

Hypothesizing Synergy between Acupuncture/ Auriculotherapy and Natural Activation of Mesolimbic Dopaminergic Pathways: Putative Natural Treatment Modalities for the Reduction of Drug Hunger and Relapse

COMMENTARY

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Abstract

Acupuncture is a very ancient form of healing which predates recorded history. The philosophy is rooted in the Taoist tradition which goes back over 8000 years. To date this practice although used world-wide to treat addictive behaviors has not been generally accepted or scientifically proven. There are however many positive reports in the literature in its effectiveness in reducing symptoms of withdrawal from alcohol, heroin and cocaine. In addition, due to known neuro-chemical mechanisms associated with acupuncture, especially its role in pain relief and endogenous opioid function, clinical benefits in reward dependence behaviors seem parsimonious. In this review article we are hypothesizing synergy between acupuncture/auriculotherapy and natural activation of mesolimbic dopaminergic pathways to reduce drug hunger and prevent relapse. Following a review of the literature involving both of these modalities the scientific and clinical community is encouraged to carry out translational research in large randomized double-blinded placebo controlled investigations coupling these two anti-craving treatment modalities.

Keywords: Acupuncture; Auriculotherapy; Dopamine; Reward Deficiency Syndrome; Neuroadaptagen Amino -Acid Therapy (NAAT); KB220

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INTRODUCTION

Is Acupuncture Effective?

In the last few years acupuncture and now auricular therapy have been used increasingly to treat substance use disorders (Unschuld, 1985, Han et al., 2011). Studies of these modalities have validated their use, and more studies are needed and in process. There is no doubt that alcoholism and drug addiction are rampant in our society. Otto (2003) has suggested that incorporating acupuncture into existing programs offers a promising approach. Proponents say ear acupuncture alleviates acute opiate withdrawal, reduces craving for all substances, and helps retain patients in treatment. Otto correctly points out that over 25 years of clinical experience have supported this claim, but scientific research has been sketchy, complicated by technical difficulties and often poorly designed. Perhaps most important for the future is the growing acceptance of this treatment and the willingness of both Drug Courts and

managed-care organizations to provide it via licensed practitioners for use with multiple addictions.

Drug addiction is a chronic brain disorder characterized by withdrawal symptoms that occur during drug abstinence and a high tendency to relapse. Compared with the currently available pharmacological interventions, acupuncture therapy has the potential to help drug addicts stay away from drugs without major adverse side effects. According to Han *et al.* (2011) "it has taken decades of research to optimize the parameters of electrical acupoint stimulation for detoxification and for relapse prevention, as well as to establish a safe and easy procedure by which drug addicts can use it on themselves". The discovery in the 1970s that acupuncture can trigger the release of opioid substances from the brain relates to the neuro-chemical underpinnings of substance seeking behavior or Substance Use Disorder (SUD). This basic research on animals made it possible to understand one of the mechanisms of action of acupuncture and to establish the procedure for treating drug addictions.

While the mechanisms of acupuncture are not fully understood, modern research has demonstrated that successful acupuncture treatment results in a number of changes in important body proteins that could, themselves, act to decrease physical symptoms. These include indications that acupuncture mobilizes the opioid peptides (i.e. enkephalins, endorphins, and dynorphins) or increases levels of other peptides such as substance P and cholecystokinin (CCK) among many others. There are also indications that acupuncture may induce alterations in certain hormones including Cortisol and ACTH to reduce stress (Han & Shao, 1990). Further, electro-acupuncture has been recently been shown to significantly reduce internet addiction while increasing self-confidence and attenuating stress (Zhu *et al.*, 2009). Interestingly the authors found in a subsequent paper that Electro-acupuncture combined with psychological intervention can significantly improve anxiety state and the mechanism is possibly related with the decrease of Norepinephrine (NE) in the body (Zhu, 2008). This has been supported by others in terms of treating multiple addictions (Handley, 2009).

While acupuncture is widely utilized to treat cocaine addiction to date the actual scientific evidence does not support its singular role. Seven studies with a total of 1,433 participants were included in a study by Gates *et al.* (2006). All were of generally low methodological quality. No differences between acupuncture and sham acupuncture were found for attrition RR 1.05 (95% CI 0.89 to 1.23) or acupuncture and no acupuncture: RR 1.06 (95% CI 0.90 to 1.26) either neither for any measure of cocaine or other drug abuse. The number of participants included in meta-analyses was low, and power was limited. Gates *et al.* suggested that there is currently no evidence that auricular acupuncture is effective for the treatment of cocaine dependence. The evidence is not of high quality and is inconclusive. Further randomized trials of auricular acupuncture may be justified. This is in agreement with the meta-analysis performed by Mills *et al.* (2005), D'Alberty (2004), Margolin (2003), Ter Riet *et al.* (1990) and Whitehead (1978).

However, a study by Lipton *et al.* (2004) provided some evidence that acupuncture had positive outcome when utilized to prevent relapse with cocaine addicts in the New York City area. They found that the efficacy of auricular (ear) acupuncture in reducing cocaine/crack craving and consumption was examined via a single-blind, placebo experiment. Specifically, one hundred and fifty individuals seeking treatment for cocaine/crack abuse were randomly assigned to receive either experimental or placebo acupuncture treatments.

Treatments were provided in an outpatient setting for a one-month period. Placebo treatments involved acupuncture at ear locations not used for drug treatment. Subjects provided urine specimens for drug content analysis after each acupuncture session. Urinalysis results over the one-month study period favored the experimental group. Experimental subjects in treatment over 2 weeks had significantly lower cocaine metabolite levels relative to placebo subjects in treatment for a comparable period. Treatment retention with both groups was similar. Relative to pretreatment usage, a significant decrease in cocaine consumption was reported by both groups.

Courbasson *et al.* (2007) found that compared to women in the control group women receiving acupuncture reported having reduced physiological cravings for substances, felt significantly less depressed, less anxious, and were better able to reflect on and resolve difficulties. The authors concluded that auricular acupuncture, as an adjunct therapy to a comprehensive psycho-educational treatment program for women with addictions, shows promise as a more viable and effective, non-drug treatment alternative to anxiolytics.

Since scientific research has shown that addiction, withdrawal, and recovery are all related to brain chemicals such as the opioid peptides and to stress regulating hormones in the body, it is reasonable, then, that use of procedures that affect these systems be explored. Some may be reluctant to trust the effectiveness and safety of acupuncture and auriculotherapy. However, the U.S. Food & Drug Administration (FDA) has recognized electrical devices used in auriculotherapy and the acupuncture needle as medical devices. Research support for the effectiveness of the procedures is abundant and will be discussed later. While there are some who claim that there are not enough sound clinical studies to support efficacy of acupuncture, ear acupuncture or auriculotherapy, others would support its use. It is our contention that, in light of the positive studies, it would be unwise to dismiss its use as being worthless and that many more controlled studies are warranted (Micozzi, 1996).

Acupuncture

Acupuncture dates back thousands of years. Specifically, acupuncture is 6000 years old and ear acupuncture is 2,500 years old. In essence, traditional Chinese healers seek to restore a dynamic balance between two complementary forces that pervade the human body and travel through meridians as CHI (life energy).

Acupuncture corrects the excess or the deficiency of CHI along meridians. Acupuncture involves stimulation of certain points on the skin, mostly with ultra fine needles that are manipulated manually or electrically (Kaptchuk, 1984, Maciocia, 1989).

Today, acupuncture is practiced internationally; its practitioners include professional acupuncturists and a variety of other health care providers including medical doctors. Upward of 2,000 acupuncture points are now recognized by licensed acupuncturists. By 1982 there were enough acupuncture schools to warrant the development of the National Council of Acupuncture Schools and Colleges, which evolved into the Accreditation Commission for Acupuncture and Oriental Medicine or ACAOM. Today over 30 programs are within ACOM's purview.

Most states permit licensed physicians to perform acupuncture as part of their medical practice, but this may vary from state to state. Most states provide for the practice of acupuncture by chiropractors on the basis of an additional 100-200 hours of training. Many states have adopted legislation to permit the practice of acupuncture by individuals who are not medical doctors or chiropractors such as doctors of naturopathy, podiatrists, physical therapists, physician's assistants, nurses and counselors, but training requirements vary.

Ear Acupuncture in the treatment of Substance Use Disorder (SUD)

As stated earlier, acupuncture has been around for thousands of years. In more recent times Hsiang Lai Wen of Hong Kong successfully applied electrical stimulation to one point in the ear to relieve opiate withdrawal symptoms. Inspired by this work, Michael Smith, an American physician, first used the Wen protocol as part of a methadone program at Lincoln hospital in Bronx, New York. Over several years, Smith and co-workers refined the detox protocol into five ear points that are needled without electrical stimulation. To promote his protocol, Smith founded the National Acupuncture Detoxification Association (NADA), and for the past 35 years he has championed the use of acupuncture detox in a wide variety of clinical settings including county jails, maximum-security prisons, outpatient drug treatment programs, homeless shelters, and mental health facilities. Smith has championed the effective use of acupuncture to treat pain (Smith and Tong, 2005).

At about the same time, Haight-Ashbury Free Clinic (HAFC) in San Francisco began to utilize acupuncture for the treatment of addiction. In fact, I published a paper with others at the HAFC on the favorable outcome of utilizing ear acupuncture in alcoholic withdrawal (Blum *et. al.*, 1978).

Auriculotherapy

The original work of Paul Nosier, M.D. of Lyon, France in 1956 provided the world with what is now called auriculotherapy. A common misconception is that auriculotherapy is ear acupuncture. While ear acupuncture depends on the use of needles inserted among a fixed set of alleged acupuncture points, auriculotherapy does not involve fixed points and does not use needles. Auriculotherapy points are created by innervations of four cranial nerves and three cervical ganglia. These are not acupuncture points. The professional uses a hand-held STIM PLUS PRO (an FDA class 11 medical device) shaped like a pen to (1) locate the auriculotherapy point, (2) diagnose the located auriculotherapy point, and (3) treat the auriculotherapy point if measured to be abnormal.

Auriculotherapy is defined as the location and treatment of neurological points in the ear by micro current stimulation. Each point is treated by the hand-held pen-shaped device (described above) for 30 seconds. The procedure is painless. Both ears are treated five days a week for 15-30 days for 10 minutes. In contrast ear acupuncture, needles must be left in place for 45 minutes to 1½ hours.

Auriculotherapy in the Treatment of Substance Use Disorder (SUD)

In 1991, in conjunction with others (Blum and Holder, 2000) my laboratory conducted the first government-funded study to formulate and further develop auriculotherapy as a treatment modality for SUD. Today, auriculotherapy is in wide use as a successful modality for both addiction treatment and detoxification. Hundreds of drug courts, residential and outpatient treatment centers, private practitioners, and addiction counselors have combined auriculotherapy with group therapy, one-on-one counseling, and psychotherapy. In 1993, the National Consortium of TASC Programs (NCTP) listed auriculotherapy as number one among 185 treatments effective as alternatives to street crime. As mentioned earlier, the National Acupuncture Detoxification Association (NADA) has selected five ear acupuncture points for the treatment of SUD and the

relief of opiate withdrawal. Today a number of clinicians are using a newer protocol. Six foundation points are stimulated transcutaneously, using frequency specific micro-currents. While research suggests that this modality can reduce a patient's physiological symptoms and physiological cravings, motivation to abstain is still required by the patient.

In certain states counselors can perform auriculotherapy for detoxification and treatment of multiple drug addictions without an acupuncture license since no needles are required. There are some other advantages:

- No risk of Hepatitis, HIV or other infections because no needles are used.
- Less than 10-minute treatment time compared to one-hour with ear acupuncture.
- Useful for both detoxification as well as treatment of multiple drug addictions, not just for opiate dependence.
- Micro current devices both locate and treat points.
- It can address the patient's drug of choice by adding or subtracting certain points accordingly.

Research Support for Acupuncture and Auriculotherapy

Since the late 1970's and the 1980's numerous studies have been performed in order to evaluate acupuncture and recently auriculotherapy in the treatment of addictive behaviors. A recent MEDLINE search found over 16,647 studies dealing with the use of acupuncture (in all forms) for SUD including alcoholism, heroin addiction, and stimulant abuse, binge eating and smoking behavior. The majority of data come from the most obvious application of acupuncture: the attempt to decrease the pain and other discomforts associated with opiate addiction. A number of positive studies by Wen in 1977 showed intense relief of withdrawal symptoms within 15 minutes of the beginning of the procedures. A subsequent one-year follow-up of the sample by Schuckit and associates revealed that 51% had been free of drugs during the interval. In 1985, Kroening and Oleson found that the combination of precipitous opiate withdrawal along with auriculotherapy was successful, with 86% of the patients withdrawing within five to seven days with a minimum of side effects. Currently the literature reveals a number of positive studies using acupuncture, ear acupuncture, or auriculotherapy

including: smoking (He *et al.*, 1997), alcoholism (Brewer, 1995); cocaine addiction (Otto *et al.*, 1998), opiate addiction (Washburn *et al.*, 1993) and SUD (Gurevish *et al.*, 1996).

In comparison, a number of negative studies involving the efficacy of both acupuncture and ear acupuncture (according to the type of addiction) include smoking (Martin & Waite, 1981), alcoholism (Worner *et al.*, 1992), cocaine addiction (Bullock *et al.*, 1999), and opiate addiction (Man & Chaung, 1980). In 1990, a meta analysis revealed that a number of studies were negative. The authors reported 22 controlled clinical negative studies in three fields of addiction: cigarette smoking (15), heroin (five), and alcohol (two).

Here are few examples of scientifically sound studies that support the use of acupuncture (in all forms) and auriculotherapy:

1. In a placebo-controlled study, 80 severe recidivist alcoholics received acupuncture either at points specific for the treatment of substance abuse (treatment group) or at nonspecific points (control group). Twenty-one of forty patients in the treatment group completed the program compared with one of forty controls. Significant treatment effects persisted at the end of the six-month follow-up: by comparison with treatment patients more control patients expressed a moderate to strong need for alcohol and had more than twice the number of both drinking episodes and admissions to a detoxification center (Bullock *et al.*, 1989).
2. In 66 residential patients using auriculotherapy and a six-point system; patients in the placebo group performed worst, with a retention rate below 65.5%. However, the auriculotherapy group had a retention rate of 96% and in comparison to the standard residential group's retention of 72%, a patient was ten times likely to complete a 30-day residential treatment program than one without auriculotherapy (Holder *et al.*, 2001).
3. A recent Yale study reported on a randomized controlled trial of ear acupuncture in cocaine-dependent subjects. Of the patients studied, 53.8% of those receiving the acupuncture treatment tested free of cocaine during the last week of the study, compared with 23.5% and 9.1% in the two control groups. Those who completed the acupuncture treatment also had longer periods of sustained

abstinence than participants in either control group (Savants *et. al.*, 2000).

4. Research published in the Journal of Substance Abuse Treatment from the Consortium Treatment Center in Klamath Falls, Oregon (Russell *et al.*, 2000), reveals that acupuncture detoxification had the following measurable outcomes among court mandated, chronic offenders: (1) increased patient retention, (2) reduced number of arrests, (3) more drug-free urinalysis, and (4) decrease in the number of days needed for successful patient progress. The authors used a five-point approved and established protocol as defined by the National Acupuncture Detoxification Association (NADA).

Drug Court and Acupuncture

The Drug Court is one of the most famous programs to incorporate the use of acupuncture detox treatment in the United States. Janet Reno, the former Attorney General, was one of the founders of the original Drug Court in Dade County, Florida in 1989. Over the past 15 years, Drug Court programs have switched the criminal justice approach to drug abuse from an approach based in punishment to one rooted in rehabilitation (US Senate Subcommittee, 1993).

In general, if drug offenders, including D.U.I. offenders, decide to participate in a typical one-year Drug Court program, their arrest will be erased from their record and they will be released from probation. For example Sacramento based Drug Court employs a licensed acupuncturist. In this program, along with drug testing and counseling, clients receive auricular acupuncture five days a week. The following are brief anecdotal remarks from a number of patients receiving acupuncture in drug courts:

Patient Comments include a number of very positive responses. In this regard here are a few to consider: "A change in attitude." "Moods are less erratic." "Feeling good from within." "Full of energy." "Headache is gone." "Now actually sleeping." "This was the quickest I kicked heroin." "It reduces my craving for booze, and it brought back my natural energy." "I feel less stress." "I'm calmer." "Before acupuncture, even though I was clean I never once stopped craving drugs. Since acupuncture, I've stopped the craving."

Counselors of drug court had this to say: "Patients are coming in more balanced emotionally, mentally and

physically." "I have seen tremendous results with acupuncture for my patients."

In reviewing the past scientific history of the potential efficacy of Acupuncture in all forms no definitive conclusion can be reached. However, because of the common neuro-chemical effects of acupuncture and mesolimbic reward impairment linked to all addictive behaviors coined Reward Deficiency Syndrome (RDS) (Blum *et al.*, 1996) it would be parsimonious to develop a research protocol that combines natural dopaminergic activation with acupuncture induced enhance opioid activity for RDS.

Reward Circuitry Opioid- Dopaminergic Connectivity as a Therapeutic Target for Reward Deficiency Syndrome (RDS)

Since the discovery of the double helix, explorations of brain function in terms of both physiology and behavioral traits have resulted in a plethora of studies linking these activities to neurotransmitter functions having a genetic basis. The mechanisms underlining gene expression and the potential impairments due to polygenic inheritance -- and as such, predisposition to addiction and self-destructive behaviors have been studied. Our studies have shown that the prevalence of the dopamine D2 receptor gene (DRD2) A1 allele in Cocaine dependent (CD) subjects (n = 53) was 50.9%. It was significantly higher than either the 16.0% prevalence (P < 10(-4)) in non-substance abusing controls (n = 100) or the 30.9% prevalence (P < 10(-2)) in population controls (n = 265) wherein substance abusers were not excluded. Logistic regression analysis of CD subjects identified potent routes of cocaine use and the interaction of early deviant behaviors and parental alcoholism as significant risk factors associated with the DRD2 A1 allele. The cumulative number of these risk factors in CD subjects was positively and significantly (P < 10(-3)) related to DRD2 A1 allelic prevalence. The data showing a strong association of the minor alleles (A1 and B1) of the DRD2 with CD indicates that a gene, located on the q22-q23 region of chromosome 11, confers susceptibility to this drug disorder (Noble *et al.*, 1993).

Over half a century of dedicated and rigorous scientific research on the mesolimbic system, has provided insight into the addictive brain and the neurogenetic mechanisms involved in man's quest for happiness (Blum *et al.*, 2009). In brief, the site of the brain where one experiences feelings of wellbeing is the mesolimbic system. This part of the brain has been termed the

“reward center”. Chemical messages including serotonin, enkephalins, GABA, and dopamine (DA) work in concert to provide a net release of DA at the nucleus accumbens (NAc), a region in the mesolimbic system. It is well known that genes control the synthesis, vesicular storage, metabolism, receptor formation, and neurotransmitter catabolism. The polymorphic versions of these genes have certain variations that could lead to an impairment of the neurochemical events involved in the neuronal release of DA. The cascade of these neuronal events has been termed “Brain Reward Cascade”. See Figure 1. A breakdown of this cascade ultimately leads to a dysregulation and dysfunction of DA. Since DA has been established as the “pleasure molecule” and the “anti-stress molecule,” any reduction in its function could lead to reward deficiency and resultant aberrant substance seeking behavior and a lack of wellness (Blum *et al.*, 2000).

It is well known that humans are biologically predisposed to drink, eat, reproduce, and desire pleasurable experiences (Tindell *et al.*, 2006, Peciña *et al.*, 2006). Impairment in the mechanisms involved in these natural processes lead to multiple impulsive, compulsive, and addictive behaviors governed by genetic polymorphisms. While there are a plethora of genetic variations at the level of mesolimbic activity, polymorphisms of the serotonergic-2A receptor (5-HTT2a), serotonergic transporter (5HTTLPR), dopamine D2 receptor (DRD2), dopamine D4 receptor (DRD4), dopamine transporter (DAT1), and Catechol-o-methyltransferase (COMT), and monoamine-oxidase (MOA) genes, as well as other genes, predispose individuals to excessive cravings and resultant aberrant behaviors.

An umbrella term to describe the common genetic antecedents of multiple impulsive, compulsive, and addictive behaviors is RDS. Individuals possessing a paucity of serotonergic and/or dopaminergic receptors and an increased rate of synaptic DA catabolism, due to high catabolic genotype of the COMT gene, or high MOA activity are predisposed to self-medicating with any substance or behavior that will activate DA release including alcohol, opiates, psychostimulants, nicotine, glucose, gambling, sex, and even excessive internet gaming, among others. Use of most drugs of abuse, including alcohol, is associated with release of dopamine in the mesocorticolimbic system or “reward pathway” of the brain (Di Chiara, 1995). Activation of this dopaminergic system induces feelings of reward and pleasure. However, reduced activity of the dopamine system (hypodopaminergic functioning) can trigger drug-seeking behavior. Variant alleles can induce

hypodopaminergic functioning through reduced dopamine receptor density, blunted response to dopamine, or enhanced dopamine catabolism in the reward pathway. Cessation of chronic drug use induces a hypodopaminergic state that prompts drug-seeking behavior in an attempt to address the withdrawal-induced state (Berridge, 2009).

Acute utilization of these substances can induce a feeling of wellbeing. But, unfortunately sustained and prolonged abuse leads to a toxic pseudo feeling of well being resulting in tolerance and disease or discomfort. Thus, normal or high DA receptors results in low craving whereas low DA receptors due to carrying the DRD2 A1 allelic genotype results in excessive cravings and consequential drug seeking behavior. In terms of preventing substance abuse, or excessive glucose craving, one goal is to induce a proliferation of DA D2 receptors in genetically prone individuals. Experiments in vitro have shown that constant stimulation of the DA receptor system via a known D2 agonist in low doses results in significant proliferation of D2 receptors in spite of genetic antecedents. In essence D2 receptor stimulation signals negative feedback mechanisms in the mesolimbic system to induce mRNA expression causing proliferation of D2 receptors (Boundry *et al.*, 1996). This molecular finding serves as the basis to naturally induce DA release to also cause the same induction of D2-directed mRNA and thus proliferation of D2 receptors in the human. This proliferation of D2 receptors in turn, will induce the attenuation of craving behavior. In fact this has been proven with work showing DNA-directed over-expression (a form of gene therapy) of the DRD2 receptors and significant reduction in both alcohol and cocaine craving-induced behavior in animals (Filtz *et al.*, 1994). These observations are the basis for the development of a functional hypothesis of drug-seeking and drug use. The hypothesis is that the presence of a hypodopaminergic state, regardless of the source, is a primary cause of drug-seeking behavior. Thus, genetic polymorphisms that induce hypodopaminergic functioning may be the causal mechanism of a genetic predisposition to chronic drug use and relapse. Finally, utilizing the long term dopaminergic activation approach will ultimately lead to a common safe and effective modality to treat RDS behaviors including Substance Use Disorders (SUD), Attention Deficit Hyperactivity Disorder (ADHD), and obesity among other reward deficient aberrant behaviors (Rothman & Glowa, 1995, Peng *et al.*, 2010).

Support for the impulsive nature of individuals possessing dopaminergic gene variants is derived from a

number of important studies illustrating the genetic risk for drug-seeking behaviors based on association and linkage studies implicating these alleles as risk antecedents having impact in the mesocorticolimbic system (see Figure 1)..

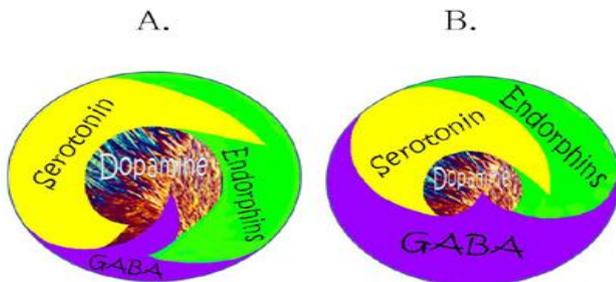


Figure 1. Schematic of Brain Reward Cascade normal and abnormal representation. (A) Represents the normal physiologic state of the neurotransmitter interaction at the mesolimbic region of the brain. Briefly, serotonin in the hypothalamus stimulates neuronal projections of methionine enkephalin in the hypothalamus that, in turn, inhibits the release of GABA in the substantia nigra, thereby allowing for the normal amount of Dopamine to be released at the Nucleus Accumbens (NAc; reward site of the 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*). Genetic variables include serotonergic genes (serotonergic receptors [5HT2a]; serotonin transporter 5HT1PR); endorphinergic genes (the mu OPRM1 gene; proenkephalin (PENK); PENK polymorphic 3' UTR dinucleotide (CA) repeats); GABergic genes (GABRB3); and dopaminergic genes (including ANKK1 Taq A; DRD2 C957T, DRD4 7R, COMT Val/met substitution, MAO-A uVNTR, and SLC6A3 9 or 10R). Any of these genetic and or environmental impairments could result in reduced (Blum *et al.* 2010).

In doing association studies that require a representative control sample for a single RDS psychiatric diagnosis or for potential subsets of RDS, one limitation relates to controls poorly screened for multiple RDS behaviors and other related psychiatric disorders (Neiswanger *et al.*, 1995). Missing behaviors that are part of the RDS subset may be the reason for spurious results when genotyping for single subsets of RDS behaviors. For example, in our unpublished study, an individual may not drink alcohol or use drugs but may have other RDS behaviors such as overeating or intensive video-gaming. In support of this, a very strong association of the dopamine D2 receptor A1 allele (100%) was found in one family (Family A) studied over five generations. In addition,

every individual in another family, Family B, also had at least one dopaminergic high risk allele (100%) (48% carried the DRD2 A1 allele). Moreover, in Family B only three adult individuals exhibited no addictive behavior. When compared to results in which 55 RDS subjects carried the DRD2 A1 allele at a frequency of 78.2% and the results of a study in which 597 severe alcoholics carried the A1 allele at a frequency of 49.3%, there was a significant difference between these two groups ($X^2=16.9$, $p<0.001$). This demonstrated that the A1 allele's prevalence increases with multiple RDS behaviors. The results from these experiments show that multifaceted non-specific RDS behaviors should be considered as the true "reward" phenotype (endophenotype) instead of a single subset RDS behavior such as alcoholism.

With this stated it is interesting that the Canadian scientists, Bruce Pomeranz and Robert Cheng (1980), found that the amino acid D-phenylalanine has been shown to potentiate the analgesic effects of acupuncture in rodents. Specifically, the D-amino acids, D-phenylalanine and D-leucine, produce naloxone reversible analgesia. Electro-acupuncture also produces analgesia which is blocked by naloxone. Combining the two treatments produces an additive effect with a larger analgesia than that produced by either treatment given alone; this combined effect is also blocked by naloxone. Moreover only 62% of the mice show electro-acupuncture analgesia and 53% show D-amino acid analgesia; 80% of the animals show marked analgesia with both electro-acupuncture plus D-phenylalanine treatment. Perhaps the combination of electro-acupuncture with D-phenylalanine will provide a potent method for the treatment of clinical pain.

With this in mind, our laboratory engaged in a scientific study to assess the result of combining neuroadaptagen - amino acid therapy (NAAT-KB220) and acupuncture to treat clients in a Drug Court setting. It is noteworthy that since the nutritional supplement component of Sacramento's Drug Court began in July 1998, the percentage of program graduates has risen by 39 percent (personal communication with Carolyn Reuben of Sacramento's drug Court Program). In one program, the combination of counseling, acupuncture, and amino acid therapy (both oral & intravenous) has produced significant positive results in preventing relapse (Blum *et al.*, 2007).

In Las Vegas, we studied a total of seventy six patients who attended a drug and alcohol treatment program. The study combined auriculotherapy and nutraceutical

brain rebalancing The precursor amines and nutrients included: DL-phenylalanine, L-glutamine, L-tyrosine, 5-hydroxytryptophane, Rhodiola *rosea* and chromium picolinate.(Blum *et al.* 2000). The clients were derived from four referral sources: Clark County District Attorney Office, Clark County Drug Court Program, US Federal Court System, and Self Referral. The patients were multiple DUI offenders and serious drug and alcohol offenders (see table 1).

Specifically, the Chen *et al.* (2007) study evaluated the effects of a putative activator of brain reward circuitry on outcomes in a one year (1y) prospective comprehensive outpatient clinical program called the Gene Narcotic Attenuation Program (GNAP), administered for the treatment of SUD. Seventy-six patients (45 males and 31 females; mean age, 33 y [standard deviation, 7.0]) who had been given a diagnosis of serious substance use disorder were recruited. After exclusion of 15 patients who dropped out before the end of the study, self-reported craving decreased from program entrance to 12 wk (visual analog scale whereby 0 represents no craving and 5, the strongest craving) for 61 compliant patients (mean decrease, 2.85, 95% confidence interval [CI], 2.65, 3.05); this improvement was significant ($P < .001$). Building up to relapse scores (each of 5 individual items and summary value) showed similar improvement after 1 y of treatment; the mean decrease in scores was significant for stress ($t=3.3$; $P=.002$), depression ($t=4.0$; $P < .001$), anger ($t=4.4$; $P < .001$), anxiety ($t=4.5$, $P < .001$), drug craving ($t=5.4$, $P < .001$), and summary building up to relapse ($t=4.1$; $P < .001$). Also, recovery score measures of energy level ($t=8.4$; $P < .001$) and ability to refrain from drug-seeking behavior ($t=7.4$; $P < .001$) showed significant mean increases from entry to 1 y. During the study, the alcoholic dropout rate was only 7% (4 of 57), which was significantly (Fisher's exact test, $P < .001$) lower than the 73% (11 of 15) dropout rate reported for psychostimulant users. Although these results are significant, any interpretation must await the performance of rigorous double-blind studies.

If we calculate the percent relapse of the entire program which included a total of 76 patients with a total of 15 patients that dropped out, it is a remarkable 19.9 % relapse rate. When we compare relapse rates obtained from the literature: 56% for alcoholics and 90% for cocaine or stimulant dependent subjects, our result is quite significant. Our finding which translates to 79.1% recovery is considered by the Court system significant. The main observation is that unlike all other treatments tried by the court system these patients after a 3month period showed great improvement in all physiological, psychological and even spiritual levels (Chen *et al.*, 2007).

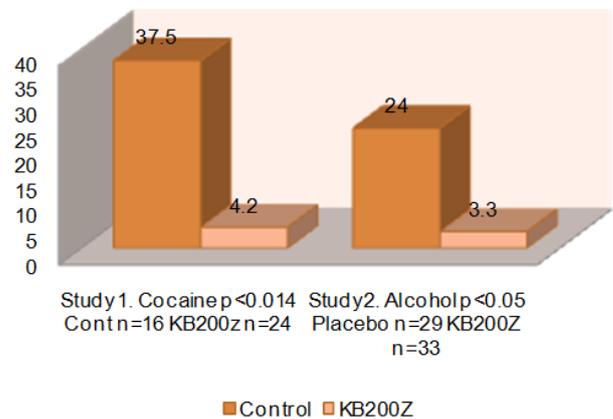
Table 1. Genetic Narcotic Attenuation Program Data

Clark County District Attorney Referral	Clark County	US Courts	Federal	Self Referral
15 patients	42 patients	10 patients		8 patients
Assessed after 11 months	Assessed after 8 months	Assessed after 5 months		Assessed after 11 months
2 patients dropped out	11 patients dropped out	2 patients dropped out		No drop out
13.33% relapse	23.2% relapse	20% relapse		No relapse

Figure 2a. Comparison AMA Rate Control vs KB200Z (Study 1. Blum *et al.*, *Curr Therp Res.*

43: 1204-1214, 1988; Study 2. Blum *et al.*, *Alcohol* 5: 481-493, 1989).

There are two important clinical outcomes using NAAT



{KB220 variant-SynaptaGenX (SGX)}: (1) reduction in Against Medical Advice (AMA) rates (Figure 2a) (2) relapse prevention (Figure 2b).

From the results of these two independent studies we cautiously suggest that KB220 variant significantly prevents AMA rate in a population of in-patient cocaine addicts. Compared to controls (no KB220 variant) whereby the AMA rate in the first five days of in-patient treatment was 37.5% of the population leaving the program, the KB220 group of subjects had only a 4.2 percentage AMA rat which was significant at the ($p < 0.014$) (Blum *et al.*, 1988). In a second double -blinded randomized placebo controlled study in alcoholic in-patients similar reduction of AMA was observed. In the placebo group the AMA rate in the first five days was 24% compared to only 3.3 percent in the KB220 group ($P < 0.05$) (Blum *et al.*, 1989).

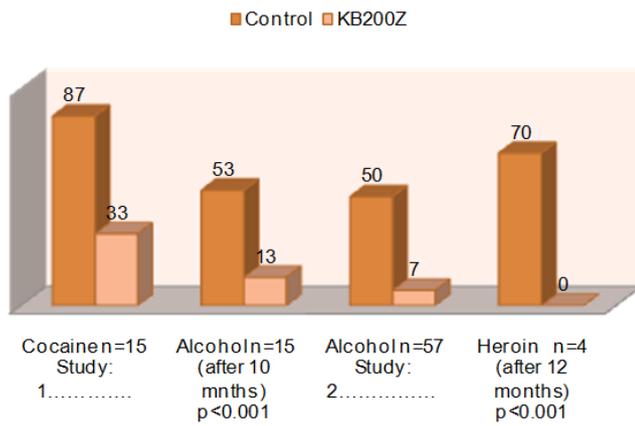


Figure 2b. Without vs with KB200Z Variant (Study 1. Brown *et al.*, Journal of Psychoactive Drugs 22:173-187 (1990); Study 2. Chen *et al.*, Adv Therp. 24:402-414 (2007))

From the results of these two independent studies we cautiously suggest that KB220 variant significantly reduces relapse rates in poly drug abusers attending out-patient clinics. In one study in cocaine and alcohol addicts attending a DUI offenders program in San Francisco evaluated over a 10 month period, the relapse rate for cocaine addicts was 33% percent compared to a Centrum® vitamin control group relapsing at 87% (P<0.001) and for alcoholics it was only 13% compared to 53% for the control group (p<0.001) (Brown *et al.*, 1990). Similarly, the relapse rate for alcoholics attending an out-patient program in Las Vegas, Nevada over a 10 month period was only 7% for the KB220 Variant group compared to 50% of literature controls (no KB220 variant) and for heroin addicts zero percent relapsed compared to 70% of literature controls (P<0.001).

Most recently our laboratory (Blum *et al.*, 2010) obtained positive outcomes demonstrated by quantitative electroencephalographic (qEEG) imaging in a randomized, triple-blind, placebo-controlled, crossover study involving oral KB220Z™ showed an increase of alpha waves and low beta wave activity in the parietal brain region (Figure 3). Using t statistics, significant differences observed between placebo and KB220Z™ consistently occurred in the frontal regions after week 1 and then again after week 2 of analyses (P = 0.03). This is the first report to demonstrate involvement of the prefrontal cortex in the qEEG response to a natural putative D2 agonist (KB220Z™), especially evident in dopamine D2 A1 allele subjects. Independently, we have further supported this finding with an additional study of 3 serious polydrug abusers undergoing protracted abstinence who carried the DRD2 A1 allele. Significant qEEG differences were found between those who received 1 dose of placebo compared with those who were administered KB220Z™. Moreover, KB220Z™ induced positive regulation of the dysregulated electrical activity of the

brain in these addicts. The results are indicative of a phase change from low amplitude or low power in the brain to a more regulated state by increasing an average of 6.169 mV(2) across the prefrontal cortical region. In the first experiment we found that while 50% of the subjects carried the DRD2 A1 allele, 100% carried ≥ 1 risk allele. Specifically, based on the proposed addiction risk score for these 14 subjects, 72% had moderate-to-severe addiction risk. Similar findings were obtained by repeating the experiment in 3 additional currently abstinent polydrug abusers carrying the DRD2 A1 allele.

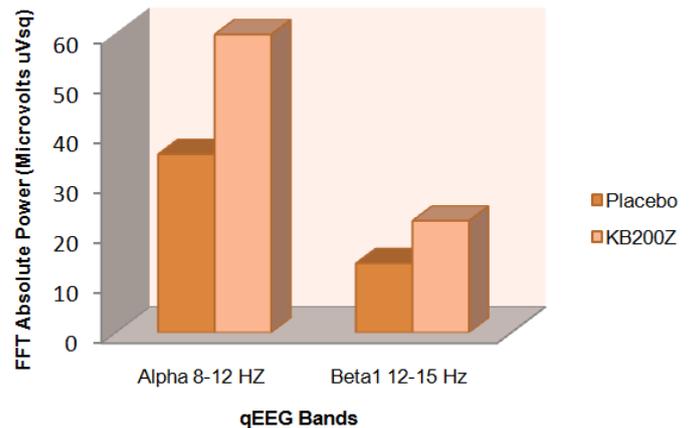


Figure 3. qEEG Study: KB220Z compared to placebo in psychostimulant addicts

We concluded that this seminal work will provide important information that may ultimately lead to significant improvement in the recovery of individuals with psychostimulant and polydrug abuse problems, specifically those with genetically induced dopamine deficiency. Based on this small sample size, we are proposing that with necessary large populations supporting these initial results it is possible incorporate a safe, nonaddicting, natural dopaminergic receptor agonist that potentially up-regulates instead of down-regulates dopaminergic receptors, preferably the D2 subtype (Blum *et al.*, 2008).

The clinical benefits of NAAT [KB220 variants] have been reviewed by Chen *et al.*, (2011) showing significant anti-RDS behaviors. Interestingly the effects are in-part attributable to meso-limbic dopaminergic activation as well as significant regulation of Prefrontal Frontal Cortex - Cingulate Gyrus dysregulation (site for addiction relapse). Moreover, unpublished data derived from preliminary pilot fMRI study in China revealed BOLD response at the Caudate -NAc brain region in heroin addicts compared to placebo, indicating dopaminergic activation.

CONCLUSION

Acupuncture is especially attractive because it does not involve long-term administration of medications. There is a potential for future studies using either acupuncture or auricular therapy, especially in the field of stimulant withdrawal. Finally, all published reports to date suggest that acupuncture (in all forms) is likely to be of optimal use when combined with additional treatments such as amino acid therapy (both oral and intravenous), psychotherapy, counseling, education, outreach to the family, and appropriate self-help groups.

There are 1200 substance abuse treatment programs in the US and abroad using acupuncture, and the number of drug treatment programs incorporating acupuncture is growing each year. Recovery from addiction is difficult and subject to relapse. People in recovery need more tools like acupuncture and auriculotherapy coupled with NAAT to improve the quality of recovery as well as to reduce the risk of relapse. This notion is based on the mutual synergistic action of both acupuncture and NAAT. Acupuncture increases enkephalinergic activation and enhances neuronal release of the opioid peptide. In fact known enhancement of opiate function through acupuncture leads to a preferential release of dopamine due to GABA inhibition via mu opiate receptor stimulation. Thus the combination of acupuncture with NAAT which indirectly activates caudate –accumbens dopaminergic pathways will result in neurochemical synergy between these two non –drug modalities. We are encouraging our peers to further investigate in randomized –double-blind placebo controlled studies this potentially novel anti-craving modality to treat RDS.

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