International Journal of Pharma Research and Technology

Review on Opioid Addiction and Therapy

Shinde V.R.[1*] , Thorat N.V.[2]
Sanjivani College of Pharmaceutical Education & Research Kopargaon, 423603
Sanjivani College of Pharmaceutical Education & Research Kopargaon, 423603
vsk.vision11@gmail.com

Abstract

The primary pharmacotherapies for treating opioid addiction are covered in this article. Treatment options include quick detoxification methods, buprenorphine, adrenergic agonists such clonidine and lofexidine, and detoxification utilising tapering methadone. Methadone is most frequently used in opioid maintenance therapy (OMT). Also mentioned is OMT using additional opioid agonists, buprenorphine, or buprenorphine with naloxone. The usage of oral and sustained-release naltrexone formulations for relapse prevention as well as the opioid antagonists naloxone (for the treatment of intoxication and overdose) and naltrexone are also taken into consideration. Although recent discoveries about the neuroscience of addiction may result in the creation of novel pharmaceutical medicines for the management of addictive diseases, improving the efficacy of currently available therapies remains a significant problem. For opioid addiction, pharmacotherapy alone is frequently insufficient; a full course of treatment should also include efficient psychological support or other therapies. The most successful approach to treating opioid addiction involves combining pharmacotherapies with patient-specific psychosocial support techniques.

Keywords: Opioid dependence. drug methadone, drug buprenorphine.

Introduction

In Europe, there are 1.5 million problem opioid users, and the downward trend that began in 2000 looks to have reversed itself in recent years[1]. On society, illicit opioid use has a significant influence. Increased illness and mortality, marginalization, and criminal activity, including a sizable black market economy fueled by drug trafficking, are all part of it. Different national initiatives have been used to offer specialized therapy for opioid addicts as well as medical services. Opioid maintenance therapy has been one of the most often employed therapeutic techniques for the control of opioid addiction (OMT). 530,000 Europeans were enrolled in OMT in 2005, and 80% of them were receiving methadone and 19% were receiving buprenorphine[2]. Opioid addiction is characterized by persistent alterations in the mesolimbic dopaminergic system, including tolerance for the euphoric effects (liking) and sensitization to the drug-use incentive (wanting). Opioid receptors become desensitized and down-regulated when they are exposed to the drug repeatedly. Unless greater amounts are consumed, opioid tolerance increases, but the temptation to use narcotics is sensitized for a considerably longer period of time. This essay examines opioid detoxification procedures, methadone and buprenorphine maintenance, as well as other agonist substitution techniques, and it also takes into account more recent methods of relapse prevention using opioid antagonists.

www.ijprt.com https://doi.org/10.5281/zenodo.7467643

Detoxification from Opioids

Drug withdrawal, often known as "detoxification," is a component of abstinence-focused therapy. Detoxification's intended function is frequently misunderstood. When a physically dependent drug user quits using drugs, detoxification should remove or significantly lessen their withdrawal symptoms. The severity of the symptoms, the length of the withdrawal phase, and the percentage of programmers that are completed should be the primary factors used to evaluate the efficiency of detoxification. Many detoxification techniques are successful in the sense that they enable abstinence transitions with relatively mild withdrawal symptoms. Detoxification may, however, be successful in terms of the aforementioned criteria, but it still doesn't address the psychosocial and other elements that could ultimately cause relapse. High rates of relapse result from treating opiate addiction alone through detoxification. Usually, relapse prevention or rehabilitation programmes are necessary to supplement detoxification. Patients who underwent detoxification consistently had lower outcomes than those who got outpatient drug-free treatment, methadone maintenance, or therapeutic communities [3]. Detoxification has been the subject of numerous therapies. These include buprenorphine, symptomatic medicines, clonidine, lofexidine, other adrenergic agonists, tapered methadone, tapered methadone plus adjunctive medication, and other opioid agonists. One of the most popular techniques is progressively lowering the oral methadone doses over the course of a few weeks (usually) while substituting an equivalent amount of methadone for the illegal opiates. The most effective pharmacotherapeutic drug currently used in detoxification has been cited as methadone [4,5]. Prior to withdrawal, methadone is typically used instead of heroin, and detoxification is accomplished by progressively lowering methadone dosages over intervals of 10 to 28 days . Due to its dual agonist and antagonist activity, buprenorphine can also be utilized for detoxification. As a detoxification treatment, buprenorphine was found to be as effective as methadone, with the benefit that withdrawal symptoms may subside more quickly with buprenorphine. In terms of detoxification, buprenorphine outperforms clonidine [6]. When receiving buprenorphine treatment rather than methamphetamine, patients who are codependent on opioids and benzodiazepines report less severe withdrawal symptoms and are more likely to successfully complete detoxification[11]. Clonidine and lofexidine, centrally acting alpha-2 adrenergic agonists, decrease noradrenergic neuronal activity and noradrenaline turnover. Clonidine quickly and significantly reduces withdrawal symptoms . Clonidine only partially relieves symptoms, therefore patients frequently need extra medicine (hypnotics are commonly needed) to treat lingering symptoms. The way that clonidine can be utilised may also be constrained by its hypotensive effects. Compared to clonidine, lofexidine has a similar clinical effectiveness but less adverse effects, most notably postural hypotension [7]. Lofexidine can be used to detoxify the body in as little as 5 days. There are now a number of investigations, including double-blind, controlled clinical trials, that have produced encouraging results regarding the efficacy of lofex-idine [8]. There have been efforts to create ultra-rapid opioid detoxification procedures that last anything from a few days to just a few hours. For instance, opioid antagonists have been used to generate a severe withdrawal state that can be mitigated by taking an alpha-2 agonist and/or benzodiazepines that cause drowsiness at the same time. The patient has been anaesthetized and mechanically ventilated while an ultra-rapid detoxification procedure has been tried. The utilization of procedures involving prolonged general anaesthesia exposure of opioid-dependent patients raises serious safety issues. Ultra-rapid detoxification has not been found to significantly increase heroin abstinence rates at follow-up compared to buprenorphine or clonidine tapering regimens, despite reports of potentially fatal side effects [9]. The use of ultra-rapid opioid detoxification outside of research settings is currently not justified due to its dubious benefits. Inpatient specialty units, mental wards, outpatient clinics, primary care settings, and jails can all offer detoxification services. Despite persistently low completion rates for outpatient programmes, outpatient detoxification for opioid

www.ijprt.com https://doi.org/10.5281/zenodo.7467643

abusers is routinely employed in several countries. Although opiate detoxification is possible in an outpatient setting, it is less likely to be successful when tried there. Outpatient detoxification programmes frequently have low success rates, with many addicts not completing care [10]. The achievement of a drug-free state is not a risk-neutral event, despite the fact that detoxification offers a variety of prospects for benefits. An initial relapse to opioid usage frequently happens very soon after leaving the programme among patients who have undergone detoxification in inpatient or residential settings [11]. The person is at danger of overdosing if they begin using opioids because of the reduction or loss of tolerance that happens during and after detoxification. Drug overdose continues to be one of the most common causes of mortality among drug users, and more fatal overdoses have been recorded among opioid abusers who have just completed detox . The possible hazards of overdose among patients who have successfully stopped using opioids and have lost their tolerance to their effects must be taken into consideration by detoxification programmes.

Opioid Maintenance Therapy (OMT)

Contrary to detoxification, the goal of opioid maintenance is not to become drug-free, but rather to prevent illicit drug usage and make it possible for the user to live without the complications that come with it. OMT aims to lessen damages and expenses for society while increasing the individual's quality of life and psychosocial functioning. Any opioid medication may theoretically work in OMT, also known as agonist replacement therapy or agonist substitution. Methadone is the most commonly utilized drug, but buprenorphine use is rising. The selection of an OMT drug should be made based on acceptability and practicability of factors such side effects, stabilizing properties, dose frequency, and control methods. Drugs that are opioids have to be secure for long-term, high dosage use**.**

Methadone

Methadone has a strong affinity for opioid receptors and is a complete agonist. It has a high bioavailability and is almost entirely absorbed when taken orally. The half-life of methadone is approximately 24 hours, with a range of 13 to 50 hours. Methadone is slowly metabolized, reaching peak plasma levels in 2 to 4 hours after injection. A patient who has been stabilized can typically take the medicine once daily without experiencing withdrawal symptoms before the next day's intake [12]. OMT with methadone was initially developed using a stringent paradigm that included controlled environment detoxification followed by gradually increasing dose beginning at 10- 30 mg per day. In clinical practice, it's crucial that doses be increased gradually, under supervision, with periodic urinary tests for the use of other medications, and with ongoing clinical effect monitoring. Patients may receive substantially bigger doses on the first day of treatment and may not have undergone a detoxification process previously. Treatment is now started in both inpatient and outpatient settings. Because methadone's slow metabolism may result in buildup and because other medications may have additive effects on sedation and respiratory depression, it is crucial to closely evaluate symptoms during the first two hours after consumption. The initial several weeks of treatment could have a higher mortality risk. Flexible, high-dose techniques are the most successful, according to meta-analyses [13]. The range of daily doses advised is 60-100 mg, occasionally up to 120 mg.

Methadone's therapeutic effects have been thoroughly examined, and two recent systematic Cochrane reviews backed up its efficacy in terms of improving treatment retention and lowering heroin use .According to the first comprehensive meta-analytic assessment [14], OMT has a favorable impact on criminal behavior, risk-taking for HIV infection, and illegal heroin usage (with moderate to large effect sizes ranging from 0.22 for HIV risk-taking to 0.70 for drug-related crime). Strong support for OMT is provided by this review for the chosen parameters. However, as the author notes, conclusions are only applicable to people who seek and continue treatment. Additionally, the results of numerous longitudinal cohort studies show that people who complete their treatment have significantly lower mortality and crime rates as well as improved health, even when an

intention-to-treat (ITT) method is used [15]. There are signs of reduced HIV risk behaviors, and some studies also indicate better life quality. Prospective longitudinal studies have found that treatment has definite advantages and that stopping treatment—especially involuntarily—is followed by an increase in mortality and crime [16]. Further research is needed on a number of issues, including the usage and frequency of urine testing, take-home dose restrictions and dispensing laws, decentralized versus centralized therapy, and the need for and nature of supplementary psychosocial support. During methadone commencement and stabilization, daily dispensing and supervised consumption are typically advised, with frequency decreasing in accordance with clinical improvement. Regular urine testing may also be necessary in this situation. Although methadone is typically thought to have few long-term issues, there have been reports of cardiac adverse effects with dose-dependent QTc prolongation[17]. Estimates of mortality show that major incidents are uncommon. It is crucial to perform routine medical exams while undergoing OMT, especially when doses are raised. Concurrent use of other drugs should be avoided if at all possible because it may extend QTc time. Opioid maintenance has been suggested for inmates who are opioid-dependent, in part to reduce risky behaviours while they are incarcerated but also to lower the high risk of relapse and overdose mortality after release. OMT should be continued for some patients while they are incarcerated, and it should be started before release for opioid-dependent prisoners who are not getting OMT [18]. For patients with HIV, OMT is advised to reduce risk behaviors such needle sharing and to improve adherence to medications like antiretroviral therapy [19]. The use of methadone during pregnancy is more debatable. OMT is useful in preventing dependent ladies from using heroin in an unrestrained manner. It shields the foetus from withdrawal, which causes intrauterine stress in women receiving methadone treatment . Neonatal abstinence syndrome, however, will require care for a significant portion of neonates [18]. Children exposed to opioid drugs are frequently born slightly prematurely with lower length and head circumference, but these issues appear to go away with proper postnatal care. There hasn't been enough study done on the long-term impacts.

Buprenorphine

An artificial opioid that binds to the -opioid receptor is buprenorphine. Buprenorphine has a lower maximal action at the receptor as a partial agonist than complete agonists do. At roughly 16–20 mg, a ceiling effect is reached. Although buprenorphine is anticipated to cause less intoxication, it might be less useful for patients who require high dosage OMT. The almost irreversible binding of buprenorphine to the receptor and the delayed dissociation from the receptor [20]. If buprenorphine is taken initially, other opioids won't be able to displace it, even in high dosages. It will displace the majority of other opioids from the receptor. Due to these factors, buprenorphine users who previously used other opioids may experience withdrawal symptoms more quickly, however buprenorphine maintenance may shield patients from overdosing on additional opioids . Buprenorphine's bioavailability is just 16% when taken orally, but when administered sublingually, it rises to 20–40% . Buprenorphine can be administered once daily or even three times per week due to its potent binding to the opioid receptor, active metabolite norbuprenorphine, recirculation in the enterohepatic system, and potential depot action in the oral mucosa [21]. The tight binding may make it difficult to utilise naltrexone or naloxone to reverse the effects of opioids. Studies comparing buprenorphine and methadone maintenance at fixed doses , flexible dosing studies of the two medications, and placebo-controlled trials have all provided evidence for the effectiveness of buprenorphine maintenance. The outcome measures for the many trials vary somewhat, although treatment retention is the result that is most usually reported. Other indicators include opiate use (self-reported and determined by a urine test), cocaine use, the use of illegal benzodiazepines, and criminal activities. When administered at medium and high doses (up to 16 mg/day), buprenorphine has been found to reduce opioid consumption more effectively than a placebo, but not in low levels [22]. In certain

www.ijprt.com https://doi.org/10.5281/zenodo.7467643

trials, buprenorphine performs worse than methadone when administered in equivalent dosages. This might be because patients are unable to obtain an appropriate degree of substitution with the help of the drug due to the ceiling effect of buprenorphine, which is reached at higher doses. Buprenorphine's partial agonist-antagonist pharmacology has been cited as support for its usage in less regulated OMT programmes, such as prescription in general practise.

Buprenorphine has been widely used in general practise in France due to particular regulatory circumstances. Buprenorphine prescriptions have been permitted by certified medical practitioners since 1996 without the need for any further training or authorization. Buprenorphine is prescribed by as many as 20% of French doctors to a small number of patients each, and they treat more than 50% of heroin addicts who have problems [23]. Although the physicians' inadequate training has drawn criticism, overall this technique has been deemed successful due to declines in mortality, criminality, and infant opioid withdrawal [24]. Rapid switching between methadone and buprenorphine may result in abstinence responses. Therefore, the methadone dosage should be gradually decreased to around 30 mg/day prior to starting buprenorphine. By doing this, the withdrawal symptoms will be minimized and might only include minor dysphoria . Buprenorphine has not been found to have any teratogenic effects[25]. Early research found little to no neonatal withdrawal symptoms following maternal buprenorphine exposure, but later research suggests that there aren't many distinctions between buprenorphine and methadone [26,27].

Buprenorphine-Naloxone

To prevent misuse by injection, methadone is typically made into syrup by combining it with sugar. Sublingual administration of buprenorphine tablets is preferred, but injections can be abused and misdirected. A substance called Suboxone that contains both buprenorphine and naloxone was created as a result of this. Buprenorphine and naloxone together are less appealing for diversion because of the limited bioavailability of naloxone when taken sublingually, but the drug has a high bioavailability when it is injected. In terms of retaining and using opioids, suboxone is probably just as effective as buprenorphine [28], and studies suggest that this medication can be administered with less supervision and with a lower risk of diversion [29].

Other Opioid Agonists

Although all opioids, in theory, may be appropriate for OMT, only four have been utilized frequently: heroin, slow-release oral morphine, codeine, and LAAM. In 1887, morphine was converted into heroin (diacetylmorphine), which has been prescribed in the UK since 1927. Heroin is a pro-drug that has no agonist effects, but it quickly crosses the blood-brain barrier and is converted within 5 to 15 minutes to the active substance 6-monoacetylmorphine (6-MAM). The elimination half-life of 6-MAM is around 30 min, whereas that of its metabolite, morphine, is 2-4 h. To prevent withdrawal, heroin must be injected every 4-6 hours. Because of its low intestinal absorption, heroin must be shot or inhaled.

Even seasoned drug users are unable to tell heroin from other short-acting opioids like hydromorphone [30]. Although it has a lengthy history, heroin is still just a minimally effective therapy choice in the UK. Its utility is suggested by some British study and more thorough studies from Germany, the Netherlands, and Switzerland, as well as Switzerland [31]. About 1,000 heroin users who had previously not participated in OMT or who had previously failed OMT were involved in the German randomized controlled trial (RCT). Participants from the two target populations were randomized to one of eight research arms, where they received psychosocial assistance, heroin-assisted treatment, or methadone maintenance. The ITT analyses revealed better gains in retention, physical and mental health for the heroin group. However, compared to the methadone group, heroin treatment participants had a higher rate of non-fatal overdoses. There was no discernible benefit to heroin over methadone maintenance, according to a Cochrane review [32]. In the UK, Spain, Canada, and other nations, more heroin trials are planned or already underway. Despite the lack of well-developed patient selection criteria, heroin seems to help users who are

hard to reach and keep on methadone maintenance. In nations with well-established methadone and buprenorphine maintenance programmes, the cost-effectiveness of heroin maintenance is more debatable, and it is likely to remain an additional choice. In a number of nations, oral morphine with a slow release has been utilized for OMT. Over the course of roughly ten years, a unique formulation (morphine sulphate pentahydrate, Substitol) has become a mainstay in OMT. Once per day, substitute is provided orally in capsule form, with supervised dispensing being advised. Despite the paucity of evidence, studies suggest that SROM is a treatment option on par with methadone [33]. Patients can switch from methadone to SROM without experiencing any subjective discomfort or worsening, and some even report feeling better. Patients who are intolerant to methadone have also been advised to try SROM. Future research will still be necessary to determine SROM's role. A mild opioid with common use is codeine. Tolerance and reliance are known issues, and it is virtually solely used to manage pain [34]. The medication has some acceptance as a maintenance drug and can be used to ease opioid withdrawal. This might be as a result of improved accessibility brought on by lax laws. Although codeine has some agonistic effects, it mostly works through the 10% fraction that the hepatic enzyme CYP2D6 converts to morphine [35]. The amount of codeine metabolized into morphine varies genetically and is influenced by this enzyme's ability to function. Nearly 10% of Caucasians have slow metabolisms and receive just a modest amount of analgesia from codeine, compared to 1% who have fast metabolisms and receive substantially larger morphine concentrations. Codeine is inappropriate for OMT due to these characteristics. There is no proof that any benefit exists beyond simple accessibility. Levomethadyl acetate hydrochloride (LAAM), an oral prodrug, breaks down into two active components over the course of two to three days. This provides the medication a desirable profile with long-lasting effects that start off gradually. In particular with well-functioning patients, LAAM has been found to have effects that are equivalent to or even superior to those of methadone [36], but it was taken off the market when it was discovered that it could result in significant cardiac arrhythmia by extending QTc intervals.

Antagonists: Naloxone and Naltrexone

Naloxone for the Treatment of Opioid Overdose and Intoxication.

Naloxone has a strong affinity for the -opioid receptor and is a short-acting, non-selective, specific opioid receptor antagonist. The oral bioavailability of naloxone is less than 1% because of the significant first-pass metabolism it undergoes in the liver [37]. The elimination half-life and duration of effect when given intravenously are around 70 minutes and 3–4 hours, respectively. Naloxone displaces opioid receptor agonists by competing with them. Through this method of action, opioid intoxication, including respiratory depression, sedation, and hypotension, is successfully reversed [38]. Naloxone is administered intravenously in doses of up to 2 mg to reverse opioid overdose. Within a few minutes, the start of the action becomes clinically obvious. Bolus injections of 0.4–2 mg can be continued until an effect is felt if no clinical impact is seen. An opioid overdose is deemed unlikely if after 10 mg there is no noticeable effect. Naloxone has a shorter half-life than long-acting opioids like methadone or SROM, thus many intramuscular injections of 0.4 mg are required to have a prolonged effect. Naloxone should be provided gradually and titrated against clinical effects, such as vigilance and the reversal of respiratory depression, because it causes withdrawal and drug seeking in opioid-dependent people.

Oral Naltrexone for Treatment of Opioid Dependence

Naltrexone is pharmacodynamically comparable to naloxone but more potent and long-lasting when taken orally. Naltrexone's oral bioavailability varies from 5 to 40%, and its peak plasma levels are attained in under one hour. Systematic reviews evaluating the effectiveness of oral naltrexone for preventing relapse to opioid addiction have been conducted, with dosages ranging from 50–100 mg of oral naltrexone taken daily to three times per week (100–150 mg). Comparisons between oral naltrexone with or without psychosocial counseling, a placebo with or without

psychosocial counseling, and psychosocial counseling alone were made [39,40].According to the Cochrane study, naltrexone alone or in combination with psychosocial counseling was more effective at reducing heroin usage than placebo alone or in combination with such counseling. When the combined data from studies without psychosocial counseling were excluded, this drop was not discernible. Comparing oral naltrexone to psychosocial counseling alone, oral naltrexone was more effective at lowering the rate of re-incarcerations. In the 10 RCTs, oral naltrexone had no positive impact on heroin relapse or treatment adherence. Patients receiving naltrexone were not shown to experience side effects any more frequently than other patients. This result is consistent with past observations of vague, mild, and temporary adverse effects, like headache, nausea, vomiting, restlessness, and muscle discomfort, which frequently resemble opiate withdrawal [41]. The superiority of buprenorphine was demonstrated in a double-blind RCT comparing oral naltrexone, buprenorphine, and placebo. Patients with heroin addiction kept on buprenorphine stayed in therapy longer and returned to heroin use later than those kept on naltrexone or a placebo. Oral naltrexone was not proven to be superior to a placebo for these outcomes. Previous studies on oral naltrexone have found substantial treatment attrition rates and limited patient interest. But specific subgroups with strong external motivation might gain from oral naltrexone therapy. Oral naltrexone treatment coupled with psychosocial counseling is said to be well tolerated by addicted business executives risking their careers and parolees [42].

Sustained-Release Naltrexone for Treatment of Opioid Dependence

In the 1970s, it was suggested that long-acting medications be created to increase oral naltrexone's poor treatment retention Sustained-release naltrexone was made available for research in bigger clinical trials by the end of the 1990s. Although encouraging, there is still a dearth of data to assess its efficacy. There have been three RCTs on two different sustained-release formulations. The injectable naltrexone depot Vivitrol was studied in the first placebo-controlled trial to treat heroin addiction [43]. The 384 mg of naltrexone in the injectable formulation was released gradually over a month. More patients who received the 384 mg depot remained in the programme than those who received the placebo. They also offered fewer urine samples that tested positive for opioids and expressed less desire for heroin. The FDA has just yet to approve this naltrexone depot for the treatment of opiate addiction. Another trial looked into an implant that released roughly 2.2 g of naltrexone over the course of 5–6 months. Naltrexone implants added to standard aftercare as a follow-up six months after inpatient treatment ended led to higher drops in heroin usage than standard aftercare alone. In a recent double-blind, double-placebo randomized experiment, it was found that an implant delivering naltrexone for 3–4 months reduced heroin usage and increased treatment retention more than oral naltrexone. Given that the use of opiate analgesia is virtually forbidden during therapy with sustained-release naltrexone, office-based pain management may be difficult. There are reports of patients who had effective analgesia from non-opioid analgesics or a regional nerve blockade [44].

Future Challenges

The more efficient distribution of methadone and other agonist medications is a significant hurdle. A comprehensive treatment should also involve adequate psychological support or appropriate pharmacotherapy's targeting other substances, notably co-dependent usage of other drugs [45]. Pharmacotherapy for opioid addiction is typically insufficient on its own. With more nations offering OMT as the primary therapy option to more patients, progress is being made in this area. But there are still some nations that limit how effectively OMT is provided. National legislation, a lack of provider knowledge, or cultural perceptions that view addiction as a morally wrong behavior rather than a medical problem that can be treated with medication are possible causes of limited access to treatment. The application of OMT in situations where there is disagreement, like prison or during pregnancy, needs

www.ijprt.com https://doi.org/10.5281/zenodo.7467643

more study. OMT must be evaluated in longitudinal cohort studies that follow patients for many years or even decades because it is a long-term treatment. Heroin maintenance seems to be a good, although pricey, option for treating difficult-to-reach subgroups. Additionally, OMT may need to be modified to accommodate addicts who are unwilling to seek assistance from current treatment providers; these adaptations depend on local or national policies. Modifications could involve switching to low- or high-threshold intake criteria, centralized specialist treatment, or France's general practice approach to prescribing buprenorphine, among other things.

Conclusion

Although many different drugs have been attempted as addiction treatments, only a small number have been proven to be successful. Agonist maintenance is the major method of treating opioid addiction, and methadone or buprenorphine are the drugs that are used the most frequently. A number of advances in recent years have aided in the advancement of the creation of drugs to treat addictions. The results of recent studies have shed light on how drugs affect the brain, which has prompted the development of new pharmacological methods for treating addiction diseases. New pharmacotherapies for the treatment of addictive disorders may be developed as a result of recent improvements in our understanding of the neuroscience of addictions. Further research is required on novel therapies such naltrexone depot injections and implants that temporarily prevent relapse. Vaccine research has been ongoing for a number of years, and they represent a sophisticated alternative to opiate therapy. But none of the upcoming pharmaceutical treatments is anticipated to act as a "miracle cure" for opiate addiction. As long as poly-drug use is not addressed, opioid maintenance medications, naltrexone, or upcoming vaccinations alone are usually insufficient. It is a tough and expensive task to combine pharmacotherapies with individualized psychosocial support techniques. However, this integrated approach to treatment is the most thorough way to support the long-term behaviour change required to effectively treat opioid addiction.

Acknowledgement

The authors are thankful to the Sanjivani College of Pharmaceutical Education & Research Kopargaon (India) for unconditional support for the work.

Reference:

1. Hedrich, Dagmar, Alessandro Pirona, And Lucas Wiessing. "From Margin To Mainstream: The Evolution Of Harm Reduction Responses To Problem Drug Use In Europe." *Drugs: Education, Prevention And Policy* 15.6 (2008): 503-517.
2. Nestler, Eric J. "Molecular Basis Of Long-Term Plasticity Underlying Addiction." *Nature Reviews Neuroscience* 2.2 (2001): 119-128.
3. Robinson, Terry E., And Kent C. Berridge. "The Psychology And Neurobiology Of Addiction: An Incentive–Sensitization View." *Addiction* 95.8s2 (2000): 91-117.
4. Simpson, Dennis Dwayne, And Saul B. Sells, Eds. *Opioid Addiction And Treatment: A 12-Year Follow-Up*. Krieger Publishing Company, 1990.
5. Ratnasabapathy, Y., Et Al. "Blood Pressure Lowering Interventions For Preventing Dementia In Patients With Cerebrovascular Disease (Protocol)." *Cochrane Database Syst. Rev* (2003).
6. Kreek, Mary Jeanne. "Methadone-Related Opioid Agonist Pharmacotherapy For Heroin Addiction: History, Recent Molecular And Neurochemical Research And Future In Mainstream Medicine." *Annals Of The New York Academy Of Sciences* 909.1 (2000): 186-216.
7. Amato, Laura, Et Al. "Methadone At Tapered Doses For The Management Of Opioid Withdrawal." *Cochrane Database Of Systematic Reviews* 2 (2003).
8. Gossop, Michael, Et Al. "Opiate Withdrawal Symptoms In Response To 10-Day And 21-Day Methadone Withdrawal Programmes." *The British Journal Of Psychiatry* 154.3 (1989): 360-363.
9. Strang, John, And Michael Gossop. "Comparison Of Linear Versus Inverse Exponential Methadone Reduction Curves In The Detoxification Of Opiate Addicts." *Addictive Behaviors* 15.6 (1990): 541-547.
10. Gowing, Linda, Robert Ali, And Jason M. White. "Buprenorphine For The Management Of Opioid Withdrawal." *Cochrane Database Of Systematic Reviews* 3 (2009).
11. Reed, Laurence J., Et Al. "Comparison Of Buprenorphine And Methadone In The Treatment Of Opiate Withdrawal: Possible Advantages Of Buprenorphine For The Treatment Of Opiate-Benzodiazepine Codependent Patients?." *Journal Of Clinical Psychopharmacology* 27.2 (2007): 188-192.
12. Gossop, Michael. "Clonidine And The Treatment Of The

Opiate Withdrawal Syndrome." *Drug And Alcohol Dependence* 21.3 (1988): 253-259.
13. Buntwal, N., Et Al. "Naltrexone And Lofexidine Combination Treatment Compared With Conventional Lofexidine Treatment For In-Patient Opiate Detoxification." *Drug And Alcohol Dependence* 59.2 (2000): 183-188.
14. Bearn, Jennifer, Michael Gossop, And John Strang. "Accelerated Lofexidine Treatment Regimen Compared With Conventional Lofexidine And Methadone Treatment For In-Patient Opiate Detoxification." *Drug And Alcohol Dependence* 50.3 (1998): 227-232.
15. Strang, John, Jenny Bear, And Michael Gossop. "Lofexidine For Opiate Detoxification: Review Of Recent Randomised And Open Controlled Trials." *American Journal On Addictions* 8.4 (1999): 337-348.
16. Bearn, Jennifer. "Rapid Opiate Detoxification Treatments." *Drug And Alcohol Review* 18.1 (1999): 75-81.
17. Collins, Eric D., Et Al. "Anesthesia-Assisted Vs Buprenorphine-Or Clonidine-Assisted Heroin Detoxification And Naltrexone Induction: A Randomized Trial." *Jama* 294.8 (2005): 903-913.
18. Unnithan, Sujata, Michael Gossop, And John Strang. "Factors Associated With Relapse Among Opiate Addicts In An Out-Patient Detoxification Programme." *The British Journal Of Psychiatry* 161.5 (1992): 654-657.
19. Chutuape, Mary Ann, Et Al. "One-, Three-, And Six-Month Outcomes After Brief Inpatient Opioid Detoxification." *The American Journal Of Drug And Alcohol Abuse* 27.1 (2001): 19-44.
20. Strang, John, Et Al. "Loss Of Tolerance And Overdose Mortality After Inpatient Opiate Detoxification: Follow Up Study." *Bmj* 326.7396 (2003): 959-960.
21. Ward, Jeff, Wayne Hall, And Richard P. Mattick. "Role Of Maintenance Treatment In Opioid Dependence." *The Lancet* 353.9148 (1999): 221-226.
22. Buster, Marcel CA, Giel HA Van Brussel, And Wim Van Den Brink. "An Increase In Overdose Mortality During The First 2 Weeks After Entering Or Re-Entering Methadone Treatment In Amsterdam." *Addiction* 97.8 (2002): 993-1001.
23. . Bao, Yan-Ping, Et Al. "A Meta-Analysis Of Retention In Methadone Maintenance By Dose And Dosing Strategy." *The American Journal Of Drug And Alcohol Abuse* 35.1 (2009): 28-33.
24. Faggiano, Fabrizio, Et Al. "Methadone Maintenance At Different Dosages For Opioid Dependence." *Cochrane Database Of Systematic Reviews* 3 (2003).
25. World Health Organization. Department Of Mental Health, Et Al. *Guidelines For The Psychosocially Assisted Pharmacological Treatment Of Opioid Dependence*. World Health Organization, 2009.
26. Ratkowsky, D. A., Et Al. "Model For Bacterial Culture Growth Rate Throughout The Entire Biokinetic Temperature Range." *Journal Of Bacteriology* 154.3 (1983): 1222-1226.
27. Amato, Laura, Et Al. "An Overview Of Systematic Reviews Of The Effectiveness Of Opiate Maintenance Therapies: Available Evidence To Inform Clinical Practice And Research." *Journal Of Substance Abuse Treatment* 28.4 (2005): 321-329.
28. Marsch, Lisa A. "The Efficacy Of Methadone Maintenance Interventions In Reducing Illicit Opiate Use, HIV Risk Behavior And Criminality: A Meta-Analysis." *Addiction* 93.4 (1998): 515-532.
29. Caplehorn, John RM, Et Al. "Retention In Methadone Maintenance And Heroin Addicts' Risk Of Death." *Addiction* 89.2 (1994): 203-207.
30. Gossop, Michael, Et Al. "Outcomes After Methadone Maintenance And Methadone Reduction Treatments: Two-Year Follow-Up Results From The National Treatment Outcome Research Study." *Drug And Alcohol Dependence* 62.3 (2001): 255-264.
31. Skeie, Ivar, Et Al. "Somatic Health Among Heroin Addicts Before And During Opioid Maintenance Treatment: A Retrospective Cohort Study." *BMC Public Health* 8.1 (2008): 1-8.
32. Clausen, Thomas, Katinka Anchersen, And Helge Waal. "Mortality Prior To, During And After Opioid Maintenance Treatment (OMT): A National Prospective Cross-Registry Study." *Drug And Alcohol Dependence* 94.1-3 (2008): 151-157.
33. Torrens, Marta, Et Al. "Methadone And Quality Of Life." *The Lancet* 353.9158 (1999): 1101.
34. Metzger, David S., Et Al. "Human Immunodeficiency Virus Seroconversion Among Intravenous Drug Users In-And Out-Of-Treatment: An 18-Month Prospective Follow-Up." *Journal Of Acquired Immune Deficiency Syndromes* 6 (1993): 1049-1049.
35. Hubbard, Robert L., S. Gail Craddock, And Jill Anderson. "Overview Of 5-Year Followup Outcomes In The Drug Abuse Treatment Outcome Studies (DATOS)." *Journal Of Substance Abuse Treatment* 25.3 (2003): 125-134.
36. Gossop, Michael, Et Al. "The National Treatment Outcome Research Study (NTORS): 4–5 Year Follow-Up Results." *Addiction* 98.3 (2003): 291-303.
37. Magura, Stephen, And Andrew Rosenblum. "Leaving Methadone Treatment: Lessons Learned, Lessons Forgotten, Lessons Ignored." *The Mount Sinai Journal Of Medicine, New York* 68.1 (2001): 62-74.
38. Ehret, Georg B., Et Al. "Drug-Induced Long QT Syndrome In Injection Drug Users Receiving Methadone: High Frequency In Hospitalized Patients And Risk Factors." *Archives Of Internal Medicine* 166.12 (2006): 1280-1287.
39. Krupitsky, Evgeny M., Et Al. "Naltrexone For Heroin Dependence Treatment In St. Petersburg, Russia." *Journal Of Substance Abuse Treatment* 26.4 (2004): 285-294.
40. Shufman, Emi N., Et Al. "The Efficacy Of Naltrexone In Preventing Reabuse Of Heroin After

Detoxification." *Biological Psychiatry* 35.12 (1994): 935-945.

41. Dolan, Kate A., Et Al. "A Randomised Controlled Trial Of Methadone Maintenance Treatment Versus Wait List Control In An Australian Prison System." *Drug And Alcohol Dependence* 72.1 (2003): 59-65.
42. Kandall, Stephen R., Et Al. "The Methadone-Maintained Pregnancy." *Clinics In Perinatology* 26.1 (1999): 173-183.
43. Comer, Sandra D., Et Al. "Injectable, Sustained-Release Naltrexone For The Treatment Of Opioid Dependence: A Randomized, Placebo-Controlled Trial." *Archives Of General Psychiatry* 63.2 (2006): 210-218.
44. O'Brien, Brian, And Caitriona Cody. "Analgesia And Sedation In The Presence Of A Naltrexone Implant: A Novel Pharmacological Challenge." *European Journal Of Emergency Medicine* 13.5 (2006): 315-316.
45. Bramness, Jørgen G., And Hege Kornør. "Benzodiazepine Prescription For Patients In Opioid Maintenance Treatment In Norway." *Drug And Alcohol Dependence* 90.2-3 (2007): 203-209.