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Buprenorphine-Naloxone Treatment of Prescription Opioid Abuse: Does Past Performance Predict Future Results?

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Misuse of prescription opioids is a national public health problem: In the United States, according to the 2012 National Survey on Drug Use and Health, 4.5 million, or 1.7%, of persons aged 12 or older reported current nonmedical use of pain relievers, and 335,000 reported currently using heroin.[1,2] This is an upward trend, as heroin use has more than doubled since 2002.[2] Transition from ingesting or insufflating (ie, snorting) prescription opioids to snorting or smoking (ie, inhaling the fumes) heroin has become more common and is driven by the increasing purity and lower cost.[3] Significant numbers of heroin users progress to intravenous use,[4,5] making prescription opioid abuse a risk factor for HIV and hepatitis C.[6] To further complicate the matter, the prevalence of injecting prescription opioids may be increasing.[6] However, compared to heroin, prescription opioid addiction has a limited literature base. In this month's Focus on Addiction section, McDermott et al[7] examine the relationship between abstinence from illicit opioids in the first and third (last) months of treatment with buprenorphine-naloxone combination tablets.[8] They found that participants not abstinent from illicit opioids in the first 2 weeks were very unlikely to achieve abstinence in weeks 9 through 12 of the trial. In addition to the potential implications for practice, the McDermott et al article highlights 2 general questions: (1) To what extent do protocols developed for heroin dependence apply to prescription opioids? and (2) What is the state of the art in the prediction of treatment response in opioid use disorders? Data reported by McDermott and colleagues are extracted from weeks 12 to 24 of the 36-week Prescription Opioid Addiction Treatment Study (POATS).[9] As a secondary analysis, McDermott is best understood in the context of POATS as it has been reported in several prior papers.[9–16] Briefly, POATS consisted of 2 phases: a "brief" phase 1 that entailed a 4-week buprenorphine-naloxone "stabilization" and taper and an 8-week follow-up. Of the 653 participants who entered phase 1, only 43 (7%) were either mostly or completely abstinent at week 12. Of the 610 patients who failed phase 1, 360 enrolled in the "extended" phase 2, which lasted 12 weeks and was followed by a 4-week taper of buprenorphine-naloxone and an 8-week follow-up. Therefore, one could describe 2 "initial" responses to treatment in POATS, 1 for each phase.

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McDermott et al found that 56% of patients who were abstinent at the 2-week timepoint were abstinent in the last 3 weeks of buprenorphine-naloxone treatment. Conversely, only 6% of those who continued using during the first 2 weeks were abstinent at the 3-month time point. Together, these results translate to a predictive value of 94% for the lack of abstinence at weeks 9 through 12, while the predictive value of early abstinence was below 60%. McDermott et al defined "lack of abstinence" as a positive test in their assigning of positive and negative predictive values. This is somewhat counterintuitive, since positive and negative predictive values are commonly used to describe a diagnostic test, in this case, urine toxicology. To rephrase McDermott and colleagues' findings from a clinician's perspective, opioid-positive urine toxicology in the first 2 weeks of treatment had a high positive and low negative predictive value for opioid-positive urine toxicology in the last 3 weeks. The predictive value of the early positive urine toxicology is in line with findings in other substance use disorders. However, the low predictive value of early abstinence contrasts similar studies in cocaine[17] and suggests that additional variables need to be considered.

Another clue that suggests unaccounted-for variables is the poor outcome of phase 1 of the POATS. A direct comparison with other studies is complicated by differences in design and outcome measures; however, Sigmon et al[18] reported between 29% and 63% improvement after a 2- to 4-week buprenorphine-naloxone taper in prescription opioid abusers, while only 7% of POATS participants were abstinent at the end of phase 1. Consistent with prior literature,[19] nearly half of POATS participants were abstinent or reduced their use at the end of the period covered by McDermott et al, but most (>90%) relapsed within 8 weeks after buprenorphine-naloxone was tapered off.[9] Therefore, the McDermott et al data can be thought of as predicting an intermediate outcome. It would be interesting to know what bearing these data have on the patient status 8 weeks later. A more immediate conclusion from McDermott and colleagues' article is that 12 weeks of buprenorphine-naloxone treatment was insufficient to achieve a sustained remission in the POATS cohort. However, it is unclear to what extent the McDermott et al sample was representative of the prescription opioid abuse demographic. More than 40% of POATS patients reported chronic pain, and approximately 30% reported lifetime prevalence of heroin or alcohol abuse and depression. All of these factors are likely to influence the prognosis of prescription opioid dependence,[20–24] with pain[20,21] playing a particularly large and complex role.[24] It would be interesting to see how these variables might have changed the McDermott et al results.

Together with other papers reporting POATS results, the article by McDermott et al is a very important step toward bridging the gap between our knowledge on heroin and on prescription opioids. Although the US Food and Drug Administration relied on data from intravenous heroin users for the approval of new pharmacotherapies (ie, buprenorphine-naloxone and injectable extended-release naltrexone) for opioid dependence, the prescribing information for these medications does not differentiate between prescription opioids and heroin or between oral, intranasal, and intravenous routes of administration.[25,26] Yet, there appear to be important sociodemographic and clinical differences between these 2 categories of opioids, though they may be on a continuum of addiction severity and duration.[27,28] On average, prescription opioid abuse begins at an earlier age than heroin abuse, with longer opioid-free intervals, smaller daily amounts, fewer psychosocial problems, and higher global function,[29–31] all of which may lead to a more favorable treatment response than is seen in heroin abuse. In the United States, open-ended agonist maintenance is the standard of practice for intravenous heroin dependence.[32] Should this standard be applied to prescription opioid users? McDermott et al can only tell us that 3 to 4 months of opioid replacement is not sufficient for most patients, which is a logical extension of prior controlled studies[19] and of the concept of addiction as a chronic relapsing illness in which even prolonged abstinence does not guarantee cure.

In addition to reporting a clinical outcome, McDermott et al touch upon the larger issue of predicting treatment adherence and outcomes in addiction.[33–35] Although initial response is an established predictor, a growing number of medical specialties use objective biological tests to plan treatment. In an example from oncology, the so-called triple-negative breast cancer (TNBC) lacks the 3 receptors targeted by the standard chemotherapies and requires alternative protocols. Until the TNBC biomarkers had been identified, oncologists had to rely on the initial response to predict treatment outcomes. While oncologists are now able to identify TNBC before starting chemotherapy, trial by error is still commonly used to guide psychopharmacology. While the value of the single-nucleotide polymorphism (SNP) of the μ-opioid receptor (OPRM1 Asn40Asp) to guide pharmacotherapy in opioid dependence remains uncertain, the search for other SNPs and more complex models integrating multiple genes with environment continues.[36–39]

Another category of predictors of addiction severity and treatment response not usually employed in clinical trials and practice includes symptom provocation, such as drug craving in response to drug-related cues.[40–43] To some extent, this is analogous to a cardiac stress test or a glucose tolerance test in medicine. Although craving and its peripheral nervous system correlates (eg, electrodermal skin response) have not produced effects robust enough for clinical applications,[44,45] neuroimaging indices of brain function, such as brain activity at rest, in response to cognitive tasks, or brain response to drug-related cues, have shown promise as pretreatment predictors of outcomes.[35,46,47] For example, prospective studies of the brain response to heroin-related cues in recently detoxified heroin addicts suggest that time to relapse may be getting longer with continued abstinence,[48,49] lending support to the feasibility of time-limited pharmacotherapy followed by abstinence as the treatment goal in prescription opioid dependence. In addition, neuroimaging may offer data on the mechanisms of addiction that could help determine the optimal length of treatment. In addition to their clinical potential, functional magnetic resonance imaging biomarkers may inform other, less invasive techniques, such as electrophysiology[50] and functional near-infrared spectroscopy.[51,52] Integrated with genetic, neuropsychological, and personality measures, these variables would advance personalized treatment protocols for prescription opioid dependence.

In conclusion, the McDermott et al article confirms the heuristic value of urine toxicology in the management of prescription opioid dependence, suggests that most prescription opioid–dependent patients may benefit from longer treatment duration, and underscores the importance of the clinical context in evaluation of biomarkers in addiction. Further studies using multiple biological and behavioral variables to enable individualized treatment protocols for prescription opioid dependence are urgently needed.

Drug names: buprenorphine-naloxone (Suboxone), injectable extended-release naltrexone (Vivitrol).

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REFERENCES

1. Substance Abuse and Mental Health Services Administration. *Results from the 2012 National Survey on Drug Use and Health: Detailed Tables*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.
2. Substance Abuse and Mental Health Services Administration. *Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings,* NSDUH Series H-46, HHS Publication No. (SMA) 13-4795. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.
3. Mars SG, Bourgois P, Karandinos G, et al. "Every 'never' I ever said came true": transitions from opioid pills to heroin injecting. *Int J Drug Policy*. 2014;25(2):257–266.
4. Jones CM. Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers—United States, 2002–2004 and 2008–2010. *Drug Alcohol Depend*. 2013;132(1-2):95–100.
5. Neaigus A, Gyarmathy VA, Miller M, et al. Transitions to injecting drug use among noninjecting heroin users: social network influence and individual susceptibility. *J Acquir Immune Defic Syndr*. 2006;41(4):493–503.
6. Bruneau J, Roy E, Arruda N, et al. The rising prevalence of prescription opioid injection and its association with hepatitis C incidence among street-drug users. *Addiction*. 2012;107(7):1318–1327.
7. McDermott KA, Griffin ML, Connery HS, et al. Initial response as a predictor of 12-week buprenorphine-naloxone treatment response in a prescription opioid–dependent population. *J Clin Psychiatry.* 2015;76(2):189–194.

8. Food and Drug Administration. Subutex (buprenorphine hydrochloride) and Suboxone tablets (buprenorphine hydrochloride and naloxone hydrochloride). 2002. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm191520.htm. Accessed October 8, 2014.
9. Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Arch Gen Psychiatry*. 2011;68(12):1238–1246.
10. Weiss RD, Potter JS, Griffin ML, et al. Reasons for opioid use among patients with dependence on prescription opioids: the role of chronic pain. *J Subst Abuse Treat*. 2014;47(2):140–145.
11. Potter JS, Dreifuss JA, Marino EN, et al. The multi-site Prescription Opioid Addiction Treatment Study: 18-month outcomes [published online ahead of print August 2, 2014]. *J Subst Abuse Treat*.
12. Meade CS, Bevilacqua LA, Moore ED, et al. Concurrent substance abuse is associated with sexual risk behavior among adults seeking treatment for prescription opioid dependence. *Am J Addict*. 2014;23(1):27–33.
13. McHugh RK, Nielsen S, Weiss RD. Prescription drug abuse: from epidemiology to public policy [published online ahead of print August 28, 2014]. *J Subst Abuse Treat*.
14. Hilario EY, Griffin ML, McHugh RK, et al. Denial of urinalysis-confirmed opioid use in prescription opioid dependence [published online ahead of print July 18, 2014]. *J Subst Abuse Treat*.
15. Griffin ML, Dodd DR, Potter JS, et al. Baseline characteristics and treatment outcomes in prescription opioid dependent patients with and without co-occurring psychiatric disorder. *Am J Drug Alcohol Abuse*. 2014;40(2):157–162.
16. Weiss RD, Potter JS, Provost SE, et al. A multi-site, two-phase, Prescription Opioid Addiction Treatment Study (POATS): rationale, design, and methodology. *Contemp Clin Trials*. 2010;31(2):189–199.
17. Plebani JG, Kampman KM, Lynch KG. Early abstinence in cocaine pharmacotherapy trials predicts successful treatment outcomes. *J Subst Abuse Treat*. 2009;37(3):313–317.
18. Sigmon SC, Dunn KE, Saulsgiver K, et al. A randomized, double-blind evaluation of buprenorphine taper duration in primary prescription opioid abusers. *JAMA Psychiatry*. 2013;70(12):1347–1354.
19. Woody GE, Poole SA, Subramaniam G, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. *JAMA*. 2008;300(17):2003–2011.
20. Younger JW, Chu LF, D'Arcy NT, et al. Prescription opioid analgesics rapidly change the human brain. *Pain*. 2011;152(8):1803–1810.
21. Ives TJ, Chelminski PR, Hammett-Stabler CA, et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. *BMC Health Serv Res*. 2006;6(1):46.
22. Maremmani I, Pacini M, Perugi G, et al. Cocaine abuse and the bipolar spectrum in 1090 heroin addicts: clinical observations and a proposed pathophysiologic model. *J Affect Disord*. 2008;106(1-2):55–61.
23. Mackesy-Amiti ME, Donenberg GR, Ouellet LJ. Prevalence of psychiatric disorders among young injection drug users. *Drug Alcohol Depend*. 2012;124(1–2):70–78.
24. Elman I, Zubieta JK, Borsook D. The missing *P* in psychiatric training: why it is important to teach pain to psychiatrists. *Arch Gen Psychiatry*. 2011;68(1):12–20.
25. Vivitrol (naltrexone for extended-release injectable suspension) [package insert]. Waltham, MA: Alkermes Inc; 2013.
26. Suboxone (buprenorphine and naloxone) sublingual tablets for sublingual administration [package insert]. Richmond, VA: Reckitt Benckiser Pharmaceuticals Inc; 2002.
27. Cicero TJ, Kuehn BM. Driven by prescription drug abuse, heroin use increases among suburban and rural whites. *JAMA*. 2014;312(2):118–119.
28. Cicero TJ, Ellis MS, Surratt HL, et al. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. *JAMA Psychiatry*. 2014;71(7):821–826.
29. Mendelson J, Flower K, Pletcher MJ, et al. Addiction to prescription opioids: characteristics of the emerging epidemic and treatment with buprenorphine. *Exp Clin Psychopharmacol*. 2008;16(5):435–441.
30. Moore BA, Fiellin DA, Barry DT, et al. Primary care office-based buprenorphine treatment: comparison of heroin and prescription opioid dependent patients. *J Gen Intern Med*. 2007;22(4):527–530.
31. Sigmon SC. Characterizing the emerging population of prescription opioid abusers. *Am J Addict*. 2006;15(3):208–212.
32. Mattick RP, Breen C, Kimber J, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2014;2:CD002207.
33. Woody GE. Progress in addiction treatment: from one-size-fits-all to medications and treatment matching. *Subst Abus*. 2014;35(2):110–113.
34. Wang AL, Ruparel K, Loughead JW, et al. Content matters: neuroimaging investigation of brain and behavioral impact of televised anti-tobacco public service announcements. *J Neurosci*. 2013;33(17):7420–7427.
35. Lerman C, Gu H, Loughead J, et al. Large-scale brain network coupling predicts acute nicotine abstinence effects on craving and cognitive function. *JAMA Psychiatry*. 2014;71(5):523–530.
36. Anton RF, Oroszi G, O'Malley S, et al. An evaluation of mu-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. *Arch Gen Psychiatry*. 2008;65(2):135–144.
37. Crist RC, Clarke TK, Ang A, et al. An intronic variant in OPRD1 predicts treatment outcome for opioid dependence in African-Americans. *Neuropsychopharmacology*. 2013;38(10):2003-2010.
38. Clarke TK, Crist RC, Ang A, et al. Genetic variation in OPRD1 and the response to treatment for opioid dependence with buprenorphine in European-American females. *Pharmacogenomics J*. 2014;14(3):303–308.
39. Schacht JP, Anton RF, Voronin KE, et al. Interacting effects of naltrexone and OPRM1 and DAT1 variation on the neural response to alcohol cues. *Neuropsychopharmacology*. 2013;38(3):414–422.
40. Meyer RE. Craving: what can be done to bring the insights of neuroscience, behavioral science and clinical science into synchrony. *Addiction*. 2000;95(suppl 2):S219–S227.
41. Elman I, Karlsgodt KH, Gastfriend DR, et al. Cocaine-primed craving and its relationship to depressive symptomatology in individuals with cocaine dependence. *J Psychopharmacol*. 2002;16(2):163–167.
42. Langleben DD, Ruparel K, Elman I, et al. Acute effect of methadone maintenance dose on brain FMRI response to heroin-related cues. *Am J Psychiatry*. 2008;165(3):390–394.
43. O'Brien C, Childress AR, Ehrman R, et al. Conditioning mechanisms in drug dependence. *Clin Neuropharmacol*. 1992;15(suppl 1 pt a):66A–67A.
44. Sofis M, Jarmolowicz DP, Martin LE. Competing neurobehavioral decision systems and the neuroeconomics of craving in opioid addiction. *Neurosc Neuroecon*. 2014;3:87-99.
45. Tiffany ST, Wray JM. The clinical significance of drug craving. *Ann N Y Acad Sci*. 2012;1248(1):1–17.
46. McGrath CL, Kelley ME, Dunlop BW, et al. Pretreatment brain states identify likely nonresponse to standard treatments for depression. *Biol Psychiatry*. 2014;76(7):527–535.
47. Morgenstern J, Naqvi NH, Debellis R, et al. The contributions of cognitive neuroscience and neuroimaging to understanding mechanisms of behavior change in addiction. *Psychol Addict Behav*. 2013;27(2):336–350.
48. Li Q, Wang Y, Zhang Y, et al. Assessing cue-induced brain response as a function of abstinence duration in heroin-dependent individuals: an event-related fMRI study. *PLoS ONE*. 2013;8(5):e62911.
49. Lou M, Wang E, Shen Y, et al. Cue-elicited craving in heroin addicts at different abstinent time: an fMRI pilot study. *Subst Use Misuse*. 2012;47(6):631–639.
50. Wang AL, Romer D, Elman I, et al. Emotional graphic cigarette warning labels reduce the electrophysiological brain response to smoking cues [published online ahead of print December 15, 2013]. *Addict Biol*.
51. Irani F, Platek SM, Bunce S, et al. Functional near infrared spectroscopy (fNIRS): an emerging neuroimaging technology with important applications for the study of brain disorders. *Clin Neuropsychol*. 2007;21(1):9–37.
52. Ernst LH, Plichta MM, Lutz E, et al. Prefrontal activation patterns of automatic and regulated approach-avoidance reactions - a functional near-infrared spectroscopy (fNIRS) study. *Cortex*. 2013;49(1):131–142.