ADDICTION: NEW ERA OF THERAPY

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ABSTRACT

Background: Drug abuse and addiction represents a major burden to the society. According to National Institute of Drug Abuse (NIDA) the economic costs alone are estimated to exceed half a trillion dollars annually in the United States, including health, losses in productivity, and crime related costs. In Egypt, the 2013 survey of substance use and addiction revealed an increased prevalence when compared to 1996 survey. Untreated substance abuse and addiction adds a significant avoidable costs and major disruptions to the families and communities. However, scientists are now poised to capitalize on recent advances in genetics, neuroscience and developmental biology to create breakthrough treatments that could revolutionize care and reduce associated public health and safety problems. These treatments will help addicts stop abusing drugs and resume their productive lives.

Aim: The aim is to provide review of recent literature on the new methods for treatment of addiction, including opiate, cocaine, nicotine; their advantages and disadvantages. Also to highlight areas for researchers interested in this field to build upon their studies.

Conclusion: Several new recent lines for treating addiction have been developed including nanotechnology approach, brain stimulation methods, yoga and mindfulness practice, vaccines against drugs of abuse, N-methyl-d-aspartate receptor modulators, acupuncture and hypnotherapy.

Key words: addiction therapy, nanotechnology, gene silencing, yoga, laser acupuncture, brain stimulation methods.

INTRODUCTION

Addiction can be defined as the continued use of mood-altering addicting substances or behaviors despite adverse consequence or a neurological impairment leading to such behaviors (**Angres and Bettinardi-Angres, 2008**).

Natural reward behaviors as well as drug reward converge on a common neural pathway, beside the mesolimbic dopamine (DA) system, in which the nucleus accumbens (NAc) plays a central role (**Kelley, 2004**). Drugs of abuse induce neuroplasticity in the mesolimbic system, which plays a central role in the transition from drug use to drug addiction (**Mameli and Luscher, 2011**).

A gene transcription factor called ΔFosB has been identified as playing a central role in the development of addictive states in both behavioral addictions and drug addictions (**Robison and Nestier, 2011**). This factor was found to be over expressed in addictions to alcohol, cannabinoids, cocaine, nicotine, phenylcyclidine, and substituted amphetamines (**Hyman et al., 2006; Steiner and Van Waes, 2013**), as well as addictions to natural rewards such as sex, exercise, and food (**Olsen, 2011; Blum et al., 2012**). A recent study also demonstrated a cross-sensitization between drug reward (amphetamine) and a natural reward (sex) that was mediated by ΔFosB (**Pitchers et al., 2013**).

Drug addiction causes an enormous medical, financial, and emotional problems on individual and society in the form of overdose and health complications, loss of employment, family disintegration, and crime (**Sussman et al., 2011**).

The increased studies of the neuronal effects of abuse drugs and the mechanisms of addiction resulted in uncovering of novel targets for treatment and prevention of addiction (**Sun et al., 2014**).

AIM OF THE WORK

To review recent literature on the new methods for treatment of addiction, including opiate, cocaine, nicotine; their advantages and disadvantages and highlights areas where future research will help the discovery of new therapeutics.

DISCUSSION

New methods for treatment of addiction:

1) *Nanotechnology approach:*

Nanotechnology has an increasing impact in the healthcare industry, especially in facilitating the targeted delivery into specific sites and across complex biological barriers **(Farokhzad and Langer, 2006)**. The first trial to use the nanotechnology in treatment of addiction was done by **Bonoiu et al. (2009).** They utilized gold nanorode-DARPP-32 siRNA (dopamine- and cyclic AMP-regulated phosphoprotein 32 small interfering RNA) complexes (nanoplexes) to target the dopaminergic signaling pathway.

The idea was based on more understanding of the molecular and genetic background of addiction. Opiate addiction involves activation of the dopaminergic signaling pathway in the brain **(Gould and Manji, 2005)**. Dopamine activates protein kinase A (PKA)-mediated phosphorylation of DARPP-32 **(Nairn et al., 2004)**. Modulation of DARPP-32, results in the activation of the extracellular signal-regulated kinase (ERK)**,** ERK activity has been known to be important in neuronal plasticity and its pharmacologic blockade prevents the behavioral and transcriptional effects of different drugs of abuse **(Valjent et al., 2005).**

Based on the previous data, **Bonoiu et al. (2009)** concluded that DARPP-32 is the central molecular "trigger" that underlies the neurobiological alterations related to drug abuse, and hypothesized that the suppression of DARPP-32 gene expression in dopaminergic neuronal cells will lead to significant behavioral inhibition of the drug addiction process.

Recently, gene therapy has been used to suppress specific gene expression in targeted organs or cells using small interfering RNA (siRNA) **(de Fougerolles et al., 2007).**

Despite promising, developing siRNA as therapeutics has proven challenging because: firstly, siRNAs are rapidly cleared by renal filtration and are susceptible to degradation by extracellular RNases leading to short half-life **(Aagaard and Rossi, 2007);** secondly, the brain which is the target organ for drug addiction therapy, represents a particularly inaccessible organ for siRNA delivery owing to the presence of the blood–brain barrier **(Pardridge, 2007),** so scientists were directed to the use of nanoparticle-based delivery of certain molecules for overcoming present therapeutic limitations.

Connor et al. (2005) showed an increasing interest to gold nanorods and nanoparticles as a site specific carrier to various therapeutic and diagnostic agents because they are biocompatible.

Their surfaces can incorporate cationic charges forming electrostatic complexation with anionic genetic materials such as siRNA, for the aim of targeted gene delivery/silencing **(Ding et al., 2007).** In addition, their complexation with genetic material and subsequent delivery and distribution within the target tissues can be monitored by the use of surface plasmon resistance phenomenon associated with gold nanoparticles and nanorods **(Sokolov et al., 2003).**

Bonoiu et al., (2009) introduced a nanotechnology-based approach for gene silencing-mediated drug addiction therapy using gold nanorodes (GNRs) electrostatically complexed with appropriate siRNA molecules (nanoplexes) for modulating the key components of the dopaminergic signaling pathway, where the aim of this study was to:

a- Confirm the formation of the nanoplexes

b- Confirm the uptake of the nanoplexes into dopaminergic neuronal cells

c- Measuring in vitro silencing of DARPP-32 and other molecules of this pathway, such as ERK and protein phosphatase

d- Measuring transmigration efficiency of the nanoplexes across an in vitro blood brain barrier model compared to the free siRNA

The results of the study were encouraging however, the efficacy of the use of GNRS as effective transport carrier for siRNA in vivo needs to be determined since **Akhtar and Benter (2007)** focused on the importance of understanding the specificity of siRNA for the target gene and whether the delivery reagent has an impact on gene silencing activity of siRNA.

The next trial to use the nanotechnology approach in treatment of addiction was performed by **Law et al. (2012)** where they used PEGlyated quantum rod (covalently conjugated with Polyethylene

glycol) with different surface functional groups (amine and maleimide) for the delivery of siRNA to human neuronal cells. The PEGlyated surface offered high biocompatibilities and negligible cytotoxicities to the formulation that may facilitate in vivo applications of these nanoparticles.

These nanoplexes integrated gene delivery and imaging into single system which is manifested by high transfection efficiency and low cytotoxicity together with high biocompatibility however, the challenge was the application of these nanoparticles in the clinical setting because of the cadmium based nature. So, it will be beneficial to replace cadmium based quantum rods with heavy metal free material such as silicon quantum dot.

Reynolds et al. (2012) have utilized gold nanorod-galectin-1 siRNA complexes (nanoplexes) to inhibit gene expression of galectin-1. Galectin-1, an adhesion molecule, is expressed in macrophages and implicated in enhancing human immunodeficiency virus (HIV-1) infection via facilitating viral adsorption to macrophages cell surface (**Mercier et al., 2008**). Studies performed by **Reynolds et al. (2007)** proved that treatment of immature dendritic cells with methamphetamine increase the expression of galectin-1 thus facilitating attachment of HIV to human macrophages thereby regulating HIV infection.

In addition, under investigation is the use of magnetic nanoparticles which can deliver anti-opioid drugs across BBB without compromising its integrity under the effect of external (non- invasive) magnetic force (**Sagar, 2013**).

2) *Brain stimulation method:*

Brain stimulation methods are gaining increasing interest as possible addiction therapeutics. Different types were used including repetitive transcranial magnetic stimulation (rTMS), cranial electrostimulation (CES), transcranial direct current stimulation (tDCS) or deep brain stimulation (DBS) (**Wing et al., 2013**).

There is nascent evidence that rTMS could be effective in reducing nicotine and alcohol craving and consumption and cocaine craving and might represent a potential therapeutic method for treating addiction. Further studies are indicated to identify the optimal parameters of stimulation for the most beneficial treatment of drug addiction (**Bellamoli et al., 2014**).

The mechanism of the therapeutic effect of rTMS is poorly understood but may be mediated through increased dopamine and glutamate function in cortico meso limbic system in the brain and modulating neuronal activity in brain circuits responsible for cognitive processes related to addiction (**Gorelick et al., 2014**)

3) *yoga and mindfulness as complementary therapies for addiction:*

Although a small number of experimental and clinical studies on effectiveness of yoga and mindfulness practice in illicit drug use, alcohol dependence and smoking, the current theoretical models suggest that they can target multiple psychological, neural, physiological, and behavioral processes implicated in addiction and relapse (**Khanna and Greeson, 2013**).

Hallgren et al. (2014) has been explored the feasibility of yoga as a part of a treatment program for alcohol dependence through a pilot study that proved decrease in alcohol consumption when adding yoga to the usual treatment but the difference was not statistically significant.

In a review of evidence based yoga intervention's impact on smoking cessation it was found that it represents a promise for smoking cessation since it was able to enhance quitting. However, there were some limitations including short term follow up and short duration of therapy (**Dai and Sharma, 2014**).

4) *Vaccines against drugs of abuse:*

Immunotherapeutic vaccines against different drugs of abuse as nicotine, cocaine, heroin, oxycodone, methamphetamine, and others are being developed. They act through inducing antibodies that sequester the drug in the blood in the form of antibody-bound drug that cannot cross the blood brain barrier,

thereby preventing psychoactive effects (**Alving et al., 2014**).

Few of these vaccines have entered clinical trials, but research is going on apace (**Kosten and Domingo, 2013**) however, **Kinsey (2014)** focused on several points that should be fully characterized before this treatment can realize its full potential including:

1- Hapten structure: should be able to induce antibodies that bind to the free drug with good degree of specificity and affinity

2- Linkage chemistry: should be simple to allow for good manufacturing practice and the linker should be stable against hydrolysis

3- Immunogenic proteins: choosing the most promising immunogenic protein that can be approved from the US Food and Drug Administration (FDA)

4- Adjuvants: which adjuvant or which combination of adjuvants is the best stimulant for the immune system.

5) *N-methyl-d-aspartate (NMDA) Receptor Modulators in the Treatment of Drug Addiction:*

Glutamate plays an important role in drug addiction (**Gass and Olive, 2008**), and the N-methyl-d-aspartate (NMDA) glutamate receptor presents a molecular target for several drugs of abuse (**Myers et al., 2011**).

These NMDA receptor ligands include receptor modulators (memantine and acamprosate), as well as the partial NMDA agonist d-Cycloserine. Review of studies testing such ligands suggests that direct NMDA receptor modulators have relatively limited efficacy in drug addiction treatment, and that partial agonist may have some efficacy (**Tomek et al., 2013**).

Studies examining novel ligands with indirect mechanisms for altering NMDA receptor function are going on apace. These ligands include metabotropic glutamate receptor 5 positive allosteric modulator (mGluR5 PAM) which indirectly enhance NMDA receptor function through biochemical and structural linkage between these two receptor subtypes (**Chen et al., 2011**).

Several studies have been published testing mGluR5 PAM for addiction treatment however these studies are in the preclinical stage (**Gass and Olive, 2009; Cleva et al., 2011; Reichel, 2011; Kufahl et al., 2012**).

6) *Acupuncture and hypnotherapy for smoking cessation:*

Acupuncture and hypnotherapy gained a great interest as a complementary and alternative medicine for use in tobacco cessation programs (**Sood et al., 2006**).

Tahiri et al. (2012) had conducted meta-analysis of trials using acupuncture and hypnotherapy in smoking cessation. The results suggested that both may help to quit smoking.

The other two Cochrane systematic reviews evaluating the effectiveness of acupuncture and hypnotherapy for smoking cessation were performed by **White et al. (2011)** and **Barnes et al. (2010)** and concluded that no consistent evidence that acupuncture and the related interventions (acupressure, laser therapy and electrostimulation) and hypnotherapy are effective for smoking cessation.

Braillon and Ernst (2013) have criticized the meta-analysis performed by **Tahiri et al. (2011),** where it included only 10 studies while the two Cochrane systematic reviews included 44 studies.

Zhu et al. (2013) referred the contradictory results in the clinical trials testing the efficacy of acupuncture in treatment of substance use disorder to the numerous administration methods and protocols performed by different acupuncture schools. Also, they advised that future animal studies and clinical trials should explain in details the acupuncture methods in order to optimize this alternative method in the clinical practice.

SUMMARY AND CONCLUSION

Drug dependence and addiction are major public health problems that do not discriminate between race, gender, ethnicity, or socioeconomic status of the drug user. Globally, the drug related problems affect more than tens of millions of people worldwide.

Despite the advances in the pharmacological and behavioral therapy of

drug addiction, this problem continue to maintain its presence in the society.

There are a number of medications approved for other medical conditions that have been tested as a possible treatment aid for addiction but there are only a handful of medications approved to treat specific addictions to substances as nicotine, opiate and alcohol.

Standard pharmacological treatments for nicotine dependence include nicotine replacement therapy, buproprion the monoamine uptake inhibitor, and the partial nicotinic acetylcholine receptor agonist. Also, standard pharmacological treatments for opiate dependence include opioid substitution therapies such as methadone and buprenorphine which is often formulated with low doses of the opiate antagonist naloxone to deter abuse. While standard pharmacological treatments for alcohol dependence include the aldehyde dehydrogenase inhibitor disulfiram, the broad spectrum opiate antagonist naltrexone, and also the NMDA receptor modulator acamprosate. Currently, there are no approved specific medications to treat addiction of marijuana, cocaine, methamphetamine, or behavioral addiction.

Also, many of the medications developed to treat drug addiction shows moderate effectiveness which is related to poor compliance to the drug and the possible side effects.

For the previous reasons it appears clearly that there was an urgent need to develop new medication. This articles reviewed different new lines of management of addiction including nanotechnology approach, brain stimulation methods, yoga and mindfulness practice, vaccines against drugs of abuse, the NMDA receptor modulators, and acupuncture and hypnotherapy.

Many studies have been performed to test the efficacy of the previous methods in addiction treatment. Some of which are in the preclinical stage and others are in the clinical stage and the results were variable.

Recommendations:

Much research is needed to test the efficacy of the previous methods to yield promising drugs for addiction treatment in the near future.

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الملخص العربى
الإدمان: حقبة جديدة من العلاج
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تعد مشكلة الإدمان من المشاكل الصحية الكبرى والتى لا تميز بين العرق أو الجنس أو الوضع الإقتصادى والإجتماعى للمدمن. تؤثر المشكلات المتعلقة بالإدمان على عشرات الملايين من البشر على الصعيد العالمى.

على الرغم من التقدم المطرد فى العلاج الدوائى والسلوكى للإدمان تستمر هذه المشكلة فى تواجدها بالمجتمع. بالإضافة إلى ذلك فإنه قد تم أختبار عدد من الأدوية المعتمدة لعلاج الحالات الطبية الأخرى كعلاج مساعد للإدمان لكن هناك فقط عدد بسيط من الأدوية المعتمدة والمتخصصة فى علاج الإدمان مثل النيكوتين والأفيون والكحول.

تشمل الأدوية المعتمدة لعلاج إدمان النيكوتين بدائل النيكوتين والبربروبيون ومثبطات امتصاص المونوامين والمناهض الجزئى لمستقبلات الاستيل كولين. كما تشمل الأدوية المعتمدة لعلاج إدمان الأفيون بدائل الأفيون مثل الميثادون والبيوبرنورفين والتى يمكن مزجها بجرعات صغيرة من مثبطات مستقبلات الافيون مثل النالوكسون. فى حين أن الأدوية المعتمدة لعلاج إدمان الكحول تشمل الدايسالفيرام مثبط انزيم الألكحول ديهيدروجينيز ومضاد الأفيون واسع المدى نالتركسون ومعدلات مستقبلات الإن ميثيل دى اسبارتات مثل الاكمبروسات. وعلى النقيض فإنه لا توجد أدوية معتمدة لعلاج إدمان الكوكايين و الحشيش والميثامفيتامين.

بالإضافة إلى ذلك فإن بعض الأدوية التى تم اختبارها لعلاج الإدمان أظهرت فاعلية متوسطة نظرا لضعف الامتثال للدواء والاثار الجانبية المحتملة.

لذلك يتضح من كل ما سبق الحاجة القصوى لاكتشاف أدوية جديدة. وقد شمل هذا الموضوع عرض للأنواع المختلفة لعلاجات الإدمان الحديثة والتى تتضمن:

- تطبيقات جزيئات النانو لعلاج الإدمان: لقد اتسع استخدام تكنولوجيا النانو فى المجال الطبى وخاصة فى توصيل الادوية للخلايا المستهدفة وقد تمت أول محاولة لاستخدام هذه التقنية فى علاج الادمان سنة ٢٠٠٩ ثم تلاها عدة محاولات واعدة فى هذا المجال

- طرق استثارة المخ: توجد العديد من الطرق لاستثارة المخ وقد وجد ان بعض هذه الطرق فعال فى تقليل استخدام النيكوتين والكحول. ربما يكون ذلك من خلال زيادة الدوبامين والجلوتامت فى الاجزاء المسؤلة عن الادمان فى المخ

- اليوجا: تعد التجارب التى اجريت لاختبار فاعلية هذه الطريقة فى علاج الادمان قليلة الى حد ما ويعد قصر مدة العلاج والمتابعة من المشاكل التى قابلت هذه التجارب

- اللقاحات المضادة للإدمان: تعمل هذه العلاجات من خلال تحفيز الجسم لانتاج اجسام مضادة حيث تتحد هذه الاجسام المضادة مع الادوية المسببة للادمان فى الدم ومنع وصولها للمخ ومن ثم منع تأثيرها

- معدلات مستقبلات الإن ميثيل دى اسبرتات: تعد هذه المستقبلات هدف جزيئى هام للكثير من أدوية الادمان. حيث تؤثر بعض الادوية عليها بطريقة مباشرة والبعض الاخر بطريقة غير مباشرة

- الوخز بالإبر والعلاج بالتنويم: تم اختبار هذه الطرق فى العديد من التجارب وكانت النتائج مختلفة نظرا لاختلاف بروتكولات العلاج المستخدمة

لذلك ومن كل ما سبق نوصى بإجراء المزيد من الأبحاث من أجل اكتشاف أدوية واعدة وفعالة لعلاج الإدمان فى المستقبل القريب.