

Do We Really Need to Continue Pharmacotherapy for Opioid Use Disorder (OUD) Indefinitely?

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Abstract

It is unclear whether pharmacotherapy for opioid use disorder (OUD) should be continued for short or long-term. Before introduction of buprenorphine, methadone was the primary pharmacotherapy for OUD in the United States. Because of its specific pharmacokinetic properties methadone was recommended for long-term use with some justification. Introduction of buprenorphine however has altered the treatment protocol because of milder adverse effects and withdrawal symptoms. The adverse effects of buprenorphine are milder but not negligible. Therefore, indefinite prescription is justified only if there is a significant benefit. Studies that have compared short and long-term treatment of buprenorphine protocols do not show a significant benefit of long-term treatment over relatively short-term (few months) treatment protocols. Obviously, the ultra short-term treatment lasting a few days has very little or no benefit on long-term treatment of buprenorphine protocols that use buprenorphine for 3 to 9 months is comparable to that of the long-term (years to lifetime) treatment without financial and medical consequences of the long-term treatment.

Keywords

Pharmacotherapy, Opioid Use Disorder (OUD), Buprenorphine/naloxone, Mood changes

Introduction

After introduction of buprenorphine and buprenorphine/naloxone combination (BUP) in the US in 2002, pharmacological treatment of opioid use disorder (OUD) has become more popular and easily accessible because it can be dispensed/prescribed in the office and individuals have to visit the clinic only once in several weeks. This is a departure from methadone treatment protocol, which requires patients to report to the clinic on a daily basis. Relatively low incidence of adverse effects and ease of prescription has made a significant difference in the way OUD is treated pharmacologically.

This change has prompted debate on appropriate treatment protocol. Because of limited data and clinical experience, determination of the dose and length of treatment with BUP remains unclear. Gustin et al. [1] recommend indefinite continuation of treatment. They argue that the chronic disease model of addiction proposed by American Society of Addiction Medicine [2] suggests that the addiction treatment should be continued for the rest of life, as is the case with the most chronic diseases like diabetes mellitus and hypertension. This is in contrast to the suggestions made by other investigators who favor short-term treatment to avoid adverse consequences associated with long-term BUP use [3].

We favor this approach and discuss some of its advantages over the long-term protocols and why we think it is not appropriate to continue pharmacological treatment for OUD indefinitely.

Methadone was introduced in the US for OUD treatment in 1947. Because of long exposure and experience, there are a number of well-designed studies that have established dosing and duration of treatment with methadone. The data on BUP is not that extensive and because it can be prescribed by only a small number of physicians (8777 in the United States as of 2008), there is limited experience. Because of this limitation most prescribers use their own experience to guide treatment protocol and duration. This has led to controversy concerning the length of treatment. Initial thought was to follow the methadone model, which requires continuation of treatment for several years. The United States Federal Guidelines for Opioid Treatment compiled by the Substance Abuse and Mental Health Services Administration recommends lifelong treatment with methadone [4].

Long-term treatment with methadone is justified on several counts: being an agonist of μ receptor it activates these receptors to full extent depending on the dose and develops tolerance and physical dependence. As a result, its withdrawal or dose reduction result in serious withdrawal symptoms and craving leading to relapse. It also has relatively short half-life of 14.3 hrs [5]. Since substances with shorter half-life have greater addictive potential [6], methadone works as a kind of substituted drug of addiction. Moreover, most methadone programs do not require patients to go for psychotherapy/counseling. It makes the treatment a substitution therapy that needs to be continued for several years if not lifelong.

Treatment of opioid addiction with BUP however is a different story. Since it is a partial agonist of μ receptors, it does not fully activate these receptors and therefore has milder withdrawal symptoms [7] but still very significant. It is significantly milder and sets in slower than that of the methadone partly due to slow dissociation from receptor sites [8, 9]. Because of the slow dissociation it has longer half-life of 27.72 hrs as compared to methadone [10]. Because of these differences treatment strategies that are effective for methadone cannot be applied to BUP.

Most independent clinics prefer the methadone model and prescribe BUP for several years without a break. The expert consensus panel convened by the US Department of Health and Human Services however recommended BUP treatment for one week, followed by a taper for two weeks [3]. It recommended long-term treatment for patients who are unable to maintain to stay clean. Since publication of this clinical guideline, several trials were conducted to examine relapse rates after a short or long term treatment. In a large study 990 patients were randomly assigned a protocol in which they received BUP either for 7 or 28 days [3]. Three months after termination of the treatment, there was no significant difference in the rate of relapse in the group that received BUP for 7 or 28 days. The two groups had similar levels of withdrawal symptoms and craving. The relapse rate however was high in both groups. Only 12.16% of the 7-day group and 13.41% of the 28-day group were opioid free three months after the treatment. While the result is disappointing, the authors concluded that the duration of treatment does not

significantly affect the outcome and treatment success does not depend on the duration of treatment.

When we examine the results of this study with the other similar studies, we did find that relatively longer duration allows more patients to stay opioid-free after cessation of treatment [11-13]. For example, if patients receive BUP for 12 weeks instead of 4 weeks more than 60% patients remain drug-free after a year of treatment termination [14]. This is encouraging data because no intervention, even BUP maintenance for life achieve 100% opioid-free outcome. Even patients on long-term treatment and on BUP maintenance treatment achieve mean abstinence of only 5.2 weeks as compared to 2.7 weeks achieved by graduates of a short-term program.

Thus no protocol at this time can make all patients opioid-free but most of them are able to stay that way following a 12-week BUP treatment [14]. A certain number of patients will not stop abusing opioid no matter what treatment strategy is employed. Therefore, we have to accept a certain degree of treatment failure. The correct approach therefore is to strike a balance between treatment outcome and adverse effect of long-term BUP use.

A reasonable approach to strike this balance is to increase the duration of treatment to include even more patients. So, if after 7 days' treatment 12.16% patients stay drug free and the number increases to 13.41 after 28-day and 60% after 12 weeks' treatment, the duration can be increased to a few more weeks to include 90% of patients. In our clinic when we tapered BUP over 6-9 months period, over 90% of patients were opioid-free after a year of treatment termination (manuscript in preparation). Achieving over 90% success following 6-9 months' treatment is the best outcome we should hope for. However, we have not accessed the possibility of transfer addiction.

These studies make it clear that there are individual differences in the ability of individuals to respond to pharmacotherapy. A number of variables are known to affect the recovery and ultimately treatment success [15]. In this context we agree with Gustin et al. [1] that the treatment protocol should be individualized but the variables that affect the outcome are difficult to quantify. It is difficult to precisely predict the length of treatment a particular individual would need. It is therefore best to use a treatment protocol that would make a vast majority of patients opioid-free (for example 90% patients in 6-9 month treatment protocol). For the patients that do not respond to this protocol, the treatment can be continue for another few months. Of course there will be few patients that will never respond. Because a few patients will not respond to any length of treatment does not justify recommending long-term (lifelong) treatment protocol for all patients as suggested by Gustin et al. [1].

Thus, a regimented relatively short-term treatment protocol not only will treat a vast majority of patients at a relatively lower cost but will also avoid long-term consequences of BUP use. In the short term BUP has relatively low adverse effects, consequences of its long-term use are still largely unknown because of a short clinical history. But there is very high probability of it making long-term alterations in the receptor activity. In laboratory animals BUP is known to down regulate

or upregulate a variety of receptors [16]. It downregulates μ receptors in several brain areas (frontal cortex, parietal cortex, thalamus, hippocampus, striatum, brain stem) and upregulate κ_1 receptors in the striatum and in the frontal, parietal, and occipital cortex. It is not yet known whether long-term use of BUP will have the same adverse effects that are associated with long-term use of opioids. Since it is a partial opioid agonist it is likely to have at least some of those adverse effects. These effects include lower immunity, hyperalgesia, prolonged QTc interval, respiratory depression and reduced levels of a number of hormones [17]. There are a number of reports of serious withdrawal symptoms in individuals using BUP [18, 19]. Additionally, long-term users of BUP (average 1.6 years) have difficulty experiencing pleasure and other emotions [20]. They discount happiness and tend to be unaware of the feeling of sadness and anxiety. Long term use therefore takes away normal pleasures of life and leads to reward deficiency syndrome [21]. Additionally since BUP inhibits the CYP2D6 and CYP3A4 enzyme systems [22], it interacts significantly with a number of medications. This is a potential problem for an individual who is on a lifelong BUP treatment. The most important problem is the possible anti dopaminergic effect of chronic administration leading to increased relapse potential [23]. Long-term treatment could therefore be counterproductive.

Conclusion

Thus, does it make sense to expose all OUD individuals to significant medical and financial stress of lifelong treatment because a small number of individuals would not respond to short-term therapy? We think that the stress of long term therapy should be restricted only to a small subset of individuals who are resistant to short-term treatment. For some of these individuals pharmacotherapy or other forms of dopamine agonistic therapy [23, 24] may be effective for some but not all, while others may benefit from psychological and social interventions, which should be used to maximize benefits of the short-term treatment. We can achieve better outcome with this approach without adverse consequences of long-term use.

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Conflict of Interest

Dr. Blum is a member of the scientific advisory board of Dominion Diagnostics, LLC and a member of the Board of Directors of RDSolutions Inc. He also serves as Chief Scientific Advisor to Dominion Diagnostics, LLC and is

currently the Chief Scientific Officer of RDSolutions, Inc. and Victory Nutrition International, LLC. There are no other conflicts of interest to report.

Authors Contribution

All the authors contributed equally.

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