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Should the United States Government Repeal Restrictions on Buprenorphine/Naloxone Treatment?

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Abstract

Attention must be focused on needed changes to the current United States law that restricts physicians who prescribe buprenorphine for the detoxification or treatment of Opioid Use Disorder, to accepting no more than100 patients. The current system does not provide comprehensive treatment as defined by the American Society of Addiction Medicine (ASAM) criteria. Additionally, it suffers from both fragmentation and stigma and will require a significant change to comply with ASAM's call for integrated delivery of comprehensive addiction treatment.

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Declaration of interest

Dr. Kenneth Blum owns stock in LaVita RDS and is owner of Synaptamine, which holds patents on KB220Z. Rajendra D. Badgaiyan are on the Scientific Advisory Board of LaVita RDS. There are no other conflicts to report.

This commentary calls for the development and implementation of “best practice,” by recommending caution in lifting the 100 patient limit until substantial achievement of this goal occurs. The authors call for an increase to 200 in the patient limit to be restricted to those physicians who are Board Certified in Addiction Medicine by the American Board of Addiction Medicine (ABAM) or in Addiction Psychiatry by the American Board of Psychiatry and Neurology (ABPN), or other responsible medical organizations. Any additional restriction lifting should follow a systemic evolution that rewards and documents competency. Such a system would involve the integration of treatment, treatment systems, and recovery with prescription medication. In addition, it should monitor emotional blunting, treatment progress and initiation of genetic addiction risk testing.

Keywords

Buprenorphine/Naloxone; United States Law; Restriction Cap; Competency; Genetic Risk; Drug Urine Testing

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There is concern that the current restrictions in the United States (US) on prescribing buprenorphine/naloxone severely reduce, access to care. It is, however, imperative for people with Opiate Use Disorder (OUD) to obtain proper care and treatment, and rural areas, where prescribers are limited and opioid dependence is prevalent, require consideration (Rosenblatt, Andrilla and Catlin et al, 2015).

Many individuals, who could benefit from the utilization of buprenorphine/naloxone, are not receiving opioid maintenance therapy. There has been an large increase in the use of prescription opioids and street heroin in across the US; buprenorphine/naloxone is considered the most viable of approved options for treatment (Shapiro, Coffa, McCance-Katz, 2013). In 2000, Congress passed the Drug Addiction Treatment Act [DATA-2000] that allows physicians to be certified to prescribe buprenorphine, a partial mu opiate receptor agonist, in combination with a very low dosage of the narcotic antagonist naloxone. If clinicians take and pass an 8-hour course and have other qualifications, they become eligible to legally prescribe this approved medication. However, this law restricts the number of patients that a physician could treat through the first year following certification to thirty, expandable to 100 patients thereafter (Zibbell, Iqbal, Patel, et al, 2015). Interestingly, no other medications have this restriction and as such, many ASAM and other physicians have called into question the benefit of such a law. The population is in the midst of an increase in hepatitis C among injection drug users (IDUs), and at least one rural county has experienced an outbreak of human immunodeficiency virus (HIV). Buprenorphine, reduces the frequency and need for injection drugs for those opioid dependent IDUs (Zibbell, Iqbal, Patel, et al, 2015; Wiegand, 2015).

The law had good intentions, primarily in consideration of the addictive potential of buprenorphine. In this regard, Blum et al and Wiegand (2015) in conjunction with Dominion Diagnostics, LLC, and some ASAM physicians, utilized a sophisticated urine drug test, “Comprehensive Analysis of Reported Drugs (CARD)™,” to evaluate both treatment compliance and abstinence from abused drugs. This study included 1,268 patients who received Suboxone®. Blum K, Han D, Femino J, et al (2014) found very high compliance of

approximately 90% with Suboxone, and longitudinal analyzes revealed a substantial drop in illicit opioid use. This finding potentially highlights the importance of having appropriate counseling in specialized Opioid Replacement Therapy (ORT) clinics. Additionally, while the question of diversion was not evaluated, high compliance with the medication seems to implicate reduced diversion.

If indeed there is a modified law to increase patient limits for buprenorphine/naloxone treatment, enhanced certification programs need to be put into place. There is evidence that counseling and substance abuse education for the patient in both residential and out-patient programs are of benefit (Blum K, Han D, Femino J, et al, 2014). Various organizations responsible for treatment oversight should develop programs that require additional counseling and substance abuse education to be provided with the expansion of access to buprenorphine/naloxone.

Undoubtedly, there could be a standard of treatment and training of new physicians that included relevant and appropriate practice standards. In this commentary we are pointing out some noted issues and potential “best practices” that may guide future programming. It is plausible that a system could be developed with the following standard practices:

1. upon entry into a pain clinic, obtain a DNA sample (swab) for subsequent pharmacogenetic/genetic risk testing (Blum et al., 2015; Blum et al., 2014);
2. during treatment, monitor both compliance to buprenorphine/naloxone and abstinence from any non-prescribed psychoactive drugs by utilizing urine drug testing, like CARD (Wiegand, 2015);
3. refer to and support patient involvement in psychosocial treatments as described in the ASAM criteria, and following that, in recovery, utilize practices tailored for the need of the individual patient (Shapiro et al., 2013; Rowe, Santos, Behar, & Coffin, 2015);
4. implementation of the ASAM continuum software and/or Addiction Severity Index (ASI) or neuropsychological indices, like, Computer Assisted Learning for the Mind [CALM], Central Nervous System Vital Signs [CNSVS], P300 Evoked Potentials; and
5. monitor for emotional blunting, perhaps utilizing “true grounded emotion detection” (Hill, Han, Dumouchel, et al., 2013).

Hill and associates (2013) found long-term buprenorphine/naloxone patients had less self-awareness of being happy, sad, and anxious, and a significantly flat affect ($p<0.01$), as compared to both general population and Alcoholic Anonymous (AA) samples.

The findings of Hill et al (2013) encourage continued research of strategies that can target the brain regions identified as responsible for relapse prevention of opioid addiction in buprenorphine/naloxone patients.

There is much research pointing to the effective treatment of opioid addiction with either buprenorphine alone or in combination with naloxone (Suboxone; Zubsolv; Bunavail) –

which is now almost unversally preferred - in the context of ongoing psychosocial therapies (Hill, Han, Dumouchel, et al., 2013). Most authors have suggested that buprenorphine/naloxone should be utilized as a long-term opioid maintenance therapy based on the chronicity of opioid dependence (Gustin, Nichols, Martin, et al., 2015), while some others do not support this “mainstream” view (Badgaiyan, Sinha, Blum, 2015).

Also, there must be caution when using buprenorphine as a treatment protocol because buprenorphine is an opioid, and may maintain or further promote opioid addiction through diversion and abuse. Additionally, buprenorphine may not prevent a future relapse because new evidence shows that buprenorphine-treated individuals had higher myo-inositol and glutamate/glutamine levels than methadone-treated patients in the right dorsal Anterior Cingulate Cortex (ACC). Furthermore myo-inositol levels were positively correlated with depressive symptoms in participants stabilized on buprenorphine (Verdejo-García et al., 2013).

The principle of recovery would suggest that the treatment should be time-limited. Prescribing buprenorphine indefinitely, therefore, should not be an option, in our opinion.. Although not mainstream thinking, there is a view that long-term treatment with buprenorphine has no therapeutic advantage over short-term treatment, but has a number of disadvantages (Badgaiyan et al., 2015; Verdejo-García et al., 2013).

The proposal is that a broad guideline should be prepared by addiction specialists to guide providers to formulate a short-term treatment protocol based on known scientific facts related to clinical outcomes, instead of extending the long-term use of buprenorphine/naloxone. This guideline should be reviewed periodically.

To date, the Food and Drug Administration (FDA) have approved buprenorphine, buprenorphine/naloxone, and methadone for opioid maintenance, however, cautions against the use of these compounds for long-term maintenance, cannot be ignored (Blum, Chen, Bailey, et al., 2011).

To advise the utilization of pharmacogenetic and risk genetic testing as a way of uncovering reward circuitry gene polymorphisms, particularly those linked to dopaminergic pathways, as well as, opioid receptor(s), is sensible as a method of bettering treatment effects (Blum, Oscar-Berman, Jacobs, et al., 2014).

Additionally, each patient entering a pain clinic could be tested for genetic risk by utilizing a sophisticated researched panel of reward genes known as Genetic Addiction Risk Score (GARS). This genetic test could be very useful as the window to the brain and may help identify patients entering a pain clinic for potential future opiate/opioid risk (Blum et al., 2015; Blum et al., 2014).

Obtaining a genetic risk profile for each patient is beneficial because it provides critical information about particular genetic vulnerabilities and gauges treatment susceptibility. Accepting the association of reward circuitry genotypes, with buprenorphine outcomes can result in enhanced clinical experience and opioid replacement therapy benefit, for patients. While pharmacogenetic testing alone (without GARS) offers some insight into the

individualized metabolism of buprenorphine/naloxone, it does not contribute to understanding the overall risk for relapse. However, coupling polymorphisms of the cytochrome P450 system with GARS seems prudent regarding pinpointing an individual's genetic risk for relapse (Zibbell et al., 2015). While it is understood that drug interactions may occur through several mechanisms, it is important to note the prominent mechanisms, to elucidate the effects of buprenorphine/naloxone treatment. The primary mechanisms of drug interactions include the effects of drugs on liver metabolism of pharmaceuticals. These include the effects on cytochrome P450 (CYP) enzymes or effects on glucuronidation, medicinal effects on drug transporters, effects on P-glycoprotein, and effects on drug absorption (Karan, McCance-Katz, & Zajicek, 2009). The opioid medications, methadone, and buprenorphine are extensively metabolized by human hepatic cellular enzymes. In particular, the CYP3A4 enzyme metabolizes methadone and buprenorphine, which is an enzyme of interest and may have clinical relevance regarding outcomes.

In unpublished data Blum's group found that a panel of ten reward gees and associated risk alleles (thousands of publications showing risk for addictive behaviors for each selected gene risk allele) revealed a novel restrictive allelic panel which significantly matched the ASI-Media Version. High GARS significantly associated with the ASI-Alcohol Severity Risk ($P<0.004$; Age adjusted $P<0.012$); family history of alcoholism ($P<0.003$); high illicit drug abuse ($P<.042$); reporting more often many RDS behaviors. The gene distribution met Hardy –Weinberg Equilibrium. Similar results were found for the ASI-Drug risk scores ($P<0.05$) and age was a covariate predictor. These significant findings provide evidence for the important value of GARS in the addiction & pain field. Sequence variation in multiple genes regulating dopaminergic signaling, influences risk, in a manner that is additive.

There are two sides to any debate: on one hand, increasing access to buprenorphine will likely help many individuals, even if it is done with limited support and monitoring. On the other hand, doing this may lead to many individuals receiving sub-optimal care. However, the proposal to increase the limit for physicians with addiction training or certification seems parsimonious, but could also increase the abuse of opioids and the current opioid epidemic in America. In 2014, data showed that more than 16,000 lives are lost each year due to opioid-related overdoses, even these overdoses are primarily due to street heroin. In 2010, two million people reported using prescription opioids non-medically for the first time—nearly 5,500 people a day (The National Drug Abuse Center for Training Resource and Development; Warner, Hedegaard, & Chen LH, 2014). Sub-optimal care is probably better than no care, but holding out for an ideal system that may never come may harm many individuals in need of this early–on treatment. Since it has been estimated that 75% of those Americans addicted to opiates/opioids do not get treatment of any kind, there is still a great concern of diversion and poor counseling in some so-called "pill mills," which need better monitoring by governing bodies (Kennedy-Hendricks, Richey, McGinty, et al., 2016). So one paradox is that some have cautioned that long-term buprenorphine/naloxone should not be utilized, and other options should be rigorously explored but waiting will increase harm in society.

Most concerning to us is the recent approval by the FDA of a abuprenorphine implant device for opioid addicts. On the positive side of the debate, the device called Probuphine is

composed of four metal rods, each smaller than a matchstick. The rods seep buprenorphine subcutaneously, easing withdrawal symptoms, lessening cravings, and reducing relapse risks in recovering opioid addicts. However, as pointed out by Judith Kramer, chairwoman of the FDA advisory committee, “I’m very concerned about the precedent this sets” (Mole B, 2016). While others on the panel believed that this device would save lives, the authors are concerned about both long-term effects of buprenorphine; anhedonia (which may be due to gene polymorphisms in the dopamine D1 receptor gene) and suicidal ideation, and fatalities due to unwanted leakage problems. In consideration of changing the law, responsible clinicians and scientists must encourage “best practice” monitoring. The authors suggest that raising the national limit to increase accessto buprenorphine/naloxone must be accompanied by careful efforts to reduce the negative impacts.

Finally, there has to be a more substantial commitment to long-term psychosocial treatment and more sophisticated approaches when buprenorphine/naloxone is used; that engage patients in individualized psychosocial treatment as recommended by ASAM. Without a commitment from the addiction treatment community to individualized, comprehensive treatment approaches, raising the cap will lead to patient mismanagement and inappropriate buprenorphine prescribing practices, negatively impacting patients who commit to recovery. Therefore, it is suggested that a more comprehensive schedule of requirements for treatment and patient assessment be enacted. Recognized organizations like the American Society of Addiction Medicine (ASAM), American Board of Addiction Medicine (ABAM), American Academy of Pain Medicine, American Academy of Pain Management, American Society of Interventional Pain Physicians, and American Board of Psychiatry and Neurology (ABPN) provide specialized training and oversight.

Monitoring the following areas are crucial; they include assessment upon acceptance into treatment, and at regular intervals throughout, identification of high-risk using genetic testing and urine drug screens, and documentation of treatment progress. While this could be difficult to fully implement, it needs to be carefully considered. Initially, physiological problems, withdrawal, and the physiological sequella to drug toxicity, like hepatotoxicity, should be assessed (albiet some have not shown a link to liver tioxicity) and treated, and psychosocial treatment as recommended by ASAM made available. Behavioral healthcare providers should conduct and discuss the results of confirmatory urinalysis to detect diversion and assess for abstinence from other psychoactive substance use. Supportive counseling involving family and community resources should be provided. Additionally, patients need to be monitored for emotional blunting and suicidal ideation.

Recently, the Obama administration proposed a rule that would increase the cap on the number of patients a physician could treat for opioid addiction. The United States Department of Health and Human Services (HHS) Secretary Sylvia Mathews Burwell stated that the rule could very likely go into effect before President Obama leaves office (Mole B, 2016). The proposed rule increases the patient limit up to 200 patients in a physician’s third year of certification to prescribe buprenorphine and could potentially lower the number of patients dying on treatment waiting lists (Cherkis, 2016; U.S. Department of Health and Human Services). With the possibility of a patient increase, black market sales of

buprenorphine would drop, allowing patients the opportunity to treat their addiction legally and seek behavioral services as well (Cherkis, 2016).

While we appreciate the short –term use of buprenorphine/naloxone, clinicians should continue to monitor a patients response since there have been a number of issues involving toxicity(DeVido, Connery, & Hill, 2015; Gangahar, 2015; Daniulaityte, Carlson, Brigham, Cameron, & Sheth, 2015; Ciftci et al., 2015; Edwards, McCormick-Deaton, & Hosanagar, 2014; Lavonas et al., 2013; Kim, Smiddy, Hoffman, & Nelson, 2012). One limited study suggests that buprenorphine does not affect the cingulate gyrus in early abstinent heroin addicts and as such may act as a true non-addicting pharmaceutical to prevent relapse (Mei, Zhang, & Xiao, 2010); clearly much more research is needed on this topic.

These recommendations regarding the conditions, under which an increase in the patient limit for treatment is prudent, should carefully follow the literature on opioid addiction and the benefits of buprenorphine treatment. For patients addicted to opioids, the buprenorphine/naloxone option is currently a first line treatment (Shapiro et al., 2013). Some addiction specialists may think that the concerns with genetic testing (Blum, 2012; Blum et al., 2013; Blum et al., 2015; Blum et al., 2012; Blum, Febo, Giordano, Hauser, Oscar-Berman, et al., 2013; Blum et al., 2010; Blum, 2015; Blum, Badgaiyan, & Gold, 2015) and psychological blunting (Rowe et al., 2015) contained within this proposal may be a barrier to treatment. These proposals are very important for the prevention of a continued rise in illegal opiate/opioid abuse and should not be ignored. We may not be there yet in terms of these proposals, but we encourage the field to help develop these important steps to insure the “best practice” principles in curtailing the opiate/opioid epidemic. This is particularly the case in pain clinics, where it is imperative that those who have at least one reward risk allele refrain from utilizing opioids as treatment, and that appropriate alternative treatment be determined. Furthermore, those with OUD who carry genetic risk alleles require opioid replacement therapy. Although there are many benefits in methadone use, it is not sustainable for addicts to use methadone treatment indefinitely. Placing limitations on the length of time that methadone can be used as treatment is prudent, especially considering the need for normalization of psychological capacities as well as resultant drug abstinence. The discontinuation of opioid maintenance therapy with methadone results in high relapse rates and even death (Magura & Rosenblum, 2001). However, we hereby propose that neuroscientists and clinicians alike should consider the development of either pharmaceutical or nutraceutical alternatives that induce dopamine homeostasis, rather than promote anti-dopaminergic activity (Blum, Oscar-Berman, Femino, et al., 2013). The recent Obama administration proposal will target some of these concerns above and improve treatment availability to those who otherwise would not have access.

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