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Review Article

Latest advances in de-addiction strategies

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In most part of the last century people who were addicted to different drugs, chemicals and substances were viewed from a moral model. An addict represented a spoilt person with anti-social attributes. Depending upon the nature of substance used they were penalized to varying extent and at the very least they were ostracized from social, occupational and family circles[1].

Most of the treatment and litigations were based on this principle and it was the official practice in most countries. It says that one is responsible for one's habit, does out of free will, and is morally bad. Either he/she should be punished or should be responsible to come out through the pain of withdrawal. Addicts used to get dumped into hospitals, rehabilitation centres and prisons. An addict was supposed go through the curse of withdrawal ("sickness") to make them realize the amount of trouble they have given to the society. "Cold turkey" was the official practice, especially in the prisons[2] .

It was not until 1960 when Jellinek published an influential book, *The disease concept of alcohol addiction*, that addicted people started being evaluated form medical model. Addicts started being viewed as people who were ill rather than wicked. With the passage of the decade of the brain in nineties and the knowledge of brain science and neurobiology, modern psychiatry attempts to treat addiction illness on the basis of medical model[3]. Addiction is a disease just like tuberculosis, typhoid, hypertension, multiple sclerosis, depression, etc[4]. It is not something that happens by choice and in the case of opioid dependence applies so much more than in the case of alcohol[5]. In the case of alcohol dependence unhealthy behaviour, lack of health education, ignorance and other psychosocial variables may be equally important. Cloninger[6] went as far as classifying two types of alcoholism and in type-II genetic predisposition was enough and irrespective of the environmental factors the risk of dependence increased by 9 fold.

There is no one-size-fits-all programme for all types of dependence, though there can be an agreement on important principles[4]. From behavioural model addiction basically is a habit of taking substances which are either harmful for the body on chronic use or socially/legally unacceptable. Though there are some cultural influences on soft drugs, the scientific basis of habit formation is clearer than before and treatment of addiction has to be contemplated on the basis of neurobiology at receptor level.

Human brain is the most sophisticated structure in the universe, as it is in interface between the mind of the owner and the external universe. It is also the master organ of the physical body and operates it on the basis of this interaction. Different parts of brain are specialized for different functions. The area called the "reward centre" located around nucleus accumbens and ventral tegmental area (VTA) has been implicated for the addiction. The future behaviour of any animal depends upon how a particular substance or event influences this reward centre. Rewarding behaviours which create a sense of pleasure, euphoria and gratification are repeated frequently and non-rewarding behaviours go into extinction[3].

The psychoactive substances exert their rewarding effect through the receptors in the reward centre. Receptors have been identified for all substances listed in International Classification of Diseases (ICD-10) and Diagnostic Statistical Manual) DSM-IV, except for the inhalants[7].

The worse aspect of substance use is that, on repeated use one develops tolerance and on stopping it suddenly, both physical and psychological withdrawal symptoms manifest. As the molecules erode away from the receptors the autonomic neural regulation is disbalanced[8] and patient experiences horrific, nasty symptoms, which compels them to keep on using the drug, because the memory of withdrawal is so much haunting.

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Detoxification is a procedure which attempts to make the recovery from withdrawal as smooth as possible. Previously when the knowledge of neurobiology was inadequate psychosocial detoxification was the standard, but today medical detoxification with sympathetic attitude is the standard practice in modern centres.

The most important part of the treatment of substance dependence really comes after the detoxification is completed, that is called relapse prevention. The longer the duration of abstinence from the point of detoxification, better the chance of recovery.
There is little information available on relative relapse rates in the reviewed studies. In the case of opioids, reports show that 75% of detoxified patients relapsed into heroin use within 1 month and 80% had relapsed within 3 months[9,10,11].

This is really a big challenge, which is not keeping up with developments in other fields of medicine and surgery. One reason for this is that the traces of memory of the reward is so badly imprinted in the brain that a slightest emotional upheaval in the psychosocial life of the patient makes them fall back on to the drugs. However long the abstinence may be, once even a single dose is reinstated, the patient is trapped in the vicious circle of psychological dependence, physical dependence, withdrawal, which would not let the patient come out of the drug habit.

Some of the latest strategies of de-addiction for substances prevalent in Nepalese context will be discussed.

Opioids
The last century has been frustrated with the very low success rate of what is called "conventional detoxification". Initially it involved intense psychosocial counselling, while the patient went through cold turkey and gradual withdrawal method. At the most few medicines like anxiolytics, anti-histamine, antispasmodics and antipsychotics were used. The rate of completion was always low. And the scientific loophole with this method was that one could never be sure whether all the receptors were completely washed out of the molecules or not. And another important aspect was whether the autonomic neural regulation has been set to the pre-addiction level. This can not be insured until the patient has been challenged with antagonists like naltrexone, naloxone and nalmefene.

Major breakthrough in the treatment of opioid dependence occurred in 1965 when Methadone was started in the treatment of opioid detoxification and withdrawal. More than making the patient abstinent from the drug use, the major philosophy behind its use was harm reduction in terms of unhealthy behaviour, criminal endeavours, sexually transmitted diseases, HIV/AIDS and Hepatitis from needle sharing and social integration. Gradually it became replaced by buprenorphine.

All these conventional methods could not make the process of detoxification short and since there was the uncertainty of complete clearance of addictive molecules from the body, induction and maintenance with opioid-antagonist could never be started. Therefore the rate of completion of detoxification was always low and relapse was alarmingly high.

The latest strategies in detoxification attempts to compact a long detoxification procedure into a very short one so that the patient could be induced into antagonist and maintained on it. This can be achieved by Rapid Opioid Detoxification (ROD) and Ultra-rapid Opioid Detoxification (UROD). In the protocol of ROD the patient is pre-treated with alfa-2 agonists like lofexidine, anti-emetics, benzodiazepines, anti-diarrhoeals, muscle relaxants, NSAIDS and taken into a state of light sedation. Depending upon the amount and frequency of use of opioids the patient is rapidly induced with intravenous naloxone, nalmefene or oral naltrexone at the dose of 12.5 to 50mg. Any aggravation in withdrawal symptoms or haemodynamic disbalance is managed with medications. Only after three supervised doses of naltrexone can one be sure that the patient is detoxified completely[12].

In the protocol of UROD the antagonist induction is done under general anesthesia[12], either with oral naltrexone or naloxone infusion. The whole process is completed within 6 hours and the patient can be discharged on the same day. According to Waisman it is a form of accelerated neural regulation (ANR). Though there is some literature highlighting the complication of this procedure, the results seem to be due to deviation from standard protocols and inadequate supervision and know-how.

There are many studies (long term and short term) in favour of these novel techniques. In a 3 month follow up study comparing UROD with Standard Methadone Maintenance Tapering (SMT), Krabbe et al. [13] found significant differences between abstinence rates. After 1 month, abstinence was 100% for UROD versus 43% for SMT; after 2 months, it was 93% versus 33% and after 3 months, it was 67% versus 33%, respectively. Gerra and colleagues[14] report similar relapse rates at 6 months between naltrexone-clonidine (47%) and clonidine (56%) detoxified patients. However, 74% of

methadone tapering patients had returned to heroin use.

Successful completion of detoxification is an equally important parameter in the overall treatment of opioid dependence. There are several definitions of successful completion of detoxification and ways of describing short-term outcomes. For the purpose of this review successful completion of detoxification is defined as induction onto naltrexone maintenance and/or completion of the detoxification protocol[15]. As may be expected given the nature of the procedure, in all UROD studies, all patients were inducted on naltrexone and completed the detoxification protocol. In the ROD studies, the majority of patients were inducted on to naltrexone, 100%[9,16] to 80%[17] to 75%[14]. In terms of rates of induction to naltrexone compared with other forms of detoxification, Gerra and colleagues[14] randomly allocated patients to detoxification using clonidine and naltrexone, clonidine alone, and 10-day methadone tapering. 75% of the clonidine-naltrexone group commenced naltrexone maintenance which was significantly higher than those commencing naltrexone in the clonidine group (53.1%, $p<.05$) and methadone-tapering group (26.4%, $p<.01$).

The high rate of relapse is the biggest challenge in opioid dependence and the era of methadone maintenance could neither decrease the relapse, neither the health or social/criminal risk behaviour. And it is not allowed in many countries including Nepal. In Nepal the government mental hospital ran it for few years but ultimately stopped it few years ago.

If we are to look at opioid addiction from a neurobiological viewpoint, methadone maintenance is less acceptable. Chronic mu-receptor stimulation is leads to alteration in autonomic homeostasis and decrease in muscle sympathetic activity (MSA) [18], which predisposes to various chronic diseases in the brain and the circulatory system. Secondly the conceptualization on methadone maintenance treatment (MMT) does not involve the idea of getting out the patient from opioid use. Third controversy is that there should be provision for indefinite supply of methadone, usually from the government side. Lastly antagonist induction and maintenance never come into the picture.

At least in the Nepalese context, use of naltrexone (or other antagonist) under supervision seems to be the only way one can make sure that the patient is no more using the opioids. Naltrexone is a complete antagonist of opioid receptor, not habit forming, long acting and minimal side effects. Fifty milligram of naltrexone can antagonize 25 mg of heroin. The draw back of oral naltrexone is that there is low compliance and constant supervision is necessary. It has been found that whenever the patient wants to restart the drug they devise ingenious methods to discard it from the mouth.

The solution to such problem is the use of slow release depot of naltrexone in the form of "implants" [19, 20, 21] which has been developed by O'Neil George. These are small pellets which are put in the subcutaneous tissue of the abdominal skin or the back of the arm. Implants for different strengths have been developed, ranging from 8 weeks to one year. This has been in use in Bangladesh and India for last 3 years and is cent percent successful in preventing the relapse[19]. With implant there is no problem of spitting out, "forgetting" to take naltrexone and reduces the craving much more than oral one because there is no point in craving for what you can't have. The disadvantages are: minor surgery; local infection and inflammation at the implant site which respond well to antibiotics; and initially appears to be more expensive. But in the long run it will turn out to be much cheaper if we take into account the amount of financial, emotional and family damage, and the repeated cost of detoxification.

Laheij et al. compared the cost effectiveness of different treatments. He found that the average intention to treat cost of UROD was US$5850 compared with US$4230 for the methadone-tapering program. However, the average cost per treatment success where success is defined as completing detoxification was US$8775 for RODA and US$12,685 for methadone tapering[13].

There are reports of naltrexone depot injections in the making[22]. The expected release of the first licensed depot preparation in May 2006 represents a real progress, albeit one for which necessary technology had existed for decades and had been successfully use in other fields. The pharmacology of naltrexone was known as far back as 1976[23].

Alcohol

Since alcohol does not have a specific antidote, conventional detoxification is still popular. For relapse prevention oral disulfiram has been used for a long time, though the success rate is low. Since the use of disulfiram is based on deterrence, many physicians do not prefer it. But from a psychiatric point of view its value is under estimated. Lately three months implant for disulfiram has become available.

Benzodiazepine

In the case of benzodiazepine, flumazenil is use for antagonist induction. Long acting oral and depot forms are yet to be available.

So, in the case of management of addiction, we are still stuck at the time wrap of 1965. This situation is in total contrast to the rest of the medicine, where enormous changes and many improvements in outcome have occurred. One major reason for this contrast is that promising technologies and medications are quickly evaluated and adopted in general medicine and surgery but not in addiction treatment. Especially in countries like Nepal and India, addiction is still widely seen as a moral or "spiritual" problem that requires exclusively spiritual and/or psychosocial interventions. This attitude does not co-exist easily with medical treatments. So new concepts in pharmacology have to be adopted and interventions started on the basis of knowledge of brain science and neurobiology. Psychiatrists should endeavour on new advancements and technologies in de-addiction programme, while recognizing the importance of specific psychosocial interventions for many patients. In fact once on maintenance in antagonist, more valuable time is available for meaningful psychosocial counselling and social and vocational integration.

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