CHAPTER TEN

"Addicted to Euphoria": The History, Clinical Presentation, and Management of Party Drug Misuse

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Abstract

Eating, drinking, sexual activity, and parenting invoke pleasure, an emotion that promotes repetition of these behaviors, are essential for survival. Euphoria, a feeling or state of intense excitement and happiness, is an amplification of pleasure, aspired to one's essential biological needs that are satisfied.

People use party drugs as a shortcut to euphoria. Ecstasy (3,4-methylenedioxymethamphetamine), γ-hydroxybutyric acid, and ketamine fall under the umbrella of the term "party drugs," each with differing neuropharmacological and physiological actions. This chapter seeks to survey the history and epidemiology of party drug use; we will then discuss the pharmacological characteristics of each drug to provide a platform for understanding the difficulties that party drug users encounter through intoxication, harmful use, dependence, and withdrawal and how these should be clinically managed.

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1. HISTORICAL ASPECTS OF PARTY DRUG USE

1.1 3,4-Methylenedioxymethamphetamine

3,4-Methylenedioxymethamphetamine (MDMA) or ecstasy was the first party drug, the term being adopted in the late 1980s (Saunders, 1993). As with many of the defining pharmacological discoveries of the twentieth century, it began with a mistake. Kollish described the synthesis of MDMA in 1912 while working for the German pharmaceutical company Merck in Darmstadt. Later, three Merck chemists became interested in MDMA: Max Oberlin in 1927, Albert van Schoor in 1952, and Wolfgang Fruhstorfer in 1959, each explored its pharmacological characteristics, though no studies were carried out on humans. Their most salient finding was that they were toxic to fruit flies (Freudenmann, Oxler, & Bernschneider-Reif, 2006).

MDMA reemerged in the United States in 1953 in the context of Cold War paranoia. Projects supported by the Army Chemical Center at the University of Michigan between 1953 and 1954 investigated physiological characteristics of MDMA in mice, rats, snakes, monkeys, and dogs, although there is no evidence that it was tested in man. The results of these tests were declassified in 1969 and published 4 years later (Hardman, Haavik, & Seevers, 1973). These studies were directed by Sidney Gottlieb director of the MK-ULTRA Project, the CIA's fabled "mind control program," which tested various psychedelic compounds for potential military use.

The first recorded human ingestion of MDMA was in the mid-1970s, by the Californian psychedelic chemist Alexander Shulgin, often referred to as the stepfather of ecstasy. He synthesized MDMA and recorded titration experiments in his Lab Notebooks (Erowid, 2009), involving his wife, friends, and colleagues, with commentaries on their subjective experiences. Subsequently, MDMA was applied both as an adjunct to the exploration of new drugs and as a subjective "control" for the assessment of new psychedelic drugs. He later published the seminal paper *Characterization of Three New Psychotomimetics*, in which he remarked "*Qualitatively, the drug (MDMA) appears to evoke an easily controlled altered state of consciousness with emotional and sensual overtones. It can be compared in its effects to marijuana, to psilocybin devoid of the hallucinatory component, or to low levels of MDMA*" (Shulgin & Nichols, 1978).

MDMA acquired an underground following among hippies, psychedelic chemists, and unconventional psychiatrists and psychotherapists in the late 1970s and early 1980s. The earliest published advocate of the use of MDMA

in psychotherapy was George Greer (Greer, 1985), who investigated the potential use of MDMA as a psychotherapeutic adjunct and is still actively involved in the therapeutic psychedelic movement at the Heffter Research Institute in Zürich. He anonymously published "*The legal, safe, and effective use of MDMA*" and later a "*Recommended protocol for MDMA sessions*" (Greer & Tolbert, 1986). Viewed as an empathogen (and labeled "empathy") by radical psychiatrists, it was thought to lower patient's defenses, thus aiding the psychotherapeutic process (Greer, 1985).

As a brand name, "ecstasy" the name coined by members of an underground East Coast distribution network in 1981 had greater consumer appeal than "empathy." Used primarily on the East and West Coasts of United States, MDMA use rapidly escalated in the 1980s among "New Age" Americans. Media attention followed and one of the first nonscientific articles was published anonymously in the counterculture magazine *Wet* in 1981. In 1984, the San Francisco Chronicle dubbed MDMA "the yuppie psychedelic." Public controversy in the United States followed with popular magazines including Newsweek and TIME magazine publishing articles, which reported recreational use among the "American middle classes" (Shulgin, 1989). The Drug Enforcement Administration used emergency measures to add MDMA to Schedule 1 of the controlled substance list in 1985, in a response to concern about its growing use. MDMA was deemed as having a "high risk of addictive abuse potential" and a New York Times article reported that it had been shown to cause brain damage. The UK followed suit, though the Misuse of Drugs Act 1971 had already been altered in 1977 to include all ring-substituted amphetamines such as MDMA and 3,4-methylenedioxyamphetamine (MDA); a further amendment was made in 1985 to refer specifically to ecstasy, which was subsequently designated as class C drug.

At this time, the United States was bearing witness to the birth of a new cultural phenomenon that would define the history and popularity of ecstasy. In Chicago, DJs such as Frankie Knuckles, at the Warehouse nightclub, created the early fusion of disco and electronic music that would become house and dance music. By 1987, house music had spread to Ibiza with a group of UK DJs exporting the Balearic mix of house sound to the United Kingdom. Clubs including the Hacienda in Manchester started hosting house music parties, ecstasy followed the music, and the United Kingdom rave scene was born (Saunders, 1993).

Having ushered in the Thatcher era in 1979, the intervening years (1978–1988) brought the Brixton riots, rising youth unemployment,

reduced manufacturing output, and the miner's strikes. The changes in fortunes for some were stoked by widening societal inequalities creating fertile ground for the emergence of a new British youth counterculture movement. Outdoor unlicensed acid house parties took place in and around the M25, and ecstasy rather than alcohol became the drug of choice as the United Kingdom experienced a melting pot of politics, music, and drugs that spawned the "Second Summer of Love" in 1988, mirroring the narrative of social change brought about by the youth counterculture movement of 1960s America that had opposed the Vietnam War and the nuclear arms race and spawned the first "Summer of Love" in 1967.

The use of ecstasy mushroomed in the United Kingdom; the oral route of administration labeling (the smiley face) and the underground marketing methods reduced the fear of harm by users. The press reaction was initially neutral, and images of the smiley face that parodied ravers as harmless hedonists were common during the early reporting of the acid house movement. Reports of harm, gangland involvement in distribution of ecstasy, and moral concern later prompted police action. The police developed a task force to close down illegal parties, often engaging in a cat and mouse game with those organizing illegal parties. Later, the Criminal Justice and Public Order Act 1994 provided the police with new powers to close down illegal parties, acknowledging the role house music played in its use. The act made public gatherings where music or "sounds wholly or predominantly characterized by the emission of a succession of repetitive beats" illegal. Acid house moved into clubs and licensed bars, but the use of ecstasy continued and disseminated further into the UK mainstream. Public concern reached its peak following the death of Leah Betts, a teenager and the daughter of a policeman, in 1995 (Davison & Parrott, 1997). In response to her death, "the Public Entertainments Licences (Drug Misuse) Act 1997" provided the police with new powers that included the ability to close venues thought to contain persons consuming illegal drugs. The global dance scene is now worth 6.2 billion pounds worldwide and is expected to be worth 18 billion pounds within the next 10 years.

1.2 γ-Hydroxybutyric Acid

Henri Laborit synthesized γ-hydroxybutyric acid (GHB) in 1960 as a potential anesthetic agent (Laborit, Buchard, Laborit, Kind, & Weber, 1960). His team subsequently synthesized GHB from butyrolactone and carried out extensive *in vivo* testing, finding that at dose of 250 mg/kg, it caused

sleepiness in several animal species and had little effect on respiration and oxygen consumption (Basil, Blair, & Holmes, 1964). His work was expanded on by Dr. Margaret Blumenfeld who noted that induction was slow (up to 45 min), sleep was indistinguishable from natural sleep (both in appearance and on the electroencephalogram), respiratory depression occurred (Cheyne–Stokes respiration in some subjects), and bradycardia and mild elevation of the arterial blood pressure were also noted. They also observed that GHB appeared to potentiate or be potentiated by hypnotic drugs, tranquilizers, and narcotics as evidenced by markedly reduced amounts of these agents necessary for anesthesia, the so-called sparing effect (Blumenfeld, Suntay, & Harmel, 1962).

Subsequent research focused on the sleep-modifying effects leading to therapeutic interventions in the form of sodium oxybate for sleep disturbances, particularly in Gelineau's syndrome of narcolepsy and cataplexy (Alshaikh et al., 2012). It was also shown to be effective in the treatment of the alcohol withdrawal syndrome (Leone, Vigna-Taglianti, Avanzi, Brambilla, & Faggiano, 2010). In contrast to its use as an anesthetic, it is limited by its lack of analgesic and muscle relaxant properties (Schep, Knudsen, Slaughter, Vale, & Mégarbane, 2012). The effects on respiration and cardiac functions and the sparing effect began to be recognized by doctors in accident and emergency departments (Galicia, Nogue, & Miró, 2011) and users of GHB on the dance floor (Wood, Nicolaou, & Dargan, 2009).

GHB reemerged as a food and dietary supplement and was sold in health food stores in tablet, capsule, and liquid forms during the 1980s and early 1990s throughout the United States (Dyer, 1991), popular with bodybuilders (Steele & Watson, 1995), due to its growth hormone-releasing properties (Van Cauter et al., 1997). Concerns about its safety as a food supplement began to surface, with reports of altered levels of consciousness and seizures being reported (Dyer, 1991; Steele & Watson, 1995). Recreational users then chanced upon euphoria and increased libido as side effects, a discovery that intersected with the emergence of the club scene.

GHB's potential as a party drug has been recognized since the early 1990s (Dyer, 1991; Steele & Watson, 1995). Ingested orally, GHB and its analogs, γ-butyrolactone (GBL) and 1,4-butanediol, are available via the Internet and drug dealers and can be readily synthesized from a number of household products. GBL and 1,4-butanediol continue to be used as industrial solvents and are important components in the production of polyurethane and pesticides and are found in nail polish removal products (Gonzalez & Nutt, 2005).

Rapidly converted to GHB once ingested, the industrial use of GBL and 1,4-butanediol has had a marked impact on the legal classification, price, and availability of GHB. In many ways, GHB is the first drug of the Internet age, with the distribution and means of preparation disseminated via the web and social media (Anderson et al., 2006). It is known by various street names including GHB, "liquid ecstasy," "liquid E," "grievous bodily harm," "fantasy," "G," "Georgia home boy," "Mils," "liquid X," and "liquid G."

Increased media attention, public health concerns, and clinical scrutiny eventually led to a change in the legal classification of GHB, GBL, and 1,4-butanediol in Europe and the United States (Anderson, Kim-Katz, Dyer, & Blanc, 2010). The deaths of American teenagers, Hillory Farias and Samantha Reid, caught the public imagination in the United States and with fears growing about the role of GHB in assisted sexual assault (the rape drug) that led to its classification under Schedule 1 in the United States. The UK followed suit and GHB was classified as a class C drug, though the discrepancy in the legal classification of GHB and its analogs between 2003 and 2009 led to the substitution of GHB with its precursors GBL and to a lesser extent 1,4-butanediol (Anderson et al., 2010).

1.3 Ketamine

Ketamine was discovered in 1962 at the University of Michigan by the chemist Calvin Stevens in a quest to find an alternative to phencyclidine (aka "PCP" or "angel dust") (Teltzrow & Bosch, 2012). Labeled CI-581, ketamine was first trialed in prisoners in 1965. Domino's description of the experiment is illuminating: "*So unique were these effects that we had to invent a new set of words to describe its anaesthetic properties. The drug produced 'zombies' who were totally disconnected from their environment, with their eyes open, and yet in a complete anesthetic and analgesic state. The observation of being disconnected from the environment gave rise to the term 'dissociative anesthesia'*" (Domino, Chodoff, & Corssen, 1965). The term "dissociative anesthesia" had also been used to describe the effects of GHB, although its lack of analgesic properties limited it to be used as an induction agent. In contrast to GHB, ketamine demonstrated properties of rapid induction, rapid recovery, and effective analgesia while having a limited effect on respiratory and cardiovascular functioning (Teltzrow & Bosch, 2012).

Its first use as a recreational drug occurred as early as 1967, acquiring street names including "mean green" and "rock masculine" by a psychedelic chemist in Michigan (Jansen, 2001), though it has been suggested that a

major catalyst for the recreational ketamine use was the Vietnam War (Sewell, 2007). Ketamine can be administered by almost any route and made an ideal battlefield anesthetic. It has continued to be used on the battlefield and in areas that have limited medical equipment (Bonanno, 2002; Mercer, 2008). From 1970s onward, ketamine was used clinically as an anesthetic, although in recent years, this has been declined mainly due to the dissociative effects (Pai & Heining, 2007).

By the early 1980s, ketamine moved from the hospital setting to the private consulting room for use by "New Age therapists" and later for recreational purposes. Karl Jansen recounts the history of ketamine in "Ketamine: Dreams and Realities" (Jansen, 2001) noting that its recreational use was relatively rare until the late 1990s when it started to be used on the United Kingdom dance and rave scene (Moore & Miles, 2004). This owes something to the variable purity of ecstasy tablets, so that experimentation with ketamine may have been as a result of taking ecstasy tablets containing little or no MDMA. Known as "K," "special K," "kit-kat," or "vitamin K," it is also sometimes referred to as "the horse tranquilizer" (Dillon & Degenhardt, 2001) due to its use by vets as an animal tranquilizer. Recreational use has grown rapidly in the last 20 years (Morgan & Curran, 2012), particularly in Asia.

More recently, ketamine has been used as a neuropharmacological simulator of psychosis in functional MRI studies (Hashimoto, 2014). It had been noted in the 1960s that PCP and ketamine produced schizophrenia-like symptoms in some healthy volunteers and cause the exacerbation of symptoms in schizophrenic patients (Lahti, Weiler, & Tamara, 2001; Pomarol-Clotet et al., 2006), supporting the glutamate dysfunction model of schizophrenia (Coyle, 2001). For example, atypical antipsychotic drugs block the neuropsychiatric symptoms of ketamine (Duncan & Miyamoto, 2000). These findings have led to ketamine being used in functional neuroimaging studies to assess the efficacy of existing and new antipsychotic drugs (Large, 2007).

2. EPIDEMIOLOGY OF PARTY DRUG USE

Ecstasy is by far the most popular "party drug" worldwide with between 19 and 29 million users and is the fourth most popular drug after cannabis, opioids, and amphetamines (and stimulants), with world prevalence estimates of between 0.4% and 0.6%. Prevalences in Europe, the United States, and Oceania (New Zealand and Australia) are higher than

the world average at 0.5%, 0.9%, and 2.9%, respectively. In the United Kingdom, the use of ecstasy is declining, with evidence that new designer drugs are taking its place. In contrast, the use of ecstasy and club drugs is increasing in Asia and developing world, though there are difficulties in obtaining accurate prevalence data (World drug report, 1997).

GHB is a relatively new drug on the party scene, becoming more popular in the last decade (McCambridge, Winstock, Hunt, & Mitcheson, 2007). Prevalence estimates of GHB in industrialized countries are 0.1–2% (WHO, 2012), with an increased prevalence among subgroups including young adults who use it in combination with other party (or designer) drugs (McCambridge et al., 2007), bodybuilders (Gonzalez & Nutt, 2005), men who have sex with men (MSM) (Palamar & Halkitis, 2006; Wood & Beaumont, 2010), and clubbers (Anderson et al., 2010; Dillon & Degenhardt, 2001). A typical GHB user is a male, in his midtwenties to early thirties and active on the party scene, though among MSM, the age range is wider as they are more likely to use GHB as a prosocial drug (Palamar & Halkitis, 2006).

Ketamine use has also been growing in Southeast Asia. It is the second most commonly used illicit drug in Hong Kong (Kalsi, Wood, & Dargan, 2011), and its use on mainland China is growing. Its use in the United Kingdom and industrialized countries remains low with UK population-based studies reporting lifetime use of 4% for 16–24-year-olds and 2% for 16–59-year-olds; this contrasts with Australia and America who report significantly lower lifetime use of below 0.5% among all age groups (World drug report, 1997). Recreational use is most prevalent in ravers, MSM, young injecting drug users, and those who work in the medical or veterinary fields. Subjects interviewed in the party drug setting report lifetime use of 67.8% in the United Kingdom, 16.4% in France, and 10.8% in Italy (Kalsi et al., 2011).

3. RECREATIONAL USE VERSUS DEPENDENCE

"Recreational drug" use is a nonclinical term describing the use of a drug with the intention of enhancing life, inducing euphoria, or creating pleasure. It is a relatively new way of describing drug use and likely came into common usage as a way of describing patterns of drug use among young people and clubbers. The term contrasts with "drug dependence" that is characterized by a cluster of physiological, behavioral, and cognitive symptoms that drive repeated drug use in the face of harmful

consequences and is a clinically defined entity that came into common usage 50 years ago.

In 1964, the WHO Expert Committee on Addiction-Producing Drugs introduced the term "dependence" to replace the terms addiction (a state of periodic or chronic intoxication produced by the repeated consumption of a drug) and habituation (a condition resulting from repeated consumption of the drug) (Berridge & Mars, 2004). WHO defined drug dependence as "a state arising from repeated administration of a drug on periodic or continuous basis" (WHO, 1964).

The diagnostic criteria for alcohol and drug dependence have evolved over time, though they remain largely derived from Edwards and Gross seminal paper on alcohol dependence (Edwards & Gross, 1976), which highlighted the key features as a narrowing in the repertoire of drug use, salience of drug-seeking behavior, increased tolerance, repeated withdrawal symptoms, repeated relief or avoidance of withdrawal symptoms by further use, subjective awareness of a compulsion to use (or cravings), and reinstatement of the use after abstinence. Both international classification of diseases (ICD) and diagnostic and statistical manual of mental disorders (DSM) criteria for drug and alcohol dependency and abuse continue to be based on these principles. Additionally, Edwards and Gross commented on the way that social processes impact on the rate of development of dependence, the secondary consequences, seeking treatment, and stigmatization (Edwards & Gross, 1976). These ideas are fundamental to understanding the nature of party drug use in its novel social settings. The history and social narrative of club culture, music, unique social settings of nightclubs, flashing lights, and restricted licensing hours (mostly open at weekends) all impact on the rates of drug dependency, consequences of drug use, pattern of use, and treatment options.

Not all drugs are equally likely to cause dependence and the influence of a party drugs' potential to cause dependence is both contextual and pharmacological (Nutt, King, Saulsbury, & Blakemore, 2007). The pleasurable effects of the drug and its propensity to produce dependent behavior are likely the most important factors, as this is the first step in the behavioral cycle of repeated administration. Drug-induced pleasure has two components—the initial, rapid effect (the rush), followed by a period of euphoria (Nutt et al., 2007). The initial rush of euphoria provides a psychological drive for repeated administration, mediated by activation of mesocorticolimbic dopaminergic reward networks underpinning abuse and dependence potential.

The faster an euphoriant drug reaches the brain, the greater the reinforcing effect or "rush" and the greater potential to cause dependence. This can be influenced by both neuropharmacological profile and route of administration. If a drug is smoked or injected, this provides rapid bioavailability by crossing the blood–brain barrier. In contrast, orally administered drugs are absorbed more slowly and present a less intense rush, though the euphoric effects may last longer. An intense rush combined with a marked experience of euphoria and short duration of action increases the likelihood of dependence (Nutt et al., 2007).

Physiological tolerance also plays a major role in the dependency potential of a drug (Edwards & Gross, 1976; Nutt et al., 2007), such that the continuing use is driven by the prevention of withdrawal symptoms coupled with compulsive drug-seeking behavior (craving). This leads to a cycle of escalating use. Drugs that are rapidly metabolized tend to produce greater tolerance and withdrawal symptoms (Nutt et al., 2007). Placing this in context, an orally administered drug (i.e., ecstasy) with a long half-life and generating limited physiological tolerance is significantly less likely to cause dependence when compared to an orally administered drug (i.e., GHB) with a short half-life and that generates marked physiological tolerance.

There has been a major conceptual shift in the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Pub Inc., 2013). The concepts of abuse and dependence have been combined under the single diagnostic entity, substance use disorder, on a continuum from mild to severe depending on the number of symptoms experienced, which now includes craving as a diagnostic feature (Hasin et al., 2013).

4. PARTY DRUGS: SUBJECTIVE EFFECTS AND HAZARDS OF USE

4.1 MDMA (Ecstasy)

4.1.1 Administration, Metabolism, and Elimination

MDMA is usually orally ingested. Ecstasy in tablet form contains 30–150 mg of MDMA (Hall & Henry, 2006). In powder form, it is often dissolved in an alcoholic beverage or soft drink. The purity of ecstasy tablets is variable, although there is evidence that the purity of tablets is increasing (Giraudon & Bello, 2007; Tanner-Smith, 2006; Wolff, Hay, Sherlock, & Conner, 1995). MDMA can also be snorted, though this requires grinding to produce a fine powder and can result in intranasal trauma, and so is relatively rare. A minority of regular users report nasal and intravenous

administration (up to 16% reporting having injected once or more); intravenous use is associated with a greater risk of overdose and physical harm (Degenhardt & Hall, 2010). When ingested orally, peak serum levels are reached 2 h postadministration (Degenhardt & Hall, 2010; Torre & Farré, 2004) and the elimination half-life of 100 mg is 8–9 h, though the effects of ecstasy may last between 2 and 12 h due to its complex metabolism (Torre & Farré, 2004).

Metabolism is hepatic and produces a number of active metabolites including MDA, making it difficult to predict the dose–response relationship in individuals. Cytochrome P450 family enzymes play a central role in the metabolism of MDMA, with the isoform 2D6-mediated O-demethylation and N-demethylation in humans (Torre & Farré, 2004). MDMA metabolism involves N-demethylation to 3,4-methylenedioxyamphetamine (MDA). This important pathway is influenced by CYPD polymorphism, for example, up to 10% of the Caucasian population has deficiency in the *CYP2D6* gene and has a reduced ability to metabolize MDMA (De La Torre et al., 2002), potentially prolonging drug effects and increasing the risk of toxicity. The major metabolites of MDMA are 3,4-dihydroxymethamphetamine, 4-hydroxy-3-methoxymethamphetamine, and 4-hydroxy-3-methoxyamphetamine that are excreted in the urine as conjugated glucuronide or sulfate metabolites (Abraham et al., 2009).

4.1.2 Neuropharmacology

MDMA is a ring-substituted amphetamine (Shulgin, 1986) and lies somewhere between traditional amphetamines (speed) and hallucinogens (mescaline) in its neuropharmacological effects; it offers mild stimulation and mild reality distortion to recreational users. In contrast to traditional amphetamines, it is a potent releaser of serotonin (5-HT) and inhibits 5-HT reuptake (Maxwell, 2005; Schifano, 2004; Torre & Farré, 2004), though unlike traditional hallucinogens, it does not directly activate postsynaptic 5-HT receptors. Its pharmacological activity results from its interaction with monoamine transporters, the serotonin transporter (SERT), norepinephrine transporter (NET), and dopamine transporter (DAT) (Verrico, Miller, & Madras, 2007).

MDMA reverses the actions of SERT, redirecting 5-HT stores into the synapse. A single dose of ecstasy can release up to 80% of the available serotonin into the synaptic cleft, acutely increasing serotonergic activity. MDMA also inhibits tryptophan hydroxylase, the rate-limiting enzymes in the synthesis of 5-HT (Green, Mechan, Elliott, O'Shea, & Colado, 2003). Animal

models suggest that after acute administration, the inhibitory effects on tryptophan hydroxylase can last for up to 1 week (Green et al., 2003). It is likely that the combination of the depletion of neuronal serotonin (SERT activity) and the inhibition of tryptophan hydroxylase contributes to the ecstasy "comedown" symptoms of sleep disturbance, low mood, and irritability reported by users (Parrott, 2013). There is evidence for long term serotonergic neural toxity (Parrott, 2002; Benningfield & Cowan, 2013).

Like other amphetamines, it also potentiates dopamine and noradrenaline activity. MDMA increases dopamine and noradrenaline levels by reversing the action of DAT and NET, though MDMA-induced release of 5-HT is higher compared with the release of dopamine or norepinephrine and depletion of neuronal stores less pronounced Verrico et al., 2007. MDMA also mediates a mild inhibition of monoamine oxidase preventing the breakdown of 5-HT, noradrenaline, and dopamine. Prefrontal and dorsal hippocampus release of acetylcholine has been reported, and there is also an evidence for the activation of glutamate and interaction with gamma-aminobutyric acid (GABA) system (Torre & Farré, 2004).

4.1.3 Use, Harmful Use, and Dependence

The subjective experience of users has been important in the investigation of ecstasy's neuropharmacological and physiological actions. The acute psychological effects of ecstasy include a sense of well-being, euphoria, and increased sense of closeness with others (or empathy), leading to ecstasy being dubbed "the love drug." A range of negative psychological effects have also been reported and these include anxiety, depressed mood, irritability, and paranoia. A dose–response relationship related to the cardiovascular effects of ecstasy occurs at doses above 1 mg/kg, whereby significant increases in heart rate, blood pressure, and cardiac output occur. Nausea and vomiting, teeth grinding, headaches, body temperature changes, palpitations, muscle aches, fatigue, dizziness, dry mouth, increase energy, sweating, and paresthesia are the most common side effects (Baylen & Rosenberg, 2006) and are more pronounced in acute intoxication.

Ecstasy use in contrast to GHB or ketamine carries a low risk of dependence. There is limited evidence to suggest that physiological dependence occurs in animal studies, but in practice, people can stop using ecstasy without the need for specific medical intervention (Degenhardt, Bruno, & Topp, 2010). Typically, ecstasy is used one to two times per week in the context of partying, clubbing, or social gatherings. Ecstasy is often used with a number of other recreational drugs including alcohol, ketamine, GHB, cocaine, and

methamphetamine. Escalation of recreational use to a level where it is deemed harmful is the most common scenario.

Bingeing behaviors include "stacking," the use of several tablets all at once, and "boosting," the use of successive tablets taken over an evening or over successive days. Comorbid psychiatric syndromes such as anxiety disorders may also play a role in facilitating the escalating use of ecstasy. People exhibiting these behaviors have reported mild/moderate subjective withdrawal symptoms during the comedown period including low mood and reduced appetite, which may be associated with taking days off work. Ecstasy dependence syndrome has been described applying the DSM-IV criteria that places an emphasis on compulsive use (use despite problems, giving up important activities because of ecstasy, unsuccessful attempts to stop, withdrawal, and excessive time spent obtaining or using it) and escalating use (tolerance and using it more often and longer than intended) (Degenhardt et al., 2010). However, presentation to treatment services with primary ecstasy dependence is rare. Ecstasy is normally the secondary or tertiary problematic drug reported by polydrug users. The course of ecstasy dependence has a tendency to differ from that of other drugs. Studies indicate that after 3 years, those initially meeting DSM-IV criteria for ecstasy dependence syndrome, 43% were still using the drug, though the majority no longer met the criteria for dependence (Degenhardt et al., 2010).

4.1.4 Intoxication and Overdose

Ecstasy use can result in acute physical health problems and psychiatric morbidity, though death is very rare (Hall & Henry, 2006). Psychiatric symptoms including an acute psychosis, flashback phenomena similar to those seen with lysergic acid diethylamide (LSD), anxiety/panic states, and depressive mood disorders may all occur (Green et al., 2003). Ecstasy can additionally precipitate psychotic and manic episodes in those with preexisting psychotic illness or precipitate a first psychosis (Rugani et al., 2012).

Clinically significant toxicity is rare and the presentation is usually in the context of polydrug use. As with other club drugs, ecstasy is often coingested with a range of other party drugs including alcohol, GHB, ketamine, methadone, cocaine, and methamphetamine. The major risks are around cardiovascular compromise. A combination of ecstasy use, hyperthermia, prolonged physical activity (in the form of vigorous dancing), and dehydration can lead to potentially fatal rhabdomyolysis and subsequent multiorgan failure and disseminated intravascular coagulation. Disturbances in sodium and water balance also occur and can be precipitated by acute water

intoxication, which may present as an acute confusional state, impaired consciousness, and seizures. This is the main cause of ecstasy-associated mortality, is a medical emergency, and may require intensive care unit support.

4.2 GHB and GBL

4.2.1 Administration, Metabolism, and Elimination

GHB is oral ingested in the form of capsules, powder, tablets, or liquid. The powder is typically dissolved in water or alcoholic beverages to hide its salty taste. Its lipophilic properties potentiate a rapid absorption by the gastrointestinal tract with a bioavailability of about 25% (Schep et al., 2012). It reaches peak plasma concentrations in 20–60 min postingestion and has a relatively short half-life of between 20 and 60 min, with its lack of hangover effect cited as a reason for use among recreation users. Intravenous use has been reported, but this is rare (Gonzalez & Nutt, 2005; Wood, Brailsford, & Dargan, 2011).

All of the neurophysiological effects of GBL and 1,4-butanediol are attributable to GHB. GBL is metabolized to GHB via serum lactonase and 1,4-butanediol in the liver by alcohol dehydrogenase. GBL conversion to GHB is measurable within 5 min postingestion; in contrast, the conversion of 1,4-butanediol requires both alcohol dehydrogenase and aldehyde dehydrogenase enzymes party to zero-order kinetics, prolonging the conversion times when ingested with alcohol.

GHB is metabolized by GHB dehydrogenase and converted to succinic semialdehyde, which is then metabolized to succinic acid by succinic semialdehyde dehydrogenase. Succinic acid then enters the Krebs cycle and is further metabolized to CO_2 and water (Parviza, Vogelb, Gibsonb, & Pearl, 2014). The elimination is mostly via the lungs in the form of CO_2. Less than 2% of GHB is excreted in urine and is not detectable in urine after 12 h, presenting a challenge for drug monitoring, and GHB is reported to be a drug favored by airline pilots (Gonzalez & Nutt, 2005; Schep et al., 2012; Fig. 1).

4.2.2 Neuropharmacology

A short-chain fatty acid is similar in structure to GABA, for which it is both a precursor and a metabolite (Wong, Gibson, & Snead, 2004), though unlike GABA, it is able to cross the blood–brain barrier (Ryan & Stell, 1997; Van Cauter et al., 1997). GHB has both a stimulatory action and a sedative action, which can be partly explained by its high affinity to GHB receptors and low affinity to GABA-B receptors. It is an agonist at the excitatory

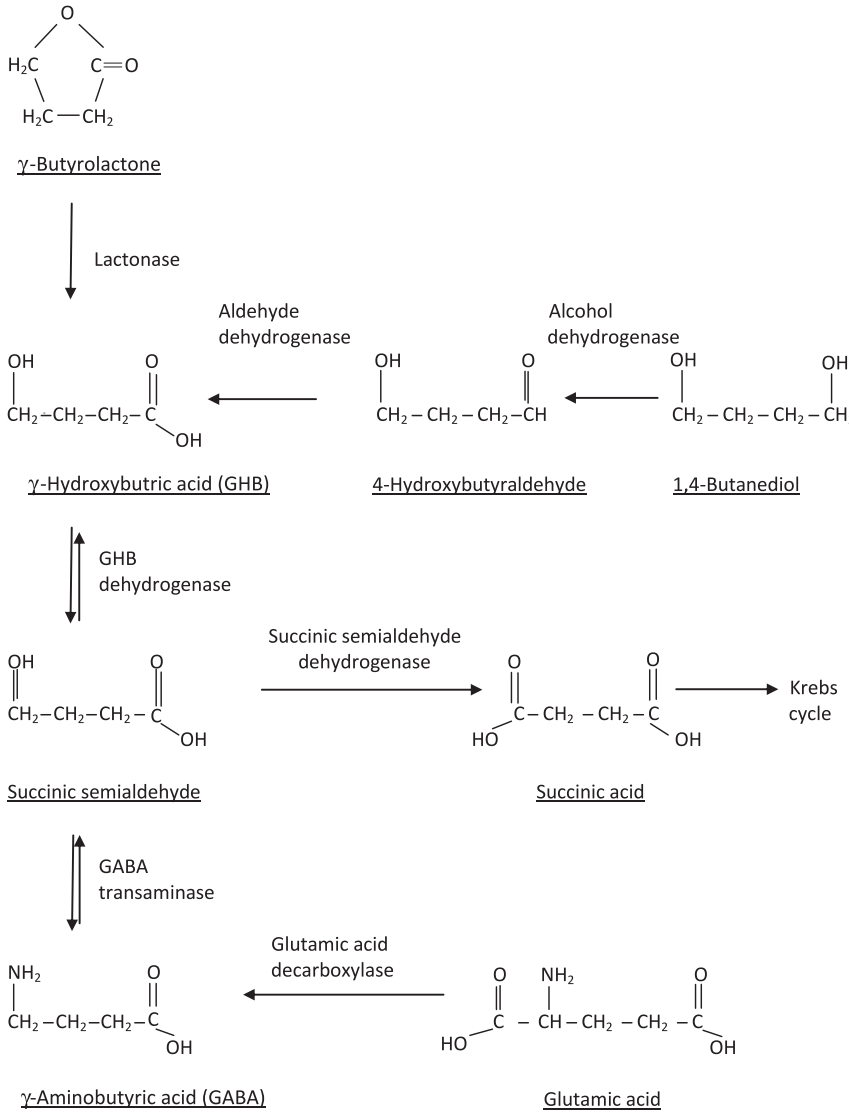

Figure 1 The metabolic pathway of GHB and precursors.

G protein-coupled GBH receptor that is widely distributed throughout the brain, with highest receptor density found in the cortex, the hippocampus, the olfactory tracts, and the cerebellum. In contrast, activity at the inhibitory GABA-B receptor is complex; it has a lower affinity for GABA-B receptors when compared to GABA-A (1000 times less than GABA), but clinical and

experimental evidences demonstrate that GHB has marked GABA-B activity (Schep et al., 2012).

At lower doses (i.e., during recreational use), GHB activates GHB receptors and potentiates dopamine release, accounting for the euphoria and nausea that are common at low doses. At high dose, GHB has a modulatory function at the GABA-B receptor (Koek, Mercer, Coop, & France, 2009) leading to reduced dopamine levels and central nervous system (CNS) depression. There seems to be a limited effect on other transmitters and receptors, although there is evidence that it increases serotonin turnover in the brain and increases total brain acetylcholine (Schep et al., 2012), though the neuropharmacological and clinical sequelae are unclear.

4.2.3 Use, Harmful Use, and Dependence

In an international survey, partying (50%), being alone (20%), sexual enhancement (16%), and body building (6%) were cited as the most common reasons for use (Anderson et al., 2010). Initially, people seek the effects of euphora, sociability, and sexual enhancement. A minority may progress to domestic recreational use (euphoric effects and sexual enhancement) and then lone use (euphoria and sleep enhancement) before the characteristic frequent administration associated with dependence (to abate withdrawal symptoms and induce sleep) (Anderson et al., 2010; Gonzalez & Nutt, 2005; Van Cauter et al., 1997).

Among recreational users, the reward currency of GHB is euphoria and it is regularly used as part of a "party drug cocktail" with alcohol, MDMA, ketamine, and cocaine widely reported as coadministered drugs (Dillon & Degenhardt, 2001; Wood et al., 2009). The average dose among recreational users is in the range of 0.75–2.5 g (Gonzalez & Nutt, 2005). Subjective and clinical effects typically occur between 15 and 45 min following oral administration, though prolonged times to intoxication can occur when 1,4-butanediol is ingested in combination with alcohol. Associated positive effects include sociability, sensory enhancement, increased libido, and euphoria, with associated negative effects such as confusion, blurred vision, aggression, ataxia, nausea, and vomiting (Schep et al., 2012). Drug effects plateau at about 3–4 h following ingestion, disappearing between 4 and 8 h postingestion.

Tolerance, severe dependence, and withdrawal are recognized features of regular GHB misuse, and the withdrawal syndrome is a potentially life-threatening withdrawal state that is associated with high mortality if left

untreated. A particular feature of GHB use, due to its short half-life and its ability to induce a rapid alcohol-like physiological tolerance, is the rapid onset of dependence in those who were previously recreational users or new to the drug (Maxwell, 2005). A typical dependent user will pipette the required dose of GHB/GBL every 4–5 h, often in response to feelings of mild agitation or anxiety (Gonzalez & Nutt, 2005). The dose is usually increased by 25–50% to induce sleep, often to counteract the insomnia that is an early feature of the withdrawal syndrome, with sleep usually lasting between 4 and 6 h. People with more severe dependence describe continuing 4–5 h dosing over a 24 h period. Dependence is typically associated with consumption of greater than 18 g in 24 h, and physiological dependence has been reported in between 4% and 21% of GHB users (Carter, Pardi, Gorsline, & Griffiths, 2010; Degenhardt, Darke, & Dillon, 2002; Miotto et al., 2001).

Recreational GHB use is associated with high-risk sexual behaviors, sex with strangers, and increased HIV risk, particularly on the MSM scene and risks of overdose and a dangerous alcohol-like withdrawal syndrome (Maxwell, 2005; Oser & Havens, 2008; Palamar & Halkitis, 2006).

4.2.4 Intoxication and Overdose

The clinical features of GHB intoxication reflect the steep dose–response relationship, though symptoms depend on the level of tolerance. They include short-term anterograde amnesia, hypotonia, nystagmus, euphoria, aggression, and ataxia at doses between 0.75 and 1.5 g (10–20 mg/kg); euphoria, drowsiness, sleep, hallucinations, and myoclonus at doses between 1.5 and 2.5 g (20–30 mg/kg); CNS depression, bradycardia, and respiratory depression at doses between 2.5 and 5 g (40–50 mg/kg); and coma/death at doses in excess of >5 g (50 mg/kg) (Schep et al., 2012).

New users face the risk of a titration trial, with the evidence suggesting that difficulties around titration continue even with regular use, so that users often present on multiple occasions to A&E with symptoms of toxicity (Korf, Nabben, Benschop, Ribbink, & van Amsterdam, 2014; Van Amsterdam et al., 2012). Presentation is more common in clinical units located in high-density urban areas, close to nightclubs, and at music/street festivals (Wood et al., 2011). Overdose is associated with the rapid ingestion of large quantities of GHB or with use of drugs that cause CNS depression including alcohol, ketamine, methadone, and benzodiazepines (Galicia et al., 2011; Korf et al., 2014).

CNS depression can progress quickly in the otherwise stable patient, and particular attention should be paid toward respiratory and cardiovascular support, with management in the ICU environment necessary if intubation and mechanical ventilation are required. Airway management is a particularly important feature of management as the loss of a gag reflex and vomiting can occur early in evolution of GHB overdose. CNS depression typically lasts for between 1 and 3 h with a typical full recovery within 4–8 h (Galicia et al., 2011). Patients should be observed for a minimum of 2 h, with supportive management being the mainstay of treatment.

There are currently no licensed antidotes for GHB, though a GABA-B antagonist SCH 5091 has shown some promise in animal studies, significantly reducing mortality in mice following the administration of fatal doses of GHB or 1,4-butanediol (Schep et al., 2012). Naloxone, flumazenil, and physostigmine have demonstrated limited benefits in GHB toxicity (Anderson et al., 2006; Schep et al., 2012).

4.2.5 The Management of GHB Withdrawal

The recognition of withdrawal states in the A&E or psychiatric ward presents a clinical challenge; in part, this is due to the limited exposure of general psychiatric and medical staff in the United Kingdom to GHB withdrawal. Additionally, patients presenting overdose may rapidly transition from states of intoxication to withdrawal. Moderate to severe withdrawal symptoms usually occur within 24 h of the last dose, though users can present with symptoms up to 4 days following the acute cessation of use. The main differential diagnoses are acute alcohol and overdose of another party drug. The distinct features of GHB withdrawal are the rapid evolution of symptoms, the absence of the physical stigmata of chronic alcohol use, and the presence of psychotic symptoms in clear consciousness. Mild to moderate withdrawal symptoms include anxiety, restlessness, nystagmus, confusion, tachycardia, nausea, and vomiting (Gonzalez & Nutt, 2005) and severe withdrawal symptoms, seizures, delirium, tachypnea, and palpitations (Bearn & Goldin, 2013; Choudhuri, Cross, Dargan, Wood, & Ranjith, 2013).

When managing acute withdrawal, cardiovascular and respiratory support is critical. First-line treatment is oral diazepam or parenteral lorazepam if oral medication is contraindicated, switching to oral diazepam when permissible. Baclofen, a GABA agonist, is helpful for agitation and the prevention of myoclonus. Second-line drugs such as phenobarbital and propofol have been used in cases not responding to high doses of benzodiazepines, and ICU support will be required if the patient requires enhanced levels

of sedation or requires continuous cardiac monitoring and ventilator support (Schep et al., 2012).

GHB detoxification can present a challenging clinical entity (Gonzalez & Nutt, 2005). Typically, mildly to moderately dependent users (<3–4 doses and <30 g GHB/15 ml GBL in 24 h, respectively) can be managed as outpatients, with a reducing regime of diazepam starting at 5–10 mg four times daily over 4–5 days (Bearn & Goldin, 2013). Moderately to severely dependent users (>3–4 doses and >30 g GHB/15 ml GBL in 24 h, respectively) and dependent users with comorbid polydrug or alcohol dependence, with a history of withdrawal seizures, epilepsy, and a comorbid psychotic or mood disorder, should be managed in the inpatient environment.

High doses of diazepam between 80 and 150 mg are often required in the first 24 h, which may need to be increased to 200 mg if there is delirium. An agitated delirium and psychiatric symptoms occur in up to 1/3 of people during withdrawal and are more common in severe dependence. Visual and auditory hallucinations, paranoid thoughts, and delusions are the most common presenting psychiatric symptoms; typically, these occur after the first 24 h and antipsychotic medication such as olanzapine or quetiapine may be indicated (Choudhuri et al., 2013).

Clinical planning should be directed toward minimizing the likelihood that a severe withdrawal syndrome emerges and treating neuropsychiatric symptoms. The guiding principles are early treatment and continuous monitoring of withdrawal symptoms. The Alcohol Withdrawal Assessment Scoring Guidelines (CIWA-Ar) can be helpful as an objective measure, as no objective evidence-based measure exists for the GHB withdrawal syndrome (Gonzalez & Nutt, 2005). The course of the withdrawal syndrome runs on average 9 days but can last up to 14 days (Bearn & Goldin, 2013; Fig. 2).

4.3 Ketamine

4.3.1 Administration, Metabolism, and Elimination

Ketamine is an arylcyclohexylamine and as a recreational drug can be administered enterally, parenterally, and intranasally. Euphoriant effects occur rapidly and are dose-dependent, due to high lipid and water solubility and rapid transition across the blood–brain barrier (WHO, 2006). Most commonly encountered on the recreational drug scene as a white powder, it is also available as a liquid. When recreational use began, ketamine was smoked with cannabis, though intramuscular and intravenous use had also been described (Lankenau & Sanders, 2007). On the club scene, ketamine is

The algorithm below shows an example of the management for both GHB and GBL withdrawal.

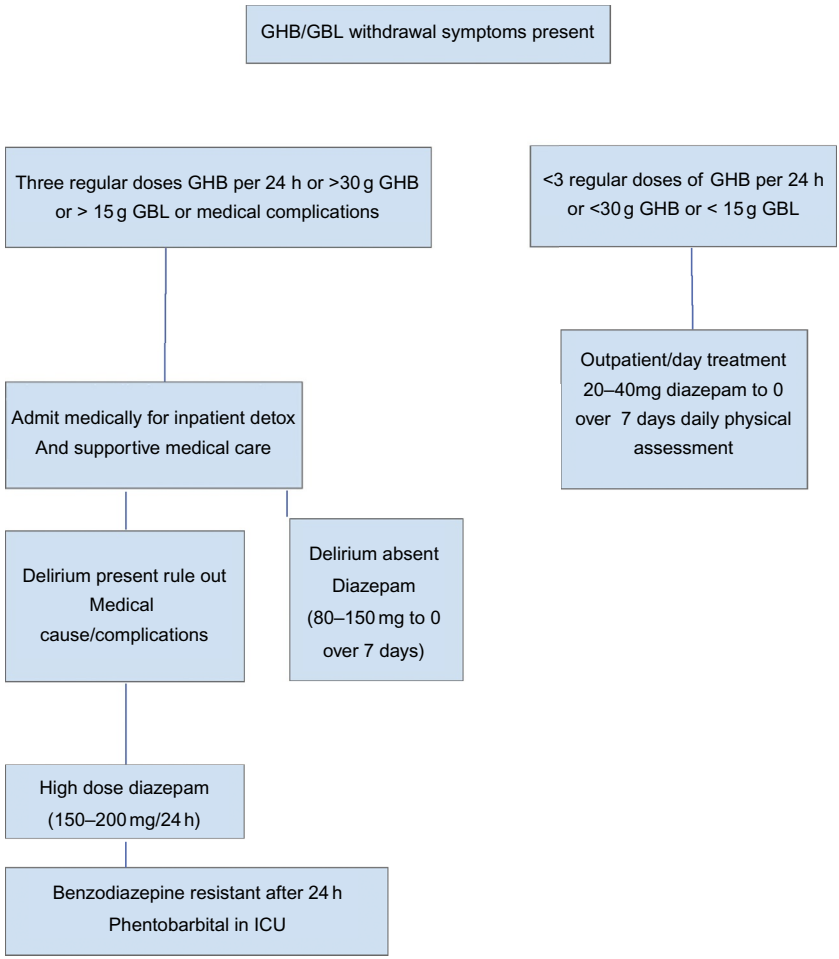

Figure 2 Algorithm for the management of GHB and GBL withdrawal (McDonough, Kennedy, Glasper, & Bearn, 2004). Guidelines for the management of GHB and GBL withdrawal.

primarily snorted, though it can be orally ingested and used rectally (Kalsi et al., 2011). Recreational doses of the drug typically range between 200 and 300 mg when ingested orally and 60–250 mg when snorted (Kalsi et al., 2011). Bioavailability via the nasal route is about 50% (Malinovsky & Servin, 1996). The initial rush occurs after 2–5 min, followed by a trance-like euphoria. When ingested orally, the bioavailability

is 17%, and following extensive first-pass metabolism (Clements, Nimmo, & Grant, 1982), the major active metabolite, norketamine, is 1/3 as potent as ketamine (Adamowicz & Kala, 2005) and induces a more sedative experience.

Ketamine has a half-life of between 2 and 16 min and the effects of the drug last about an hour. It is metabolized via N-demethylation by cytochromes CYP3A4, CYPB6, and CYP2C9 to its active metabolite norketamine and inactive metabolite dehydronorketamine (Bokor & Anderson, 2014). Renally excreted mostly as glucuronide conjugates (80%), dehydronorketamine (16.2%), ketamine (2.3%), and norketamine (1.6%) (Wieber, Gugler, Hengstmann, & Dengler, 1975; Wood et al., 2009), ketamine is detectable in urine for up to 48 h following a single dose and norketamine is detectable for between 6 and 14 days (Adamowicz & Kala, 2005).

4.3.2 Neuropharmacology

Ketamine is a noncompetitive receptor antagonist at the *N*-methyl-D-aspartate receptor (NMDA) PCP binding site (Trujillo et al., 2011) and has an R- and S-isomer. While the S-isomer has greater receptor affinity and potency, both isomers demonstrate similar pharmacokinetic profiles (Morgan & Curran, 2012). The NMDA complex is activated by the endogenous agonists glutamic acid, aspartic acid, and glycine and plays a central role in the modulation of synaptic plasticity and memory function (Morgan & Curran, 2006); the receptor is also involved in the processing of sensory inputs at the spinal and thalamic levels (Dougherty & Palecek, 1992). The activity of ketamine at the NMDA receptor has impact on memory, emotion, sensation, and perceptions (Morgan et al., 2013).

Our understanding of mechanisms of action and potential role in the understanding of psychiatric disorders is incomplete. Initially, it was assumed that ketamine inhibited glutamate release, the hypoglutamatergic hypothesis (Trujillo et al., 2011). More recently, it has been suggested that due to its blockade of NMDA receptors on GABAergic neurons, ketamine potentiates glutamate release (Trujillo et al., 2011). This underpins the glutamate hypothesis of schizophrenia and may contribute to psychedelic effects (Deakin et al., 2008).

The analgesic properties of ketamine are likely to occur via its direct and modulatory effect on opioid receptors on spinothalamic pathways. Ketamine has been demonstrated to be a weak agonist at opioid receptors and

is able to prevent opiate tolerance in animal models. Ketamine can reduce the amount of opioid medication required (Trujillo et al., 2011) and has been used to treat complex regional pain syndrome (Sigtermans et al., 2009).

Ketamine also activates dopaminergic reward networks. With repeated administration, dopamine supplies are depleted promoting both euphoric effects and the development of tolerance (Ross, 2008). In contrast, repeated administration of ketamine enhances serotonin levels, and a single dose of ketamine has been demonstrated to improve depressive symptoms for up to 1 week (Zarate et al., 2006).

4.3.3 Use, Harmful Use, and Dependence

Ketamine's emergence as a party drug is curious partly owing to the diversity of experience reported by users. Euphoria features high on subjective reporting, though dissociative experiences are also commonly described. The dissociative effects are thought to be a result of an electrophysiological dissociation between the limbic and the thalamoneocortical systems (Kalsi et al., 2011; Mercer, 2008). In one study of the subjective psychological and behavioral effects of ketamine, a range of experiences were described. The absence of time (70%), unusual thought content (60%), psychomotor dissociation (57%), euphoria (55%), derealization (53%), visual hallucinations (49%), weightlessness (47%), and auditory hallucinations (46%) were the seven most commonly reported effects (Dillon, Copeland, & Jansen, 2003). Users have also reported the subjective experience of feeling like they are "flying" or "becoming god" and being "stuck in a K-hole," a zombie-like psychedelic twilight zone particularly associated with intravenous ketamine use (Lankenau & Sanders, 2007). Ketamine use is associated with cognitive dysfunction, particularly difficulties in working and episodic memory (Morgan & Curran, 2006).

Ketamine dependence does occur and reinforcing effects have been demonstrated in both animals and humans. In particular, the short half-life and buzz associated with snorting ketamine can lead to a compulsive binge pattern of use or continuous use in spite of repeated harms. Tolerance is rapid and common among users, with the occasional user doubling their dose in the first year of use and regular users increasing but more (Kalsi et al., 2011). There is limited evidence for a physiological withdrawal syndrome. Anxiety, sweating, and palpitations have been reported on cessation of the drug that may be ameliorated by low doses of benzodiazepines.

4.3.4 Intoxication and Overdose

A psychotic-like state or excited delirium can be signs of overdose. Common psychological and behavioral symptoms include agitation, aggression, grandiosity, persecutory and paranoid delusions, and auditory and visual hallucinations (Dillon et al., 2003; Pomarol-Clotet et al., 2006). Dissociative states may present as feelings of impaired somatic or psychic control (passivity phenomena).

Ketamine is a mild respiratory depressant and cardiovascular stimulant inducing increases in heart rate, cardiac output, and blood pressure. Palpitations are sometimes a presenting complaint. Pulmonary edema has been described in ketamine overdose, and this may be related to a combination of increased cardiac output and respiratory depression (Kalsi et al., 2011). The median lethal therapeutic dose in animals is 100 times the average therapeutic dose, and no adverse effects were observed in nine children who had been injected with 100 times the intended dose (Green et al., 1999; Morgan & Curran, 2012). Mortality associated with ketamine is often the result of use within a polydrug cocktail as previously described with MDMA and GHB (Morgan & Curran, 2012). Between 1996 and 2006, only four cases of death associated with ketamine were reported in the United Kingdom (Bokor & Anderson, 2014; Schifano, Corkery, Oyefeso, Tonia, & Ghodse, 2008). Although there was a 10-fold increase in deaths mentioning ketamine as a cofactor between 1999 and 2008 (2–22), this is likely to reflect the increasing use of the drug on the club scene (Morgan & Curran, 2012).

Management of ketamine toxicity is targeted at psychiatric symptoms including auditory and visual hallucinations. As agitation or aggression can also be a feature, benzodiazepines can be used for sedation and the patient should be nursed in a low-stimulus environment. Evidence suggests that both typical and atypical antipsychotic medications may have a role in the treatment of acute ketamine intoxication, haloperidol (Giannini, Underwood, & Condon, 2000), and atypical antipsychotics (Duncan & Miyamoto, 2000) have been used, though low doses are advised as there is a risk of neuroleptic malignant syndrome in the neuroleptic naive patient.

Accidents are a common cause of injury or death in ketamine users, arising in the context of reduced pain perception combined with psychomotor aberration, reduced environmental awareness, grandiosity, perceptual disturbance, and thought disorder. Falls, drowning (Trujillo et al., 2011), jumping off buildings (Kalsi et al., 2011), and car accidents have been recorded as causes of death in ketamine-intoxicated patients. In Hong Kong,

9% of fatal crashes recorded over a 5-year period involved ketamine use (Cheng, Ng, Chan, Mok, & Cheung, 2007; Morgan & Curran, 2006).

Problems with chronic use include ketamine-induced ulcerative cystitis that can present as painful hematuria and suprapubic pain; the course of the condition is variable. Sometimes, this is resolved by abstaining from ketamine use; although up to 1/3 may have long-term difficulties and are at risk of obstructive nephropathy, K-cramps describe a vague abdominal pain associated with the long-term use of ketamine, which again abate following a period of abstinence (Morgan & Curran, 2012).

5. THE FUTURE OF PARTY DRUGS

The use of drugs to induce altered states is interwoven with human history, a history driven by human needs and wants and shaped by social evolution. Timothy Leary's call to "Turn on, tune in, drop out" has become a central ideology of dance or party drug culture, spawning metaphysical association between music, dance, underground culture, and freedom of expression. The emerging pattern is that of an increase in "party drug" use in countries with increasing disposable income and a greater acceptability of party drug use in developed countries. More people are using recreational drugs to induce particular desired feelings or states of mind.

Ecstasy, ketamine, and GHB have a range of pharmacological and physiological effects, abuse potential, clinical uses, and social consequences but have been collected under a label that focuses on the social use and historical and legal classification rather than the properties of the drugs themselves. The three party drugs explored in this chapter are currently being reexplored and investigated, and their potential therapeutic and research value has become a hot topic in psychiatry. In this regard, the history of ecstasy, GHB, and ketamine provides an important narrative for the future of drug use, particularly with the rapid emergence of new designer drugs in the Internet age.

REFERENCES

Abraham, T. T., Barnes, A. J., Lowe, R. H., Kolbrich Spargo, E. A., Milman, G., Pirnay, S. O., et al. (2009). Urinary MDMA, MDA, HMMA and HMA excretion following controlled MDMA administration to humans. *Journal of Analytical Toxicology*, *33*, 439–446.

Adamowicz, P., & Kala, M. (2005). Urinary excretion rates of ketamine and norketamine following therapeutic ketamine administration: Method and detection window considerations. *Journal of Analytical Toxicology*, *28*(August), 31–33.

Alshaikh, M. K., Tricco, A. C., Tashkandi, M., Mamdani, M., Straus, S. E., & BaHammam, A. S. (2012). Sodium oxybate for narcolepsy with cataplexy: Systematic review and meta-analysis. *Journal of Clinical Sleep Medicine: JCSM: Official Publication of the American Academy of Sleep Medicine*, *8*(4), 451–458.

American Psychiatric Pub Inc. (2013). *Diagnostic and statistical manual of mental disorders: DSM5*. Arlington, VA: American Psychiatric Pub Inc.

Anderson, I. B., Kim, S. Y., Dyer, J. E., Burkhardt, C. B., Iknoian, J. C., Walsh, M. J., et al. (2006). Trends in gamma-hydroxybutyrate (GHB) and related drug intoxication: 1999 to 2003. *Annals of Emergency Medicine*, *47*(2), 177–183.

Anderson, I. B., Kim-Katz, S. Y., Dyer, J. E., & Blanc, P. D. (2010). The impact of gamma hydroxybutyrate (GHB) legal restrictions on patterns of use: Results from an international survey. *Drugs: Education, Prevention, and Policy*, *17*(5), 455–469.

Basil, B., Blair, A. M., & Holmes, S. W. (1964). The action of sodium 4-hydroxybutyrate on spinal reflexes. *British Journal of Pharmacology and Chemotherapy*, *22*, 318–328.

Baylen, C. A., & Rosenberg, H. (2006). A review of the acute subjective effects of MDMA/ecstasy. *Addiction*, *101*(7), 933–947.

Bearn, J., & Goldin, M. (2013). *GHB: What psychiatrists need to know*. CPD Online Royal College of Psychiatry, Maney publishing.

Benningfield, M. M., & Cowan, R. L. (2013). Brain serotonin function in MDMA (ecstasy) users: Evidence for persisting neurotoxicity. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *38*(1), 253–255.

Berridge, V., & Mars, S. (2004). History of addictions. *Journal of Epidemiology and Community Health*, *58*(9), 747–750.

Blumenfeld, M., Suntay, R. G., & Harmel, M. H. (1962). Sodium gamma-hydroxybutyric acid: A new anesthetic adjuvant. *Anesthesia and Analgesia*, *41*(6), 721–726.

Bokor, G., & Anderson, P. D. (2014). Ketamine: An update on its abuse. *Journal of Pharmacy Practice*, *27*(6), 582–586.

Bonanno, F. G. (2002). Ketamine in war/tropical surgery (a final tribute to the racemic mixture). *Injury*, *33*(4), 323–327.

Carter, L. P., Pardi, D., Gorsline, J., & Griffiths, R. R. (2010). Illicit gamma-hydroxybutyrate (GHB) and pharmaceutical sodium oxybate (Xyrem): Differences in the characteristics of misuse. *Drug and Alcohol Dependence*, *104*(501), 1–10.

Cheng, W.-C., Ng, K.-M., Chan, K.-K., Mok, V. K.-K., & Cheung, B. K.-L. (2007). Roadside detection of impairment under the influence of ketamine—Evaluation of ketamine impairment symptoms with reference to its concentration in oral fluid and urine. *Forensic Science International*, *170*(1), 51–58.

Choudhuri, D., Cross, S., Dargan, P. I., Wood, D. M., & Ranjith, G. (2013). Psychiatric aspects of acute withdrawal from gamma-hydroxybutyrate (GHB) and its analogue gamma-butyrolactone (GBL): Implications for psychiatry services in the general hospital. *International Journal of Psychiatry in Clinical Practice*, *17*(2), 154–156.

Clements, J. A., Nimmo, W. S., & Grant, I. S. (1982). Bioavailability, pharmacokinetics, and analgesic activity of ketamine in humans. *Journal of Pharmaceutical Sciences*, *71*(5), 539–542.

Coyle, J. T. (2001). Reviews and overviews. The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. *The American Journal of Psychiatry*, *158*(9), 1367–1377.

Davison, D., & Parrott, A. C. (1997). Ecstasy (MDMA) in recreational users: Self-reported psychological and physiological effects. *Human Psychopharmacology*, *12*(3), 221–226.

Deakin, J. F. W., Lees, J., McKie, S., Hallak, J. E. C., Williams, S. R., & Dursun, S. M. (2008). Glutamate and the neural basis of the subjective effects of ketamine. *Archives of General Psychiatry*, *65*(2), 154–164.

De La Torre, R., Farré, M., Ortuño, J., Mas, M., Brenneisen, R., Roset, P. N., et al. (2002). Non-linear pharmacokinetics of MDMA ("ecstasy") in humans. *British Journal of Clinical Pharmacology*, *49*(2), 104–109.

Degenhardt, L., Bruno, R., & Topp, L. (2010). Is ecstasy a drug of dependence? *Drug and Alcohol Dependence*, *107*(1), 1–10.
Degenhardt, L., Darke, S., & Dillon, P. (2002). GHB use among Australians: Characteristics, use patterns and associated harm. *Drug and Alcohol Dependence*, *67*(1), 89–94.
Degenhardt, L., & Hall, W. (Eds.), (2010). *The health and psychological effects of "ecstasy (MDMA) use"*. Sydney: NDARC.
Dillon, P., Copeland, J., & Jansen, K. (2003). Patterns of use and harms associated with non-medical ketamine use. *Drug and Alcohol Dependence*, *69*, 23–28.
Dillon, P., & Degenhardt, L. (2001). Ketamine and GHB: New trends in club drug use? *Journal of Substance Use*, *6*(1), 11–15.
Domino, E. F., Chodoff, P., & Corssen, G. (1965). Pharmacologic effects of CI-581, a new dissociative anaesthetic, in man. *Clinical Pharmacology and Therapeutics*, *6*, 279–291.
Dougherty, P., & Palecek, J. (1992). The role of NMDA and non-NMDA excitatory amino acid receptors in the excitation of primate spinothalamic tract neurons by mechanical, chemical, thermal, and electrical stimuli. *The Journal of Neuroscience*, *12*(8), 3025–3041.
Duncan, G., & Miyamoto, S. (2000). Comparison of the effects of clozapine, risperidone, and olanzapine on ketamine-induced alterations in regional brain metabolism. *The Journal of Pharmacology and Experimental Therapeutics*, *293*(1), 8–14.
Dyer, J. E. (1991). Gamma-hydroxybutyrate: A health-food product producing coma and seizure like activity. *The American Journal of Emergency Medicine*, *9*(4), 321–324.
Edwards, G., & Gross, M. M. (1976). Alcohol dependence: Provisional description of a clinical syndrome. *British Medical Journal*, *1*(6017), 1058–1061.
Erowid, E. (2009). *Alexander Shulgin's pharmacology notebooks*. http://www.erowid.org/library/books_online/shulgin_labbooks.
Freudenmann, R. W., Oxler, F., & Bernschneider-Reif, S. (2006). The origin of MDMA (ecstasy) revisited: The true story reconstructed from the original documents. *Addiction*, *101*(9), 1241–1245.
Galicia, M., Nogue, S., & Miró, O. (2011). Liquid ecstasy intoxication: Clinical features of 505 consecutive emergency department patients. *Emergency Medicine Journal: EMJ*, *28*(6), 462–466.
Giannini, A. J., Underwood, N. A., & Condon, M. (2000). Acute ketamine intoxication treated by haloperidol: A preliminary study. *American Journal of Therapeutics*, 7(6), 389–391.
Giraudon, I., & Bello, P.-Y. (2007). Monitoring ecstasy content in France: Results from the National Surveillance System 1999–2004. *Substance Use & Misuse*, *42*(10), 1567–1578.
Gonzalez, A., & Nutt, D. J. (2005). Gamma hydroxy butyrate abuse and dependency. *Journal of Psychopharmacology*, *19*(2), 195–204.
Green, S. M., Clark, R., Hostetler, M. A., Cohen, M., Carlson, D., & Rothrock, S. G. (1999). Inadvertent ketamine overdose in children: Clinical manifestations and outcome. *Annals of Emergency Medicine*, *34*(4 Pt 1), 492–497.
Green, A. R., Mechan, A. O., Elliott, J. M., O'Shea, E., & Colado, M. I. (2003). The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). *Pharmacological Reviews*, *55*(3), 463–508.
Greer, G. (1985). Using MDMA in psychotherapy. *Advances*, *2*, 57–59.
Greer, G., & Tolbert, R. (1986). Subjective reports of the Effects of MDMA in a clinical setting. *Journal of Psychoactive Drugs*, *18*, 319–327.
Hall, A. P., & Henry, J. A. (2006). Acute toxic effects of "Ecstasy" (MDMA) and related compounds: Overview of pathophysiology and clinical management. *British Journal of Anaesthesia*, *96*(6), 678–685.
Hardman, H. F., Haavik, C. O., & Seevers, M. H. (1973). Relationship of the structure of mescaline and seven analogs to toxicity and behaviour in five species of laboratory animals. *Toxicology and Applied Pharmacology*, *25*(2), 299–309.

Hashimoto, K. (2014). Targeting of NMDA receptors in new treatments for schizophrenia. *Expert Opinion on Therapeutic Targets*, *18*, 1049–1063, 1–15.
Hasin, D. S., O'Brien, C. P., Auriacombe, M., Borges, G., Bucholz, K., Budney, A., et al. (2013). DSM-5 criteria for substance use disorders: Recommendations and rationale. *The American Journal of Psychiatry*, *170*(8), 834–851.
Jansen, K. (2001). *Ketamine: Dreams and realities*. Sarasota, FL: Multidisciplinary Association for Psychedelic Studies.
Kalsi, S. S., Wood, D. M., & Dargan, P. I. (2011). The epidemiology and patterns of acute and chronic toxicity associated with recreational ketamine use. *Emerging Health Threats Journal*, *4*, 7107.
Koek, W., Mercer, S. L., Coop, A., & France, C. P. (2009). Behavioural effects of gamma-hydroxybutyrate, its precursor gamma-butyrolactone, and GABA(B) receptor agonists: Time course and differential antagonism by the GABA(B) receptor antagonist 3-aminopropyl(diethoxymethyl)phosphinic acid (CGP35348). *The Journal of Pharmacology and Experimental Therapeutics*, *330*(3), 876–883.
Korf, D. J., Nabben, T., Benschop, A., Ribbink, K., & van Amsterdam, J. G. C. (2014). Risk factors of γ-hydroxybutyrate overdosing. *European Addiction Research*, *20*(2), 66–74.
Laborit, H., Buchard, F., Laborit, G., Kind, A., & Weber, B. (1960). Use of sodium 4-hydroxybutyrate in anesthesia and resuscitation. *Agressologie: Revue Internationale de Physio-Biologie et de Pharmacologie Appliquées aux Effets de L'agression*, *1*, 549–560.
Lahti, A., Weiler, M., & Tamara, M. (2001). Effects of ketamine in normal and schizophrenic volunteers. *Neuropsychopharmacology*, *25*(4), 455–467.
Lankenau, S. E., & Sanders, B. (2007). Patterns of ketamine use among young injection drug users. *Journal of Psychoactive Drugs*, *39*(1), 21–29.
Large, C. H. (2007). Do NMDA receptor antagonist models of schizophrenia predict the clinical efficacy of antipsychotic drugs? *Journal of Psychopharmacology (Oxford, England)*, *21*(3), 283–301.
Leone, M. A., Vigna-Taglianti, F., Avanzi, G., Brambilla, R., & Faggiano, F. (2010). Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses. *The Cochrane Database of Systematic Reviews*.
Malinovsky, J., & Servin, F. (1996). Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. *British Journal of Anaesthesia*, *77*, 203–207.
Maxwell, J. C. (2005). Party drugs: Properties, prevalence, patterns, and problems. *Substance Use & Misuse*, *40*(9–10), 1203–1240.
McCambridge, J., Winstock, A., Hunt, N., & Mitcheson, L. (2007). 5-Year trends in use of hallucinogens and other adjunct drugs among UK dance drug users. *European Addiction Research*, *13*(1), 57–64.
McDonough, M., Kennedy, N., Glasper, A., & Bearn, J. (2004). Clinical features and management of gamma-hydroxybutyrate (GHB) withdrawal: A review. *Drug and Alcohol Dependence*, *75*, 3–9.
Mercer, S. (2008). "The Drug of War"—A historical review of the use of Ketamine in military conflicts. *Journal of the Royal Naval Medical Service*, *95*, 145–150, September 1970.
Miotto, K., Darakjian, J., Basch, J., Murray, S., Zogg, J., & Rawson, R. (2001). Gamma-hydroxybutyric acid: Patterns of use, effects and withdrawal. *The American Journal on Addictions/American Academy of Psychiatrists in Alcoholism and Addictions*, *10*(3), 232–241.
Moore, K., & Miles, S. (2004). Young people, dance and the sub-cultural consumption of drugs. *Addiction Research & Theory*, *12*(6), 507–523.
Morgan, C. J. A., & Curran, H. V. (2006). Acute and chronic effects of ketamine upon human memory: A review. *Psychopharmacology*, *188*(4), 408–424.
Morgan, C. J. A., & Curran, H. V. (2012). Ketamine use: A review. *Addiction*, *107*(1), 27–38.

Morgan, C. J. A., Noronha, L. A., Muetzelfeldt, M., Fielding, A., & Curran, H. V. (2013). Harms and benefits associated with psychoactive drugs: Findings of an international survey of active drug users. *Journal of Psychopharmacology (Oxford, England)*, *27*(6), 497–506.

Nutt, D., King, L. A., Saulsbury, W., & Blakemore, C. (2007). Development of a rational scale to assess the harm of drugs of potential misuse. *Lancet*, *369*(9566), 1047–1053.

Oser, C., & Havens, J. (2008). HIV sexual risk behaviours among ketamine and non-ketamine using criminal offenders prior to prison entry. *Addiction Research & Theory*, *16*(3), 289–302.

Pai, A., & Heining, M. (2007). Ketamine. *Continuing Education in Anaesthesia, Critical Care & Pain*, *7*(2), 59–63.

Palamar, J. J., & Halkitis, P. N. (2006). A qualitative analysis of GHB use among gay men: Reasons for use despite potential adverse outcomes. *The International Journal on Drug Policy*, *17*(1), 23–28.

Parrott, A. C. (2002). Recreational Ecstasy/MDMA, the serotonin syndrome, and serotonergic neurotoxicity. *Pharmacology, Biochemistry, and Behavior*, *71*(4), 837–844.

Parrott, A. C. (2013). Human psychobiology of MDMA or "Ecstasy": An overview of 25 years of empirical research. *Human Psychopharmacology*, *28*(4), 289–307.

Parviza, M., Vogelb, K., Gibsonb, K. M., & Pearl, P. L. (2014). Disorders of GABA metabolism: SSADH and GABA-transaminase deficiencies. *Journal of Pediatric Epilepsy*, *3*(4), 217–227.

Pomarol-Clotet, E., Honey, G. D., Murray, G. K., Corlett, P. R., Absalom, A. R., Lee, M., et al. (2006). Psychological effects of ketamine in healthy volunteers. Phenomenological study. *The British Journal of Psychiatry: The Journal of Mental Science*, *189*, 173–179.

Ross, S. (2008). Ketamine and addiction. *Primary Psychiatry*, *15*, 61–69.

Rugani, F., Bacciardi, S., Rovai, L., Pacini, M., Maremmani, A. G. I., Deltito, J., et al. (2012). Symptomatological features of patients with and without Ecstasy use during their first psychotic episode. *International Journal of Environmental Research and Public Health*, *9*(7), 2283–2292.

Ryan, J. M., & Stell, I. (1997). Gamma hydroxybutyrate—A coma inducing recreational drug. *Journal of Accident & Emergency Medicine*, *14*(4), 259–261.

Saunders, N. (1993). *E for Ecstasy*. London: W.B. Saunders.

Schep, L. J., Knudsen, K., Slaughter, R. J., Vale, J. A., & Mégarbane, B. (2012). The clinical toxicology of γ-hydroxybutyrate, γ-butyrolactone and 1,4-butanediol. *Clinical Toxicology (Philadelphia, Pa.)*, *50*(6), 458–470.

Schifano, F. (2004). A bitter pill. Overview of ecstasy (MDMA, MDA) related fatalities. *Psychopharmacology*, *173*(3–4), 242–248.

Schifano, F., Corkery, J., Oyefeso, A., Tonia, T., & Ghodse, A. H. (2008). Trapped in the "K-hole": Overview of deaths associated with ketamine misuse in the UK (1993–2006). *Journal of Clinical Psychopharmacology*, *28*(1), 114–116.

Sewell, R. (2007). Ketamine: Peril and promise. *MAPS Bulletin*, *17*(1), 23–27.

Shulgin, A. T. (1986). The background and chemistry of MDMA. *Journal of Psychoactive Drugs*, *18*(4), 291–304.

Shulgin, A. (1989). History of MDMA. In S. Peroutka (Ed.), *Ecstasy: The clinical, pharmacological and neurotoxicological effects of the drug MDMA* (pp. 1–20). Boston: Kluwer, Springer Science & Business Media (p. 244).

Shulgin, A., & Nichols, D. (1978). Characterization of three new psychotomimetics. In R. C. Stillman, & R. E. Willette (Eds.), *The psychopharmacology of hallucinogens* (pp. 1–9). New York: Pergamon Press.

Sigtermans, M. J., van Hilten, J. J., Bauer, M. C. R., Arbous, M. S., Marinus, J., Sarton, E. Y., et al. (2009). Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. *Pain*, *145*(3), 304–311.

Steele, M. T., & Watson, W. A. (1995). Acute poisoning from gamma hydroxybutyrate (GHB). *Missouri Medicine*, *92*(7), 354–357.
Tanner-Smith, E. E. (2006). Pharmacological content of tablets sold as "ecstasy": Results from an online testing service. *Drug and Alcohol Dependence*, *83*(3), 247–254.
Teltzrow, R., & Bosch, O. (2012). Ecstatic anaesthesia: Ketamine and GHB between medical use and self-experimentation. *Applied Cardiopulmonary Pathophysiology*, *16*, 309–321.
Torre, R. D. la, & Farré, M. (2004). Human pharmacology of MDMA: Pharmacokinetics, metabolism, and disposition. *Therapeutic Drug Monitoring*, *26*(2), 137–144.
Trujillo, K. A., Smith, M. L., Sullivan, B., Heller, C. Y., Garcia, C., & Bates, M. (2011). The neurobehavioral pharmacology of ketamine: Implications for drug abuse, addiction, and psychiatric disorders. *ILAR Journal/National Research Council, Institute of Laboratory Animal Resources*, *52*, 366–378.
Van Amsterdam, J. G. C., Brunt, T. M., McMaster, M. T. B., Niesink, R., van Noorden, M. S., & van den Brink, W. (2012). Cognitive impairment due to intensive use and overdoses of gammahydroxybutyric acid (GHB). *Tijdschrift voor Psychiatrie*, *54*(12), 1001–1010.
Van Cauter, E., Plat, L., Scharf, M. B., Leproult, R., Cespedes, S., L'Hermite-Balériaux, M., et al. (1997). Simultaneous stimulation of slow-wave sleep and growth hormone secretion by gamma-hydroxybutyrate in normal young Men. *The Journal of Clinical Investigation*, *100*(3), 745–753.
Verrico, C. D., Miller, G. M., & Madras, B. K. (2007). MDMA (Ecstasy) and human dopamine, norepinephrine, and serotonin transporters: Implications for MDMA-induced neurotoxicity and treatment. *Psychopharmacology*, *189*(4), 489–503.
WHO (1964). *WHO expert committee on addiction-producing drugs: Thirteenth report*.
WHO (2006). *Critical review of ketamine*. (September 2002, pp. 1–30).
WHO (2012). *Gamma-hydroxybutyric acid (GHB) critical review report* (June, pp. 4–8).
Wieber, J., Gugler, R., Hengstmann, J. H., & Dengler, H. J. (1975). Pharmacokinetics of ketamine in man. *Der Anaesthesist*, *24*(6), 260–263.
Wolff, K., Hay, A. M., Sherlock, K., & Conner, M. (1995). Contents of "ecstasy" *The Lancet*, *346*(8982), 1100–1101.
Wong, C. G. T., Gibson, K. M., & Snead, O. C. (2004). From the street to the brain: Neurobiology of the recreational drug γ-hydroxybutyric acid. *Trends in Pharmacological Sciences*, *25*(1), 29–34.
Wood, D., & Beaumont, P. (2010). Recreational drug use presentations during a large outdoor festival event: Reduction in hospital emergency department transfer where medical physicians are present. *Journal of Substance Use*, *15*(6), 434–441.
Wood, D. M., Brailsford, A. D., & Dargan, P. I. (2011). Acute toxicity and withdrawal syndromes related to γ-hydroxybutyrate (GHB) and its analogues γ-butyrolactone (GBL) and 1,4-butanediol (1,4-BD). *Drug Testing and Analysis*, *3*(7–8), 417–425.
Wood, D., Nicolaou, M., & Dargan, P. (2009). Epidemiology of recreational drug toxicity in a nightclub environment. *Substance Use & Misuse*, *44*(11), 1495–1502.
World drug report. (1997). *Trends in Organized Crime*, *3*, 11–14.
Zarate, C. A., Singh, J. B., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A., et al. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of General Psychiatry*, *63*(8), 856–864.