

Long-Term Use of Naltrexone For Opiate Dependence

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Introduction

Opioid dependence causes several familial, occupational, social and medical complications among dependent individuals and their families. One of the treatment options available to treat such individuals is the use of maintenance medication (substitution with an orally active opioid drug, like methadone and buprenorphine), which has proven to be the most effective treatment for opioid dependence. However, opiate antagonists like naltrexone offer a treatment approach that is distinctly different from that of agonist maintenance. These opiate antagonists have been used for some time as antidotes after opiate overdose, but their application in the treatment of opioid dependence is more recent.

Opiate antagonists are substances that bind to the opiate receptors but do not produce morphine like effects. The first clinically useful antagonist was nalorphine, which reduced morphine effects, but also produced some agonist effects. Because of its potential for increasing rather than decreasing respiratory depression, nalorphine has been replaced by naloxone as an antidote for opioid overdose. Naloxone and naltrexone are relatively pure antagonists in that they produce little or no agonist activity at usual doses. Naloxone however has limited utility as a maintenance agent because it is poorly absorbed and has a duration of only a few hours following oral administration. Among the opiate antagonists, naltrexone, which became available for general use in 1985, has emerged as the most extensively studied agent to prevent relapse in opiate dependent patients. Naltrexone is an orally active and long acting potent pure narcotic antagonist.

Structure

Naltrexone was developed by substituting an N-methyl group on the opiate agonist oxymorphone with a methylcyclopropyl moiety.

Pharmacokinetics

Naltrexone is rapidly and completely absorbed following oral administration and reaches peak plasma concentration within an hour. It has high first pass metabolism and oral bioavailability is 60%, with 20% of the drug being bound to plasma proteins.

Naltrexone undergoes first-pass metabolism in the liver via glucuronic acid conjugation with transformation to the active metabolite 6-beta naltrexol. The half-life of this drug is about 4 hours and that of its active metabolite is 10-12 hours.

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Pharmacodynamics

Naltrexone is a non-specific opiate antagonist that binds to all three opiate receptors sites () as a function of dose administered.

The pharmacological duration of naltrexone is longer than might be predicted by the plasma kinetics. The plasma half-life of naltrexone is 4 hours, but the duration of opioid receptor blockade is much higher and a 50 mg dose of naltrexone blocks 25 mg of heroin for 24 hours, 100 mg for 48 hours and 150 mg for 72 hours. This pharmacodynamic property of naltrexone makes it easy to be administered in simple and convenient regimens.

Indications

1. Maintenance treatment for detoxified patients with Opiate dependence.
2. Prevent relapse in patients with Alcohol dependence
3. Opiate detoxification protocols: It has established usefulness when combined with clonidine as part of outpatient detoxification protocols.

Preparations of Naltrexone

50 mg oral tablet in package of 10 tablets

Trade name: Naltima (Intas pharma), Noddict (Sun Pharma)

Cost: Rs 40-45/ tablet depending on the brand.

Long-term use of naltrexone for opiate dependence(as a maintenance agent)

Rationale for use

As an opiate antagonist, naltrexone selectively competes with both exogenously administered opiates for central nervous system (CNS) and non-CNS opiate receptors and blocks their activity. If an individual stabilized on opiate antagonist consumes an opiate agonist like heroin, he will not experience the euphoric effects as the opiate receptors are already blocked and hence not available for the opiate agonist to act. In this manner, over time, the *drug seeking behaviour* becomes extinct. This blockade eventually reduces *craving* and *de-conditioning of cue related craving* as patients are exposed to people, places and things formerly associated with opiate use while being protected from opiate effects. In addition due to the constant occupation of opiate receptors by antagonists, *physical dependence* is not re-established. Since the medication is without any addictive property, diversion is not an issue. Tolerance does not appear to develop to the antagonism of opioid effects even after more than one year of naltrexone ingestion. Cravings for opiates, opiate seeking and using behaviour, if viewed as conditioned responses, should then extinguish as a consequence of not being reinforced.

Thus, a long acting drug like naltrexone is ideal for use in preventing relapse to opioid use.

Evidence base

Patients involved in meaningful relationships, employed full time, or attending school and living with family members are most likely to benefit from naltrexone treatment. Follow up of naltrexone treated patients indicates that 30-40% are opioid free for 6 months after terminating treatment.

However, naltrexone treatment has a very high early dropout rate. Only 10-20% take naltrexone for 6 months or longer, although certain specific motivated populations like **addicted professionals** and **former prisoners** on probation have significantly higher rates of accepting naltrexone and remaining in treatment. This may be due to the fact that naltrexone has no reinforcing properties of its own and is perceived as a subjectively neutral drug that prevents addicts from getting high. Kirchmayer and colleagues in 2002 systematically reviewed controlled clinical trials that there was insufficient evidence to justify naltrexone use in the maintenance of addicts, except to decrease the possibility of reincarceration of prisoners treated with combined behaviour therapy and naltrexone. However a metaanalysis of fifteen studies involving 1071 patients in 2006 found significant heterogeneity in the efficacy of naltrexone. The authors attributed this to the potential moderating effect of treatment retention. This study concluded that retention was the key variable for understanding the mechanisms of the effect of naltrexone in opioid dependence and that the drug may be effective if the retention rate is increased above a certain level.

Patient Selection

Naltrexone therapy is suitable and recommended for patients with the following characteristics:

- ⊙ Younger persons at early stages of opiate dependence.
- ⊙ Persons currently abstinent but concerned about possible relapse and willing to be on a medication that does not produce a high.
- ⊙ Employed individuals and professionals (healthcare workers, lawyers, pilots, business people) facing loss of employment or licensure due to opiate abuse.
- ⊙ Former opiate dependent persons who have been drug-free e.g., in a rehabilitation centre, therapeutic community, or prison and wishing to remain abstinent.
- ⊙ Opiate-dependent persons who prefer to try alternative pharmacotherapy, other than methadone or buprenorphine.
- ⊙ Individuals who have been drug-free but recently relapsed on opiates.

Patients, as well as their support persons, need education on how naltrexone works and the critical importance of compliance with the dosing regimen. *It is advisable to supervise the ingestion of naltrexone either from the treatment centre (by the nurse/pharmacist) or tell a family members like wife, parent to administer the medication.*

Dosage and Administration

Naltrexone is available in 50 mg tablets and the recommended daily dose is 50 mg per day. *Initiating naltrexone maintenance requires that the patient be opiate free.* An opiate antagonist like naltrexone can precipitate an acute withdrawal syndrome in patients who are dependent on or are regular users of opioids. So patients should be detoxified and should be abstinent from short acting opiates (e.g. heroin) for about 3 days and from longer acting opiates (e.g. methadone) for about 7 days or more as judged by self report, urine toxicology screening test and Naloxone Challenge test.

Naloxone testing for residual dependence (Naloxone Challenge test)

It has been advocated that an intravenous or subcutaneous challenge of 0.4-0.8 mg of Inj. Naloxone (if available in the centre) be given prior to the administration of naltrexone to test for residual opioids so that withdrawal signs and symptoms are not precipitated. A positive test indicative of residual opioids would consist of typical signs and symptoms of opiate withdrawal. These include yawning, abdominal cramps, irritability, anxiety, chills etc. These signs and symptoms often last only 30-60 minutes and in such a situation naltrexone should be withheld for at least 24 hours.

Intravenous:

Inject 0.2 mg naloxone.

Observe for 30 seconds for signs or symptoms of withdrawal.

If no evidence of withdrawal, inject 0.6 mg of naloxone.

Observe for an additional 20 minutes.

Subcutaneous:

Administer 0.8 mg naloxone.

Observe for 20 minutes for signs or symptoms of withdrawal.

Note: The naloxone challenge test should not be performed in a patient showing clinical signs or symptoms of opioid withdrawal, or in a patient whose urine contains opioids.

Naltrexone Induction

When the required period of abstinence from opioids is complete as judged by clinical examination and self report, urine toxicology screening test (if available), negative naloxone challenge test (if available), naltrexone can be initiated carefully in the dose of 25mg and if no withdrawals occur after 1 hour then another dose of 25 mg is given. The recommended dosage subsequently is 50mg/ day.

After the first 1-2 weeks, it is usually possible to graduate the patient (50, 75, 100 mg on subsequent days) to three doses per week (100mg on Mondays and Wednesdays and 150mg on Fridays). It may also be give in the dosing regimen of 100mg every other day or 150 mg every third day. As compliance is often poor, these flexible

dosage regimens makes it possible to supervise the ingestion of naltrexone from the treatment centre (directly observed treatment.)

Progress in treatment is determined by psychosocial parameters (e.g finding a job, job performance) and absence of drug abuse as confirmed by urine tests.

Retention/Compliance

Naltrexone maintenance is effective as long as the drug is taken regularly. Despite it's relatively pure antagonist activity and minimal side effects, naltrexone has not been widely accepted by addict and has a very high early dropout rate. This may in part be due to the fact that naltrexone does not have any agonist properties and thus does not induce euphoria. In large multimodal programmes in USA, only 5-10% of opiate dependent patients show an interest in naltrexone at any given point in time and many patients drop out early. Only 10-20% takes naltrexone for 6 months or longer, although its acceptance among (opiate users) certain target groups such as health professionals, employed individuals and former prisoners on parole is high. Retention and compliance have been best in motivated individuals with strong support systems. Conversely, individuals with poor socio-economic supports or few incentives for rehabilitation tend to fare poorly.

However, even short term (30 days or more) treatment with naltrexone has been associated with improved outcome at 6-month follow up. Appropriate patient selection and explanation of need for adequate duration of therapy can reduce the drop out rate. Naltrexone works best in the presence of a structured rehabilitation programme.

Guidelines for providing naltrexone maintenance treatment

- ⊙ Good occupational functioning
- ⊙ Good social support
- ⊙ Higher motivation
- ⊙ Short duration of drug use (3years or less)
- ⊙ Been on agonist maintenance for several months and has achieved good occupational and social functioning
- ⊙ Opts for antagonist maintenance when given a choice
- ⊙ Clearly prepared for abstinence

One or more of the above criteria may be satisfied.

These guidelines should be used along with clinical judgment.

Therapy Duration

No standard duration of therapy is recommended although it is generally used for 6-12 months. It has to be used for a minimum period of 3 months. The guiding principles for discontinuation of therapy are an extended period of opiate abstinence and achievement of stable and significant psychosocial recovery.

Naltrexone as part of a comprehensive treatment programme

Naltrexone works best within a comprehensive treatment programme that deals with all aspects of a patient's problems. Adjunctive psychiatric evaluations, counseling, relapse prevention sessions, coping skills, significant family member involvement and participation in psycho-education group sessions are vitally important and these must be tailored to individual patient needs. Counselling involving families and/or significant others has been repeatedly recommended as beneficial because these persons serve as support and/or coercive agents fostering treatment retention and compliance.

Side effects and contraindications

It has few side effects. Most patients report no symptoms at all and the profile of reported adverse effects includes gastrointestinal distress (nausea, vomiting, diarrhoea, and abdominal pain), anxiety, restlessness, dysphoria, mild hypertension, headache and insomnia. It has been suggested that some effects might be attributed to a mild, temporary abstinence syndrome influenced by naltrexone's complete opiate blockade. These adverse effects are most prominent in the first several days of use and improve rapidly for patients remaining in treatment. Adverse effects can be minimized by ensuring an adequate interval between cessation of opiate use and initiation of naltrexone therapy and by a graduated initial dosage schedule starting with 12.5 or 25 mg daily for the first few days.

The potential for hepatotoxicity at high doses has been raised as a more serious concern. However convincing reports of elevated liver function test results have been limited to patients receiving 250mg to 300mg daily, five to six times higher than the recommended maintenance dosage for opiate dependence. As a precaution, patients should receive a full battery of liver function tests prior to receiving naltrexone, and it is *contraindicated* in patients with liver failure or acute hepatitis. Caution should be exercised in using naltrexone with patients whose levels of liver enzymes are 2-3 times above normal values.

As a guideline, liver function tests should be repeated monthly for the first 3 months and every 3 to 6 months thereafter, if there is no evidence of rising enzyme levels. If persistent elevation in liver enzyme occurs, naltrexone should be discontinued.

Because naltrexone is excreted through the kidneys, caution should be used in patients with severe renal impairment.

It is contraindicated also in persons who are taking opiate agonists

Patients taking naltrexone will lose their tolerance to opioids just as will drug free patients. This means, by definition, that they will be more sensitive and thus vulnerable to overdose if they resume heroin use at

previous levels. Patients should be advised that taking large quantities of exogenous opiates in an attempt to overcome blockade provided by naltrexone can be dangerous. Life threatening opiate intoxication may result including respiratory arrest or circulatory collapse.

In patients requiring elective surgery, cessation of naltrexone 72 hours prior to surgery is recommended.

Safety in pregnant women and in children and adolescents

It is advisable to avoid use in this population as safety and efficacy of naltrexone in this population has yet to be adequately established.

Drug interactions

Because naltrexone is an opiate antagonist, it blocks the pain relieving effects of opiate analgesics. In patients maintained on naltrexone, non-opiate pain medications or approaches should be tried when possible.

The safety and efficacy of combined use of disulfiram and naltrexone are unknown and given that both medications are potentially hepatotoxic, their concomitant use is not routinely recommended.

Increased lethargy and somnolence have been reported with the combined use of naltrexone and thioridazine. If a neuroleptic were required in combination with naltrexone, a nonsedating neuroleptic is preferable. Although formal drug interaction studies have been not been conducted with antidepressant medication the incidence of adverse events reported by patients receiving naltrexone in addition to antidepressants was similar to that of patients receiving naltrexone in a large safety study.

Depot naltrexone

As medication compliance with the oral preparation has been low, the safety and effectiveness of a depot formulation of naltrexone is currently under study.

Characteristics of Naltrexone treatment

- ⊙ Once daily or less frequent oral administration.
- ⊙ Blocks the euphoric effects of opiates.
- ⊙ No psychotropic or reinforcing effects.
- ⊙ Non-addicting with no withdrawal symptoms on cessation.
- ⊙ No tolerance to opiate antagonism.
- ⊙ Absence of serious adverse effects or toxicity even on long-term use.
- ⊙ Essentially no abuse liability.
- ⊙ No potential for diversion.
- ⊙ Relatively easy availability.

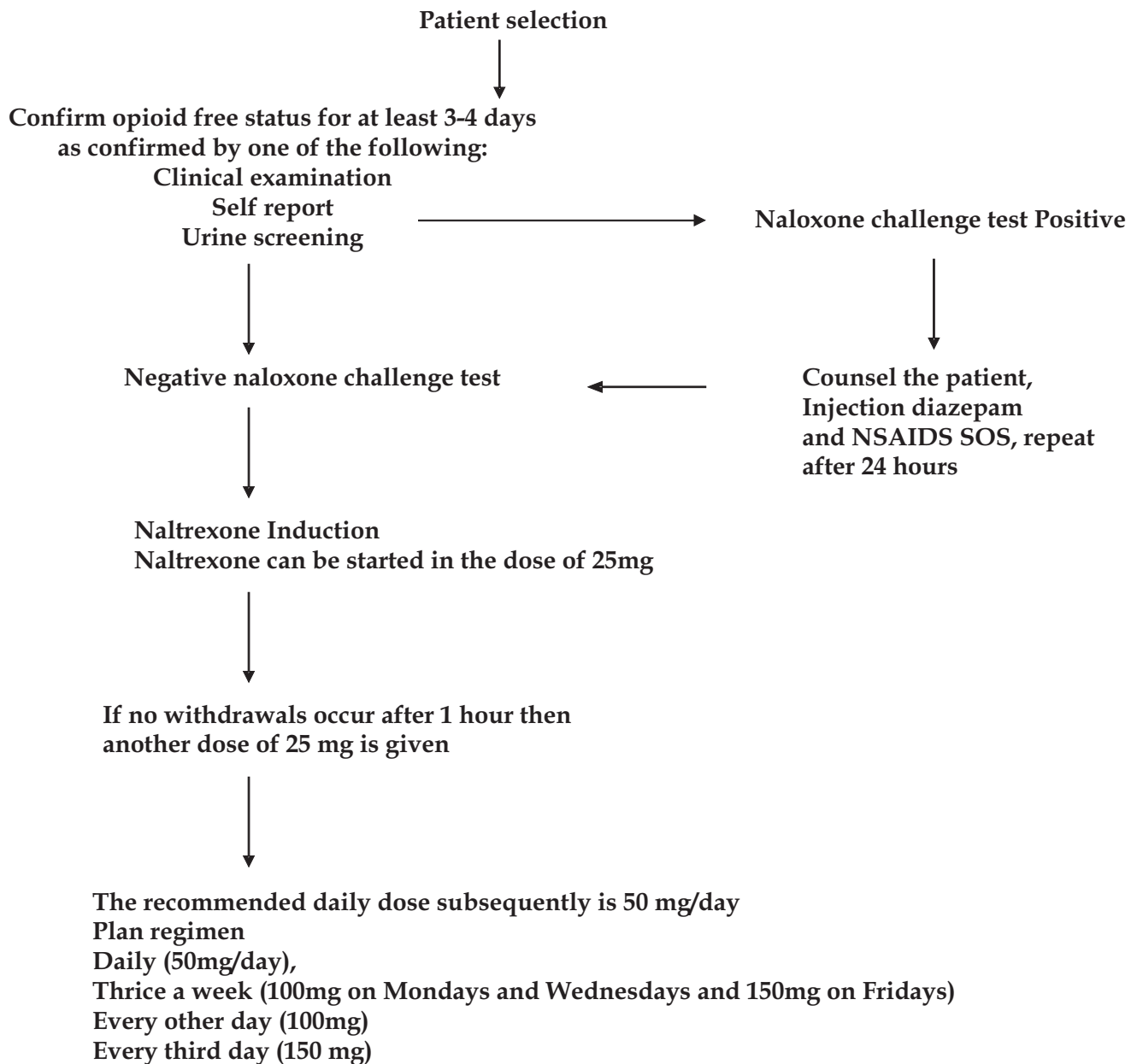
Steps for clinical action

- ⊙ Instill sufficient motivation among patients to begin treatment;
- ⊙ Successfully withdrawing patients from illicit opiates or agonists, and keeping them opiate-free until it is safe to start naltrexone;
- ⊙ Maximizing retention in treatment and compliance while taking naltrexone;
- ⊙ Involving family and/or significant others in the therapeutic process.

The practitioners should consider the following evidence-based conclusions:

1. Naltrexone is effective in a variety of treatment settings where motivation to stay in treatment, avoiding opiate use and taking medications is supported by appropriate psychosocial support.
2. Therapy providing coping skills to identify triggers and avoid relapse if opiate and/or other drug use occurs may be more beneficial than a strict abstinence orientation.
3. Patients and their support persons need education on how naltrexone works and how to use it.
4. Individualized flexible dosing schedules are possible and may be helpful.

Treatment Algorithm for Naltrexone Maintenance for Opioid Dependent Patients



In cases of Buprenorphine/Pentazocine dependence upto 5mg of Naloxone is required for precipitating Opioid withdrawal symptoms

Frequently asked questions

Q1. What should be done if the information regarding opioid use given by the patient and the family member differs in the patients being considered for naltrexone treatment?

Ans. The usual requirement of naltrexone induction is the presence of opioid-free status in the patient for at least for 3-4days (for patients using longer acting opioids up to 7 days of opioid free period are required). If there is any discrepancy in the accounts given by the patient and the family member about opiate-free period, the patient needs to be explained regarding the possibility of precipitated opioid withdrawal syndrome with shorter opioid-free period. In case of further doubts, naltrexone induction may be postponed and initiated after the required period of abstinence.

Q2. What is naloxone challenge test (NCT)?

Ans. Naloxone is an opioid antagonist with plasma half-life of 1 hour in adults. It is inactive orally because of high first pass metabolism in liver. Injected i.v, it acts in 2-3 min. Presence of residual opioid in the body precipitates opioid withdrawal syndrome if intravenous or subcutaneous injection of 0.4-0.8 mg of naloxone is given. These signs and symptoms often last only 30-60 minutes and in such a situation naltrexone should be withheld for at least 24 hours. When the naloxone challenge test is negative, naltrexone can be started immediately.

Q3. What should be done if naloxone is not available at the centre?

Ans. If there is no doubt about opioid-free period, naltrexone can be started without doing naloxone challenge test (NCT). If there is any doubt about opioid-free period, naltrexone induction can be withheld for another 1-2 days.

Q4. Can naltrexone induction be undertaken on the out-patient basis?

Ans. Naltrexone induction can be undertaken at the out-patient or the in-patient basis. For patients being considered for naltrexone induction on the out-patient basis, the most important task lies in ensuring the adequate opioid-free period. As a precautionary measure, naloxone challenge test can be done. If naloxone is not available at the centre, minimum required opioid-free period can be increased to avoid precipitated opioid withdrawal syndrome.

Q5. How long does naltrexone take to work?

Ans. Naltrexone's effect on blocking opioid receptors occurs shortly after taking the first dose. However, it is advisable to allow the drug to reach a steady state levels(i.e. 3-4 days) for complete blockade of exogenous opioid effects.

Q6. At what time of the day, should naltrexone be taken?

Ans. The timing of day has nothing to do with effect/side-effect of naltrexone. However, it should be taken on a fixed time everyday.

Q7. What does it feel like to be on naltrexone?

Ans. Aside from side-effects, which are usually short-lived and mild, patients usually report that they are largely unaware of being on medications. Naltrexone usually has no psychological effects and patients don't feel either "high" or "down" while they are on naltrexone.

Q8. What should be done if a dose of naltrexone is missed?

Ans. After the achievement of steady blood level of naltrexone (i.e. within a week), if a patient misses a single dose, adding up the missed dose is not required. Rather the patient is required to take the usual dose regularly

Q9. For how long does the effect of naltrexone persists after stopping it?

Ans. The effect of naltrexone persists for 24-72 hours depending on the dose of naltrexone used.

Q10. Will the patient get sick if he stops naltrexone suddenly?

Ans. Naltrexone does not cause physical dependence and it can be stopped at any time without withdrawal symptoms.

Q11. What will happen if the patient uses opioids while on naltrexone?

Ans. After stabilization with naltrexone is achieved, use of opioids by the patient will not be able to produce any effect due to blockade of opioid receptors by naltrexone. However, if the patient uses very high doses of opioids to overcome the blockade of receptors produced by naltrexone, life threatening opioid intoxication may result, including respiratory arrest and circulatory collapse.

Q12. What should be done if the patient is regularly using opioids while on naltrexone?

Ans. In such situation, first thing to do would be to check the compliance on naltrexone. The family members should be advised to supervise the intake of naltrexone. After ensuring the compliance, if the situation remains the same, it would be useful to check with the patient if he perceives the effects of opioid. If the patient perceives the effects of opioid, this mean that effective blockade of opioid receptor has not been achieved. In such circumstances, increasing the daily dose of naltrexone to 75-100 mg/day should be considered. Alternatively, patient's motivation to stop using the opioid should be assessed as well.

Q13. What should be done if the patient starts using alcohol or relapses to alcohol use following cessation of opioid use with naltrexone?

Ans. One of the clinical uses of Naltrexone is to reduce craving for alcohol as well. However the above situation may still arise and here it is useful to discuss with the patient the harm due to alcohol use and to motivate him to get additional treatment for alcohol use as well.

Q14. What should be done if the liver function tests (LFT) get deranged while the patient is on naltrexone?

Ans. Convincing reports of elevated liver function test due to naltrexone have been limited to patients receiving 250mg to 300mg daily, five to six times higher than the recommended maintenance dosage for opiate dependence. As a precaution, however patients should receive a full battery of liver function tests prior to receiving naltrexone, and it is *contraindicated* in patients with liver failure or acute hepatitis. If enzyme level rises 2-3 times above normal value, naltrexone should be discontinued till the LFT returns to normal. However, the other potential causes of LFT derangement such as viral hepatitis and alcoholic hepatitis should also be explored and treated accordingly.

Q15. What should be done if the patient needs medication for pain or surgery while on naltrexone?

Ans. In such cases, the patient should carry a card explaining that he is on naltrexone and that should also instruct the physician on pain management. Many pain medications that are not opioids are available for use. If the patient is going for elective surgery, naltrexone should be discontinued at least 72 hours beforehand.

Q16. Are there some people who should not take naltrexone?

Ans. Naltrexone should not be used with pregnant women, individuals with severe liver or kidney damage or with patients who cannot achieve abstinence for at least 3-5 days prior to initiating medications. Also, people who are dependent on opioid drugs, like heroin or morphine must stop their drug use at least 3-7 days prior to starting naltrexone.

Q17. How long should the patient continue naltrexone?

Ans. There is no general rule about exact duration of treatment with naltrexone although most studies recommend a period of 6 months-1 year. The guiding factors are significant period of abstinence from illicit drugs along with stable and significant psychosocial recovery like doing a job, fulfilling family and financial commitments etc.

Suggested reading

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