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The Addictive Brain: All Roads Lead to Dopamine

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Abstract — This article will touch on theories, scientific research and conjecture about the evolutionary genetics of the brain function and the impact of genetic variants called polymorphisms on drug-seeking behavior. It will cover the neurological basis of pleasure-seeking and addiction, which affects multitudes in a global atmosphere where people are seeking "pleasure states."

Keywords — brain reward cascade, dopamine, mesolimbic system, orbital prefrontal cortex-cingulate gyrus, relapse, reward deficiency syndrome (RDS)

When almost half of the U.S. population have indulged in illegal drug practices, when presidential candidates are forced to dodge the tricky question of their past history involving illegal drug use, and when most Americans have sloshed down a martini or two in their lifetime, there must be a reason, there must be a need—this must be a natural response for people to imbibe at such high rates. Even more compelling questions surround the millions who seek out high-risk novelty. Why do millions of us have this innate drive in the face of putting themselves in harm's way? Why are millions paying the price of their indiscretions in jails, hospitals, wheel chairs or cemeteries? What price must be paid for pleasure seeking or just plain getting "high"? Maybe the answer lies within the brain, and in particular the genome.

Once it was true that all roads led to Rome. Recently it has been said (with regard to understanding the brain) that all roads lead to dopamine. Thus, this simple truth is not

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too dissimilar to considerations of the reward circuitry of the brains of homo sapiens. Numerous experiments in the scientific literature have established that the brain's major reward neurotransmitter pathway —the road to Rome—is indeed dopamine (Kirsch et al. 2006).

Dopamine was first synthesized in 1910 by George Barger and James Ewens at the Wellcome Laboratories in London, England. It was named dopamine because it is a monoamine whose precursor is levodopamine. In 1958 at the National Heart Institute of Sweden, Arvid Carlsson and Nils-Ake Hillarp were the first to recognize dopamine's function as a neurotransmitter (Benes 2001). In 1978 one of the present authors (KB) invited Arvid to present at the first Gordon Conference on Alcoholism in Santa Barbara, California, for a discussion of the important role of dopamine in alcoholism. Twenty-two years later in 2000 Carlsson was awarded the Nobel Prize for Physiology or Medicine.

EVOLUTIONARY GENETICS OF DOPAMINE

Currently throughout the neuroscience literature dopamine is considered both a "pleasure molecule" and an "antistress molecule." The role of dopamine in brain function has been fraught with controversy but is arguably very interesting and mind expanding (Blum et al. 2000). There are many unanswered questions related to what makes us human and what drives our unique behaviors. While many brain theories have focused on the role of brain size and genetic adaptations, Fred Previc (2009), explored the provocative concept of a "dopaminergic society." According to Previc, the dopaminergic mind hypothesis seeks to explain the differences between modern humans and their hominid relatives by focusing on changes in dopamine. It theorizes that increased levels of dopamine were part of a general physiological adaptation due to an increased consumption of meat around two million years ago by homo habilis and later (beginning approximately 80,000 years ago) by dietary changes and other environmental and social factors. This theory is supported by recent discoveries about the seaside settlements of early man where evidence of dietary changes, like the inclusion of fish oils—known to increase dopamine receptors—could have further enhanced dopamine function (Kuperstein et al. 2005).

Previc's theory is that the "high-dopamine" society is characterized by high intelligence, a sense of personal destiny, a religious/cosmic preoccupation, and an obsession with achieving goals and conquests. High levels of dopamine are proposed to underlie increased psychological disorders in industrialized societies. According to this hypothesis, a "dopaminergic society" is an extremely goal-oriented, fast-paced, and even manic society, "given that dopamine is known to increase activity levels, speed up our internal clocks and create a preference for novel over unchanging environments"(Previc 2009).

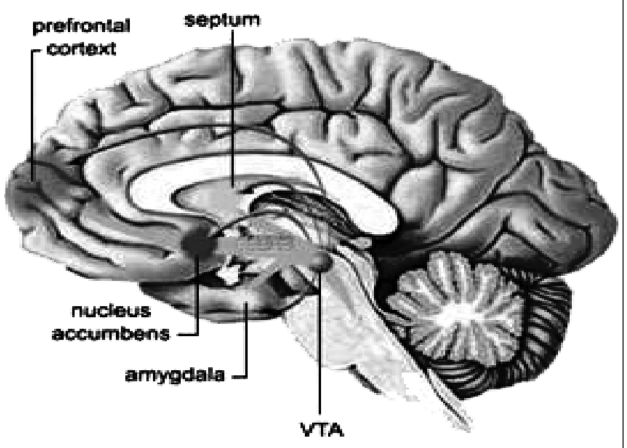
Although behavioral evidence and some indirect anatomical evidence like the enlargement of the dopamine-rich striatum in humans revealed by the work of S.I. Rapoport (1990) support a dopaminergic expansion in humans, according to M.A. Raghanti and associates (2008) there is still no direct evidence that dopamine levels are markedly higher in humans relative to apes. However, the recent discoveries about seaside settlements of early man may provide evidence of dietary changes consistent with this hypothesis.

There are a number of studies that report the positive relationship between omega 3 fish oil and dopamine D2 receptor density. Specifically, decreased tissue levels of n-3 (omega-3) fatty acids, particularly docosahexaenoic acid (DHA), are implicated in the etiologies of nonpuerperal and postpartum depression. Davis and colleagues (2010) examined the effects of a diet-induced loss of brain DHA content and concurrent reproductive status on dopaminergic parameters in adult female Long-Evans rats. Decreased brain DHA produced a significant main effect of decreased density of ventral striatal D(2)-like receptors. Virgin females with decreased DHA also exhibited higher density of D(1)-like receptors in the caudate nucleus than virgin females with normal DHA. These receptor alterations are similar to those found in several rodent models of depression, and are consistent with the proposed hypodopaminergic basis for anhedonia and motivational deficits in depression.

EVOLUTIONARY GENETICS AND THE DRD2 GENE

The possibility does exist that prehistoric ancestral species over two million years ago carried the low dopamine brain function due to low dopamine receptors (Blum et al. 2012). Dopamine functions as a neurotransmitter, activating the five known types of dopamine receptors (D1 through D5) and their variants. Dopamine from l-tyrosine, abundant in meat, is produced in several areas of the brain, including the brain reward site in the nucleus accumbens (NAc) which is located in the reptilian, old brain region called the mesolimbic system (see Figure 1). It now well known that there are two major variant forms of the human dopamine D2 receptor gene (DRD2) that regulate the synthesis of D2 receptors; they are the A1 and A2 alleles. As these forms (polymorphisms) exist in pairs, there at least are three variants of the dopamine D2 receptors: the A1/A1, the A1/A2, and the A2/A2. DRD2, the most widely studied gene, accounts for major aspects of modern human behavior. The DRD2 A2 form, which in today's world is considered the "normal" variation, is carried by 2/3 of the United States population. Carriers of the DRD2 A1 form

FIGURE 1
The Brain Reward Site*



*Modified from Comings 2008 with permission

about 1/3 of today's U.S. population and have 30% to 40% lower D_2 receptors; this is a subset of approximately 100 million people (Blum 2011). However, within this subset, the prevalence varies significantly between Caucasians, African Americans, Hispanics, Asians and Native Americans (Castiglione et al. 1995). It is prudent to speculate that the older gene form (DRD2-A1) leading to low dopamine function may have afforded certain survival benefits. But as homo habilis or Australopithecus sediba (Berger et al. 2010) increased their meat consumption, feeding the brain with the needed l-tyrosine to synthesize more dopamine required to overcome the D_2 receptor deficit (competitive edge), a new society was born—the "high dopamine society" carrying the DRD2 A2 form of this gene (Blum et al. 1996a, b).

David Comings (1996) writing in his popular book *The Gene Bomb* suggests that while it may be true that genetic adaptations are very slow there may be some exceptions like the Tibetan altitude gene that allowed for adaptation to high altitudes. Comings also discussed the future of the DRD2 gene. Let us assume that the a gene variant called X causes addiction, and that individuals with this X gene drop out of school earlier, cohabitate with others carrying the same genotype (this is known as "birds of a feather flock together," another characteristic of the DRD2 A1 form; Fowler, Settle & Christakis 2011) and start having children earlier than individuals who do not carry that gene. Let us also assume that the average age at birth of the first child of X gene carriers is 20 years, while for those not carrying the variation it is 25 years. As a result, the X form of the gene will reproduce faster, namely every 20 years, while the normal form of the gene will reproduce every 25 years. The ratio of 25/20 is 1.25. Although this gene X may seem to not have any selective benefit one must consider the fact that having low D2 receptors in our current society may confer certain competitive advantages like enhanced aggression, novelty seeking and risk taking, leading to greater survival as it did in the past (Comings 1996).

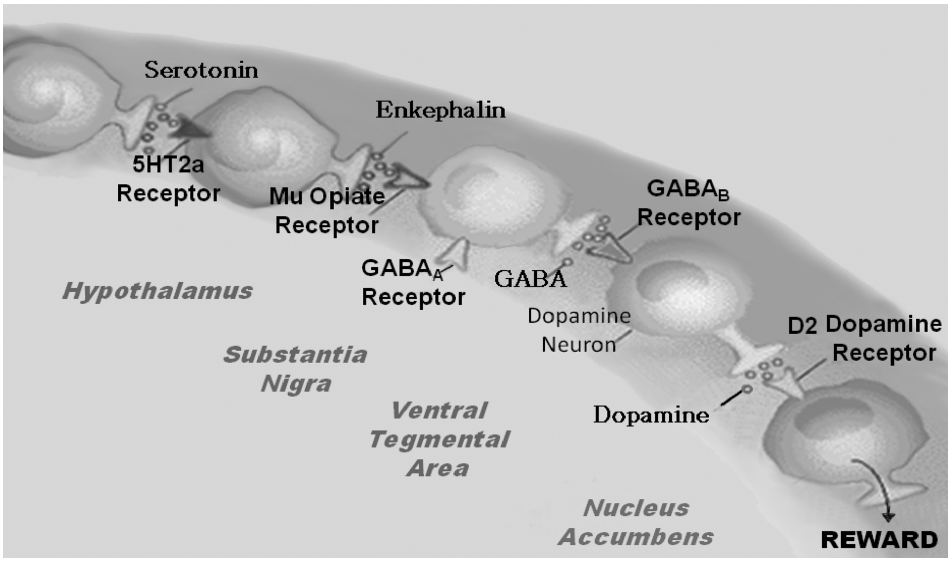
WHAT IS THE DOPAMINE-ADDICTION CONNECTION?

The conviction that drug and alcohol dependence was a disease rather than a symptom of moral weakness was growing in the late nineteenth and early twentieth century, there was no knowledge of how the disease might be acquired or treated. Importantly, the therapies used to treat this disease remained focused solely on psychological factors and lifestyle behavior modification (with the help of drugs) as if it were still a psychiatric condition rooted in moral weakness. The good news today is that understanding that low dopamine function leads to impulsive, compulsive and addictive behaviors paves the way to defining addiction as a brain disorder involving impairments in so-called "reward circuitry" (Blum et al. 2000). This definition of addiction has now been adopted by the American Society of Addiction Medicine (ASAM 2011), which was founded by the San Franciscan visionary David E. Smith (Sturges 1993).

This new definition is based in part on our initial conceptualization of the "brain reward cascade" (see Figures 2 and 3 and Blum 2011) and the discovery in 1990 in collaboration with Earnest Noble of the genetic association between alcohol addiction and the reward gene DRD2 (Blum et al. 1996a,b, 1990). This was the first evidence of the link between addictive behavior genes and neurotransmitters. Subsequently, in 1995 Blum coined the term "reward deficiency syndrome" (RDS), an umbrella term for behaviors that are associated with genetic antecedents that result in a hypodopaminergic state and a predisposition to obsessive, compulsive and impulsive behaviors (see Table 1). All of these behaviors have been linked with low dopamine function due to an association with the presence of the DRD2-A1 gene form (Blum et al. 2012, 2011b, 1996 a, b).

Based on an abundance of literature indicating that low brain dopamine function confers a high vulnerability to substance use and aberrant behavior seeking, it is not surprising that every known abusable drug as well as gaming, sex and even music all cause the neuronal release of dopamine at the brain reward site. In essence this helps explain the concept of self-medication. An individual with low dopamine function will seek out substances and/or behaviors known to boost dopamine function. This can be temporarily achieved through alcohol, drugs, food, smoking, sex and gaming. These drugs and behaviors provide a pseudo feeling of well-being that could in the short-term asymptotically reach a so-called feeling of "normalization"

FIGURE 2
The Interaction of Various Neurotransmitter Including Serotonin, Enkephalins, GABA and Dopamine Constitute the "Brain Reward Cascade"



The brain reward cascade starts in the hypothalamus of the brain sitting in the midbrain called the mesolimbic system where serotonin acts as the neurotransmitter activating the enkephalins (one type of brain endorphin); the enkephalins are released in the hypothalamus and stimulate mu receptors in another part of the brain called substania nigra that contains the neurotransmitter GABA (an inhibitory neurotransmitter) that stimulates $GABA_B$ receptors that projects to the ventral tegmental area (VTA) brain region where dopamine neurons are inhibited to allow for just the right amount of dopamine to released at the nucleus accumbens (reward site of brain).

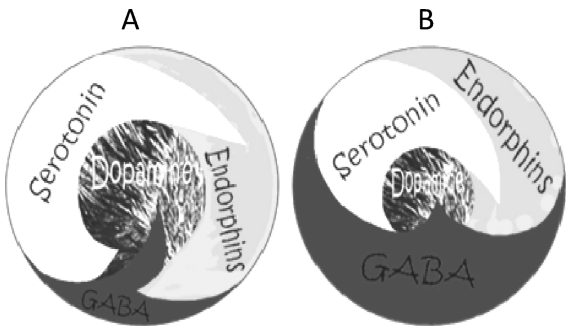
(Blum et al. 2012). This fact is coupled with the understanding that dopamine functions in the brain to provide a feeling of pleasure and promotes general well-being and happiness (Blum et al. 2012; see Figure 3).

An orgasm is the primary natural blast of dopamine available to all of us. Accordingly, J.R. Georgiadis (2006) scanned the brains of people having orgasm. He said they resembled scans of heroin rushes. These individuals experienced one of the most addictive substance ever produced: dopamine. Orgasms and addictive substances or behaviors have two things in common. They produce an initial pleasurable experience, and both are followed by neurochemical fluctuations that appear to continue for a week or two. According to some sexual satisfaction is innate, or what we have always experienced. That is one reason many never notice its effects—they have always been there.

"What goes up must come down." It's simple: *biological systems must return to balance*, or homeostasis. In this case dopamine (or sensitivity to dopamine) rising and falling that can play around with your mood and most importantly, your love life, including the way in which you perceive and treat your partner. In terms of love and relationships there are two brain chemical messengers involved: oxytocin and dopamine (Ross & Young 2009). In fact, oxytocin and dopamine are the yin and yang of bonding and love. Dopamine furnishes the kick, oxytocin makes a *particular* mate appealing, in part by triggering feelings of comfort. It is necessary to have both acting on the reward circuitry at ideal levels to stay in love. In animal experiments, if scientists block either oxytocin or dopamine, mothers will ignore their offspring (Heather et al. 2009).

While having any genetic deficit in the reward site of the brain may predispose an individual to a higher risk for RDS, it is always the combination of our genes and their interaction with environmental elements that predict not only addictive behaviors in general but specificity of the type of drug or behavior of choice. A Bayesian mathematical formulation developed by a sixteenth century monk was used to predict the life-time risk for any RDS behavior for those carrying the A1 polymorphism of the DRD2 gene, which causes low D_2 receptors in the reward site. The total risk for any behavior was predicted to be as high as 74% (Blum et al. 1996a). However, as Steve Sussman of the University of Southern California points out, RDS is highly

FIGURE 3
Brain Reward Cascade*



Happy Brain A represents the normal physiologic state of the neurotransmitter interaction at the mesolimbic region of the brain. Briefly, serotonin in the hypothalamus stimulates neuronal projections of methionine enkephalin in the hypothalamus that, in turn, inhibits the release of GABA in the substania nigra, thereby allowing for the normal amount of dopamine to be released at the nucleus accumbens (NAc), reward site of the brain.
Unhappy Brain B represents hypodopaminergic function of the mesolimbic region of the brain. The hypodopaminergic state is due to gene polymorphisms as well as environmental elements, including both stress and neurotoxicity from aberrant abuse of psychoactive drugs (i.e. alcohol, heroin, cocaine etc) and genetic variables.
*Adapted from Blum et al. 2010 with permission.

impacted by environmental epigenetic factors affecting our *RNA* rather than just genetic factors involving our *DNA* (Sussman & Sussman 2011). While one is not doomed because of their genes to become addicted, they are definitely at high risk and as such may require this genetic knowledge earlier rather than later in life.

PROBING THE MYSTERIES OF RECOVERY

The problem regarding addiction in society is global and widespread. The total population of the United States at the turn of the twenty-first century was 281,421,906. The total number of people above the age of 12 was estimated at 249 million (US Census Bureau 2011). The National Institutes on Drug Abuse and the Substance Abuse and Mental Health Services Administration (SAMHSA) have surveyed persons age 12 and older and found that in the year 2001, a total of 104 million people had ever used illegal drugs in their life, 32 million had used a psychoactive drug in the past year (2000–2001) and 18 million had used a psychoactive drug in the past 30 days (NIDA 2010). Interestingly this does not include alcohol. Children of alcoholics are 50% to 60% more likely to develop alcohol use disorder than people in the general population. Similarly children of parents who abuse illicit drugs may be 45% to 79% more likely to abuse drugs themselves than the general population. In the United States in 2008 the highest percent prevalence of any alcohol use disorder was 18.4 and any drug use disorder was 7.0 at ages 18–24. Men are more likely than women to have problems with alcohol, drugs or two substances combined (US DHHS 2008). In 2007, 182 million prescriptions were written for pain meds. (NIDA 2010). There is a growing concern among addiction professionals about a new epidemic in America involving prescription of pain medication. We must ask then, who are the people that could just say "no."

John Giordano, in thinking about the recovery process, emphatically stated, "Can you imagine jumping out of a plane without a parachute?" (Giordano & Blum 2010). Mark Gold accurately stated, "In spite of all the effort and progress made by the addiction community, as a whole, it has failed to both comprehend and willingly incorporate well established, evidence-based medical modalities into treatment, especially as it relates to relapse prevention" (Blum et al. 2011b).

We now know that the patient who carries certain high-risk genetic deficits, such as low dopamine function ("dopamine resistance") in the brain reward site, is at a high risk of relapse. Following treatment—residential or nonresidential—where no attempt is made to enhance the function of brain dopamine, the patients who most likely carry gene variants that cause low dopamine function in the brain are released back into society and are probably doomed to relapse. Are we approaching the time when, along with "love needs care" (coined by David Smith), providers can supply a much-needed parachute?

Science Meets Recovery

It is encouraging that for the first time in this millennium the addiction community is about to embrace newer scientific and clinically proven modalities. In this regard the following areas must be adequately addressed by treatment providers:

- Genetic testing to determine risk for RDS
- Safe and effective nutrigenomic and neuromodulation solutions to activate dopaminergic pathways in the brain
- Holistic modalities that promote well-being
- Drug testing to assist in determining medication adherence and use as outcome measures
- Tests related to alterations of reward gene expression as a molecular outcome measure
- Continued utilization of self-help organizations
- Psychological, behavioral and spiritual therapy

While this is a profound wish list, significant progress is being made in a global thrust to characterize, delineate and develop through necessary rigorous investigation those elements required to translate research from the bench to bedside.

TABLE 1
The Reward Deficiency Syndrome Behaviors (RDS)*

Addictive Behaviors	Impulsive Behaviors	Compulsive Behaviors	Personality Disorders
Severe Alcoholism	Attention-Deficit Disorder & Hyperactivity	Aberrant Sexual Behavior	Conduct Disorder
Polysubstance Abuse	Tourette Syndrome	Internet Gaming	Antisocial Personality
Smoking	Autism	Pathological Gambling	Aggressive Behavior
Obesity			Generalized Anxiety

*Reproduced from Blum et al. 1996a with permission

Understanding Diagnosis, Prevention and Treatment Strategies

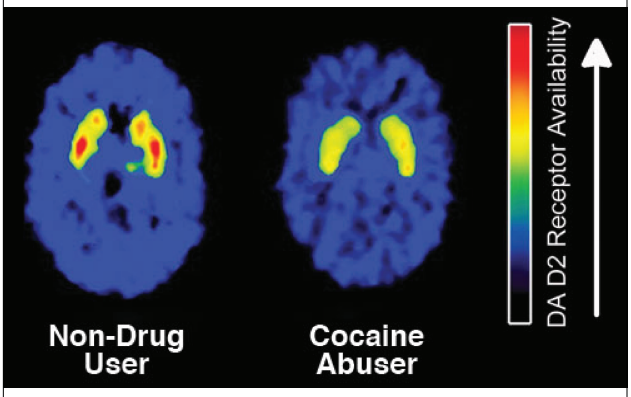
In general people begin taking drugs for a variety of reasons: to feel good, to feel better, to do better, and because others are doing it. Importantly, at first, people may perceive what seem to be positive effects from drug use. They also may believe that they can control their use; however, when drug abuse takes over, a person's ability to maintain prudent executive function and exert self-control can become seriously impaired. Brain imaging studies from drug-addicted subjects show physical changes in areas of the brain that are critical to judgment, decision-making, learning, memory and behavior control (see Figure 4). Cocaine prevents dopamine reuptake by binding to proteins that normally transport dopamine. Not only does cocaine "bully" dopamine out of the way, it hangs on to the transport proteins much longer than dopamine does. As a result, more dopamine remains to stimulate neurons, which causes prolonged feelings of pleasure and excitement. Amphetamine also increases dopamine levels. Again, the result is overstimulation of these pleasure pathway nerves in the brain (NIH/NIDA 2010).

Why do some people become addicted to drugs, (or any aberrant RDS behavior noted in Table 1 above) while others do not? As mentioned earlier, vulnerability to addiction differs from person to person and is influenced by both environmental (home, family, nutrition, availability of drugs, stress, and peer pressure in school, early use and method of administration) and genetic risk factors. Researchers estimate that genetic factors account for between 40% to 60% of a person's vulnerability to addiction, (especially alcoholism) including the effects of environment on gene expression and function. It is noteworthy that both adolescents and individuals with comorbid mental disorders are at greater risk of drug abuse and addiction than the general population (Pickens et al. 1991).

Genetic Test to Determine Risk for RDS

One very important preventive tactic is to develop a genetic-based test to determine risk and vulnerability to substance abuse and harmful behaviors during adolescence.

FIGURE 4
Brain Images Showing Decreased Dopamine (D_2) Receptors in the Brain of a Person Addicted to Cocaine Versus a Nondrug User (color figure available online)



The dopamine system is important for conditioning and motivation, and alterations such as this are likely responsible, in part, for the diminished sensitivity to natural rewards that develops with addiction (NIDA 2010).

One of the brain areas still maturing during adolescence (from age five to 20) is the prefrontal cortex—the part of the brain that enables one to assess situations, make sound judgments, and maintain emotions. Thus use of drugs while the brain is still developing may have profound and long-term consequences. Drug abuse often starts as early as 12 years and peaks in the teen years. This has added real impetus for the development of a test to determine a "genetic addiction risk score" (GARS) as an early preventive tool. The GARS test will also have relevance for treatment of addicted patients to reduce both guilt and denial and to determine levels of support required for maintenance and relapse prevention. This test coupled with the message that drugs are harmful to the brain (having both short and long-term consequences) should lead to a reduction of youthful drug use or abuse (Blum et al. 2010).

Given that about 30% of people in the U.S. are born with genetically induced low dopamine brain function (Noble et al. 1991), how can we overcome this survival variant of human nature and prevent excessive craving behavior? Certainly, the human brain is the most complex organ in the body. The brain is a communications center consisting of billions of neurons, or nerve cells. Unfortunately drugs can alter brain areas: *the brain stem* that is necessary for sustaining life through motor and sensory control, *the limbic system* that regulates the ability to feel pleasure, and the *cerebral cortex* that powers the ability to think. Pleasure produced from drugs of abuse occurs because most of these drugs target the brain's reward system by flooding the circuit with dopamine (Budygin et al. 2012). When some drugs like cocaine are taken, they can release two to ten times the amount of dopamine; the resultant effects on the brain's pleasure circuit dwarfs those produced by natural rewards such as food and even sex. This fact alone strongly motivates people to take drugs again and again. Independent of one's genetic makeup, if one keeps taking drugs the brain adjusts to the overwhelming surge in dopamine and other neurotransmitters causing a breakdown in the natural process of brain reward by producing less dopamine or by reducing the number of dopamine (D2) receptors. This process causes abnormally low dopamine function, high cravings and reduced ability to perceive pleasure (Chen et al. 2011).

Dopamine Agonist Therapy

Scientists across the globe, including Dr. Nora Volkow the director of NIDA, have suggested that dopamine agonist therapy would reduce cravings and prevent relapse and drug-seeking behavior (Thanos et al. 2008). The bottleneck to date is that typical pharmaceutical agents that have dopaminergic activation qualities are too powerful and as such have profound side effects. Studies are beginning to support the idea that the dopaminergic system can be stimulated with a patented natural, nonaddictive D2 agonist KB220 neuroadaptogen. Neuroimaging tools (qEEG, PET, and fMRI) are being used to demonstrate the impact of KB220IV and KB220Z oral (SynaptaGenX™; see Table 2) as a safe activator of brain reward dopamine. One hour after administration KB220Z "normalizes" aberrant electrophysiological activity in subjects undergoing protracted abstinence from alcohol, heroin and cocaine at the prefrontal cortex–cingulate gyrus, the site in the brain for relapse, by increasing alpha and low beta waves with effects similar to ten to 20 sessions of neurofeedback (Figure 5). Moreover, preliminary data from China using fMRI imaging is showing that KB220Z induces activation of dopamine pathways in the reward site of the brain (Blum et al. 2012; Chen et al. 2011).

In terms of genetically-induced low D2 receptors, we believe that based on 26 clinical trials with KB220 variants, long-term activation of dopaminergic receptors with this natural substance will result in the proliferation of D2 receptors leading to enhanced "dopamine sensitivity" and thus, an increased sense of happiness, particularly for carriers of the DRD2 A1 gene form who have 30% to 40 % less D2 receptors (Chen et al. 2011). This is also true for certain brain-stimulating devices such as Trans-Magnetic Stimulator (TMS) and a newly developed neuro-modulator –NEAT 12 (cranial electrical stimulator) in unpublished research showing dopamine activation in the brain reward site and relapse site respectively.

TABLE 2
KB220Z (SynaptaGenX™) Ingredients*

Gras Nutrients	Neurotransmitter Pathway
D-Phenylalanine	Opioid Peptides
L-Phenylalanine	Dopamine
L Tryptophane	Serotonin
L-Tyrosine	Dopamine
L-Glutamine	GABA
Chromium	Serotonin
Rhodiola rosea	COMT and MOA
Pyridoxine	Enzyme catalyst

*Reproduced from Chen et al. 2011 with permission.

FIGURE 5
KB220Z Normalizes qEEG Dysregulation by Increasing Alpha and Low Beta Bands

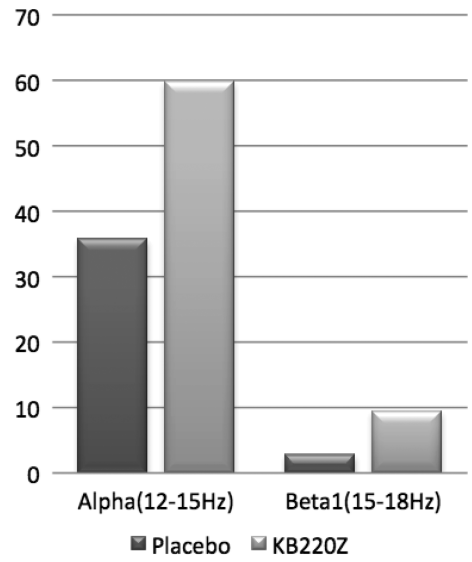


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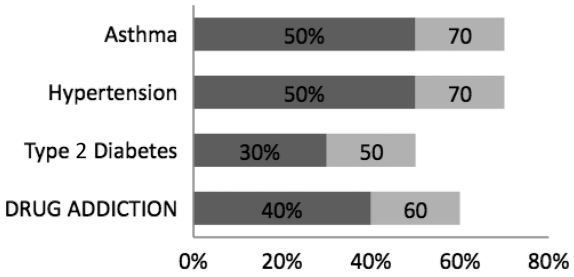
TABLE 3
FDA Approved Addiction Medications

Drug and Alcohol	**Tobacco**
Naltrexone	Bupropion
Acamposate	Varenicline
Campral	Chantix
Disulfirm	
Opioids	**Nicotine Replacement**
Methodone	Patches
Buprenorphine	Inhaler
Naltrexone	Gum

FIGURE 6
Addiction Relapse Rates Compared to Other Chronic Illnesses



Numbers shown are range in percents.

Holistic Modalities that Promote Well-Being

Moreover, meditation (Kjaer et al. 2002), yoga, exercise, diet, music therapy, relaxation using Audio Therapy (Morse et al. 2011), acupuncture (Blum et al. 2011a) and potentially hyperbaric oxygen therapy (HBOT) are known holistic modalities that could induce dopamine release. Coupling talk therapy, behavioral therapy (cognitive behavioral therapy, motivational incentives, motivational interviewing, and group therapy) with treatment medications (see Table 3) and whole body testing for peripheral markers (i.e. adrenal function, thyroid function, tissue levels of heavy metals, hormones and brain mapping) provides the clinician with a blueprint for successful treatment.

One of the most powerful elements about recovery is the understanding of the 12-Step program. To many in recovery this is essential. However, some individuals are conflicted about the acceptance of spirituality and the "higher power" concepts. Nevertheless, it is important to realize that the quality of and dependence on the cognisant connection to such a belief system can be significantly influential in an individual's ability to achieve a state of peace and happiness.

Comings and associates (2008) were the first group to identify the role of a specific gene in spirituality. The gene was the dopamine D4 receptor gene (DRD4) gene, which was found to play a role in *novelty seeking*. Others have also found evidence for what was called the "God gene" or the dopamine vesicular transporter gene (VMAT2), which was reported to be associated with spirituality (Hamer 2005). In fact those individuals who scored high on self-transcendence are less likely to abuse alcohol or drugs. That dopamine is the "feel good" neurochemical may help explain why spirituality plays a powerful role in the human condition and why the majority of people derive great comfort and happiness from a belief in a God (Comings 2008).

Drug Testing to Assist in Medication Adherence and Overall Outcome Measures

Drug and urine testing are important to determine treatment outcomes and compliance. Different types of medications may be useful at different stages of treatment to help a patient stop abusing drugs, stay in treatment and avoid relapse. Figure 6 illustrates a comparison of relapse rates between drug addiction and other chronic illnesses. Relapse rates for drug-addicted patients are compared with rates for those suffering from other chronic illnesses (McLellan et al. 2000). Relapse is common and is similar across Type 2 diabetes, hypertension and asthma and is dependent in part to adherence to treatment medication. Certainly the relapse rates of approximately 22% for physicians due to mandates of potentially losing a professional license is better than the general population, which is much higher and varies across different drugs of abuse (DuPont et al. 2009). Thus it is very important to determine not only adherence to medication but unexpected use of drugs during treatment, which is a trigger for relapse. Most recently utilizing the Comprehensive Analysis of Reported Drugs (CARD™; Dominion Diagnostics), in unpublished work it was discovered that in at least six east coast states there was a significant nonadherence to treatment medication, but significant use of unexpected drugs was noted across all states evaluated.

Self-help Organizations, Psychological and Spiritual Therapy

The use of KB220Z™ in treatment facilities should enhance well-being, improve cognition and judgment, and most importantly, facilitate adherence for acceptance of the 12-Step program. It is important to find dopamine D2 activators that will not down regulate D2 receptors like bromocryptine. We propose that a reduction in stress will impact one's state of happiness and spirituality. Thus agents that reduce stress such as known natural dopamine agonists should have benefits for craving reduction, relapse prevention and quite possibly prevention of other RDS behaviors, especially in adolescents.

CONCLUSION

Finally, the scientific understanding of addiction and all its ramifications and the incorporation of these new techniques and concepts into diagnosis, treatment, and most importantly prevention strategies may ultimately lead to not only reduced relapse but importantly enhance quality of life for many.

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