model only included data for the 71 studies with follow-up periods of two years or less due to a paucity of studies with >2-year follow-up periods.[*]

[*] Additional methodological details: The meta-regression model was a binomial generalized linear mixed model run in R version 4.4.0 using the glmmTMB package. The model included linear and quadratic fixed effect terms to allow for a curvilinear relationship between time and retention, which provided better fit than a linear term alone (likelihood ratio test, $\chi^2(1) = 483.5$, $p < .001$; AIC = 7440 (linear) vs. 6958 (quadratic)). Random slopes were included for follow-up period within study, weighted by sample size; the random slopes model provided better fit than a random-intercepts-only model ($\chi^2(2) = 1788.8$, $p < .001$; AIC = 8743 (random intercepts) vs. 6958 (random slopes)). Of note, one records-based study of 6-month retention had a very large sample (Chua et al., 2023, $n > 3M$); excluding this study had a negligible effect on predicted values.

Figure One. Predicted trajectory of retention in MOUD treatment based on a convenience sample of MOUD studies, 2014-2024



Predicted probability of MOUD retention by time from a meta-regression model of studies in Table A1. The shaded area represents the 95% confidence interval. Points represent rates reported in individual studies, scaled to study sample size.

The available MOUD retention and post-treatment outcome studies suggest several tentative conclusions.

Paucity of Patient Perspectives There are far more studies of MOUD retention rates and their clinical and social consequences than there are studies eliciting MOUD patient perspectives on incentives and disincentives to continue MOUD participation.

Paucity of Long-term MOUD Retention Studies Most studies of MOUD retention focus on the early months of treatment: only 37 of 77 of the studies in Table A1 report retention at one year or longer, only 19 reported data for more than one year, and only six reported retention rates beyond three years. This focus on early retention reflects an acute care orientation and leaves unanswered patient status years into or after discontinuation of MOUD.

High Rates of Short-Term Medication Discontinuation The challenge of MOUD is to retain patients during early stages of induction when personally optimal medication dosages have not yet been determined, medications have yet to take full effect, and experiences of withdrawal distress, drug craving, or medication side-effects may trigger continued illicit drug use and treatment disengagement.[98] Based on the meta-regression model, over a fifth of patients discontinued supervised medication use in the first month of treatment (predicted retention = 79%, 95% confidence interval [74%, 84%]. Predicted

retention dropped to 71% [65%, 76%] at three months, 38% [31%, 44%] at one year, and 27% [18%, 37%] at two years from admission. The sample-size-weighted mean of eight studies reporting retention beyond two years (range from 3 to 35 years) was 14% (weighted *SD* = 10 percentage points).

The days, weeks, or months required for full homeostatic stabilization pose significant challenges for continuing MOUD. The same challenge is faced in medication maintenance for other chronic medical and psychiatric conditions, including alcohol use disorder.[99] In the authors' collective clinical experience, a significant portion of MOUD patients discontinue treatment during induction as a consequence of medication underdosing and its biopsychological consequences. Avoiding withdrawal distress is possible with concomitant high rates of early retention with higher medication dosages by using more aggressive medication protocols. Close clinical supervision is critical to avoid the danger of over-medication.

Individual and Program Variability of MOUD Outcome In a systematic review of MOUD retention rates as a program process measure, Timko and colleagues found a wide range of reported patient retention rates at three months (19% to 94%) and at one-year (37% to 91%).[100] In a separate review, Bailey et al., also found wide retention variability, ranging from 31.6% to 73.3% at one month and from 26.2 to 58.5% at 3 months.[101] Individual responses to MOUD vary widely and may be influenced by genetic variation.[102] This spectrum of change spans:[103]

1) continued OUD—progressive clinical deterioration and high risk of treatment disengagement,
2) languishing/floundering—unstable or partial remission of OUD and related problems but no enhancement of global health and functioning—what patients have described to us as a sense of stasis, limbo, confinement, being stuck, or flatness rather than a feeling of incremental progress,[104]
3) incremental progress (remission of OUD and related problems with time-dependent progressive enhancement of global health and social functioning), and
4) flourishing (remission of OUD and related problems with exceptional enhancement of global health, quality of life, social functioning, service to family and community, and life meaning and purpose).[105]

Many MOUD patients vacillate in their personal goals between harm reduction, OUD remission, and OUD recovery[106]—caught within the coexistence, resignation and resistance to both addiction and recovery.[107]

Retention Variability by Country, State, Medication Type, Setting, Service Protocol and Clinical Subpopulations. Retention rates vary internationally, across medication type, service setting, demographic and clinical subpopulations, medication dosage levels, scope and intensity of ancillary services provided, the legal/regulatory frameworks under which OUD medications are authorized, and the duration of study follow-up.[108]

Retention rates in methadone treatment are generally higher than those in buprenorphine treatment,[109] with only a minority of reviews reporting no difference in retention rates across methadone, buprenorphine, and buprenorphine/naloxone.[110] In a recent review of retention in buprenorphine treatment, Kenney and colleagues found

that nearly half of buprenorphine patients were no longer in treatment 24 weeks after admission.[111] Rates of buprenorphine discontinuation are high across diverse treatment settings including outpatient primary care physicians, psychiatry, and specialty OUD treatment settings.[112] Comparisons of outcomes for sublingual daily buprenorphine versus extended-release buprenorphine injections suggest the latter has similar or superior rates of patient retention[113] and a higher level of patient satisfaction,[114] but retention remains a challenge. In a study of patients transitioning from sublingual buprenorphine to injectable buprenorphine, Stein et al., found that 48% of patients had discontinued treatment at three-month follow-up.[115] Extended-release subcutaneous buprenorphine injections may have advantages for patients who have used fentanyl.[116] Retention with naltrexone is lower than that with methadone or buprenorphine naloxone,[117] but naltrexone may have special utility in the treatment of certain OUD populations, e.g., physicians with OUD in states that are opposed to allowing physicians to resume practice while on methadone and buprenorphine, patients lacking stable shelter.[118]

Comparisons of the two most frequently used OUD medications (methadone and buprenorphine) are challenged by racial, class and gender disparities in access,[119] with communities of color (Non-Hispanic Black people, non-Hispanic American Indian or Alaskan Native/Asian/Hawaiian/Pacific Islander people, and Hispanic people) and lower income communities most often having access to methadone while white and more affluent communities are more likely to have access to buprenorphine.[120] There is a marked absence of research on Asian American patients entering MOUD in spite of increasing rates of opioid overdose.[121] Bart and colleagues. in a comparison of Hmong and non-Hmong methadone patients did report lower OUD problem severity and higher retention and recovery rates among Hmong patients.[122]

Retention rates in MOUD are lower for Black men and women who identify as Black, Latino, or Other,[123] women with histories of developmental and interpersonal trauma,[124] and women with prior histories of psychiatric illness and criminal offending.[125] Women entering MOUD have higher rates of cooccurring psychiatric illness than men entering MOUD treatment.[126]

Clinical Outcomes by Treatment Duration Progress in illicit opioid reduction/cessation, diagnostic remission of OUD, and reduction/cessation of ancillary drug use is enhanced with duration of MOUD treatment.[127] Reduction in drug use, rates of abstinence, and improvements in global health and quality of life increase incrementally with each month/year of medication support.[128] Initial improvements in quality of life following MOUD initiation are observed in the first two to three months, with incremental improvement continuing over the early years of medication maintenance.[129]

Areas of improvement following MOUD initiation span many of the conditions that compromise quality of life in active addiction:[130] elevation of physical health (including reduced craving, weight control, exercise, sleep quality, and enhanced sexual functioning); diminution of the chaotic addiction lifestyle; normalization and stabilization of family life; and improved psychiatric status, living conditions, and social functioning.[131] Enhancements in quality of life during maintenance on MOUD are associated with treatment adherence and treatment duration,[132] social support of at

least one recovery-supportive friend, structured daily activities, and meaningful employment.[133]

The ideal duration of MOUD continues to be debated with related ethical issues raised regarding the polar harms of premature termination (clinical abandonment) and unnecessarily prolonged treatment (as an alleged form of cultivated institutional dependency for purposes of financial exploitation), as well as concerns related to client autonomy/preferences and the limits of shared decision-making.[134]

Retention and Completion Compared to Alternative Treatments Research reviews conclude that all three primary OUD pharmacotherapies generate higher treatment adherence and retention rates and related clinical outcomes than psychosocial OUD treatments lacking medication support.[135] That said, as noted earlier treatment system data reports in the U.S. show lower rates of treatment completion and higher rates of discontinuation of MOUD treatment compared to OUD patients receiving non-MOUD treatment. MOUD treatment compared to psychosocial treatment retains OUD patients in treatment longer but is less likely to end in a completed treatment episode at discharge.[136] A 2005 review of available evidence concluded that psychosocial treatment of OUD was insufficient without the availability of medication support.[137]

Treatment Retention versus Treatment Completion This pattern of higher *retention* but lower *completion* in MOUD relative to non-MOUD treatment may appear paradoxical. It in part reflects that other treatment modalities, such as residential or intensive outpatient treatment, generally have shorter expected durations and more clearly defined end points. In contrast, there is no consensus on the optimal duration of MOUD treatment. Beyond detailing the mechanics of medication tapering, there exists no widely accepted model that maps pathways of exit from MOUD and provides alternative modes of long-term recovery maintenance in the absence of medication support. As such, while treatment completion for non-pharmacological addiction treatment modalities is associated with positive post-treatment outcomes,[138] the parallel story of MOUD is far more complex. The literature on MOUD, which contains thousands of books and published articles on seemingly every aspect of methadone, buprenorphine, and naltrexone maintenance, is remarkably sparce on the subject of MOUD treatment completion and the status of MOUD patients years after medication discontinuation.[139]

Early studies of methadone maintenance concluded that between 80-90% of patients who discontinued treatment via drop out or administrative discharge experienced OUD recurrence within a year.[140] Other early studies linked MOUD treatment completion to positive long-term outcomes.[141] In a five-year MOUD follow-up study published in 2017, only 20% of patients successfully completed treatment and were not re-admitted in the following six months.[142] A more recent study by Andraka-Christou and colleagues of methadone maintenance treatment discharges in the state of Florida found a completion rate of only 11%.[143] Beyond detailing the mechanics of medication tapering, there exists no widely accepted model that maps pathways of exit from MOUD and provides alternative modes of long-term recovery maintenance in the absence of medication support.

In the largest national U.S. data set on U.S. treatment discharges, the discharge categories and related results for MOUD and non-MOUD treatment among persons reporting opioid use at intake in 2022 span six categories: treatment completion (19%

vs. 32%); dropped out (37% vs. 25%), terminated by facility [administrative discharge] (5% versus 5%), transferred to another treatment program (29% versus 33%), incarcerated (2% versus 2%), and death (1% vs. 0%).[144] The completion rate for outpatient MOUD treatment was just 12%. In line with an earlier analysis by Krawczyk and colleagues, retention time was an important predictor of completion; the majority of episodes (65%) had a treatment duration of less than six months, which was associated with a completion rate of only 9%.[145] The completion rate among those with treatment duration of more than six months was almost double this, but still only 17%. Treatment completion among OUD patients is often associated with external coercion to complete and end treatment (e.g., pressure from criminal justice or child welfare authorities).[146]

Patients who are therapeutically discharged (treatment completion) after MOUD have increased odds of sustaining opioid abstinence and OUD remission/recovery compared to those with non-therapeutic discharges, e.g., drop-out, disciplinary discharge, arrest/incarceration—48% versus 22%.[147] That said, discontinuation of MOUD under any circumstances is associated with increased risks of OUD recurrence and related mortality risks.[148]

Racial disparities exist in the MOUD treatment completion in some studies, with Black and Hispanic patients less likely to complete treatment[149] and more likely to be administratively discharged,[150] while other reviews have found similar rates of MOUD retention across all gender and racial groups and across all three primary OUD medications.[151] Rigg et al., in drawing upon data from the Florida Minority Health Survey, found three deeply imbedded views of methadone within African American communities that could affect MOUD initiation and retention: 1) prescribed methadone is similar to heroin in its intoxicating properties, 2) methadone patients should remain on the drug for as short a time as possible, and 3) methadone is a "crutch."[152] Much more positive attitudes exist towards extended release naltrexone, which is less accessible in African American communities.[153]

OUD patients treated with methadone are twice as likely to be administratively discharged from treatment as those treated with buprenorphine, which may reflect differences in problem severity and differences in patient demographics.[154] Historically, the rate of administrative discharge in some programs providing MOUD has exceeded fifty percent of admitted patients.[155] Administrative discharges increase in tandem with counselor caseload size, suggesting a weaning process of the most demanding, most "resistant," and least stabilized patients.[156] Of greatest concern is that administrative discharge is often followed by clinical deterioration, OUD recurrence, and increased mortality risks across OUD treatment settings.[157] Patients who experience discharge as punishment for non-adherence are often embittered by the experience and discouraged from future help-seeking.[158]

Post-MOUD Treatment Outcomes Given the robust body of published scientific and clinical research on MOUD and on MOUD retention, the limited literature on the clinical course of OUD following cessation of MOUD is quite striking. It is hoped that research currently underway by the Clinical Trials Network of the National Institute on Drug Abuse and other private research organizations linked via the Recovery Research Networks will help fill this void.[159] Readiness for cessation of MOUD has historically been judged by the patient's desire and decision to discontinue medication support, judgement of the clinical staff of the patient's readiness to taper off medication, evidence of substantial

and sustained rehabilitative progress, and the patient's motivation and confidence in sustaining OUD recovery without the aid of medication support.[160] What is known from the limited studies reviewed here is that most patients who taper from MOUD resume opioid use following cessation of medication support,[161] and that morbidity and mortality risks and related social costs rise in tandem with illicit opioid resumption.[162]

Flynn and colleagues, in a rigorous five-year follow-up study of 432 patients across 18 methadone maintenance clinics, reported that 28% of those studied were found to be in stable OUD remission.[163] In an earlier 10-year follow-up study of 95 former methadone patients, Maddux and Desmond found only seven percent had achieved continuous heroin abstinence in the three years preceding follow-up.[164] In studies comparing outcomes by medication types, rates of resumed opioid use post-treatment were higher following buprenorphine cessation than methadone cessation.[165] A five-year follow-up study of MOUD in England found five patterns of post-treatment heroin use: 'gradual decreasing' (20.9%), 'decreasing then increasing' (21.7%), 'continued low-level' (17.0%), 'rapid decreasing' (25.6%), and 'continued high-level' (14.8%).[166] Mohseni and colleagues, in an Iranian study comparing outcomes of methadone maintenance and participation in Narcotics Anonymous (NA), found lapses (isolated episodes of non-medical opioid use) higher in methadone treatment, while relapses (recurrence of continued non-medical opioid use and OUD) were higher in NA than in methadone treatment.[167] However, this study included both discharged and current MOUD patients. Studies by Maddux and Desmond and Clark and colleagues found follow-up abstinence rates higher in MOUD programs than in behavioral treatments not providing medication support.[168]

Reported post-MOUD abstinence rates vary widely—22%-86% with a pooled abstinence rate of 33% in Kornør & Waal's review of 14 studies conducted between 1973-2003.[169] Rates of abstinence or stable remission/recovery following discontinuation of MOUD vary by medication, length of follow-up period, and by definition of abstinence. A sample of reported post-MOUD abstinence rates are displayed in Table A2 in the Appendix.

Widely varying definitions of *abstinence* span opioid abstinence, abstinence from all illicit drugs, abstinence from illicit drugs and alcohol, enduing abstinence throughout the follow-up period, abstinence for the past year, and abstinence at a set time period prior to follow-up.[170] What is clear from Table A2 is that only a minority of patients who complete and discontinue MOUD treatment successfully achieve sustained OUD remission/recovery maintenance without medication support. Those who complete a planned tapering process (therapeutic discharge) have more than twice the post-treatment abstinence rates as those who drop-out or are administratively discharged.[171]

Studies of post-MOUD outcomes report as few as 10% of patients maintaining opioid abstinence, with nearly half exhibiting uncontrolled drug use or lost to follow-up.[172] The majority of MOUD patients are discharged with suboptimal treatment duration, without a planned or complete tapering process, and without a monitored plan for post-treatment recovery support.[173]

The low rates of post-treatment opioid abstinence extend across methadone, buprenorphine, and naltrexone treatment.[174] However, such rates are similar or higher than abstinence rates in OUD treatment within psychosocial modalities that do not provide medication support[175] and similar to rates of stabilization for other chronic

illnesses such as adult-onset asthma and hypertension in which treatment adherence problems parallel those for OUD treatment and where up to 50% of patients experience symptom recurrence each year.[176] Recent updates of OUD treatment guidelines suggest MOUD as the primary OUD treatment of choice and that psychosocial treatments be considered only as adjunctive to MOUD and not used in isolation of MOUD.[177] It is not yet possible to identify patient characteristics predictive of long-term post-MOUD abstinence and remission/recovery outcomes due to conflicting findings across available studies.[178]

MOUD Treatment and Retention in Adolescents The outcomes we have reviewed are based primarily upon studies of adult OUD populations. Research interest has recently increased in the use of MOUD in the treatment of OUD in adolescents and transition age youth,[179] in part due to the confluence of increased opioid-related deaths among adolescents and lowered rates of MOUD utilization.[180] Adolescents admitted to MOUD treatment report a high rate of adverse childhood experiences, which may be linked to early onset of OUD, opioid overdose risk, and high rates of treatment nonadherence.[181] Findings on MOUD retention among adolescents are mixed. While several studies note the acceptability of MOUD among adolescents and young adults[182] and treatment adherence and retention rates on par with those reported for adults,[183] other studies report lower retention rates.[184] Adolescents treated for OUD with approved medications , with or without concomitant behavioral interventions have higher retention.[185] Retention rates for adolescent and young adults who are Black, Indigenous, and/or People of Color (BIPOC) have been found to have slightly higher retention rates in methadone treatment than white patients.[186]

In spite of reports of positive treatment outcomes, there is considerable hesitancy among practitioners to prescribe MOUD to adolescents, which limits MOUD accessibility for youth experiencing OUD.[187] Access to MOUD among adolescents who could benefit from them is quite low.[188] McCarty et al., confirmed low MOUD access for Black youth and also found lower rates of MOUD retention among young adults compared to older adults.[189] There has also been a noted preference amongst some providers for use of naltrexone over both buprenorphine and methadone in the treatment of adolescent OUD patients, despite the limited data to support greater effectiveness of naltrexone in this population.[190] While rates of buprenorphine treatment of OUD for adults are increasing, such rates actually declined for adolescents between 2015-2020.[191] Factors that increase the probability of adolescents being treated with MOUD include being male, lower levels of education, and prior arrests—potential proxies for greater problem severity.[192]

Studies of adolescents and young adults confirm many of the general findings in this report: low rates of MOUD utilization and adherence, equivalent or low rates of retention, the import of dosage of both MOUD and psychosocial services, the ineffectiveness of short tapering protocols, and the high risk of post-treatment OUD recurrence.[193] Significant advancements have been made in the treatment of adolescent SUDs, including widely available training in the use of manualized evidence-based behavioral interventions such as motivational enhancement therapy, cognitive behavioral treatment, and adolescent community reinforcement approach.[194] However, there have been no comparable efforts related to the manual-guided treatment of adolescents with integrated MOUD and psychosocial therapies.[195]

Factors Influencing Medication Retention

Most striking in the voluminous studies on obstacles to retention in MOUD treatment is the sheer volume of such obstacles and their span across personal, institutional, and contextual (geographic, regulatory, cultural) factors.[196]

Personal factors that contribute to higher rates of MOUD treatment discontinuation begin with a cluster of patient demographics: age (younger), gender (male), race (African American, Hispanic), lower educational achievement, housing instability, and living a greater travel distance to the medication dispensing location. These are further complicated by key clinical characteristics found in those at highest risk of attrition: greater confidence in maintaining opioid abstinence without support of medication, high opioid craving, lower motivation to cease drug use, prior use of illicit methadone or buprenorphine, lower social support (recovery capital), past history of drug injection, past overdose history, and, in some reports, psychiatric co-morbidity. As suggested by a brief review by Stauffer,[197] some MOUD attrition factors associated with lack of motivation or recalcitrance may in fact result from brain injuries and neurocognitive impairments associated with past opioid overdoses.

Other retention-inhibiting factors include exposure to street myths about methadone or buprenorphine, experience of or fear of medication acute or long-term side-effects, fear of medication effects on unborn or newborn children, concerns about still being "drug dependent" (fear of "substituting one addictive drug for another" / not being in "full recovery"), fear of future medication inaccessibility, unfulfilled expectations related to improved quality of life, and the desire to finally feel "cured"—free of control by drugs, medication, and the treatment program. Studies of MOUD attrition also note such factors as payment unaffordability, the burden of daily dosing, work/school schedule conflicts, and encouragement to end use of medication by family members, friends, and members of recovery communities.[198]

In one of the most in-depth studies of patient reasons for MOUD discontinuation, Reisinger and colleagues found the following: disagreement with inflexible program rules; conflict with staff; "feetox" (discharge for non-payment of fees); schedule conflicts with work, school and family responsibilities; desire to escape dependence on the medication and the program; and incarceration.[199] The multiplicity of inhibiting factors identified in these studies suggests the need for individualized evaluation of and assertive clinical responses to personal expectations of medication effects on quality of life, obstacles related to meeting those expectations, and each patient's evolving experience of MOUD.[200]

Polydrug use (concurrent or sequential use of multiple licit and illicit drugs) is common among those experiencing OUD.[201] As many as half of MOUD patients report concurrent use of prescribed MOUD and heroin[202] or methamphetamine.[203] Polydrug use patterns span periodic episodes of such use or a continual pattern throughout maintenance on MOUD.[204] Polydrug use is particularly prominent among males[205] and among those entering MOUD treatment with higher risk factors e.g., history of daily injection drug use, public injection, sharing of injection equipment, psychiatric comorbidity, or past overdose.[206]

Polydrug use is a prominent factor in MOUD attrition.[207] Studies conclude that continued use of illicit opioids, concurrent or sequential use of cocaine / methamphetamine and benzodiazepines, and excessive drinking even at reduced levels is a major contributing factor in MOUD treatment discontinuation.[208] Polydrug use in the context of MOUD treatment has been linked to worse in-treatment and post-treatment outcomes, more severe psychopathologies, and increased mortality risks.[209] Testing positive for one drug during MOUD treatment doubles the risk of treatment discontinuation, and testing positive for multiple drugs quadruples the risk of attrition.[210] Remission from one SUD reduces but does not eliminate the risk of development of another SUD—a risk particularly associated with being a young, unmarried male with psychiatric comorbidity.[211] Though clinicians have expressed concerns about drug substitution following cessation of MOUD, some studies report no such increased risk in post-MOUD outcomes.[212] Such contradictory findings could reflect differences in study methodology and differences across clinical populations.

A rarely addressed issue is the potential influence of smoking (concurrent nicotine dependence) on MOUD retention and related clinical outcomes. Studies to date confirm the following:

- The majority (80%-98%) of adult and adolescent MOUD patients report tobacco dependence at admission[213]—four to six times the smoking rate in the general population.[214] They also report early onset of smoking (13 or younger), high smoking intensity (20+ cigarettes a day), and near-universal choice of menthol cigarettes, but high awareness of smoking health risks and high interest in smoking cessation.[215]
- MOUD patients who smoke are at increased risk of experiencing tobacco-related disease and death (e.g., cancer, respiratory disease, heart disease, liver disease).[216] A long-term follow-up study of 53,172 hospitalized patients with opioid use disorder found that 39% died of smoking-related conditions.[217]
- The number of cigarettes a day smoked by MOUD patients rises in tandem with the number of psychiatric symptoms experienced;[218] smoking among MOUD patients is also associated with hazardous drinking.[219]
- A majority of MOUD patients express a desire to stop smoking,[220] yet rates of smoking cessation are low among opioid users and MOUD patients[221]—far lower than rates for the general population.[222]
- The high smoking rates and low quit rates among MOUD patients may be linked to nicotine's potentiation of opioid effects and its reduction of restlessness, irritability, and depression.[223] Smoking intensity (number of cigarettes per day) is higher among patients on agonist medication than those on antagonist medication,[224] and smoking intensity reduces by nearly a third when antagonist medication is initiated.[225] Heavy-smoking methadone patients require higher dosages of methadone,[226] and those with higher smoking intensity report more frequent opioid withdrawal symptoms and higher anxiety than those with lower smoking intensity—factors that could influence treatment adherence and retention.[227] Cigarette consumption increases in the two-hour window prior to methadone dosing, again suggesting its potential role in withdrawal and related anxiety management.[228]

- Nicotine replacement therapy combined with counseling increase rates of successful smoking cessation among MOUD patients[229] but is rarely provided within the context of MOUD.[230]
- Patients undergoing inpatient opioid withdrawal who smoke have a higher rate of opioid withdrawal discomfort which could be a factor in treatment retention.[231]
- MOUD patients who achieve tobacco abstinence have higher rates of MOUD adherence than those who are current smokers.[232] Smoking is associated with higher risk of MOUD non-adherence (e.g., in-treatment illicit opioid use) than among current MOUD non-smoking patients.[233] Compared to nonsmokers, smokers are more likely to report past-month heroin use.[234]
- Smoking cessation and MOUD retention are associated in some studies,[235] but not in others;[236] the exact nature and mechanisms involved in the smoking and MOUD retention relationship remain unclear due to insufficient investigation.

Motivations for illicit opioid use and polysubstance use among MOUD patients are similar to those for pre-treatment illicit opioid use: intensification of pleasure (pharmacological reward), relief/release (self-medication of stress-induced craving and other physical/emotional distress),[237] and impulsive use in the face of family/social influence and high availability.[238] Concurrent drug use in the context of MOUD treatment may indicate efforts to manage withdrawal distress, craving, pain, medication side effects (e.g., sleep disturbance), or anxiety[239]—a pattern that may reflect suboptimal medication dosing and the potential need for dosage elevation.[240] Broad patterns of polydrug use during treatment signal the potential for worse treatment outcomes—a potential proxy for medical/psychiatric comorbidity[241] and the need for intensified recovery support services.[242] For example, motivation for benzodiazepine use in as much as twenty-five percent of MOUD patients has been linked to greater problem severity and complexity, efforts to enhance medication effects, and efforts to manage anxiety and depression.[243]

Included within the rubric of polydrug use among MOUD patients is past self-treatment with diverted methadone or buprenorphine. Obtained in the illicit drug markets, the motivations for such unsupervised but often therapeutic use include preventing withdrawal, reducing the intensity of withdrawal distress, and self-tapering off heroin or prescription opioids when professionally directed MOUD treatment is unavailable, unaffordable, undesirable, or perceived as too burdensome in its requirements.[244]

In contrast to other drugs (e.g., cocaine, methamphetamine, illicit benzodiazepines), there is no clear nexus between concurrent cannabis use during MOUD and treatment adherence or retention, with mixed results across studies.[245] Published reports to date link daily cannabis use to increased MOUD retention,[246] report therapeutic effects of cannabis during early MOUD treatment,[247] find negative effects on retention,[248] or find no effects on in-treatment illicit opioid use or MOUD retention.[249] The primary motivations for cannabis use during MOUD is management of withdrawal distress and related anxiety and efforts to reduce the needed dosage of more dangerous substances[250]–functions that may be related to under-medicating of withdrawal

symptoms Cannabis use tends to increase during MOUD induction but then decline with medication stabilization.[251]

Similarly, although rates of OUD and psychiatric comorbidity are high (nearly 60%),[252] there is no clear evidence that co-occurring depression or other psychiatric disorders lower rates of MOUD treatment retention,[253] with studies showing mixed results based on specific diagnosis and specific types of MOUD.[254] Peles et al., found that psychiatric comorbidity and increased rates of pain actually increased long-term MOUD retention.[255] Prescribing psychiatric medications (e.g., antidepressants) along with MOUD may enhance treatment retention for some patients.[256] Ramey et al., similarly found that diagnosis of anxiety or depression increased MOUD retention rates among adolescents and young adults.[257]

Many addiction treatment providers and people who use opioids reject MOUD or advocate MOUD only as a temporary tool of stabilization until the “real work of recovery” can progress, at which time MOUD can be discontinued. Scientific and clinical support for that position would require: 1) evidence that long-term OUD remission and recovery are possible for the mass of OUD patients without medication support, 2) identification of the essential ingredients of “recovery work” and that such elements are attainable for the majority of people experiencing OUD, and 3) an effective protocol for transitioning from MOUD to remission and recovery maintenance without medication support in a way that also lowers risk of post-MOUD morbidity and mortality. To date, these three requirements have yet to be met.

Stigma attached to MOUD dissuades help-seeking, creates a preference for suboptimal medication dosages, leads to misinterpretation of normal physical/emotional discomforts as medication side-effects, exaggerates fears about medication withdrawal, and exerts pressure to discontinue medication support.[258] Such stigma may be even more pronounced in communities of color and in rural communities where patients experience multiple interacting barriers to MOUD engagement and retention.[259] Women, particularly women of color, may also fear the double bind of being encouraged to use MOUD during pregnancy only to then be penalized for MOUD involvement after delivery.[260]

Stigma attached to MOUD permeates the popular culture and the illicit drug culture, operates to inhibit and shorten MOUD treatment, and can even pervade the OUD treatment milieu.[261] Some routine practices in MOUD treatment (e.g., mandatory supervision of urine drops for drug testing and medication consumption, distrust based on exaggerated fears of medication diversion, etc.) can leave MOUD patients feeling more like a recalcitrant child or criminal than a medical patient and contribute to treatment flight.[262]

Public stigma attached to MOUD is often linked to widespread perception of “substituting one addictive drug for another” (a view held by 66.6% of U.S. adults[263]). and the related view that MOUD patients remain on medications for too long—a view shared by many addiction counselors[264] and many MOUD patients.[265] There are, however, marked differences between MOUD and illicit opioids in terms of their effects and safety, and the majority of MOUD patients receive medication support for periods too brief to receive full therapeutic effects and protection from OUD-related mortality risks.[266] The safer route of administration, slower onset of action, and longer half-life of MOUDs create a zone of stability in which the MOUD patient can function normally

without impairment from the vacillating periods of intoxication, sedation, and withdrawal distress characteristic of active OUDs.[267]

Stigma-related beliefs encountered and internalized by MOUD patients may lead to medication discontinuation out of fear of prolonged dependence on the medication and the treatment program.[268] Stigma related to MOUD encountered in recovery mutual aid groups may account for the low rate (10.4%) of patients who concurrently participate in medication support and recovery support groups[269] and for the tendency of some MOUD patients to sample, select, and do well in support groups in which less stigma is attached to MOUD, e.g., Alcoholics Anonymous, Methadone Anonymous, or Medication-Assisted Recovery Anonymous versus Narcotics Anonymous.[270] MOUD stigma encountered within mutual aid groups can take many forms: denying the right of MOUD patients to share in group meetings, encouraging discontinuation of MOUD treatment in member-to-member communications, refusal to sponsor MOUD patients, denying MOUD patients' right to sponsor others or fulfill other service roles, and denial of right to celebrate "clean time".[271] Denial of access to support or limitations on level of participation is also evident within other recovery support institutions, including recovery residences.[272] Added to the import of such restrictions is the emergence of these new recovery support institutions (recovery residences, recovery high schools and collegiate recovery programs, recovery community centers, the Recovery Café Network, sober active communities (The Phoenix), recovery ministries, and recovery-focused projects in the arts and music as prominent features of the culture of recovery in the United States and other countries.[273] Psychological safety—an antidote to stigma—is a critical ingredient mediating recovery outcomes within these new recovery support mechanisms.[274]

Attitudes toward OUD treatment medications among people in SUD recovery vary widely and can include negative attitudes that dissuade treatment seeking and retention.[275] Personal recovery status per se is not a barrier to belief in MOUD effectiveness among addiction counselors,[276] but a stronger 12-Step orientation, lower levels of education, and working in non-MOUD addiction treatment settings or faith-affiliated organizations are associated with decreased perception of MOUD effectiveness and acceptability, even though such attitudes may be softening.[277] There are MOUD treatment programs in which recovery mutual aid participation is high and perceived by patients to be supportive of treatment goals.[278]

Although many factors in the future could lessen OUD- and MOUD-linked stigma—new medications freed from the social taint of history, new protocols of medication administration, and enhanced public and professional knowledge of the value of MOUD, it is doubtful that MOUD-related stigma will lessen substantially until a vanguard of people in medication-supported recovery participate in public and professional educational and advocacy efforts that offer living proof by putting a positive face and voice on the role of medications in OUD recovery.[279] Long-acting injectable medications may have different stigma dynamics, but research is still inconclusive on such effects.[280] At present, social stigma has left people recovering from OUD the least comfortable of all those in SUD recovery from publicly disclosing their recovery status and stories.[281]

In spite of such obstacles, patients cite multiple reasons for continuing MOUD, including positive achievements while in treatment, fear of physical and emotional difficulty withdrawing from MOUD, prior failed attempts at medication discontinuation,

knowledge of others who were unsuccessful with medication tapering, and low self-confidence in one's ability to maintain abstinence without medication support.[282] In brief, MOUD patients balance fears related to current medication use against fears of addiction recurrence and its consequences in their decision to continue or discontinue medication support.[283]

Program-related factors related to high rates of MOUD dropout include low dose medication policies/practices (at a time when fentanyl is precipitating the need for higher MOUD dosages),[284] arbitrary limits on duration of MOUD, an inconvenient or unsafe medication dispensing location, limited or inconvenient dispensing hours, a peer treatment milieu that encourages illicit drug use, punitive policies (e.g., reducing medication dose for rule infractions), patient feelings of being disrespected and disempowered within the care process, mandatory group counseling, punishment for alcohol or illicit drug use (e.g., withholding medication, medication dosage reduction, administrative discharge), and encouragement by treatment staff for medication tapering/cessation.[285] MOUD patient attrition is greater within "high threshold programs" that require counseling, drug testing at every visit, or have other requirements that increase demands for patients' time and tolerance.[286]

Attrition and retention may also be related to a program's preferred protocol for tapering off MOUD. Slower and smaller dose reductions over longer periods of time are associated with higher retention rates, less opioid use during the tapering process, and successful treatment completion,[287] but may not have an effect on other post-treatment treatment outcomes.[288] Rapid tapering is also associated with higher risk of overdose mortality.[289]

Environmental, cultural and professional factors associated with discontinuation of MOUD include social stigma attached to opioid dependence and OUD medications, particularly methadone maintenance; negative attitudes toward MOUD from treatment professionals working in abstinence-based programs;[290] and remote travel distances to access MOUD (e.g., more than five miles).[291]

Negative attitudes toward OUD medications within mainstream recovery support institutions (recovery mutual aid groups, recovery residences, etc.), including a requirement for medication cessation prior to full participation, may inhibit help-seeking or limit duration of medication support.[292] Despite the risk of encountering such attitudes, participation in recovery mutual aid groups and other recovery support institutions is associated with better MOUD clinical outcomes and a planned treatment completion.[293] Limited MOUD knowledge and lack of expressed support for MOUD are pervasive within community systems of care and add to forces that inhibit MOUD initiation and retention.[294] Additional factors include difficulty affording treatment costs in lower resourced areas and high-deductible insurance coverage for MOUD.[295]

A challenge at the policy level is how to shape MOUD reimbursement schemes that encourage retention without incentivizing exploitive practices, such as organizations shrinking the scope and quality of services offered to maximize profits. Such exploitive quality dilution could enhance retention by lessoning required levels of participation at the expense of treatment adherence and treatment outcome. This could at a systems level such practices could set the stage for a future public backlash regarding all MOUD.

MOUD retention rates decline as the number and intensity of personal, program, and environmental barriers increase.[296] The majority of people seeking MOUD treatment present with OUDs of significant severity, complexity and chronicity and experience multiple barriers to treatment initiation and retention, including programmatic and community barriers. Such barriers may particularly inhibit help-seeking among special OUD subpopulations such as adolescents and young adults.[297] The volume of such obstacles suggests the need for a comprehensive menu of support services and regular in-treatment "checkups" and assertive responses to identified barriers to enhance retention and long-term remission and recovery outcomes.[298]

Psychosocial Support and MOUD Retention

In 1981, Paul Cushman, Jr. described the wide-ranging quality of methadone maintenance programs—from little more than methadone filling stations to vibrant recovery supportive environments.[299] That depiction seems equally applicable today and also encompasses the variability of psychosocial support within office-based treatment of OUD with buprenorphine or naltrexone. Psychosocial support continues to be a required component of specialized opioid (methadone) treatment programs, and office-based treatment programs utilizing buprenorphine are recommended but not required to provide support services. The former most often provide in-house non-pharmacological support services, and the latter provide a mix of in-house and external referrals for support services that include individual/group counseling and self-help meetings.[300] Most providers of buprenorphine treatment believe psychosocial services improve treatment outcomes, but that they are not able at present to provide an adequate level of such services within their service setting.[301] Private for-profit organizations that now make up the bulk of MOUD delivery in the United States are less likely to have a comprehensive range of support services than nonprofit organizations.[302]

The potential role of psychosocial support in enhancing MOUD retention remains unclear.[303] A number of studies and study reviews conclude that psychosocial support interventions enhance MOUD retention and other clinical outcomes.[304] Even when clearly recommended, the exact content of MOUD-based counseling and related services, their dose and duration, and best qualifications for their delivery remain unclear.[305]

Other studies find no evidence or only limited evidence supporting such services or report untoward effects of psychosocial services on MOUD retention.[306] Effectiveness of psychosocial services provided in tandem with MOUD differ across types of interventions, medications, clinical subpopulations, and service delivery settings.[307] Counseling frequency and intensity have not been consistently linked to improved outcomes from MOUD,[308] except in distinct clinical subpopulations (e.g., patients with PTSD or other cooccurring psychiatric disorders[309] or patients lacking stable shelter[310]). The fact that the majority of studies of the effects of psychosocial support linked to MOUD focus only on during-treatment outcomes also contributes to the ambiguity of their role in OUD remission and recovery. What remains unclear is whether and the extent to which such in-treatment services affect outcomes for MOUD patients after medication discontinuation.

As a result of equivocal findings, SAMHSA and the FDA have relaxed mandated counseling requirements, and MOUD clinical guidelines have moved to an expectation of availability of psychosocial support services rather than mandating such services.[311] Relaxation of counseling requirements does not inevitably lead to a dramatic reduction in MOUD patients' utilization of counseling services.[312]

The ambiguity of findings may be related to differences in definitions of "psychosocial support," clinical subpopulations studied, types and quantity of support offered, and differences in cultural contexts. Existing studies on psychosocial support in conjunction with OUD medications most frequently include routine counseling or case management, 12-Step facilitation, cognitive behavioral therapy, motivational interviewing, and relapse prevention. The one psychosocial adjunct with strong evidence for positive effects on medication retention is contingency management (CM), but CM is not a mainstream practice within most OUD treatment settings.[313]

Programs including psychosocial components vary widely in quality, and clinical outcomes vary even among counselors working within the same program. McLellan and colleagues conducted a study to determine the range of clinical outcomes across a selection of addiction counselors working in a methadone maintenance program. Evaluation based on multiple performance measures found a wide range of clinical outcomes depending on the counselor to which a methadone patient was assigned.[314] MOUD "treatment as usual" and the included psychosocial services constitute a "black box" with only vaguely defined elements, dosages, and undefined levels of fidelity monitoring. That ambiguity compromises the ability to isolate and evaluate the role of particular psychosocial services within MOUD.[315] Questions remain unanswered related to the most potent mechanisms of psychosocial support, the optimum dosage and duration of psychosocial support provided in tandem with medication support, whether service outcomes differ across voluntary and coerced participation, and the value of matching (in a stepped care approach) particular psychosocial support services to levels of problem severity and recovery capital.[316]

It is not clear how mainstream addiction counseling is practiced in the MOUD context and whether there have ever been rigorous evaluations of high-quality addiction counseling guided by rigorous clinical supervision within that context. Numerous factors suggest the lack of a true test of the effects of addiction counseling on MOUD retention and remission and recovery outcomes.

First is the lack of a model of counseling within MOUD treatment settings. Carroll and colleagues introduced a technology model of psychotherapy research that exerted considerable influence on the refinement of addiction counseling via the development of motivational enhancement therapy, cognitive behavioral therapy, 12-Step facilitation, and various family therapy approaches.[317] This model required each counseling approach to define its active ingredients, operationalize those ingredients within a prescriptive counseling procedure manual, provide competency-based training of all individuals delivering the counseling, assure fidelity to counseling procedures via rigorous clinical supervision, utilize standardized instruments to measure client responses to counseling, and to individualize counseling based on client responses to clinical interventions. To date, no such specific counseling model has been developed for MOUD patients that meets elements contained in other evidence-based SUD counseling manuals. Additionally, while considerable attention has been devoted to the

effects of medication dosage on treatment outcomes, little comparable attention has been given to the dosage effects of psychosocial interventions, with many studies evaluating what the authors would consider a sub-therapeutic dosage of such support, e.g., one hour per week or “as needed” counseling. Reports that efforts to create a “patient-centered” approach to counseling within MOUD programs require a significant adjustment by counselors are themselves quite telling.[318]

Second is the wide variability of backgrounds of those providing counseling and allied services within the context of MOUD. The lack of a homogeneous addiction counselor entity means that MOUD patients will be served by people of widely varying educational and experiential backgrounds and widely varying skill levels, from counselors with little prior experience (given the high rate of counselor turnover) to counselors with general SUD counseling backgrounds but not expertise with OUD treatment to tenured counselors with both educational and lived experience of OUD remission and recovery.[319] The limited availability and unknown quality of onsite “counseling” delivered in conjunction with opioid medications[320] makes it difficult to draw definitive conclusions about their value. This is particularly the case with counseling delivered by medical personnel with unknown levels of counseling-related training in office-based buprenorphine treatment.[321] Guidelines related to psychosocial support within MOUD do not specify the level of education, training, and experience required to deliver such services.

Third is the high counselor to patient ratio in methadone maintenance programs—typically 1:40-60 with some caseloads reported to be in excess of 100 patients (compared to a 1:5 to 1:8 for counselors working in inpatient or residential SUD rehab programs and an average caseload of 32 for all outpatient addiction counselors in the U.S.[322] Challenges posed by excessive caseloads are intensified by methadone programs having fewer PhD- and Master’s-trained therapists and fewer therapists that are licensed or certified.[323] Excessive caseloads lower counseling dose per patient—important given that higher hours of received counseling is linked to lowered rates of in-treatment and post-treatment SUD recurrence.[324] Excessive patient caseloads erode treatment processes and outcomes and are a catalyst for treatment staff turnover.[325] Counselor caseloads in methadone maintenance are larger in part due to longer treatment duration and continuation of highly stabilized patients in less need of counseling support. However, there is little data on allocation of patients across phases of treatment within what appears on the surface quite excessive caseloads for counselors working within medication maintenance programs.

Fourth is the large portion of counselor time in MOUD programs consumed by non-clinical roles and activities.[326] These demands include liaison with referral sources, arranging public assistance applications, assuring payment authorization and patient payment of service fees, addressing scheduling problems, tracking down patients who missed dosing appointments, assisting patient access to medication while traveling, supervising urine drops, enforcing program rules, keeping up with a “suffocating” level of paperwork to assure compliance with all regulatory and billing requirements, resolving patient-patient and patient-staff conflicts, attending untold numbers of non-clinical meetings, all while fending off questions from patients, family members, other professionals, and the public regarding the legitimacy of MOUD.[327] All such activities may be needed in the context of MOUD treatment, but these activities do not constitute

the essence of recovery-focused addiction counseling. Reports of only sporadic, subtherapeutic counselor-patient contact (e.g., billed “counseling sessions” that are little more than brief exchanges while a patient is standing in line for medication) are particularly troubling.[328]

Finally, there is the paucity of attention to the frequency and quality of clinical supervision of MOUD counselors within studies of psychosocial support as a component of MOUD. Given these circumstances, how could there ever have been a legitimate test of the role of addiction counseling in MOUD adherence, retention, remission, and recovery? Many patient factors considered as prerequisites to positive MOUD counseling outcomes (e.g., motivation, medication adherence, participation in counseling sessions, etc.) are in actuality consequences and outcomes of high-quality addiction counseling. As such, these so-called “patient factors” are instead measures of MOUD program effectiveness.[329]

Also of note is that recovery mutual aid participation, peer recovery support services, or participation in allied recovery support institutions (e.g., recovery residences, collegiate recovery programs, recovery community centers, recovery ministries, etc.) are less likely to be included in reviews of psychosocial support in MOUD.[330] This omission ignores evidence that activities such as participation in Narcotics Anonymous and related service work (e.g., sponsoring others), peer recovery coaching, peer navigation, and family support services enhance OUD remission and recovery outcomes, including treatment initiation, adherence, and retention.[331] Enhanced recovery outcomes supported by prolonged mutual aid participation are a product of such mechanisms of change as exposure to recovery role models, increased recovery capital, reconstruction of identity and social networks, heightened commitment to long-term recovery, enhanced coping skills, and increased meaning and purpose in life.[332] Such resources are noteworthy for their wide geographical and online availability, their low threshold of access (no fees, intake procedures, or waiting lists), their collaborative role as an adjunct or alternative to professional treatment, and the growing body of research on their effects on long-term recovery outcomes.[333]

Thirty-eight percent of a survey of 24,495 members of Narcotics Anonymous reported regular opioid use before joining NA,[334] yet few rigorous studies exist on this population, the mechanisms of change within NA-facilitated OUD remission and recovery, and NA members’ past or concurrent participation in MOUD treatment. In 2022, only 21% of U.S. MOUD patients attended a self-help group in the 30 days prior to their discharge compared to 29% of OUD patients in non-MOUD treatment settings.[335] Assertive in-treatment and post-treatment linkage of OUD patients to mutual aid resources is missing or weak in both MOUD and non-MOUD settings. Studies are also limited of the role of groups other than NA and AA (e.g., Methadone Anonymous, Heroin Anonymous, Opiates Anonymous, Prescription Drugs Anonymous, and Medication-Assisted Recovery Anonymous), including secular and religious mutual aid alternatives (e.g., SMART Recovery, Celebrate Recovery).[336] AA and NA remain the most available and utilized of recovery mutual aid groups.[337]

A study by Peles and colleagues compared long-term (10 years+) methadone patients with a sample of people in long-term OUD recovery (10 years+, mostly NA members) without MOUD.[338] Methadone patients reported higher rates of psychiatric illness, chronic pain, sleep disturbance, and cognitive impairment; the non-MOUD

subjects were younger, reported greater problem severity and higher rates of polydrug and opioid use and were more likely to have also quit smoking as part of their recovery process. The study of the relationship between MOUD and recovery mutual aid participation is at an early stage. It remains unclear the extent to which combining MOUD and mutual aid participation enhance treatment retention and outcomes as well as the extent, direction, and durability of such influence. For example, does mutual aid participation enhance MOUD adherence, retention, abstinence, and quality of life outcomes for MOUD patients? Do medications approved for OUD treatment enhance NA retention and OUD remission and recovery outcomes of NA members? Are the combined effects greater than that which could be expected from their effects in isolation? Are the effects additive or synergistic? Do combined effects differ across medications or particular recovery mutual aid organizations? At present, we simply do not have definitive answers to such questions.

A number of studies of peer-based recovery services delivered in conjunction with medication support suggest their potential to elevate MOUD initiation,[339] medication continuation, and related clinical outcomes,[340] while other studies report no effects of a peer intervention on MOUD retention.[341] A study by Berge and colleagues examining the effects of inclusion of staff with lived experience of addiction and recovery found that such inclusion significantly improved treatment retention.[342] Variations in outcome reports on the role of peer-based recovery support services in MOUD remission and recovery may spring from diverse definitions of “peer”; widely varying practices related to screening, selection, training, and supervision of peers; different role definitions within peer-based services; and different effects of peer services across diverse clinical populations and cultural settings.[343]

Treatment initiation has been linked to the density of recovery support within one’s social network and depletion of network members who use drugs,[344] but this role has not been fully confirmed in the MOUD treatment context. Medication support alone is not assurance that enhanced social functioning will increase in tandem with OUD remission,[345] but studies do reveal increases in recovery capital over time among most patients participating in MOUD treatment.[346] Bing et al., found improved quality of life during early stages of MOUD but a ceiling effect on incremental improvements for those in long-term MOUD maintenance.[347] It is possible that psychosocial support could enhance continued quality of life enhancements when such a ceiling has been reached from the effects of medication. Cumulative service dose—adherence, retention and combined effects of medication and psychosocial support—may be critical to long-term optimal outcomes.[348]

The potential import of psychosocial support on recovery outcomes related to MOUD is found in this singular finding: many of the obstacles to MOUD retention are precisely the areas in which psychosocial support services can exert their greatest influence—minimizing misconceptions/stigma regarding MOUD; motivational enhancement; resolving traveling, scheduling, and other logistical barriers to MOUD adherence; improving self-reported quality of life; elevating self-efficacy and self-image; enhancing educational/employment/income opportunities; helping achieve and maintain housing stability; improving management of co-occurring substance use, psychiatric, or medical conditions; elevating family health and reducing conflict; disconnecting from drug-supportive relationships; and building a recovery-supportive social network.[349] In the

literature reviewed in this report, most reported gains achieved by MOUD patients occurred in the first year to two years of treatment with much smaller increments of improvement in subsequent years. Is it possible that there is a ceiling on gains achieved through MOUD that can only be raised by the addition of psychosocial support services and that additional gains are most likely to occur in later stages of recovery—long after the short periods of psychosocial services are most accessible?

Enhancing MOUD In-treatment and Post-treatment Remission and Recovery Outcomes

In a 2001 review of the OUD recurrence vulnerability of patients following discharge from methadone maintenance, Magura and Rosenblum declared: “The hard fact is that we do not yet know how to improve post-treatment outcomes for methadone patients.”[350] Nearly a quarter century later, the same could be said for all MOUD patients. Studies underway may help illuminate the processes and outcomes of patients wishing to discontinue medication support,[351] but the present review underscores how little is known about the long-term trajectory of the lives of patients who discontinue OUD medication support beyond the risk of OUD recurrence and death. There is a critical need for updated studies that test and extend present findings in light of transitions in the illicit opioid market, changes in the characteristics of OUD patients, refinements in OUD treatment protocol, and the evolving menu of OUD treatment options.

What is known at present would suggest several directions in the future of OUD care with a particular focus on MOUD retention and its scientific evaluation.

1. Expand Treatment Goals and Measure Retention Outcomes Across the OUD Severity Spectrum. This step would extend measurement of MOUD treatment effects beyond the binary indicator of illicit opioid use or illicit opioid abstinence to encompass gradations in drug use; the severity of personal, family, and community injury; as well as the accrual of remission and recovery assets (personal, family, and community recovery capital). We know little, for example, about the application of MOUD to those experiencing opioid-related problems that do not yet meet diagnostic criteria for an OUD.[352] Questions could be answered regarding why some people who use opioids develop OUD and others do not, and why some develop brief periods of opioid problems resolved via natural resources while others go on to decades of severe, complex and chronic OUDs in spite of multiple and varied treatment approaches. How do such patterns differ in their pathogenesis, course, response to treatment, and long-term outcome? Could OUDs be further delineated with differential treatment responses based on the number or particular combinations of diagnostic criteria in a manner similar to what Hoffman and Kopak have suggested for alcohol use disorders?[353] Would, for example, time-limited, low-dose buprenorphine maintenance at early stages of subclinical, opioid-related problems prevent the development of an OUD? Would non-abstinent OUD treatment approaches prove to be particularly effective with those seeking assistance with lower problem severity, shorter duration of opioid use, and greater evidence of control over drug use decision making? Would such delineation of clinical subpopulations help delineate who is and is not a good candidate for MOUD or their psychosocial alternatives?

Medication effectiveness measures could ideally be expanded to consistently include quality of life measures as well as reductions in frequency, quantities, and high-risk circumstances of opioid use that fall short of continuous abstinence but result in clinically meaningful enhancements of global health and social functioning. The expanded goals of MOUD treatment could span: 1) reduce harm and protect life and health, 2) promote OUD remission, 3) promote OUD recovery, 4) break cycles of intergeneration transmission of SUD and related problems, with discrete measurements developed within each of these categories. Explicitly expanding the goals of MOUD would link treatment retention to a broad spectrum of outcome measures, including personally and socially meaningful outcomes that do not rely on complete abstinence.[354]

Evaluating such expanded treatment goals would be greatly enhanced if professional consensus could be reached on definitions of *adherence*, *retention, abstinence, recurrence,* and *recovery* as used in the context of MOUD evaluation studies as well as more detailed elucidation of the stages of long-term OUD remission and recovery. Also missing from the literature are focused studies of people who achieve OUD remission/recovery without the aid of medication support (e.g., on their own, through alternative treatments, or in Narcotics Anonymous or a faith-based recovery pathway) and comparisons of those who succeed or fail in the transition from MOUD to remission/recovery maintenance without continued medication support.
It may also be time to recognize that for some people OUD is irreversible,[355] to achieve a consensus definition of *refractory OUD*, and to formulate appropriate clinical responses to such irreversibility within the context of MOUD as is done within palliative care models for other chronic and potentially terminal illnesses.[356] That interest aligns with increased investigations of non-abstinent approaches to OUD treatment and the cross-fertilization and integration of harm reduction, OUD treatment, and recovery support services.[357] The American Society of Addiction Medicine has recently taken the position that MOUD should be available to individuals across all stages of change and that abstinence should not be a precondition for admission or a condition for retention.[358]

A wide variety of measures mark existing MOUD evaluation studies,[359] but most studies use subtraction measures as indicators of efficacy and effectiveness.[360] Such measures focus on reduced rates of opioid and other illicit drug use and OUD/SUD diagnosis, infectious disease (HIV/HCV) status and related risk behaviors, emergency room visits, hospitalizations, adverse fetal outcomes for pregnant women, drug-related deaths, arrests/incarcerations, child neglect/abuse, unemployment, and homelessness.[361] Far fewer studies focus on addition measures: positive changes in emotional and relational health, educational achievement, employment and professional advancement, civic involvement, social contribution, sustained improvements in quality of personal and family life, happiness, and life meaning and purpose.[362]

Traditional MOUD/SUD clinical evaluations focus on what opioid use did <u>to</u> the patient and the extent to which this damage may be ameliorated and future damage prevented through the vehicle of specialized professional treatment. New innovations in service delivery might come from examining what opioid use did <u>for</u> the individual and addressing the extent to which such functions may be addressed within the context of OUD treatment and related recovery support services.[363] Such “doing for” effects in the authors’ clinical experience include the experiences of pleasure, protection,

performance enhancement, relief, release, respite, wholeness, belonging, and purpose.[364] Within the most severe patterns of OUD, the drug relationship becomes everything until it becomes nothing—when the perceived instrument of one's salvation becomes an instrument of one's own destruction.

The anticipated and experienced rewards that serve as catalysts of opioid experimentation and maintenance are numerous and often evolve over time. Such rewards span pleasure/ecstasy/joy/laughter/excitement/exhilaration within an otherwise bleak life; a trigger for artistic/musical expression; relief and transient release from physical and emotional distress—including a balm for unimaginable and unforgiveable traumatic wounds; a buffer or protective shield against the insults of an arduous life; an aid in the search for transcendence and meaning; an act of protest/defiance against social injustice, political disillusionment, or personal despair; respite from the perpetual demands and threats posed by the street hustles and straight (licit) hustles required for addiction maintenance; a sense of completeness/wholeness/subjective wellbeing—as if missing pieces of one's self were being filled in; a source of courage to face difficult or unpleasant tasks (e.g., commonly used by sex workers);[365] the experience of connection/acceptance/belonging/camaraderie/community—being "at home" with kindred spirits in a subterranean culture of outsiders; and a sense of structure and purpose that drives daily activities and priorities. Differing levels of personal vulnerability and the intensity of such needs separate those with deep commitment to and entrapment within "the life" from the occasional "chipping" of heroin and other transient drug experimentation.[366] When the former commitment occurs, neurobiology of addiction maintenance trumps all other motivations. Once reduced or fully quelled via medication support, those other motivations may again come into play in affecting MOUD retention and risk of OUD recurrence.

In thinking of such needs and functions and their replacement, it is interesting to contrast the rigors of hustling in active addiction to the passivity of waiting in queue to receive one's medication at a methadone clinic. Do some MOUD patients disengage from treatment simply from boredom and the seductive call to action within "the life"—like an aging athlete pulled repeatedly back to the game? In the lead author's early role as a "streetworker" among the mid-twentieth century OUD population, I often witnessed OUD as a lifestyle choice before it became a profoundly debilitating disorder. This lifestyle extoled the outsider identity; exuded a sense of independence and contempt for "squares/civilians," conventional lifestyles and racial/ethnic or gender stereotypes; required a high degree of motivation, technical knowledge, and skills (to succeed in the "rippin' and runnin" / "taking care of business" lifestyle); offered daily excitements and challenges; provided a sense of coherence and meaning; and elicited pride in mastering the argot, communication channels ("the wire"), geography (e.g., "copping corners", "shooting galleries," clubs and other street institutions), etiquette, ethics, and refinement of one's role "in the game/life"[367]—all before one became too burnt out or too impaired to sustain the rigors of the lifestyle. For many, opioids and the illicit drug culture in which they are nested also constitute the ultimate relationship—a lover, an old friend, a surrogate family that provides enormous emotional sustenance and security—one that in remission and recovery must be mourned and replaced.[368] This latter function takes on clinical significance with the finding that adverse childhood experiences, subsequent PTSD, isolation, loneliness, and "feeling unloved" are collective indicators of prolonged

addiction careers and worse MOUD outcomes.[369] This discussion of what opioid use has done for the OUD patient underscores the key point that while from the outside such addictive behavior may appear bizarrely incomprehensible, it is from the inside purposeful and driven by intense needs for which other alternatives have yet to be personally discovered—needs which must be effectively addressed in the context of any scheme of OUD treatment.

Given the power of such drug-related experiences, the question becomes how to initiate and sustain motivation for relief, repair, and eventual transformation of values, identity, intimate and social relationships, and lifestyle via the manipulation of treatment and environmental contingencies until remission and recovery can meet those same needs and become self-rewarding and self-perpetuating. Professionally-directed addiction programs would be well served to examine how such needs are addressed within the context of indigenous recovery mutual aid societies. There may be non-addicting psychoactive substances or non-pharmacological devices of the future that achieve these historical functions while enhancing physical, cognitive, and emotional health and exacting minimal adverse consequences. Such advances could render both existing illicit drugs and MOUD relics of the past.[370] Until then, strategic efforts must be mounted to enhance treatment retention by more effectively competing with the multidimensional power of the illicit drug experience and the power of the illicit culture in which it is nested.

Finally, the import of retention for all OUD treatment will not be fully realized until the prevalence, pathways, styles, and stages of long-term OUD remission and recovery—with and without MOUD—are fully charted by independent investigators. We need to confirm the scientific possibility of lifetime OUD remission and recovery without lifelong MOUD (and the personal, programmatic, and community factors that make this possible) or confirmation of the need for such lifelong medication support—or more probably, delineate the variability of responses across particular demographic and clinical characteristics. This must be part of the emerging recovery research agenda.

2. View Retention in Context of the Long-term Trajectory of Addiction, Treatment and Recovery Careers. Ideally, MOUD evaluations would shift measurement of retention from its current focus on a single episode of care provided by a single treatment entity to cumulative retention across episodes of care and potentially across multiple treating and recovery support organizations. This would extend the retention definition beyond a single treatment site[371] and shift the retention measure to percentage of days of remission/recovery engagement per year[372] or “cumulative dose” of treatment and recovery support across multiple episodes and levels of care.[373] This takes on import given the pattern of cycling in and out of treatment over extended periods of time that is common among OUD patients[374] as well as evidence of cumulative effects across multiple episodes of treatment.[375] In 2022, 65% of all publicly funded addiction treatment admissions in the U.S. were for individuals with one or more prior treatment admissions; among those with opioid-related admissions, the rates of one or more prior treatments were 76.9% for MOUD and 65.2% for non-MOUD admissions respectively, with 25.3% and 21.3% having five or more prior admissions.[376]

Motivations for seeking MOUD vary over the trajectory of opioid addiction and influence treatment expectations, adherence, retention, and outcomes. Soloway described the role of methadone in the context of addiction career progression—a stage

in which the addicted person is no longer able to master the rigorous demands of the addiction/hustling lifestyle, finds themselves cornered, and seeks treatment as a "pharmacological crisis intervention center".[377] Whether the person is seeking escape and planned respite from the lifestyle or seeking something beyond that lifestyle will exert a great influence on whether motivation for continued MOUD is strong enough to reach a tipping point of sustainable remission and recovery. MOUD patients may also seek treatment for one reason and then discover other reasons to continue treatment through experiences within the treatment process. This can reflect a transition from a superficial style of "doing treatment" as part of one's addiction career to experiencing transformative or incremental change processes that lead to permanent recovery.[378]

Most MOUD patients 1) enter treatment in a state of crisis, 2) experience substantial benefits from treatment, 3) leave treatment with stable or unstable remittance at discharge, 4) experience opioid use recurrence and related problems, and 5) re-enter treatment but with less severity than in earlier admissions.[379] Patients experiencing multiple treatment episodes also stay in treatment longer in later episodes of treatment, creating opportunities for greater recovery stability and sustainability.[380] While former MOUD patients who enter psychosocial treatment settings continue to have high risks for treatment discontinuation, a subset of these patients achieve sustainable recovery without lifelong medication support.[381]

Studies that examine these longer trajectories find a common pattern of recycling in and out of treatments over a span of years.[382] In a nine-year MOUD follow-up study, 64% of patients were in care at six months and 70% were in care at nine years, even though there were many episodes of medication discontinuation, with an average time out of treatment of 33 days following each disengagement.[383] In a 10/11-year follow-up study of 615 OUD patients, Teesson and colleagues reported 22.1% exhibited continual use of heroin throughout the study period, 16.1% were heroin abstinent during that period, and 61.8% fluctuated between periods of use and periods of treatment engagement.[384] In a study of 1,512 patients enrolled in 14 methadone clinics in China, Zhang and colleagues found that 79% of patients dropped out of treatment over the course of seven years, but 82% of dropouts had subsequently re-enrolled in MOUD treatment.[385] Studies that evaluate MOUD based on a single care event fail to grasp this larger trajectory of OUD treatment careers in which cycles of help-seeking and remission are interrupted by periods of remission instability, recurrence of opioid use, and related morbidity and mortality risks.[386]

McLellan and colleagues have argued that 1) the expectation of prolonged effects from a single acute episode of SUD treatment is misconceived for many if not most SUD patients; 2) SUD treatment adherence, symptom recurrence, and retention rates are similar to those found in the treatment of such chronic disorders as hypertension, diabetes, and asthma; 3) treatment for severe and complex SUDs should resemble the chronic care processes used in the treatment of other chronic medical illnesses; and 4) SUD treatment evaluation measures should focus on the degree to which symptoms are reduced and social functioning and quality of life enhanced *during the period of active care provision* and the degree to which patients are *retained in a long-term process of recovery management (*continuing care aimed at symptom amelioration and enhanced social functioning and quality of life without expectation of permanent cure).[387] Within

this framework, treatment “discharge,” “graduations,” and “aftercare” are replaced with the vision and practice of “sustained and assertive recovery management.”[388]

MOUD treatment must ideally shift from an acute care event focus to models of sustained and assertive recovery management over the long-term course of addiction, treatment, remission/recovery careers.[389] Examples of such a shift include integrating harm reduction and outreach strategies and clinical treatment,[390] concurrent in-treatment recovery monitoring,[391] assertive continuing care and post-treatment recovery management checkups, early detection of illicit substance recurrence, assertive linkage to treatment re-entry, and continuing expansion of recovery support resources across episodes of care.[392] The technologies involved in achieving 90% retention rates in long-term treatment follow-up studies could be mobilized within such extended treatment and recovery support models,[393] but such technology transfer is not yet a mainstream practice within international MOUD programs.

There is value in seeing attraction, engagement, induction, adherence, retention, remission, and recovery as index points in the therapeutic alliance that is often the hidden dimension in long-term personal and family recovery or in the failure to achieve or sustain such outcomes. That alliance could go beyond alliance with a particular clinician or a particular program to be reconceptualized and measured as alliance with the treatment system and recovery culture as a whole spanning multiple organizations and episodes of support over time.

3. Evaluate MOUD Retention in Context of other Treatment and Post-Treatment Process Measures. Ten MOUD treatment/recovery process measures that reflect this extended time perspective and their respective rationales are presented in Table One. These measures underscore the relationship between in-treatment and post-treatment process measures and long-term remission and recovery outcomes.[394] The proposed retention-linked measures incorporate elements from Hoffman and Moolchan’s phased model of methadone maintenance[395] and Williams and colleagues’ performance measures within the OUD cascade of care model,[396] as well as performance elements recommended by the Washington Circle,[397] the American Society of Addiction Medicine,[398] the American Psychiatric Association,[399] and the National Quality Forum.[400]

Table One: MOUD Treatment Process Measures

Early Identification and Attraction: a) annual percentage of OUD population accessing MOUD treatment; b) annual percentage of MOUD admissions voluntarily seeking treatment at early stages of problem progression as measured by age at first admission and the average number of OUD diagnostic criteria met at patient admission.

- Most opioid-affected individuals begin treatment only after years of opioid use and at advanced stages of OUD.[401]
- The earlier treatment begins in OUD progression, the better the long-term outcomes and the lower the cumulative harm to self, family, and community, including its related economic costs.[402]
- Entering SUD treatment in the first decade of use shortens addiction careers by as much as half.[403]
- Assertive outreach and initiation of MOUD in non-specialty settings (e.g. emergency rooms, primary care offices), linkage to longer-term

treatment resources, and policies that normalize OUD treatment in mainstream community service settings enhance OUD treatment outcomes.[404]
- MOUD enrollment decisions depend upon perceptions of medication effectiveness, medication safety, and consistency with the goal and meaning of abstinence and recovery.[405]

Therapeutic Engagement: a) continuity of contact with a core recovery support team across levels of care[406] e.g., measurement of MOUD clinical workforce stability, b) percentage of people seeking MOUD who get through admission and medication induction, c) average cumulative hours of addiction counseling by OUD severity levels, and d) average patient ratings of therapeutic alliance.

- Rates of preadmission attrition are high among those seeking MOUD, with as many as 60% of those calling about treatment entry disengaging before admission.[407]
- The practice of "creaming" (denying admission to persons seeking medication support who present with high problem severity and complexity or who are perceived to be non-compliant) is a form of pre-admission attrition / clinical abandonment.[408]
- Dropout rates are particularly high in the first 30 days of MOUD induction.[409]
- Strong therapeutic alliance is associated with treatment adherence, retention/completion, and positive post-treatment outcomes, particularly among patients with the most severe and complex disorders.[410] Confrontational (versus empathic/supportive) styles of counseling are associated with higher rates of non-adherence and treatment dropout.[411]
- Patient participation in setting treatment goals and evaluating treatment process enhances treatment outcomes.[412]
- Any break in therapeutic continuity (e.g., transfer to another level of care or other program) poses risk of treatment dropout and increased mortality risks.[413]

Family and Social Network Engagement: percentage of patients with family and social network involvement in their treatment.

- The risk of nonadherence, treatment dropout, and OUD recurrence increases with density of drug users within one's family, extended family, and social network.[414]
- Family members can increase or decrease patient misunderstandings about OUD medications and undermine or support MOUD adherence and retention.[415]
- OUD of a family member inflicts profound and prolonged trauma upon affected families/children that warrants a parallel recovery support process.[416]
- Drug-free family members can be mobilized to support family members in MOUD treatment.[417]

- Drug-free family and social network expansion and engagement enhances individual outcomes via increased treatment adherence and retention, enhancement of family recovery via increased rates of family reunification; positive changes in family roles, rules, and relationships; lowered peer pressure for resumption of opioid use; and increased social support for recovery.[418]
- High levels of social support, expanding non-drug social ties, and positive involvement in family and community life reduce the risk of opioid use episodes and strengthen treatment adherence, retention, and recovery maintenance.[419] In-treatment elevation of recovery capital decreases opioid cravings and strengthens commitment to OUD recovery, which in turn increases adherence and lowers risk of treatment discontinuation.[420]
- Adherence and retention among one's treatment peers increase individual adherence and retention, suggesting the potential of strategic mobilization of peer support for remission/recovery within the MOUD treatment milieu.[421]
- Reducing adverse experiences of children through the mechanism of parental OUD recovery stability potentially reduces family clustering of opioid use and intergenerational transmission of OUD and related problems.[422]
- Technology is emerging to identify future addiction risk levels, which could facilitate targeted prevention and early interventions strategies and reduce intergenerational cycles of addiction and related problems.[423]

Assertive Linkage to Recovery Mutual Support Resources: Percentage of patients participating in a community-based and peer-based recovery mutual aid group for more than 90 days.

- Participation in recovery mutual support resources enhances MOUD treatment adherence, retention, and long-term recovery outcomes.[424]
- While barriers exist for MOUD patients seeking participation in recovery mutual aid groups, the gulf between MOUD and such groups is narrowing.[425]

Adherence: a) percentage of compliance with medication dosing appointments, b) percentage of patients who complete induction without excessive (sedation) or suboptimal (withdrawal distress, craving, sleep disturbance) medication dosing, c) percentage of drug tests free of illicit opioids and other illicit substances.

- Missed medication doses increase opioid cravings, the odds of illicit opioid and other drug use, and related health care events, which in turn increase odds of treatment drop-out or administrative discharge.[426]
- As patient adherence increases, the risk of illicit drug use and medication discontinuation is lowered.[427] Adherence in final stages of medication tapering is predictive of post-treatment remission and recovery outcomes.[428]

- MOUD adherence and related outcomes rise in tandem with time in treatment and increases in social support.[429]

Treatment Retention/Duration: percentage of patients who meet period of minimum duration set in MOUD maintenance standards.

- Duration of MOUD treatment is predictive of a broad spectrum of clinical outcomes;[430] positive outcomes in treatment increase incrementally with time in treatment.[431]
- Increasing cumulative treatment "dose" across levels of care increases remission/recovery outcomes.[432]

Level of Care Completion/Transition: a) percentage of patients completing a planned tapering process, b) percentage of patients following continuing recovery plan.

- Treatment completion as planned increases odds of post-treatment remission stability but does not fully ameliorate OUD recurrence and related morbidity/mortality risks following medication discontinuation.[433]
- Psychological preparation for post-MOUD remission and recovery maintenance is associated with higher rates of post-treatment opioid abstinence.[434]

Post-Treatment Monitoring and Support: a) percentage of discharged patients receiving post-treatment recovery management checkups (RMCs), b) percentage of patients participating in continuing care appointments, c) percentage of patients achieving sustained remission/recovery status at multiple time points, d) average time span from post-treatment opioid use and OUD recurrence to treatment readmission for those needing a return to medication support.

- Participation in post-treatment assertive continuing care activities elevates short- and long-term SUD remission/recovery outcomes for adolescents and adults.[435]
- Continuing care outcomes improve with duration of participation, with a minimum recommended duration of up to 12 months.[436]
- RMCs increase remission/recovery outcomes and if/when needed shortens the time to treatment readmission and remission/recovery re-stabilization.[437]
- Quality of life improvements in recovery are non-linear, with key periods of increased distress warranting amplified support to reduce risk of OUD recurrence.[438]
- The sooner treatment re-admission occurs after recurrence of OUD, the better the long-term MOUD treatment outcome.[439]
- There are no post-MOUD treatment continuing care models or MOUD guidelines that contain standards for long-term recovery management of MOUD other than medication maintenance, e.g., only three sentences reference continuing care, aftercare, and post MOUD recovery planning in SAMHSA's 2024 *Federal Guidelines for Opioid Treatment Programs*.

Early Re-intervention and Remission Restabilization: percentage of patients experiencing opioid use recurrence or OUD who are readmitted to treatment within 30 days of resumed use.

- Early reintervention and timely treatment re-admission lessen OUD severity and morbidity risks, enhance rates of abstinence, and preserve accumulated recovery capital.[440]

Positive MOUD treatment Experiences: Percentage of patients who record high continued satisfaction ratings of their treatment experience.[441]

- Motivation for and degree of positive response to treatment ebbs and flows over the course of MOUD, suggesting the need for frequent monitoring and adjustments of clinical interventions to achieve the best clinical outcomes.[442]
- Patient retention is enhanced by shared goal-setting and shared tapering decisions related to if, when, and how medication tapering occurs.[443]
- Patient satisfaction is predictive of positive MOUD treatment outcomes.[444]

The most glaring omission within the above treatment process measures is the lack of clear evidence-based consensus on minimal and optimal duration of MOUD and the current gap between those recommendations and the average duration of MOUD across clinical populations and cultural contexts. Moreover, while the issue of MOUD retention is the focus of the current review and commentary, retention cannot be adequately addressed in isolation. Efforts to address any of the major MOUD limitations are inextricably linked to other key dimensions noted in Table One.[445]

In-treatment and post-treatment process measures constitute a service scaffolding within which the work of OUD remission and recovery can occur. Developmental tasks of long-term recovery unfold over time within five zones of action and experience: 1) physical health, 2) psychological health, 3) spiritual health (life meaning and purpose / worldview), 4) relational health, and 5) lifestyle reconstruction.[446] The work of recovery extends across five overlapping stages of remission and recovery: precovery (remission/recovery priming during final stages of uncontrolled illicit opioid use), remission initiation and stabilization, transition to remission maintenance, enhancement of global health and social functioning in long-term recovery, and efforts to break intergenerational cycles of addiction, trauma, and related problems.[447]

The MOUD treatment process measures in Table One address dimensions of treatment that have a strong nexus to proximal and distal OUD remission and recovery outcomes. Monitoring and managing progress and regress across these zones and stages, assertive outreach to patients following missed appointments, and periodic telephonic check-ups on patients who have disengaged from treatment could all potentially elevate retention rates within MOUD treatment.

4. Support Future Advancements in Medication and related Neuropsychological Interventions While technical advancements in MOUD are inhibited by pharmaceutical company concerns about association with a stigmatized condition and the cost-profit ratio of MOUD development, advances in neuroscientific research portend a future of once unthinkable medical breakthroughs in the treatment of OUD and other

SUDs.[448]Targets of future OUD medication development include medications that affect treatment retention by achieving rapid induction and stabilization, simultaneously treat opioid withdrawal and opioid craving, provide time-extended effects, and concurrently treat OUD, co-occurring SUDs, and other medical/psychiatric conditions.[449]

A target for future technological advancement is in the area of agonist dosing protocol and the potential for dosing algorithms based on a combination of genetic phenotypes and clinical presentation.[450] Historically, there have been broad discussions and debates about widely divergent low- and high-dose MOUD policies,[451] with the latter associated with elevated rates of retention.[452] Less attention has been devoted to calculating the most individually tailored medication doses. Personally optimal dosages of methadone and buprenorphine provide a period of neuropsychological harmony through three mechanisms: 1) suppressing opioid withdrawal, 2) suppressing opioid craving, and 3) blocking the euphorigenic effects of illicit opioids. The therapeutic effects of MOUD remain for a duration that is dependent upon the rate of medication metabolism, which is genetically influenced, varies from individual to individual, and can change within the same individual over time and circumstances.[453] This means, for example, that the same dosage of prescribed methadone could in a span of 24 hours produce perfect stabilization in one MOUD patient, impairment due to acute withdrawal distress in another, and impairment from acute intoxication/sedation (and mortality risk) in yet another. Fast metabolizers on inadequate dosages of medication will experience breakthrough symptoms that trigger self-medication with illicit opioids and other drugs, treatment non-adherence and increased risk of treatment discontinuation, particularly during the induction phase of MOUD.[454] Suboptimal dosing of MOUD remains a too common practice, with as many as a third of patients reporting breakthrough withdrawal symptoms and related illicit drug use.[455] Any such use should trigger a reevaluation of medication dosage, as such adjustments have been found to decrease unprescribed drug use and increase rates of retention.[456]

The rate of medication metabolism can be calculated by genetic markers and measures of the peak and troughs of medication effects, but the use and frequency of such tests are limited by their costs and capabilities of MOUD providers.[457] Treatment adherence and retention are influenced by the speed and precision with which adjustments in MOUD dosage can be made, particularly for those exhibiting ultra-rapid or ultra-slow MOUD metabolism.[458] MOUD retention is dependent upon how quickly individually optimal medication dosage can be determined, stabilized and sustained with each patient.[459] New technological and cost-effective advances to make such determinations would mark a dramatic elevation in the quality of MOUD and OUD patient retention.[460]

Particularly promising but not yet clinically available are advances in immunotherapy, including the potential for vaccines that trigger the immune system to create antibodies in response to opioid exposure, prevent or reduce their pharmacological reward, and reduce the risk of opioid exposure progressing to OUD recurrence by preventing the passage of opioids into the brain.[461] Also promising are medications that do not temporarily correct or cure OUD but provide a protective shield against overdose death and injury to body organs. Naloxone (Narcan) is now available and regularly administered to reverse opioid overdose and prevent death; medications of the future might prevent the overdose before reversal was needed. Assessment is also underway

of new formulations of existing OUD medications and the potential repurposing of medications currently used for other conditions for OUD treatment.[462]

New medical protocols could provide a neurobiological reset that breaks the cycles of withdrawal distress, drug craving, compulsive drug seeking, and ever-escalating drug consequences. Such developments would obviate the need for long-term medication adherence, but would raise difficult medical, ethical, and legal issues regarding the potential for unforeseen long-term side-effects and the degree to which such "cures" could be legally coerced.[463] Reports of such a long-lasting reset from a single or short series of medication administrations have been reported for some novel treatments of SUD (e.g., treatments involving, psilocybin, ketamine, and ibogaine),[464] but some have resulted in adverse medical events.[465] Current SUD medications are SUD-specific (e.g., for opioid use disorder or alcohol use disorder), not available for some SUDs (e.g., stimulant use disorder, cannabis use disorder), and not recommended for treating multiple co-occurring SUDS. Future medications might transcend these limitations.

Beyond the realm of intrapersonal transformation, a long-term goal would be the development of medical and social interventions that can prevent the intergenerational transmission of OUD/SUD risk, particularly within families with dense inter-and intra-generational clustering of OUDs/SUDs.[466] The distress of parents in MOUD treatment regarding the feared risks of their children developing substance-related problems could be lessened in the short term by including education about intergenerational risks and parent-based strategies of substance use prevention and early intervention within the treatment process.[467]

Other potential developments include:

- new models of understanding and treating OUD and related disorders (e.g., reward deficiency syndrome[468])
- increased adoption of genetic screening instruments to measure OUD susceptibility that could reduce patient denial and enhance family understanding of OUD as well as aid advancement of precision treatment[469]
- CRISPR-facilitated gene editing
- biomarker identification of OUD phenotypes responsive to different medications and dosages
- expanded medication delivery routes (e.g., longer acting implants) that alleviate or reduce travel barriers and the burden of frequent clinic attendance
- transcranial magnetic stimulation, transcranial focused ultrasound, electroencephalography neurofeedback, and real-time functional magnetic resonance imaging neurofeedback
- surgical alteration of brain reward centers
- increased sophistication of wearable electronic risk/use/overdose detection and in-the-moment recovery support apps specifically tailored to provide medication-assisted recovery support; and
- virtual reality therapy as an adjunct in relapse prevention training.[470]

Heightened specificity of craving measurement and ecological momentary assessment of craving intensity may also allow early identification of MOUD adherence and retention risks.[471] The potential of identifying a single biomarker to identify patients who are ultra-

rapid medication metabolizers and who could be effectively stabilized with split dosing would also be an important clinical advancement affecting rates of patient retention.[472]

The advent of personalized precision medicine could capitalize on genetic and metabolic data in the choice of medication, dosage, duration, and preferred medication delivery protocol to create improved matches that enhance MOUD treatment retention.[473] Artificial intelligence (AI), a tool now being used to expand the illicit drug menu,[474] will be increasingly harnessed to aid the development of new OUD treatment medications and related medical procedures.[475] AI will also make predictive analytics possible—algorithms that analyze patient data to identify risks for MOUD discontinuation and OUD recurrence. Through such processes, issues such as craving, pain, and sleep disturbances could be preemptively identified and addressed that could otherwise lead to resumed drug use and treatment discontinuation.[476] All of these developments suggest a future in which new technologies will be available to enhance MOUD retention or eliminate the clinical need for long-term treatment retention.

The question that will arise in the face of technological advancements in the treatment of OUD and other SUDs is whether such innovations can be equally applied to the full spectrum of drug problem severity, complexity and chronicity or whether terms such as opioid use disorder or substance use disorder constitute a clustering of convenience for what are actually multiple disorders that respond to different treatments. As noted, the term *addiction* is commonly applied to the most severe, complex and prolonged OUDs/SUDs. Is this a distinct subpopulation/phenotype? And how would MOUD, other SUD medications, and alternative treatments of the future be allocated differently across this high to low spectrum of severity, complexity, and duration? Will they be available, accessible, and affordable for all those who experience an OUD? Interventions of the future that alter brain structures affected by addiction could potentially revolutionize addiction treatment by triggering the shift from managing addiction and recovery to actually curing addiction and related comorbidities.[477] Until then, advances will be needed that enhance long-term treatment adherence and retention.

5. Investigate Potent Service Combinations and Sequences Medication development and its related regulatory frameworks tend to examine each new medication candidate in isolation, but a new area of promise is the use of integrative therapies—bundling particular combinations and sequences of medications and other treatments that may have dramatically amplified effects in supporting OUD remission and recovery.[478] The future of MOUD treatment will lie not just in increased utilization of a currently available medication or a new medication, but in the precision through which particular medications are matched to particular patients at particular dosages and durations and uniquely combined and sequenced in tandem with other allied medical and psychosocial interventions across the stages of OUD remission and recovery[479]—across what Osher and Kofoed broadly described as stages of engagement, persuasion, treatment, and relapse prevention.[480] A simple example of such stepped care within MOUD would be providing a rich menu of recovery support services and volunteer service opportunities for patients who have completed tapering. At present, how many MOUD patients remain in treatment during the months following medication discontinuation, the period at highest risk for opioid use recurrence and mortality?

Stahler and Mennis found that adding MOUD to treatment plans of OUD patients admitted to residential treatment increased their retention in treatment by 34% and treatment completion by 40%.[481] Klein and Seppala reported enhanced retention and abstinence outcomes of OUD patients who received integrated medication support within a traditional 12-Step treatment system.[482] Similarly, both MOUD and participation in recovery mutual aid organizations enhance OUD abstinence outcomes and can be combined for potential additive or synergistic effects.[483] Collins and colleagues have also reported positive results in the use of buprenorphine as a bridge of entry for opioid dependent prospects entering a long-term residential therapeutic community.[484] Galanter and Seppala et al., have independently suggested that uniquely combining and sequencing previously siloed approaches to harm reduction, treatment, and post-treatment recover support based on individualized assessment of problem severity/complexity/chronicity and recovery capital could elevate treatment and recovery outcomes beyond those now being achieved.[485] Such integration would replace the current status in which MOUD patients have only limited psychosocial support services available and patients within psychosocial treatment modalities are frequently denied access to medication support. Theoretically, unique service combinations and sequences have the potential to mobilize multiple mechanisms of change that underly long-term processes of OUD remission and recovery.

Discovery of such potent combinations and sequences would be aided by research on OUD remission/recovery success without MOUD support, which could lead to new clinical tools (instruments and algorithms) to identify patients who are or are not good candidates for sustained remission/recovery maintenance with or without medication support. For example, if as earlier noted, 38 percent of members of Narcotics Anonymous report a past primary drug choice of opioids, how do these individuals differ from MOUD patients in clinical characteristics, methods of remission/recovery initiation and maintenance, and long-term remission and recovery outcomes? Findings of such studies could help expand such pathways and also help guide those who are considering the transition from MOUD to remission/recovery maintenance without medication support.

6. Address Personal, Programmatic, and Community Barriers to Retention MOUD retention efforts begin with personalized and continual assessment and response to retention obstacles via assertive case management and peer-based recovery support services, as well as modifications in MOUD protocol to accommodate individual needs in full recognition that the number and intensity of treatment obstacles ebb and flow over time.

We begin this discussion of retention barriers with the need to assertively and effectively address the role of medication side effects in MOUD attrition. A wide scan of the scientific, professional and lay literature on opioid addiction can leave the impression that the opioid epidemic could be stemmed if we could just increase MOUD dissemination, provide appropriate doses of MOUD, reduce burdensome MOUD regulatory requirements, and expunge MOUD-related stigma at professional and public levels. As noted in this report, those are all important steps, but even if achieved, there remains the role of medication side effects in the failure to seek or sustain MOUD treatment.

In spite of the worldwide dispersion of medication-based treatment of OUDs, there is a marked paucity of rigorous research on MOUD side effects and adverse events.[486] Such effects and events range from the rare and extreme (death during medication induction)[487] to medication side-effect concerns expressed by most MOUD patients.[488] The latter include restlessness, mood changes, bone and muscle pain, headache, nausea, sedation, fatigue, lethargy, constipation, dry mouth and related dental problems, excessive sweating, sleep disruption, and decreased sexual libido, performance, and satisfaction.[489] While some of these symptoms could be attributed to excessive or inadequate medication dosage,[490] vulnerability to such effects may also be related to genetic anomalies that in the future may be routinely identified and used to guide clinical decision making[491] or to interactions with other medication taken by those maintained on MOUD. MOUD side effects are more frequent and more intense among MOUD patients who are continuing illicit opioid use, making this group particularly high risk for MOUD discontinuation.[492] Such side effects may also be exacerbated among older MOUD patients due to changes in drug metabolism, co-occurring medical disorders, and interactions with multiple medications.

What is clear in the literature is the bidirectional relationship between MOUD retention and health-related quality of life reported by MOUD patients.[493] While the risks of illicit opioid use far outweigh the medication side effects experienced by some MOUD patients, resolving the challenges of medication adherence and retention requires a far more assertive and sophisticated approach to preventing, identifying, and managing such effects. Strategies to enhance retention include rigorous identification and management of MOUD side effects and their implication for medication choice, dosage, timing of administration, and the need for ancillary interventions to eliminate, reduce, or more effectively cope with medication side effects.[494]

Beyond the burdens imposed by the illness and the medications used to treat it, MOUD patients experience burdens of treatment that few patients seeking help for other medical conditions would tolerate. There are commonly long waiting lists for admission, prolonged intake and induction procedures, life-disrupting requirements for daily medication pick-up, limited medication dispensing hours, long lines for medication dispensing, required supervision of medication consumption, required face-to-face counseling as a condition of medication access, the machinations surrounding observed urine drops, and unannounced calls for return of take-home medicine bottles. Such experiences collectively convey to MOUD patients that they are unworthy of care, unable to be trusted, and deserving of shame. Such procedures may prevent or weaken therapeutic alliance between MOUD staff and patients and sow the seeds of treatment discontinuation.[495]

The treatment organization and the illicit drug connection compete for the attention and loyalty of the MOUD patient, with each entity relying financially on customer retention. The personal tipping point in this competition from the patient's judgement rests upon which entity can provide what one needs with the least pretense, pain, and contempt. In which setting can one find the fastest personal relief and greatest expected benefit at the lowest personal cost? Calls for "lower thresholds of MOUD initiation"[496] and "minimally disruptive OUD care"[497] reflect the recognition that regulatory- and program-imposed burdens (excessive time, emotional energy, and money) stand as major obstacles to prolonged MOUD participation. Efforts to reduce the burdens of care

have been positively evaluated by MOUD patients[498] and are a promising strategy to enhance MOUD retention.

At present, any enhancement of MOUD retention hinges on reducing the burden of what is required for admission, regular medication administration, and if and when needed, readmission. For example, greater MOUD treatment flexibility during the COVID pandemic (e.g., increased outreach / methadone vans, rapid access to medication, enhanced medication take-home privileges, flexible dosing, medication self-administration, virtual or tele-counseling support that reduced clinic visit requirements) enhanced MOUD patient quality of life and patient satisfaction without an increase in adverse events or increased medication diversion.[499] Regulatory frameworks guiding MOUD could and should continue to be relaxed in the future. Similarly, studies of the viability of telehealth, telemedicine, and teletherapy to deliver OUD treatment and enhance treatment retention in rural areas also suggest promise in overcoming obstacles to the geographical accessibility of traditional MOUD services.[500] Telemedicine advantages include increase accessibility (particularly in rural and frontier communities and in other medical deserts), convenience for patients and providers, and opportunity for more frequent monitoring and support.

Stigma-related countertransference on the part of staff that can trigger treatment disengagement can be reduced via increased staff training in conflict resolution/mediation/de-escalation, enhanced clinical supervision, and on a more prolonged basis via sustained MOUD educational efforts directed at patients, family members, addiction and allied professionals, recovery community members, and the public.[501]

It would similarly be helpful to abandon the practice of extruding patients (via administrative/disciplinary discharge) for exhibiting the primary symptoms for which they are being treated, i.e., inability to abstain from drug use and loss of healthy decision-making once drug use begins. Such a practice is unprecedented in the treatment of other medical conditions, a potential breach of medical ethics, and reflects a fundamental misunderstanding of the role of volition in OUD progression.[502] Administrative discharge may also constitute a proxy for problem severity and complexity (e.g., co-occurring personality disorders, a chaotic lifestyle that leads to missed dosing appointments), suggesting that this practice extrudes from treatment precisely those patients most in need of treatment.[503] Administrative discharge would ideally be replaced, except related to threats to safety, with refinements in treatment that facilitate remission/recovery re-stabilization and/or harm minimization.[504] In this way retention would be enhanced by responding to non-adherence therapeutically (e.g., alterations in treatment plan, movement to another level of care) rather than by clinical abandonment masked as punishment or defended as a patient “learning experience.” Extrusion for perceived low recovery motivation would similarly be replaced by clinical interventions that increase motivation, e.g., motivational interviewing and seeding MOUD levels of care with peers (“recovery carriers” / “recovery champions”) who make OUD remission and recovery socially infectious.[505]

Studies of MOUD providers underscore the import of strengthening therapeutic alliance as a primary means of enhancing MOUD retention. This would involve such interventions as pre-treatment contracting, increasing caregiver time in direct service to patients, using text and calls to maintain contact with patients between face-to-face

appointments (e.g., teleprompts for appointments), improved methods of resolving patient-patient and patient-staff conflicts, patient-centered scheduling, and rewards for medication adherence.[506] There is also the question of the broader aspect of the service culture within which MOUD is delivered. Qualitative studies of patients' experience of medication-supported treatment often reveal experiences of being discredited, humiliated, shamed, and punished rather than encouraged and supported.[507] Building and sustaining a contempt-free, affirming MOUD milieu is a critical step in enhancing MOUD retention.

The journey from opioid addiction to recovery is an intrapersonal journey but is often also a journey between two physical and cultural worlds—a journey from the culture of addiction to the culture of recovery—each with its own unique history, physical landscapes, language, literature, music, art, values, symbols, roles, rules, rituals, and relationship patterns.[508] The MOUD patient is often caught in limbo between these two worlds.[509] Unaddressed in the literature on MOUD retention is the question of whether MOUD milieus reinforce the culture of addiction and contribute to MOUD dropout or serve as a welcome portal into the culture of recovery.[510] Michael Agar has described that in addition to being a pharmacological pathway out of the street addiction lifestyle in New York City, methadone also was incorporated into the illicit drug culture in ways that could serve to sustain addiction careers.[511] Rosenbaum and Murphy and Mayock et al., have similarly suggested that traditional MOUD settings have all too often been closer to the former than the latter, via encouragement of drug use, drug dealing and related illicit hustling within the context of methadone clinics, as well as in the striking absence of visible recovery role models.[512] It is possible in such circumstances that an individual seeking recovery could flee treatment or a mutual aid setting not to return to addiction but to escape the milieu that poses the greatest threat to their efforts to escape "the life." OUD recovery resources, whether a methadone clinic or an NA group, ought to be judged by the degree to which people have access to visible role models who are successfully maintaining recovery. Strategies to reduce MOUD attrition must include assertive efforts to infuse and refine a contagious recovery culture within the MOUD milieu.

Treating a condition like OUD in a cultural context in which the disorder and its treatment are highly stigmatized and in which innumerable obstacles exist to treatment initiation, adherence, and retention increases the odds of poor clinical outcomes. It does so by delaying help-seeking until OUD presents in its most severe, complex and chronic forms—the equivalent of only treating cancer when it has reached its most advanced stages of progression. Antidotes to this situation require new technologies of patient engagement but also require "treating" the community itself via expanded efforts at public education, the expansion of community-based recovery support services, and the expansion of recovery landscapes/spaces in which long-term recovery can flourish.[513] Few existing SUD treatments address the ecology of OUD addiction and recovery, with the possible exception of some of the family-oriented treatments and the community reinforcement approach,[514] which are rarely available within MOUD treatment settings.[515]

There are examples of successful efforts to enhance acceptance of diverse pathways of recovery, including those supported via OUD medications, within recovery support institutions and the larger community.[516] The long-term goals include altering

the community environment—to create *recovery-oriented systems of care* and *inclusive recovery cities* that welcome medication-supported pathways of recovery and challenge the cultural forces that inhibit MOUD treatment-seeking, encourage suboptimal MOUD medication dosages, and shorten MOUD treatment duration.[517] Such recovery support landscapes include virtual recovery communities.[518]

Finally, another helpful resource with suggestions for addressing particular obstacles to retention is the American Society of Addiction Medicine's report, *Engagement and Retention of Nonabstinent Patients in Substance Use Treatment: Clinical Consideration for Addiction Treatment Providers*.[519] This monograph offers many helpful strategies to enhance treatment retention, so don't be dissuaded by the limitations suggested by its title.

7. Design and implement protocol for post-MOUD remission maintenance and recovery management. Elements within such a protocol could include:

- Engaging family and intimate social network and recovery support specialists (e.g., mutual aid sponsors, recovery coaches, pastors, etc.) in post-MOUD recovery management planning
- Assuring inclusion of a primary care physician within the post-MOUD recovery management process
- Providing harm reduction interventions in tandem with MOUD tapering (e.g., mortality risk education, naloxone distribution, etc.)
- Assertively linking MOUD patients to an expanded menu of recovery support resources during the tapering and post-tapering period, to include choices of MOUD-friendly mutual aid groups, recovery residences, recovery community centers, recovery cafes, recovery advocacy and celebration events, recovery ministries, collegiate recovery programs, etc.[520]
- Exploring the pros/cons and approaches to medication disclosure prior to patient exposure to settings (e.g., NA meetings) in which medication use may be discouraged[521]
- Monitoring patient response to recovery support resources and providing linkage to alternative resources as needed
- Encouraging patient involvement in pro-social community service activities
- Concentrating the in-person and telephonic recovery check-ups during final stages of tapering and first 90 days following MOUD discontinuation
- Providing addiction counseling to support self-efficacy in the initial, intermediate and longer-term post-medication phases of OUD care[522]
- Continuing recovery management check-ups at personally planned intervals for at least five years following MOUD discontinuation and titrating frequency based on recovery stability and patient preferences,[523] and
- Facilitating early reentry into MOUD or alternative treatment in response to resumed opioid use.

Assertively linking MOUD patients to drug-free social relationships and activities offers protection against the influence of prior drug-saturated social networks or against the

social isolation often chosen by MOUD patients as a strategy to avoid addiction recurrence and the social stigma attached to OUD and MOUD.[524]

The epidemic of opioid overdose deaths has created deserved preoccupation with expanding onramps to MOUD, but a barrier to treatment seeking and retention is the lack of professionally directed and peer-supported offramps. This leaves the field several choices: 1) determining that MOUD for life is the best choice for all those experiencing OUD and launching a massive professional and public education campaign with the science supporting such a stance, 2) scientifically and clinically delineating those for whom MOUD and is best sustained for a lifetime and those who may transition to recovery maintenance without medication support, or 3) in the case of the latter, defining and mapping pathways of remission maintenance and enhanced quality of life in long-term recovery without medication support. Such offramps are not visible today for most MOUD patients.

Limitations

Every effort has been made in this monograph to present an accurate summary of the state of MOUD research internationally, with a particular focus on the critical issues of treatment adherence, retention, and post-MOUD remission and recovery outcomes. There are, however, significant limitations to what can be concluded from the standpoint of science. As we have noted, the lack of consensus on defining key concepts and their measurement make comparing study findings difficult and at times impossible. Sample sizes, diversity of study samples, and duration of follow-up vary widely across studies and limit the conclusions that can be drawn from individual studies. Most critical is the paucity of long-term follow-up data on the life trajectories of both people who maintain long-term medication support as well as those who discontinue medication support. As with the larger body of addiction-related research, we know the most about the earliest stages of treatment and the least about the long-term processes of personal and family recovery—with and without medication support.

Conclusions

In 1978, Vincent Dole and Herman Joseph summarized the state of OUD treatment as follows:

> *Most patients will be discharged after relatively short periods of treatment and most of them will relapse to use of illicit opiates. The problem therefore reduces to the re-treatment of subjects who have relapsed or are in danger of relapse after detoxification. Unfortunately, most of the methadone programs examined in this study had failed to develop any consistent long-term plan for follow-up and re-treatment of relapsed subjects.*[525]

In spite of technical advancements in OUD treatment, that statement is as applicable today as it was when originally composed. The bottom line? For most MOUD patients, the successful psychopharmacological treatment of OUD with evidence-based medications is contingent upon continued treatment adherence and retention. The

current global MOUD practice reality often fails to achieve those contingencies. MOUD drop-out rates are high. Most patients express intentions of ending medication support in the near future. Most will discontinue treatment prior to stable and sustainable OUD remission. Many will disengage before completing a planned tapering process. And most will experience post-treatment recurrence of opioid use and related morbidity and mortality risks. A clear consensus does not exist on the types and intensity of psychosocial services that could be added to MOUD treatment to elevate rates of adherence and retention, but there is a near universal call for more effective methods of post-treatment monitoring and support.

Medication supported recovery from OUD disorder rests upon a progressive series of disconnections and connections: disconnection from illicit drugs, connection to a potentially lifesaving and life transforming medication; severing drug-enabling relationships, building a recovery-supportive social network; shedding the chaotic lifestyle of active addiction, forging a new identity via story reconstruction and storytelling and a new daily lifestyle. Stages of recovery engagement include precovery—a "crystallization of discontent"[526] fueled by addiction related pain and rising hope in the possibility of a life beyond one's present circumstances, self-experiments in reducing harm by altering use patterns, abstinence sampling, engagement in one or more pathways/styles of recovery initiation and maintenance as well as enhancement of global health and social functioning.

The MOUD treatment process is itself marked by a continuum of connections/alliances/relationships—from early identification (treatment attraction), medication induction (treatment engagement), bonding with caregivers and caregiving organization (therapeutic alliance), working through ambivalence regarding both addiction and recovery (treatment adherence), overcoming obstacles to long-term clinical support (treatment retention), and embracing radical changes in life and lifestyle, including one's view of self and the self-world relationship. Each stage in this process is marked by opportunities for progression or regression, the key to which is marshaling the internal and external resources (recovery capital) to sustain a movement toward health and wholeness. In personal terms, this requires fortitude and persistence and in clinical terms it is contingent upon prolonged treatment adherence and retention.

Seen as a whole, this review underscores a powerful lesson of clinical history in the treatment of OUD: underpowered (low intensity) and inadequately sustained (low duration) interventions create the illusion of effectiveness but produce two unintended effects. Like antibiotics taken at too low a dosage and too short a duration, the illness remains unchecked, or symptoms are temporarily suppressed but return in a more virulent and intractable form. In contrast, disease/recovery management models use MOOUD similar to the use of insulin to achieve prolonged stabilization of diabetes. Since their international dispersion over the past half-century, medications used in the treatment of the most severe and complex opioid use disorders have been plagued by suboptimal medication dosages, suboptimal psychosocial support provided in tandem with and following medication support, and suboptimal duration of integrated medication and psychosocial support. It is our belief that the future of effective OUD treatment adherence and retention rests upon seven critical steps:

1) expanding treatment choices across the problem severity / complexity / chronicity and recovery capital spectrums and providing patients informed choice regarding medication continuation or discontinuation
2) reconceptualizing MOUD retention within the broader understanding of addiction/treatment/recovery careers
3) evaluating retention within the context of other treatment and post-treatment process measures
4) advancing medication development and related neuropsychological interventions
5) identifying the most potent serviced combinations and sequences that facilitate pathways of long-term OUD remission and recovery across diverse clinical phenotypes
6) assertively addressing personal, programmatic, and community obstacles to treatment retention, and
7) designing and implementing protocol for post-MOUD remission maintenance and long-term recovery management.

The “gold standard” designation for MOUD as presently practiced internationally is warranted only when compared to currently available alternatives, whose key process and outcome measures are worse than MOUD. It stretches the limits of credulity to declare a medical treatment the “gold standard” if the overwhelming majority of people needing it will not voluntarily seek it; will fail to overcome the physical, emotional, and financial burdens demanded by it; will discontinue the treatment before its optimum benefits are achieved; and will experience increased morbidity and mortality following treatment discontinuation. That stark reality does not mean that medication-supported treatments for OUD should be abandoned. On the contrary, it means that their quality, including their adherence, retention, and long-term clinical benchmarks must be elevated to the point that the “gold standard” designation is warranted. That will require bridging the gaps between MOUD attraction/induction, the processes of long-term personal and family recovery, and the expansion of community/cultural spaces in which all pathways and styles of OUD remission and recovery are welcomed and can flourish.

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Appendix

Table A1: Sampling of MOUD Retention Studies, 2014-2024

Study	Setting	Medication	*n*	Rate
Follow-up: 2 weeks				
Sadek & Sanders, 2022	Nova Scotia Prescription Monitoring Program	Buprenorphine	359	77%
Sadek & Sanders, 2022	Nova Scotia Prescription Monitoring Program	Methadone	1,527	78%
Follow-up: 1 month				
Chan et al., 2024	Telehealth	Buprenorphine	100	97%
Chan et al., 2024	Non-telehealth	Buprenorphine	54	94%
Fine et al., 2021		Buprenorphine	1,467	45%
Lira et al., 2023	Telehealth	Buprenorphine	1,816	75%
Ivasiy et al., 2024		Methadone	53,568	89%
Jennings et al., 2021		Buprenorphine	522	43%
Lone et al., 2024		Naltrexone	100	83%
Noe et al., 2020		Buprenorphine	350	65%
Reuter et al., 2022		Buprenorphine	279	54%
Samples et al., 2018		Buprenorphine	17,329	72%
Steiger et al., 2024		Methadone	93	88%
Tierney et al., 2023		Methadone	52	74%
Vu et al., 2023	Vietnam	Methadone	1,069	99%
Zhang et al., 2022		Buprenorphine	11,619	81%
Follow-up: 2 months				
Hamid-Reza Esmaeili et al., 2014	Iran	Methadone	207	76%
Hamid-Reza Esmaeili et al., 2014	Iran	Buprenorphine	104	59%
Ker et al., 2021	Outpatient treatment initiation	Buprenorphine	2,409	50%
Ker et al., 2021	Inpatient/IOP treatment initiation	Buprenorphine	2,749	25%
Follow-up: 3 months				
Burns et al., 2015	Australia	Methadone	7,183	70%
Burns et al., 2015	Australia	Buprenorphine	8,417	44%
Chan et al., 2024	Telehealth	Buprenorphine	99	97%
Chan et al., 2024	Non-telehealth	Buprenorphine	51	92%
Dayal et al., 2017	India	Buprenorphine	68	34%
Ivasiy et al., 2024		Methadone	53,568	66%

Study	Setting	Medication	*n*	Rate
Kaliamurthy et al., 2024	Pediatric Addiction Clinic	Buprenorphine, Naltrexone	21	58%
Lira et al., 2023	Telehealth	Buprenorphine	1,816	62%
Lone et al., 2024		Naltrexone	100	64%
Lynch et al., 2021		Buprenorphine, Naltrexone	40	93%
Marcovitz et al., 2016		Buprenorphine	202	72%
Morgan et al., 2021		Extended-release Buprenorphine	204	50%
Morgan et al., 2021		Extended-release Naltrexone	1,173	64%
Morgan et al., 2021		Mucosal Buprenorphine	12,171	34%
Morgan et al., 2021		Methadone	810	58%
Mudiope et al., 2024	Uganda	Methadone	343	83%
Reuter et al., 2022		Buprenorphine	279	43%
Schuman-Olivier et al., 2014	Emerging adults	Buprenorphine	223	56%
Schuman-Olivier et al., 2014	Older adults	Buprenorphine	71	78%
Rowe et al., 2025		Buprenorphine	742	73%
Tierney et al., 2023		Methadone	50	52%
Zhang et al., 2022		Buprenorphine	11,619	66%
Zheng et al., 2025		Buprenorphine	3,255	57%
Follow-up: 6 months				
Alexander et al., 2023	BIPOC patients	Methadone	156	62%
Alexander et al., 2023	White patients	Methadone	301	57%
Brenna et al., 2024	Norway	XR-Naltrexone	161	61%
Chambers et al., 2023		Buprenorphine	6,499	42%
Chan et al., 2024	Telehealth	Buprenorphine	98	96%
Chan et al., 2024	Non-telehealth	Buprenorphine	48	88%
Chua et al., 2023	US retail pharmacy claims data	Buprenorphine	3,006,629	22%
Crepeault et al., 2024	Canada	Buprenorphine	78	18%
Crepeault et al., 2024	Canada	Methadone	76	18%
Dayal et al., 2017	India	Buprenorphine	68	19%
Esmaeili et al., 2014	Iran	Methadone	311	66%
Fendrich et al., 2021		Primarily Buprenorphine	423	59%

Study	Setting	Medication	*n*	Rate
Fine et al., 2021		Buprenorphine	1,467	22%
Gryczynski et al., 2014		Buprenorphine	297	58%
Haddad et al., 2024		Buprenorphine	1,451	64%
Hamid-Reza Esmaeili et al., 2014	Iran	Methadone	207	56%
Hamid-Reza Esmaeili et al., 2014	Iran	Buprenorphine	104	35%
Hawkins et al., 2024		Buprenorphine	2,880	58%
Hayes et al., 2024		Buprenorphine	31,797	50%
Hser et al., 2014		Buprenorphine	738	46%
Hser et al., 2014		Methadone	529	74%
Ivasiy et al., 2024		Methadone	53,568	50%
Johnson et al., 2021		Methadone	25,866	38%
Ker et al., 2021	Outpatient treatment initiation	Buprenorphine	2,409	27%
Ker et al., 2021	Inpatient/IOP treatment initiation	Buprenorphine	2,749	9%
Kermode et al., 2020		Buprenorphine	74	68%
Lehmann et al., 2021	Germany	Slow-release Morphine	180	61%
Lira et al., 2023		Buprenorphine	1,816	52%
Mudiope et al., 2024	Uganda	Methadone	343	72%
Nateghi Haredash et al., 2024	Stanford Electronic Health Record Data (STARR)	Buprenorphine	1,800	61%
Nateghi Haredash et al., 2024	NeuroBlu Longitudinal Behavioral Health Database	Buprenorphine	7,957	58%
Noe et al., 2020		Buprenorphine	350	35%
Reuter et al., 2022		Buprenorphine	279	38%
Samples et al., 2018		Buprenorphine	17,329	35%
Scheibe et al., 2020	South Africa	Methadone	54	81%
Shakya et al., 2024		Buprenorphine, Methadone	130	64%
Sullivan et al., 2019		XR-Naltrexone	28	57%
Sullivan et al., 2019		Oral Naltrexone	32	28%
Vu et al., 2024	Vietnam	Methadone	1,069	89%
Williams et al., 2024		Buprenorphine	19,487	39%
Yang et al., 2023	Vietnam	Methadone	315	34%
Zhang et al., 2022		Buprenorphine	11,619	53%
Follow-up: 9 months				
Chan et al., 2024	Telehealth	Buprenorphine	97	94%

Study	Setting	Medication	*n*	Rate
Greiner et al., 2022		Buprenorphine	120	23%
Greiner et al., 2022		Injectable Naltrexone	88	53%
Håkansson et al., 2016		Buprenorphine	36	83%
Mollajavadi et al., 2016	Iran	Methadone	74	24%
Mudiope et al., 2024	Uganda	Methadone	343	64%
Vu et al., 2024	Vietnam	Methadone	1,069	84%
Follow-up: 11 months				
Chan et al., 2024	Telehealth	Buprenorphine	89	84%
Tehrani et al., 2023	Iran	Opium Tincture	90	83%
Follow-up: 12 months				
Brummer et al., 2024	Denmark	Heroin Maintenance	432	70%
Dayal et al., 2017	India	Buprenorphine	68	12%
Fine et al., 2021		Buprenorphine	1,467	11%
Hoseinie et al., 2017	Iran	All MOUD	242	30%
Ker et al., 2021	Outpatient treatment initiation	Buprenorphine	2,409	14%
Ker et al., 2021	Inpatient/IOP treatment initiation	Buprenorphine	2,749	4%
Lopian et al., 2019		Buprenorphine	108	73%
Manhapra et al., 2018		Buprenorphine	16,190	45%
Montalvo et al., 2019		Buprenorphine	321	53%
Mudiope et al., 2024	Uganda	Methadone	343	55%
Noe et al., 2020		Buprenorphine	350	25%
Pashaei et al., 2014	Iran	Methadone	260	76%
Reuter et al., 2022		Buprenorphine	279	35%
Radfar et al., 2023	Iran - patients referred from compulsory residential centers	Methadone	58	12%
Radfar et al., 2023	Iran - nonreferred patients	Methadone	47	21%
Schiff et al., 2021		Methadone	2,314	64%
Schuman-Olivier et al., 2014	Emerging adults	Buprenorphine	223	17%
Schuman-Olivier et al., 2014	Older adults	Buprenorphine	71	45%
Seiri et al., 2014	Iran	Opium Tincture	90	83%
Shakya et al., 2024		Buprenorphine, Methadone	130	46%
Stone et al., 2020	Fentanyl-exposed	Methadone	121	53%
Stone et al., 2020	Non-fentanyl-exposed	Methadone	30	47%
Vu et al., 2024	Vietnam	Methadone	1,069	78%

Study	Setting	Medication	*n*	Rate
Weinstein et al., 2017		Buprenorphine	1,605	54%
Williams et al., 2024		Buprenorphine	19,487	26%
Wyse et al., 2023		Methadone	1,004	28%
Young et al., 2024		Buprenorphine	37,955	43%
Zhang et al., 2022		Buprenorphine	11,619	32%
Follow-up: 18 months				
Boyett et al., 2023		Buprenorphine	529	33%
Noe et al., 2020		Buprenorphine	350	18%
Shakya et al., 2024		Buprenorphine, Methadone	130	39%
Vu et al., 2024	Vietnam	Methadone	1,069	61%
Follow-up: 24 months				
Busch et al., 2021	Australia	Methadone, Slow-release Morphine	4,778	61%
Cao et al., 2014	China	Methadone	1,511	36%
Farrell et al., 2024	Australia	Buprenorphine	100	47%
Hasan et al., 2021		Buprenorphine	5,134	25%
Montalvo et al., 2019		Buprenorphine	321	36%
Nosyk et al., 2024	British Columbia, Canada	Buprenorphine	30,891	11%
Nosyk et al., 2024	British Columbia, Canada	Methadone	30,891	19%
Shakya et al., 2024	India	Buprenorphine, Methadone	130	29%
Williams et al., 2024		Buprenorphine	19,487	17%
Follow-up: 36 months or more				
Cope et al., 2022	3 years	Buprenorphine	152	48%
Manhapra et al., 2018	3 years	Buprenorphine	16,190	14%
Rao et al., 2020	6 years - South Asia	Buprenorphine	150	36%
Zhang et al., 2015	7 years – China	Methadone	1,512	21%
Haddad et al., 2024	9 years	Buprenorphine	169	70%
Pilarinos et al., 2023	13 years - Canada	Methadone	160	36%
Jiménez-Treviño et al., 2023	15 years – Spain	Methadone	120	75%
Zhou et al., 2024	18 years – China	Methadone	9,435	10%
Jiménez-Treviño et al., 2023	25 years – Spain	Methadone	90	48%
Jiménez-Treviño et al., 2023	35 years – Spain	Methadone	49	4%

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Table A2: Past-MOUD Abstinence Rates at Follow-up

Study	Setting	Medication	Abstinence Definition	Follow-up Period	*n*	Rate
Breen et al., 2003	Australia	Methadone to Buprenorphine Transition	Not using heroin	1 month	51	31%
Davison et al., 2006	VA Medical Center	Clonidine	Toxicology-verified abstinence from opioids	90 days	112	≤3%
Ghandi et al., 2003		Buprenorphine	Opioid-free urine test	6 months	123	12%
Coviello et al., 2011		Methadone	No heroin or other opioid use	9 months	230	71%
De Jong et al., 2007		Naltrexone	Self-report of no heroin and/or methadone use, confirmed with urine analysis	10 months	272	28%
Ling et al., 2020	35 US-based sites	Buprenorphine	Sustained opioid abstinence over 12 months	12 months	425	51%
Cushman, 1981		Methadone	No use of heroin or other narcotics	14 months	1,740	25%
De Jong et al., 2007		Naltrexone	Self-report of no heroin and/or methadone use, confirmed with urine analysis	16 months	272	32%
Pashaei et al., 2014	Iran	Methadone	No illicit opioid use	26 months	198	25%
Clausen et al., 2014	Norway	Methadone	Opioid-free without maintenance treatment	2.8 years	103	11%
Eklund et al., 1994	Sweden	Methadone	Opiate-free and well-ordered live	3 years	50	42%
Riordan et al., 1976		Methadone	No illicit drug use	44 months	38	11%
Stimmel & Rabin., 1974		Methadone	“Drug free”	47 months	490	7%
Judson et al., 1980		Methadone	No heroin use	5 years	260	24%
Dole & Joseph., 1978		Methadone	Heroin abstinence and doing well	Up to 6 years	1,413	8%
Stimmel et al., 1977		Methadone	Narcotic-free	6 years	269	35%
Cushman, 1978a		Methadone	“Stable and narcotic free”	8 years	161	23%

Study	Setting	Medication	Abstinence Definition	Follow-up Period	*n*	Rate
Maddux & Desmond, 1992	Methadone for >1 year	Methadone	Continuous heroin abstinence x 3 years	10 years	95	7%
Maddux & Desmond, 1992	Methadone for ≤1 year	Methadone	Continuous heroin abstinence x 3 years	10 years	77	26%
Jiménez-Treviño et al., 2023		Methadone	No heroin use	15 years	120	60%
Jiménez-Treviño et al., 2023		Methadone	No heroin use	25 years	90	77%
Jiménez-Treviño et al., 2023		Methadone	No heroin use	35 years	49	96%

Bibliography of Table A2

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