Journal of Behavioral Addictions 2(2), pp. 117–124 (2013)
DOI: 10.1556/JBA.2.2013.2.8

Hypothesizing repetitive paraphilia behavior of a medication refractive Tourette's syndrome patient having rapid clinical attenuation with KB220Z-nutrigenomic amino-acid therapy (NAAT)

THOMAS MCLAUGHLIN[1], MARLENE OSCAR-BERMAN[2], THOMAS SIMPATICO[3], JOHN GIORDANO[4], SCOT JONES[4], DEBMAYLA BARH[5], WILLIAM B. DOWNS[6], ROGER L. WAITE[6], MARGARET MADIGAN[6], KRISTINA DUSHAJ[8], RAQUEL LOHMANN[8], ERIC R. BRAVERMAN[8], DAVID HAN[9] and KENNETH BLUM[3–8,10–11]*

[1]Center for Psychiatric Medicine, North Andover, Massachusetts, USA
[2]Department of Psychiatry, Anatomy & Neurobiology, Boston VA and Boston University School of Medicine, Boston, Massachusetts, USA
[3]Department of Psychiatry, Global Integrated Services Unit of Vermont Center for Clinical & Translational Science, University of Vermont College of Medicine, Burlington, Vermont, USA
[4]Department of Holistic Medicine, G & G Health Care Services LLC, North Miami Beach, Florida, USA
[5]Center for Genomics and Applied Gene Technology, Institute of Integrative Omics and Applied Biotechnology (IIOAB), Nonakuri, Purba Medinipur, West Bengal, India
[6]Department of Nutrigenomics, LifeGen, Inc., Austin, Texas, USA
[7]Department of Psychiatry and McKnight Brain Institute, University of Florida, College of Medicine, Gainesville, Florida, USA
[8]Department of Clinical Neurology, PATH Foundation NY, New York, New York, USA
[9]Department of Management Science and Statistics, the University of Texas at San Antonio, San Antonio, Texas, USA
[10]Dominion Diagnostics, LLC, North Kingstown, Rhode Island, USA
[11]Department of Addiction Research & Therapy, Malibu Beach Recovery Center, Malibu Beach, California, USA

(Received: March 18, 2013; revision received: April 28, 2013; second revision received: May 2, 2013; accepted: May 3, 2013)

Background and aims: Many patients presenting multiple behaviors including drug and food abuse as well as other pathological repetitive unwanted activities such as gambling, self-mutilation and paraphilias may not be appropriately diagnosed. Here we present a case of a male presenting many of these seemingly diverse behaviors and finally diagnosed with reward deficiency syndrome (RDS) by his attending physician. *Methods:* The use of the dopamine agonist, ropinirole after two weeks showed improvement in terms of sexual behavior but tolerance set in and was discontinued especially when an infraction occurred with the patient's insurance. In this article, we carefully explore the potential of ropinirole to downregulate dopamine receptors causing adenylate cyclase receptor supersensitivity and tolerance a feature of neurotransmitter cross-talk. Based on previous scientific evidence showing KB220Z-nutrigenomic amino-acid therapy (NAAT) to rapidly (post one-hour) activate dopaminergic pathways in both the pre-frontal cortex cingulate gyrus (relapse loci) and ventral tegmental area–caudate–accumbens–putamen (craving and emotion loci) the patient was prescribed NAAT. *Results and discussion:* Within one week of utilization the repetitive paraphilia was eliminated. There were also a number of other positive effects such as enhanced focus that persisted even after the patient stopped using KB220Z suggesting neuroplasticity (e.g. altruistic thoughts). However, these observed profound benefits require more in-depth study, especially in a large cohort against a placebo. While this report focused on a rapid response rather than long-term benefits previously associated with NAAT, it is somewhat encouraging and longer term required follow-up and larger placebo controlled studies are warranted before any definitive conclusions could be gleaned from this case report.

Keywords: aggressive sexual behavior, repetitive paraphilia behavior, Tourette's, dopamine activation, NAAT, reward deficiency syndrome (RDS)

BACKGROUND

It is difficult to define deviant sexual behavior. For thousands of years cultures define and describe what is normal and what is deviant. According to Bhugra, Popelyuk and McMullen (2010), these definitions of normality vary across cultures and are influenced by a number of factors, such as religion and other familiar factors. Most importantly, the role and development of paraphilias across cultures is variable, with cultures mandating what is legal or illegal.

Paraphilia (from Greek para [παρά] = beside and -philia [φιλία] = friendship, meaning love) describes sexual arousal to objects, people, or situations, that are not part of normative stimulation. According to DSM-IV, paraphilia includes sexual arousal and gratification, involving a sexual behavior that is atypical or extreme (American Psychiatric Association, 2000–2006). Historically, the term was coined by Stekel in the 1920s (1930). Furthermore, Money (1990) a sexologist, popularized the term as a nonpejorative designation for deviant or unusual sexual interests ("a sexuoerotic embellishment"). It is noteworthy, that before the introduc-

* Corresponding author: Kenneth Blum, Department of Psychiatry, College of Medicine, University of Florida, and McKnight Brain Institute, Gainesville, Florida, USA; E-mail: drd2gene@aol.com

tion of the term paraphilia in the DSM-III (1980), the term *sexual deviation* was used to refer to paraphilias in the first two editions of the manual (Spitzer, 1981). Indeed paraphilia has been described (Moser & Kleinplatz, 2005) as "recurrent, intense sexually arousing fantasies, sexual urges, or behaviors generally involving":

1. Non-human objects.
2. The suffering or humiliation of oneself or one's partner.
3. Children.
4. Non-consenting persons.

Finally, the DSM-5 Paraphilias Workgroup reached a "consensus that paraphilias are not *ipso facto* psychiatric disorders", and suggested "that the DSM-5 make a distinction between *paraphilias* and paraphilic *disorders*". Thus, a paraphilia by itself would not automatically justify or require psychiatric intervention. As such a *paraphilic disorder* is a paraphilia that causes distress or impairment to the individual or harm to others like other addictions as proposed in reward deficiency syndrome, RDS) (Blum et al., 1996). The workgroup further proposed that one would *ascertain* a paraphilia (according to the nature of the urges, fantasies, or behaviors) but *diagnose* a paraphilic disorder (on the basis of distress and impairment). In this new conception, "having a paraphilia would be a necessary but not a sufficient condition for having a paraphilic disorder".

Recently, our laboratory reviewed the commonality of drugs, food, music, and other behavioral addictions including sex referring to the concept of "sex, drugs and rock 'n' roll" (Blum, Werner et al., 2012). In essence, the nucleus accumbens (NAc), a site within the ventral striatum, plays a prominent role in mediating the reinforcing effects of drugs of abuse, food, sex, and other addictions. It is generally believed that this structure mandates motivated behaviors such as eating, drinking, and sexual activity, which are elicited by natural rewards and other strong incentive stimuli. We hypothesized, a common underlying mechanism of action for the powerful effects that all addictions have on human motivation. Moreover, biological drives may have common molecular genetic antecedents, which if impaired, lead to pathological behaviors. We pointed out that based on scientific support, dopaminergic genes, and possibly other candidate neurotransmitter-related gene polymorphisms, affect both hedonic and anhedonic behavioral outcomes.

We firmly believe genotyping studies already have linked gene polymorphic associations with alcohol and drug addictions and obesity (Gardner, 2011), and we anticipate that future genotyping studies of sex addicts will provide evidence for polymorphic associations with specific clustering of sexual typologies based on clinical instrument assessments (Daw & Guo, 2011; Guo & Tong, 2006; Miller et al., 1999).

While there is a paucity of genetic research on paraphilia behavior *per se,* there are studies relating polymorphisms of dopaminergic genes (e.g. DRD2 and DRD4 genes) and sexual behavior especially related to onset of sexual intercourse (Miller et al., 1999; Guo & Tong, 2006) and unprotected sex (Daw & Guo, 2011). Specifically, Daw and Guo (2011) found in the Longitudinal Study of Adolescent Health that variants in the dopamine transporter gene DAT1, the dopamine receptor gene DRD2, and the monoamine oxidase gene MAOA are associated with unprotected sexual intercourse. Interestingly, the genotypes DRD2*A1/A2, DRD2*A2/A2, DAT1*9R/10R, and MAOA*2R/ are associated with higher odds of unprotected sexual intercourse than other genotypes at these loci. Their data also revealed that the DRD2 associations apply to both men and women, whereas the other associations apply to women only.

It is our opinion that both scientists and clinicians embark on research coupling the use of neuroimaging tools with dopaminergic agonistic agents to target specific gene polymorphisms systematically for normalizing hyper- or hyposexual behaviors.

Brief description of KB220Z

KB220Z is a neuroadaptogen consisting of amino-acid neurotransmitter precursors and catechol-O-methyltransferase (COMT)/monamine-oxidase (MOA) inhibition therapy called "neuroadaptogen amino-acid therapy™" (NAAT) that works in synchrony with brain reward function (see Table 1). It is becoming increasingly clear that this novel formulation is the first neuroadaptogen known to activate the brain reward circuitry (Chen et al., 2011). Ongoing research repeatedly confirms numerous clinical effects that ultimately result in significant benefits for victims having genetic antecedents for all addictive, compulsive and impulsive behaviors. As mentioned earlier, these behaviors are correctly classified under the rubric of "reward deficiency syndrome" (Blum et al., 1996), involving hypodopaminergic function in the meso-limbic system of the brain. Activation of brain reward circuitry using NAAT (KB220Z) has been demonstrated in the United States using qEGG (Blum, Stice et al., 2011) and in preliminary findings in China using fMRI in victims of "substance use disorder" (SUD). In unpublished data using an fMRI 2X2 design at resting state (Chen et al., 2011) NAAT in comparison to placebo showed activation of the caudate brain region and potentially a smoothing out of heroin-induced abnormal connectivity in the putamen (a site for emotionality). Although awaiting final analysis, if confirmed by ongoing studies in China coupled with published qEEG results in America, showing an increase in alpha and low beta, as well as fMRI studies ongoing in the United Sates, NAAT may be shown to impact treatment outcomes and relapse.

Table 1. KB220Z-nutrigenomic amino-acid therapy (NAAT)

GRAS nutrient pathway	
D-phenylalanine	Opioid peptides
L-phenylalanine	Dopamine
L-tryptophane	Serotonin
L-tyrosine	Dopamine
L-glutamine	GABA
Chromium	Serotonin
Rhodiola rosea	COMT/MOA
Pyridoxine	Enzyme catalyst

OBJECTIVES

Based on these and 25 earlier clinical trials (Chen et al., 2011) we decided to test the potential of using KB220Z-NAAT as a safe natural modality to attenuate refractive paraphilia behavior of a medication refractive

Tourette's syndrome patient. We hypothesized that since this complex has been shown to activate dopaminergic pathways and enhance decision-making as a result of PFC-cingulate gyrus regulation, that it may reduce paraphilias rapidly.

It is not uncommon for patients with Tourette's to display obsessive–compulsive tendencies including sexual obsessions (James, 1995; Mack et al., 2010). Furthermore, Comings (1994) reported that individuals with Tourette's show deviant sexual behaviors (paraphilias) in some cases including magnitude of sex drive, sex orientation, exhibitionism, transvestitism, transsexualism, sadism, masochism, pedophilia, fetishism, aversion to being touched, and aversion to sex. Accordingly (Comings, 1994), there was a significant positive correlation between each behavior examined and the degree of genetic loading for the Tourette's gene(s). In fact unlike our patient there is evidence for recurrent paraphilic masturbatory fantasy (Kerbeshian & Burd, 1991). In terms of potential neurochemical correlates of paraphilic behavior in Tourette's it has been shown that the opiate receptor blocker naltrexone ameliorated paraphilic behaviors in patients refractive to conventional anti-Tourette's drugs including haloperidol and clonidine (Sandyk, 1988). There is evidence for the role of dopaminergic signaling and behavior, attractiveness to opposite or same gender and bonding in animal models (Banerjee, 1974; Chen, Liu, Ren & Guo, 2012; Wang & Aragona, 2004).

Essential features and uniqueness of the case

The patient is a 35-year-old male, living with his ex-girlfriend. During his initial evaluation, 6 years ago, he stated that "I have bipolar, mood disorder". Prior to this, he had been treated with venlafaxine and sertraline, without a clinical effect. He reported a tendency to spend all his money at once and had $46,000 in credit card debt. The onset of his depressed mood followed the death of his father, when the patient was 16 years old. He developed a lack of motivation as well as insomnia and stated that these symptoms became worse each year. He also reported social anxiety and panic attacks.

Social history

Patient is a high school graduate with a history of learning disabilities. He worked as a carpenter and cabinet maker. He tended to miss work, intermittently, and was placed on Social Security Disability. He never married and had no children. He was living with his ex-girlfriend and described their relationship as "just friends". He denied any court involvement.

Substance abuse history

Patient denied current use of alcohol but reported a prior history of alcoholism for four years, when he drank to the point of intoxication on weekends. He denied current use of illicit drugs, but reported a history of using ecstasy about 30–40 times. He admitted to using LSD twice, with one bad trip. He had been using marijuana regularly for the previous six months. He reported a history of prescription, drug abuse but denied any use of cocaine, angel dust, crystal meth, or heroin.

Past psychiatric history

His first psychiatric treatment occurred three years prior, when he was hospitalized because of suicidal ideation. He saw a psychiatrist 2 years prior to this, following a brief attempt at psychotherapy.

Past medical history

Patient denied any history of asthma, hypertension, coronary artery disease, seizures, or serious head injury. He took medication for hypothyroidism. There were no known allergies.

Family psychiatric history

Father was an alcoholic and a substance abuser. Patient's mother suffered from social anxiety disorder and had also abused drugs and alcohol.

Family history

Patient's mother was 57 years old and is described as "quiet, private, and unable to show her feelings". She had a history of alcoholism and never engaged in any playful activities with the patient nor was she affectionate. His father died at the age of 45 from cancer. He had a history of alcoholism and the patient described him as "cold, distant, cruel and sadistic". He did not engage in any activities with the patient when he was a child and was not affectionate. His father was physically abusive and would smack the patient. He was verbally abusive and would call his son, a "faggot". He reported his father would tease him and say that he "looked like a fairy". His father would hit 2 to 3 times a week and, at age 11, his father threw him across a room. When asked whether he had suffered sexual abuse as a child, he stated "I wonder". He has two siblings, a brother and sister, with whom he has normal relationships.

Mental status examination

Patient was alert and oriented in all three spheres. He was pleasant and cooperative. His mood was moderately depressed. He denied suicidal or homicidal ideation, but admitted to passive wishes to die. He denied auditory hallucinations, but reported visual hallucinations, involving animals. He also reported ideas of reference but denied delusions, obsessive–compulsive symptoms, or panic symptoms. He denied periods of full-blown mania. He admitted to social anxiety and reported decreased sleep (five hours), with recently increased appetite.

Diagnoses

Axis I: major depressive disorder, social anxiety disorder and rule out bipolar disorder.
Axis II: deferred.
Axis III: hypothyroidism.
Axis IV: moderate-symptom management.
Axis V: CGAF 45.

Review of psychopharmacology progress notes

Initially, the patient weighed 230 pounds (104.326 kg) and was 5 feet 10 inches tall (177.8 cm). He reported a strong

need for pornography. His father was also addicted to pornography. The patient had experienced a 50% decrease in his interest in pornography, when his primary care physician had increased from his venlafaxine from 75 mg to 150 mg. He later reported his interest in pornography had decreased by 80%, out of consideration for his live-in girlfriend. One month into treatment, he reported he had had no sexual relations for two weeks and that his interest in pornography had decreased to one episode within the past week. Two months into treatment, he viewed pornography about once a week. Three months into treatment, he viewed pornography one to two times a week. He reported that he was overly preoccupied with computers. Six months into treatment, he was prescribed dextropropoxyphene, following a tooth infection. He became suicidal, when he ran out of dextropropoxyphene. At this time, his interest in pornography had increased. He stated that his interest in sex would fluctuate. Ten months into treatment, he watched pornography daily and his sexual relations with his girlfriend had been on hold, because of her medical issues. Eleven months into treatment, he admitted to occasional pornography viewing on the Internet. There seemed to be no relationship with the frequency of his relations with his girlfriend. Eighteen months into treatment, because of a new diagnosis of Tourette's syndrome and, because of one of the authors' (TM) familiarity with the rubric, "reward deficiency syndrome", the dopamine agonist, ropinirole, was started at the recommended titration rate. Two weeks later, AC reported an improvement in his hygiene (teeth brushing) and more motivation to organize things around the home. Ropinirole was increased to 1 mg at HS. After 2 weeks, he stated that he felt sexually "more tender" towards his girlfriend. Twenty months into therapy, he complained of no libido. Twenty-two months into treatment his ropinirole was increased to 1.5 mg and, then 2 mg. Initially, he felt his sexuality was more sensual but then he complained about feeling "more hyper" and his ropinirole was tapered to 1 mg. Twenty-three months into treatment, he continued to feel sexually more tender towards his girlfriend. Twenty-four months into treatment, he complained of racing thoughts and decreased sleep. Ropinirole was discontinued and quetiapine was started at 100–400 mg at HS. Dextroamphetamine/amphetamine was added, because of the patient's complaint of long-standing difficulties in concentrating. He was also diagnosed with ADHD. Twenty-five months into treatment, ropinirole titration was re-instituted. Paroxetine was prescribed for social anxiety disorder. Twenty-six months into treatment, the patient reported a history of vocal tics, involving throat clearing. He also described finger twitching, finger waggling, a compulsive need to touch everything as well as an impulsive tendency to blurt out sexually inappropriate comments and engage in sexually inappropriate behaviors. Twenty-six months into treatment, paroxetine was added to his regimen, because of increased sexual urges. Ropinirole was again increased to 1.5 mg at HS. Along treatment hiatus ensued. Twenty-eight months into treatment, he reported a long-standing hypersensitivity to certain smells. Ropinirole had to be re-titrated, because of non-compliance as well as insurance problems. Twenty-nine months into treatment, the patient's concentration was "almost perfect". He had decreased hyperfocusing, e.g. videogame watching. Thirty months into treatment, the patient reported continued, decreased interest in video games. He was increasingly affectionate (vs. sexually aggressive) towards his girlfriend. Thirty-one months into treatment, the patient reported increased motivation and excellent concentration. He again stopped both his dextroamphetamine/amphetamine (because he was feeling "hyper") and his ropinirole (because of insomnia). He resumed playing the "World of Warfare" and reported greater disinhibited sexuality and renewed hyperfocusing. A long treatment hiatus ensued. Thirty-six months into treatment, the patient's dextroamphetamine/amphetamine and anti-depressant (duloxetine) had again to be tapered, because of insurance reasons. At this time the relevance of reward deficiency syndrome was again discussed, along with the potential use of KB220Z-nutrigenomic amino-acid therapy (NAAT), a natural D2 agonist, and other nutraceuticals like L-tryptophan as substitutes for his prescription medications. The patient's ongoing insurance denials, need for prior approvals, being in and out of the "doughnut hole" made this seem like a worthwhile solution. The patient was, unfortunately, could not afford to purchase these products and one of us (TM) did not at that time have access to samples. Dextroamphetamine/amphetamine was later re-introduced along with ropinirole, when insurance difficulties had been resolved.

Thirty-eight months into treatment, his dextroamphetamine/amphetamine and duloxetine were regularly added and decreased, primarily for insurance and financial reasons. When maintained on both medications, he was relatively more able to focus and be euthymic. Forty months into treatment, he was abusing benzodiazepine and had not taken dextroamphetamine/amphetamine for three weeks. Dextroamphetamine/amphetamine was again re-initiated. Along hiatus in treatment ensued.

Fifty-three months into treatment, dextroamphetamine/amphetamine was discontinued and lisdexamfetamine 60 mg was prescribed for 10 days, with an increase to 70 mg.

Fifty months into treatment, the patient reported he was stable and felt "more mellow" on the lisdexamfetamine. He also noted, increased motivation as well as decreased procrastination and social anxiety. Following this, lisdexamfetamine was denied by his insurance company and his medications again changed to dextroamphetamine/amphetamine and duloxetine, the latter in the form of samples.

Fifty-seven to sixty months into treatment, the patient had been off stimulants for three months. He reported decreased motivation. For insurance and regional shortages reasons, methylphenidate 10 mg was started, along with L-tyrosine 500 mg for one week and, then 1000 mg. The rationale was derived from the literature on reward deficiency syndrome. Methylphenidate was increased to 10 mg twice a day and L-tyrosine increased to 1500 mg. He continued on duloxetine samples at 60 mg bid. In the sixtieth month of treatment, he reported a chronic tendency to pull his hair, both pubic and otherwise as well as pull on scabs. In the sixty-second month of treatment, the patient overdosed on his girlfriend's meds in combination with alcohol. He also threatened to cut his wrists, because she was breaking up with him. The patient was involuntarily hospitalized. In the sixty-fourth month of treatment, the patient reported a decrease from daily pornography watching to weekly watching. Methylphenidate, which had to be again substituted for dextroamphetamine/amphetamine was 10 mg a day. His methylphenidate was increased to 10 mg twice a day. In the sixty-fifth month of treatment, he reported decreased sexual

impulsivity. His methylphenidate was discontinued due to side effects. Dexedrine had been initiated and increased from 10 mg a day, eventually in 10 mg doses to 20 mg bid.

In the sixty-sixth month of the treatment, the patient stated that, as a child of between 8–9 years of age, he would defecate behind the sofa in the living room. He and his family would blame the dog. This was explained as another manifestation of his limbic disinhibition (Comings, 1994). In the seventieth month of treatment, the patient stated that he was increasingly sexually disinhibited and he complained of an increase in his pornography addiction. Methylphenidate was increased to 10 mg three times a day. The regional shortage of all stimulants worsened.

History of sexually disinhibited behavior, history according to patient's girlfriend

GF had been dating her boyfriend at the time for six years, prior to his psychiatric intake evaluation by TM. Eighteen months into their treatment, GF states the patient was engaging "sadistic tickling near her vagina". Twenty-four months into their treatment, patient complained of the patient increased sexual impulsivity and blatant and provocative exhibitionism in their apartment. He would also express sexual interest in the GF's younger niece. Twenty-five months into treatment, the patient was sexually disinhibited, impulsive and exhibiting vocal and motor tics. Forty months into treatment, GF broke up with the patient, because of his "hypersexuality" and because he was off his medications due to ongoing, insurance problems. Forty-two months into treatment, GF complained of the aggressive and impulsive nature of the patient's sexual approach to her. Fifty months into treatment, GF complained of a sexual assault by the patient. Fifty-one months into treatment, GF complained of boyfriend's sexually disinhibited behavior and her willingness to call the police. The patient continued to be sexually inappropriate on another occasion that month. The patient also threatened suicide, because GF refused to continue their romantic relationship. Fifty-two months into treatment patient was again sexually disinhibited and exhibitionistic.

A lengthy treatment hiatus ensued. Seventy-two months into treatment, patient complained about the ex-boyfriend entering into her room despite her protestations. Eighty-two months into treatment, GF complained that her boyfriend was "hypersexual".

Rapid clinical response to KB220Z-NAAT

Then TM provided free KB220Z-NAAT. GF agreed to ensure that tablets were taken on an empty stomach by the patient. One week later, GF reported that the patient was taking KB220Z-NAAT faithfully. After one week, GF noted that the patient 1) was able to shovel her car out from the snow/blizzard (a rare event); 2) went shopping with her (a rare event); 3) had cleaned the cat litter box (a rare event); 4) took the trash out (a rare event); 5) was checking for travel websites to visit places they had planned to go to together a number of years prior; 6) did not engage in his frequent habit of hugging her against her wishes, exposing himself to her, taunting about sex, etc. In addition, he no longer attempted to hug against her will but would instead, occasionally caress her cheek with his hand.

Protracted positive response to KB220Z

The patient stated that he took the KB220Z, two pills twice a day faithfully for three weeks. He followed the instructions, always taking the pills on an empty stomach. Nevertheless, for unclear and, possibly, motivational reasons, he stopped taking them for the fourth week, despite their salutary effects (Fig. 1).

His current, live-in, former girlfriend was present for the most recent interview. She confirmed the patient's behavior was consistent with his subjective report about the effects of KB220Z on his mental, motivational and libidinal functioning.

As an example of his perceived effect of KB220Z, the patient reported a marked improvement in concentration for the entire three-week period, rating his new ability at 90%, out of a maximum 100%.

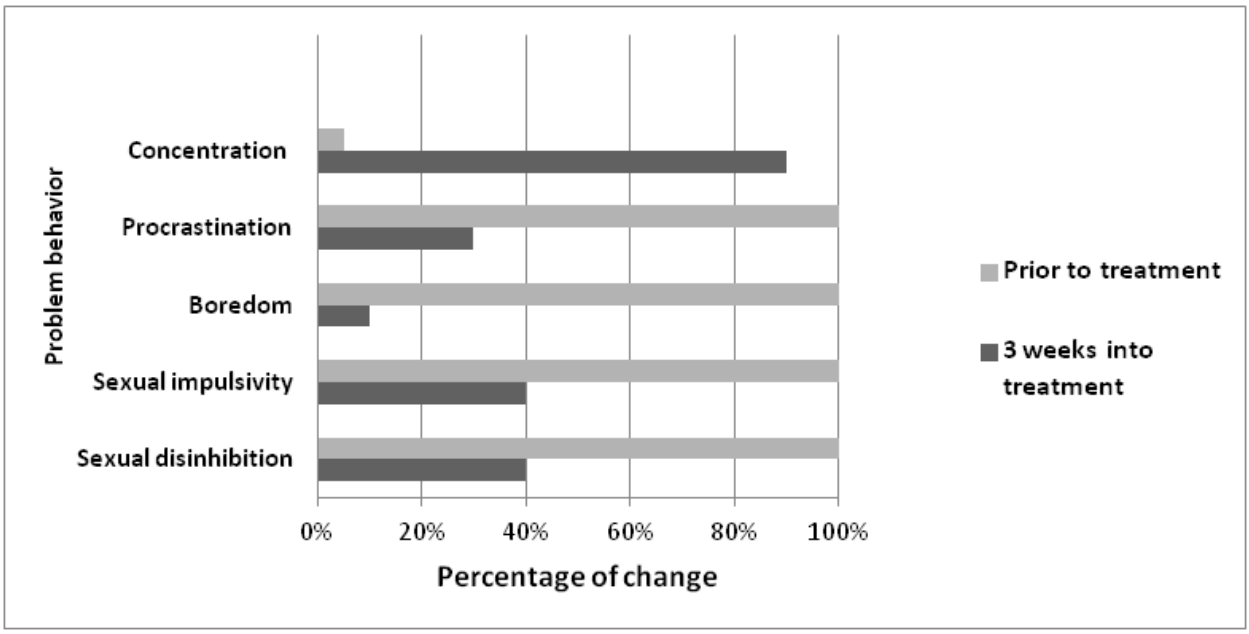

Figure 1. Illustrates positive benefits in a medication refractive Tourette's patient with paraphilias during a three-week treatment with KB220Z

In addition, he stated his procrastination tendency, which had been a severe motivational problem, was reduced to 30% out of a maximum 100%. He noted that boredom was significantly reduced for the three weeks to 10% of maximum 100%.

He reported that his sexual impulsivity was significantly reduced from 100% to 40% for three weeks on KB220Z. This estimate was emphatically confirmed by his female friend, who had had to endure his disinhibition for many months.

The patient also noted that his addiction to pornography was more under control and had decreased to only once a day from a much greater need. He added that he had a decreased need to "taunt" (tease) former girlfriend, which effect lasted for the entire month, i.e., even after he stopping the KB220Z.

His female friend stated that, on KB220Z, his sexual aggressiveness and disinhibition, which they both rated as 100% = maximum, was reduced to 40%, with respect to his pestering her, verbally and behaviorally. For the third week of the month, when he was no longer taking the KB220Z, his sexual aggressiveness returned to 85% of his maximal, baseline state.

Interestingly, the patient added, for the three weeks he took the KB220Z: "I was taking things from the back of my mind to the front of my mind". By this he meant, he was able to put himself in the position of, for example, the couple's cat (who had to endure a dirty litter box) and that he could also put himself in the position his female friend and attend more to her needs. In addition and remarkably, even though he stopped taking the KB220Z for the last week of his month's supply, the patient reported: "I am still able to think in terms of others, such as, cleaning the cat litter box and do the dishes for my (former) girlfriend".

To summarize, the patient stated that for the week when he stopped his KB220Z, his sexual impulsiveness had now returned to 85% of maximum (confirmed by female friend). His concentration was now reduced to 5% of 100% maximum and procrastination was 80% maximum debilitating effect. Boredom did not constitute a significant problem.

Questions raised by this patient's response to KB220Z center around his, possibly, new-found ability to think altruistically i.e., from the point of view of the other, namely, in this case, his cat and his female friend. Even more remarkable is his report that this new-found attitude was persisting, even though he had stopped taking KB220Z for one week.

An important consideration, of course, concerns the half-life of KB220Z, which other than rhodiola, especially the amino-acid precursors have a short 4-hour half-life. We do not expect that this attitude change is due to pharmacologically mediating his new psychological perspective. On the other hand, if it is 5 1/2 half-lives have dissipated in one week, it is possible that the patient was able to learn new behaviors and attitudes and begin to think more altruistically, in terms of the needs and perspective of others. It is possible that such newly learned behaviors might continue into the future.

In addition, even though off the KB220Z, he was still able to vacuum a donated but dirty car. Finally, the patient was able to come to his medical appointment for the first time in five weeks and did not evidence any lack of enthusiasm or lack of motivation as he related to the physician. (Prior to taking KB220Z, even though he was taking maximal dextroamphetamine/amphetamine, attending his appointment was inconsistent. The effects described above occurred without any additional dopamine agonist, pharmacological agent.)

While this is a profound clinical response it is short lived and requires more in-depth study especially in a large cohort against placebo control.

DISCUSSION

A recent article from the Cross-Disorder Group of the Psychiatric Genomics Consortium (2013), suggest that genetic contributions to psychiatric disorders do not in all cases map to present diagnostic categories. The authors aimed to identify specific variants underlying genetic effects shared between the five disorders in the Psychiatric Genomics Consortium: autism spectrum disorder, attention deficit-hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia. They analyzed genome-wide single-nucleotide polymorphism (SNP) data for the five disorders in 33,332 cases and 27,888 controls of European ancestry. SNPs at four loci surpassed the cutoff for genome-wide significance ($p < 5 \times 10^{-8}$) in the primary analysis: regions on chromosomes 3p21 and 10q24, and SNPs within two L-type voltage-gated calcium channel subunits, *CACNA1C* and *CACNB2*. Polygenic risk scores showed cross-disorder associations, notably between adult-onset disorders. Pathway analysis supported a role for calcium channel signaling genes for all five disorders. Their findings suggest that specific SNPs are associated with a range of psychiatric disorders of childhood onset or adult onset. In particular, variation in calcium-channel activity genes seems to have pleiotropic effects on psychopathology. These results provide evidence relevant to the goal of moving beyond descriptive syndromes in psychiatry, and towards a nosology informed by disease cause (Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013).

We point out this new finding because the suggestion of a common genetic antecedent as proposed by Blum et al. (1990, 1996) over 18 years ago on reward deficiency syndrome seems pivotal to the mechanisms involved in psychiatric disorders uniting potential therapeutic targets. Our laboratory continuously highlights the importance of providing dopaminergic agonist therapy for all behavioral addictions. The primary clinical issue in terms of dopaminergic agonist therapy has been the utilization of powerful agonists such as pharmaceuticals such as ropinirole, whereby long term use may result in down regulation D2 receptors (Blum, Gardner, Oscar-Berman & Gold, 2012). We on the other hand do not support the concept of reducing dopaminergic activation in the long term (Blum et al., 2008), which has now been suggested by utilizing for example, Calcium channel blockers (Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013). We refer to the development of rimonabant (Li & Cheung, 2011) which blocks dopamine release via GABAergic stimulation, which induces suicide ideation and as such rejected by the US FDA (Derosa & Maffioli, 2012).

It is noteworthy that ropinirole acts as a D_2, D_3, and D_4 dopamine receptor agonist with highest affinity for D_2. It is weakly active at the 5-HT_2, and α_2 receptors and virtually no affinity for many other neurotransmitter receptors (Eden et al., 1991). Long-term exposure to quinpirole, pramipexole and ropinirole (which possess negligible affinities for D (1)

sites) elicited supersensitivity of adenyl cycles by interacting at $D_1/D_2/D_3$ receptors. Interpretation of these result suggests that ropinirole following chronic use may induce down regulation of D_2 receptors and central tolerance to its effects (Aloisi, Silvano, Rossi, Millan & Maggio, 2011). We have suggested earlier that supersensitivity will induce relapse of addictive behaviors (Blum et al., 2009).

Given the long history of refractive response to psychotropic medication and the potential of overall RDS behaviors including drug abuse as well, one of us (TM) thought that a natural less powerful D_2 agonist such as KB220Z might provide some rapid relief of "hypersexuality" and repetitive paraphilia behavior. Based on a number of recent neuroimaging articles published (Blum et al., 2010; Miller et al., 2010) concerning the rapid onset of dopaminergic activation occurring one hour post administration, it is not surprising to obtain rapid relief of AC's paraphilias. However, while the outcome looks promising it could be short lived and must await larger long-term placebo controlled studies before any real interpretation could be garnished. We are encouraged because many previous clinical trials on KB220Z-NAAT and variants have shown long-term effects without dangerous side effects such as suicide ideation with links to reward circuitry improvements (Blum, Giordano et al., 2012; Blum & Gold, 2011; Blum, Liu, Shriner & Gold, 2011; Blum, Oscar-Berman et al., 2012).

CONCLUSIONS

Based on previous scientific evidence showing KB220Z-nutrigenomic amino-acid therapy (NAAT) to rapidly (post one-hour) activate dopaminergic pathways in both the pre-frontal cortex cingulate gyrus (relapse loci) and ventral tegmental area–caudate–accumbens–putamen (craving and emotion loci) the patient was prescribed KB220Z-NAAT. Within one week of utilization the repetitive paraphilia was eliminated. While this report focused on a rapid response rather than long-term benefits previously associated with NAAT, it is somewhat encouraging and longer term required follow-up and larger placebo controlled studies are warranted before any definitive conclusions could be gleaned from this case report.

Funding sources: The writing of this paper was supported in part by funds from the National Institutes of Health, NIAAA (RO1-AA07112 and K05-AA00219) and the Medical Research Service of the US Veterans Affairs awarded to Marlene Oscar-Berman. Kenneth Blum and Eric Braverman are the recipients of a grant from Life Extension to PATH Foundation NY.

Conflict of interest: Kenneth Blum, Roger L. Waite, William B. Downs, and John Giordano have financial ties to LifeGen, Inc. the worldwide distributors of patented KB220Z-NAAT.

REFERENCES

Aloisi, G., Silvano, E., Rossi, M., Millan, M. J. & Maggio, R. (2011). Differential induction of adenylyl cyclase supersensitivity by antiparkinson drugs acting as agonists at dopamine D1/D2/D3 receptors vs D2/D3receptors only: Parallel observations from co-transfected human and native cerebral receptors. *Neuropharmacology, 60,* 439–445.

American Psychiatric Association (2000–2006). *Diagnostic and statistical manual of mental disorders-IV (text revision).* Arlington, VA: American Psychiatric Publishing, Inc.

Banerjee, U. (1974). Modification of the isolation-induced abnormal behavior in male Wistar rats by destructive manipulation of the central monoaminergic systems. *Behavioral Biology, 11,* 573–577.

Bhugra, D., Popelyuk, D. & McMullen, I. (2010). Paraphilias across cultures: Contexts and controversies. *Journal of Sex Research, 47,* 242–256.

Blum, K., Chen, A. L., Chen, T. J., Braverman, E. R., Reinking, J., Blum, S. H., Cassel, K., Downs, B. W., Waite, R. L., Williams, L., Prihoda, T. J., Kerner, M. M., Palomo, T., Comings, D. E., Tung, H., Rhoades, P. & Oscar-Berman, M. (2008). Activation instead of blocking mesolimbic dopaminergic reward circuitry is a preferred modality in the long term treatment of reward deficiency syndrome (RDS): A commentary. *Theoretical Biology and Medical Modelling, 12,* 24.

Blum, K., Chen, T. J., Downs, B. W., Bowirrat, A., Waite, R. L., Braverman, E. R., Madigan, M., Oscar-Berman, M., DiNubile, N., Stice, E., Giordano, J., Morse, S. & Gold, M. (2009). Neurogenetics of dopaminergic receptor supersensitivity in activation of brain reward circuitry and relapse: Proposing "deprivation-amplification relapse therapy" (DART). *Postgraduate Medicine, 121*(6), 176–196.

Blum, K., Chen, T. J., Morse, S., Giordano, J., Chen, A. L., Thompson, J., Allen, C., Smolen, A., Lubar, J., Stice, E., Downs, B. W., Waite, R. L., Madigan, M. A., Kerner, M., Fornari, F. & Braverman, E. R. (2010). Overcoming qEEG abnormalities and reward gene deficits during protracted abstinence in male psychostimulant and polydrug abusers utilizing putative dopamine D_2 agonist therapy: Part 2. *Postgraduate Medicine, 122,* 214–226.

Blum, K., Gardner, E., Oscar-Berman, M. & Gold, M. (2012). "Liking" and "wanting" linked to reward deficiency syndrome (RDS): Hypothesizing differential responsivity in brain reward circuitry. *Current Pharmaceutical Design, 18,* 113–118.

Blum, K., Giordano, J., Oscar-Berman, M., Bowirrat, A., Simpatico, T. & Barh, D. (2012). Diagnosis and healing in veterans suspected of suffering from post-traumatic stress disorder (PTSD) using reward gene testing and reward circuitry natural dopaminergic activation. *Journal of Genetic Syndrome and Gene Therapy, 3,* 1000116.

Blum, K. & Gold, M. S. (2011). Neuro-chemical activation of brain reward meso-limbic circuitry is associated with relapse prevention and drug hunger: A hypothesis. *Medical Hypotheses, 76,* 576–584.

Blum, K., Liu, Y., Shriner, R. & Gold, M. S. (2011). Reward circuitry dopaminergic activation regulates food and drug craving behavior. *Current Pharmaceutical Design, 17,* 1158–1167.

Blum, K., Oscar-Berman, M., Giordano, J., Downs, B., Simpatico, T., Han, D. & Femino, J. (2012). Neurogenetic impairments of brain reward circuitry links to reward deficiency syndrome (RDS): Potential nutrigenomic induced dopaminergic activation. *Journal of Genetic Syndrome and Gene Therapy, 17,* 4.

Blum, K., Sheridan, P. J., Wood, R. C., Braverman, E. R., Chen, T. J., Cull, J. G. & Comings, D. E. (1996). The D2 dopamine re-

ceptor gene as a determinant of reward deficiency syndrome. *Journal of the Royal Society of Medicine, 89,* 396–400.

Blum, K., Stice, E., Liu, Y., Giordano, J., Morse, S., Downs, B. W., Waite, R. L., Madigan, M., Braverman, E. R., Kerner, M., Oscar-Berman, M., Miller, D., Stokes, S., Gant, C., Thompson, T., Allen, C., Smilen, A., Bowirrat, A. & Gold, M. (2011). "Dopamine Resistance" in brain reward circuitry as a function of DRD2 gene receptor polymorphisms in RDS: Synaptamine complex variant (KB220) induced "Dopamine Sensitivity" and enhancement of happiness. Washington, D.C.: XIX World Congress of Psychiatric Genetics, September 10–14.

Blum, K., Werner, T., Carnes, S., Carnes, P., Bowirrat, A., Giordano, J., Oscar-Berman, M. & Gold, M. (2012). Sex, drugs, and rock 'n' roll: Hypothesizing common mesolimbic activation as a function of reward gene polymorphisms. *Journal of Psychoactive Drugs, 44,* 38–55.

Chen, B., Liu, H., Ren, J. & Guo, A. (2012). Mutation of drosophila dopamine receptor DopR leads to male-male courtship behavior. *Biochemical and Biophysical Research Communications, 423,* 557–563.

Chen, T. J. H., Blum, K., Chen, L. C. H., Bowirrat, A., Downs, B. W., Madigan, M. A., Waite, R. L., Bailey, J. A., Kerner, M., Yelandi, S., Giordano, J., Morse, S., Miller, D. & Braverman, E. R. (2011). Neurogenetics and clinical evidence for the putative activation of the brain reward circuitry by amino-acid precursor-catabolic enzyme inhibition therapeutic agent (a neuroadaptogen): Proposing an addiction candidate gene panel map. *Journal of Psychoactive Drugs, 43,* 108–127.

Comings, D. E. (1994). Role of genetic factors in human sexual behavior based on studies of Tourette syndrome and ADHD probands and their relatives. *American Journal of Medical Genetics, 54,* 227–241.

Comings, D. E. & Blum, K. (2000). Reward deficiency syndrome: Genetic aspects of behavioral disorders. *Progress in Brain Research, 126,* 325–341.

Cross-Disorder Group of the Psychiatric Genomics Consortium, Smoller, J. W., Craddock, N., Kendler, K., Lee, P. H., Neale, B. M., Nurnberger, J. I., Ripke, S., Santangelo, S. & Sullivan, P. F. (2013). Identification of risk loci with shared effects on five major psychiatric disorders: A genome-wide analysis. *The Lancet, 381,* 1371–1379.

Daw, J. & Guo, G. (2011). The influence of three genes on whether adolescents use contraception, USA 1994–2002. *Population Studies (Camb), 65,* 253–271.

Derosa, G. & Maffioli, P. (2012). Anti-obesity drugs: A review about their effects and their safety. *Expert Opinion on Drug Safety, 11,* 459–471.

Eden, R. J., Costall, B., Domeney, A. M., Gerrard, P. A., Harvey, C. A., Kelly, M. E., Naylor, R. J., Owen, D. A. A. & Wright, A. (1991). "Preclinical pharmacology of ropinirole (SK&F 101468-A) a novel dopamine D2 agonist". *Pharmacology Biochemistry and Behavior, 38,* 147–154.

Gardner, E. L. (2011). Addiction and brain reward and antireward pathways. *Advances in Psychosomatic Medicine, 30,* 22–60.

Guo, G. & Tong, Y. (2006). Age at first sexual intercourse, genes, and social context: Evidence from twins and the dopamine D4 receptor gene. *Demography, 43,* 747–769.

James, W. H. (1995). Sexual expression, genetics, and testosterone in Tourette syndrome. *American Journal of Medical Genetics, 60,* 593.

Kerbeshian, J. & Burd, L. (1991). Tourette syndrome and recurrent paraphilic masturbatory fantasy. *Canadian Journal of Psychiatry, 36,* 155–157.

Li, M. F. & Cheung, B. M. (2011). Rise and fall of anti-obesity drugs. *World Journal of Diabetes, 2,* 19–23.

Mack, H., Fullana, M. A., Russell, A. J., Mataix-Cols, D., Nakatani, E. & Heyman, I. (2010). Obsessions and compulsions in children with Asperger's syndrome or high-functioning autism: A case-control study. *The Australian and New Zealand Journal of Psychiatry, 44,* 1082–1088.

Miller, D. K., Bowirrat, A., Manka, M., Miller, M., Stokes, S., Manka, D., Allen, C., Gant, C., Downs, B. W., Smolen, A., Stevens, E., Yeldandi, S. & Blum, K. (2010). Acute intravenous synaptamine complex variant KB220™ "normalizes" neurological dysregulation in patients during protracted abstinence from alcohol and opiates as observed using quantitative electroencephalographic and genetic analysis for reward polymorphisms: Part 1, pilot study with 2 case reports. *Postgraduate Medicine, 122,* 188–213.

Miller, W. B., Pasta, D. J., MacMurray, J., Chiu, C., Wu, H. & Comings, D. E. (1999). Dopamine receptor genes are associated with age at first sexual intercourse. *Journal of Biosocial Science, 31,* 43–54.

Money, J. (1990). *Gay, straight, and in-between: The sexology of erotic orientation*. New York: Oxford University Press.

Moser, C. & Kleinplatz, P. J. (2005). DSM-IV-TR and the paraphilias: An argument for removal. *Journal of Psychology and Human Sexuality, 17,* 91–109.

Sandyk, R. (1988). Naltrexone suppresses abnormal sexual behavior in Tourette's syndrome. *The International Journal of Neuroscience, 43,* 107–110.

Spitzer, R. L. (1981). The diagnostic status of homosexuality in DSM-III: A reformulation of the issues. *The American Journal of Psychiatry, 138,* 210–215.

Stekel, W. (1930). *Sexual aberrations: The phenomenon of fetishism in relation to sex disorders of the instincts and emotions the parapathiac disorders.* New York: Liveright Publishing.

Wang, Z. & Aragona, B. J. (2004). Neurochemical regulation of pair bonding in male prairie voles. *Physiology and Behavior, 83,* 319–328.