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Neurosurgical Research in De-Addiction - A Innovative Intervention in Habit Induced Potentially Malignant Disorders

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Abstract

Public health is a matter of concern in medical science. Several health issues are of global concern. One such vital problem is substance abuse commonly referred to as drug addiction.

Drug addiction has become a worldwide problem and the leading cause of death. Preventive programs and de-addiction centers are the key management measures. However recalcitrant patients who seek lateral management are subjected to a variety of pharmacological and behavioral measures. Emerging among these is the principle of Deep brain stimulation using brain pacemakers. Deep Brain Stimulation (DBS) is controlled stimulation of specific centers in cerebral cortex to alter the functioning of the brain for beneficial purposes. Currently the concept is being used as a therapy for neurological and psychiatric disorders. Among the various stimulated centers are the nucleus accumbens, Subthalamic Nucleus (STN), dorsal striatum and lateral habernula. Stimulation is done by application of a specific electric voltage passed across implanted electrodes in these regions. Transcranial Magnetic Stimulation (TCM) is one of the most commonly employed method in stimulating the surgically implanted electrodes and results are much alike those achieved by DBS. This stimulation therapy has shown numerous advantages over conventionally treatment modalities in experimental animals and recently human trials too. The mechanism of BDS in anti-depressive action, anti-anxiety actions were explained due to alterations in neurotransmitters in the Hypothalamo Pituitary (HP) axis. One of the most essential roles of DBS lies in drug de-addiction therapy which is reviewed in this article. This paper unveils deep brain stimulation of lateral habernula as a personalised treatment target for treating devastating drug addiction which is a burning problem of social concern simultaneously reviewing on relevant patents on DBS systems which targets these areas of the brain. In the hands of dentists, imaging DBS implanted sites in cephalograms or CBCT scans and referral of a victim to alcohol / smoking addictions leading to cancers or one with an existing unbearable oral cancer pain on addictive regimens of opioids for DBS team is all beyond the frontiers of future.

Keywords: Deep Brain Stimulation (DBS); Drug Addiction; Lateral Habernula; Neuromodulation; Public Health

Introduction

Public health is a matter of concern in medical science. Several health issues are of global concern. One such vital problem is substance abuse commonly referred to as drug addiction.

Drug addiction has become a worldwide problem and the leading cause of death. Preventive programs and de-addiction centers are the key management measures. However recalcitrant patients who seek lateral management are subjected to a variety of pharmacological and behavioral measures. Emerging among these is the principle of Deep brain stimulation using brain pacemakers.

Drug addiction is referred to as "substance dependence" by the World Health Organization [1] and the American Psychiatric Association [2]. Substance dependence is defined by the American Psychiatric Association definition as to have a patient to meet at least three of the seven criteria:

Craving (psychological dependence), physical or physiological dependence, priming (new exposure to a formerly abused substance), relapse is a resumption of drug-seeking behavior after a period of abstinence, reward (an intrinsically positive stimulus interpreted by brain), sensitization (increase in expected effect of a drug after repeated administration and lastly withdrawal syndrome after abrupt discontinuation of the drug. The behavioral component is best connoted as "Drug addiction" and it is not to be misinterpreted for physical dependence [3]. According to DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) Drug addiction which is part of Substance abuse is defined as a cluster of cognitive, behavioral, and physiological symptoms indicating that an individual continues to use a substance despite significant substance-related problems [4].

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Beyond the biased boundary wherein addiction is always assumed as a negative allegation lies an astounding but acceptable concept which concisely connotes addiction as highly devoted to an activity and involving habitually in a behavior both of which possibly portray even a positive picture of it. Scientifically it is initiated as a consensual Central nervous system imbalance. However specifically it is a neurobiological reflection of nucleus accumbens and lateral habernula. This paper unveils deep brain stimulation of specific targets for management of drug addiction, reviewing on relevant literature and patents on BDS systems used for the same.

Implications of Substance Abuse

Substance abuse triggers pleasure or relieves distress [5]. It predominantly causes dependence and tolerance which reduces the positive reinforcing effects, in other words increases negative reinforcement resulting in withdrawal symptoms [6,7] and significant systemic effects such as chronic heart and liver disease, blood-borne bacterial and viral infections, and psychiatric disorders [8]. Beyond all physical effects, drug addiction is a significant health burden not just on the individual concerned but the family and society at large. Also road-traffic accidents, suicides, and violence are unpredicted problems related to drug addiction [9].

In dentistry many patients who have addictions (tobacco smoking or chewing, alcohol) are noted on routine dental examinations. Oral pre cancers and cancers are commonly caused due to failure to cease these habits and continued addiction.

Mechanism of Drug Addiction

In the incipient stage, abuse of drug starts as a voluntary behavior later it continues as a compulsive behavior [10] thus indicating the impairment of neural function which is represented by an unbalanced interaction between brain regions implicated in goal-directed behaviors. This region includes a complex network of structures such as striatum, Ventral Tegmental Area (VTA), Substantia Nigra (SN), amygdala, hippocampus, Prefrontal Cortex (PFC), and the Lateral Habernula (LHb) [11]. Drug addiction is reflected by impaired function in reward and pleasure which is mediated by the neurotransmitter Dopamine distributed in midbrain, ventral tegmental area, cerebral cortex and hypothalamus. Addictive drugs causes large but temporary increase in Dopamine from VTA neurons that project primarily to the Nucleus Accumbens (NAc) of the ventral striatum, but also to the dorsal striatum, amygdala, hippocampus, hypothalamus, lateral septal area, and PFC [12]. Drugs of abuse increase dopamine release in a more prolonged and unregulated way than natural stimuli [13]. Human brain is the most mysterious master organ responding to external environment and experiences in a complex and confounding manner through the scientific synergy of neurotransmitters which are chemical messengers of information to brain. As part of addiction, the astounding role of neurotransmitters is a never ending exploration with emphasis on Dopamine which is associated with feeling of pleasure, reward, movement, attention and memory. A relapse in drug addiction is associated with anterior insula [14]. As part of addiction pathophysiology, glutamatergic inputs from the LHb to the VTA have been implicated [15]. The chronic use of addictive drugs leads to habenular hyperactivity, which may promote a negative emotional state during drug withdrawal [12]. Long-term changes in the amygdala and medial PFC may be associated with significant drive for drug addiction, even after longer duration of drug withdrawal [13].

Nucleus Accumbens and Lateral Habernula

Stimulation of nucleus accumbens has been shown to be an important phenomenon in attenuation of drug addiction. Also deep brain stimulation of lateral habernula causes attenuation of drug seeking behavior by interfering with axonal degeneration of the Fasciculus Retroflexus (FR), which connects the NA to the VTA [15] thereby resulting in degeneration of FR [16].

Limelight to behavioral science is shed by lateral habernula which is a dorsal diencephalic structure that is located lateral to the third ventricle and adjacent to the pineal gland. It is the region in the brain which is associated with reward and sense of pleasure. The exploration of the promising outcome related to lateral habernula is associated with the inhibition of this midbrain dopaminergic activity which is associated with addiction leading to a pathetic pentagonal psychological pathologies which include loss of control, feeling indifferent, preoccupation with a behavior, transcient satiation and pessimistic consequence.

Another significant area of interest is the PFC which if subjected to stimulation is associated with attenuation of drug seeking behavior. It is a noteworthy triad of deep stimulation related to nucleus ambiens, lateral habernula and pre frontal cortex which reduces drug addiction with minimal or seldom side effects. Significant results were noted with respect to abstinence of alcohol and smoking tobacco [17,18].

Apart from common addictions such as tobacco and alcohol significant drug addictions are associated with Cannabis, cocaine, opioids, sedatives, hallucinogens and hypnotics [8].

A dreary link to this clinical scenario is drug addiction which is a dicey devastating dependency. Despite dynamic treatment plans for drug addiction there is always a dearth and debacle in response to the multifarious management modalities.

Emerging beyond pharmacological interventions such as methadone, naltrexone, and buprenorphine and other modalities such as cognitive behavioral therapy [9] are the neuropsychological intervention reflected by deep brain stimulation which is associated with direct manipulation of the neural circuits implicated in substance abuse behavior.

Genetic Mechanism in Drug Addiction

The mechanism of drug addiction is proposed to be resulting from dysregulation of the reward mechanism [19,20] which becomes hyper sensitized and associated cognitive disturbances (related to decision making) due to deficits in the activation of prefrontal cortex area [21,22]. Apart from the above mechanism, genetic factors such as Leu7Pro polymorphism neuropeptide Y gene (alcohol dependence); deficiency in the cytochrome P-450 2D6 gene (codeine abuse); defective cytochrome P-450 2A6 *2 and *4 alleles (nicotine dependence); a single-nucleotide polymorphism in the gene encoding fatty acid amide hydrolase (recreational use of illegal drugs) [23]; minor (A1) allele of the Taq IA D2 dopamine receptor gene (severe alcoholism, opioid, nicotine and poly substance abuse) do play a role in substance abuse. Ionotropic and metabotropic mechanisms are postulated to play a significant role in drug abuse. As part of molecular

mechanism involved in the sensitization and relapse it is noted that alterations in the functional activity of the mesocorticolimbic dopamine system, especially glutamate and dopamine transmission in the nucleus accumbens [24,25] and elevated levels of the R1 subunit of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subtype of glutamate receptors is found to be involved [26].

Deep Brain Stimulation

Emerging as a dynamic neuropsychological intervention in drug addiction in hopeless situations is deep brain stimulation in defending this disaster. Deep brain stimulation is a phenomenon of targeted neuromodulation that involves manipulation and tailoring of pathological neural networks in human brain.

Deep Brain Stimulation (DBS) is controlled stimulation of specific centres in cerebral cortex to alter the functioning of the brain for beneficial purposes. DBS is achieved by initial surgical implantation of a medical device called a neurostimulator or 'brain pacemaker' and later stimulation of the same via electrical impulses to desirable parts of the brain for the treatment associated disorders. DBS in selected brain regions has provided therapeutic benefits over conventional treatment-resistant neurological disorders such as Parkinson's disease dystonia, chronic pain, major depression and obsessive-compulsive disorder [27]. DBS is used on experimental animals to explain probable hypothesis for treating above mentioned diseases when they seem to resist conventional pharmacotherapy, however underlying principles and mechanisms of DBS are still not clear [28,29]. DBS when achieved by proper technique will alter the brain activity in a controlled manner, its effects are reversible and thus is used as a therapy for neurological and psychiatric disorders.

Mechanism Behind DBS System-Electric Stimulation of Implants

Exact mechanism of DBS systems is unknown as stated above. However various hypotheses exists which tend to explain on the mechanisms by which existing neural pathways could be altered by stereotactic surgeries and DBS. Firstly, Depolarization blockade mechanism, where in electrical currents block the neuronal output at or near the electrode site. Next synaptic inhibition which causes an indirect regulation of the neuronal output by activating axon terminals with synaptic connections to neurons near the stimulating electrode. Third de-synchronization of abnormal oscillatory activity of neurons [30].

Components of DBS System

The DBS system consists of three components namely an Implanted Pulse Generator (IPG), Lead (L) and Extension (E). The IPG is a battery-powered neurostimulator in a titanium housing, which sends electrical pulses to the brain cortex to interfere with existing neural signaling activity at the desired site. The lead is a coiled wire insulated in polyurethane with about four platinum iridium electrodes and is placed in desired sites namely nuclei of the brain. The lead is connected to the IPG by the extension, an insulated wire that runs below the skin, from the head, down the side of the neck, behind the ear to the IPG, which is placed subcutaneously below the clavicle or in some cases, the abdomen [31].

DBS associated devices are incorporated in to master organ of the humans, by neurosurgeons under appropriate local anesthesia for the leads and under general anesthesia for IPG systems. Brain tissue visualization under MRI imaging is done while the procedure is being done for accuracy into target sites [31,32].

Medicinal Values of Tageted Neuro-Centeres: Drug Deaddiction and Dystonic Disorders

Among the various stimulated centers are the nucleus accumbens, Subthalamic Nucleus (STN), dorsal striatum and lateral habernula. Stimulation is done by application of a specific electric voltage passed across implanted electrodes in these regions [32,33] Trans Cranial Magnetic stimulation (TCM) is one of the most commonly employed method in stimulating the surgically implanted electrodes and results are much alike those achieved by DBS. The mechanism of DBS in anti-depressive action, anti-anxiety actions were explained due to alterations in neurotransmitters in the Hypothalamo Pituitary (HP) axis [33]. Thus, Parkinson's diseases and other associated dystonic disorders, addictive disorders and obsessive disorders with major depression and chronic unbearable pain (cancer induced) all are problems that can be addressed by DBS. The Food and Drug Administration (FDA) [34] approved DBS as a treatment for tremors, Parkinson's disease, dystonia and Obsessive Compulsive Disorder. DBS is also used in research studies to treat chronic pain and major depression which are not approved by US-FDA, but have demonstrated significant results in terms of recovery for specific tested human trails also [34,35,36].

Young et al (1986) [37] have shown in their study on seventeen patients with intractable cancer pain that thirteen were virtually pain-free and only four required opioid analgesics on release from hospital after the intervention with DBS. Similar way, Anderson et al (1920) [38] have demonstrated similar results for phantom limb pain. Wittet al (2002) [39] have conducted a multicentric randomized control trail for DBS in Parkinson's disease and reported positive associations for the same while Just et al (2002) [40] assessed on improving life quality of patients with parkinson's disease with DBS. Plaha et al (2006) [41] have demonstrated other centers such as caudal zona incerta to be better than tradition regions mentioned above for management of Parkinson's disease tremors, however surgical procedure required is very complex.

Numerous Studies [42,43,44] have demonstrated use of DBS in major depression and currently numerous experimental studies are in progress to determine risk *vs* benefit of DBS in Tourette syndrome [44]. Vassoler et al (2008) [45] have shown in rodent models effect of DBS on cocaine admistered. The results indicated that DBS of the nucleus accumbens shell attenuated the reinstatement of cocaine seeking; DBS of the dorsal striatum had no influence on cocaine reinstatement, DBS of the nucleus accumbens shell did not affect the reinstatement of food seeking and that DBS of the accumbens shell in the absence of a cocaine-priming injection did not promote the reinstatement of cocaine seeking. Gao et al (2003) [46] have reported similar effects of alleviating from opoid dependency by stimulating the nucleus accumbens using a stereotactic surgery. Kuhn et al (2011) [47] have reported a case of a patient with severe alcohol addiction with Deep Brain Stimulation (DBS) of the Nucleus Accumbens (NAc). Before and one year following the surgery, the effects of DBS was assessed within the NAc on the addiction as

well as on psychometric scores and electrophysiological measures of cognitive control. Here the result supports the hypothesis that DBS of the NAc could have a positive effect on addiction trough a normalization of craving. Lu et al (2009) [48] have reported that Stereotactic neurosurgery has shown promising results in reducing drug addiction, but it has also caused severe side effects, also authors concluded recent developments in stereotactic technique and Deep Brain Stimulation (DBS) may make stereotactic neurosurgery a viable and reversible treatment for drug addiction. Mantione et al (2010) [49] have reported smoking cessation and weight loss after chronic deep brain stimulation of the nucleus accumbens in a case report. This shows DBS in de addiction for smoking habit. Similar studies on tobacco and alcohol de addiction also are reported in literature [50] Heinze et al (2009) [51] have reported on severe cases of alcohol addiction and dependency managed similarly by stimulating the nucleus accumbens using a stereotactic surgery. DBS may have potential benefits for these disorders when traditional therapy fails to work, but surgical procedures do carry harmful long term side effects.

Burn et al (2004) [52] stated that there is also the potential for neuropsychiatric side effects, including apathy, hallucinations, compulsive gambling, hyper sexuality, cognitive dysfunction, and depression. However, these may be temporary and related to correct placement and calibration of the stimulator and so are potentially reversible. Doshiet al (2007) [53] have listed on the major complications like intracranial haemorrhage (1-2%) and site infection (3-5%) are life treating complications. The expanding applications of deep brain stimulation include epilepsy, parkinson's disease, essential tremor, obsessive compulsive disorder, untreatable pain, excruciating cluster headaches, dystonia, tourette's syndrome, addiction and obesity. The ethical issues in the practice of deep brain stimulation includes various risks such as bleeding in the brain-subdural, subarachnoid and intra parenchymal hemorrhage, infections, seizure, intracranial air and brain shift. Also other ethical issues include the induction of euphoria and even frank mania which can be induced by deep brain stimulation. Worldwide, approximately over 7,00,000 stimulation devices are in use with revenue nearing three billion dollars. The cost of deep brain stimulation in India ranges between 10 -20 lakhs. Ultimately careful selection of stimulation parameters for chronic stimulation, decision making abilities in patient selection, patient consent, voluntariness, compliance assessment, patient satisfaction are important in deep brain stimulation.

Conclusion

Neurosurgical intervention using deep brain stimulation is an attempt to tackle drug addiction which is a growing public health disaster. It is needless to mention, most patients who have addictions (tobacco smoking or chewing, alcohol) are noted on routine dental examinations. Oral pre cancers and cancers are commonly caused due to failure to cease these habits and continued addiction. Neuroscience comes to rescue in this regard through the treatment modality called as neuromodulation which is the use of electrical stimulation of target areas in brain by implanted stimulators. To conclude, deep brain stimulation is one form of targeted neuromodulation involving manipulation or alteration of the pathological neural connections through an implanted device called as deep brain stimulation pacemakers or brain pacemakers which is a revolution in the challenge faced by conventional existing treatment modalities in treating the public health disaster, drug addiction [54].

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