JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 25, Number 4, 2015

Pp. 286–292
DOI: 10.1089/cap.2014.0146

Review Article

Neurogenetic and Epigenetic Correlates of Adolescent Predisposition to and Risk for Addictive Behaviors as a Function of Prefrontal Cortex Dysregulation

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Abstract

As addiction professionals, we are becoming increasingly concerned about preteenagers and young adults' involvement with substance abuse as a way of relieving stress and anger. The turbulent underdeveloped central nervous system, especially in the prefrontal cortex (PFC), provides impetus to not only continue important neuroimaging studies in both human and animal models, but also to encourage preventive measures and cautions embraced by governmental and social media outlets. It is well known that before people reach their 20s, PFC development is undergoing significant changes and, as such, hijacks appropriate decision making in this population. We are further proposing that early genetic testing for addiction risk alleles will offer important information that could potentially be utilized by their parents and caregivers prior to use of psychoactive drugs by these youth. Understandably, family history, parenting styles, and attachment may be modified by various reward genes, including the known bonding substances oxytocin/vasopressin, which effect dopaminergic function. Well-characterized neuroimaging studies continue to reflect region-specific differential responses to drugs and food (including other non-substance-addictive behaviors) via either ''surfeit'' or ''deficit.'' With this in mind, we hereby propose a ''reward deficiency solution system'' that combines early genetic risk diagnosis, medical monitoring, and nutrigenomic dopamine agonist modalities to combat this significant global dilemma that is preventing our youth from leading normal productive lives, which will in turn make them happier.

Introduction

Recently, our laboratory (Gold et al. 2014) has called for a united effort to consider both genetic testing and early dopamine agonist therapy in early childhood, especially for those diagnosed with attention-deficit disorder (ADD) with and without hyperactivity: a known subset of reward deficiency syndrome (RDS). The impetus for the current article is the increasing concern of escalated substance seeking and even non-substance-addictive behaviors in youth, especially in those with attention-deficit/hyperactivity disorder (ADHD) (Jordan et al. 2014). It is well-known that ADHD is comorbid with cocaine abuse. As such, questions

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Funding: Marcelo Febo is the recipient of National Institutes of Health (NIH) DA019946 and is funded by the McKnight Brain Institute Foundation. Kenneth Blum is the co-recipient of a grant from Life Extension Foundation, Fort Lauderdale to the Pat Foundation, New York. Subhash C. Pandey is supported by National Institute of Alcohol Abuse and Alcoholism (NIAAA) Grant AA-019971 (Neurobiology of Adolescent Drinking in Adulthood [NADIA] project) and by the Department of Veterans Affairs (Merit Review Grant; Research Career Scientist award). Rajendra D. Badgaiyan is supported by NIH grants 1R01NS073884 and 1R21MH073624; and VA Merit Review Awards CX000479 and CX000780.

have been raised concerning the long-term consequences of ADHD medications such as methylphenidate. Jordan et al. (2014) correctly points out that whereas the prescribed use of methylphenidate has preventive symptomology benefits, teens on this medication seem to be at risk for cocaine abuse in later life. This notion that adolescent methylphenidate treatment increases adult cocaine self-administration, as is espoused by many scientists, is supported by observations in the spontaneously hypertensive rat (SHR) model of ADHD (Harvey et al. 2013; Gold et al. 2014; Krasnova et al. 2014).

As clinicians and scientists working in the addiction medicine field, we are cognizant of the growing global endemic not only of substance seeking but also of other devastating addictive behaviors, including the newly categorized psychopathology and self-destructive behaviors in adolescent populations (Kaess et al. 2014). Specifically, it is well known that there are rising global rates of pathological internet use (PIU) and related psychological impairments. Kaess et al. (2014) observed that suicidal ideation and attempts, depression, anxiety, conduct problems, and hyperactivity/inattention were independent predictors of PIU. The correlation among PIU, conduct problems, and hyperactivity/inattention was stronger in young females, whereas the association among PIU and symptoms of depression, anxiety, and peer relationship problems was stronger in males. This notion has been further underscored by the work of Taylor et al. (2014), which showed significant links among self-reported histories of self-harm, suicidal ideation, and suicide attempts in severe ADHD. Moreover these behaviors were mediated by mood, anxiety, drug and alcohol abuse, and an inability to cope with emotions.

True phenotypes for all addictive behaviors may not be carved out as independent disorders using the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) classifications (under Substance or Non Substance Use Disorder[s]) (American Psychiatric Association 2013). Instead, genetically and environmentally induced (epigenetic) brain reward impairment promises better functional delineation, as espoused by the new definition of the American Society of Addiction Medicine (ASAM) (Smith 2012) and as originally defined by Blum et al. (1996, 2012a–3) in discussing RDS.

It has been suggested by Daily (2012) that, at least in part, the root cause of addictive behavior in adolescents may be early childhood attachment (social) experiences, which are mediated by interactions with the environment (epigenetic), and by neurogenetic factors that impact a child's psychological trait/state, requiring both parental and peer co-regulation (e.g., parenting providing responsive caregiving to facilitate attention, emotion, and arousal). Interestingly, to survive after birth, mammalian infants need a mother to act as a caregiver. In this realm, we intend to show the importance of the following: 1) Key genetic components of mammalian mother–infant interactions, 2) the role of epigenetics in modulating gene expression during rearing and attachment, and 3) the role of functional connectivity in addictive behaviors (Lucion and Bortolini 2014).

Neurogenetics of Parental Rearing and Attachment

It is well known that adolescents and young adults with addiction also experience affect dysregulation resulting in an inability to reach out to others for emotional soothing and comfort, and possibly involving emotional circuitry (the amygdala) (Koob and Volkow 2010). The latter contributes significantly to the onset of drug use, continued use, and relapse. Certainly, for sustained recovery to occur, affect regulation should be a treatment focus.

There are many molecular neurobiological studies that address the important issues of attachment and parenting (Suzuki et al. 2012). In this article, we will briefly review some of the pertinent data, with a primary focus on the neurogenetic factors. The neuropeptides oxytocin and vasopressin mediate very complex social and cognitive behaviors, and recent work suggests a role for the gene polymorphisms of these neuropeptides (Donaldson and Young 2008).

It is of interest that a child's social bonding with friends (reciprocity) is associated with the child's oxytocin plasma levels, the mother's oxytocin-related genes (rs2254298, rs1042778) and hormones, and child–mother bonding (Feldman et al., 2013). These were not found to be associated with the father's genes, hormones, or behavior. Moreover, gender-specific associations were also found by Love et al. (2012), revealing that polymorphisms within the oxytocin gene explain differential dopaminergic responses to stress associated with anxiety traits linked to attachment behavior and emotional well-being in females, but not in males. In another study, Feldman et al. (2013) also found that parents reporting greater parental care showed higher plasma oxytocin, low-risk CD38 alleles, and more touch toward their infants. Furthermore, it was observed that infants ($n = 1000$) carrying the COMT-Val/Met genotype (representing a hypodopaminergic trait) showed a greater disorganization attachment style than those carrying the slower catabolism COMT genotype.

Gillath et al. (2008) have shown that although certain polymorphisms of the oxytocin gene were not associated with attachment insecurities, anxious attachment was associated with a polymorphism of the DRD2 dopamine receptor gene, and avoidant attachment was associated with a polymorphism of the 5HT2A serotonin receptor gene. The avoidant attachment is of interest because Blum et al. (1997) showed significant association between the DRD2 TaqA1 and the DAT1 10 alleles and schizoid-avoidant behavior in patients attending a neurological clinic. The concept of reward genes (dopaminergic, serotonergic, monoamine oxidase A [MAO]) and attachment style has been verified in the literature (Merikangas 1990; Merikangas et al. 1990; Letourneau et al. 2014).

It is known that overeating (food) and drugs of abuse share common neurochemical mechanisms in terms of withdrawal and responsivity in brain reward circuits as examples of RDS behaviors (Campbell et al. 2013). Along these lines, it is important to recognize the role of parenting in emotional eating in adolescence. It was found in adolescents that DRD2 A1 allele carriers only showed an increase in emotional eating, in relation to high parental psychological control, if they carried at least one DRD2 A1 allele. This suggested that a relationship between adverse rearing experiences and emotional eating might be dependent on genetic makeup (van Strien et al. 2010). Further evidence for dopamine D2 genotype and novelty seeking (thrill seeking) has also been shown by Finish investigators. Specifically, Keltikangas-Järvinen et al. (2009), observed a significant association between DRD2 and strict maternal disciplinary style in predicting novelty seeking. The investigators showed that when the child-rearing was punitive, participants carrying any A1 allele of the DRD2 gene had higher scores on novelty seeking than carriers of the A2/A2 genotype. Lucht et al. (2006) revealed earlier work also showing interaction between negative parenting and dopaminergic and GABA-ergic gene polymorphisms. They found an association between DRD2 and GABRA6 (Pro385Ser) genotypes and perceived parental rearing behavior. Only female probands with DRD2 A/A genotype showed higher scores for father rejection, parent overprotection, and father overprotection in the total group. An interaction between DRD2

and GABRA6 genotypes on father rejection and parent rejection was found. It is interesting that certain reward gene polymorphisms might, for example, be linked to thrill seeking, because of environmental issues related to childhood rearing by fathers with alcohol abuse problems. Lahti et al. (2005) showed more frequent alcohol consumption or drunkenness at age 17 and/or 14 years before the novelty-seeking assessment, and an association between the short (two- or five-repeat) alleles of the DRD4 gene and extremely high novelty seeking scores. Moreover, the genotype was not associated with less frequent alcohol consumption/drunkenness or less novelty seeking.

It is well known that adolescence is a turbulent stage of development. During these years, young people expand their social networks of peers and try out new ways of connecting to others. They tend to explore their identities through testing of their values, beliefs, ideas, and behavior. The question of genotypes and homophily (friendships) was independently explored by Blum et al. (2011, 2013) and Fowler et al. (2011) with similar findings. Specifically, Blum et al. (2012c) found substance use disorder among the genotyped family members (probands); the DRD2 Taq1 and the DAT1 10/10 alleles were more prevalent ($p < 0.015$) in the RDS families than in the controls. Interestingly, the TaqA1 allele occurred in 100% of one family, revealing that every subject who carried the A1 allele married a carrier of the same A1 genotype, suggesting homophily. It is known that humans (e.g., teenagers) associate with other humans who have similar characteristics, but it is unclear whether this tendency has consequences for the distribution of genotypes in a population. This question was evaluated by Fowler et al. (2011) wherein they showed that maps of friendship networks clustered according to genotypes. Their results indicate that one genotype (DRD2) was positively correlated (homophily) and one genotype (CYP2A6) was negatively correlated (heterophily).

Olsson et al. (2013) investigated the combined effect of: 1) An exon III variable number tandem repeat in the dopamine receptor gene (DRD4) and 2) an insecure attachment style on risk for tobacco, cannabis, and alcohol use problems in young adulthood. Their results are in agreement with genetic reward deficit hypothesis of drug addiction, for which the 7R+ risk allele interacts with attachment insecurity, and intensifies risk for problematic tobacco and cannabis use, but not alcohol binge drinking.

A consensus in the literature reveals that social interaction from birth to adulthood involves early experiences, such as childhood maternal nurturance, and genetics. Salo et al. (2011) found that high childhood maternal nurturance predicted high reward dependence and low avoidant attachment in carriers of the serotonin receptor gene (HTR2A) T/T genotype, but not in the T/C or C/C genotype. As such, T/T genotype carriers were more influenced by their childhood nurturing environment than were their C allele carrying counterparts. However, this finding was not confirmed with polymorphisms of the serotonin transporter and MAO A genes using the Temperament and Character Inventory (Samochowiec et al. 2004).

Epigenetics of Parental Rearing and Attachment

Epigenetics is an emerging area in the neuroscience field that has been provided with important clues as to how drugs of abuse, including alcohol, interact with epigenomes and modulate the genetic functions and regulate addictive endophenotypes (Renthal and Nestler 2008; Krishnan et al. 2014). Epigenetic modifications, such as histone and DNA chemical modifications, also play an important role in neurodevelopment (Kofink et al., 2013; Szyf, 2013). Epigenetics explains how environmental and psychological factors regulate the activity of our genomes without inducing changes in the DNA sequence. It has been suggested that epigenetics mediate our behavior, in part, and have long-term effects on the regulation of the genome function. González-Pardo and Pérez Álvarez (2013) indicate that epigenetics impact nature–nurture, genotype–phenotype, and pathogenesis–pathoplasty. Furthermore, ''epigenomics'' has been defined by Gomase and Tagore (2008) as the study of the ''effects of chromatin structure, including the higher order of chromatin folding and attachment to the nuclear matrix, packaging of DNA around nucleosomes, covalent modifications of histone tails and DNA methylation. This has evolved to include any process that alters gene activity without changing the DNA sequence, and leads to modifications that can be transmitted to daughter cells.'' Recent studies indicate epigenetic inheritance through the male germ line during alcohol exposure (Rachdaoui and Sarkar, 2014).

Lickliter (2008) and Toth et al. (2013) have provided important information concerning the issues related to child maltreatment and its known significant deleterious effects for the child and for society, as well as the subsequent impact on the child's social bonding (attachment). Moreover, Saveanu and Nemeroff (2012) correctly suggest that a history of childhood trauma along with a number of polymorphic reward genes significantly contributes to depressive behaviors from birth to adulthood (Apter-Levy et al. 2013). Clinically, certain environmental interventions that provide a support network (maternal care, a positive family environment, the support of a close friend) have been shown to reduce the impact of childhood abuse.

It is well known that epigenetic factors affect subsequent infant behaviors; extrapolation from many animal studies indicates that a take-away message ''lick your pups'' could have really important meaning even in terms of human interaction, and in shaping adolescent behavior (Pena et al. 2014). This concept is underscored by work from Hao et al. (2011), showing that rodent dams lick male pups more than they lick female pups in the anogenital and other regions of the body. Importantly, the mu-opioid receptor is encoded by the OPRM1 gene, and is known to contribute to mother–infant behaviors. Utilizing this animal model, they clearly show that male pups have higher DNA methylation on the OPRM1 gene, especially in the nucleus accumbens (NAc), than do female pups. This epigenetic hypermethylation may have relevance to addiction, stress regulation, motivation, and, potentially, all subtypes of RDS.

Recently, Peña et al. (2014) have suggested that environmental-induced stress or prior drug exposure impacts the onset of addiction. This exposure to environmental insults mediates stable changes in gene expression, neural circuit function, and, ultimately, behavior; these subsequent maladaptations are distinct between developmental and adult exposures. Along these lines, the same group showed that cocaine-mediated repression of the histone methyltransferase (HMT) G9a is implicated in transcriptional, morphological, and behavioral responses to chronic cocaine administration. G9a repression by cocaine was observed in both DRD1-expressing (striatonigral) and DRD2-expressing (striatopallidal) medium spiny neurons. Based on this work, the authors suggest a critical function for cell type-specific histone methylation patterns in the regulation of behavioral responses to environmental/epigenetic stimuli (Maze et al. 2014). Although psychosocial–spiritual factors play a significant role in the addiction process, so does biology. Given that that the former factors induce epigenetic effects (including ''cellular or molecular memory'' brain-region-specific alterations via chromatic structural effects), future intervention must be considered (especially at early developmental

stages) in terms of drug- related memories specific to the anterior cingulate gyrus and potential relapse (Nestler 2013).

Most recently, our laboratory (Blum et al. 2014) showed that drug abuse relapse rates were linked to the level of educational achievement. Importantly, it was pointed out that achievement of education was in part mediated by the dopamine D2 receptor gene polymorphism (TaqA1). Shanahan et al. (2007) revealed the power of epigenetics whereby genetic propensity for risky behaviors was modified by helping relationships (G×E). Their results show a number of important epigenetically related findings: DRD2 A1+ (A1A1 and A1A2 genotypes) is associated with reduced school continuation compared with male counterparts with DRD2 A1-; mentors compensate for this negative association; and youth with DRD2 A1+ are less likely to have a mentor than their counterparts with DRD2 A1-.

In humans, environmentally induced insults to dopaminergic pathways in the PFC by dopamine antagonistic therapy (haloperidol) result in an induction of ΔFosB, which has been linked to negative behavioral outcomes. Viral-mediated overexpression of ΔFosB in the PFC of rodents induces cognitive deficits and anxiety (Dietz et al. 2014).

Finally, it is known that adolescence is a developmental period with real risk for all RDS behaviors, including drug and alcohol abuse. Pascual et al. (2009), concerned about the dopaminergic mesolimbic system (a region under change during adolescence), found that repeated ethanol administration to rodents causes changes to dopaminergic and glutaminergic systems. They found that repeated ethanol administration also downregulates the expression of DRD2 and Nmdar2b phosphorylation in the PFC of adolescent animals, but not of adult rats. More interesting is their finding that ethanol treatment during adolescence alters the acetylation of histones H3 and H4 in the frontal cortex, NAc, and striatum. This suggests that epigenetics may have a differential effect in remodeling chromatin in the adolescence brain compared with the adult brain. These studies further suggest that abnormal plasticity in reward-related processes and epigenetic mechanisms could contribute to the vulnerability of adolescents to alcohol addiction.

Sakharkar et al. (2014) showed that that reduced sensitivity to anxiolysis and the lack of rapid tolerance to the anxiolytic effects of ethanol and the inhibition of histone deacetylase (HDAC) and DNA methyltransferase (DNMT) functions may play a role in engaging adolescents in binge drinking patterns. Also HDAC and DNMT inhibitors are emerging potential therapeutic agents to combat addictive behaviors, including alcoholism (Renthal and Nestler 2008; Warnault et al. 2013; Krishnan et al. 2014).

PFC Dysregulation in Youth

Unlike developed adults, preteens entering the adolescent phase of life may not be equipped to make appropriate decisions, because their brains are not fully developed and myelinated. This is especially true for the PFC (the area known to support executive function and decision making) also known as the ''braking/inhibitory system.'' The PFC can be hijacked by the subcortical structures of the midbrain. The midbrain region is known to regulate social and emotional responses, and impairments can lead to a deficit of neurotransmitter function. We must be cognizant of how stress can influence the developmental process of the brain, and also of how abuse of certain drugs, such as alcohol and cocaine, alter the integrity of white and gray matter volume (Mackey et al. 2014; Maksimovskiy et al. 2014). Moreover, it is well known that the PFC is developing before people are in their early 20s: the time when myelination is initiated (Pfefferbaum et al. 1994; Giedd et al. 1996; Spear 2000; Yurgelun-Todd et al. 2002). Myelination, which is involved in the regulation of brain speed, is compromised by stress and or drugs; even prenatally, and especially in predevelopment periods (Melo et al. 2006; Xu et al. 2013). During the turbulent years before becoming an adult, people have many stressful unanswered questions, and the resulting frustration, and possible genetic and epigenetic risks, are antecedents to subsequent drug abuse (De Bellis et al. 2005; Kofink et al. 2013).

Dopamine Agonist Therapy: Reasons for Blocking Reward

Therapy for addictive behaviors often offers the possibility of blocking the reward system by antagonistic agents (e.g., naltrexone). However, the rationale of such a blockade always remains questionable, as it strengthens the hypodopaminergic state of the brain reward circuits, and thus sustains the craving rather than helping the person achieve relief. Moreover, a recent study observed emotional impairment utilizing a sophisticated voice recognition method in long-term (average 1.6 years) patients on Suboxone maintenance therapy (Hill et al. 2013). From this perspective, the importance of utilizing dopamine agonist therapy to treat addictive disorders instead of blocking natural dopaminergic activity seems more prudent in the long term (Blum et al, 2014a). With this in mind, Blum et al. (2012e) have developed a natural putative dopamine agonist, KB220Z™, which has a number of very important anti addictive effects.

As reported in a detailed review article, KB220 variants have been shown to enhance brain enkephalin levels in rodents, reduce alcohol-seeking behavior in C57/BL mice, and pharmacogenetically convert ethanol acceptance in preferring mice to emulate nonpreferring mice, such as DBA/2J mice (Blum et al. 1987).

In humans, KB220Z has been reported to reduce drug and alcohol withdrawal symptomatology (i.e., lower the need for benzodiazepines and reduce days with withdrawal tremors, which is evidence of a lower BUD score [building up to drink], with no severe depression on the Minnesota Multiphasic Personality Inventory [MMPI]). Patients in recovery treatment had a reduced stress response, as measured by the skin conductance level, and significantly improved physical scores and behavioral, emotional, social and spiritual (BESS) scores. After detoxification, there was a sixfold decrease in Against Medical Advice (AMA) rates when comparing KB220 variant to placebo groups. Healthy volunteers demonstrated an enhanced focus. There is also evidence of reduced craving for alcohol, heroin, cocaine, and nicotine. Also, reductions in inappropriate sexual behavior and reduced posttraumatic stress disorder (PTSD) symptoms such as paraphilia have been reported (McLaughlin et al. 2013). Quantitative electroencephalographic (qEEG) studies in humans have found that KB220Z modulates theta power in the anterior cingulate cortex. In abstinent heroin addicts, a single dose of KB220Z compared with placebo in a pilot study (Blum et al. 2014b) resulted in activation of the NAc as well as activation and improvement of the prefrontal–cerebellar–occipital neural network. In addition, it was found that carriers with the DRD2 A1 allele showed a significant Pearson correlation in terms of enhanced compliance to KB220Z treatment relative to carriers of the normal compliment of DRD2 receptors in known obese patients (Blum et al. 2014b). This suggests that low dopamine function equates to better treatment outcome with KB220Z.

The recognition that in the mammalian brain there are complex genomic networks that intimately interact with functional neural networks has led to a rising endeavor to increase our knowledge of the fundamental neural mechanisms of addiction. Genes are under the regulatory control of epigenetic networks that may constitute a ''code'' that shapes, and may even define, functional features of neural networks (Colvis et al. 2005). Failure at the genomic and epigenomic levels, through hereditary mechanisms or via exposure to environmental insults such as drugs of abuse, may impact the relationship between gene regulatory networks and widespread brain neural networks. Causal relationships bridging these genomic and functional levels are missing, and are needed to enable effective treatments that are tailored to specific individual and population mental health diseases (Blum et al., in press).

Recent research (Lu and Stein 2014) has shown that the brain's intrinsic resting state activity, which is organized as functionally interrelated network states showing slow synchronous activity (Biswal et al. 1997), is reduced in addiction to several licit and illicit drugs. We reproduced this phenomenon in animal models, and have discovered that a natural dopaminergic enhancing complex, KB220Z, increases resting state functional connectivity (rsFC) in brain reward and memory networks in both human subjects addicted to heroin and in animal models. KB220Z contains tailored ingredients that supplement specific intermediary steps in the brain's natural reward cascade, and was developed to normalize dopaminergic activity under a state referred to as RDS (Blum et al. 2012b, 2012d). Conditions in which underlying genomic networks are altered in such a way that impacts the brain's intrinsic connectivity within the reward system can potentially be screened and adjusted with natural compounds such as KB220Z (Blum et al., in press).

Before this powerful strategy is enabled for human applications, basic science experiments that apply high spatial-temporal resolution functional brain imaging and genetic interrogation tools are needed. Although many laboratories across the United States and abroad are starting to apply optogenetic tools to examine the relationship between specific neuronal populations and disease modeling behaviors in rodents, there is a critical lack of optogenetic studies conjoined with noninvasive high field imaging to further our understanding the undeveloped young brain.

Conclusion

As addiction professionals, we are becoming increasingly concerned about preteenagers' and young adults' involvement with substance use disorders as a way of relieving stress and anger. The turbulent underdeveloped central nervous system, especially in the PFC, provides impetus not only to continue important neuroimaging studies in both human and animal models, but also to encourage preventive measures and cautions embraced by governmental and social media outlets. It is well known that before people are in their 20s, PFC development is undergoing significant changes and, as such, it can hijack appropriate decision making in the adolescent population. We are further proposing that early genetic testing for addiction risk alleles will offer important information that could be utilized by parents and caregivers potentially prior to indulgence of psychoactive drugs by our youth. Understandably, family history, parenting, and attachment may be modified by various reward genes, including the known bonding substances oxytocin and vasopressin, which effect dopaminergic function. Well-characterized neuroimaging studies continue to reflect brain-region-specific differential responsivity to drugs and food (including other non-substance-addictive behaviors), either a ''surfeit'' or a ''deficit.'' Similarly, early life alcohol exposure or adversity may modulate epigenetic processes that are essential for proper neurodevelopment, thereby predisposing a person to addictive behaviors at adulthood. With this in mind we hereby propose a ''reward deficiency solution system'' that couples early genetic risk diagnosis, medical monitoring, and dopamine agonist (nutrigenomic) modalities to combat this significant global dilemma that is preventing our youth from leading normal productive lives, which will in turn make them happier.

Acknowledgment

We appreciate the expert editing of Margaret A. Madigan.

Disclosures

Kenneth Blum, through his companies Synaptamine Inc. and KenBer LLC, holds a number of United States and foreign patents issued and pending on both genetic testing and solutions to RDS. Kenneth Blum, David E. Smith, and John Femino are on the Dominion Diagnostic, LLC, Scientific Advisory Board and are paid consultants. Kenneth Blum and Mark Gold are paid consultants for Malibu Beach Recovery Center. Gozde Agan and James Fratantonio are employed by Dominion Diagnostics. The other authors have nothing to disclose.

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