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Epigenetic Repair of Terrifying Lucid Dreams by Enhanced Brain Reward Functional Connectivity and Induction of Dopaminergic Homeostatic Signaling

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Abstract

During Lucid Dreams, the dreamer is aware, experiences the dream as if fully awake, and may control the dream content. The dreamer can start, stop, and restart dreaming, depending

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CONFLICT OF INTEREST

KB is a chairman and CSO of the Geneus Health Board of Directors and CSO. He is the inventor of GARS and the Pro-dopamine regulator (KB220PBM) and credited with the patents issued and pending. Through their company, Igene KB owns stock in Geneus Health RB and KB are members of the GeneUs Health LLC Board KB is also the Chairman of the Board of Directors and Scientific Advisory Board of Geneus Health that includes MGL, EJM, PKT, RDB, and DB. There are no other conflicts to report.]

on the nature and pleasantness of the dream. For patients with Reward Deficiency Syndrome (RDS) behaviors, like Attention Deficit Hyperactivity Disorder (ADHD), Tourette's- Syndrome, and Posttraumatic Stress Disorder (PTSD), the dream content may be pleasant, unpleasant, or terrifying. A sample of psychiatric center patients identified as having RDS reported the effectiveness of a neuronutrient, dopamine agonist, KB200Z, in combating terrifying, lucid dreaming. These reports motivated the study of eight clinical cases with known histories of substance abuse, childhood abuse, and PTSD. The administration of KB200Z, associated with eliminating unpleasant or terrifying lucid dreams in 87.5% of the cases. Subsequently, other published cases have further established the possibility of the long-term elimination of terrifying dreams in PTSD and ADHD patients. Induction of dopamine homeostasis may mitigate the effects of neurogenetic and epigenetic changes in neuroplasticity, identified in the pathogenesis of PTSD and ADHD. The article explores how relief of terrifying lucid dreams may benefit from modulation of dopaminergic signaling activated by the administration of a neuronutrient. Recently, precision formulations of the KB220 neuronutrient guided by Genetic Addiction Risk Score (GARS) test results have been used to repair inheritable deficiencies within the brain reward circuitry. The proposition is that improved dopamine transmodulatory signaling may stimulate positive cognitive recall and subsequently attenuate the harmful epigenetic insults from trauma.

Keywords

Lucid dreams; pro-dopamine regulation (KB220); functional connectivity; neuroplasticity; Genetic Addiction Risk Score (GARS); dopaminergic homeostatic signaling

1. INTRODUCTION

1.1. Background

During Lucid Dreams, the dreamer becomes aware of dreaming within a dream. As if fully awake, the dreamer can control the dream content; start, stop, and restart dreaming, depending on the dream's nature. The dream content may be pleasant, unpleasant, or terrifying. Lucid dreaming is a symptom of Reward Deficiency Syndrome (RDS) behaviors, like Attention Deficit Hyperactivity Disorder (ADHD), Tourette's- Syndrome, and Posttraumatic Stress Disorder (PTSD) [1].

Humans have evolved through many adaptations to evolutionary pressures and, many of the genetic polymorphisms that currently exist, represent survival alleles that load onto "Selfishness" [2]. These ancient alleles, especially those tied to dopaminergic function, such as the 7R DRD4 gene and others, while previously advantageous for survival, today represent a risk for addictive behaviors. In detail, Opazo *et al.* [3] reported that according to a phylogenetic tree, the DRD2l and DRD4rs gene lineages would have originated in the ancestor of gnathostomes between 615 and 473 million (mya) years ago. Conservation of sequences required for dopaminergic neurotransmission and small changes in regulatory regions suggest a functional refinement of the dopaminergic pathways during evolution [4]. Comprehension of the role of dopaminergic function, from then until now, makes possible the epigenetic induction of required homeostatic balance in the brain reward circuitry of *Homo sapiens*.

However, presently DNA polymorphisms remain in the human genome, which can signify a high risk for drug and non-drug RDS behaviors [5]. Research studies have demonstrated that iterations of pro-dopamine regulator KB220 increased functional connectivity in both animal [6] and human brains [7] and prolonged neuroplasticity changes [8]. This consequential evidence of this neuro-plastic effect combined with prolonged cessation of terrifying lucid dream after short term use of KB220 heralds a new research area involving Lucid Dream therapeutics.

1.2. Evidence for Alleviating Terrifying Lucid Dreams: A Snapshot

A sample of psychiatric center patients identified as having RDS behaviors reported that the neuronutrient dopamine agonist KB200Z could effectively combat terrifying, lucid dreaming. These reports motivated the study of eight clinical cases with known histories of substance abuse, childhood abuse, and PTSD. The administration of KB200Z, associated with the elimination of unpleasant or terrifying lucid dreams in 87.5% of the cases [9]. In two additional cases, similar alleviation of terrifying lucid dreams in patients with PTSD was reported [10]. In the first case, a 51-year-old, obese woman diagnosed with PTSD and depression had a history of attempted suicide. She complained of terrifying, lucid nightmares, reminiscent of the sexual/physical abuse she had suffered in her early childhood from family members, including her alcoholic father. Her vivid, “bad dreams” remained refractory to treatment, despite six months of Dialectical Behavioral Therapy (DBT) and standard pharmaceutical agents, including prazosin and clonidine. Within one month of treatment with KB220, there was a total alleviation of her terrifying, lucid dreams. A similar reduction of terrifying lucid dreams occurred in a 39-year-old female with PTSD [10].

In four additional cases, dramatic and persistent alleviation of terrifying lucid dreams in patients diagnosed with ADHD, PTSD, and opioid use disorder (OUD) with KB220 could well have been permanent. Although the patients had stopped taking the nutraceutical for between 10 to 12 months, they no longer reported any recollection or recurrence of terrifying lucid dreams. In the first of these cases, the patient was a 47-year-old married male who required continued buprenorphine-naloxone combination treatment, the second a 32-year-old female with the sole diagnosis of ADHD, the third a 38-year-old male, diagnosed with ADHD and Substance Use Disorder (SUD). The fourth case was a 50-year-old female diagnosed with Alcohol Use Disorder (AUD), ADHD, and PTSD [11].

The most dramatic case involved C.J., a 38-year-old, single female, living with her mother, who had a history of SUD and ADHD, inattentive type. Her SUD and ADHD had been stable on buprenorphine/naloxone combination as well as dextro-amphetamine mixed salts for many years. When CJ unexpectedly lost her job for oversleeping and not calling into work, she became depressed and unmotivated. After taking the KB200 nutraceutical for four weeks, she noticed a marked improvement in her mental and motivational status. Also, she noted that her previously unreported shopping and hoarding addictions had dramatically decreased. Moreover, KB220 eliminated her life-long history of terrifying lucid dreams. Finally, she felt more empowered, with her locus of control shifting from an external to a more internal one [12].

One goal of this review is to provide imaging data related to the function of KB220, discuss the neuro-genetics of lucid dreaming as a sub-type of RDS, and advocate for the adoption of a pro-dopamine lifestyle to sustain dopamine homeostasis, despite evolutionary genetics.

1.3. Molecular Neurobiology of Lucid Dreams

While Freud (1899) portrayed dreams as the royal road to the unconscious and a means of “wish fulfillment,” *nightmares* have been regarded by many as a psychic means of processing threatening information, which, brought into cognitive consciousness, would increase anxiety [13]. A more recent explanation of prolonged, intense nightmares is that they might reduce the physiological responses associated with frightening stimuli and reduce anxiety [14].

Previous studies have considered the role of neurotransmitters in lucid dreams [9–12]. Also, Blum *et al.* characterized the pathogenesis of PTSD as a severe polygenic disorder triggered by environmental factors [15]. An abundance of polymorphic genes, in particular, the alleles that are the genetic determinants of low dopamine function (hypodopaminergia) associate with a predisposition to PTSD as well as SUD [16]. An early study by Comings *et al.* [17] screened subjects exposed to severe combat conditions in Vietnam for PTSD; 58.3% of the 24 subjects who met the criteria for PTSD carried the D2A1 allele, of eight who did not 12.5% carried the D2A1 allele ($p = 0.04$). In a replication study of 13 subjects with PTSD, 61.5% carried the D2A1 allele; of the remaining 11, none had a PTSD diagnosis and, zero% carried the D2A1 allele ($p = 0.002$). In the combined group, 59.5% with PTSD carried the D2A1 allele, vs. 5.3% who did not have PTSD ($p = 0.0001$) carried the allele. These results suggest that a DRD2 variant in linkage disequilibrium with the D2A1 allele confers an increased risk for PTSD, and the absence of the D2A1 variant confers resilience, relative resistance to PTSD.

Despite substantial literature on the neurobiology of dreams currently, we do not fully understand the neurological mechanisms involved in nightmares or their function. It is noteworthy that the release of norepinephrine and acetylcholine from the ascending fibers are strongly activated during wakefulness; however during rapid-eye-movement sleep, the neocortical tone is sustained mainly by acetylcholine. Concentrations of acetylcholine, dopamine, and cortisol increase, and serotonin and noradrenaline are absent during Rapid Eye Movement (REM) [paradoxical] sleep. The paradox is that even though activity in the forebrain and midbrain during the REM stage of sleep is intense and consumes large amounts of energy, the muscles are relaxed, and the body remains inactive except for the diaphragm and eye muscles. Cycles of REM often comprise the smallest portion of the sleep, occur several times during sleep, and more frequently towards the morning.

Sil’kis [18] agrees that nightmares involve altered concentrations of acetylcholine, noradrenaline, dopamine, serotonin, and glutamate. These neurotransmitter changes may impair contextual memory through hippocampal involvement in dreams during REM sleep [18, 19]. Paradoxical sleep occurs due to cholinergic neurons’ activation in the pedunculopontine nucleus, disinhibited from the output basal ganglia nuclei. Sil’kis [18, 20] suggests that improved episodic memory and reduced nightmares might occur with the introduction of a neurotransmitter or neuropeptide capable of promoting potentiation in all

components of the polysynaptic pathway through the hippocampus, especially at CA1 and CA3 pyramidal cells.

In the absence of signals from the retina, the disinhibition of neurons in the pedunculopontine nucleus and superior colliculus allows the signals to excite neurons in the lateral geniculate body and other thalamic nuclei projecting to the primary and higher visual cortical areas, prefrontal cortex, and back into the striatum. Thus, dreams as visual images and motor hallucinations result from an increase in the activity of groups of thalamic and neocortical neurons. The involvement of dopamine is paramount in that its homeostasis provides synaptic transmission efficacy during the circulation of signals in closed interconnected loops, each which includes one of the visual cortical areas, one of the thalamic nuclei, limbic regions, and a region of the basal ganglia.

1.4. Can Pro-dopamine Regulation Induce Neuroplasticity and Attenuate Terrifying Dreams?

Remarkably, in at least three of the original cases mentioned earlier, it seems that this profound elimination of terrifying lucid dreams and conversion to happy dreams continued for ~ 9 months after cessation of KB220z administration. This prolonged nature of the effect of KB220 variation is perplexing.

1.4.1. Brain Function following Traumatic Events and As Such PTSD—A

review of the existing literature regarding brain function following traumatic events such as PTSD may inform understanding of the prolonged nature of the KB220 effect. Bowirrat *et al.* [21] pointed out that early life trauma provokes neurochemical responses to later stressful events. Long term, several biological systems, including mesolimbic brain structures and various neurotransmitters, are affected. These effects include the size and duration of the Dopamine /Norepinephrine catecholamine response and the extent of the cortisol response [22].

Many relevant studies revealed profound long-term neurotransmission abnormalities in PTSD. Mueller *et al.* [23] reported that male veterans with a positive diagnosis of PTSD compared to negative controls (no PTSD) had a thinner rostral anterior cingulate and insular cortex but no hippocampal volume loss. Moreover, PTSD was characterized by decreased nodal degree (orbitofrontal, anterior cingulate) and clustering coefficients (thalamus) but increased nodal betweenness (insula, orbitofrontal) and a reduced *small-world index* in the whole-brain analysis and by orbitofrontal and insular nodes with an increased nodal degree, clustering coefficient and nodal betweenness in the restricted analysis.

Mueller's group [24] recently investigated the polygenic risk score (PRS) for PTSD. They used the latest summary statistics from the most extensive published genome-wide association study (GWAS) conducted by Psychiatric Genomics Consortium for PTSD (PGC-PTSD). Interestingly, they found the PRS of a cohort comprising veterans of recent wars ($n = 244$) explained some variations in PTSD onset (Nagelkerke $R^2 = 4.68\%$, $P = 0.003$) and severity (Nagelkerke $R^2 = 4.35\%$, $P = 0.0008$) except for an African ancestry sub-cohort. These findings demonstrate the importance of the Genetic Addiction Risk Score (GARS) test results that identify polygenic risk for hypodopaminergia.

Moreover, in agreement with the work of Mueller *et al.* [23, 24], Du *et al.* [25] revealed in the Wenchuan earthquake survivors that while three weeks after the disaster, functional connectivity changes involved both frontal-limbic-striatum and default-mode networks (DMN). Only changes in the DMN persisted at the two-year follow-up, despite complete recovery from high initial anxiety levels. Taken together, this crucial new evidence demonstrates that post-trauma anxiety experienced by survivors alters functional connectivity in the frontal-limbic-striatal network; however, parallel changes in the DMN persist despite the apparent absence of anxiety symptoms [25]. The authors suggest that changes in disaster survivor neural networks, involved in core aspects of self-processing, cognitive and emotional functioning, are long-term, independent of anxiety symptoms, and may also increase subsequent development of PTSD.

Bierer *et al.* [26], evaluating brain functionality in Gulf War Veterans diagnosed with PTSD reported a significantly lower mean diffusivity (MD) [average molecular motion independent of any tissue directionality] in the right cingulum bundle. Still, no significant differences in MD or fractional anisotropy (FA) [direction] in the left cingulum bundle, and PTSD symptom severity scores both clinician and self-rated were associated significantly with increased FA and reduced MD and in the right cingulum. Along similar lines, Saar-Ashkenazy *et al.* [27] found a reduction in corpus-callosum (CC) white matter volume in PTSD patients compared to controls correlated with lower associative memory performance. Admon *et al.* [28] found that Israeli soldiers with diagnosed PTSD compared to non- PTSD soldiers had decreased hippocampal (HC) volume, displayed more PTSD-related symptoms post-exposure and reduced HC functional connectivity with the ventromedial prefrontal cortex (vmPFC). Chao *et al.* [29] found a significant reduction of left occipital gray matter compared to the controls and correlated negatively with the severity of PTSD symptoms. Abe *et al.* [30, 31] evaluated victims of the Tokyo subway sarin gas attack with PTSD. They reported that compared to non-PTSD matched controls, the voxel-based analysis revealed that FA increased significantly in the left anterior cingulum and the subjacent left anterior cingulate cortex (ACC) gray matter. Previously, these investigators had found a volume decrement in PTSD subjects.

Synaptic plasticity known to occur at glutamate synapses throughout the brain, including the neocortex, has a probable role in neurodevelopment and a broad spectrum of adult neural functions [32]. Thus, prolongation of the KB220 effect on lucid nightmares may be the consequence of neuro-plastic mechanisms that can repair some of these deficits caused by trauma. From the review of PTSD studies, polygenic risk score (PRS) can explain variations in onset and severity of PTSD, and functional connectivity changes in the DMN persist despite the apparent absence of anxiety symptoms after three months. Increases in FA and reduced MD in the right cingulum associate with PTSD symptom severity and decreased HC volume reduced HC functional connectivity and lowered associative memory performance. Also, a reduction of left occipital gray matter volume significantly correlates with increased PTSD symptom severity. A voxel-based analysis revealed FA increased significantly in the left anterior cingulum, subjacent to the left anterior cingulate cortex (ACC) gray matter.

Attention Deficit Hyperactivity Disorder (ADHD) is a developmental illness associated with cortical gray matter volume deficits that may represent a state of diminished dopamine

stimulation that is equally disruptive to healthy synaptic plasticity mechanisms [33–39]. In PTSD, however, long term potentiation necessary for conditioned fear-extinction is thought to be impaired. Evidence suggests that genetic polymorphisms related to hypodopaminergic neurotransmission (as determined by the GARS test) confers vulnerability to PTSD. Thus, “hypodopaminergic” trait and state thwart some of the synaptic plasticity that underlies consolidation and retention of fear extinction. Therefore, dopamine--modulated synaptic plasticity is essential, and when disrupted, either precipitates or is symptomatic of neuropsychiatric illness. Novel treatments that can restore balanced synaptic plastic modulation may be preventative as a therapeutic intervention for Lucid Dreams associated with PTSD and ADHD abnormal behaviors [12].

Also, many of the patients described herein are victims of childhood parental abuse, and there is evidence in this population of deficits in gray and white matter volume. The deficits are most prominently in the dorsolateral and vmPFC and hippocampus, amygdala, and corpus callosum (CC) regions of the brain. Diffusion tensor imaging (DTI) studies show evidence of structural interregional connectivity deficits between these areas, suggesting neural network abnormalities [40].

The function and structure of the lateral and ventromedial frontolimbic brain areas and networks that mediate effect and behavioral control are also prominent deficits associated with early childhood abuse [41]. These environmental events may also impact the future development of terrifying lucid dreams [42]. The Prefrontal Cortex (PFC) undergoes significant changes during development and may compromise appropriate decision making in an adolescent population. The potential for environmental insults to affect mRNA expression of dopaminergic genes, reported in the literature, may serve as a possible therapeutic target for unwanted lucid dreams. Specifically, Wiers *et al.* [43] showed that peripheral DAT1 promoter methylation might be predictive of striatal DAT availability in adults with ADHD. Moreover, Weder *et al.* [44] showed that with experiences of maltreatment, epigenetic changes (DNA methylation) in ID3, GRIN1, and TPPP genes, may confer risk for depression and adversity in children, which could then lead to nightmares [45]. These studies add to a growing body of literature supporting a role for epigenetic mechanisms in the pathophysiology of stress-related psychiatric disorders.

Although epigenetic changes are frequently long-lasting, they are not necessarily permanent, and interventions to reverse the adverse biological and behavioral sequelae associated with child maltreatment and future problems, including nightmares, deserve consideration. Soldiers with a background of violence during childhood or with a familial susceptibility risk would benefit from being genotyped for high--risk alleles utilizing the GARS test before combat [22].

Importantly, since hypodopaminergic function in the brain's reward circuitry due to gene polymorphisms associates with substance use disorder (SUD) in individuals with co-occurring PTSD, and administration of dopaminergic agonist to effect gene expression (mRNA) and overcome dopamine deficiency might be prudent. One practical issue is that pre-screening with the GARS test to identify individuals at risk before combat could be a prophylactic measures. Soldiers with PTSD, as well as recruits determined by the GARS test

as at high genetic risk for PTSD, can be treated with neuronutrient precision pro-dopamine (KB220) regulation to induce “dopamine homeostasis.”

Early genetic testing for hypodopaminergic risk alleles could also offer valuable information that parents, and caregivers may find helpful in early life. They may modify parenting styles and enhance attachment affecting dopaminergic function and known bonding substances like oxytocin and vasopressin [33, 46] (Fig. 1).

Neuroimaging studies continue to reflect region-specific differential responses (dopamine surfeit or deficit) to substance and non-substance-addictive behaviors that are impediments, preventing healthy productive lives [49, 50].

2. PTSD A SUBSET OF REWARD DEFICIENCY SYNDROME: NEUROIMAGING EVIDENCE OF FUNCTIONAL CONNECTIVITY & NEUROPLASTICITY

Finally, based on studies that deprived rats of sleep for one month, lack of sleep on a chronic basis can induce fatal insomnia [51]. However, despite the impact of restricted sleep on immune and hormonal function, the most powerful effect occurs in the brain, especially working memory. Tucker *et al.* [52] showed that sleep-deprived human subjects had a 40% decline in working memory compared to non-deprived healthy controls. These studies and many others [53, 54] suggest the importance of eliminating PTSD/ ADHD induced Lucid Dreams of a terrifying nature by in the induction of dopamine homeostasis and neuroplasticity as recently observed in abstinent heroin addicts (see Fig.2) and rat studies (see Figs. 3,4).

To help understand the importance of agonist therapy to treat terrifying dreams, we refer to the work of Willuhn *et al.* [55], who reported that cocaine use and even non-substance-related addictive behavior increases as dopaminergic function reduces. Chronic cocaine exposure has been associated with decreases in D2/D3 receptors and was also associated with lower activation of cues in the occipital cortex and cerebellum in a recent PET study by Volkow *et al.* [56, 57]. Therefore, treatment strategies, like dopamine agonist therapy that might conserve dopamine function, maybe an exciting approach to treat RDS behaviors, including abnormal dreams. Blum *et al.* [7] evaluated the effect of KB220Z™ on reward circuitry of ten heroin use disordered (HUD) subjects undergoing protracted abstinence (average 16.9 months). A placebo-controlled, crossover, triple-blinded study of KB220Z in five subjects found that KB220Z induced increased BOLD activation in caudate-accumbens-dopaminergic pathways and a reduction of resting-state activity in the cerebellum compared to placebo 1-hour after acute administration. In the second phase of this pilot study of all ten abstinent HUD subjects, activation increased significantly from resting-state by KB220Z compared to placebo in three brain regions of interest ($p < 0.05$). The increased functional connectivity was observed in a putative network, including the dorsal anterior cingulate, medial frontal gyrus, nucleus accumbens, posterior cingulate, occipital cortical areas, and cerebellum. These results and other Quantitative Electroencephalography (qEEG) study results [58] suggest a putative anti-craving/anti-relapse role of KB220Z in addiction by

direct or indirect dopaminergic interaction. These preliminary results may also help explain our previous findings, including the prolonged nature of the KB220 anti-terrifying nightmare effect. Due to the small sample size, we caution definitive interpretation of these preliminary results, and confirmation, with additional research and ongoing rodent and human studies of KB220Z, is required.

The literature supports dopaminergic dysfunction in RDS behaviors. There is evidence that alterations in synchronous neural activity between brain regions subserving reward and various cognitive functions may significantly contribute to substance-related disorders and other hypodopaminergic disorders, PTSD, and ADHD [59]. The Febo *et al.* [6] rodent study represents the first evidence showing that a pro-dopaminergic nutraceutical (KB220Z) significantly enhances, above placebo, functional connectivity between reward and cognitive brain areas in the rat (see Fig. 3 and 4). These areas include the nucleus accumbens, anterior cingulate gyrus, anterior thalamic nuclei, hippocampus, prelimbic, and infralimbic loci. Significant functional connectivity increased brain connectivity volume recruitment and potential neuroplasticity. See Fig. 4 showing increased neuronal recruitment and dopaminergic functionality across the brain reward circuitry. Increases in functional connectivity were specific to these regions and not broadly distributed across the brain. While these robust initial findings are observed in drug naïve rodents, the selective response implies clinical relevance for individuals at risk for RDS behaviors, including nightmares, who show reductions in functional connectivity [9–12, 60].

3. A CLINICAL PERSPECTIVE

As described by the American Association of Sleep Disorders [2005], Lucid dreams are vivid and life-like and may be associated with an awareness that one is dreaming and an ability to control the onset or offset of the dream. The teaching of lucid dreaming is, in fact, a method of overcoming nightmares. Furthermore, there is currently some controversy about whether lucid dreaming may represent a brief, wakeful state [61].

In our sample, the dreams reported were uniformly terrifying in their content. Some were PTSD patients, so a distinction must be made as to whether “the use of KB220z ameliorated lucid dreams” or the “PTSD dreams” (nightmares)?

Thus, the question posed by these findings is: “Do patients with RDS diagnoses, who report terrifying and unpleasant, lucid dreams have their dreams ameliorated by a trial of KB220z” [9–12]?

Future analyses of lucid terrifying dreams in this population should focus on the *symbolic nature* of the dream content and its relevance to the PTSD trauma. If the dreamer is terrified by dinosaurs, for example, this content would not be consistent with that of a trauma-induced dream and not easily interpreted as relevant to the PTSD, historical trauma. With these caveats in mind, we, the authors, discuss the nature of dreaming and traumatic dreams and leave aside the question of the origin and function of terrifying, lucid dreams.

Previous papers [9–12] have discussed the literature related to lucid dreams and provided two cases that showed complete elimination of Lucid dreams with KB220Z [9, 10]. While

we do not want to reiterate the same description, the following references will serve as a useful resource related to Lucid Dreams and neurotransmitter function [62–73].

3.1. Standard Treatment Options for Nightmares

In an attempt to provide medical guidelines to treat unwanted “bad dreams,” especially in PTSD patients, Aurora *et al.* [74] the following treatment options [see Table 1].

4. SUMMARY

Based on the clinical experience of one of us (TM) decided to incorporate a well-researched putative natural, safe dopamine agonist, known as KB220Z [63], in a diagnosed PTSD and RDS patient’s treatment plan to determine if this complex would provide any beneficial effects to combat reoccurring lucid nightmares (“bad dreams”), otherwise refractory to other pharmaceutical agents.

In some published case series [9–12], we describe patients who report lucid dreams, which are mainly unpleasant or terrifying. Rendering the scientific question even more problematic is that these patients have all suffered some form of psychological trauma and, as such, epigenetics (untested) was most likely involved in the promotion of terrifying lucid dreams.

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Fig. (1).

Is a schematic that represents a treatment model that includes early genetic risk diagnosis, medical monitoring, and nutrigenomic dopamine agonist modalities to combat addiction, ADHD, and PTSD, including terrifying lucid dreams [1, 9–12, 47] may make the lives of our children happier [48].

Fig. (2).

Illustrates one dose of KB220Z (Synaptose Variant) compared to placebo in ten abstinent heroin-dependent patients studied. The placebo group (n=5) notices a blue circle showing no BOLD activation of Dopamine in Caudate and an overactive BOLD activation of dopamine in the cerebellum (pink circle). In contrast, the KB220Z group (n=5) notice a BOLD activation (blue circle) in the caudate and an attenuated BOLD activation in the cerebellum (pink circle). Based on this representation, the authors suggested a putative induction of “dopamine Homeostasis.” Comparative resting-state fMRI one hour after one dose of placebo or KB220z study abstinent Chinese Heroin addicts, with permission [7].

Fig. (3).

Representative cross-correlation maps show four subjects: placebo compared to KB220Z treated rats. Maps correspond to resting-state connectivity for the left nucleus accumbens (highlighted in green in the atlas map above the figure). Note the distributed but significant connectivity between various brain regions and the nucleus accumbens in the placebo subjects. KB220Z improved connectivity, especially between left-right accumbens, dorsal striatum, and limbic cortical areas, including the anterior cingulate, prelimbic, and infralimbic regions. Correlation maps for characteristic participants presented at a threshold between $0.35 \leq r \leq 0.9$ (Fisher's z transformed), with permission [6].

Fig. (4).

Plots differences in functional connectivity between various ROI and three seed regions.

Data presented here as a mean correlation (z transformed) $\pm$ standard error. * Significantly different than placebo $t_{221} > 2.1$ $p < 0.05$ (p values FDR corrected at $q = 0.05$), with permission [6].

Table 1.

Treatment option recommendations.

Treatment Options	Nightmare Types
• Prazosin	PTSD-associated nightmares.
• Image Rehearsal Therapy (IRT)	Nightmare disorder
• Systematic Desensitization and Progressive Deep Muscle Relaxation training	Idiopathic nightmares
• Clonidine considered for	PTSD-associated nightmares
• Consider the following medications: trazodone, atypical antipsychotic medications, topiramate, low dose cortisol, fluvoxamine, triazolam and nitrazepam, phenelzine, gabapentin, cyproheptadine, and tricyclic antidepressants.	PTSD-associated nightmares, but the data are low grade and sparse
• Consider the following behavioral therapies ed: Exposure, Relaxation, and Re-scripting Therapy (ERRT); Sleep Dynamic Therapy; Hypnosis; Eye-Movement Desensitization and Reprocessing (EMDR); and the Testimony Method.	PTSD-associated nightmares based on low-grade evidence
• Consider the following behavioral therapies: Lucid Dreaming Therapy and Self-Exposure Therapy.	Nightmare disorder based on low-grade evidence
Clonazepam and individual psychotherapy	No recommendation is made based on sparse data
Venlafaxine	not suggested for PTSD-associated nightmares