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Meta-Analysis on Predatory Date-Rape Drugs: Pharmacodynamics and Counteractive Studies of *Liquid Ecstasy-GHB (γ-hydroxybutyrate)* and *Ecstasy (3, 4-methylenedioxy-N-methamphetamine, or MDMA)*

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Abstract: ***The purpose of this research is to investigate developing misuse of certain psychotropic substances, depressants, hypnotics & stimulant drugs. The research is intended to generate a uniform understanding over cruel usage of certain drugs; in diminishing attentiveness, reducing senses & disturbing logical / cognitive skills. This guide is essential to understand how predatory drugs initiate control, to develop strategies & to counteract criminal intent. The goal is to establish more safety on streets and in medical facilities. The research was developed through literature searches, reviews of existing government and private documents, interview-notes with victims and in-depth case studies of these drugs and their interactions. The study consists of quantitative studies of two drugs namely; GHB (gamma-hydroxyButyrate) & Ecstasy (methylenedioxymethamphetamine). it also includes qualitative analysis of counteractive studies for these drugs & the protective measures over these drug-effects. The main body of this report consists of: conceptual; cross-sectional decriptive study of these drugs - to induce pure & structured explanatory review. The seccondary part consists of: emprical; longitudnal exploratory study - to deduce; control & counteractive studies on these substances; medically and personally. Our study aims a way to regulate recent illicit substances & generate social barrier along with awareness.***

Keywords: Ecstacy, GHB, date rape drugs, narcotics substances, liquid ecstacy, forensic toxicology, MDMA

Abbreviations
1,4-BD : 1,4-butanediol
NADP+ : Nicotinamide Adenine Dinucleotide phosphate
NMDA : N-methyl-D-aspartate receptor of glutamate for synaptic plasticity (neurotransmitter)
MEAP : Opiod peptite
BDNF : Brain derived neurotropic factor for learning and memory
MMDA : 3-methoxy-4,5-methylenedioxyamphetamine
CSF : cerebro-spinal fluid
Antagonist : a substance that counteracts another substance
MDA : 3,4-methylene- dioxyamphetamine
5-HTT : 5-hydroxy tryptamine transporterGBL : Gamma-Butyrolactone
cGMP : Guanosine 3,5 - cyclic monophosphate
PTSD : Post traumatic syndrome
MCT : Mono carboxylate transporter
LSD : Lysergic Acid Diethylamide
TMA : Trimethoxyamphetamines
Vitro : Study done without involving living organisms
Agonist : a substance that mimic another substance
CNS : central nervous system
NDPS : Narcotics Drugs and Psychotropic Substances
ActREM : Rapid Eye Movement
SSA : Succinic Semialdehyde
GABA : Gamma-aminobutyric acid
PMA : Para-methoxyamphetamine
MDEA : Methyldiethanolamine
Vivo : Studies involving living organisms
5,7-DHT : 5,7-dihydroxytryptamine
5-HT : 5-hydroxy tryptamine
HMMA : 4-hydroxy-3-methoxymethamphetamine

1. Introduction

Need For Research

The overall purpose of this research is to develop deeper understanding on symptoms, nomencleture, chemical properties, pharmacokinetics and effects on performance of mind, physique & behaviour. To study mechanism of action of GHB & Ecstasy on the subject, its interaction & counteractive measures for its psychological impacts on humans. To study the absorption, tolerance, withdrawal, overdose treatment, metabolic effects and analytical studies; to determine right approach on using and eleminating these drugs.

The objective is to find ways to recognize being drugged; to bring back attentiveness and the methods for theraputic rehabilitation from the after-shocks of GHB & Ecstasy. Another significance lies in developing measures for flushing out the drug & retriving attentiveness after the exposure.

The potential the research may help the society in developing drug-resistance, safety measures against rapists and investigate deeper on the effects of these drugs in theraputic uses. The study explains the modest and control usage of GHB & Ecstacy; and its overdose treatments. The main aim is to formulate coutneractive drugs that reduce the effects of these predatory drugs and retain cognitive functions of the brain.

2. Literature Review

Various articles carry a wholesome information about GHB & Ecstasy. Talking about GHB; various scholars have explained its usage in fighting with alcohol dependence. Addolorato G, Capristo E, Gessa GL, Caputo F, Stefanini GF, Gasbarrini G; experimented long terms administration of GHB & muscular mass changes in alcoholics and proved it to be efficient in increasing groth hormone release in alcoholics.

Fiona J Couper & Barry K Logan gave a precise reports in journal of analytical toxicology with case reports; to explain the presence of GHB in urine and blood speicimen of live subjects and those of postmortems. It showed prnounced effect along with alcohols or other drugs, whereas every subject was seen disoriented, confused and lacked cognitive functions.

Laureen J Marinetti, Daniel S Isenchmid, Bradford R Hepler & Sawait Kanluen mentioned in thier study of GHB & GBL in postmortem matrices after long term storage that GHB concentrations were well seen in heart blood, urine but less in femoral blood & Bile. They mentioned many methods to identify GHB concentrations & validation techniques.

In an analysis "Recommendations for toxicological investigations of Drug-facilitated Sexual assaults" in Journal of forensic sciences; cited many drugs including GHB & MDMA and their symptoms on victims demanding a cohesive approach on it.

G Bustos & R H Roth explained in their article "Release of monoamines from striatum and hypothalamus : effect of gamma hydroxybutyrate" and explained how these drugs disoriented the brain chemicals creating a dopamine pool as GHB goes in the superfusion medium and shows the washing out of Calcium 2+ tissues.

Murrin LC, Roth RH cited in "Dopaminergic neurons: reversal of effects elicited by gamma butyrolactone by stimulation of the nigro-neostriatal pathway" that GBL activates triosine hydroxylase and increase in endogenous dopamine levels by blocking impluse flow in central dopaminergic neurons. Hence, we deduce that by increasing the impulse flow; decreaing tryosine hydroxylase activity, we can bring the subject's attentiveness back to normal (Still experimental and developing).

Furthermore, Jenny Johannson, wrote a detail analysis of GHB & its effects in "the impact of Growth hormone and GHB in system related to cognition" where she cited numerous dissertations in this field of drug and gave a detailed report on how it affects the human mind and its post-effects on behaviour.

We tend to devise certain chemical compositions and combinations which can alter the effects of GHB doses & counteract neuronal pathways to its normal working and cognitive functions.

Hayner, G. N., & McKinney, H. (1986). MDMA: The dark side of ecstasy. *Journal of Psychoactive Drugs* mentions about various mental disorders due to MDMA. long term uses tend to give tachycardia, hypotension and certain respiratory diseases.

J.C. Cole and collegues states in Altered State : the clinical effects of ecstasy that usually serotoninergic fibers and transporters site are damaged due to prolonged use of Ecstasy.

Nichols, D. E. (1986). Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens: Identification of a new therapeutic class: Entactogens. *Journal of Psychoactive Drugs, 18*(4), 305–313; states that MDMA comes into a new category of drug called enactogens which are not readily found naturally in brain but synthesized by humans.

In Pharmacology Of MDMA in Humans; de la Torre R, M Farre, P N Roset, C H Lopez, M Mas, J Ortuno, E Menoyo, N Pizzaro, J Segura and J Cami explains that plasma cortisol and prolactin concentrations are increased in subjects with MDMA.

In Cardiovascular and neuroendocrine effects and pharmacokinetics of 3, 4 methylenedioxymethamphetamine in humans; M Mas, M Farre, R de la Torre, P N Roset, and collegues state that placebo was given for 1 week after the washout of MDMA and it showed improvement in 8 to 9% of doses of MDMA in subject. This showed that withdrawals are not friendly and easy.

M Hiramatsu and his collegues in Stereochemical differences in metabolism of 3,4-methylenedioxymethamphetamine in vivo and in vitro : a pharmacokinetic analysis suggest that "in vivo N-demethylation of (+) & (-) isomer to MDA was calculated. Thereafter, the levels of MDA formed from (+) isomer was 3 times greater than those formed from (-) isomer. Similarly in liver metabolism; the (+) isomer showed major role. On the contarary, in vitro; enantioselectivity was opposite and MDA was not formed majorly from (+) isomer." This suggested that active metabolite plays important role in the effects of (+) MDMA.

K Kreth, K Kovar, M Schwab, U M Zanger; in their work identification of human cytochrome P450 involved in the oxidative metabolism of "ecstasy" - related designer drug claims - "In addition to CP2D6 as the sole high-affinity demethylenase, several other P450 isozymes have the capacity to contribute to microsomal oxidative metabolism of methylenedioxyamphetamines. This may be of particular importance in individuals genetically lacking functional CYP2D6." This shows interindividual variation of MDMA effects in humans.

3. Aim and Objective

Our Aim is to develop studies on predatory drugs; like **GHB (gamma-hydroxybutyrate)** and **Ecstasy (3,4-Methylenedioxy-N-methamphetamine);** its *chemical effects on brain, psychiatry & anatomy*. To devise a module of *it's identification,* bring light to: *changes caused by them in psychoneuro transmission* and *develop counteractive compunds,* to reduce its effect on - the mind and body. Such drugs are extensively used by rapists and criminals to nullify / reduce the cognitive decision-making skills in humans and extort physical, financial and emotional gains out of them. Our aim is to understand the way; these drugs interact the body's chemical structure; brain's thinking pattern and make sure we develop enough resistant-drugs for them.

Initally, *GHB and Ecstasy were party drugs or club drugs*; as they provide dopaminergic boost in neurons by creating a pool of dopamine. However, it also showed *prominent decrease in cognitive skills*, *increase in the feeling of lovey-dovey* (By disturbing chemical compounds in the brain) and also showed *psychomotor impairmants* at high doses. This was the main attraction to criminal activites and these drugs became a source of weapon for predators. Hence, they were names "**Predatory Drugs**".

Our objective is to study *the effects of these drugs and suggest a counteractive drug* that might help in reducing the levels of GHB and MDMA from the body and bring back; normal state of consciousness and awareness on subjects with initial, higher and severe doses of these drugs. Our study plans to *achieve a probable counteractive drug for GHB and MDMA to help in withdrawals and victim stabilization*.

What is GHB? How it Originated?
γ-Hydroxybutyrate, also known as *liquid ecstasy, easy lay, cheery meth, G-juice, liquid-X, somatomax or just GHB* is a **hypnotic** and a **CNS depressant.** It is sold as chemically made *sodium oxybate or sodium oxybutyrate.* However, it is naturally present in mammalian CNS and peripheral tissues as a minor precursor of inhibitory neurotransmitter γ-aminobutyric acid (GABA). A french scientist accidentally discovered it while trying to formulate GABA synthetically. However, since last 10 years, it has been used as a date-rape drug on streets.

What are the Metabolic Effects of GHB and How is it's Mechanism of Action?
The chief metabolic effect of this compound is that; *it can readily cross the blood-brain barrier;* unlike GABA.[A39] Its first inductive use was for intravenous anaesthesia. However, due to frequent vomitting[A38] and inability to produce analgesia[A35, A36, A37] and seizure-like activity in animals; it was not recommended.

What are the Pharmacodynamics of GHB Associated with Cognition & Memory?

However, GHB was used for treatment of *narcolepsy* and to induce *slow-wave sleep at night*.[A37] It was also alleged to increase the production of GH and used in muscle building compounds and energy powders. In 90s, it was recreationally used *to treat dependance and withdrawal of alcohol and opiods*.[A34] Sometimes, it was also used in alternative of tryptophan as a hypnotic but was removed because of eosinophilia-myalgia syndrome.[A33]

How is the elimination of GHB?
There is a very short half-life and *there is no accumulation of GHB with repeated doses upto 100mg/kg* & is no longer detected in blood from 2-8 hours and in urine after 8-12 hours.[A16, A32] Less than 2% is eliminated unchanged from urine. It may also have interindividual variability.[A15,A32]

What is MDMA? How it Originated?
MDMA is a synthetic chemical that acts like a **mescaline hallucinogen** and an **stimulant amphetamine**. It is famous for increasing sexual arousal and feelings of euphoria due to serotonin release in the brain. Commonly called as Ecstasy, molly or mandy; is an empathogen.

What are the Pharmacodynamic Parameters of Ecstasy?
Unlike GHB, it does not cross the blood brain barrier; however it alters serotonin, noradrenaline and somewhat dopamine in the brain. It gives higher attentiveness; yet increasing sexual arousal and emotional social skills.

What are the Subjective Effects of Mdma in Psychotropic Domain?
Recreational use of this drug is still tested in psychotic realm. However, no permanent changes were seen in patients with MDMA after 10 years of testing. Although it may help to reduce depression and anxiety for time being.

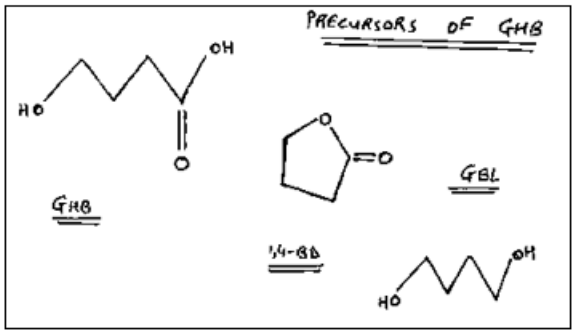
How is the Treatment of MDMA?
MDMA is a serotonin agonist, hence certain antagonist have shown results in reducing the effects of MDMA. However, long term use of MDMA needs medical attention & proper rehabilitation for repairing damaged neurons and altered enzymatic functions in amgdala, hippocampus and thallamus.

4. Meta-Analysis of GHB

4.1 Chemistry Behind GHB

GHB is *a hydroxylated short chained carbo-oxylic acid* which is *soluble in water.* However, it is poorly soluble in lipids and organic compounds. GHB is often found *as* sodium salt ($C_4H_7NaO_3$) with *MW:126.1*. There are two metabolic precursors of GHB; named **Gamma-Butyrolactone (GBL)** and **1,4-butanediol (1,4-BD)**. *GBL is* $C_4H_6O_2$ and *1,4-BD is* $C_4H_{10}O_2$. These 2 metabolic precursors are also a source of illicit uses and usually found in liquid form (clear or colored). It is mixed with strong tasting drinks and alcohol to hide their strong salty chemical taste. Since these two liquids are industrial solvents; they can be readily found in bulk market. Alternatively, GHB is found in solid form as white powder or capsule.

GHB does not exist in static state; weather inside or outside the body. It co-exists with its precursor lactone GBL. Since blood contains enzyme lactonase; it readily converts GBL to acid; hence the ratio of GHB:GBL contains more GHB. However, in stomach, urine or other water medium; the ratio remains nearly equal. *This ratio depends on ingestion, temperature and pH of the matrix.* On the other hand, 1,4-BD does not exist with GHB and as its ingested; it gets fully converted into GHB.[A8]



In humans, the free fraction of GHB in plasma is around 0.99, indicating a lack of significant protein binding. **The half-life of GHB is 22-28 minutes after an oral dose of 25mg/kg.** The half-life slightly increases as the dosage increases.[A32, A40]

There has been observed capacity-limited absorbtion of GHB and it is highly dependant on the liver function of the patients. With some liver dysfunction; the elemination channel gets saturated.[A41] GHB is also found in kidney, heart, skeletal muscle and brown fat.[A48]

4.2 Recreational & Illicit Uses

At first, GHB was used as *anaesthetic* in European countries while its effect on narcolepsy was analyzed. Later on, it started to be used as a treatment for narcolepsy since *it induced slow-wave sleep without causing disruptions in REM sleep.* Certain drugs like alcohols produce distortions in REM sleep but GHB showed no such activity; and produced state 3 and stage 4 natural psychological sleep.[A9, A8]

It is also used for *the treatment of alcohol withdrawal symptoms*.[A1] Medically formulated sodium oxybate; sold as **Xyrem** is used for this purpose. The recommended dosage is 25-50mg/kg every 12 hours. Studies on rats and clinical study have found to improve ethanol dependency and reduce withdrawal syndrome.[A25 A8 A42]

It is also said to be used in *opiate dependance and its rehabilitation*.[A25] It was earlier shown to increase the growth hormone during its relaxation phase. Hence, it was also used as a supplement *for muscle building and an alternative to anabolic steroids*.[A31] Since GHB showed peak increase in GH levels in plasma after 45 minutes and persisted for 15 minutes. These 15 minutes gave increase in activity levels and yet after 120 minutes; the levels dropped; but were still above baseline. However, some studies show that GH increase does not take place before the sleep.[A9]

Illicit uses of GHB occours either with GHB tablets, powders or its precursor GBL or 1,4-BD (since they are readily available as industrial solvents). They are mixed with alcohols or citric drinks to hide their taste and induces sleep-like state in victims.

4.3 Pharmacodynamics & Pharmacokinetic

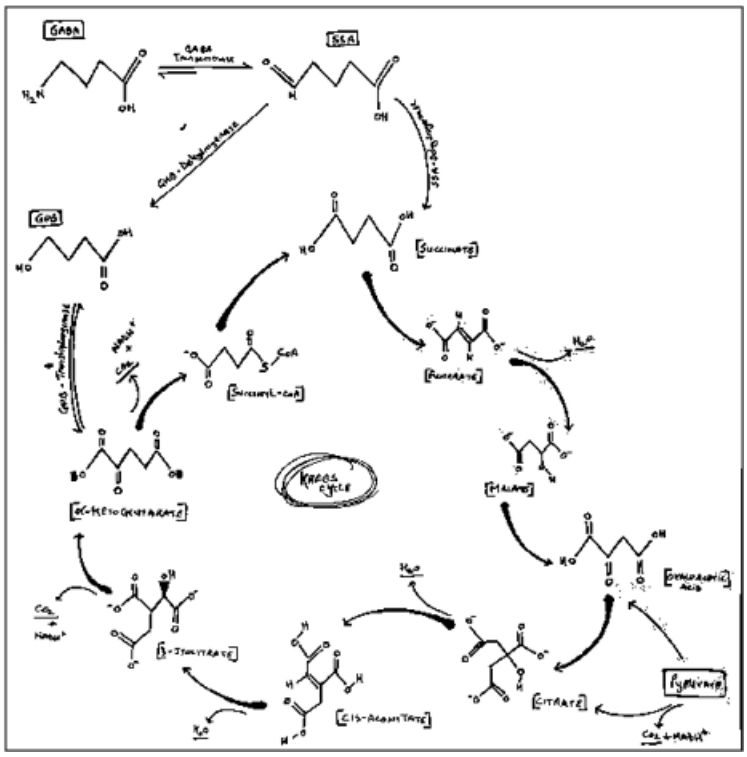
The main distinguishing factors of GHB from other sedatives and hypnotics is it's sleep induction. It produces **natural psychological stage 3 and 4 slow-wave sleep** *with low REM disturbances;* unlike other benzodiazepines and hypnotics.

GHB is a naturally occouring product of GABA metabolism in the brain. An intermediate compound SSA is formed by the neurotransmitter compound GABA. This SSA synthesizes GHB by emzymatic reduction in the mammalian brain. [A45]

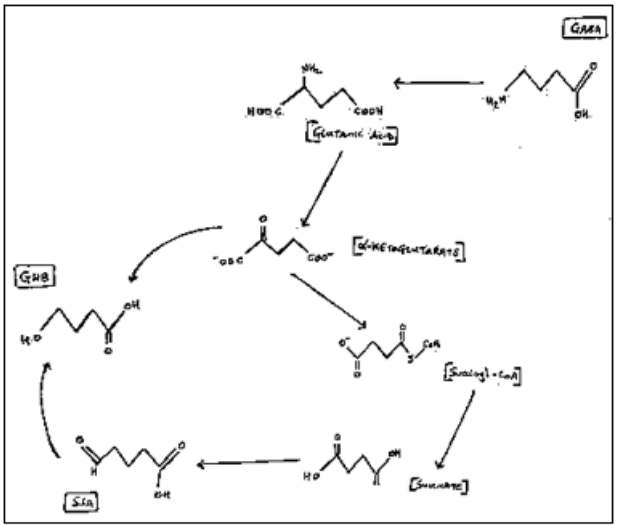
GHB has weak agonist activity at $GABA_B$ receptors and *produces an alteration in dopamine transmission.* It has been noted that GHB appears to have a distinct GHB-receptor site in the brain with both: high & low affinity components. Currently, it is known that G-Protein coupled presynaptic receptor is responsible for GHB & dopaminergic disturbances.[A43]

It also alters cerebral glucose metabolism, temperature regulations, sleep patterns and blood flow. Since it changes the plasma growth hormone and prolactin concentrations in humans (Hightens with a peak and ends with slightly higher than baseline). These changes alter the state of synchronicity.[A21, A31]

However, it is still debatable weather GHB is a neurotransmitter or a neuromodulator. This is because it functions with various roles like *synthesis, release, uptake and degradation within CNS*.[A41] However, it has a high affinity to brain receptors. Thus, it might be possible that its exact location may be in **cytosol** (if it acts as neurotransmitter) or **mitochondria** (if it acts as neuromodulator). [A44]



SSA is formed by transamination of GABA neurotransmitter. It is further metabolized to succinic acid or reduced to form GHB (by enzyme SSA reductase; which is a reducing source NADPH dependant enzyme.) However, the highest concentration of GHB is found in substantia nigra (a critical brain region to produce dopamine) and hypothallamus (manages autonomous nervous systems and hormone control).[A45 A41 A46] However, the uptake of GHB is highest in striatum (region responsible for decision making, reward system, social interactions & complex cognitive tasks). **Hence, we can make assumptions that GHB shows neurotranmitter type activity in striatum (to act the release on specific neurons) and neuromodulator type activity in substantia nigra & hypothallamus (to affect neuronal signaling)**.



GHB binds to $GABA_B$ (produces slow and prolonged inhibitory signals via G-Proteins and 2nd messengers) receptors but not with $GABA_A$ (ligand-gated chloride channel; that mediates fast inhibitory signals through rapid post synaptic membrane hyperpolarization) receptors.[A49] *Hence, GHB binds with proteins but not with chlorides; and uses sodium channel or proton-dependent channels.* However, it has affinity to bind with 2 receptor sites : **(a) cGMP : cyclic guanosine 3,5-monophosphate** {cyclic nucleotide derived from GTP & secondary messenger in phototransduction; which is degraded by light activated phosphodiesterase}; the activation of which leads to the activation of myosin phosphatase, which in-turn releases clacium from intracellular stores in smooth muscle cells. **(b) IP3 : Inositol phosphate intracellular pathway** {which terminates Ca2+ releasing action by its metabolism and is a major role playing compound in cellular decision making, mRNA frameworking and neucleous functioning}[A50, A51] which are either lipid-anchored or soluble innature.

It is seen that **GHB alters dopaminergic activity** - in some, it increases whereas in some; it decreases. Dopamine is **synthesized** after 1-2 hours without substantial increase in serotonin (norepinephrine) levels. However, it may also inhibit dopamine **release** after it's synthesis and hence; it accumulates in the tissue. *Dopamine is synthesized quickly but is not allowed to be released; creating a pool of dopamine in the tissue. It is released in striatum region*.

Another mechanism for GHB production is via glutamic acid and alpha-ketoglutarate. This compound readily converts with the help of GHB-Transhydrogenase and it is a reversible reaction. It acts as an abrupt release from citric acid cycle before it releases NADP+ ion along with carbon dioxide. This acts as a cytosolic pathway whereas the previous pathway was through

mitochondrial enzyme SSA. Hence, GHB serves as dual agent in the brain.

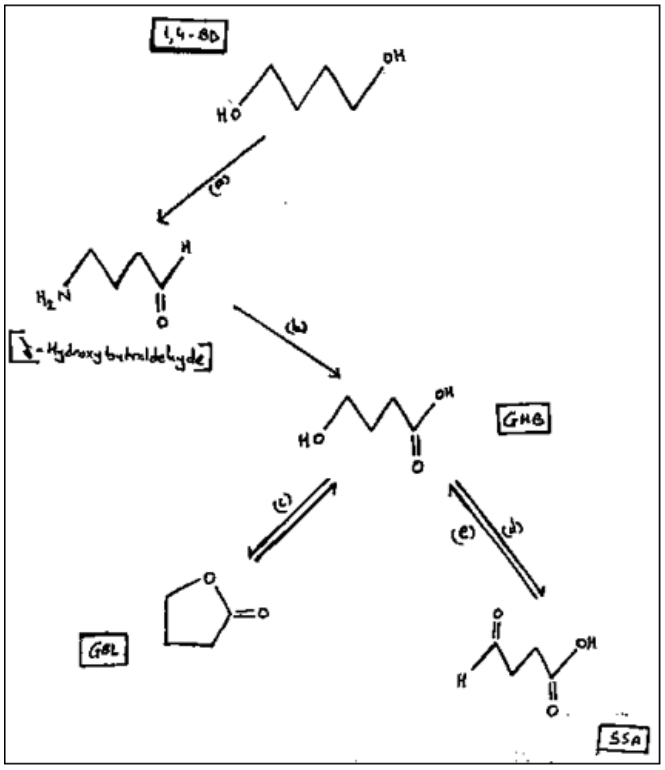
Hence, GHB is either formed by loosing a double bond with the help of Dehydrogenase enzyme from SSA or from enzyme transhydrogenase by adding hydrogen from alpha-ketoglutarate.

Thereby, we come to an assumption that GHB acts as a neurotransmitter and a neuromodullator by its method of synthesis and its metabolic activity.

We also conclude that it works on both the type of receptors (Ca2+ activating and inhibiting) differently.

4.4 Victims Of GHB

For sleep induction, the theraputic dose of GHB is 1.5-2.25g orally (30-40mg/kg for a 70kg person); along with additional 1-1.5g given after 3-4 hour interval. However, as the dosage increases to 75-100mg/kg (around 5-7g for 70kg person); a prolonged deep sleep is observed. *Moreover, for anaesthetic dosage; it must go above 100mg.* Perpetrators usually take advantage of this prolonged sleep condition to commit crimes such as rape, burglary, abuse, etc.[A25, A8]



GHB, its precursor GBL or 1,4-BD are also industrial solvents. They are used as organic cleaners, household scented solvents and cleaning solutions. Perpetrators use these items to indulge the subject into a state of slow sleep, nausea and induce criminal activity. *At higher doses, the dopamine pools induces forgetfulness, problem in psycho-motor controls and a state of mild unconsciousness or complete unconsciousness.* At this stage, the criminal uses its criminal intent to pursue the crime.

Usually, **GHB promoted periodic breathing** which made it difficult to identify its effect from respiratory system. Less than 2% GHB excreted from urine over a period of 24 hours. *Light sedative sleep, moderate hypnotic sleep and deep sleep was recorded with different doses.* Occasional opening of eyes was seen in subjects and a few had increased GHB levels in blood if theopental was given intravenous[A15].

Patients with post-GHB effects must undergo a usual Detox from kidneys, bladder and urinary tract (Pref. take flushing powdered suspension like Uritop Flush®); may induce serotonin uptake to regulate the brain tissues from dopamine levels and can be adviced to take cognitive booster micronutrients like (Ginkocer® plus or Neurozan®). Those with memory impairments and trauma shall be given psychological counselling to reduce PTSD and Bi-Polar Disorder. Those with vomitting shall be prescribed with gastrointestinial medicines for gag-reflex and stomach reflux.

Victims suffer from *lack of memory, disorientation, respiratory change, change in diet, sleep pattern and occassional mood swings. Tremors, tunnel vision, increase in sex drives and ataxia* is also seen. With higher doses, even **unconsciousness or coma.**

4.5 Toxicology & Dependance

Oral doses of GHB are absorbed from *gastrointestinial tract.* It exibits first-pass metabolism [A32] and capacity limited process with increase in dose. Peak concentration arises with increase in dosage. In humans, GHB is absorbed faster on empty stomach.[A8] This gives faster peak concentration in plamsa levels. The distribution of GHB in CSF lags behind. It is first seen in tissues and then crosses the blood-brain barrier. This shows that a passive diffusion of GHB takes place from serum / brain to CSF[A54]. Concentration of GHB is 15-20 times higher in kidney, heart, skeletal muscle and brown fat[A6].

The peak level of GHB in blood explained that it is a metabolite and not a parent compount to induce sleep state in humans[A15].

Evidence has been found that endogeneous GHB is stored in presynaptic vesicles and are released upon depolarization of neurons in Ca2+ dependant manner. This releases dopamine. However, it is also seen that large uptake of GHB stops dopamine release; predominantly mediated by low affinity $GABA_B$ receptors. This is due to G-Protein coupled inhibition of neurotransmitter release which includes dopamine. The involvement of $GABA_A$ receptors have also been discussed; indirect activation of $GABA_A$ takes place that induces alteration in neurosteroids (allopregnanalone).

However, because if its corelation with mesolimbic and nigrostriatal pathways, its dopaminergic activity causes change in reward system and addiction tendencies. Hence, some motoric impairments like muscle relaxation & dystonia is seen.

Moreover, its relation with opiod system is also complicated and unknown; but it causes sedation and euphoria for some extent.

One may also see some memory impairments explained by alteration in cholingeric and glutametergic systems. Decreased extracellular levels of acetylcholine, NMDA synaptic activity & NMDA receptor density in hippocampus, frontal cortex and striatum has also been reported. Lower concentrations of GHB increases glutamate levels in hippocampus whereas higher dosage decreases extracellular glutamate in hippocampus. An increase in GH has also been reported due to cholingeric mechanisms. The fact that GHB is used for relaxative and anxiolytic effects can be explained by the alterations in amygdala[A29].

GHB increases the level of MEAP in frontal cortex and creates and imbalance between MEAP and DynB in amgdala, hippocampus and hypothallamus. These are most important structures for creating learning, addiction and cognitive functions.[A29]

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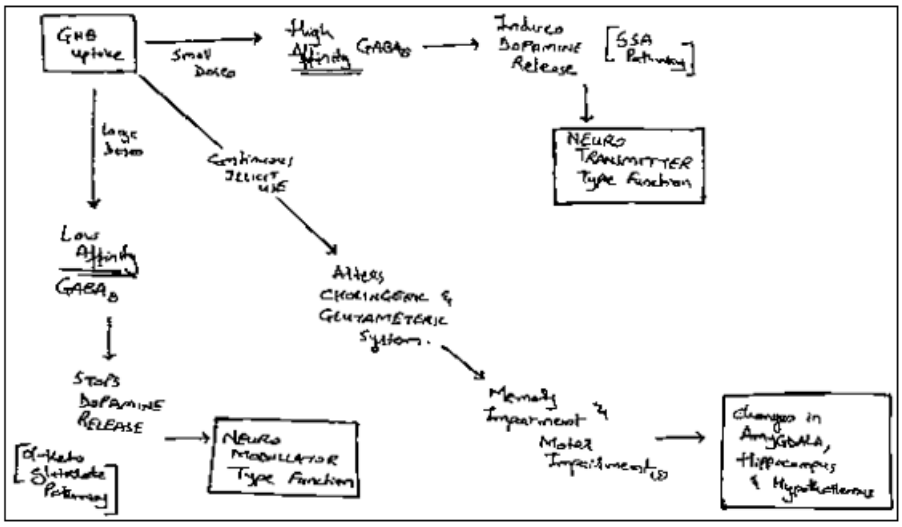
4.7 Treatments & Withdrawal

The uptake of GHB in the striatum was facilitated by sodium dependent active transport system. **Mono carboxylate transporter** (MCT) acts as a substrate for GHB generating an organic reaction. In the absence of sodium, GHB uptake increased at lower pH; suggesting proton-gradient dependent transport. Sodium Dependent MCT substrates were inhibited by *D-Lactate, L-Lactate, Pyruvate, Butyrate & non-steroidal anti-inflammatory drugs (ibuprofen, ketoprofen, naproxen)*. However, MCT is also a substrate for sodium-gradient transport system like Luteolin & Alpha-cyaano-4-hydroxycinnimate.[A47]

It is also seen that *alpha-methyltriosine;* blocks the activity of triosine hydroxylase and almost blocks the rise in brain dopamine due to GHB. This can serve as a GHB blocking mechanism as trisosine hydroxylase acts as a carrier for dopaminergic acitivty due to GHB.[A52]This shows that - release of this chemical may aid in inhibiting GHB effects in brain.



Moreover, it is also noted that when GHB releases dopamine in striatum; it is accompanied by endogneous opiods. Hence, opiod-receptor antagonists like *Naloxone or Nalorphine* may block some effects of GHB in human brain. [A53]

Some researchers say that GHB is not a particular neurotransmitter and it's effect *can be reduced by caffine, dextro-amphetamine and naxalone* experimentally[A6]. Some antagonist like *trimethadone and valporate antagonists* have also been seen to give electroencephalographic changes produced by GHB.

It is also seen that the reuptake of NA+ dependant neurons terminate the activation of Ca2+ dependant neuron receptors of GHB[A29].

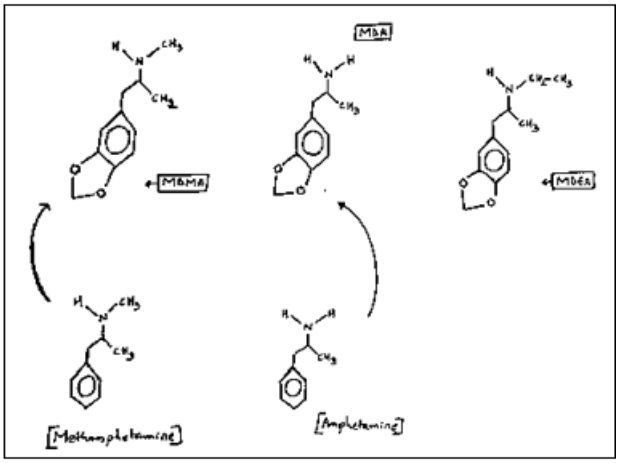
Withdrawal symptoms may include anxiety, insomnia, increase heart rate / blood pressure, physical tremors, hallucinations, extreme confusion, delirium, psychosis, aggression, change in mood, and neurological disorders. Inital symptoms may reseolve in 2-3 days and emotional and thiking clarity can resolve in 4-5 days. Sleep cycle is balanced after that. Extreme symptoms may have depression, seizures and numbness or tingling which resolves with medical attention.

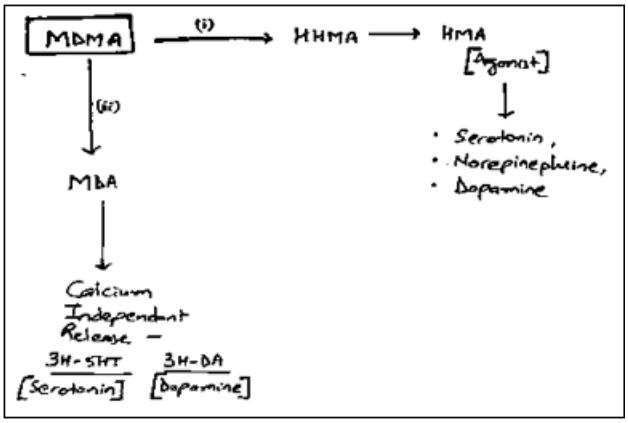
5. Meta-Analysis Of MDMA

5.1 Chemistry Behind MDMA

Ecstasy is a ring substituted amphetamine analog, commonly taken as recreational drug of abuse. It was synthesized in 1912 and patented in 1914; but became popular after 1970s.

The chemical designation of Ecstasy is : **N-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane.** It resembles dual nature - (a) *Stimulant amphetamine* and (b) *Hallucinogen mescaline*. MDMA is optically active with *dextro-rotatory isomer* {S+}. It has higher central acitivty than its levo-rotatory isomer[B4].





5.2 Subjective Effects & Recreational Use

It is alleged to improve self-esteem, communication and significant emotional relations[B3]. It also affects memory, learning and rememberance due to disruptions in hippocampal function.

MDA was patented as a tranquilizer, appetite inhibitor and a cough suppresant. However, amphetamine was also patented as weight reductive drug. However, due to addictive nature, they

were made Schedule I drugs[B14].

It marks increase in **wakefulness, endurance, sexual arousal and a sense of energy.** This is why it is mostly used as a date-rape drug. It gives **heightened sense of euphoria, sharpened sensory perceptions, greater sociability; increases closeness to people and tolerance towards emotions and feelings.** This is one of the main reasons why it is used illicit manner in clubs, parties and raves.

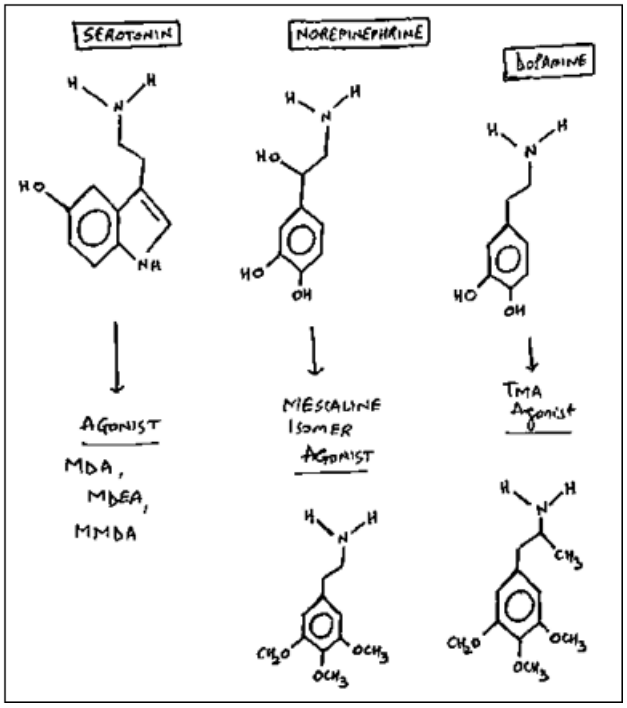
Those who voluntarily take MDMA are addicted to the greater serotonin release and simultaneous inhibition of serotonin after the elemination of drug. This creates an addiction for the need of serotonin and its transporter in the brain. However, no long term changes in serotonin receptors was seen after 10 day emprical data[B19].

5.3 Toxicology & Adverse Effects

The drug is commonly distributed as small tablet, capsule or white powder. Other similar chemicals can be sold in the name of ecstasy with similar effects like MDA & MDEA. Sometimes, mixed with other chemicals like caffiene, ephedrine, phenylpropanolamine,methamphetamine, amphetamine, ketamine, cocaine and diazepam. Hence, this intoxication can vary from the type of drug ingested and it's complete formulation.

The maximum concentration was found to be 105.6ng/ml after a dose of 330mg ecstasy[B6]. The main reason of neuronal toxicity is due to the production of free radicals that causes a dysfunction in the nervous system. These free radicals cause death of neurons by inhibiting mitochondrial energy activation (Causing neuron / cell death). It is also seen that neuronal nitric oxide elevation due to dopaminergic nigrostriatal system also causes neuronal damage. An increase in cortisol levels due to hypothallamic-pituitary-adrenal also causes stress. The loss of parvalbumin intraneurons in Dentate Gyrus causes diminishning number of neurons. Long term uses, reduced serotonin in CSF; and may also cause structural damage to serotonin neurons.

Serotonin toxicity is a main concern on long-term usage. Inital rise in serotonin may help in elevating mood and depression but a continuous increase in serotnin disrupts the neuron and cell metabolism and chemical stabilityl giving psychotic symptoms. A degenrating serotonergic molecules and axon terminals have been reported after excessive release of serotonin (somewhat dopamine too). The levels of serotonin in CSF was seen higher after some postmortem studies of MDMA users.



Memory impairment, lack of executive function, increase in impulsivity, problem in decision making, panic attacks, paranoia, flashbacks, severe depression and depersonalization was seen after large doses or long term higher exposure of MDMA. *Tooth grinding, muscular spasms, poorer control of autonomic nervous system (heart rate), neurological leisons and sometimes; parkinsons* was seen as physical issues after chronic use of MDMA.

5.4 Treatments & Withdrawal

Memory impairments of MDMA use were seen for like 6 months; however, for chronic exposures, decreased performance in declarative memory was seen. **There was a reduction in dopaminergic markers in substantia nigra.** A chronic user was also seen with impairments of passive avoidance learning due to diminished hippocampus calcium and calmodulin-dependant kinase II (CaMKII). This showed **alterations in recognition memory.** *Dextromethorphan* and its metabolite - *dextrophan* protected the toxicity produced by MDMA[B13].

Furthermore, *Ketoprofen* has reduced the number of parvalbumin positive GABA interneurons in DG in hippocampus due to repeated MDMA abuse. However, it was unable to prevent the depletion of serotonin 5-HT.

A global lesion of the 5-HT system by 5,7-DHT restricts (+/−) MDMA-induced locomotor stimulation. Pretreatment with the SSRI, fluoxetine, also restricted the hyper-locomotor effects of (+/−) MDMA but potentiated those of (+) MDMA. There is evidence for an inhibitory role of 5-HT1A-receptor antagonist pretreatment with *propranolol* and *pindolol* on (+) MDMA-induced hyper-locomotion[B17].

Henceforth, serotonin reuptake inhibitors like *citalopram, duloxetine, fluoxetine and paroxetine* have been seen to block many effects of MDMA. Anatagonist for serotonin work well with MDMA treatment.

[B14]Elimination of the drug from the body is moderately slow, the half-life for MDMA disappearance from the blood being of the order of 8 hours. It takes about 5 half-lives (i.e., about 40 hours for MDMA) for over 95% of the drug to be cleared from the body. Hence, the persistence of troublesome after-effects for one or 2 days after use can be seen. Some of the metabolites of MDMA are still pharmacologically active, especially its first metabolite, MDA, so that the duration of action may be somewhat longer than the duration of MDMA itself in the body. Everything depends on the purity of drug.

6. Outcome and Prospects

The results of our study shows that :

a) GHB acts on dopaminergic activities via GABAergenic pathway to increase the dopamine release and stop its reuptake by creating a pool of dopamine in the tissue. This trigger the reward mechanism into certain regions of the brain making you less rational and logical. This drug induces stage 3 or 4 sleep where one can act on his/her criminal intent.
b) MDMA acts on serotonergic activities and inhibits the reuptake of 5-HT. This creates serotonin pool within the brain to give euphoria. However, it also acts on noradrenaline and dopamine (certain extent). Hence, with right antagonists for 5-HT and 5-HT transporter; one can treat MDMA effects. For higher and longer detoxication and withdrawal; fluoxetine can be used. MDMA acts in increasing sexual arousal and emotional instability wher one can act on his/her criminal intent.

Hence, certain drugs can be formulated that can act as a party safety drug; which counteracts with predatory drugs and can have safety doses which do not harm or create permanent alterations in CNS. If any drug is formulated to stop over-excessive agonist action of 5-HT, 5-HT transporter, acts as antagonist for opiod receptor at smaller doses and do not alter permament change in neuronal pathway; a safety drug can be devised to act against the illicit and criminal use of predatory drugs. Further research in this field to create a combination drug for mescaline antagonist, opiod antagonist and smooth regulation of serotonin transporter and regulator of a dopaminergic pathway can act as a safety drug in small doses. Such innovations are important to increase public safety among predators moving in social environment. Such drugs help retaining partial attentiveness; even after being drugged with hallucinogens and amphetamines.

7. Discussion

The methylenedioxy group in MDMA, raises the boiling point of the free base so high; that it is impossible to use it by sniffing the vapour. Hence, it is used as tablet form. Usually direct or diluted into any drinks. Drugs sold as illicit use may not be purely MDMA but may also be: MDEA, MDA, PMA (para-methoxyamphetamine), MBDB (3,4-methylenedioxy-phenyl-N-methylbutanamine), ephedrine or varying mixtures of these. Hence, a victim falls under variety of neurological alterations and needs proper disgnosis before the treatment.

The latter effects have given rise that MDMA comes under different class of drug called "**empathogens**" or "**entactogens**". Since it aids in psychotherapy. However, no lasting study was found in 10-Year trial. Thus, due to its usual use to increase feelings and sexual arousal; it becomes famous for rape-drugs or predatory drugs. Women tend to not deny for sex and get increase in sexual drive after a dose; specially along with alcohols when the senses are diminished and arousal is at peak. However, heart beat and blood pressure tend to fluctuate after the use of MDMA.

When dopamine upsurge is seen; one can try treating with *phenothiazines* (prochloroparazine, chloropromazine, promethazine), *butyrophenones*(droperidol, haloperidol) and *metoclopramide*. Some studies show that lower doses of MDMA causes upsurge of dopamine and higher doses shows upsruge of serotonin. This is because of dual metabolic pathway of interaction. Hence, it is necessary to know dosage and dependence before withdrawal treatments and rehabilitation.

Rilmenidine, one of the anti-depressants have been found to protect 5-HT serotonin due to MDMA abuse and help relieve certain dysfunctions. Alongside, Ginger was seen to reduce activation of caspase cascade that results in cell death.

Some studies clain that there is an alteration as increase in number of glial cells, reduce in serotonin transport molecules (in cerebral cortex) and change in glucose metabolism and blood flow in the brain. There was decrease in bilateral symmetry of wave pattern and changes in auditory stimulus. The prolactin and cortisol response was reduced. Hence, *cortisol or prolactin* treatments can mildly help the MDMA chronic users to repair few alterations caused in CNS.

Some researchers say that GHB is not a particular neurotransmitter and it's effect *can be reduced by caffine, dextro-amphetamine and naxalone* experimentally[A6]. Some antagonist like *trimethadone and valporate antagonists* have also been seen to give electroencephalographic changes produced by GHB.

It is also seen that the reuptake of NA+ dependant neurons terminate the activation of Ca2+ dependant neuron receptors of GHB[A29]. It is also seen that *alpha-methyltriosine;* blocks the activity of triosine hydroxylase and almost blocks the rise in brain dopamine due to GHB. This can serve as a GHB blocking mechanism as trisosine hydroxylase acts as a carrier for dopaminergic acitivty due to GHB.[A52]This shows that - release of this chemical may aid in inhibiting GHB effects in brain.

8. Forensic Significance and Admissability

Since there has been a substantial increase in the usage of drugs; we need awareness programs and forensic aid to help stop these abuses. Certain signs that show you might have been drugged are : Feeling sudden nausea, loss of bowel and bladder control, difficulty breathing, feeling drunk without consumption of alcohol or any other drugs, sudden increase in dizziness and blurred vision, sudden body temperature change, sweatting and teeth chattering, waking up with large chunks of missing memory and hard time with motor controls.[B1] All drugs have different times of leaving the body; Rohypnol leaves within 36-72 Hours, GHB leaves within 10-12 Hours and GBL leaves the urinary system within 6 hours and bloodstream within 24 Hours. Hence, quick approach is needed to test these drugs in victims. Around 50-60% of MDMA is recovered in urine. Although MDMA is metabolized in the body; a single oral dose is excreted in urine within 72 hours. Upto 50-150mg dose, HMMA was recovered in urine rather than MDMA.

Hence, it is important to study these drugs as a forensic point of view to engage in observation, interaction, elemination and restoration of these predatory drugs. Counteractive studies help us to formulate compounds that act as antagonist for these drugs and help to generate more safer party spots. Chemical reactions to determine such drugs from blood, urine and serums should be studied in order to catch druggies, padlers and sellers. All such evidences that detect a NDPS criminal is admissable in court. For Date-Rape drugs case, rape victims can also get more admissability over the detection of drug consumed & can help linking the criminal to the victim and to the drug found.

9. Conclusion

We hereby deduce our findings on Liquid ecstasy (GHB) and Ecstssy (MDMA). GHB acts more prominent on dopaminergic activity along with GABAergenic activity in brain; inducing relaxation, sleep and inactivity in motor controls. On the other hand, Ecstasy acts more prominent on serotonin pathway and transporter to make one feel more euphoric, increase sexual arousal and give more emotional instability. Partially, MDMA also acts on noradrenaline to make one more energetic, yet sexually aroused. On the contarary, GHB makes one dull and sleepy and inattentive. On both these cases, differently, criminal can take advantage of the victims.

We hereby, deduce certain conclusions on various drugs which can help antagonising the functioning of MDMA and GHB in brain. Further research done in developing a combination of drug that well-interacts with the pathway of these predatory drugs can act as a safety drug druing parties, raves and social gatherings.

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