

Case Report

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

Jeelani S*

Department of Oral Medicine and Radiology, Sri Venkateshwara Dental College, Ariyur, Puducherry, India

***Corresponding author:** Jeelani S, Department of Oral Medicine and Radiology, Sri Venkateshwara Dental College, Ariyur, Puducherry, India**Received:** May 17, 2020; **Accepted:** June 16, 2020;**Published:** June 23, 2020**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 habenula. 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 habenula 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 Habenula; 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].

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 habenula. 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 Habenula (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 Habenula

Stimulation of nucleus accumbens has been shown to be an important phenomenon in attenuation of drug addiction. Also deep brain stimulation of lateral habenula 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 habenula 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 habenula 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, transient 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 accumbens, lateral habenula 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 Targeted Neuro-Centers: Drug Deaddiction and Dystonic Disorders

Among the various stimulated centers are the nucleus accumbens, Subthalamic Nucleus (STN), dorsal striatum and lateral habenula. 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 administered. 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 through 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].

References

1. World Health Organization. The ICD-10 classification of mental and behavioral disorders: clinical descriptions and diagnostic guidelines. Geneva: World Health Organization. 1992.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed., text revision: DSM-IV-TR. Washington, D.C.: American Psychiatric Association. 2000.
3. Maddux JF, Desmond DP. Addiction or dependence? *Addiction*. 2000; 95: 661-5.
4. American Psychiatric Association & American Psychiatric Association. DSM-5 Task Force. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. American Psychiatric Association. 2013.
5. Volkow ND, Wang GJ, Tomasi D, Baler RD. Unbalanced neuronal circuits in addiction. *Curr Opin Neurobiol*. 2013; 23: 639-4.
6. Voges J, Muller U, Bogerts B, Munte T, Heinze HJ. Deep brain stimulation surgery for alcohol addiction. *World Neurosurg*. 2013; 80: e21-31.
7. Miller NS, Summers GL, Gold MS. Cocaine dependence: alcohol and other drug dependence and withdrawal characteristics. *J Addict Dis*. 1993; 12: 25-35.
8. Degenhardt L, Hall W. Extent of illicit drug use and dependence, and their contribution to the global burden of disease. *Lancet*. 2012; 379: 55-70.
9. In pathways of addiction: opportunities in drug abuse research. The National Academies Collection: Reports funded by National Institutes of Health 1996.
10. Volkow ND, Baler RD. Addiction science: uncovering neurobiological complexity. *Neuropharmacology*. 2014; 76: 235-49.
11. Ikemoto S, Bonci A. Neurocircuitry of drug reward. *Neuropharmacology*. 2014; 76: 329-41.
12. Vanegas N, Zaghoul KA. Deep Brain Stimulation for Substance Abuse. *Curr Behav Neurosci Rep*. 2015; 2: 72-79.
13. Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology*. 2010; 35: 217-38.
14. Naqvi NH, Bechara A. The hidden island of addiction: the insula. *Trends Neurosci*. 2009; 32: 56-67.
15. Friedman A, et al. Electrical stimulation of the lateral habenula produces enduring inhibitory effect on cocaine seeking behaviour. *Neuropharmacology*. 2010; 59: 452-9.
16. Lax E. Neurodegeneration of lateral habenula efferent fibers after intermittent cocaine administration: implications for deep brain stimulation. *Neuropharmacology*. 2013; 75: 246-54.
17. Kuhn J, R Bauer, S Pohl, D Lenartz, W Huff, E H Kim, et al. Observations on unaided smoking cessation after deep brain stimulation of the nucleus accumbens. *Eur Addict Res*. 2009; 15: 196-201.
18. Kuhn J, Doris Lenartz, Wolfgang Huff, SunHee Lee, Athanasios Koulousakis, Joachim Klosterkoetter, et al. Remission of alcohol dependency following deep brain stimulation of the nucleus accumbens: valuable therapeutic implications? *J Neurol Neurosurg Psychiatry*. 2007; 78: 1152-3.
19. Robinson TE, Berridge KC. Incentive- sensitization and addiction. *Addiction*. 2001; 96: 103-14.
20. Iden. *Addiction*. *Annu Rev Psychol*. 2003; 54: 25-53.
21. Franklin TR, Acton PD, Maldjian JA, Jason G. Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. *Biol Psychiatry*. 2002; 51: 134-42.
22. Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry*. 2002; 159: 1642-52.

23. Sipe JC, Chiang K, Gerber AL, Beutler E, Cravatt BF. A missense mutation in human fatty acid amide hydrolase associated with problem drug use. *Proc Natl Acad Sci USA*. 2002; 99: 8394-9.
24. Hyman SE, Malenka RC. Addiction and the brain: the neurobiology of compulsion and its persistence. *Nat Rev Neurosci*. 2001; 2: 695-703.
25. Konipsky KL, Hyman SE. Molecular and cellular biology of addiction. In: Davis KL, Charney D, Coyle JT, Nemeroff C, eds. *Neuropsychopharmacology: the fifth generation of progress*. Philadelphia: Lippincott Williams & Wilkins. 2002: 1367-79.
26. Carlezon WA Jr, Nestler EJ. Elevated levels of GluR1 in the midbrain: a trigger for sensitization to drugs of abuse? *Trends Neurosci*. 2002; 25: 610-5.
27. Kringsbach ML, Jenkinson N, Owen SLF, Aziz TZ. "Translational principles of deep brain stimulation". *Nature Reviews Neuroscience*. 2007; 8: 623-635.
28. Hammond C, Ammari R, Bioulac B, Garcia L. "Latest view on the mechanism of action of deep brain stimulation". *MovDisord*. 2008; 23: 2111-21.
29. Garcia MR, Pearlmutter BA, Wellstead PE, Middleton RH. "A Slow Axon Antidromic Blockade Hypothesis for Tremor Reduction via Deep Brain Stimulation". *PLoS ONE*. 2013; 8: e73456.
30. McIntyre CC, Thakor NV. "Uncovering the mechanisms of deep brain stimulation for Parkinson's disease through functional imaging, neural recording, and neural modeling". *Crit Rev Biomed Eng*. 2002; 30: 249-81.
31. McIntyre CC, Savasta M, Walter BL, Vitek JL. How does deep brain stimulation work? Present understanding and future questions. *J Clin Neurophysiol*. 2004; 21: 40-50.
32. Starr PA, Martin AJ, Ostrem JL, Talke P, Levesque N, Larson PS. "Subthalamic nucleus deep brain stimulator placement using high-field interventional magnetic resonance imaging and a skull-mounted aiming device: technique and application accuracy". *J Neurosurg*. 2010; 112: 479-90.
33. Vassoler FM, White SL, Hopkins TJ, Guercio LA, Espallergues J, Berton O, et al. Deep brain stimulation of the nucleus accumbens shell attenuates cocaine reinstatement through local and antidromic activation. *J Neurosci*. 2013; 33: 14446-14454.
34. Pereira EA, Green AL, Nandi D, Aziz TZ. Deep brain stimulation: indications and evidence. *Expert Rev Med Devices*. 2007; 4: 591-603.
35. Encinas JM, Hamani C, Lozano AM, Enkilopov G. Neurogenic hippocampal targets of deep brain stimulation. *J Comp Neurol*. 2011; 519: 6-20.
36. Eapen V, Crncec R. Strategies and challenges in the management of adolescent depression. *Curr Opin Psychiatry*. 2012; 25: 7-13.
37. Young RF, Brechner T. Electrical stimulation of the brain for relief of intractable pain due to cancer. *Cancer*. 1986; 57: 1266-72.
38. Anderson RJ, Frye MA, Abulseoud OA, Kendall H Lee, Jane A McGillivray, Michael Berk, et al. "Deep brain stimulation for treatment-resistant depression: efficacy, safety and mechanisms of action". *Neurosci Biobehav Rev*. 2012; 36: 1920-33.
39. Witt K, Daniels C, Reiff J, Paul Krack, Jens Volkmann, Markus O Pinski, et al. Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre trial. *Lancet Neurol*. 2008; 7: 605-614.
40. Just H, Ostergaard K. Health-related quality of life in patients with advanced Parkinson's disease treated with deep brain stimulation of the subthalamic nuclei. *MovDisord*. 2002; 17: 539-545.
41. Plaha P, Ben-Shlomo Y, Patel NK, Gill SS. "Stimulation of the caudal zona incerta is superior to stimulation of the subthalamic nucleus in improving contralateral parkinsonism". 2006; 129: 1732-47.
42. Anderson RJ, Frye MA, Abulseoud OA, Lee KH, McGillivray JA, Berk M, et al. "Deep brain stimulation for treatment-resistant depression: efficacy, safety and mechanisms of action". 2012; 36: 1920-33.
43. Schlaepfer TE, Cohen MX, Frick C, Kosel M. "Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression". *Neuropsychopharmacology*. 2008; 33: 368-77.
44. Singer HS. "Tourette syndrome and other tic disorders". *HandbClin Neurol*. 2011; 100: 641-57.
45. Vassoler FM, Schmidt H D, Gerard M E, Famous K R, Ciraulo D A, Kornetsky C, et al. Deep Brain Stimulation of the Nucleus Accumbens Shell Attenuates Cocaine Priming-Induced Reinstatement of Drug Seeking in Rats. *The Journal of Neuroscience*. 2008; 28: 8735-8739.
46. Gao G, Wang X, He S, Li W, Wang Q, Liang Q, et al. Clinical study for alleviating opiate drug psychological dependence by a method of ablating the nucleus accumbens with stereotactic surgery. *Stereotact Funct Neurosurg*. 2003; 81: 96-104.
47. Kuhn J, Gründler TO, Bauer R, Huff W, Fischer AG, Lenartz D, et al. Successful deep brain stimulation of the nucleus accumbens in severe alcohol dependence is associated with changed performance monitoring. *Addict Biol*. 2011; 16: 620-3.
48. Lu L, Wang X, Kosten TR. Stereotactic neurosurgical treatment of drug addiction. *Am J Drug Alcohol Abuse*. 2009; 35: 391-3.
49. Mantione M, Van de Brink W, Schuurman PR, Denys D. Smoking cessation and weight loss after chronic deep brain stimulation of the nucleus accumbens: therapeutic and research implications: case report. *Neurosurgery*. 2010; 66: E218.
50. Kuhn J, Bauer R, Pohpl S, Lenartz D, Huff W, Kim EH, et al. Observations on unaided smoking cessation after deep brain stimulation of the nucleus accumbens. *Eur Addict Res*. 2009; 15: 196-201.
51. Heinze HJ, Heldmann M, Voges J, Hinrichs H, Marco-Pallares J, Hopf JM, et al. Counteracting incentive sensitization in severe alcohol dependence using deep brain stimulation of the nucleus accumbens: clinical and basic science aspects. *Front Hum Neurosci*. 2009; 3: 22.
52. Burn DJ, Tröster AI. "Neuropsychiatric complications of medical and surgical therapies for Parkinson's disease". *J Geriatr Psychiatry Neurol*. 2004; 17: 172-80.
53. Doshi PK. "Long-term surgical and hardware-related complications of deep brain stimulation". *StereotactFunctNeurosurg*. 2011; 89: 89-95.
54. Saah T. The evolutionary origins and significance of drug addiction. *Harm Reduct J*. 2005; 2: 8.