Vivitrol Completion Protocol

Prepared for the Florida Alcohol and Drug Abuse Association

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LITERATURE REVIEW

The Relationship Between Duration & Outcome

Adherence is defined by the World Health Organization (WHO 2003) as “the extent to which a person’s behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.”

WHO differentiates adherence from compliance, because adherence requires the patient’s agreement to the recommendations, i.e., patients should be active partners in their care and therefore strong patient-provider communication is a must. The US Centers for Substance Abuse Treatment consensus report noted that, “Treatment success depends on the achievement of specific goals that are agreed on by both the patient and the physician”(CSAT 2004).

This also requires multi-disciplinary team collaboration, since patients interact with and engage in self-care decision-making as a result of inputs and relationships with many providers, and even multiple agencies.

In general, federal experts recommend that, “Under ideal conditions, discontinuation of medication should occur when a patient has achieved the maximum benefit from treatment and no longer requires continued treatment to maintain a drug-free lifestyle”(CSAT 2004).

A psychological manifestation of this state exists within the Stages of Change and is known as the Maintenance Phase.

This Transtheoretical Model holds that, “Maintenance requires prolonged behavioral change by remaining abstinent…and continued vigilance for a minimum of 6 months to several years.” (CSAT 2004)

Persistence on daily oral naltrexone has traditionally been viewed as effective mainly for a narrow group of good prognosis patients, such as healthcare professionals who are highly motivated with good social supports or patients receiving intensive behavioral treatments that reinforce adherence.

The extended-release naltrexone (XR-NTX) formulation (Vivitrol®), however, was developed to achieve successful month-long adherence in all patients (Nunes, Krupitsky et al. 2015).

Indeed, XR-NTX persistence has proven efficacious in trials and effective in community evaluations (e.g., Los Angeles County Vivitrol Evaluation, accessed at: https://admin.publichealth.lacounty.gov/sapc/resources/VivitrolPilot1FinalReport.pdf).

Duration of Retention: In general, retention on medication in addiction recovery (MAT), however, tends to be short. Over 50% of XR-NTX patients persist on it for 6 months in published trials (Krupitsky, Nunes et al. 2013, Lee, Friedmann et al. 2016). This persistence on XR-NTX does not appear substantially different from persistence on methadone or buprenorphine.

In an analysis of 1,605 inner-city office-based buprenorphine opioid treatment (OBOT) episodes, 55% lasted less than a year (Weinstein, Kim et al. 2017) and in the largest retrospective insurance claims analysis, direct comparison showed that buprenorphine (N = 7,596) and methadone (N = 1,916) persistence averaged only 69 and 63 days, respectively, which was not significantly different from XR-NTX (N=165), at 61 days (Baser, Chalk et al. 2011).

Some differences between the two agonists have been reported, such as a large study of 1267 opioid-dependent individuals who were randomized to receive open-label BUP or MET. By the end of 24 weeks treatment completion was 74% for MET versus only 46% for BUP ($P < 0.01$)(Hser, Saxon et al. 2014). Buprenorphine retention consistently tends to be shorter methadone, according to a large systematic review (Mattick, Breen et al. 2014), which is problematic.

Despite some clarity on the above issues, these early dropout rates and studies examining only 6-month durations do not address at all the question of when should providers consider treatment “completed”.

Data on longer-term retention on XR-NTX indicate good safety and efficacy. In the XR-NTX pivotal FDA trial, patients who remained on XR-NTX for 18 months continued to benefit without significant laboratory abnormalities or health issues (Krupitsky, Nunes et al. 2013).

Longer-term study patients, including those who were treated for alcohol use disorder, have been safely and effectively treated for as long as 5 continuous years.

Patient concerns that the active ingredient, naltrexone, might diminish pleasure appear unfounded. In a cohort with alcohol dependence who received XR-NTX continuously for an average of 3.5 years, patients felt the least amount of gratification for drinking and gambling, with significantly greater pleasure for a variety of daily activities including exercise, listening to music, eating, and sex (O'Brien, Gastfriend et al. 2011).

Thus, it appears that OUD patients do not necessarily *have to be* on XR-NTX long-term, *but they can*, and *can do so without fear* that healthy pleasurable activities will be suppressed as are drinking and using opioids.

The Roles of MAT: It is important to consider the question:
What is the role of these medication in OUD treatment?
-- Reducing craving and drug use is fundamental.

During agonist MAT, illicit drug use is suppressed, which is desirable (Mattick, Breen et al. 2014); however, with XR-NTX, relapse is actually prevented (according to the FDA-approved label), which is a categorical or definitive benefit.

Relapse prevention is not the only needed beneficial effect of XR-NTX. Also important is protecting time to allow therapeutic relationships to develop and to allow the work needed to stabilize safe, healthy patterns of living.

Some have assumed that it is necessary for patients to first "test" the blockade with illicit opioids and experience the disappointment of feeling nothing, in order for XR-NTX treatment to be effective. Sullivan et al., observed however, that high treatment retention among naltrexone-treated patients who do not test the blockade suggests XR-NTX may exert direct effects on opiate-taking behavior that do not depend on extinction, perhaps by attenuating craving or normalizing dysregulated hedonic or neuroendocrine systems (Sullivan, Bisaga et al. 2013).

This is supported by functional MRI (fMRI) scans, in which brain reward regions, during treatment with XR-NTX, show decreased responsiveness to drug cues and other regions actually increase executive function and self-referential processing. This suggests that the clinical effects of XR-NTX may ensue, in part, by not only decreasing brain reward system response to environmental drug-associated cues, but also via increasing one's capacity for conscious self-regulation (Langleben, Ruparel et al. 2014).

If this is so, presumably there is a time frame during which such improved self-regulation might become established, after which it might no longer require medication support.

XR-NTX's absence of withdrawal and the possible benefit of improving self-regulation might imply that, unlike with agonist treatment, XR-NTX patients may and should complete medication treatment after some duration.

Many certainly seek to do so, but either stop without discussing with providers, or lack clear objectives or criteria from their providers.

The literature is quiet on what the ideal duration should be.

Duration of Treatment

Fixed vs. Individualized Duration: A particular fixed duration of treatment for opioid maintenance pharmacotherapy is not supported by general clinical consensus (Kampman and Jarvis 2015).

The US Dept of HHS Center for Substance Abuse Treatment noted this with respect to buprenorphine: "For many patients, it may be inappropriate to decide arbitrarily on the length of treatment… patients will need to be started in treatment within a flexible timeframe that responds to the progress and needs of the patient."

Furthermore, "as treatment progresses, it may become a more appropriate time to assess the duration of various aspects of treatment, including medications, counseling therapies, and self-help groups.

Therefore, it is important to assess initially, and to reassess periodically" (CSAT 2004).

In the CSAT TIP-40 consensus guideline (2004), experts believed that decisions to conclude buprenorphine should be based on a patient's wishes and commitment to being medication-free, and on the provider's confidence that a taper would succeed.

The data on both buprenorphine and methadone indicate that longer durations of medication is associated with less illicit drug use and fewer complications (CSAT 2004).

The timeframe for agonist therapies, however, *is clearly impacted by a fundamental side effect of these agents*: withdrawal and its tendency to provoke relapse.

How then should an antagonist be regarded when it comes to determining effective treatment conclusion?

Researchers have identified some characteristics of patients who are prone to premature dropout from agonist MAT.

In one large study, patients who were younger, Hispanic and who used heroin or other substances during treatment were more prone to drop out (Hser, Saxon et al. 2014).

In another, women, older patients and those with a psychiatric diagnosis had a greater odds of 1 year retention or longer. The unemployed, patients carrying Hepatitis C, and of African/American or Hispanic race/ethnicity had lower retention odds (Weinstein, Kim et al. 2017).

Also, generally, the greater the degree of pre-treatment drug use severity, the lower the likelihood of successful discontinuation, at least in the agonist medication literature (Nosyk, Sun et al. 2012).

Patient Perceptions of Duration of MAT: Patients have a variety of concerns about the duration of treatment. Little is known about their views of XR-NX treatment duration, but there is some study of patient concerns regarding buprenorphine duration of treatment.

Patients are open to longer treatment durations if they:
-- started drug use at a later age,
-- spent longer time in medication maintenance,
-- had pain concerns, and concerns about relapse.

Patients who had shorter intended durations of buprenorphine were prone to discussing discontinuation with a treatment provider, had prior attempts to discontinue it, concerns about withdrawal symptoms, and experienced pleasurable effects from taking buprenorphine, or perceived that it conflicted with their life, work, or school obligations (Bentzley, Barth et al. 2015).

Although there is a very limited literature that questions whether psychosocial treatment is necessary for buprenorphine MAT effectiveness, the FDA and the ASAM National Practice Guidelines clearly recommend psychosocial treatment with all MAT, including XR-NTX (Kampman and Jarvis 2015).

Similarly, a systematic review of 3 prominent prior reviews and 27 recent publications of empirical studies concluded that evidence-based counseling, particularly contingency management and cognitive behavioral therapy (mostly studied in methadone treatment), are generally efficacious in combination with medications to treat opioid addictions (Dugosh, Abraham et al. 2016).

To reduce the likelihood of premature patient discontinuation, researchers have recommended frequent counseling about the high probability of a patient's relapse if MAT is discontinued too early. This may improve retention in treatment and prevent the relapse to illicit opioid use that is likely to follow premature discontinuation (Bentzley, Barth et al. 2015).

Determining Duration of MAT: A general principle for determining the duration of MAT for XR-NTX is that it "depends on clinical judgment and the patient's individual circumstances" (Kampman and Jarvis 2015). Since there is no physical dependence associated with naltrexone, it can be stopped abruptly without withdrawal symptoms. This is a clear advantage over agonists, whose withdrawal symptoms emerge rapidly upon cessation, even following a slow taper, and provoke relapse in the vast majority of patients.

The largest clinical trial of taper and cessation outcomes was the NIDA Clinical Trials Network Prescription Opioid Analgesic Treatment Study. In this trial, 92% of buprenorphine-treated patients relapsed to opioid use within 8 weeks after a 1-month taper and discontinuation (Weiss, Potter et al. 2011).

In a larger database analysis of 25,545 completed methadone maintenance treatment episodes, 95.6% of all episodes initiating a taper were unsuccessful (Nosyk, Sun et al. 2012). The authors concluded, "The majority of patients attempting to taper from methadone maintenance treatment will not succeed." The adverse effect of withdrawal with agonists necessitates indefinite treatment with these agents, however, this is not necessarily a response to the primary brain disease of the addiction; rather, it is an artifact of the withdrawal side effect of the medication itself.

Therefore, the question remains, is indefinite treatment a biological necessity of addiction? If not, when can XR-NTX cessation be considered?

Patient Selection Factors for Discontinuation

There are no clear predictor variables as to which patient will do better with XR-NTX, or will do better with shorter vs. longer durations of XR-NTX treatment.

The XR-NTX pivotal FDA trial examined 25 different putative predictors of successful treatment. While the authors' hypothesis was that XR-NTX would be more efficacious for patients with low severity, this did not turn out to be the case; none of the tested variables predicted which patients would be more successful (Nunes, Krupitsky et al. 2015).

In other words, with XR-NTX, patients with high severity at baseline had as good a rate of successful clinical outcome than those with low baseline severity.

Thus, it is not necessarily useful to look at baseline problems for determining who should be offered XR-NTX or how long they should be on it. This includes variables such as: age, gender, marital status, living arrangement, addiction severity (medical, employment, substance use, legal, family/social, psychiatric), opioid use duration, craving, prior treatment, pain, anxiety/depression or HIV status.

Recovery as a Determinant: Instead of considering a patient' baseline characteristics,
it may be more important to consider subsequent factors, i.e., during or as a result of treatment.
One such major composite characteristic may be the extent to which a patient has achieved "recovery."

Recovery is defined by ASAM as, "A process of sustained action that addresses the biological, psychological, social and spiritual disturbances inherent in addiction. Recovery aims to improve the quality of life by seeking balance and healing in all aspects of health and wellness, while addressing an individual's consistent pursuit of abstinence, impairment in behavioral control, dealing with cravings, recognizing problems in one's behaviors and interpersonal relationships, and dealing more effectively with emotional responses.

An individual's recovery actions lead to reversal of negative, self-defeating internal processes and behaviors, allowing healing of relationships with self and others". (This set of objectives is a helpful expert consensus perspective, although it does not specifically distinguish parameters for MAT completion.

Spiritual recovery's intangibility makes it particularly challenging for research, but asking whether the patient has grappled with his/her existential sense of purpose in life can be a revealing window into philosophical resilience. Despite being complex constructs, recovery components are sensible considerations and have emerged elsewhere in more empirical studies.

Some initial, simple expectations are logical and may be extrapolated from the studies mentioned above: the patient should have established abstinence and longitudinal adherence to the medication (Rothenberg JL 2002).

Basic considerations would also certainly include (as per the CSAT TIP-40 Buprenorphine Consensus Panel):

-- stable housing and income,
-- adequate psychosocial support,
-- and the absence of legal problems (CSAT 2004).

Patients who have not achieved such stabilization will usually require a longer period of maintenance, to work through these barriers.

Behavioral Naltrexone Therapy was developed to foster adherence and persistence with oral naltrexone (Rothenberg et al., 2002). The extended phase of medication treatment ("Maintenance Phase") was proposed to last 9 months.

During Maintenance, the patient should address:

-- broader life-style changes and goals,
-- attending weekly psychosocial sessions,
-- coping with cravings,
-- learning to monitor thoughts about drug use,
-- planning for emergencies,
-- and building a supportive network.

An important category of effort is developing problem-solving skills, including:
drug refusal skills, awareness and management of anger, moods, negative thinking,
increasing pleasant activities, and job-seeking skills. The importance of developing these skills and responses is not simply an expert clinical observation; it is also consistent with current understanding of neurophysiology of addiction and recovery (Volkow, Koob et al. 2016).

Neurophysiologically, a key disruption of addiction is the conditioning of brain circuitry to instant gratification for drug rewards.

1) Much of this damage occurs through dysregulation in the firing of dopamine cells and the eventual decreased release of dopamine.
2) Drugs trigger neuroplastic changes in the crucial brain-reward region, the nucleus accumbens.
3) They also disrupt function in a region implicated in the encoding of habits and routines – the dorsal striatum.
4) Other key areas that are affected are the amygdala, which is involved in emotional, stress and desire responses and the memory region, the hippocampus.
5) Finally, drugs also disrupt self-regulation and the attribution of salience managed by the prefrontal cortex.

In sum, addiction disrupts the local function and the aggregate coordination across these brain regions, producing conditioning, craving and loss of drive, i.e., motivation (Volkow, Koob et al. 2016).

A key implication of this brain science is that in order to achieve stable recovery, ordinary, healthy rewards must regain normal physiologic motivational power – either regaining this, or, if the patient has used substances since early adolescence, maybe for the first time (Volkow, Koob et al. 2016).

The attenuated release of the neurotransmitter dopamine diminishes brain sensitivity to stimulation by both drug-related and non–drug-related rewards. Therefore, addicted individuals lose the euphoria from their drugs over time and also become less motivated by normal daily stimuli such as relationships and activities.

Since these brain disruptions become deeply ingrained, they cannot be quickly reversed simply via detoxification. Medication treatment should therefore continue until the team has determined that the patient is achieving normal gratification and pleasure from healthy, everyday activities, and that these are motivating and sustaining.

Ongoing psychoeducation and counseling are critical to helping patients persist on medication. Scientists who have analyzed some of the largest datasets of OUD longitudinal treatment note the many reasons why patients may wish to discontinue MAT; however, the relapse risks should be communicated – even to the extent of conducting an informed consent process (Nosyk, Sun et al. 2012).

Given the importance of sustaining adherence long enough for effective long-term recovery, providers should implement multiple strategies, including:

-- interventions in individual sessions with the patient,
-- external reinforcements, such as positive and negative contingencies, and
-- involvement of family members or significant others (Weiss 2004).

Organizing XR-NTX Completion Criteria: A widely-used organizing schema for evaluating substance use disorders and treatment planning is the ASAM Criteria.

These 6 dimensions of assessment are highly relevant to consideration of patients' readiness for concluding XR-NTX treatment, and therefore, this will be the organizing outline for the proposed XR-NTX Completion Protocol.

Based on the limitations of the available empirical literature, this protocol will necessarily be qualitative, rather than quantitative. The elements that should be considered are nevertheless logical, clinically relevant, and broad.

Ideally, teams composed of all providers with direct knowledge of the patient should jointly review these parameters – including and particularly with the patient. Significant supportive others, e.g., spouse and close family members, will also be valuable in providing input and supporting the patient.

These questions are presented below.

After Concluding MAT: Finally, upon conclusion of MAT, the providers' work is hardly finished.

Experts urge that, "Patients should be assessed for continued stability in maintaining their drug-free lifestyle. Patients should then be followed with psychosocial services and/or the reintroduction of medication, if needed, for continued progress."(CSAT 2004)

Relapse may require re-initiation of not only medication, but also earlier stage levels of care. "After a return to substance use, clients usually revert to an earlier change stage —not always to maintenance or action, but more often to some level of contemplation. They may even become precontemplators again."(CSAT 2004)

VIVITROL COMPLETION PROTOCOL

The following protocol is designed for the entire provider team – starting with the patient.

During treatment, the items below may be thought of as therapeutic prompts to help the patient consider his/her treatment objectives and progress.

The full team includes prescribers, individual and group counselors, coaches, and other team members.

When the time comes for a decision to be made, the team must work with the patient to conduct a collaborative, patient-centered review. This review should include the patient's wishes, strengths and needs, in order to determine readiness for medication treatment completion.

Questions are organized according to the ASAM Criteria.

Each question should first be asked, answered, and considered within its individual dimension.

Then, the net set of findings within each dimension should be considered
in relation to the other 5 dimensions.

The goal is not simply to choose between a binary “yes” vs. “no” decision
– since a “no” determination may be discouraging to the patient, provoking premature discontinuation.

The principles of Motivational Enhancement Therapy call for empowering patients to understand and seek to pursue their own health objectives, rather than comply with the mandate of experts.

Instead, consideration within each dimension may reveal specific key areas in need of continued focus.

This information can give the patient clarity on what more is needed, so that the patient sees the feasibility of specific targets, and feels encouraged to persist long enough to achieve a comprehensive readiness for XR-NTX treatment completion.

ACHIEVED	NEEDS WORK	
DIMENSION 1 – INTOXICATION/WITHDRAWAL		
❑	❑	1. Has the patient overcome withdrawal symptoms, such as craving, both overt and subtle?
❑	❑	2. Has the patient maintained longitudinal adherence to Vivitrol injections?
❑	❑	3. Does the patient wish to complete Vivitrol?
DIMENSION 2 - BIOMEDICAL CONDITIONS AND COMPLICATIONS		
❑	❑	4. Has the patient considered and successfully managed or resolved biomedical issues that pose relapse risks in the foreseeable future, including consistent adherence to healthcare treatments and medications, if relevant?
❑	❑	5. Has the patient secured and reliably used resources to address any biomedical needs?

DIMENSION 3 - EMOTIONAL, BEHAVIORAL OR COGNITIVE CONDITIONS AND COMPLICATIONS			
❑	❑	6.	Has the patient considered and successfully managed or resolved psychological issues that pose relapse risks in the foreseeable future, including consistent adherence to psychosocial treatments and psychiatric medications, if relevant?
❑	❑	7.	Has the patient secured and reliably used resources to address any emotional, behavioral and/or cognitive needs?
DIMENSION 4 – READINESS TO CHANGE			
❑	❑	8.	Does the patient have a clear acceptance of his/her opioid use disorder?
❑	❑	9.	Does the patient have a good understanding of his/her disorder?
❑	❑	10.	Is the patient realistically aware of his/her risk factors for relapse and his/her self-care responsibilities?

DIMENSION 5 – RELAPSE, CONTINUED USE OR CONTINUED PROBLEM POTENTIAL		
❑	❑	11. Has the patient achieved a demonstrated period of abstinence from the drug(s) for which the medication is being prescribed – and for any other drugs that pose serious risk for relapse or, in combination with opioids, pose serious risk for overdose?
❑	❑	12. Has the patient learned a variety of new, healthy, and adaptive coping skills, such as monitoring thoughts about drug use, planning for emergencies, drug refusal skills, and anger, anxiety and mood management?
❑	❑	13. Has the patient addressed negative, self-defeating internal processes and behaviors?
❑	❑	14. Has the patient developed and engaged in healthier routines, activities and behaviors/practices (e.g., exercise, meditation, etc.) that improve coping capacities?
❑	❑	15. Is the patient able to identify the risks, behaviors or other conditions – even prior to return to actual drug use (e.g., upon the return of or increases in craving or overwhelming stress) – under which s/he would agree to restart XR-NTX in the future?

DIMENSION 6 – RECOVERY/LIVING ENVIRONMENT		
❑	❑	16. Has the patient addressed critical environmental needs, such as stable housing and income, adequate psychosocial support, and the absence of legal problems?
❑	❑	17. Has the patient resolved prior obstacles, reduced burdens/pressures, disengaged from relationships that jeopardize recovery, to reduce risks for future relapse?
❑	❑	18. Has the patient formed new relationships or resolved/improved prior relationships and built a supportive network, e.g., mutual help group and sponsor, in ways that support recovery?
❑	❑	19. Has the patient endured meaningful stress – both distress and eustress (i.e., healthy, positive stress) – and managed successfully without relapse?
❑	❑	20. Has the patient begun to consider spiritual or existential issues in his/her life, e.g., whether life has a particular meaning or purpose?

EVALUATION:

In the absence of empirical data and quantitative indicators,
clinical review by the team and patient of the above questions will determine
if the patient has achieved a preponderance of these objectives,
such that the patient's desire to conclude Vivitrol and continue with psychosocial management
alone is more likely than not to be successful.

TREATMENT PLANNING:

If key items are yet to be achieved, the team should explicitly discuss with the patient what to focus on in the next phase of the therapeutic work
– in an empowering manner, such that the patient can feel a sense of optimism.

This should review both:

1) What has the patient successfully achieved?
2) What specific, concrete steps can the patient take next
   to feasibly achieve readiness for medication completion?

REFERENCES

1. Baser, O., M. Chalk, D. A. Fiellin and D. R. Gastfriend (2011). "Cost and utilization outcomes of opioid-dependence treatments." American J Managed Care **17**: S235-248.

2. Bentzley, B. S., K. S. Barth, S. E. Back, G. Aronson and S. W. Book (2015). "Patient Perspectives Associated with Intended Duration of Buprenorphine Maintenance Therapy." J Subst Abuse Treat **56**: 48-53.

3. Bentzley, B. S., K. S. Barth, S. E. Back and S. W. Book (2015). "Discontinuation of buprenorphine maintenance therapy: perspectives and outcomes." J Subst Abuse Treat **52**: 48-57.

4. CSAT (2004). Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Rockvill MD, US DHHS.

5. Dugosh, K., A. Abraham, B. Seymour, K. McLoyd, M. Chalk and D. Festinger (2016). "A Systematic Review on the Use of Psychosocial Interventions in Conjunction With Medications for the Treatment of Opioid Addiction." J Addict Med **10**(2): 93-103.

6. Hser, Y. I., A. J. Saxon, D. Huang, A. Hasson, C. Thomas, M. Hillhouse, P. Jacobs, C. Teruya, P. McLaughlin, K. Wiest, A. Cohen and W. Ling (2014). "Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial." Addiction **109**(1): 79-87.

7. Kampman, K. and M. Jarvis (2015). "American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use." J Addict Med **9**(5): 358-367.

8. Krupitsky, E., E. V. Nunes, W. Ling, D. R. Gastfriend, A. Memisoglu and B. L. Silverman (2013). "Injectable extended-release naltrexone (XR-NTX) for opioid dependence: long-term safety and effectiveness." Addiction **108**(9): 1628-1637.

9. Langleben, D. D., K. Ruparel, I. Elman, J. W. Loughead, E. L. Busch, J. Cornish, K. G. Lynch, E. S. Nuwayser, A. R. Childress and C. P. O'Brien (2014). "Extended-release naltrexone modulates brain response to drug cues in abstinent heroin-dependent patients." Addict Biol **19**(2): 262-271.

10. Lee, J. D., P. D. Friedmann, T. W. Kinlock, E. V. Nunes, T. Y. Boney, R. A. Hoskinson, Jr., D. Wilson, R. McDonald, J. Rotrosen, M. N. Gourevitch, M. Gordon, M. Fishman, D. T. Chen, R. J. Bonnie, J. W. Cornish, S. M. Murphy and C. P. O'Brien (2016). "Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders." N Engl J Med **374**(13): 1232-1242.

11. Mattick, R. P., C. Breen, J. Kimber and M. Davoli (2014). "Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence." Cochrane Database Syst Rev(2): CD002207.

12. Nosyk, B., H. Sun, E. Evans, D. C. Marsh, M. D. Anglin, Y. I. Hser and A. H. Anis (2012). "Defining dosing pattern characteristics of successful tapers following methadone maintenance treatment: results from a population-based retrospective cohort study." Addiction **107**(9): 1621-1629.

13. Nunes, E. V., E. Krupitsky, W. Ling, J. Zummo, A. Memisoglu, B. L. Silverman and D. R. Gastfriend (2015). "Treating Opioid Dependence With Injectable Extended-Release Naltrexone (XR-NTX): Who Will Respond?" J Addict Med **9**(3): 238-243.

14. O'Brien, C. P., D. R. Gastfriend, R. F. Forman, E. Schweizer and H. M. Pettinati (2011). "Long-Term Opioid Blockade and Hedonic Response: Preliminary Data from Two Open-Label Extension Studies with Extended-Release Naltrexone." American J Addictions **20**(2): 106-112.

15. Rothenberg JL, e. a. (2002). "Behavioral naltrexone therapy: An integrated treatment for opiate dependence." J Subst Abuse Treat **23**: 351-360.

16. Sullivan, M. A., A. Bisaga, J. J. Mariani, A. Glass, F. R. Levin, S. D. Comer and E. V. Nunes (2013). "Naltrexone treatment for opioid dependence: does its effectiveness depend on testing the blockade?" Drug Alcohol Depend **133**(1): 80-85.

17. Volkow, N. D., G. F. Koob and A. T. McLellan (2016). "Neurobiologic Advances from the Brain Disease Model of Addiction." N Engl J Med **374**(4): 363-371.

18. Weinstein, Z. M., H. W. Kim, D. M. Cheng, E. Quinn, D. Hui, C. T. Labelle, M. L. Drainoni, S. S. Bachman and J. H. Samet (2017). "Long-term retention in Office Based Opioid Treatment with buprenorphine." J Subst Abuse Treat **74**: 65-70.

19. Weiss, R. D. (2004). "Adherence to pharmacotherapy in patients with alcohol and opioid dependence." Addiction **99**(11): 1382-1392.

20. Weiss, R. D., J. S. Potter, D. A. Fiellin, M. Byrne, H. S. Connery, W. Dickinson, J. Gardin, M. L. Griffin, M. N. Gourevitch, D. L. Haller, A. L. Hasson, Z. Huang, P. Jacobs, A. S. Kosinski, R. Lindblad, E. F. McCance-Katz, S. E. Provost, J. Selzer, E. C. Somoza, S. C. Sonne and W. Ling (2011). "Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial." Arch Gen Psychiatry **68**(12): 1238-1246.

21. WHO (2003). Adherence to long-term therapies: evidence for action. Geneva, WHO.

