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Buprenorphine for opioid dependence

Walter Ling, MD

Integrated Substance Abuse Programs (ISAP), University of California at Los Angeles, CA, USA,
Tel.: +1 310 267 5888, Fax: +1 310 312 0552

Walter Ling: lwalter@ucla.edu

Abstract

As a treatment agent for opioid dependence, buprenorphine is a nearly ideal medication at our current stage of medication development. Unlike methadone, buprenorphine dosage can be rapidly adjusted with minimal potential for inducing severe consequences. In addition to its intrinsic safety, buprenorphine's relatively low abuse liability in the combination product (i.e., with naloxone as Suboxone®) makes it even more acceptable in regulatory quarters as well as to prescribing physicians. The approval of buprenorphine as a pharmacotherapy for opioid dependence returns to physicians the ability to treat their opioid-dependent patients with an effective opioid-based treatment for the first time in nearly 100 years. Buprenorphine is an opioid, however, and potential for misuse remains, even in combination with naloxone. Whether buprenorphine will be increasingly accepted as a treatment for opioid-dependent patients depends on clinicians recognizing the advantages of its uniquely useful properties while still heeding the need to manage their patients' therapy with reasonable vigilance.

Keywords

buprenorphine; heroin addiction; opioid dependence; pharmacotherapy; Suboxone®

Buprenorphine is a recent addition to the armamentarium for the treatment of opioid dependence, following legislation authorizing office-based prescribing in 2000 and subsequent approval in 2002 by the US FDA. As the buprenorphine–naloxone combination or in the monotherapy form, the medication boasts a unique pharmacological profile characterized by high levels of safety and a ceiling effect on respiratory suppression [1]. Thus, buprenorphine-based pharmacotherapy is well suited for use in clinical settings, with patients requiring less stringent oversight than is required for methadone maintenance [2–4]. Most importantly, buprenorphine is the first opioid-based medication in nearly a century to become available to clinicians in the USA for treatment of opioid dependence in the general practice setting. Buprenorphine offers physicians an acutely needed clinical tool, but

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exploiting its therapeutic potential still requires clinical vigilance and the avoidance of some pitfalls, including potential abuse.

This article offers a description of what buprenorphine is, how it was developed to become a safe and effective pharmacotherapy for opioid dependence and some key considerations for its clinical application.

Chemistry of the buprenorphine preparation used to treat opioid dependence

The most widely used formulation of buprenorphine to treat opioid dependence in the USA is the combination of buprenorphine hydrochloride (HCl) with naloxone HCl dihydrate as Suboxone® for sublingual administration, manufactured by Reckitt Benckiser Healthcare Ltd (Hull, UK). Suboxone tablets contain buprenorphine and naloxone in a ratio (free bases) of 4:1 buprenorphine:naloxone [101]. Buprenorphine HCl is a white powder, weakly acidic with limited solubility in water (17 mg/ml). Chemically, buprenorphine is 17(cyclopropylmethyl-a-(1.1 dimethylethyl)-4,5-epoxy-18, 19-dihydro-3-hydroxy-6-methoxy-a-methyl-6, 14-ethenomorphinan-7-methanol, HCl [5a, 7a (S)]. Buprenorphine HCl has the molecular formula $C_{29}H_{41}NO_4HCl$ and the molecular weight is 504.10. Naloxone HCl dihydrate is a white to slightly off-white powder that is soluble in water, in dilute acids and in strong alkali. Chemically, naloxone is 17-allyl-4,5 epoxy-3, 14-dihydroxymorphinan-6-one HCl. Naloxone HCl dihydrate has the molecular formula $C_{19}H_{21}NO_4HCl_2H_2O$ and the molecular weight is 399.87.

Pharmacokinetics & metabolism

Taken orally, buprenorphine is not well absorbed, and much of it is metabolized in the liver and small intestine [101]. Buprenorphine is well absorbed through the mucosa of the oral cavity, however, and when the tablet is given sublingually, bioavailability ranges from 50 to 80% of a 30% ethanolic solution [5–8]. The absolute bioavailability of the sublingual tablet is approximately 40% following a single dose [9]. After absorption, buprenorphine is widely distributed throughout the body with peak plasma concentration reached at approximately 60 min and with a terminal half-life of approximately 32–37 h [7,10]. It is highly bound to plasma proteins and is inactivated by enzymatic transformation, specifically *N*-dealkylation and conjugation. Buprenorphine undergoes *N*-dealkylation to norbuprenorphine and glucuronidation. The *N*-dealkylation pathway is mediated by cytochrome P450 3A4 isozyme. Norbuprenorphine, an active metabolite, can be further metabolized via glucuronidation. Naloxone undergoes direct glucuronidation to naloxone 3-glucuronide, as well as *N*-dealkylation and reduction of the 6-oxo group.

Plasma levels of buprenorphine increase similarly when administered sublingually alone (Subutex) or when combined with naloxone (Suboxone), and plasma levels of naloxone increase with sublingual doses of Suboxone [10–12]. Large intersubject variability exists with regard to sublingual absorption of both buprenorphine and naloxone [6], but there is less intrasubject variability [11]. Thus, the large intersubject variability is not clinically relevant when buprenorphine is titrated to clinical effect, as recommended. Both C_{max} and

AUC of buprenorphine appear to increase in a linear fashion with an increase in dose (in the 4–16 mg range), although the increase is not directly dose proportional [10,11].

Naloxone does not affect the pharmacokinetics of buprenorphine, and both Subutex and Suboxone deliver similar buprenorphine plasma concentrations. The levels of naloxone were too low to assess dose proportionality in clinical trials [10,11]. At the naloxone doses of 1, 2, and 4 mg tested by Jones and colleagues, levels above the lower limit of quantification (LLOQ) were detected beyond 2 h in none out of eight subjects, two out of eight subjects and five out of eight subjects, respectively [11]. In one subject at the 4-mg dose, the last measurable concentration was at 8 h. In a similar trial performed by Hitzemann and colleagues using naloxone doses of 1, 2, 4 and 6 mg, levels above the LLOQ at 2 h were observed in four out of 14, seven out of 14, 13 out of 14, and ten out of 12 subjects with samples available at this time point, respectively. With each subject across the doses, there was a trend toward an increase in naloxone concentration with increase in dose. Mean peak naloxone levels ranged from 0.11 to 0.28 ng/ml in the dose range of 1–4 mg in the study performed by Jones *et al.*, and from 0.12 to 0.44 ng/ml in the dose range from 1 to 4 mg in the study performed by Hitzemann *et al.* [10,11].

Buprenorphine's metabolites are excreted mainly via the fecal route. A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing [13]. Almost all of the dose was accounted for by assays quantifying buprenorphine, norbuprenorphine and two unidentified buprenorphine metabolites. In urine, most of the buprenorphine and norbuprenorphine were conjugated (buprenorphine: 1% free and 9.4% conjugated; norbuprenorphine: 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine: 33% free and 5% conjugated; norbuprenorphine: 21% free and 2% conjugated) [13].

Pharmacodynamics

Buprenorphine is a partial agonist at the μ -opioid receptor and an antagonist at the K receptor. A major advantage of buprenorphine is that it does not produce the familiar opioid 'rush' effect characteristic of full agonists at the μ -opioid receptor, but it does have a reinforcing effect that renders it acceptable to opioid addicts. Daily sublingual doses have been demonstrated to be effective in suppressing heroin self-administration while not producing clinically significant physical dependence such that only a mild abstinence syndrome occurs following abrupt discontinuation. Buprenorphine's ceiling effect on respiratory depression in the absence of other CNS depressants renders it safe with low potential for overdose [1]. The low level of physical dependence should theoretically make it easier to discontinue the medication for patients who desire to stop treatment. However, prolonged administration of high doses of buprenorphine (including those used in the treatment of opioid dependence) can lead to physical dependence and withdrawal symptoms if treatment is stopped abruptly, although these symptoms are typically milder than those seen with full agonists. Both gradual and abrupt medication withdrawal has been used. Gradual dose taper (36 vs 12 days) was associated with better outcomes in an early trial [14], and slowly tapering the buprenorphine dose over 12 or 16 weeks has been effective in

maintaining treatment retention and preventing relapse of opiate use [15,16]. However, a recent multicenter study showed that patients stabilized physiologically on a range of buprenorphine doses can be tapered successfully over 7 days and there is no advantage of prolonging the tapering schedule for several weeks [17]. The decision to discontinue the buprenorphine component of therapy after a period of stabilization or maintenance therapy should be made as a part of a comprehensive treatment plan.

Buprenorphine products are available in two sublingual tablet formulations: buprenorphine alone (Subutex) or in combination with naloxone (Suboxone). Subutex contains 2 or 8 mg buprenorphine and Suboxone contains 2 or 8 mg of buprenorphine combined with 0.5 or 2 mg naloxone, respectively. The rationale for the combination product Suboxone is the reduction of parenteral abuse liability without inducing withdrawal symptoms when properly administered sublingually. This is possible because of the difference between the sublingual absorption of buprenorphine and naloxone; the former is well absorbed sublingually while the latter product is not. Consequently, if the combination tablet is taken sublingually as indicated, there is a negligible amount of naloxone absorbed (if any) and the net clinical effect is virtually equal to taking buprenorphine alone. If Suboxone is illicitly injected, however, the naloxone effect will be felt immediately and a precipitated opioid withdrawal syndrome ensues in individuals dependent on an opioid, thus discouraging intravenous abuse of the product. Recent work has indicated a potential for Suboxone-precipitated withdrawal in cases of high levels of opioid dependence (e.g., methadone 100 mg daily) and finding that split dosing at clinically advised levels appear to be safe and better tolerated [18].

Developing buprenorphine as a pharmacotherapy for opioid dependence

For four decades, methadone has been available as a treatment for opioid addiction, but its use is highly regulated. Attempts to use nonopioid pharmacotherapies, notably the antagonist naltrexone, and the off-label use of the antihypertensive clonidine, have been largely unsuccessful. Consequently, there was – and still is – a need for additional pharmacotherapies to address the problem, which has been recognized by the WHO in its 2007 World Drug Report to include at least 15 million addicts around the world. Although originally intended to treat heroin addiction, buprenorphine also has a role in the treatment of prescription opioid abuse, which has arisen as an unfortunate consequence of the increased prescription of opioids to treat a wide range of pain conditions.

Buprenorphine has been used in many parts of the world for many years as an analgesic, and it has been available in the USA in a parenteral formulation for acute postsurgical pain. In the late 1970s, Jasinski and colleagues postulated that the partial opioid agonist properties of buprenorphine could be useful for the treatment of opioid dependence, having the combined clinical profiles of the agonist methadone and the antagonist naltrexone [19]. The National Institute on Drug Abuse (NIDA) and Reckitt and Colman entered a Cooperative Research and Development Agreement in 1993 to develop the medication in the USA for the treatment of opioid dependence. Subsequent clinical studies have demonstrated its safety and efficacy for such use [4,20,21], and with legislation in 2000, buprenorphine became the first opioid-based medication available to clinicians in the USA in nearly 100 years. Its

clinical success has stimulated the development of a sustained-release preparation in implant form (Titan Pharmaceuticals), and undoubtedly there will be interest in generic preparations once its status as an 'orphan drug' expires in 2010.

Clinical studies of efficacy & utility

Early clinical trials by Jasinski and colleagues proved buprenorphine's ability to substitute for morphine and suppress withdrawal from opiate (i.e., heroin) while producing only a mild withdrawal syndrome of its own [19]. In the early 1980s, Mello and Mendelson conducted a series of human laboratory studies showing that addicts maintained on buprenorphine reduced their consumption of heroin [22,23]. A subsequent series of controlled clinical trials comparing buprenorphine to methadone [4,20,21,24,25] and buprenorphine to placebo [26,27], as well as various buprenorphine dose-ranging studies [28,29], all provided data confirming its safety and efficacy and led to its approval by the FDA and to the passage in 2000 of the Drug Addiction Treatment Act (DATA). DATA allowed buprenorphine to become the first opioid-based drug available to physicians for treatment of opioid dependence in a private practice medical setting.

Most of the early clinical studies of buprenorphine for treatment of opiate dependence were conducted with a liquid preparation [30], but the liquid preparation became discolored with storage and was inconvenient for general clinical administration. A tablet formulation was thus developed and studies were conducted to compare the relative bioavailability of the two formulations. Results generally showed that the tablet delivers a sufficient level of active medication and that blood levels associated with chronic dosing of the tablet formulation approach those resulting from the liquid formulation [8,31].

To further reduce buprenorphine's abuse liability when used for treatment of opioid dependence, a formulation was developed combining buprenorphine and naloxone (Suboxone, as noted previously). This strategy had precedence since a formulation of buprenorphine–naloxone was already available in some parts of the world for analgesic use. Extensive research evaluated the ratio of buprenorphine to naloxone needed to best treat opioid dependence [9,30,32–34].

Mendelson and colleagues administered intravenous buprenorphine–naloxone combination in different ratios to groups of experienced heroin users maintained on a steady dose of morphine [35]. Subjects were asked to rate their liking of the combination preparation and how much they would pay for the effect. The subjects showed increasingly less liking for the combination product as the ratio of naloxone increased, and at the 4:1 buprenorphine:naloxone ratio the product was rated as mostly unrewarding and undesirable. Thus, this 4:1 ratio was adopted for the combination product.

Currently, the combination tablet is the product marketed in North America. The buprenorphine mono-product, under the trade name Subutex, has been available for some time in other countries, notably in France since 1996 and in Australia since 2002. The bulk of clinical research supporting the approval of buprenorphine and the buprenorphine–naloxone combination has been conducted by US investigators, although other studies in Europe [36–38] and Australia [39] add to the weight of evidence for its clinical efficacy and

safety. Some of the more crucial studies have been summarized in the Cochrane reviews [16].

A major focus of buprenorphine's clinical development centered on the setting in which it would be delivered [40,41], since it was anticipated that it would be made available to general physicians [42,43]. To that end, several large-scale studies were conducted in community-based offices of general practice physicians. One of these, dubbed the 'best practice protocol', was published in the *New England Journal of Medicine* and attests to the feasibility of implementing buprenorphine treatment in general medical settings [44].

Another recent effort in clinical research with buprenorphine relates to its implementation in the community-based drug abuse treatment facilities that had little prior experience conducting research on the use of opioid medications. Some of the programs were philosophically opposed to the use of any medications to treat addicts. The NIDA Clinical Trials Network (CTN) compared short-term use of the combination product to clonidine for opiate detoxification in an in- and an out-patient treatment setting [2,3]. Several hundred heroin users seeking detoxification were enrolled in this protocol, each randomly assigned to either buprenorphine-naloxone or clonidine over a 2-week course of treatment. Using a composite outcome measure of being present on the last day of the treatment and yielding an opiate-free urine sample as an indication of good outcome, the results were in favor of buprenorphine. In total, 59 out of the 77 patients assigned to buprenorphine in the in-patient setting were successful compared with only eight of the 36 patients similarly treated with clonidine, and 46 out of the 157 patients in the outpatient buprenorphine group were successful compared with only four out of 74 patients on clonidine. This study showed that implementing opioid-based treatment in the community setting is readily feasible. An unexpected result was that a number of facilities that previously had shunned pharmacological treatment adopted buprenorphine as an integral part of their treatment strategy.

Postmarketing surveillance

The approval of buprenorphine came at a time when there were serious public and regulatory concerns about the rise of prescription opioid abuse, and its approval was accompanied by an imposed mandate to conduct certain postmarketing surveillance. Early returns from these efforts suggest that the extent of buprenorphine's street diversion and abuse has been minimal and does not pose a public health concern [33]. It must be recognized, however, that this was due at least in part to slow market penetration after its initial introduction. More reports of abuse and diversion have since appeared, and some clinicians and regulators have reacted with alarm. Clearly, it would be unrealistic to assume that buprenorphine, which is an opioid, will never be abused. While the incorporation of naloxone into the combination product greatly reduces the abuse liability of Suboxone, the risk of abuse that is intrinsic to any opioid-based medication cannot be entirely eliminated, and clinicians must be aware of the potential for misuse or diversion. A recent examination of more than 1000 treatment-seeking prescription opioid addicts found that buprenorphine-treated patients were similar to methadone-treated patients in terms of seeking intoxication via buprenorphine (30–35%) but only for a short duration until the rate dropped to below

20%, well below the continued rate for methadone-treated patients [45]. Fewer than 3% of the sample reported buprenorphine becoming a primary abused drug, confirming the notion that the insufficiency of buprenorphine's euphorogenic capacity ultimately constrains its attraction as an abusable substance.

Owing to concerns about liver function affected by buprenorphine, the NIDA CTN was charged with the investigation of related phenomena [46]. No evidence has thus far been found for hepatotoxicity of buprenorphine.

Regulatory affairs

Buprenorphine poses some interesting and challenging regulatory issues. In the analgesic dose range originally marketed for the treatment of pain, there was little, if any, concern about buprenorphine's abuse potential and it was designated a Schedule V drug in the Drug Enforcement Agency (DEA) registration, in spite of reports of abuse of the analgesic preparations. The formulations that were approved for treatment of opioid dependence contain much higher buprenorphine dosages, however, and the potential for abuse led to its being given a schedule III designation. To prescribe buprenorphine for treatment of opioid dependence, physicians in the USA must have a special designation on their DEA registration, although the medication itself has remained at a less restrictive schedule level than most narcotics, and it does not require the triplicate prescription necessary for medications such as morphine and methadone. This equivocal classification continues to generate controversies from regulatory bodies and clinicians striving to balance its clinical access against the concerns about its abuse. Scheduling to a higher category (i.e., schedule II) would pose a serious barrier to its use by clinicians treating opioid dependence. While there have been reports of diversion and abuse of both formulations, the extent of buprenorphine abuse appears to be minimal and there is no indication that such abuse poses a serious public health concern. Thus, a sensible regulatory approach at present appears to call for leaving things where they are while continuing to keep a watchful eye. Agency officials may remain somewhat nervous about the abuse potential, but careful clinical management, which is merely an expectation of responsible practice, can lessen the prevalence and degree of buprenorphine abuse. Improved training of buprenorphine-prescribing physicians will assist in this process.

Conclusion

Of all the advancements in opioid pharmacotherapy that have been made since the introduction of methadone, none has been as momentous as the introduction of buprenorphine. The partial agonist properties of buprenorphine confer on it a high clinical safety profile and its tight receptor binding ensures a relatively long duration of action. Together, these characteristics make buprenorphine appealing to clinicians, patients and society as a whole. For the clinician, buprenorphine's ceiling effect on respiratory depression translates into less concern for overdose deaths and allows clinicians greater flexibility in treatment delivery. For the patient, the relatively slow onset of generally mild symptoms of withdrawal when doses are missed or when the medication is discontinued mitigate against one of the most anxiety-provoking drawbacks of opioid pharmacotherapy. For society at

large, buprenorphine's lower abuse liability, especially with the combination product, also makes it more acceptable. The true significance of the availability of buprenorphine to clinicians, however, is not that it offers them a new medication, but it returns to them the ability to treat their opioid-addicted patients with an effective opioid-based treatment for the first time in nearly a 100 years.

However, buprenorphine remains an opioid and is not free of the dual nature that justifies its being known as the 'Janus drug'. Whether buprenorphine will be a widely utilized clinical success in treating opioid addiction depends on the extent to which clinicians will understand buprenorphine and make best use of it for the benefit of their patients, taking advantage of its unique properties while respecting the need for caution and vigilance in its use.

Expert commentary

The introduction of buprenorphine into the opioid addiction treatment system is arguably the most important development in opioid pharmacotherapy since the introduction of methadone more than 40 years ago. Approval of buprenorphine in 2000 is most significant for heralding a paradigm shift in the medical management of opioid dependence made possible by evolving societal values and attitudes. The approval of buprenorphine represented a manifestation of wider understanding and acceptance of opioid addiction as a chronic disease deserving of medical treatment, thus returning treatment of opioid addiction into the hands of the physician. Buprenorphine is not just a new medication, its acceptance for treating heroin addiction signals a new approach to treating these patients; buprenorphine is but a tool.

The sea change was not a simple process, however, and resistance came from many quarters, from both inside the realm of addiction medicine as well as from external forces. It literally took an act of Congress to make buprenorphine available to clinicians, but even then, cautionary restrictions were included, such as the requirement for special training and qualification of prescribing physicians. Much of the hesitation to implement buprenorphine appears to have related to the fact that most treatment strategies require changes on the part of the patients, whereas the use of buprenorphine as a clinical tool demands certain changes on the part of the caregivers. The tentative implementation of this useful medication must be understood in this context.

As a treatment agent for opioid addiction, buprenorphine probably comes as close to an ideal medication as could be imagined, at least at this point in medication development. Its great advantage is its safety, which allows for flexible dosing and therefore confers a degree of autonomy in clinical management not available with methadone, the mainstay pharmacotherapy. With buprenorphine, the clinician has the ability to rapidly escalate dosage levels, with minimal potential for inducing severe consequences, in order to manage a particular patient's emergent needs. Similarly, dosage reductions to accommodate a patient's developments and ultimate cessation of pharmacotherapy is a strength unique to buprenorphine.

From the patient's perspective, buprenorphine is ideal even for those not totally committed to giving up drugs completely. Its pharmacological properties are such that an addict who is maintained on it can still experience some opioid effect on occasion of street use while suffering little withdrawal symptoms when such use is not available. For an addict who fears withdrawal more than anything else, this is a compelling characteristic of buprenorphine. It is, therefore, not surprising that a number of patients maintained on buprenorphine continue to seek occasional use of illicitly obtained opioids. This behavior is anathema to societal mores and is disconcerting to clinicians as well, especially for those who errantly believe that placing a patient on buprenorphine should equate to their immediate and absolute abstinence.

The incorporation of naloxone into the formulation was meant to inhibit intravenous abuse and probably does help to lessen illicit diversion for injection use, but it was never thought to completely eliminate the abuse of buprenorphine, intravenously or otherwise. Perhaps that message was never clearly stated, which leaves ground for criticism by those who held the view that a medical treatment is useless if it does not work flawlessly. The surprise should not be that there are reports of buprenorphine abuse, but that clinicians who claim to know addicts should be surprised by that reality and, as a result, take negative attitudes toward buprenorphine's clinical utility. Buprenorphine is neither perfect nor harmless. As with everything else, the medication has its attributes as well as its limitations and hazards, although they are certainly within reason when managed by a thoughtful, reasonably capable clinician.

A few issues do warrant comment at this juncture. The availability of buprenorphine came at a time when prescription opioid abuse was on the rise as a result of resurgent enthusiasm for prescribing opioids to treat chronic pain, and the subsequent copious supplies of opioid analgesics on the market and thus more available for diversion. The FDA had mandated a postmarketing surveillance of abuse and diversion as part of the buprenorphine approval. As described previously, reports on the results of these efforts suggest that diversion and abuse of buprenorphine occur minimally. Initial findings have been subject to a great deal of criticism from many quarters, in part because the number of reports of numbers of incidents during the time that market penetration was still small. Increases in the extent of abuse could be expected as buprenorphine is more widely used. More accurate reporting is needed, and our surveillance system needs improving. In addition, pharmaceutical controls can be improved. Certainly, there needs to be continued vigilance in tracking potential abuse and diversion, and it may well be that diversion and abuse have increased, but that does not suggest that buprenorphine as a pharmacotherapy for opioid addiction has failed. There is no justification for a knee-jerk reaction that buprenorphine products should be rescheduled to a category indicating greater abuse and addiction risk.

For clinicians, some of the more salient clinical issues regarding the use of buprenorphine are as follows. The partial agonist nature of the medication means that buprenorphine could physiologically act as an agonist or antagonist depending on the physiological milieu of the patient. This has important implications in the initial dosing of the patient, which is called induction. Practically, what this means is that there is a potential for buprenorphine to act as an antagonist and precipitate an acute opioid withdrawal, which would be highly

undesirable. This can happen in a patient who presents to the clinician with a significant amount of opioid on board. Therefore, the admonition to clinicians has been to give the initial dose when the patient is showing some definitive signs and symptoms of opiate withdrawal. In practice, it means at least 8 or 10 h after the last use of heroin or 1–3 days after the last dose of methadone or prescription opioids. While the amount and time of the last use and the nature of the opioids used are important, the critical issue is to be certain that the patient actually shows some reliable signs of opioid withdrawal. The better indicators are a pulse rate of 80 bpm or more, some degree of elevated blood pressure, perhaps elevated respiratory rate and some dilatation of the pupils. The idea is that the more discomfort the patient is experiencing from the withdrawal, the more therapeutic benefit will be attained from the initial dose of buprenorphine.

Once patients are inducted onto buprenorphine, the speed with which an adequate therapeutic dose is reached has a direct bearing on how the patient will feel and is an important determinant of retention, which is crucial in treatment of any drug-use disorder, but especially in opioid addiction. Early retention is critical and can best be attained by providing patients with an adequate dose to suppress symptoms of withdrawal. Almost unique to buprenorphine treatment is the clinical observation that the daily dose tended to decrease rather than increase after patients have been in treatment for a period of time.

It is universally recommended that psychosocial treatment be provided as part of the pharmacotherapy. This is certainly important, but the nature and extent to which psychosocial support should be a required element of treatment is debatable, since it inevitably requires the patient's frequent visits to the prescribing physician or other clinician, and these visits can be a burden in themselves. Physicians should reflect on why we sometimes demand frequent clinical contact. Is it to ease our own anxiety or is it for the patient's benefit?

Recently, there have been concerns raised about prolongation of the QTc intervals among patients maintained on methadone. Inevitably, the same concerns are being directed toward buprenorphine. There is little indication, however, that prolonged QTc intervals are a clinical concern when buprenorphine is used properly [47].

The paucity of drug–drug interactions between buprenorphine and antiviral medication that is used in treating HIV/AIDS is another advantage of buprenorphine worthy of clinical consideration.

Finally, a frequently asked question is how long buprenorphine treatment should be provided. The answer is as long as the patient needs it. This is not the same as saying the patient should be treated for life, but it does mean one should have a very clear indication by several measures that the patient no longer needs treatment. Neither the dose nor the length of treatment is a determinant of such a decision. The important points to consider are to what extent the clinician and the patient can be certain that medication is no longer required. This means determining not only that the use of illicit opioids is no longer an issue but also the extent to which the patient's life has become stabilized with regard to health, self-care, relationships, employment and improvement in other social domains.

Five-year view

The exclusivity enjoyed by the manufacturer of Subutex and Suboxone will expire in the next 2 years. Generic manufacturers will undoubtedly enter the market and make the product more widely available and perhaps more affordable. There will also be continued development of other formulations, such as Probuphine® (the long-acting implant form of buprenorphine in combination with naloxone), and off-label use of the product will likewise continue. Changes will come slowly, however, as has been the case to this point.

The implementation of buprenorphine treatment in the USA has been slow. Cost, regulatory barriers and training requirements have understandably been cited as factors that contribute to reticent acceptance of the medication [43,48,49], but philosophical resistance appears to have played an important role, and this is more difficult to comprehend. Logic would argue that an entity that has advocated agonist therapy would welcome and embrace buprenorphine, but reluctance remains. Personal philosophy and life experience often get in the way of logic, even among addiction experts who commonly remark that “pharmacotherapy is not recovery”. Such is the paradox. If any group of physicians should understand the relationship between medication, brain chemistry and addiction, it is the experts in addiction medicine. Addiction is often called ‘chemical dependence’ by addiction medicine professionals, and it is by definition brain chemistry gone awry. It seems almost incomprehensible that these same experts would insist that pharmacotherapy has no place in recovery.

In the end, for this newest advance in opioid pharmacotherapy to succeed, the changes in attitude and practice must come from within the ranks of clinicians. Much of the effort in developing effective medications has been directed toward changing the patients, but in this case the physicians must also adapt. The introduction of buprenorphine had been called a “great social experiment”. That endeavor is not a drastic innovation in medication development, it is an experiment involving the medical community to see whether it can respond with a new attitude, philosophy and approach to patients. Physicians will have to change in order to best capitalize on the ability of buprenorphine to treat patients with opioid dependence. New attitudes and practices among physicians may help drive a new societal attitude toward opioid-dependent individuals and the treatment of addiction. This would be a real and meaningful advance.

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- Website of manufacturer of Suboxone® (Reckitt Benckiser): www.suboxone.com

Key issues

- The approval of buprenorphine as a pharmacotherapy for opioid dependence returns to physicians the ability to treat their opioid-dependent patients with an effective opioid-based treatment for the first time in nearly 100 years.
- Early retention is critical and can best be attained by providing patients with an adequate dose to suppress symptoms of withdrawal.
- The use of buprenorphine as a clinical tool demands certain changes in attitude and practice on the part of the caregivers, such as having greater flexibility in requiring patients to attend clinics or visit the office, as well as in philosophy about addiction and the appropriateness of pharmacotherapy to manage addiction.
- Clinicians should understand and deal with occasional, infrequent use of illicit opioids by buprenorphine-maintained individuals—no medication is perfect.
- Buprenorphine is a partial opioid agonist thus has some abuse potential - reasonable clinical management, which is merely an expectation of responsible practice, can lessen buprenorphine abuse, and improved training of buprenorphine-prescribing physicians will assist in this process.