Review Article

Long-acting Preparations in Substance Abuse Management: A Review and Update

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ABSTRACT

Many pharmacological approaches have been used in managing substance use disorders. Conventional pharmacological agents have relatively short durations of action which make them vulnerable to non-adherence and relapse to substance use disorder. To overcome this problem, long-acting preparations have been developed with the aim of reducing the frequency of use and hence improving adherence. This review takes a broad overview of the long-acting preparations available for the management of substance use disorders. The pharmacology, advantages and disadvantages of these preparations are discussed. Many of these preparations hold promise for improving patient outcomes.

Key words: *Depots, implants, long acting preparations, pharmacoprophylaxis, substance use disorders*

INTRODUCTION

Substance use disorders continue to exact a heavy toll on the user, his family, and society.[1] In trying to manage substance use disorders, a plethora of therapeutic measures have been used, ranging from pharmacotherapy to psychotherapy, to alternate and complementary medicine.[2] Among pharmacological approaches, many agents have been utilized. These include agonist medications like buprenorphine, antagonists like naltrexone, deterrents like disulfiram, and others.

Pharmacological agents used conventionally face a number of hurdles. Most agents used presently have relatively short durations of action, leading to the need for frequent dosing. They hence need to be taken regularly for a long duration of time, raising the possibility of poor adherence, and hence a high chance of relapse. Attempts to overcome these, by increasing the monitoring and supervision of use of medication has had limited benefit.[3,4] Furthermroe, many agents meant for treatment, for example, buprenorphine and methadone, have themselves been misused.[5]

The above issues have contributed significantly to the limited effectiveness of conventional pharmacological approaches in altering the course of substance abuse. With the aim of overcoming the problem, workers have attempted to develop preparations which once administered, can act longer, and reduce the frequency of dosing. Hence, by decreasing the chances of omission of dosages, they have the potential to improve treatment adherence and prognosis.

Intending to bring attention to this exciting topic, we have reviewed relevant literature from all over the world focusing on long acting preparations. The term 'long-acting' has been variously defined and used.[6] In this review, we have defined a long-acting preparation for substance abuse management as one that decreases or stops drug seeking or drug taking behavior in the

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context of a target drug which is abused, and does away with or decreases the frequency of need of a more conventional method of pharmacological treatment.

Long-acting preparations can be classified variously-depending on the type of formulation used, such as depot injections, implants, patches; depending on what purpose the preparation is used for, such as detoxification, substitution, or abstinence promotion; depending on the target drug of abuse-and so on. For simplicity, and clarity, we have classified the various preparations under the parent molecules, describing at the end, some 'novel' agents.

NALTREXONE

Modified dosage
Flexible dosing regimens of naltrexone tablets have been employed to enhance compliance. Instead of the usual 50 mg/day regimen, there are anecdotal reports of workers having seen benefit while using regimens such as 100 mg every alternate day, 150 mg every 3rd day, 100 mg on Monday, 100 mg on Wednesday, and 150 mg on Friday, etc.

Injectable depots
Depot formulations of naltrexone were first developed in the mid-1970s and were tried in laboratory animals. These initial formulations were abandoned because of wide between subject variability in plasma concentrations of naltrexone and lack of tissue compatibility.[7,8] Injectable formulations have since been developed, containing microspheres of naltrexone with lactide and glycolide polymers. These formulations contain naltrexone in various strengths of 192 mg, 384 mg, 380 mg, etc., depending on the manufacturer.[9] After being administered as an intra-muscular injection, naltrexone is released from the microspheres in multiple phases by a combination of diffusion and polymer erosion. Drug release under *in-vitro* conditions occurs in three distinct phases: An initial release of surface drug within 24 h of injection, a hydration phase that occurs during the first week following injection, and lastly, a sustained-release phase with a near constant rate of release during 2-4 weeks post-injection. Therapeutically relevant near-constant plasma concentrations of naltrexone (above 1 ng/ml) are seen to be provided, over a course of 4 weeks. As the polymer erodes, lactide and glycolide monomers are formed, which are metabolized and eliminated from the body as carbon dioxide and water.

These depot formulations have been used in the treatment of alcohol and opioid dependent patients. In alcohol dependent individuals, two multi-center,

double-blind, placebo-controlled trials were conducted investigating once-a-month injectable naltrexone.[10,11]

In the first trial with 315 participants over 3 months, the naltrexone (300 mg) group reported fewer days to the first drink and more abstinent days compared to placebo.[10] However, time to first heavy drinking day showed no difference between the groups. In both groups the γ-glutamyl transferase values improved throughout the study indicating clinically significant reductions in alcohol consumption.

In another trial, 624 alcohol-dependent subjects received up to 6 monthly injections of naltrexone depot in two dosages (190 or 380 mg) or placebo.[11] The rate of heavy drinking days was found to be 25% lower in the 380-mg group compared to placebo. However, naltrexone treatment did not show a significant advantage in terms of reduction in risky drinking (more than one or two drinks per day) or any drinking. Also, γ-glutamyl transferase values showed no additional improvement. In the subgroup that achieved abstinence before treatment start, the 380-mg naltrexone group maintained abstinence significantly longer and reported a greater reduction in alcohol consumption and craving than the placebo group.[12] In the full sample, quality of life showed improvement in mental health, but not on physical health scores for the naltrexone group compared to placebo.[13]

The reduction in alcohol drinking and craving that was found in both studies hence did not unequivocally support the advantages of the naltrexone injections compared to placebo. This finding is in line with the inconsistent results from oral naltrexone studies.[14]

In opioid dependent subjects, non-randomized investigations have shown the ability of slow-release naltrexone injections to block opioid effects and help maintain abstinence in different populations of opioid dependent patients.[8] Few randomized trials have since studied the efficacy of these agents. Comer, *et al*.[15] randomized 60 heroin dependent patients to receive placebo, 192 mg, or 384 mg of extended-release naltrexone. The treatment effect was however observed to be insignificant. This lack of significance most probably occurred because the study was not adequately powered, given the small sample size and three conditions of treatment.[16] Newer randomized controlled trials (RCTs) have had more optimistic results. Brooks, *et al*.[17] utilizing a quasi-experimental uncontrolled design, compared treatment retention and opiate use confirmed by urine in opioid dependent patients in two concurrent RCT's of oral and extended-release injectable naltrexone. Overall, patients receiving injectable naltrexone had

better results in terms of days retained in treatment, and opiate use. Patients with more severe heroin use had better treatment retention with oral naltrexone therapy. The authors attributed the improved retention to the intensive psychosocial treatments received by the severe heroin use group in addition to oral naltrexone. In another multisite RCT,[18] monthly injections of extended-release naltrexone or placebo were combined with biweekly sessions of drug counseling. Overall, extended-release naltrexone was found to have a significant benefit in maintaining abstinence, improving retention, decreasing craving, and preventing relapse over weeks 5-24 of the study period.

Common adverse events associated with injectable naltrexone include tissue reactions around the site of drug administration, in the form of tenderness and tissue induration. Other adverse effects are those associated with naltrexone *per se*. A disadvantage of these depots is difficulty in their reversal, which can be problematic in situations such as a planned surgery (requiring the use of opioid analgesia), or when the patient develops an adverse effect to the components of the depot naltrexone.[19] Some subjects have been observed to increase the dose of opioids in a bid to overcome the block with naltrexone, raising the possibility of accidental overdose and its consequences, including death.[20] It has also been reported that the risk of accidental overdose increases after cessation of chronic treatment with naltrexone, either via loss of opioid tolerance or increased sensitivity to opioid agonist administration.

Naltrexone depot injections are available variously as Depotrex (Biotek, Inc.), Naltrel (Elbion NV), Vivitrol (Alkermes, Inc.) in USA, Russia, Australia and some European countries.[21] Vivitrol received US Food and Drug Administration (FDA) approval for treatment of alcohol dependence in 2006 and for relapse prevention in opioid dependent patients in 2010.[16] It is not yet available for sale in India.

Implants
Available naltrexone implants contain naltrexone either in a magnesium stearate matrix, or with a special biodegradable polymer such as a poly-lactic-based polymer. They require surgical insertion in the sub-cutaneous tissue, usually in the anterior abdominal wall, under local anesthesia. Most contain 1000-3600 mg of naltrexone and maintain therapeutically effective levels of naltrexone (above 1 ng/ml) for long durations, ranging from 2 to 10 months.

Many uncontrolled studies conducted suggest the superiority of naltrexone implants over oral naltrexone. Implants have been demonstrated to maintain opioid dependent individuals in an opiate-free state up to 12 months after initiating treatment. These benefits have also been shown in large populations.[22,23] Non-randomized trials have tested the feasibility of the treatment,[24] showing short- and long-term positive outcomes.[25-27]

Three randomized clinical trials have compared implants to oral naltrexone, placebo, or treatment as usual. Hulse, *et al.*,[20] in a 6 month RCT, randomized 70 heroin-dependent patients to receive 50 mg/day oral naltrexone plus placebo implants (*n*=35) or a single-dose of 2.3 g naltrexone implant plus placebo tablets (*n*=35). Plasma naltrexone levels were found in the range of 1-2 ng/ml for a longer time in the naltrexone implant group. Results showed that more patients receiving oral naltrexone had plasma naltrexone levels below 2 ng/ml in the first 2 months of treatment and a higher proportion of them had resumed heroin use by the end of the study compared with the naltrexone implant group. Time to relapse was shorter among oral naltrexone patients. Considering the association of consistent plasma naltrexone levels with opioid abstinence, the authors suggested the effectiveness of the treatment to be associated with more effective μ-opioid receptor blockade. Secondary data analysis showed that effective treatment was achieved at naltrexone levels between 1 and 3 ng/ml and that implant treatment was associated with reduced craving and relapse.[28]

Kunoe *et al.*[29] randomly and openly assigned 56 patients who completed inpatient treatment for opioid dependence to receive either a 6-month naltrexone implant or the usual no-naltrexone after-care, including counseling and vocational services. Patients on naltrexone implant had on average 45 days less heroin use and 60 days less opioid use than controls in the 180-day period. Blood tests showed naltrexone levels above 1 ng/ml for the entire duration of the study.

Krupitsky *et al.*[30] conducted a 6-month RCT in which patients were divided into 3 groups (*n*=102 per group). Patients received naltrexone implant (1000 mg, implanted every other month), oral naltrexone (50 mg/day) or placebo. Opiate-positive urines at 6 months were lowest in the naltrexone implant group (63%) and higher in the oral naltrexone and placebo groups (87% and 86%, respectively). Retention was also significantly higher in the naltrexone implant group compared with the other groups.

Some common adverse effects are those associated with the parent naltrexone molecule and include nausea, vomiting, headache, fatigue, and muscle cramps. Others, such as pain, induration, allergic tissue reaction, wound infection, and cosmetic defects have been observed. Other observed disadvantages are the possibility of the

individual removing the implant soon after its insertion, and like depot naltrexone, the possibility of accidental overdose. An advantage over the depot preparation is the option of immediate reversal, in case of intolerable adverse effects, or a planned surgery (requiring the use of opioid analgesia).[16]

Naltrexone implants, available variously as the O'Neil Implant (GoMedical Industries, Australia), Wedgewood Implant (Wedgewood Pharmacy, USA), and Prodetoxon (Fidelity Capital, Russia)[31] is not approved for use in India as of now.

Deaths and overdoses are a potential concern during long-acting naltrexone treatment and following its discontinuation.[32] There is retrospective data showing no significant increase in overdose-related deaths with these formulations,[33] but attempts of self-testing the competitive antagonist blockade have been reported.[34]

The cost of the above preparations of naltrexone may significantly surpass that of the oral formulation and may contribute to their reduced use. For example, the cost per day of the FDA-approved injectable depot naltrexone formulation is 10-15 times higher than that of the oral preparation. However, cost-effective analyses have confirmed significantly reduced health care expenses.[35] The formulations of naltrexone are summarized in Table 1.

BUPRENORPHINE

Depots
A subcutaneous depot of buprenorphine has been developed, made of microcapsules consisting of buprenorphine base and a biodegradable polymer, poly L(-)lactide-coglycolide. The depot contains 58 mg of buprenorphine. After being administered as a sub-cutaneous injection, the plasma buprenorphine level increases gradually, peaks at 2-3 days and then decreases gradually, becoming undetectable by 6 weeks.

As compared to placebo, the depot provides effective relief from opioid withdrawal.[36] On opioid challenge, the depot appears to produce substantial opioid blockade that persists for 6 weeks post-administration. Adverse effects noted include transient pain and tenderness at the injection site, and rash, itching, bumps and peeling of skin on non-depot sites.[36-38]

Implants
A rod-shaped implant (26 mm × 2.5 mm) has been developed which contains 80 mg or 90 mg of buprenorphine in a polymeric matrix composed of ethylene vinyl acetate.[39,40] The implant is placed in the sub-dermal space (2-3 mm below the skin) in the inner side of the non-dominant arm and is seen to deliver buprenorphine at a steady rate, over 6 months. In a multi-center RCT using the implants,[40] withdrawal symptoms and craving were found to remain low throughout the 6 months follow-up. Significantly more urine samples were negative for illicit opioids in patients with implants as compared to placebo. Adverse effects included bruising, itchiness, redness, swelling, hematoma, soreness, and pain in the injection sites in about half of patients.

Patches
A transdermal patch has also been developed for buprenorphine.[41] The patch has been utilized for detoxification of opioid dependent subjects. A single patch with application for 7 days has been utilized. The buprenorphine plasma levels peaked 48 h after patch application. This formulation was found to be effective in reducing withdrawals in the patients, and was safe and well tolerated.

These above-described long acting preparations of buprenorphine seem promising. However, they are not yet approved for use in India. The various formulations of buprenorphine are depicted in Table 2.

DISULFIRAM

Modified dosage
Flexible dosing regimens of Disulfiram tablets have been employed to enhance compliance. Instead of the popularly used 250 mg/day regimen, higher doses such as 600-800 mg used twice a week, and once a week regimens have been used, improving treatment adherence. There is anecdotal evidence of regimens

Table 1: Long acting naltrexone preparations

Depot injections	Implants
IM injection-easy	Surgical insertion ↓ local anesthesia-difficult
1 month	2-10 months
Almost impossible to reverse	Easily removable

IM – Intra-muscular

Table 2: Long acting buprenorphine preparations

Attribute	Depot injections	Implants	Patches
Duration of action	6 weeks	6 months	1 week
Mode of administration	Subcutaneous injection	Surgical insertion in sub-dermal space	Transdermal application
Used for	Detoxification and long-term management	Long-term management	Detoxification
Characteristics	Not rapidly reversible	Reversible rapidly	Reversible rapidly

such as 500 mg every 2nd day, 750 mg every 3rd day, etc., having been used with benefit, instead of the more conventional daily dosing regimen.[42,43]

Implants

Disulfiram implants had been developed as early as 1968. Though, the implantation of disulfiram tablets in the sub-cutaneous tissue of patients had been suggested to be a solution to problems of adherence to oral disulfiram, the results of the studies on disulfiram has been mixed. Wilson *et al*.[44] have conducted studies in which they have used disulfiram implantation in comparison to sham surgeries. Wilson *et al*.[45] utilized a randomized placebo controlled methodology using either disulfiram implantation or sham surgery. Of the patients who resumed drinking alcohol, only those with disulfiram implants experienced disulfiram ethanol reaction (DER). Sham operation subjects continued to drink after their first drink on follow-up, while most of disulfiram implant recidivists remained abstinent following their experience of a DER showing efficacy of implant. The same group showed efficacy of disulfiram in prolonging abstinence using a placebo controlled trial.[46]

Johnsen and Mørland,[47] conducted a randomized, placebo controlled trial in which both groups were led to believe that they were receiving disulfiram implants. The intervention group received implantation of disulfiram tablets while placebo group received calcium tablets. No significant differences were found in drinking measures or the time to first relapse. It was seen that both groups reduced their drinking significantly. The authors suggested a psychological effect of disulfiram rather than the pharmacological effect being the primary therapeutic action of disulfiram in decreasing the amount of drinking.

One of the common problems associated with disulfiram implantation has been wound infections and inflammation at surgery site.[48] Ethical issues have been raised regarding the use of DER, a potentially fatal complication, as a deterrent measure to prevent alcohol use.[49]

Hughes and Cook[50] assert that the lack of disulfiram implant efficacy in many trials could be ascribed to insignificant absorption of disulfiram implant or inadequate amount of disulfiram being released in the body. This has been reflected in the infrequent disulfiram-ethanol reaction in the studies.

Recent research has focused on developing improved formulations of depot disulfiram. In animals, using poly-glycolic lactic acid as a vehicle a new biodegradable polymer, a sustained systemic delivery of disulfiram has been achieved for 3 months. In humans, a depot preparation using normal saline containing 0.1% polysorbate, combined with an oral loading dose, has been shown to be clinically effective. The depot induced sensitivity to alcohol for 28 days following a single treatment.

The disulfiram implants being developed are not yet available for use in India.

NICOTINE

Patches

Nicotine, as replacement therapy, is also available in the form of patches apart from gums, lozenges, spray, sublingual tablets and inhalers. The transdermal patches are applied to the skin and deliver nicotine at a relatively steady rate. They are usually applied to a clean, dry skin site on the upper torso or outer part of the upper arm. Currently many formulations are available that vary widely in their design, pharmacokinetics and duration of wear.[51] Commonly available patches are 24 and 16 h wear formulations, coming in variable dosages, e.g., 24 h formulation available in 7, 14 and 21 mg patches. This gives flexibility of using progressively lower doses to provide weaning over a long period.

In a meta-analysis of 123 studies using various nicotine replacement therapy formulations,[52] nicotine patches have been shown to be quite effective. The pooled relative risk of abstinence for patients using the different formulations regularly was 1.66 for the patch compared to 1.43 for the gum, 1.90 for inhaler, 2.00 for lozenges and 2.02 for the nasal spray.

The advantages of the nicotine patch include ease of administration, few side effects, and once daily dosing, all of which may lead to better compliance.[51,52] However, the patches do not provide protection against acute craving provoked by smoking related stimuli. Since cue provoked craving appears to be a major factor in relapse, many authors have suggested supplementing patch with acute dosing forms of NRT, like gums.[53,54]

The adverse effects of the patches include mild to moderate sleep disturbances, dyspepsia, body aches, increased cough, nausea, vomiting, dizziness, headache, transient itching or burning at skin sites, erythema and contact sensitization. Transdermal nicotine treatment has not been associated with any consistent changes in electrocardiogram or routine hematology and chemistry blood tests.[55]

Nicotine patches (Nicotinell transdermal therapeutic system (TTS) patch, Novartis) are available for use in India.

NEWER FORMULATIONS AND PREPARATIONS

Vaccines

In the last decade, vaccines are being developed that produce antibodies with high affinity for the drug, bind the drug molecule in the circulation and prevent it from crossing the blood brain barrier. This prevents the access for the drug to the receptor in the brain. Vaccines have been developed for nicotine, cocaine, morphine, methamphetamine and phencyclidine. Of these, nicotine and cocaine vaccines have reached human trials.[56-60]

Clinical trials demonstrate that antibodies attenuate effects of cocaine and nicotine for several months after vaccination in significant number of patients who achieve therapeutic levels. The vaccines have a potential benefit of a long duration of effect. However, significant amount of inter-subject variability in amount of antibody produced has been reported. Furthermore, intrinsic immunogenicity of the present vaccine formulations has been found to be poor. There is a possibility of surmounting the blockade by increasing the dose of the drug and therapeutic effect requiring some time to establish.[56-60] Hence, we may need to wait for some time before such vaccines are widely used.

Certain ethical questions have been raised as to administration of the vaccines to unwilling subjects like incarcerated substance users as means to effectuate control. Furthermore, question has been raised about parents being given authority for vaccinating their young children so that they do not become substance users.[57] Such questions perhaps would be dealt in the future when effective vaccines are available.

Monoamine transport inhibitors

For treatment of cocaine dependence syndrome, monoamine transport inhibitors have been developed.[61,62] The abuse potential of cocaine derives from blockade of monoamine transporters, especially dopamine transporters, leading to an increase in extracellular nucleus accumbens dopamine. Monoamine or dopamine transport inhibitors may serve as agonists, much in the same way methadone acts for opioid dependence. Though, many molecules have been developed, until date none has proven successful, largely because of significant abuse liability of these molecules themselves, and significant side-effects. Recently, many newer molecules have been under study, having much slower onset and longer durations of action, ranging from 1 day (e.g., compound 31,345) to 30 days (e.g., GBR12909).[61,62] However, these molecules also have dose-dependent stimulation of various reward areas leading to the possibility of abuse. They are also observed to augment the action of cocaine, as compared to methadone in opioid abuse

which inhibits their action. This group of molecules do however shows promise and there is scope for the development of a molecule, which may be the first drug effective in cocaine dependence.

Other formulations

Methadone implant formulations have been evaluated *in-vitro* and *in-vivo* in animals.[63] These have been made of polylactide-co-glycolide and polylactic acid with methadone release at a steady rate for 1 week and 1 month duration respectively with the formulation.

Long acting injectable risperidone has been tried in patients with cocaine dependence in a 12 week trial,[64] wherein 25 mg of risperidone was injected every alternate week. However, long acting risperidone was not associated with reduction in cocaine use or craving in the trial, rather was associated with worsening of depressive symptoms and weight gain as compared to placebo.

DISCUSSION

As pharmacotherapeutic agents became available for managing substance use disorders a few decades ago, researchers also started developing long acting preparations. Many long-acting preparations have since been found to be promising.

An 'ideal' long-acting preparation for use in substance abuse management can be conceptualized as one that is safe, effective, and easy to use, releasing the drug at a relatively constant rate for as long a duration as necessary, not causing any adverse event after completion of the desired action and being reversible.[65] Is there an 'ideal' preparation available at present? If no, how close are we to finding one?

Many of the preparations described above do seem to be near to this 'ideal' preparation, at least in research and developmental studies. However, there is negligible data available on their benefit in the real-world scenario.

Among the preparations mentioned above, most literature is available on nicotine patches, naltrexone depot injections and implants. Studies with respect to the other preparations are few in number. Though, they fulfill their intentions with adequate methodologies, the small sample sizes used, the sheer lack of studies, and the absence of 'real-world' studies makes it difficult to comment on, or foresee the effectiveness of these agents in clinical use.

Regarding nicotine patches, there is a relatively larger amount of research data available. A number of studies strong in methodology and using large sample-sizes have

compared them with other preparations of nicotine. The demonstration of their use in these studies assist the clinician in prescribing them to an index patient, after taking into consideration their particular strengths and weaknesses.

Long-acting preparations of naltrexone have been used in patients with opioid dependence and alcohol dependence. In patients with alcohol dependence, there have been studies demonstrating the use of depot injections. They are few in number, most studies having small study populations, and inadequate methodologies. Those few with strong methodologies have not been able to establish a clear advantage over conventional naltrexone preparations. The scenario in opioid dependent patients is somewhat similar. In 2008, Lobmaier, *et al*.[66] conducted a Cochrane meta-analysis of naltrexone sustained release preparations (included depot injections and implants). After analysis, the authors could comment that depot injections seemed promising, though the overall data was insufficient. Only one study met the inclusion criteria for efficacy analysis. Since then, there have been a few more studies of these agents in opioid dependent patients, with adequate quality of methodology. These studies have shown significant advantages of both implants and depots. Weaknesses remain-the small sample sizes used, the 'artificial' study environment, and the lack of head-to-head comparison studies of these agents with conventional oral naltrexone (especially in the case of depot injections). In addition, the relatively small number of studies makes it premature for us to arrive at any firm conclusions.

The long-acting preparations mentioned in this paper have not become as popular among clinicians as they would be expected to, considering their theoretical promise. Viewing from different perspectives, various explanations seem plausible. Problems inherent to the preparations-their pharmacology, mode of use, possibility of reversal, and adverse effect profile may be a handicap. The reason may be related to the problems inherent to substance use itself. When medications such as disulfiram, naltrexone and buprenorphine initially came into use, pharmacology, mechanisms of action, and effectiveness of these molecules in research trials brought along with them, an air of optimism in the ability of the pharmacological agents to control substance abuse. However, over the years, observing their use in patients, they seem not to have lived up to expectations. A range factors thought to be responsible for the poor performance of these conventional preparations (out of scope of the present paper) may make the long-acting preparation vulnerable too.

Research in this area seems to be vastly insufficient, more so in India. Even the simplest of methods of making a preparation longer acting, by modifying its dosage (described under naltrexone and disulfiram above), which has possible advantages in improving adherence, seems to have found minimal attention in formal clinical study. Other technically more complex methods described above, mostly developed in USA, Europe and other countries, also find little mention in Indian literature.

Many long-acting preparations developed in recent years do have the scope for becoming useful in everyday clinical practice. Further research is vital to devise, develop, and implement safer and more effective agents. Among the preparations developed, studies with strong methodology and adequate patient populations are needed. A greater number of head-to-head comparison trials of the newer agents with the conventional preparations are needed, to identify and establish their benefits and weaknesses. In addition, for all the different medications and target substances of abuse, the optimal blood levels needed are not established. An important research question would be what levels are optimally required, and their degree of correlation with different outcomes (such as reduced craving, reduced frequency of use, complete abstinence, or adverse effects).

Substance use appears eminently suitable for pharmacotherapy with long-acting preparations, as these agents hold promise for better adherence in substance users. This will require focused research and spreading of knowledge, enthusiasm and commitment from all concerned.

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