Opioid Dependence: Is Engaging the Receptor Necessary for Treating the Patient?

Maria A. Sullivan, M.D., Ph.D.

Video: https://www.youtube.com/watch?v=pR_3-z92Z0s&feature=em-upload_owner

At this year's annual Area 2 meeting of the AAAP, held May 28, 2014 at the Columbia University Faculty House, the topic for discussion was: ***"What should be the first-line treatment for opioid dependence?"*** The goals of the Area 2 meeting are to allow members to share clinical and professional information and to encourage prospective members to join AAAP.

This Area 2 workshop was designed to provide members with an update on the current state of medication-assisted treatments for opioid dependence, describing the strengths and limitations of each treatment approach. Building on the experience of clinicians working with several medications, a panel of three physicians sought to elicit clinical experience-based input from the audience with a goal to assess the need of developing a more formal opioid dependence treatment guidelines that clinicians may find useful in their practice. Many practitioners find it challenging to determine which strategy – agonist, antagonist, or non-medication-assisted – should be the first-line treatment for patients with opioid dependence.

Medication-free Treatment. Grace Hennessy, M.D., Director of the Substance Abuse Recovery Program at VA New York Harbor Healthcare System, described what is historically the first treatment approach for opioid use disorders, namely non-pharmacologic treatments including 12-step work and psychosocial interventions. She began by acknowledging the drawbacks to treating opioid addiction without pharmacologic support, including high rates of relapse (65-85% in the first month) post-detoxification and post-discharge from residential treatment and mortality associated with ongoing heroin or illicit opioid use. She then reviewed several medication-free treatments offered for opioid dependence, including Enhanced Outreach Counseling Program to re-enroll methadone clinic drop-outs and Cue-exposure Therapy. Two of the most structured treatments are: Reinforcement-based Treatment (RBT; intensive day treatment programs offering individual and group counseling, urine drug testing, recreational activities, meals, and skills training for employment) and Recovery Housing (structured drug-free housing contingent on abstinence). While the first few months of RBT and Recovery Housing are characterized by high retention and negative UDTs –50% abstinence at 6 months for combined RBT + Recovery Housing in one study -- retention and abstinence drop significantly after abstinence-based contingencies end.

Returning to the question, "Is Medication-free Treatment feasible?" Dr. Hennessy concluded that while it can be effective, this form of treatment requires a wide array of services combined vocational, housing, medical and psychiatric services which are labor-intensive and costly; 3 months of RBT + Recovery Housing can cost up to $2300.

And these programs also require a high level of motivation on the part of patients. Further, there is little research to guide us in assessing the short- or long-term benefits of 12-step Programs, which represent by far the most common form of medication-free treatment to which opioid-dependent patients are referred following detoxification.

Agonist Strategies. Edwin A. Salsitz, MD, FASAM (Attending Physician at Mount Sinai Beth Israel in the Chemical Dependency Division) spoke next, humorously titling his talk "Confessions of an Opioid Agonist Provider." He presented data showing that long-term methadone maintenance reverses the neurochemical abnormalities associated with short-acting opioids. The several advantages of methadone maintenance include: decreased mortality; reduced intravenous drug use (IVDU); less crime; decreased HIV seroconversion; reduced likelihood of relapse to IVDU; improved health, occupational and social functioning; and overall harm reduction. But Dr. Salsitz acknowledged that the restrictive settings in which methadone is prescribed have contributed to its stigma.

He emphasized that the particular advantages for patients of receiving methadone in an office-based general medical practice, a treatment model in which Dr. Salsitz is a pioneer. Dr. Salsitz argued that personal benefits to patients of receiving methadone in a medical setting similar to that used for other chronic illnesses include the dignity of a standard professional atmosphere and the potential for flexible dosing. Overall, such a setting allows for more individualized treatment of the methadone-maintained patient.

Concerning buprenorphine treatment, Dr. Salsitz hailed the use of this office-based agonist treatment as a major paradigm shift in favor of the medical model. He noted that the number of buprenorphine-maintained patients (300,000) now exceeds that of methadone-maintained patients (250,000). While buprenorphine has a favorable side effect profile compared to methadone, and carries fewer risks for cardiac arrhythmias, it has been associated with diversion and misuse problems.

Dr. Salsitz concluded by discussing the unresolved issues that still plague Opioid Agonist Treatment, including questions about optimal duration of treatment or most effective tapering strategies. He also highlighted the stigma and prejudice that patients in agonist-based treatment face in some AA or NA settings, in which they receive the message that being "in recovery" should not involve maintenance on an opioid.

Antagonist Strategies. The next speaker was Maria A. Sullivan, M.D., Ph.D., Associate Professor of Psychiatry at Columbia University Medical Center, who also serves as the Chair of the Clinical Expert Panel for the Providers' Clinical Support System for Medication-assisted Treatment (PCSS-MAT). This is an SAMHSA-sponsored training initiative in which several professional organizations are collaborating, with AAAP taking the lead. She reviewed findings from early studies with oral naltrexone, showing that its use in combination with behavioral therapy boosted retention rates, but that adherence was a significant limitation to its efficacy. Advantages to injection naltrexone (XR-NTX) include the fact that it blocks opioids without agonist effects, that naltrexone is

incompatible with ongoing illicit opioid abuse, and that no tolerance or withdrawal develops. ***In spite of these advantages, only 15.8% of treatment facilities in the U.S. report using naltrexone in either oral or injectable form (SAMHSA 2009).***

Several types of candidates for naltrexone were proposed: patients not interested in, or unable to access, agonist maintenance; those who have successfully used agonist, but are now interested in becoming non-dependent; patients who have failed prior treatment with agonist; patients who are abstinent but at high risk for relapse (e.g. just released from detoxification unit or prison; acute or worsening psychiatric status); and individuals with a shorter history of opioid use or less severe form of the disorder.

XR-NTX, FDA-approved for the treatment of opioid dependence since 2010, doubles rates of treatment retention compared to the oral formulation. XR-NTX achieves 6-month retention rates of 50-70%, comparable to those seen with buprenorphine. Dr. Sullivan presented data from an ongoing randomized trial (N=100 to date) she has conducted with Dr. Bisaga, comparing two strategies for outpatient induction onto injection naltrexone. They have found that oral naltrexone-assisted detoxification significantly outperforms a buprenorphine taper (70% vs. 40%; p=.008) in allowing patients to achieve successful induction onto injection naltrexone.

Dr. Sullivan concluded that XR-NTX is an effective, cost-effective pharmacotherapy for patients in primary care and psychiatric treatment settings and should be a first-line treatment for opioid-dependent patients seeking to become non-dependent. In contrast to detoxification without pharmacologic support – which carries a significant risk of overdose and death – XR-NTX is protective against overdose, carries no risk of abuse or diversion, and is not compatible with relapse.

New Treatment Guidelines. The final speaker was Adam Bisaga, M.D., Professor of Psychiatry at Columbia and the Chair of the Mentoring Program of PCSS-MAT. Dr. Bisaga opened his summary remarks by observing that while opioid dependence can be the most devastating addiction, it also has the most effective medication-assisted treatments (MAT). However, few patients (<20%) are receiving MAT because the majority of programs offer a single treatment, in a "one size fits all" approach. Dr. Bisaga took direct aim at the dominant treatment model in the U.S. of detoxification followed by psychosocial treatment, noting that despite the considerable ineffectiveness of this model – marked by >90% relapse and increased risk of death –it remains the dominant treatment across the U.S.

Dr. Bisaga observed that opioid-dependent patients seeking treatment encounter a "silo" system, in which they are relegated to one of three kinds of treatment, depending upon the venue in which they initially present. Patients presenting to a detox unit or rehab will very likely be discharged without any medication. On the other hand, patients at an Opioid Treatment Program (OTP) are assigned to receive methadone or buprenorphine at the window. And patients in an addiction physician's

office are usually offered buprenorphine, and only very rarely naltrexone. A patient who fails to respond to the first treatment offered is likely to be referred out, or to drop out, rather than having an opportunity to try an alternative approach. Comprehensive treatment programs are needed, which would offer multiple options and facilitate the smooth transition from one option to another. What is important is that such guidelines are based on the currently available scientific evidence and consensus-based, rather than based on convenience, tradition, belief system.

Dr. Bisaga proposed a decision tree for first-, second-, and third-line treatments for opioid dependence. He argued that patients who are not physically dependent when they present for treatment (such as those released back to the community from a controlled setting, i.e. rehab or prison) should undergo a risk stratification assessment, based on environmental risk factors as well as medical and psychiatric risks. Patients deemed to be at low risk for relapse could be referred to relapse prevention therapy or CBT in conjunction with support groups. But those at higher risk should be offered injection naltrexone, in combination with the same behavioral treatments.

By contrast, patients who are physically dependent when they present for treatment should receive a comprehensive evaluation, which includes a through discussion of all available medications. The patient's preference for a specific medication should be determined, along with an assessment of patient-specific prognostic factors. A first line of treatment could consist of either abstinence induction using an agonist, or detoxification/relapse prevention using an opioid antagonist. Dr. Bisaga suggested that the agonist pathway should begin with a trial of buprenorphine for 1-2 months. Responders would continue on BUP maintenance, but non-responders would be offered intensive behavioral treatment to complement buprenorphine; if they continue to lapse or relapse, they should be transitioned to methadone. Patients who choose instead the antagonist approach could be inducted onto XR-NTX and continued for 12-18 months if they do well (and otherwise transitioned to buprenorphine). After successful maintenance on XR-NTX for this extended period, patients can be offered oral naltrexone to take in high-risk situations. And finally, patients who have done well on BUP and wish to discontinue agonist maintenance should be offered the alternative of induction onto XR-NTX, in preparation for medication-free treatment.

In summary, the panel concluded that (1) the current delivery system for treating opioid dependence needs restructuring to allow patients to be make more informed choices, taking into account evidence-based medicine, regarding their choice of treatment; and (2) clinicians treating opioid dependence deserve to be informed by treatment guidelines which integrate all FDA-approved medications to allow a given individual to achieve abstinence and avoid relapse.

A lively discussion followed the panel's presentation, with some practitioners attesting to the benefits of agonist treatment, while others expressed concern at the underutilization of antagonist strategies. Some in attendance were frank in admitting

that they are not familiar with induction protocols for injection naltrexone. Drs. Sullivan and Bisaga encouraged interested physicians to access the **pcssmat.org** website, which offers clinical guidances on the use of antagonist and agonist treatments as well as a training video that demonstrates how to deliver the long-acting naltrexone injection. In addition, Dr. Bisaga reminded the AAAP members in attendance that PCSS-MAT offers free-of-cost mentoring to clinicians seeking to broaden their practice in opioid dependence treatment to include newer pharmacotherapies such as injection naltrexone or buprenorphine.

This panel discussion generated a high level of interest among AAAP members, and Dr. Lawrence Westreich, President of AAAP, expressed his thanks to the speakers for presenting "substantive data and clinical wisdom in a very short time" and for leading a discussion that was "frank, curious, respectful – academic, in the best sense of the word." Both Dr. Westreich and Dr. Michael Scimeca, AAAP Area 2 Director, graciously encouraged the panel members to bring this engaging discussion to a wider stage at the AAAP national meeting in December. Plans are underway for a workshop, and we hope that AAAP members who missed the Area 2 meeting will consider attending this presentation and taking part in what promises to be another lively discussion on the evolving roles for pharmacotherapy in the treatment of opioid addiction.

Q. Have there been any studies following each of these tracks – that is, buprenorphine vs. methadone vs. naltrexone – and looking at death rates? Which one leads to the best survival for patients long-term?

Dr. Adam Bisaga: There are very few comparative trials on different medications to treat opioid dependence, except a couple comparing buprenorphine to methadone over 6 to 12 months. And they do show that methadone is a more effective at retaining patients in treatment when used at high doses. But then there are the long-term psychiatric, medical, and addiction outcomes to consider. You need to define the outcome you are looking at: retention or whether people are compliant and abstinent from illicit opioids. There is an ongoing NIDA CTN study in which patients randomly assigned on an inpatient basis to injection naltrexone (Vivitrol) vs. buprenorphine and then discharged and followed for six months.

Dr. David Gastfriend (Treatment Research Institute, formerly of Alkermes): We conducted a health economic study, which was a naturalistic trial looking at methadone vs. buprenorphine vs. XR-NTX vs. oral naltrexone and those without medication. The hospitalization rates (as proxy for medical morbidity rates) were worst for the non-medicated group. Of medicated groups, rates of hospitalization were lowest for XR-NTX treatment. Hospitalization rates were substantially higher for agonist treatment. During the 6-month period, the average patients were maintained on meds for approximately 2-3 months of the 6-month, so this therefore includes a period of about 3 months when they were not on medication. Hospitalization rates were substantially higher in those on the agonist treatment, both during and after they went off.

Q. Can buprenorphine also be used for patients who need pain management, and what have people's experience been? We often have patients on buprenorphine who need pain management, also.

Dr. Salsitz: I recall that Dr. Comer has published in this area. Using adequate doses of s.l. buprenorphine both adequately treated the pain and reduced people's cravings for oxycodone or other opiates. I would say this is an emerging area: buprenorphine for pain. And then, there is the transdermal buprenorphine patch, which is approved only for pain and not for addiction, and this has some efficacy.
Dr. Sullivan: We found sublingual buprenorphine given in divided doses to be effective in pain. Patients experienced about a 30% reduction in pain scores from baseline. People were very pleased with the analgesic effects of buprenorphine. We gave it QID but it can be given TID; what's essential is that it be given in multiple divided doses because the analgesic effects will wear off in 6-9 hours. So, it is like methadone in that respect. In terms of side effects, people who had experienced other prescription opioids appreciated the fact that they felt cognitively clearer. A number of those patients went out to seek buprenorphine maintenance for pain management after the trial.

Q. Like Dr. Salsitz, I would make the disclosure that I am an ***internist and opioid prescriber.*** I would be curious to know more about the efficacy of naltrexone, and in which groups it seems to be most effective. And also, it seems like there's a pretty high rate of dropout from naltrexone, so has there been any investigation of overdose following treatment, or what happens to those folks who are falling off?

Dr. Bisaga: The data you have seen are probably from the era of oral naltrexone; the perception from that era has kind of gotten carried forward to the present and to XR-naltrexone. It is true that with oral naltrexone there is high rate of treatment non-compliance, treatment dropout and possibly increased risk of overdose. That risk has been much lower with the extended-release naltrexone preparations. There are mixed findings about mortality following treatment discontinuation. We know that mortality is higher after discontinuation from any treatment, but there is no clear indication that mortality that would be higher following XR-NTX naltrexone. And some people would even argue that the effect of the blockade is much longer than the tolerance being reduced with agonist. So it can be protective in some cases, but at this time I think there is no clear indication one way or the other.

Dr. Sullivan: Yes, I would just add that the problem with the oral product was that you could be fully blocked one day and use 2-3 bags without any effect, and the next day you are unblocked, and you shoot up 5-6 bags, and it may an adverse outcome. But that doesn't happen with the injectable product because you are getting this trailing off that goes on for a number of days. So, if you choose to relapse, at least you are doing it in a context that is safer than a sudden unexpected shift in tolerance.

Dr. Bisaga: So, to the question about the efficacy of injectable NTX, the studies we quote were done is a kind of optimal setting, in research clinics with lots of support staff. So we are not sure how this will translate into community programs. But if you think about programs that have been doing this for a while, the question is: what is the starting point? Thirty percent of people don't make it through detox., and this is no different for people who are detoxing with the intention of going onto injectable naltrexone. But once people receive XR-NTX, studies show that retention is 50-70% at 3-6 months, which is very comparable with buprenorphine given in the office. But the difference is that most people who remain on XR-NTX are drug-free, vs. 30-50% of people on buprenorphine continue to use opioids. It depends how you define the clinical response.

Dr. Gastfriend: There are two studies in the real community, and not clinical trials, that are worth knowing about. Los Angles County had 399 patients evaluated by UCLA. They looked at patients started in rehab and detox and as outpatients. The overall conclusion was that the outcomes were sufficiently good that they recommended expansion to the full LA County, which has happened. CRC, a national for-profit chain that owns 150 treatment programs, have reported that of 160+ opioid-dependent patients started on XR-NTX prior to discharge from rehab. There was an 80% drop in AMA departures and a 50% increase in engagement in the next level of care within 10 days. CRC is not interested in spending more money than they have to, and these are real-world findings.

Q. What about using buprenorphine on a PRN basis? It makes me nervous.

Dr. Sullivan: I thought you might ask a question that often comes up: What if you have a pain crisis, on top of moderate pain – can buprenorphine work? In the study I did with Dr. Comer, we found that in an experimental paradigm, we had people immerse their hands in ice-cold water as a proxy for acute pain. And what we found was that you can layer oxycodone on top of buprenorphine, if you need to, to manage an acute pain crisis, but the participants did not experience positive subjective effects from oxycodone – and these were people who were former prescription opioid abusers. So, these were encouraging data, that you really are protecting pain patients who have a history of opioid abuse, against a return to misuse of the opioids. And you still have the liberty of dosing on top of the buprenorphine to manage severe acute pain, if you need to.

Regarding PRN dosing, I would worry a little that if someone is not opioid-dependent, it doesn't take too many doses to engender dependence. But, theoretically, I suppose you could use it for intermittent pain management.

Comment: Dr. Herbert Kleber: I have a problem with many doctors who prescribe buprenorphine, and that's all they do. Be careful what you wish for. We have always wanted addiction treated like a chronic, relapsing disease. How is hypertension or diabetes treated? Once a month for 15 minutes. The majority of

people who are on buprenorphine these days are treated once a month without any therapy. That may be a group of chickens coming home to roost: a source of diversion.

Q. What is the route of treatment given to physicians themselves? What are "our own brethren" getting when they have an opioid addiction, and how well do they do? And how does this compare to others' response rates?
Dr. Jeffery Seltzer: The landmark study on this was done by Tom McLellan and Bob DuPont. They looked at outcomes for physicians who could negotiate getting into Physician Health Programs. They found that with very little Medication-Assisted Treatments, the outcomes were much better than those reported here this evening for non-medication-assisted treatments. My colleagues who work in this field tell me that, in their hands, with good residential treatment and close monitoring afterward, -- an important guideline to consider -- the outcomes at 5 years are that physicians typically never have a positive drug screen, and 75% of those who do have one positive screen, never have a subsequent positive screen. We have to keep a flexible, open mind. There is certainly much more use of XR-NTX now in physician health programs. My own belief is that there is a bias against agonist treatment that is not justified by the data. I don't think it is clear that agonists are associated with cognitive problems; we need to look at those data. I worry about the old argument that agonist treatment does not really result in abstinence, whereas antagonist treatment does. And I worry about our incorporating that value. In New York State, the state licensing board does not have a firm position on this. So physicians are able to return to work on agonist treatment.

I would worry about physicians who were lost to the programs I cited because they were not withstand the rigors. The first goal is to get physicians well, to treat them as patients, rather than their return to practice as being the ultimate goal. But my own view is that we want to keep all the options open for physicians, whether or not they return to practice.

Dr. Michael Scimeca: I would like to thank everyone for a lively discussion this evening, and our panel for a wonderful and timely presentation.