buprenorphine. Both of these treatments are more effective than drug-free treatment for opioid addiction. All forms of treatment are significantly less costly and more effective than no treatment (Butler 2008).

A review of the literature regarding the use of buprenorphine and methadone in medication assisted therapy (MAT) programs for opiate addiction shows that such programs have proven effective when looking at the following primary and secondary outcome indicators (USHHS Report 2003):

- **a.** Primary Outcome Measures
  - **1.** Abstinence from illicit opiate use
  - **2.** Reduction in illicit opiate use
  - **3.** Reduction in the severity of withdrawal from opiate use
  - **4.** Retention in treatment for persons enrolled in opiate withdrawal or opiate cessation programs.
- **b.** Secondary Outcome Measures
  - **1.** Level of injecting
  - **2.** Employment status
  - **3.** Housing status
  - **4.** Educational status
  - **5.** Criminality
  - **6.** Quality of life

However, the need to find a substance that not only blocks opiate-type receptors (mu, delta, etc.), but also provides agonistic activity, afforded the impetus for the development of a combination of narcotic antagonism and mu receptor agonist therapy (SAMHSA, 2007).

It is noteworthy that until 2000, medications for opioid dependence were limited to two opioid agonists, methadone and LAAM (withdrawn from market in 2003), or the narcotic antagonist naltrexone used for both opiate (Judson and Goldstein, 1984) and alcohol dependence (Blum et al., 1977). At that time, and even today, prescribing methadone is restricted to hospitals and federal- and state-approved opioid replacement substance abuse treatment programs. Currently, physicians can prescribe naltrexone, but patients must be opioid-free for several days prior to starting its use. According to Arfken et al. (2010), prior to 2002, the only pharmacological options for physicians treating opiate addicts were the antagonist naltrexone or the agonist methadone, both under strict regulations.

The federal Drug Abuse Treatment Act 2000 (DATA) opened a window of opportunity for patients with addiction disorders by providing increased access to options for treatment. DATA allows physicians to become certified to prescribe buprenorphine, by taking a short specialty-training course. Certified physicians can prescribe buprenorphine and buprenorphine/naloxone (Subutex, Suboxone) in a traditional office setting when treating patients with opioid dependence. Clinical studies indicate buprenorphine maintenance is as effective as methadone maintenance in retaining patients in substance abuse treatment and reducing illicit opioid use. Sublingual buprenorphine is more effective than Clonidine or Clonidine/naltrexone in short-term opioid detoxification treatment. Buprenorphine provides an additional tool to treat opioid addiction and improve the quality of lives of these patients. When the FDA approved the monoformulation of buprenorphine and buprenorphine/naloxone for the treatment of opioid dependence and placed both formulations in Schedule

that impulsive, compulsive, and addictive behaviors are commonly linked and support the emerging concept of Reward Deficiency Syndrome (RDS) as an umbrella term to characterize and classify these commonly linked genetically induced behaviors (Comings & Blum, 2000; Bowirrat & Oscar-Berman, 2005; Green et al., 1999). In this scenario, any and all of these abusable psychoactive drugs or pathological behaviors are candidates for addiction (tolerance/dependence) and are chosen by the individual as a function of genetic and environmental factors (e.g., availability, peer pressure, etc) (Blum et al., 2000).

While DA is critical to maintain normalization of natural rewards, the neuronal release of DA into NAc synaptic sites is somewhat complex. In 1989 our laboratory proposed an interactive cascade of events of mesolimbic function that lead to net DA release (Blum and Kozlowski, 1990). It was termed the [a]brain reward cascade' (see Figure 1).

The interactions of activities in the separate subsystems mentioned above merge together into the much larger global system. These activities take place simultaneously and in a specific sequence, merging like a cascade. The end result is a sense of peace, pleasure, and well being when these systems work normally. Other research has confirmed that the reward sensation is related to complex cascade reactions involving several neurotransmitters and structures in the limbic system (Volkow et al. 2002). The ultimate result of the process is the activation of the mesolimbic DA pathway, which starts in the tegmental ventral area and ends at the DA D2 receptors on the cell membranes of neurons located in the NAc and the hippocampus (Volkow et al. 2007).

The process, as described by Blum and Kozlowski (1990), starts in the hypothalamus with the excitatory activity of serotonin-releasing neurons. This causes the release of the opioid peptide met-enkephalin in the ventral tegmental area, which inhibits the activity of neurons that release the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). The disinhibition of DA-containing neurons in the ventral tegmental area allows them to release DA in the NAc and (*via* amygdala) in certain parts of the hippocampus, permitting the completion of the cascade and the development of the reward sensation (Carelli, 2002). Usually, if the cascade is working properly, the reward or feeling of well-being is obtained provided certain basic conditions are fulfilled (Blum & Kozlowski, 1990)

5. Traditional Long-Term Blockade Leads to Mood Changes and Suicide Ideation

Most recent examples of pharmaceuticals that block DA release and or receptor activation include Acomplia (Rimonabant), the cannabinoid (CB1) receptor blocker, and possibly Gabapentin. While there are numerous studies supporting the therapeutic benefits of Acomplia as an anti-craving drug, the long-term adverse effects resulted in a recent rejection by the United States Federal Drug Administration (FDA). A recent PUBMED search revealed 1007 papers on Acomplia. Since the prevalence of obesity continues to increase, there is a demand for effective and safe anti-obesity agents that can produce and maintain weight loss and improve co morbidity. Christensen et al. (2007) conducted a meta-analysis of all published randomized controlled trials to assess the efficacy and safety of the newly approved anti-obesity agent Rimonabant. They searched the Cochrane database and Controlled Trials Register, Medline (*via* Pubmed, Embase (*via* WebSpirs, Web of Science, Scopus, and reference lists up to July 2007. They collected data from four double-blind, randomized controlled trials (including 4105 participants) that compared 20 mg per day Rimonabant with placebo. Patients given Rimonabant had a 4.7 kg (95% CI 4.1±5.3 kg; p < 0.0001) greater weight reduction after 1 year than did those given placebo. Rimonabant caused significantly more adverse events than did placebo (Odds Ratio (OR) = 1.4; 0.0007; number needed to harm = 25 individuals [95% CI 17±58]), and 1.4 times more

serious adverse events (OR = 1.4; $p = 0.03$; number needed to harm = 59 [27–830]). Patients given Rimonabant were 2.5 times more likely to discontinue the treatment because of depressive mood disorders than were those given placebo (OR = 2.5; $p = 0.01$; number needed to harm = 49). Furthermore, anxiety caused more patients to discontinue treatment in Rimonabant groups than in placebo groups (OR = 3.0; $p = 0.03$; number needed to harm = 166). Their findings suggest that 20 mg per day of Rimonabant increases the risk of adverse psychiatric events – i.e., depressed mood disorders and anxiety; despite depressed mood being an exclusion criterion in these trials. Taken together with the recent US Food and Drug Administration finding of increased risk of suicide during treatment with Rimonabant, these researchers recommended increased alertness by physicians to these potentially severe adverse psychiatric reactions. Concerning this report, we propose that the negative effects on mood are due to the continued blockade of naturally required DA release at the NAc.

Gabapentin is a gamma-aminobutyric acid (GABA) analogue, with GABAmimetic pharmacological properties. Gabapentin is used for the treatment of seizures, anxiety and neuropathic pain. It has been proposed that Gabapentin may be useful in the treatment of cocaine dependence. However, clinical trials with Gabapentin have shown conflicting results, while preclinical studies are sparse. In one study, Peng et al. (2008) investigated the effects of Gabapentin on intravenous cocaine self-administration and cocaine-triggered reinstatement of drug-seeking behavior, as well as on cocaine-enhanced DA in the NAc. They found that Gabapentin (25–200 mg/kg, i.p., 30 min or 2 h prior to cocaine) failed to inhibit intravenous cocaine (0.5 mg/kg/infusion) self-administration under a fixed-ratio reinforcement schedule or cocaine-triggered reinstatement of cocaine-seeking behavior. *In vivo* microdialysis showed that the same doses of Gabapentin produced a modest increase (approximately 50%, $p < 0.05$) in extracellular NAc GABA levels, but failed to alter either basal or cocaine-enhanced NAc DA. These data suggest that Gabapentin is a weak GABA-mimic drug. At the doses tested, it has no effect in the addiction-related animal behavioral models. This is in striking contrast to positive findings in the same animal models shown by another GABAmimetic – gamma-vinyl GABA – by Garner's group (see Blum et al., 2000 for review). Based on our current theoretical model we are opposed to the use of Gabapentin to treat substance seeking behavior especially in long term care.

Other than a few scientific groups that suggest serotonergic/dopaminergic agonist therapy (Rothman et al., 2007), most strategies embrace dopaminergic receptor blockade/attenuation of DA release (Malhorta et al., 2007; Koob et al., 2008; Blum et al., 2000; Comings & Blum, 2000; Bowirrat & Oscar-Berman, 2005; Green et al., 1999; Suzuki et al., 2010). We propose that, in most circumstances, utilization of amino acid precursors affecting positive dopaminergic activation is a better alternative (Chen et al., 2011)

6. Proposed Relapse Mechanisms

It is well known that after prolonged abstinence, individuals who use their drug of choice experience a powerful euphoria that often precipitates relapse. While a biological explanation for this conundrum has remained elusive, we hypothesize that this clinically observed "supersensitivity" might be tied to genetic dopaminergic polymorphisms. Another therapeutic conundrum relates to the paradoxical finding that the dopaminergic agonist bromocriptine induces stronger activation of brain reward circuitry in individuals who carry the DRD2 A1 allele compared with DRD2 A2 allele carriers. Because carriers of the A1 allele relative to the A2 allele of the DRD2 gene have significantly lower D2 receptor density, a reduced sensitivity to DA agonist activity would be expected in the former (Kirsch et al., 2006). Thus, it is perplexing that with low D2 density there is an increase in reward sensitivity with the DA D2 agonist bromocriptine. Moreover, under chronic or long-term therapy with D2 agonists, such as bromocriptine, it has been shown *in vitro* that there is a

Blum K, Briggs AH, DeLallo L. Clonidine enhancement of ethanol withdrawal in mice. Subst Alcohol Actions Misuse. 1983; 4:59–63. [PubMed: 6684796]

Blum K, Chen ALC, Bowirrat A, Downs BW, Waite RL, Reinking J, et al. Genes and Happiness. Gene Ther Mol Biol. 2009; 13:91–129.

Blum K, Chen TJ, Downs BW, Bowirrat A, Waite RL, Braverman ER, Madigan M, Oscar-Berman M, DiNubile N, Stice E, Giordano J, Morse S, Gold M. Neurogenetics of dopaminergic receptor supersensitivity in activation of brain reward circuitry and relapse: proposing "deprivation-amplification relapse therapy" (DART). Postgrad Med. 2009; 121:176–96. [PubMed: 19940429]

Blum K, Chen TJ, Meshkin B, Waite RL, Downs BW, Blum SH, Mengucci JF, Arcuri V, Braverman ER, Palomo T. Manipulation of catechol-O-methyl-transferase (COMT) activity to influence the attenuation of substance seeking behavior, a subtype of Reward Deficiency Syndrome (RDS), is dependent upon gene polymorphisms: a hypothesis. Med Hypotheses. 2007; 69:1054–60. [PubMed: 17467918]

Blum K, Futterman S, Wallace JE, Schwertner HA. Naloxone-induced inhibition of ethanol dependence in mice. Nature. 1977; 265:49–51. [PubMed: 556802]

Blum K, Mark S, Gold MS. Neuro-chemical activation of brain reward meso-limbic circuitry is associated with relapse prevention and drug hunger: A commentary. Med Hypotheses. 2011 (in press).

Blum, K.; Kozlowski, GP. Ethanol and neuromodulator interactions: a cascade model of reward. In: Ollat, H.; Parvez, S.; Parvez, H., editors. Alcohol and Behavior. Utrecht, Netherlands: VSP Press; 1990. p. 131-149.

Blum K, Wallace JE, Schwerter HA, Eubanks JD. Morphine suppression of ethanol withdrawal in mice. Experientia. 1976; 32:79–82. [PubMed: 942927]

Bowirrat A, Oscar-Berman M. Relationship between dopaminergic neurotransmission, alcoholism, and Reward Deficiency Syndrome. Am J Med Genet B Neuropsychiatr Genet. 2005; 132B:29–37. [PubMed: 15457501]

Bruce RD, Altice FL, Moody DE, Morse GD, Andrews L, Lin SN, Fang WB, Ma Q, Friedland GH. Pharmacokinetic interactions between buprenorphine/naloxone and once-daily lopinavir/ritonavir. J Acquir Immune Defic Syndr. 2010; 54(5):511–4. [PubMed: 20672450]

Bruijnzeel AW, Marcinkiewcz C, Isaac S, Booth MM, Dennis DM, Gold MS. The effects of buprenorphine on fentanyl withdrawal in rats. Psychopharmacology (Berl). 2007; 191:931–41. [PubMed: 17211652]

Butler, M.; Kane, RL.; McAlpine, D.; Kathol, RG.; Fu, SS.; Hagedorn, H.; Wilt, TJ. AHRQ Publication No 09-E003. Rockville, MD: Agency for Healthcare Research and Quality; Oct. 2008 Integration of Mental Health/Substance Abuse and Primary Care No. 173. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-02-0009.)

Carelli RM. The nucleus accumbens and reward: neurophysiological investigations in behaving animals. Behav Cogn Neurosci Rev. 2002; 1:281–296. [PubMed: 17712985]

Chang Y, Moody DE, McCance-Katz EF. Novel metabolites of buprenorphine detected in human liver microsomes and human urine. Drug Metab Dispos. 2006; 34:440–448. [PubMed: 16381669]

Chen JF, Aloyo VJ, Qin ZH, Weiss B. Irreversible blockade of D2 dopamine receptors by fluphenazine-N-mustard increases D2 dopamine receptor mRNA and proenkephalin mRNA and decreases D1 dopamine receptor mRNA and mu and delta opioid receptors in rat striatum. Neurochem Int. 1994; 25:355–66. [PubMed: 7820070]

Chen TJH, Blum K, Chen LCH, Bowirrat A, Downs BW, Madigan MA, Waite RL, Bailey JA, Kerner M, Yelandi S, Giordano J, Morse S, Miller D, Braverman ER. Neurogenetics and clinical evidence for the putative activation of the brain reward circuitry by a neuroadaptagen: proposing an addiction candidate gene panel map. J Psychoactive Drugs. 2011; 43(2):108–27. [PubMed: 21858957]

Chen TJ, Blum K, Payte JT, Schoolfield J, Hopper D, Stanford M, Braverman ER. Narcotic antagonists in drug dependence: pilot study showing enhancement of compliance with SYN-10, amino-acid precursors and enkephalinase inhibition therapy. Med Hypotheses. 2004; 63:538–48. [PubMed: 15288384]

Chen AL, Chen TJ, Waite RL, Reinking J, Tung HL, Rhoades P, Downs BW, Braverman E, Braverman D, Kerner M, Blum SH, DiNubile N, Smith D, Oscar-Berman M, Prihoda TJ, Floyd JB, O'Brien D, Liu HH, Blum K. Hypothesizing that brain reward circuitry genes are genetic antecedents of pain sensitivity and critical diagnostic and pharmacogenomic treatment targets for chronic pain conditions. Med Hypotheses. 2009; 72:14–22. [PubMed: 18951726]

Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. Lancet. 2007; 370:1671–1672. [PubMed: 18022023]

Ciraulo DA, Hitzemann RJ, Somoza E, Knapp CM, Rotrosen J, Sarid-Segal O, Ciraulo AM, Greenblatt DJ, Chiang CN. Pharmacokinetics and pharmacodynamics of multiple sublingual buprenorphine tablets in dose-escalation trials. J Clin Pharmacol. 2006; 46:179–92. [PubMed: 16432270]

Chiang CN, Hawks RL. Pharmacokinetics of the combination tablet of buprenorphine and naloxone. Drug Alcohol Depend. 2003; 70(2 Suppl):S39–47. [PubMed: 12738349]

Comings DE, Blum K. Reward deficiency syndrome: genetic aspects of behavioral disorders. Prog Brain Res. 2000; 126:325–341. [PubMed: 11105655]

Comings DE, Muhleman D, Gysin R. Dopamine D2 receptor (DRD2) gene and susceptibility to posttraumatic stress disorder: a study and replication. Biol Psychiatry. 1996; 40:368–372. [PubMed: 8874837]

Conrad KL, Tseng KY, Uejima JL, Reimers JM, Heng LJ, Shaham Y, Marinelli M, Wolf ME. Formation of accumbens GluR2-lacking AMPA receptors mediates incubation of cocaine craving. Nature. 2008; 454:118–121. [PubMed: 18500330]

Costa-Mallen P, Costa LG, Checkoway H. Genotype combinations for monoamine oxidase-B intron 13 polymorphism and dopamine D2 receptor TaqIB polymorphism are associated with ever-smoking status among men. Neurosci Lett. 2005; 385:158–162. [PubMed: 15955630]

Cowan A. Buprenorphine: new pharmacological aspects. Int J Clin Pract. 2003; (Suppl133):3–8. [PubMed: 12587932]

Dackis C, O'Brien C. Neurobiology of addiction: treatment and public policy ramifications. Nat Neurosci. 2005; 8:1431–1436. [PubMed: 16251982]

da Silva Lobo DS, Vallada HP, Knight J, Martins SS, Tavares H, Gentil V, Kennedy JL. Dopamine genes and pathological gambling in discordant sib-pairs. J Gambl Stud. 2007; 23:421–33. [PubMed: 17394052]

De Ridder D, Vanneste S, Kovacs S, Sunaert S, Dom G. Transient alcohol craving suppression by rTMS of dorsal anterior cingulate: an fMRI and LORETA EEG study. Neurosci Lett. 2011; 496(1):5–10. [PubMed: 21458537]

Dole VP, Nyswander ME. Rehabilitation of heroin addicts after blockade with methadone. N Y State J Med. 1966; 66:2011–2017. [PubMed: 5220498]

Doehring A, Hentig N, Graff J, Salamat S, Schmidt M, Geisslinger G, Harder S, Lötsch J. Genetic variants altering dopamine D2 receptor expression or function modulate the risk of opiate addiction and the dosage requirements of methadone substitution. Pharmacogenet Genomics. 2009; 19:407–414. [PubMed: 19373123]

Dow-Edwards DL, Milhorat TH, Freed LA, Gintzler AR. Regional brain glucose utilization during and following chronic naltrexone administration: preliminary observations in rat brain. Life Sci. 1989; 44:571–577. [PubMed: 2522577]

Elkader A, Sproule B. Buprenorphine: clinical pharmacokinetics in the treatment of opioid dependence. Clin Pharmacokinet. 2005; 44:661–80. [PubMed: 15966752]

Epstein LH, Temple JL, Neaderhiser BJ, Salis RJ, Erbe RW, Leddy JJ. Food reinforcement, the dopamine D2 receptor genotype, and energy intake in obese and nonobese humans. Behav Neurosci. 2007; 121:877–889. [PubMed: 17907820]

Everitt BJ, Robbins TW. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat Neurosci. 2005; 8:1481–1489. [PubMed: 16251991]

Feigenbaum J, Yanai J. The role of dopaminergic mechanisms in mediating the central behavioral effects of morphine in rodents. Neuropsychobiology. 1984; 11(2):98–105. [PubMed: 6090975]

Fang WB, Chang Y, McCance-Katz EF, Moody DE. Determination of naloxone and nornaloxone (noroxymorphone) by high-performance liquid chromatography-electrospray ionization- tandem mass spectrometry. J Anal Toxicol. 2009; 33:409–17. [PubMed: 19874646]

Garavan H, Pankiewicz J, Bloom A, Cho JK, Sperry L, Ross TJ, Salmeron BJ, Risinger R, Kelley D, Stein EA. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. Am J Psychiatry. 2000; 157:1789–1798. [PubMed: 11058476]

Gaulier JM, Marquet P, Lacassie E, Dupuy JL, Lachatre G. Fatal intoxication following self-administration of a massive dose of buprenorphine. J Forensic Sci. 2000; 45:226–228. [PubMed: 10641946]

Gold MS. Opiate addiction and the locus coeruleus. The clinical utility of clonidine, naltrexone, methadone, and buprenorphine. Psychiatr Clin North Am. 1993; 16:61–73. [PubMed: 8456048]

Gold MS, Dackis CA, Pottash AL, Sternbach HH, Annitto WJ, Martin D, Dackis MP. Naltrexone, opiate addiction, and endorphins. Med Res Rev. 1982; 2:211–46. [PubMed: 6289026]

Goldstein A. Heroin addiction: neurobiology, pharmacology, and policy. J Psychoactive Drugs. 1991; 23:123–33. [PubMed: 1662715]

Green AI, Zimmet SV, Strous RD, Schildkraut JJ. Clozapine for comorbid substance use disorder and schizophrenia: do patients with schizophrenia have a reward-deficiency syndrome that can be ameliorated by clozapine? Harv Rev Psychiatry. 1999; 6:287–296. [PubMed: 10370435]

Hans G. Buprenorphine--a review of its role in neuropathic pain. J Opioid Manag. 2007; 3:195–206. [PubMed: 17957979]

Harris DS, Jones RT, Welm S, Upton RA, Lin E, Mendelson J. Buprenorphine and naloxone co-administration in opiate-dependent patients stabilized on sublingual buprenorphine. Drug Alcohol Depend. 2000; 61:85–94. [PubMed: 11064186]

Hervé S, Riachi G, Noblet C, Guillement N, Tanasescu S, Goria O, Thuillez C, Tranvouez JL, Ducrotte P, Lerebours E. Acute hepatitis due to buprenorphine administration. Eur J Gastroenterol Hepatol. 2004; 16:1033–1037. [PubMed: 15371928]

Heidbreder CA, Hagan JJ. Novel pharmacotherapeutic approaches for the treatment of drug addiction and craving. Curr Opin Pharmacol. 2005; 5:107–118. [PubMed: 15661634]

Hume SP, Lingford-Hughes AR, Nataf V, Hirani E, Ahmad R, Davies AN, Nutt DJ. Low sensitivity of the positron emission tomography ligand [11C]diprenorphine to agonist opiates. J Pharmacol Exp Ther. 2007; 322:661–7. [PubMed: 17488881]

Jasinski DR, Pevnick JS, Griffith JD. Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction. Arch Gen Psychiatry. 1976; 35:501–516. [PubMed: 215096]

Judson BA, Goldstein A. Naltrexone treatment of heroin addiction: one-year follow-up. Drug Alcohol Depend. 1984; 13:357–65. [PubMed: 6479015]

Kosarac B, Fox AA, Collard CD. Effect of genetic factors on opioid action. Curr Opin Anaesthesiol. 2009; 22:476–82. [PubMed: 19502975]

Kintz P. Deaths involving buprenorphine: a compendium of French cases. Forensic Sci Int. 2001; 121:65–69. [PubMed: 11516889]

Kirsch P, Reuter M, Mier D, Lonsdorf T, Stark R, Gallhofer B, Vaitl D, Hennig J. Imaging gene-substance interactions: the effect of the DRD2 TaqIA polymorphism and the dopamine agonist bromocriptine on the brain activation during the anticipation of reward. Neurosci Lett. 2006; 405:196–201. [PubMed: 16901644]

Kreek MJ. Methadone-related opioid agonist pharmacotherapy for heroin addiction. History, recent molecular and neurochemical research and future in mainstream medicine. Ann N Y Acad Sci. 2000; 909:186–216. [PubMed: 10911931]

Kreek MJ, LaForge KS, Butelman E. Pharmacotherapy of addictions. Nat Rev Drug Discov. 2002; 1:710–726. [PubMed: 12209151]

Koob GF, Le Moal M. Addiction and the Brain Antireward System. Annu Rev Psychol. 2008; 59:29–53. [PubMed: 18154498]

Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology 2010. 2010 Jan; 35(1):217–38.

Lesscher HM, Bailey A, Burbach JP, Van Ree JM, Kitchen I, Gerrits MA. Receptor-selective changes in mu-, delta- and kappa-opioid receptors after chronic naltrexone treatment in mice. Eur J Neurosci. 2003; 17:1006–12. [PubMed: 12653976]

Lingford-Hughes A. Human brain imaging and substance abuse. Curr Opin Pharmacol. 2005; 5:42–46. [PubMed: 15661624]

London ED, Cascella NG, Wong DF, Phillips RL, Dannals RF, Links JM, Herning R, Grayson R, Jaffe JH, Wagner HN Jr. Cocaine-induced reduction of glucose utilization in human brain. A study using positron emission tomography and [fluorine 18]-fluorodeoxyglucose. Arch Gen Psychiatry. 1990a; 47:567–74. [PubMed: 2350209]

London ED, Broussolle EP, Links JM, Wong DF, Cascella NG, Dannals RF, Sano M, Herning R, Snyder FR, Rippetoe LR, et al. Morphine-induced metabolic changes in human brain. Studies with positron emission tomography and [fluorine 18]fluorodeoxyglucose. Arch Gen Psychiatry. 1990b; 47:73–81. [PubMed: 2403775]

Malhotra AK, Lencz T, Correll CU, Kane JM. Genomics and the future of pharmacotherapy in psychiatry. Int Rev Psychiatry. 2007; 19:523–530. [PubMed: 17896232]

Mavridis M, Besson MJ. Dopamine-opiate interaction in the regulation of neostriatal and pallidal neuronal activity as assessed by opioid precursor peptides and glutamate decarboxylase messenger RNA expression. Neuroscience. 1999; 92:945–66. [PubMed: 10426535]

McNicholas L. SAMHSA clinical guidelines for the use of buprenorphine in the treatment of opioid addiction. Treatment Improvement Protocol. 2004; 40 DHHS Publication No. (SMA) 04–3939.

Mei W, Zhang JX, Xiao Z. Acute effects of sublingual buprenorphine on brain responses to heroin-related cues in early-abstinent heroin addicts: an uncontrolled trial. Neuroscience. 2010; 170(3): 808–815. [PubMed: 20678551]

Miller DK, Bowirrat A, Manka M, Miller M, Stokes S, Manka D, Allen C, Gant C, Downs BW, Smolen A, Stevens E, Yeldandi S, Blum K. 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. Postgrad Med. 2010; 122:188–213. [PubMed: 21084795]

Nestler, EJ. Reinforcement and addictive disorders. In: Nestler, EJ., et al., editors. Molecular neuropharmacology: a foundation for clinical neuroscience. New York, NY: McGraw-Hill; 2009.

O'Brien CP. Anticraving medications for relapse prevention: a possible new class of psychoactive medications. Am J Psychiatry. 2005; 162:1423–1431. [PubMed: 16055763]

Orman JS, Keating GM. Spotlight on buprenorphine/naloxone in the treatment of opioid dependence. CNS Drugs. 2009; 23:899–902. [PubMed: 19739698]

Poisnel G, Dhilly M, Le Boisselier R, Barre L, Debruyne D. Comparison of five benzodiazepine-receptor agonists on buprenorphine-induced mu-opioid receptor regulation. J Pharmacol Sci. 2009; 110:36–46. [PubMed: 19443999]

Ponce G, Jimenez-Arriero MA, Rubio G, Hoenicka J, Ampuero I, Ramos JA, Palomo T. The A1 allele of the DRD2 gene (TaqI A polymorphisms) is associated with antisocial personality in a sample of alcohol-dependent patients. Eur Psychiatry. 2003; 18:356–360. [PubMed: 14643564]

Peng XQ, Li X, Li J, Ramachandran PV, Gagare PD, Pratihar D, Ashby CR Jr, Gardner EL, Xi ZX. Effects of gabapentin on cocaine self-administration, cocaine-triggered relapse and cocaine-enhanced nucleus accumbens dopamine in rats. Drug Alcohol Depend. 2008; 97:207–15. [PubMed: 18065162]

Peyrière H, Tatem L, Bories C, Pageaux GP, Blayac JP, Larrey D. Hepatitis after intravenous injection of sublingual buprenorphine in acute hepatitis C carriers: report of two cases of disappearance of viral replication after acute hepatitis. Ann Pharmacother. 2009; 43:973–977. [PubMed: 19383935]

Radwan GN, Setouhy ME, Mohamed MK, Hamid MA, Israel E, Azem SA, Kamel O, Loffredo CA. DRD2/ANKK1 TaqI polymorphism and smoking behavior of Egyptian male cigarette smokers. Nicotine Tob Res. 2007; 9:1325–1329. [PubMed: 18058350]

Ritchie T, Noble EP. Association of seven polymorphisms of the D2 dopamine receptor gene with brain receptor-binding characteristics. Neurochem Res 2003. 2003; 28:73–82.

Ritchie T, Noble EP. [3H]naloxone binding in the human brain: alcoholism and the TaqI A D2 dopamine receptor polymorphism. Brain Res. 1996; 718:193–197. [PubMed: 8773786]

Rothman RB, Blough BE, Baumann MH. Dual dopamine/serotonin releasers as potential medications for stimulant and alcohol addictions. AAPS J. 2007; 9:E1–10. [PubMed: 17408232]

Shahmoradgoli Najafabadi M, Ohadi M, Joghataie MT, Valaie F, Riazalhosseini Y, Mostafavi H, Mohammadbeigi F, Najmabadi H. Association between the DRD2 A1 allele and opium addiction in the Iranian population. Am J Med Genet B Neuropsychiatr Genet. 2005; 134B:39–41. [PubMed: 15704216]

Schottenfeld RS, Chawarski MC, Pakes JR, Pantalon MV, Carroll KM, Kosten TR. Methadone versus buprenorphine with contingency management or performance feedback for cocaine and opioid dependence. Am J Psychiatry. 2005; 162:340–349. [PubMed: 15677600]

Spangler R, Wittkowski KM, Goddard NL, Avena NM, Hoebel BG, Leibowitz SF. Opiate-like effects of sugar on gene expression in reward areas of the rat brain. Brain Res Mol Brain Res. 2004; 124:134–142. [PubMed: 15135221]

Seeman P. Dopamine D2 receptors as treatment targets in schizophrenia. Clin Schizophr Relat Psychoses. 2010; 4:56–73. [PubMed: 20643630]

Spitz MR, Shi H, Yang F, Hudmon KS, Jiang H, Chamberlain RM, Amos CI, Wan Y, Cinciripini P, Hong WK, Wu X. Case-control study of the D2 dopamine receptor gene and smoking status in lung cancer patients. J Natl Cancer Inst. 1998; 90:358–363. [PubMed: 9498485]

Stock C, Shum JH. Bupreorphine:a new pharmacotherapy for opioid addictions treatment. J Pain Palliat Care Pharmacother. 2004; 18:35–54. [PubMed: 15364630]

Swan GE, Jack LM, Valdes AM, Ring HZ, Ton CC, Curry SJ, McAfee T. Joint effect of dopaminergic genes on likelihood of smoking following treatment with bupropion SR. Health Psychol. 2007; 26:361–368. [PubMed: 17500623]

Suzuki H, Han SD, Lucas LR. Chronic passive exposure to aggression decreases D2 and 5-HT 1B receptor densities. Physiol Behav. 2010; 99(5):562–570. [PubMed: 20114057]

Theile JW, Morikawa H, Gonzales RA, Morrisett RA. GABAergic transmission modulates ethanol excitation of ventral tegmental area dopamine neurons. Neuroscience. 2011; 13;172:94–172103.

Tracqui A, Tournoud C, Flesch F, Kopferschmitt J, Kintz P, Deveaux M, Ghysel MH, Marquet P, Pépin G, Petit G, Jaeger A, Ludes B. Acute poisoning during substitution therapy based on high-dosage buprenorphine. 29 clinical cases--20 fatal cases. Presse Med. 1998; 27:557–61. [PubMed: 9767947]

Umbricht A, Montoya ID, Hoover DR, Demuth KL, Chiang CT, Preston KL. Naltrexone shortened opioid detoxification with buprenorphine. Drug Alcohol Depend. 1999; 56:181–190. [PubMed: 10529020]

US Department of Health and Human Services. Substance Abuse and Mental Health Services Administration (SAMHSA). [Accessed February 26, 2003] Opioid agonist therapy (OAT) with methadone or LAAM. Available at: http://dpt.samhsa.gov/001025o.ptx.htm

Van den Oever MC, Lubbers BR, Goriounova NA, Li KW, Van der Schors RC, Loos M, et al. Extracellular matrix plasticity and GABAergic inhibition of prefrontal cortex pyramidal cells facilitates relapse to heroin seeking. Neuropsychopharmacology. 2010; 35:2120–33. [PubMed: 20592718]

Volkow ND, Fowler JS, Wang GJ, Goldstein RZ. Role of dopamine, the frontal cortex and memory circuits in drug addiction: insight from imaging studies. Neurobiol Learn Mem. 2002; 78:610–624. [PubMed: 12559839]

Volkow ND, Fowler JS, Wang GJ. The addicted human brain: insights from imaging studies. J Clin Invest. 2003a; 111:1444–1451. [PubMed: 12750391]

Volkow ND, Fowler JS, Wang GJ, Baler R, Telang F. Imaging dopamine's role in drug abuse and addiction. Neuropharmacology. 2009; 56(Suppl 1):3–8. [PubMed: 18617195]

Volkow ND, Wang GJ, Ma Y, Fowler JS, Zhu W, Maynard L, Telang F, Vaska P, Ding YS, Wong C, Swanson JM. Expectation enhances the regional brain metabolic and the reinforcing effects of stimulants in cocaine abusers. J Neurosci. 2003b; 23:11461–11468. [PubMed: 14673011]

Volkow ND, Wang GJ, Ma Y, Fowler JS, Wong C, Jayne M, Telang F, Swanson JM. Effects of expectation on the brain metabolic responses to methylphenidate and to its placebo in non-drugabusing subjects. Neuroimage. 2006a; 32:1782–1792. [PubMed: 16757181]

Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Jayne M, Ma Y, Pradhan K, Wong C. Profound decreases in dopamine release in striatum in detoxified alcoholics: possible orbitofrontal involvement. J Neurosci. 2007; 27:12700–12706. [PubMed: 18003850]

Walley AY, Alperen JK, Cheng DM, Botticelli M, Castro-Donlan C, Samet JH, Alford DP. Office-based management of opioid dependence with buprenorphine: clinical practices and barriers. J Gen Intern Med. 2008; 23:1393–1398. [PubMed: 18592319]

Walsh SL, Gilson SF, Jasinski DR, Stapleton JM, Phillips RL, Dannals RF, Schmidt J, Preston KL, Grayson R, Bigelow GE, et al. Buprenorphine reduces cerebral glucose metabolism in polydrug abusers. Neuropharmacology. 1994; 10:157–170.

Weiss F. Neurobiology of craving, conditioned reward and relapse. Curr Opin Pharmacol. 2005; 5:9–19. [PubMed: 15661620]

Wilson SJ, Sayette MA, Fiez JA. Prefrontal responses to drug uses: a neurocognitive analysis. Nat Neurosci. 2004; 7:211–214. [PubMed: 15001989]

Wood E, Li K, Palepu A, Marsh DC, Schechter MT, Hogg RS, Montaner JS, Kerr T. Sociodemographic disparities in access to addiction treatment among a cohort of Vancouver injection drug users. Subst Use Misuse. 2005; 40:1153–67. [PubMed: 16040375]

Xiao C, Zhang J, Krnjeviæ K, Ye JH. Effects of ethanol on midbrain neurons: role of opioid receptors. Alcohol Clin Exp Res. 2007; 31:1106–1113. [PubMed: 17577392]

Xu K, Lichtermann D, Lipsky RH, Franke P, Liu X, Hu Y, Cao L, Schwab SG, Wildenauer DB, Bau CH, Ferro E, Astor W, Finch T, Terry J, Taubman J, Maier W, Goldman D. Association of specific haplotypes of D2 dopamine receptor gene with vulnerability to heroin dependence in 2 distinct populations. Arch Gen Psychiatry. 2004; 61:597–606. [PubMed: 15184239]

Yassen A, Olofsen E, Romberg R, Sarton E, Danhof M, Dahan A. Mechanism-based pharmacokinetic-pharmacodynamic modeling of the antinociceptive effect of buprenorphine in healthy volunteers. Anesthesiology. 2006; 104:1232–42. [PubMed: 16732095]

Yoburn BC, Shah S, Chan K, Duttaroy A, Davis T. Supersensitivity to opioid analgesics following chronic opioid antagonist treatment: relationship to receptor selectivity. Pharmacol Biochem Behav. 1995; 51:535–539. [PubMed: 7667382]

Yücel M, Lubman DI, Harrison BJ, Fornito A, Allen NB, Wellard RM, Roffel K, Clarke K, Wood SJ, Forman SD, Pantelis C. A combined spectroscopic and functional MRI investigation of the dorsal anterior cingulate region in opiate addiction. Mol Psychiatry. 2007; 12:611, 691–702. [PubMed: 17245325]

Zhou SF, Liu JP, Chowbay B. Polymorphism of human cytochrome P450 enzymes and its clinical impact. Drug Metab Rev. 2009; 41:89–295. [PubMed: 19514967]

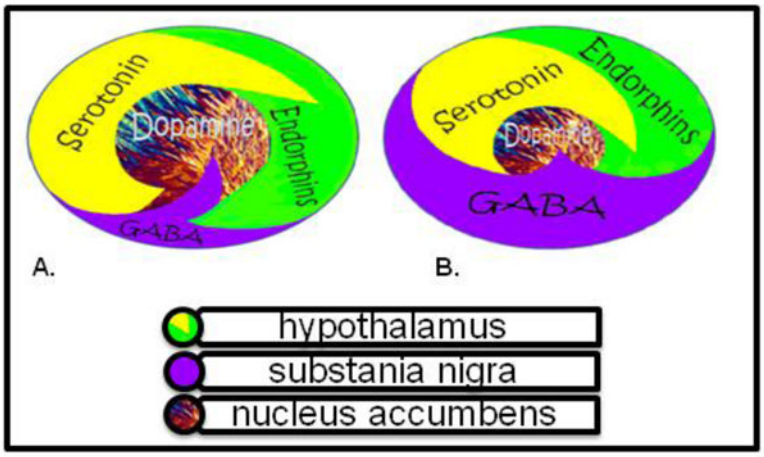

Fig 1. Brain Reward Cascade

Fig 1a. Schematic represents the normal physiologic state of the neurotransmitter interaction at the mesolimbic region of the brain. Briefly in terms of the "Brain Reward Cascade" first coined by Blum and Kozlowski [90]: serotonin in the hypothalamus stimulates neuronal projections of methionine enkephalin in the hypothalamus which in turn inhibits the release of GABA in the substania nigra thereby allowing for the *normal* amount of DA to be released at the NAc (reward site of Brain). Fig 1b Represents hypodopaminergic function of the mesolimbic region of the brain. It is possible that the hypodopaminergic state is due to gene polymorphisms as well as environmental elements including both stress and neurotoxicity from aberrant abuse of psychoactive drugs (*i.e. alcohol, heroin, cocaine etc).* Genetic variables could include serotonergic genes (serotonergic receptors [5HT2a]; serotonin transporter 5HTlPR); endorphinergic genes (mu OPRM1 gene; proenkephalin (PENK) [PENK polymorphic 3′ UTR dinucleotide (CA) repeats}; GABergic gene (GABRB3) and dopaminergic genes (ANKKI Taq A; DRD2 C957T, DRD4 7R, COMT Val/met substation, MAO-A uVNTR, and SLC6A3 9 or 10R). Any of these genetic and or environmental impairments could result in reduced release of DA and or reduced number of dopaminergic receptors. (**Brain reward cascade -modified with permission from IIOAB Journal, Blum et al. IIOAB, 2010, 11(2) 1–14.)**

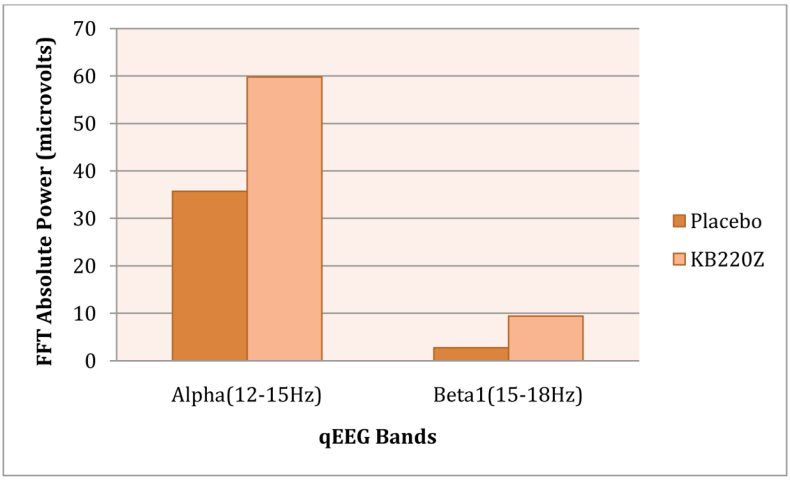

Fig 2. KB220Z compared to Placebo in Psychostimulant Abusers

Illustrates positive response of KB220Z compared to placebo in triple blind randomized placebo -controlled study in psychostimulant abusers undergoing protracted abstinence. Modified from data presented by Blum et al (2010).

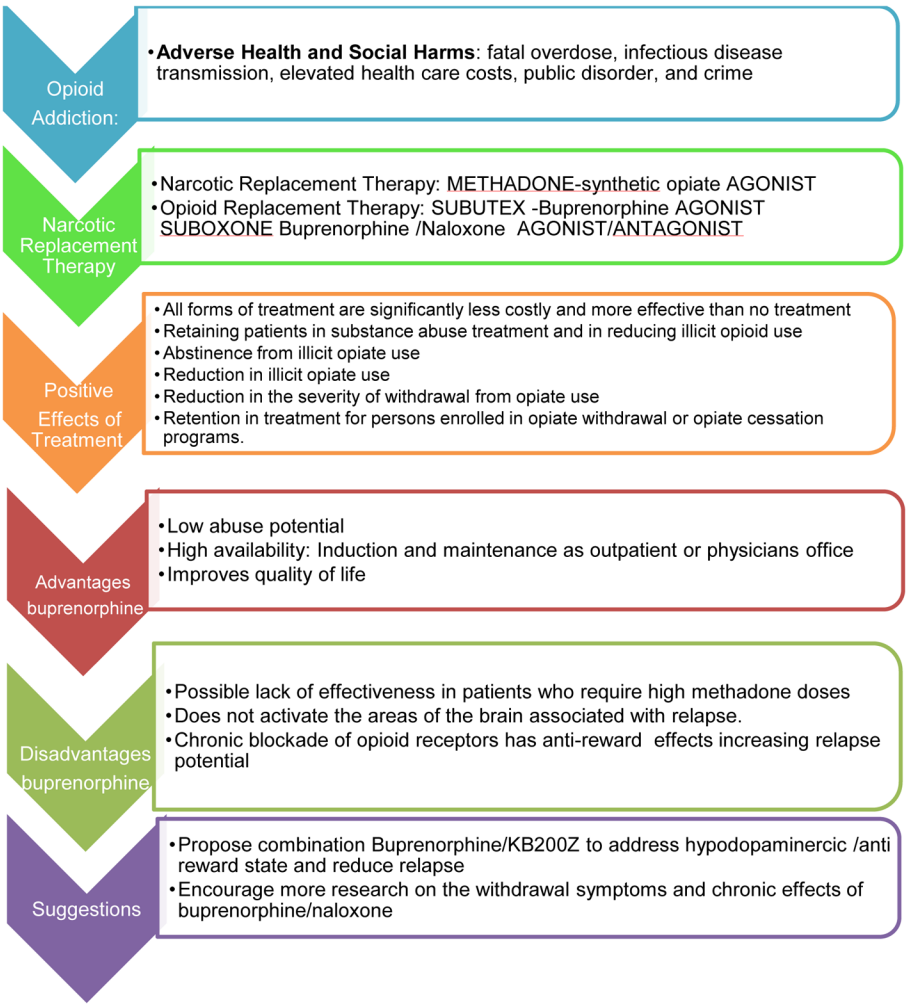

Fig 3.

Represents a thumb nail schematic of the salient points expressed in this commentary to assist in the understanding opioid addiction, opioid substitution therapy and an alternative modality.

The figure shows the Opioid addiction adverse effects (fatal overdose, infectious disease transmission, elevated health care costs, public disorder, and crime) and the available treatments. The traditional narcotic substitution therapy (*e.g.* methadone maintenance), does not target or block delta or mu receptors but provides agonistic activity. However, the new combination treatment of narcotic antagonism and mu receptor agonist therapy (even at very low doses of Naloxone) seems parsimonious. Clinical studies indicate that buprenorphine maintenance is as effective as methadone maintenance in retaining patients in substance abuse treatment and in reducing illicit opioid use. The figure delineates the negative effect on reward circuitry whereby chronic blockade of opioid receptors, even with partial opioid agonist action, may ultimately block dopaminergic activity, causing anti-reward effects and increasing relapse potential. Based upon initial results with large populations receiving D2 agonist therapy withKB220/KB220Z, we propose that offering a safe, nonaddicting, natural dopaminergic receptor agonist that potentially up-regulates instead of down-regulates dopaminergic receptors, could be at least one option to utilize in the long term to prevent relapse rather than the combination of buprenorphine/naloxone alone.