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GHB: a new and novel drug of abuse

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Abstract

There has been increasing attention in the United States to problems of abuse of *gamma*-hydroxybutyrate (GHB), with some evidence for problems in other parts of the world as well. In vitro and animal research show that, while GHB shares some properties with abused central nervous system depressant drugs, it has unique aspects of its pharmacology as well, including actions at a specific neural receptor which probably mediates many of its effects. Abuse potential assessment of GHB using standard animal models has not yielded a picture of a highly abusable substance, but little human testing has yet been done. Very little systematic data exist on tolerance and dependence with GHB, but both have been seen in human users. Quantitative data on the prevalence of GHB abuse is incomplete, but various qualitative measures indicate that a mini-epidemic of abuse began in the late 1980s and continues to the present. GHB is often included with the group of 'club drugs', and can be used as an intoxicant. It also has been used as a growth promoter and sleep aid and has been implicated in cases of 'date rape', usually in combination with alcohol. Undoubtedly the easy availability of GHB and some of its precursors has contributed to its popularity. Recent changes in the control status of GHB in the US may reduce its availability with as yet unknown consequences for the scope of the public health problem. Drug abuse experts need to familiarize themselves with GHB as possibly representing a new type of drug abuse problem with some unique properties.

Keywords: *Gamma*-hydroxybutyrate; GHB, abuse potential, pharmacology; Patterns of use and abuse; Epidemiology; Review

1. Introduction

Gamma-Hydroxybutyrate (sodium hydroxybutyrate; sodium oxybutyrate; GHB) is a naturally occurring, short-chained fatty acid found in mammalian tissue (Bessman and Fishbein, 1963; Roth and Giarman, 1970). It was initially isolated and investigated by Laborit in 1960 in an effort to develop a *gamma*-aminobutyric acid (GABA) congener which would readily cross the blood brain barrier (Fig. 1). Early testing demonstrated that GHB could produce a dose-dependent sedation and anesthesia in laboratory animals and humans (Laborit et al., 1960; Laborit, 1964). GHB's action as a CNS depressant was in some ways similar to those of classical sedative/hypnotics such as barbiturates and benzodiazepines. Because of the behavioral effects of exogenously administered GHB, coupled with its chemical similarity to and metabolic relationship with GABA, GHB was initially classified with and often compared to GABAergic compounds (Anden and Stock, 1973; Roth and Nowycky, 1977). While GHB does share some cellular and behavioral effects with classical sedative/hypnotics, many now consider GHB to represent a unique pharmacological entity, which is believed to function as a distinct neurotransmitter or neuromodulator (Vayer et al., 1987; Tunnicliff, 1992; Feigenbaum and Howard, 1996a; Maitre, 1997; Bernasconi et al., 1999).

GHB has a 30-year history of use in medicine, particularly in Europe, and it was also available for many years in the US as a consumer product sold as a dietary supplement. Until the early 1990's, GHB had received only modest attention from medical scientists and little concern from public health officials. There have been several developments over the past 10 years in the US which have changed this situation (Luby et al., 1992; Hernandez et al., 1998). Increasing consumer use of GHB as a growth promoter and mild sedative has generated concerns about its safety and effectiveness for these uses without medical supervision. As word of its

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intoxicating effects become more widely known, GHB came to be touted as a new recreational 'club drug' with increasing attention being paid to it in nearly all media, particularly the Internet. Over this same period, reports began to emerge that GHB had been used, often in combination with alcohol, to render women more vulnerable to sexual assault. This served to further heighten public attention to its availability and use. All of this led the US Food and Drug Administration (FDA) in 1990 to declare GHB-containing products as unsafe and ban public sale (Food and Drug Administration, 1991; Center for Disease Control, 1991). This was not entirely effective as Internet sites and certain stores continued to sell GHB which had become known by street names such as liquid X, liquid ecstasy, GBH-grievous bodily harm, scoop, cherry meth, soap, salty water, organic quaalude and growth hormone booster. One method to circumvent the prohibition on the sale of GHB was through the sale of 'chemistry kits' containing precursors of GHB, *gamma*-butyrolactone (GBL) or 1,4-butanediol, along with instructions on how to convert them to GHB. This has led to increased availability of liquid formulations of GHB for street purchase.

As this is written, there is an active public debate in the US about the abuse liability and dangers of GHB, and it can be expected that this will emerge as a worldwide issue in the near future. This discussion is occurring at the same time that GHB is being developed with the trade name Xyrem® as a new medical treatment for narcolepsy under the FDA's Orphan Drug Program. The challenge has been to formulate a public health response to the GHB abuse problem that is proportional to its risks and that minimally interferes with its legitimate uses and those of its precursors. Since GHB represents a new drug of abuse unfamiliar even to many experts in the field, and because additional research is needed to more fully understand the properties of this compound, we have undertaken this review of its neurobehavioral pharmacology and its effects in humans.

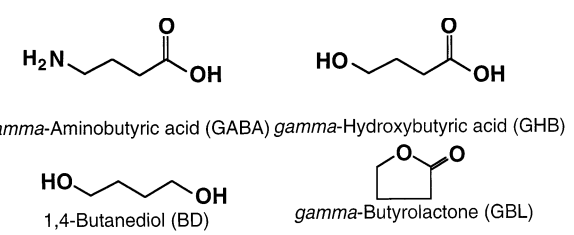

Fig. 1. Shown are the structures of the neurotransmitter *gamma*-aminobutyric acid, *gamma*-hydroxybutyrate and its structurally related precursors *gamma*-butyrolactone and 1,4-butanediol.

2. Biological activity of GHB

2.1. Physiological role of GHB

A variety of findings suggest that GHB functions as a neurotransmitter or neuromodulator. GHB is heterogeneously distributed in the CNS with levels highest in the hippocampus, basal ganglia, hypothalamus and substantia nigra (Vayer and Maitre, 1988; Mamelak, 1989; Maitre, 1997) with systems present for synthesis and vesicular uptake and storage in synaptic terminals (for review see Maitre, 1997). The primary source of GHB in the brain is believed to be metabolism of GABA, which is first deaminated to succinic semialdehyde (SSA) by GABA aminotransferase. The majority of the SSA produced is converted to succinate and incorporated into the Kreb's cycle. However, a small portion, less than 2%, is converted by a specific neuronal cytosolic enzyme, SSA reductase (EC 1.1.1.1.2), to GHB (Gold and Roth, 1977; Cash et al., 1981; Bernasconi et al., 1999). Some investigations suggest that there are alternative sources of GHB, which may play a very significant role in GHB production (Snead et al., 1982; Feigenbaum and Howard, 1996a), especially in the periphery, since GHB levels there are so high yet peripheral levels of GABA are very low to absent. 1,4-Butanediol, a naturally occurring aliphatic alcohol, has been demonstrated to serve as a source of GHB (Poldrugo and Snead, 1984) and GBL, a naturally occurring lactone precursor, is readily and irreversibly metabolized to GHB by peripheral lactonases (Roth and Giarman, 1968, 1970). Both 1,4-butanediol and GBL are present in rat brain at levels 1/10 those of GHB (Maitre, 1997).

Many pharmacological studies have used GBL administration instead of GHB since GBL is more readily absorbed. The behavioral and physiological effects of GHB and GBL are generally assumed to be equivalent. However, some studies suggest that differences do exist in both the neurochemical (Sethy et al., 1976; Ladinsky et al., 1983) and behavioral (Ban et al., 1967; Winter, 1981) effects of these two compounds. Perhaps most importantly, GBL has negligible affinity for the GHB receptor (Maitre et al., 1990). The significance of these findings is uncertain, but they should be taken into consideration when evaluating the numerous animal studies to be reviewed below which used GBL instead of GHB administration.

GHB has been shown to be released in a Ca^{++} dependent manner following depolarization of neurons (Maitre et al., 1983; Vayer and Maitre, 1988). Subsequent to neuronal release, GHB binds reversibly to specific GHB receptors. The highest levels of receptors are present in the hippocampus and the lowest in the cerebellum (Benavides et al., 1982a; Snead and Liu, 1984; Hechler et al., 1987). Despite high levels of GHB

in peripheral tissue, GHB receptors appear to be completely absent outside the CNS. GHB has been shown to bind to these neuronal receptors, now reported to be G-protein receptor coupled (Ratomponirina et al., 1995), with evidence for both high ($k_i = 95$ nM) and low ($k_i = 16$ μM) affinity sites, suggesting the presence of two different receptor populations. Neither GABA nor GBL demonstrate appreciable affinity for the GHB receptor nor is there evidence of significant overlap in the regional distributions of GABA and GHB receptors in the brain other than in layers I-III of the cerebral cortex (Benavides et al., 1982a; Hechler et al., 1987). Thus far, the only other compounds demonstrating binding activity at GHB receptors are GHB analogs, the selective antagonist NCS-382 (6,7,8,9-tetrahydro-5-[H]benzocycloheptene-5-ol-4-ylidene acetic acid) and several benzamide neuroleptics (Maitre et al., 1990; Hechler et al., 1993; Maitre et al., 1994). The isolation of the GHB-specific antagonist has provided further evidence of GHB's classification as a unique pharmacological entity. NCS-382 displaces GHB binding and dose-dependently reverses the in vitro and in vivo effects of GHB, including catalepsy, sedation, opioid release and dopamine accumulation (Maitre et al., 1990; Hechler et al., 1991; Schmidt et al., 1991). In addition, analysis of GHB analogs demonstrates a correlation between GHB receptor affinity and their potency to alter dopaminergic transmission which is produced following GHB receptor activation (Hechler et al., 1993).

While GABA fails to bind to GHB receptors, GHB can bind to $GABA_B$ receptors, but with an affinity ($k_i = 80–120$ μM) sufficiently low that endogenous levels are most likely irrelevant (Bernasconi et al., 1992, 1999). It has been suggested that some of the actions of exogenously administered GHB, such as absence seizure-like effects in rodents, may be partially related to weak $GABA_B$ agonist activity because some GHB effects can be antagonized by $GABA_B$ antagonists and mimicked by the $GABA_B$ agonist baclofen (Engberg and Nissbrandt, 1993; Nissbrandt and Engberg, 1996; Erhardt et al., 1998).

Following release, GHB activity is terminated by active uptake from the synaptic cleft. This cellular uptake is by means of a high affinity, energy/Na^+-dependent mechanism specific for GHB and its analogs (Benavides et al., 1982b; Hechler et al., 1985). Once within the cell, the cytosolic enzyme, GHB dehydrogenase (EC 1.1.1.19), catalyzes the conversion of GHB into SSA which then is further metabolized primarily to succinate as well as GABA (Doherty et al., 1975; Mohler et al., 1976; Kaufman and Nelson, 1991). The succinate is further degraded to CO_2 and H_2O. These reactions proceed rapidly resulting in a half life of 30–50 min for GHB in the body with clearance in the CNS proceeding even more rapidly (Doherty et al., 1975; Palatini et al., 1993; Scharf et al., 1998). An important point when considering the half-life of GHB is that it demonstrates nonlinear kinetics of elimination due to saturability of the elimination pathway (Ferrara et al., 1992; Palatini et al., 1993). Because of this, the half-life becomes dose-dependent, similar to ethanol and salicyclic acid, and could be expected to be appreciably longer in cases of overdose.

2.2. Neurochemical effects of GHB

Endogenous GHB release and exogenous administration act both pre- and post-synaptically to diminish CNS activity levels (Xie and Smart, 1992). Initially, activation of GHB receptors results in alterations in second messenger systems, elevating cGMP levels and stimulating inositol phosphate turnover in the hippocampus (Vayer and Maitre, 1989). Subsequently, GHB receptor activation results in modulation of the activity of various other neurotransmitter systems.

One of the primary effects of GHB appears to be modulation of dopaminergic neurotransmission. GHB and its analogs have been shown to increase brain dopamine levels (Hechler et al., 1993). This is believed to occur secondary to an inhibition of dopamine neuron firing in the substantia nigra and mesolimbic regions resulting in an accumulation of dopamine in the presynaptic cells (Roth et al., 1980; Hechler et al., 1991; Howard and Feigenbaum, 1997). Because dopamine autoreceptors are also indirectly inhibited, there is stimulation of tyrosine hydroxylase activity resulting in an increase in dopamine production (Walter and Roth, 1972; Morgenroth et al., 1976). This attenuation of dopamine neurotransmission may underlie the production of certain GHB-associated behavioral effects in animals, such as immobility and catalepsy, similar to those produced by antipsychotic compounds (Hechler et al., 1993; Feigenbaum and Howard, 1996b). Also consistent with reduced dopaminergic neurotransmission are results from studies that show dopamine agonists antagonizing some in vivo effects of GHB (Menon et al., 1973; Dudek and Fanelli, 1980; Feigenbaum and Howard, 1996b). While diminished dopaminergic activity is the primary response reported following GHB exposure, some studies suggest that dose and time can influence the ultimate response. For instance, it has been reported that, after an initial decrement in dopamine release, a second phase of GHB modulation occurs in which there is enhanced release of dopamine in the striatum and corticolimbic structures (Hechler et al., 1991; Nissbrandt et al., 1994; Maitre, 1997). This enhancement of dopaminergic activity might play a role in GHB's reported euphoric effects and abuse potential as well as in its ability to alleviate withdrawal from and craving for other drugs. However, concerns have been raised regarding the effect of anesthetics and other

experimental parameters in these studies which can cause dopamine release independent of GHB. At this time it is unclear whether GHB's biphasic effect on dopamine release represents a valid response or an artifact associated with the experimental procedure (Feigenbaum and Howard, 1996b).

In addition to GHB's interaction with $GABA_B$ receptors discussed previously, evidence of interplay between the GHB and GABA systems can be seen in GHB modulation of GABA concentrations. GHB has been shown to inhibit GABA release in the thalamus (Banerjee and Snead, 1995). Similarly, Gobaille et al. (1999) found that low dose administration of GHB resulted in a decrease in extracellular GABA levels in the frontal cortex, although higher doses of GHB enhanced GABA levels in this area. GHB can also influence GABA neurotransmission by serving as a precursor for GABA. This modulatory action on the GABA system may mediate GHB's anxiolytic actions, particularly since these effects have been shown to be antagonized by flumazenil (Schmidt-Mutter et al., 1998).

GHB has been shown to affect serotonin systems by increasing turnover rates without altering absolute serotonin levels (Waldmeier and Fehr, 1978; Hedner and Lundborg, 1983). While the precise mechanism for this effect is unclear, it is most likely due to elevated tryptophan levels (Maitre, 1997). Some studies suggest that the increase in serotonin turnover may be an effect of only high GHB doses and mediated by the $GABA_B$ receptor, either through direct stimulation or increased metabolism to GABA, since baclofen has also been shown to alter serotonin turnover (Waldmeier and Fehr, 1978). However, because baclofen and GHB show different regional distributions of serotonin modulation and because nonmetabolisable GHB analogs cause GHB-like serotonergic effects, a unique mechanism probably exists for GHB's effects (Waldmeier and Fehr, 1978; Maitre, 1997). GHB is also purported to produce increases in brain acetylcholine levels due to decreased firing of cholinergic neurons (Giarman and Schmidt, 1963). While this has been demonstrated with GBL, it has not been reliably demonstrated with GHB itself (Sethy et al., 1976; Ladinsky et al., 1983).

Interestingly, some of the neurochemical and behavioral actions of GHB, including changes in dopamine neuron firing and catalepsy, have been shown to be attenuated or eliminated by administration of the opioid antagonists, naloxone and naltrexone (Snead and Bearden, 1980; Feigenbaum and Howard, 1997). This occurs despite GHB having no affinity for opioid receptors (Feigenbaum and Simantov, 1996) and naloxone having no affinity for the GHB receptor (Maitre et al., 1990). GHB has been shown in vitro and through in vivo microdialysis to stimulate an increase in release of various endogenous opioids in different brain regions (Lason et al., 1983; Hechler et al., 1991; Gobaille et al., 1994). It has been proposed that it is through modulation of opioid interneuron activity that dopamine neuron firing is inhibited (Snead and Bearden, 1980, 1982) thus explaining opioid antagonists' reversal of GHB's effects on dopamine levels. However, some studies argue against a central role for opioid modulation in GHB-induced effects because naloxone antagonism of GHB effects and dopaminergic changes are not entirely consistent (Devoto et al., 1994). As with GHB, the sedative effects of GABAergic sedative/hypnotics, including barbiturates, benzodiazepines and ethanol, can also be attenuated by naloxone under some conditions, but only at doses sufficiently high to suggest a nonopioid receptor mechanism (Dingledine et al., 1978; Ho and Ho, 1979).

3. Preclinical pharmacology and abuse potential studies

3.1. In vivo depressant effects of GHB

GHB possesses sedative and, at sufficiently high doses, anesthetic properties. However, clear differences can be found in the profile of depressant effects produced by GHB versus those produced by barbiturates and benzodiazepines. In some laboratory animals (rodents, cats and monkeys), primarily at higher doses, GHB produces EEG changes reminiscent of epileptiform patterns (Winters and Spooner, 1965; Godschalk et al., 1977; Snead, 1978) supporting the idea that GHB actually induces a cataleptic state rather than a true sedation (Godschalk et al., 1977). In fact, many believed that the nonresponsive state induced by GHB was more reflective of a petit mal absence seizure than sedation/anesthesia. This was further supported by the ability of the anti-petit mal drugs valproate and ethosuximide to block these characteristic EEG changes (Godschalk et al., 1976). At sufficiently high doses, GHB produces CNS excitation and hypersynchronous firing, and myoclonic jerks and clonic seizures can be elicited (Drakontides et al., 1962; Ban et al., 1967; Snead et al., 1976). In a study by Winters and Kott (1979) comparing the characteristics of the sedation and/or anesthesia produced by diazepam, pentobarbital and GHB, it was demonstrated that there are significant differences in the dose-dependent changes in the CNS states produced by the different compounds. GHB sedation possessed distinct excitatory properties, in some ways more suggestive of the ketamine-induced dissociative state, whereas increasing doses of diazepam and pentobarbital, after a brief initial excitation stage, produced a progressive depression of CNS activity. Further evaluation of GHB's EEG effects in different species (rabbits and humans) and at lower doses (cats), however, has shown the EEG pattern produced to be most consistent with physiological sleep (Vickers, 1969;

Mamelak et al., 1977; Godbout and Pivik, 1982). In addition, testing of GHB in monkeys showed that, despite production of what appeared to be epileptiform EEG changes, the sedation produced by GHB was not consistent with absence seizures (Nakamura et al., 1987). In humans, GHB has been shown to increase slow wave sleep, stages 3 and 4, and increase and consolidate REM episodes (Laborit, 1973; Mamelak et al., 1977). This is unlike other hypnotics, such as benzodiazepines and ethanol, which typically interfere with the stages of the sleep cycle and diminish REM sleep resulting in less restful and beneficial sleep patterns. The effect of GHB to normalize sleep is the basis for its development as a treatment for narcolepsy.

Similar to GABAergic depressant drugs, GHB and GBL have been shown to possess anxiolytic effects in various animal models, although less consistently than with benzodiazepines. For example, GBL altered the timid behavior exhibited by isolation-reared mice (Krsiak et al., 1974). GHB was shown to increase open arm entries and the time rats spent in the open arms of a radial arm or plus maze at doses which did not produce sedative effects or decrease total arm entries (Agabio et al., 1998; Schmidt-Mutter et al., 1998). McIntire and colleagues (1988) evaluated the effects of GBL on punished and unpunished responding in rats and found that it produced increased responding during punished components of the sessions. In other studies, however, increases in punished responding were not observed. For example, GBL did not increase responding under a Geller-Seifter procedure as did chlordiazepoxide and other benzodiazepines (Iversen, 1980; McIntire et al., 1988). At this time, insufficient testing has been done to conclude whether these drugs can produce robust anxiolytic effects like those of classical CNS depressants.

3.2. Drug discrimination studies

Drug discrimination studies have been shown to be useful animal models for evaluation of similarities and differences in the acute behavioral effects of drugs and are considered to be predictive of subjective effects in humans (Brady and Fischman, 1985; Schuster and Johanson, 1988; Balster, 1991b). When the discriminative stimulus effects of drugs are compared, classifications based on the results can be predictive of commonalities in cellular sites of action. In addition, drug discrimination studies in animals can be useful for abuse potential assessment (Schuster and Johanson, 1988; Holtzman, 1990; Balster, 1991a). If GHB can be shown to share discriminative stimulus properties with other abused drugs, this would support the prediction that it would have abuse liability similar to that of the reference drugs. Of particular interest are drug discrimination studies that compare GHB and GBL to abused depressant drugs such as ethanol and barbiturates.

Winter (1981) trained rats to discriminate GHB (200 mg/kg, i.p.) from saline and tested compounds from many different drug classes for their ability to substitute for GHB. None of the drugs tested fully substituted for GHB. Morphine, LSD, chlordiazepoxide and direct GABA agonists produced, at best, partial substitution; *d*-amphetamine and ethanol produced a very low partial substitution and barbital and PCP-like compounds failed to support GHB-lever responding at any dose tested. Evidence of some overlap between the discriminative stimulus effects of $GABA_B$ agonists and GHB was seen in rats trained to discriminate either a high (700mg/kg, i.g.) or low (300 mg/kg, i.g.) dose of GHB from saline (Lobina et al., 1999). Baclofen fully substituted in both groups but was more potent in producing GHB-like effects in the high-dose group. The $GABA_B$ antagonist, CGP 35348, partially blocked GHB discrimination for the low-dose group and fully for the high-dose group. These results are consistent with GHB binding to $GABA_B$ receptors with low affinity. These data would support the conclusion that, at low doses, GHB's discriminative stimulus effects would be mediated primarily by activity at the GHB receptor, whereas at higher doses, $GABA_B$ receptor occupation and activation plays a more important role. In these same rats, the $GABA_A$ agonist diazepam produced partial substitution in the low-dose group while the NMDA antagonist dizocilpine and the cannabinoid WIN 55,212-2 both failed to produce any substitution for GHB in either training group.

GHB has also been tested in rats trained in drug discrimination procedures with other drugs. Testing of GHB in both heroin- and phencyclidine-trained rats failed to demonstrate any substitution with GHB (Beardsley et al., 1996). Colombo et al. (1995c) compared the discriminative stimulus effects of ethanol and GHB. They found cross generalization could be produced between the two drugs but only over a very narrow range of doses. One intermediate dose of GHB (300 mg/kg, i.g.) fully substituted in low-dose (1000 mg/kg, i.g.) ethanol-trained rats while in high-dose (2000 mg/kg, i.g.) ethanol-trained rats, GHB produced little if any drug lever responding at any dose. Reciprocal testing of ethanol in GHB-trained (300 mg/kg, i.g.) rats also produced full substitution at one dose (1000 mg/kg, i.g.), with higher and lower doses of ethanol producing primarily saline-lever responding. However, Metcalf et al. (1999) were unable to replicate this finding, with at most partial substitution being produced by GHB and ethanol in ethanol- and GHB-trained rats, respectively, results similar to those of Winter (1981). The results to date in rats suggest that GHB administration produces unique discriminative stimulus effects with some characteristics most similar to those of ethanol and some GABAmimetic drugs with different cross substitution patterns occurring at different doses of GHB.

The discriminative stimulus effects of GHB have also been examined in nonhuman primates. Rhesus monkeys were trained to discriminate either oral *d*-amphetamine or pentobarbital (Woolverton et al., 1999). GHB tests were conducted using the same route at doses of 1.0 mg/kg up 170 mg/kg. In *d*-amphetamine-trained monkeys, GHB produced a maximum mean of 50% drug lever responding. This partial substitution for *d*-amphetamine was not dose-related, with low or intermediate doses producing maximum levels of substitution. GHB completely failed to substitute for pentobarbital, producing no pentobarbital-lever responding in any subject at any dose. The discriminative stimulus effects of GHB were also compared to those of triazolam and flumazenil in rhesus monkeys with all drugs being administered subcutaneously (Woolverton et al., 1999). Only one of the three monkeys showed any evidence for triazolam-like effects of GHB and the effect was not clearly dose-related. For the flumazenil discrimination study, monkeys were given daily oral doses of diazepam resulting in diazepam dependence. Thus, flumazenil injections would precipitate a mild withdrawal that was discriminated from saline. GHB did not substitute for flumazenil helping to rule out the possibility that GHB is a GABA antagonist.

As a means of determining possible cellular mechanisms for GHB's discriminative stimulus effects, various receptor antagonists have been tested in combination with GHB or GBL. In GBL-trained rats, naloxone failed to antagonize GBL and *d*-amphetamine only partially attenuated its discriminative stimulus effects (McIntire et al., 1988) despite the ability of these drugs to counteract other in vivo GBL/GHB effects (Snead and Bearden, 1980; Hechler et al., 1993; Feigenbaum and Howard, 1997). In GHB-trained rats, the $GABA_B$ antagonist bicuculline partially attenuated GHB's effects while the antagonists pizotyline (serotonin), phentolamine (α-adrenergic) and butaclamol (dopamine) had no effect (Winter, 1981). In a related study (Beardsley et al., 1996), GHB administration failed to antagonize the discriminative stimulus effects of cocaine. Evidence that the discriminative stimulus effects of GHB are mediated by GHB receptors is provided by a study by Colombo et al. (1995b) in which NCS-382 dose-dependently antagonized the discriminative stimulus effects of GHB.

3.3. Drug self-administration and related studies

The behavioral effects of GHB have also been examined in animal models predictive of the reinforcing properties of drugs. Conditioned place preference (CPP) relies on the pairing of drug administration with a specific environment, and subsequently testing for preference for that environment over one paired with the nondrug condition. In a study by Martellotta et al. (1997), GHB was shown to induce a CPP. Under similar testing conditions, other sedative hypnotics, such as diazepam, have also been shown to induce CPP (for review see Schechter and Calcagnetti, 1993). Typically, drugs with known strong reinforcing effects, such as cocaine and opiates, will produce a CPP after only 2–3 drug exposures (Blander et al., 1984; Nomikos and Spyraki, 1988). In the study with GHB, a minimum of six drug exposures were required to produce a CPP, suggesting a weaker effect compared to highly abused drugs like cocaine.

The reinforcing effects of GHB have been directly examined in self-administration studies. The results of drug self-administration studies have demonstrated a good correlation between drugs self-administered by laboratory animals and those abused by humans and includes heroin, morphine, cocaine, amphetamine, PCP, ethanol, barbiturates and benzodiazepines (Brady et al., 1975; Johanson and Balster, 1978; Griffiths et al., 1979; Balster, 1991a). A series of studies has been done in which different strains of rats were shown to drink GHB solutions. This occurred more readily in rats selectively bred to self-administer alcohol (Colombo et al., 1995a, 1998). In this series of studies, rats were given forced exposure to GHB (1% w/v) for a period of two weeks and then given a two-bottle choice between 1% (w/v) GHB and water. The rats alternately drank higher amounts of GHB than water and then higher amounts of water than GHB on a 1- to 2-day cycle. When only three days of forced exposure were followed by free choice, only the alcohol-preferring strain of rats eventually showed the previous pattern of consumption (Colombo et al., 1998). It is possible that this pattern of results could indicate periods of GHB-reinforced drinking, but it is not clear what the results would be if there were no preference between the two solutions. Although bottles were swapped to prevent position maintained behavior, the degree of correlation between bottle position and solution preference would need to be examined to determine if it contributed to the alternating pattern of GHB and water consumption. On the other hand, doses in the range of 500–750 mg/kg/day were obtained, generally consumed in binges of 100–300 mg/kg. These doses are within the low to middle range of doses shown to be pharmacologically relevant in drug discrimination studies. Thus, this alternate day self-administration may be due to true reinforcing effects of GHB. That self-administration is not maintained over more than one to two days may be due to accumulation of drug and/or metabolites; however, nothing known about the metabolism of GHB supports either of these possibilities (Lettieri and Fung, 1979). It is also possible that the GHB drinking which occurred was not due to centrally-mediated reinforcing effects. GHB solutions have a salty taste which may have influenced GHB's ability to maintain behavior. Indeed,

Colombo et al. (1998) demonstrated that both alcohol-preferring and nonpreferring rats would self-administer saline solutions in a two-choice procedure with water in volumes equal to those of the GHB solution on GHB-preferring days. Because of these uncertainties about the interpretation of these drinking studies, it is difficult to unambiguously conclude that they provide evidence for reinforcing effects of GHB mediated by CNS effects.

There has been a report of i.v. self-administration of GHB in mice (Martellotta et al., 1998b). In this study, drug-naive mice were temporarily catheterized and able to receive i.v. infusions of vehicle or GHB in response to nose-pokes. The number of nose-pokes by actively self-administering mice increased significantly relative to a yoked control group which passively received the drug solution. GHB-reinforced responding was dose-dependent and could be prevented by preadministration of the GHB receptor antagonist NCS-382, resulting in levels of nose-pokes similar to those for vehicle. The doses, which supported self-administration were unexpectedly low when compared to i.v. self-administration studies in nonhuman primates and other behavioral tests in rodents. Unfortunately, no data were provided detailing the number of infusions received or the total dose of drug received to assure that the effects obtained were centrally mediated.

Further evaluation of GHB's reinforcing effects has been made in several i.v. self-administration studies in rhesus monkeys using a substitution procedure widely used for abuse potential assessment (Johanson and Balster 1978; Balster, 1991a). In one study, monkeys experienced in PCP self-administration were tested with a wide range of doses of GHB (Beardsley et al., 1996). The results were negative. In only one of 18 substitution tests was the rate of GHB self-infusion greater than for vehicle, and even in this case the rate of responding was very much lower than was obtained with PCP. Behaviorally relevant doses of GHB were tested since some observable sedation was seen in the monkeys. A second self-administration study was performed in rhesus monkeys trained to lever-press to obtain i.v. infusions of methohexital (Woolverton et al., 1999). The number of infusions of various doses of GHB that were self-administered was approximately the same as the number of infusions of saline and considerably less than the number of infusions of methohexital. In only two tests did the rates of GHB self-administration exceed those for saline. Even then, the infusion rates were quite low and did not approach those seen with methohexital. The authors of both primate studies concluded that GHB was, at most, only a weak positive reinforcer.

GHB has also been examined for its ability to attenuate self-administration of other drugs of abuse. Non-hypnotic doses of GHB and/or GBL have been observed to reduce ethanol intake in rats and humans as well as decrease cocaine self-administration in rats (Fadda et al., 1983; Biggio et al., 1992; Gallimberti et al., 1992; Addolorato et al., 1996; Agabio et al., 1998; Martellotta et al., 1998a). In humans, this effect was associated with a decrease in craving (Biggio et al., 1992; Gallimberti et al., 1992; DiBello et al., 1995). Various explanations have been advanced for these potentially therapeutic effects of GHB. One is that GHB may be mimicking the effect of the abused drug. For example, because of some similarities in the behavioral effects of ethanol and GHB discussed above, ethanol consumption may be diminished due to a substitution effect. Another is that GHB may alleviate some of the distress associated with discontinued alcohol use. Agabio et al. (1998) contend that, because ethanol's anxiolytic actions may contribute to its own oral self-administration in rats, it is GHB's anxiolytic activity that alleviates ethanol withdrawal signs and attenuates ethanol consumption. Alternatively, GHB may truly alter the reinforcing efficacy of some drugs of abuse, either by direct receptor interaction or by indirect CNS effects. This is certainly a possibility for the effects on both alcohol and cocaine self-administration given GHB's ability to diminish dopamine neurotransmission as discussed above. Yet another possibility is that decreases in drug self-administration are a nonspecific effect of GHB. In the operant studies (Biggio et al., 1992; Martellotta et al., 1998b), no control tests were conducted to determine if GHB could have decreased responding for any reinforcer because of its response rate decreasing effects.

4. Tolerance and dependence

There have been relatively few controlled studies examining the ability of GHB to produce tolerance and dependence in either animals or humans. Colombo et al. (1995d) showed that tolerance develops to motor impairment effects in rats following 9-day repeated i.g. administration of a high dose (1.0 g/kg) of GHB. GHB was given before daily tests on the rota-rod, therefore the tolerance seen may reflect both cellular neuroadaptive changes as well as learning to perform the task while impaired. Results of testing an acute dose of ethanol in these same rats, as well as testing of GHB in ethanol-tolerant rats, demonstrated the development of cross-tolerance between the two drugs. However, while an apparent cross-tolerance developed to a similar extent, the pattern of tolerance acquisition over 9 days was different for the two drugs, with more extensive and repeated exposure to GHB required for tolerance development than with ethanol. In another study examining the ability of GHB to alleviate withdrawal in ethanol-dependent rats, tolerance to the sedative effects

of GHB was noted (Fadda et al., 1989). In this study, the highest dose of GHB tested (1.0 g/kg, i.p.), which would typically produce anesthesia in a control rat, produced only a modest sedative response in the ethanol-dependent rats. These results are generally consistent with earlier studies evaluating the ability of GBL to induce tolerance. Gianutsos and Moore (1978), Gianutsos and Sudzak (1984) tested the ability of GBL to induce tolerance in mice as measured by effects of acute GBL and GABAmimetic drugs on locomotor activity and elevation of presynaptic dopamine levels. In both studies, tolerance developed to the effects of GBL as well as cross-tolerance to baclofen and muscimol. However, a subsequent study (Wood et al., 1988) failed to show tolerance development to GBL-induced alterations in dopaminergic neurotransmission in mice, despite twice daily administration of GBL. This discrepancy may reflect that the former studies involved a minimum of 13-day exposure to GBL whereas the latter study only involved 7-day exposure. These results may reflect the slower acquisition of tolerance that was seen previously with chronic GHB (Colombo et al., 1995d). Following 4-week exposure to GBL in drinking water, Nowycky and Roth (1979) showed tolerance development in rats to the sedative effects and increased dopamine synthesis produced by acute GBL administration. These results were confirmed by Giorgi and Rubio (1981) who showed that the anesthetic effects of acute GBL administration were greatly attenuated after 3-week chronic administration and the brain levels of GHB at time of recovery were 50% greater than the levels in control rats.

Primary physical dependence to GHB has not been directly examined in controlled animal studies. None of the tolerance studies described above in which repeated administration of GHB was used noted any withdrawal symptoms after discontinuing treatment. For example, in the study by Nowycky and Roth (1979), where GBL was administered daily in drinking water for 4 weeks at about 3 g/kg/day, there was no mention of withdrawal effects however it is not clear from the report if they looked for them.

No formal studies in humans have investigated the ability of GHB to produce tolerance and dependence. The evidence provided indirectly through case reports and clinical investigations has thus far been contradictory and inconclusive. Case reports include comments suggestive of tolerance development, with abusers reporting dose escalation in order to maintain the desired effects of GHB (Galloway et al., 1997). Sporadic reports of physical dependence are also present among case reports. Galloway et al. (1997), Friedman et al. (1996) and Craig et al. (2000) each reported signs of physical dependence in high-dose chronic GHB users which included abstinence-induced insomnia, anxiety and agitation, tremors and, in one case, tachycardia and elevated blood pressure. Several other possible cases of dependence have been described in the literature, presenting with an array of withdrawal symptoms, including hallucinations (Hernandez et al., 1998) but most consistently with insomnia which generally resolves within three days (Friedman et al., 1996; Galloway et al., 1997). Even less heavy users have reported experiencing some decrease in the ability to sleep for several days subsequent to cessation of GHB administration (Galloway et al., 1997). In a clinical trial, Mamelak and colleagues (1986) reported no tolerance to GHB's effects in 48 patients during a 9-year clinical study in narcoleptic patients. Following cessation of a 3 month clinical investigation of GHB for treatment of alcohol withdrawal, patients did not express any problems suggestive of withdrawal (Gallimberti et al., 1992), nor was any abstinence syndrome reported following a similar 6-month long study (Addolorato et al., 1996). Gallimberti et al. (1994) further reported not having noted any GHB-related abuse behavior being exhibited by the subjects during their clinical investigations. Addolorato et al. (1996), however, did report an escalation of GHB consumption and some GHB craving in 10% of the patients during the chronic study. Follow up on patients which escalated their dosing showed that if this abuse was terminated early on, it resulted in mild anxiety and insomnia which resolved without treatment (Addolorato et al., 1997). Addolorato et al. (1999b) also report one patient with prolonged exposure who experienced anxiety, tremors, sweating and nausea subsequent to cessation following escalation of GHB doses up to 18 g/day. The insomnia and anxiety associated with abstinence were readily alleviated by benzodiazepine administration.

There is more information on the ability of GHB to show cross-dependence with alcohol. GHB has been shown to alleviate the abstinence syndrome following cessation of alcohol intake in both rats and human subjects (Gallimberti et al., 1989; Fadda et al., 1989). In a study by Fadda and colleagues (1989), GHB dose-dependently attenuated audiogenic seizures and overt behavioral signs of withdrawal in ethanol-dependent rats, 7 h after cessation of ethanol administration. Drugs used to treat the alcohol withdrawal syndrome, such as benzodiazepines and barbiturates, typically show cross-dependence and -tolerance with ethanol (Kramp and Rafaelsen, 1978; Shaw, 1995). GHB's ability to ease alcohol withdrawal, as recounted in anecdotal reports as well as in controlled preclinical and clinical studies, suggests a potential cross-tolerance/dependence with alcohol (Fadda et al., 1989; Colombo et al., 1995d). In case reports presented by Galloway et al. (1997) and Friedman et al. (1996), patients reported spontaneous decreases in craving and consumption of alcohol subsequent to initiation of GHB use. Gallimberti et al. (1989, 1992) and Addolorato et al. (1996, 1999a) have shown,

in controlled double-blind studies, that non-hypnotic doses of GHB are able to alleviate withdrawal symptoms and decrease alcohol consumption and craving in alcoholics. In addition, in a comparative study with diazepam, GHB was shown to be equally effective to diazepam in alleviating withdrawal symptoms, with evidence of a more rapid relief of anxiety and depression (Addolorato et al., 1999a). This effect of GHB may reflect its ability to mimic the central effects of ethanol similar to the effect seen with other sedative hypnotics such as benzodiazepines (Newman et al., 1986). Typically, however, true cross-tolerance/dependence is demonstrated by drugs with common neural sites of action. Ethanol and GHB as yet show no pertinent overlap in their cellular actions. Ethanol has been shown to have significant activity at the $GABA_A$ receptor (Ticku, 1989) and as an NMDA antagonist (Lovinger et al., 1989; Gonzales and Woodward, 1990) while GHB has no activity at the $GABA_A$ receptor and only very low affinity for the NMDA receptor ion channel (Gessa et al., 1993). This suggests that the apparent cross-dependence between GHB and alcohol may be more reflective of GHB's ability to selectively attenuate some of the signs and symptoms of alcohol withdrawal (Agabio et al., 1998), much as clonidine does for opioid withdrawal (Rosen et al., 1996a).

GHB has also been investigated for the treatment of opiate withdrawal. GHB was found to alleviate the abstinence syndrome following spontaneous but not precipitated opiate withdrawal in humans (Gallimberti et al., 1993, 1994; Rosen et al., 1996b). Similar results were obtained in morphine-dependent rhesus monkeys where lower, but not higher, doses of GHB were able to significantly attenuate withdrawal signs (Aceto et al., 2000). There are no indications that GHB has any direct activity at opiate receptors to explain this effect (Feigenbaum and Simantov, 1996). It has been suggested instead that this effect is associated with GHB-stimulated modulation of endogenous opioid release as discussed earlier (Lason et al., 1983; Hechler et al. 1991; Gobaille et al., 1994). This idea is supported by GHB's ability to prevent spontaneous opioid withdrawal but an inability to prevent precipitated withdrawal. Under the latter conditions, GHB's amelioration of opioid withdrawal through stimulation of endogenous opioid release would be blocked by naloxone (Rosen et al., 1996a).

5. Enhancement of the effects of alcohol and other depressant drugs

Concern has been raised regarding the interactive effects of GHB with other CNS depressants. Much of this concern comes from reports that GHB or GBL has been added to alcoholic beverages of women without their knowledge and the combined CNS effects have rendered them vulnerable to assaults (see below). Not unexpectedly, GHB and depressant drug combinations result in greater CNS depressant effects than seen with either drug alone. Combining GHB/GBL with barbiturates produces a prolongation of pentobarbital and hexobarbital sleep time (Drakontides et al., 1962; Ban et al., 1967) as well as an enhancement of phenobarbital's anticonvulsant activity (Czuczwar et al., 1984). Low doses of diazepam combined with GHB given once daily to rats resulted in a decreased overall waking time and an increase in slow wave sleep time (Monti et al., 1979). In addition, GHB and GBL administration prolong ethanol sleep time (Serebryakov, 1965; Ban et al., 1967; McCabe et al., 1971). This enhancement of sleep time is also commonly seen when ethanol is combined with benzodiazepines and barbiturates (Smith and Herxheimer, 1969; Okamoto et al., 1985). It is well known that combinations of ethanol with benzodiazepines or barbiturates in humans result in a dose additive impairment of motor coordination (Linnoila and Mattila, 1973; Saario and Linnoila, 1976). A study in humans evaluating the effects of GHB on psychomotor performance found that low doses of GHB failed to diminish driving skills. However, the doses of GHB used (1.0 and 2.0 g) may have been too low to be active. When combined with ethanol, 1.0 g GHB did not augment the effects of low-dose alcohol (0.5 g/kg), however significant impairment of coordination and manual proprioception was produced when 2.0 g GHB was used in the combination, suggesting an enhancement of alcohol's effect (Mattila et al., 1978). Nonetheless, there are no scientific studies that suggest that the ability of GHB to enhance the effects of ethanol is any greater than is typically observed with a wide range of depressant drugs. Because there have been clinical reports of adverse effects with this combination (Chin et al., 1992; Greenblatt, 1997; Louagie and Verstraete, 1997), the issuance of warnings about concurrent use of GHB with depressant drugs and alcohol can be supported by the animal research literature.

Conflicting reports have been published regarding the metabolic interaction of GHB and alcohol. Some studies suggest that alcohol dehydrogenase (ADH) plays a role in the formation of GHB from SSA in the brain (Taberner, 1974). Subsequent studies have found that ethanol does not interact with the enzymes responsible for GHB formation or degradation in the brain (Doherty et al., 1975; Poldrugo and Snead, 1986). However, ethanol does competitively interfere with the NADPH-/NAD^+-dependent formation and degradation of GHB in the liver which may involve ADH (Poldrugo and Addolorato, 1999). This interaction may explain a prolonged degradation time of either GHB or ethanol when administered simultaneously (Vree et al., 1976; Hoes et al., 1978) as well as elevation of blood levels of

endogenous alcohol compounds following GHB administration in alcoholics (Burov et al., 1983). Also of relevance, given the current increase in abuse of GHB precursors, is the competitive inhibition of 1,4-butanediol conversion to GHB by ethanol which has been demonstrated both in vitro (Poldrugo and Snead, 1986) and in vivo (Vree et al., 1975; Poldrugo and Snead, 1984). The clinical impact of these interactions in acute users of GHB/ethanol or 1,4-butanediol/ethanol combinations has yet to be fully investigated.

A series of studies was done to investigate whether GHB would alter the analgesic effects of morphine or the expression of morphine tolerance (Aceto et al., 1999). These studies utilized a mouse tail-flick procedure. In the first study, various doses of GHB were tested in combination with doses of morphine that produced about 25% maximal antinociception when given alone. GHB did not produce appreciable antinociception at any dose, but it dose-dependently enhanced morphine's effects. In mice made tolerant to morphine antinociception, GHB in combination with morphine restored some of morphine's antinociceptive effects. These studies are not directly related to abuse potential assessment, but do speak to the safety of GHB in combination with opiates and also could suggest additional therapeutic uses.

6. Clinical reports of GHB use, misuse and abuse

There is a fairly extensive history of use of GHB for a variety of purposes, many of which are consistent with claims made for its potential therapeutic actions as a sleep enhancer and growth promoter. GHB had been in clinical use in Europe for decades without reports of severe side-effects and incidents of abuse. Indeed, based on early evaluations of GHB, Vickers (1969) commented on the safety of the compound. However, in the US, when it became widely available as a dietary supplement in the 1980's, reports of adverse events began to emerge. In 1990, based on reports of abuse and adverse effects, the FDA ordered the removal of GHB from the market. The escalation of use of GHB as an anabolic agent in the U.S. was undoubtedly stimulated by the placement of androgenic steroids under drug abuse control laws as well as the removal of L-tyrptophan from the market. Just as with other dietary supplements, human use of GHB products at that time was not prohibited by US food and drug laws. Therefore, use of GHB as a growth enhancer and sedative, at least prior to 1990, cannot all be described as instances of drug abuse and might best be termed misuse. The use of GHB as an intoxicant and enhancer of sexual activity is more reasonably viewed as an instance of drug abuse, especially after 1990 when an illegal market developed. Since that time, the misuse/abuse of GHB has continued and been the focus of a great deal of media and government attention in the US.

Illicit use, thus far, has only involved oral administration of GHB which is available as the sodium salt in either powder or, increasingly, liquid form. Following ingestion, GHB is rapidly absorbed and begins to have effects within 15–30 min (Vickers, 1969; Lettieri and Fung, 1979) with peak levels being reached in 25–45 min (Ferrara et al., 1992; Palatini et al., 1993). GHB has a relatively short duration of action with it being ultimately metabolized to CO_2 and eliminated through the lungs (Vickers, 1969; Lettieri and Fung, 1979). The intensity of the effects of GHB depends on the dose taken and can be significantly affected by types and amount of any coingestants. In humans, GHB produces a dose-related alteration of CNS activity with as little as 10 mg/kg producing some muscle relaxation (Dyer, 1991). Doses in the 20–30 mg/kg range generally induce sleep and have also been reported to produce some euphoria (Lapierre et al., 1990; Chin et al., 1992). High doses of 60 mg/kg and above can produce unarousable sleep or coma which lasts from 1–5 h with lethal doses estimated to be 5–15 times the dose producing unconsciousness (Vickers, 1969; Mamelak et al., 1977; Dyer, 1991). When it has been administered for therapeutic purposes, GHB has generally been given in the 15–30 mg/kg range, with 1.5–2.25 g/70 kg being recommended for sleep induction.

6.1. Growth promoter

GHB was initially marketed in the US as a steroid replacement for body builders and weight lifters. GHB was purported to promote muscle growth and decrease body fat, the latter also making GHB use attractive as a means of weight loss (Chin et al., 1992; Luby et al., 1992; Friedman et al., 1996). GHB has been shown to stimulate the release of human growth hormone from the anterior pituitary, most likely because growth hormone release occurs during slow wave sleep which is increased by GHB (Takahara et al., 1977; Bluet-Pajot et al., 1978; Gerra et al., 1994). However, there is no evidence that the short-term elevations in growth hormone produced by GHB result in any increase in muscle mass. Despite this, GHB has been widely used among the body building community and is believed by some to be the primary focus of recent GHB misuse (Friedman et al., 1996).

6.2. Sleep aid

Consistent with its reported sedative actions, GHB has also been used as a sleep-inducing agent (Chin et al., 1992; Mack, 1993), in some cases replacing L-tryptophan for insomniacs and others with sleep disturbances. There also have been occasional reports of

GHB use as a sleep aid for amelioration of the after effects of methamphetamine or MDMA (Galloway et al., 1997). Oral doses of 30–50 mg/kg GHB generally produce sleep, which is readily reversed by external stimuli and is virtually indistinguishable from normal sleep. EEG patterns, behavior and subjective evaluations all suggest that GHB-induced sleep mimics physiological sleep, increasing slow wave sleep (stages 3 and 4) and REM sleep (Laborit, 1964; Yamada et al., 1967; Vickers, 1969; Mamelak et al., 1977). This characteristic is not true for classical sedative hypnotics, such as benzodiazepines, which suppress REM and slow wave sleep. Therefore, GHB should not result in REM rebound with nightmares, as is seen with discontinuation of benzodiazepines (Bonnet et al., 1981; Grozinger et al., 1998).

GHB was initially proposed for the symptomatic treatment of narcoleptic patients in the late 1970's. While this therapeutic approach might initially appear counterintuitive, the ability of GHB to induce a physiological sleep at night underlies its use to alleviate the symptoms of narcolepsy (Mamelak, 1989). The etiology and pathology of narcolepsy have yet to be fully elucidated; however, it is known that these patients experience sleep disturbances throughout the night resulting in abnormal sleep patterns. During waking hours, because of this nonrestorative sleep pattern, patients are subject to extreme daytime sleepiness, cataplexy, sleep paralysis and hypnagogic hallucinations. GHB taken at night serves to consolidate sleep and restore a more normal sleep pattern such that the incidence of daytime symptoms is decreased (Mamelak, 1989; Lapierre et al., 1990). GHB has been examined in clinical trials for treatment of narcolepsy and found to be safe and effective in reducing cataplexy, daytime sleepiness and hypnagogic hallucinations (Scharf et al., 1985; Mamelak et al., 1986; Scrima et al., 1990; Lammers et al., 1993). The only Treatment Investigational New Drug currently approved by the FDA in the US is held by Orphan Medical, Inc. (Minnetonka, MN) who are developing GHB (Xyrem®) for treatment of narcolepsy under the FDA's orphan drug program.

6.3. Intoxicant

GHB has been reported to be euphorigenic, producing a pleasurable intoxication generally without residual toxic effects, i.e. no hangover (Dean et al., 1998). In both a controlled study as well as numerous anecdotal reports, the subjective effects of GHB have been compared to those of benzodiazepines, opiates and alcohol (Friedman et al., 1996; Galloway et al., 1997; Rosen et al., 1997). In interviews with GHB users, they said GHB made them 'feel good' and in some cases, they had initially begun GHB use for other effects (i.e. sleep or muscle growth) but enjoyed the euphoric effect so increased their consumption (Dyer, 1991; Chin et al., 1992; Galloway et al., 1997). GHB has also been reported to enhance the effects of alcohol and stimulants (Frederick et al., 1994; Galloway et al., 1997). Because of these characteristics, GHB has achieved popularity for use as one of the new 'club drugs', and is sometimes available at 'raves' and in nightclubs (Stell and Ryan, 1996; George, 1996; Galloway et al., 1997; Marwick, 1997). This has led to increased reports of GHB use in combination with the other 'club drugs', ketamine and MDMA. GHB has also attained a reputation as an aphrodisiac. Case reports have noted subjective reports of increased libido (Luby et al., 1992; Galloway et al., 1997; Chin et al., 1998) as well as a similar 'sexually enhancing' effect being noted by Laborit (1972) as a side-effect. This sexual effect is most likely due to disinhibition, but needs additional study.

6.4. Drug-facilitated sexual assault

In recent years there have been an increasing number of reports of drug-facilitated assault with several drugs taking the forefront in the media. GHB has been characterized by the media as being one of the 'date-rape' drugs (Anonymous, 1997Wall Street Journal) and there have been some reports of surreptitious GHB administration in clubs (Center for Disease Control, 1997). The purported enhancement of sexuality, coupled with a possible abrupt coma-inducing effect, ease of administration and enhancement of ethanol's behavioral effects (McCabe et al., 1971) have resulted in the use of GHB as an assault related drug (Marwick, 1997; Anonymous, 2000). A study examining the presence of various drugs in urine following sexual assault found ethanol to be the most common 'date-rape' associated drug, being present in over 40% of the assault cases tested (ElSohly and Salamone, 1999). GHB was present in only 4.1% of the cases, a lower rate than reported for benzodiazepines (8.2%), cocaine (8.2%) and marijuana (18.5%). While rapid metabolism of GHB may have underestimated the presence of GHB in these victims, this report suggests that GHB's involvement in drug-facilitated assault, while certainly occurring in some cases, may be less common than what is being promulgated by the media. Additionally, this study tested only for the presence of drugs and did not investigate what role the drug(s) played in the assault or if they were administered unknowingly.

6.5. Adverse reactions

Ferrara et al. (1999) examined the subjective, cognitive and motor effects in humans following administration of typical therapeutic doses. Oral doses of 12.5 and 25 mg/kg had no effect on attention, vigilance, alertness, short-term memory or psychomotor skills based

on the tests used. The only adverse effects noted were slight dizziness and dullness. Counterintuitive to reports of euphoric effects in abusers, GHB showed a dose-dependent decrease in reported levels of contentedness in this sample. There is suggestion of cognitive impairment, however, when GHB is administered at higher doses. An earlier study in humans, using 10 mg/kg i.v., found a significant impairment of short-term memory. Even so, this effect was only noted at the earliest time-point and had dissipated by 15 min post injection (Grove-White and Kelman, 1971).

Illicit use of GHB, however, has been associated with little consistency and precision in the doses consumed. When marketed as a food supplement in powdered form, a dose of 0.5–1 teaspoon (1.4–2.8 g) was recommended for body building; however in reported cases, users said they had taken from 0.25 teaspoon to 4 tablespoons (Mack, 1993; Galloway et al., 1997), demonstrating a wide variation in GHB consumption even without taking into account individual definitions of 'teaspoon' and 'tablespoon'. An evaluation of liquid GHB samples showed a high inconsistency in mg/ml (Thomas et al., 1997) also contributing to the highly variable dosing. The ready availability of GHB, coupled with frequently inexact dosing, have resulted in cases of acute intoxication requiring medical attention, however, over half of these cases were associated with coingestion of another drug (Center for Disease Control, 1991; Steele and Watson, 1995; Ross, 1995; Chin et al., 1998). Adverse effects reported included mild hypothermia, dizziness, nausea, vomiting, weakness, loss of peripheral vision, confusion, agitation, hallucinations, decreased respiratory effort, unconsciousness and coma (Dyer, 1991; Luby et al., 1992; Ross, 1995; Chin et al., 1998; Li et al., 1998). Some cases have reported the occurrence of tonic-clonic seizure activity (Dyer, 1991; Steele and Watson, 1995); however, in humans, GHB is not generally associated with seizure production. The seizures reported may have been due to concurrent sympathomimetic drug ingestion and/or a misinterpretation of clonic movements which can be produced by high doses of GHB (Vickers, 1969; Li et al., 1998; Kleinschmidt et al., 1999). During anesthetic induction, these movements are typically seen but occur without concurrent epileptiform EEG patterns (Vickers, 1969; Entholzer et al., 1995). Overdose cases generally are responsive to supportive care, and patients typically recover consciousness within 1–5 h, although reports range from 2–96 h for complete recovery dependent upon dose and the presence of other intoxicating drugs (Chin et al., 1992; Ross, 1995; Thomas et al., 1997; Chin et al., 1998; Li et al., 1998). Recovery is spontaneous, frequently abrupt, and is not usually associated with any adverse sequelae (Dyer, 1991; Louagie and Verstraete, 1997; Marwick, 1997; Li et al., 1998).

Deaths related to GHB ingestion have been reported in the medical literature (Adornato and Tse, 1992; Ferrara et al., 1995; Marwick, 1997; Li et al., 1998). The majority of these incidents involve mixing of GHB with other drugs, with only one published case believed to be due exclusively to GHB ingestion (Center for Disease Control, 1997). For example, the death reported by Ferrara and colleagues (1995) involved ingestion of GHB in combination with heroin by an already debilitated individual. In the majority of the toxicity cases reported (Dyer, 1991; Chin et al., 1992; Ross, 1995; Steele and Watson, 1995; Galloway et al., 1997; Thomas et al., 1997; Chin et al., 1998), GHB was the presumed cause of the adverse reactions but this was based on the description of the incident, time of onset, etc. Because laboratory tests for GHB intoxication are not generally available to clinicians, only rarely were actual blood/tissue levels of GHB determined (Stephens and Baselt, 1994; Dyer et al., 1994; Li et al., 1998). This makes evaluation of the true risk associated with GHB use difficult, especially when considering that the majority of cases resulting in hospitalization involved the coingestion of alcohol or another drug (frequently a stimulant such as methamphetamine or MDMA) (Einspruch and Clark, 1992; Steele and Watson, 1995; Thomas et al., 1997; Chin et al., 1998; Li et al., 1998; Hernandez et al., 1998).

7. Epidemiology of GHB abuse

It is difficult to obtain quantitative data on the prevalence of GHB use and abuse from traditional databases used to monitor drug abuse behaviors in the US. As of 1999, questions about GHB have not been included in the nationwide Monitoring the Future survey of high school students conducted annually. There are plans to add it to the next survey (Johnston et al., 1999). There is also no information available about rates of GHB abuse in reports of the National Household Survey on Drug Abuse through the most recent report of the 1998 survey (Substance Abuse and Mental Health Services Administration, SAMHSA, 1999c), although survey respondents may include GHB under one of the 'other' drug categories. Since the use of GHB is not queried specifically, however, it is not even possible to know whether the prevalence of abuse is below the threshold of about 0.1% of the population which is capable of being detected in the Household Survey.

Because GHB abuse is a recently emerging problem, information about it should be more readily found in epidemiological instruments designed for identifying new drugs of abuse. GHB is not mentioned at all in any of the most recent publicly available primary reports of the Drug Abuse Warning Network (DAWN) system,

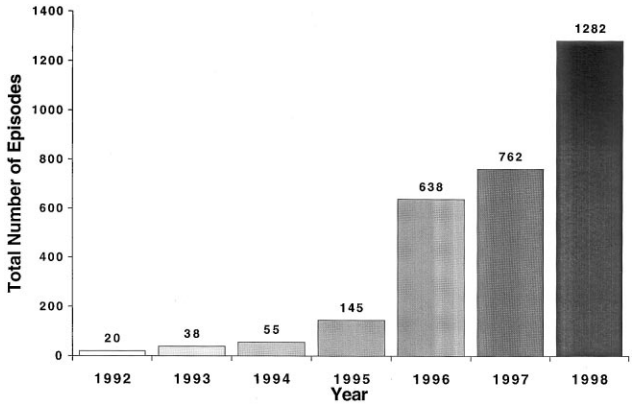

Fig. 2. Shown are the number of GHB-related emergency room episodes reported annually for the time period 1992 through 1998. Data are based on reports from the Substance Abuse and Mental Health Services Administration Drug Abuse Warning Network compiled from various sources (see text).

either in the 1998 year-end emergency department data (SAMHSA, 1999b) or the 1997 medical examiner (ME) data (SAMHSA, 1999a). This does not mean that there were no mentions of GHB in either of these data sets, but rather that the frequency was insufficient to be included in the published reports. Indeed, a secondary analysis of both DAWN data sets for 1992 through 1996 conducted by the Office of Applied Statistics of SAMHSA (Greenblatt, 1997) shows a rise in GHB involvement with emergency department cases over that period (Fig. 2). In 1992, there were 20 mentions of GHB; however by 1995 and 1996 the number of mentions had increased to 145 and 638 respectively. The GHB mentions in 1996 were primarily located in cities throughout the midwest, south and west coasts of the US, but few in east coast cities (Greenblatt, 1997). To place these 638 GHB emergency department mentions in 1996 into perspective, this value would place GHB as 76th in rank among drugs included in that database, accounting for about 0.1% of all mentions for that year (SAMHSA, 1998). More recent reports describing data from the DAWN emergency department survey list an increase to 762 GHB mentions in 1997 (Nordenberg, 2000) and to 1282 mentions in 1998 showing that the increase seen in this database beginning in 1995 has continued (Fig. 2). One must always keep in mind when interpreting data from the DAWN system that 'mentions' do not imply that the substance mentioned was involved in the reason the person came to the attention of the emergency department nor whether GHB alone was involved in a case. In addition to drugs of abuse which are identified in the DAWN system, other commonly used drugs which always receive mentions include aspirin, ibuprofen, and fluoxetine (SAMHSA, 1999a). Nonetheless, the dramatic increase in GHB mentions over the period of 1995–1998 is the clearest quantitative evidence we have of a nationwide epidemic.

There are somewhat conflicting data on the number of deaths attributable to GHB. No GHB deaths are contained in the published DAWN ME data sets through the most recently available report for 1997 (SAMHSA, 1999a). The secondary analysis by Greenblatt (1997) for the period of 1992 through 1996 found that there was only one ME mention of GHB, and that death occurred in a young women who took GHB in combination with alcohol. In contrast to this lack of evidence for mortality from GHB abuse, the US Drug Enforcement Administration (DEA, 2000) reports that their staff have identified 65 GHB-related deaths since 1990. This figure does not come from standard epidemiological survey instruments such as DAWN but rather from aggressive case-finding when deaths have been brought to the attention of agency officials. This method is likely to be far more effective in identifying GHB-related deaths than a more passive reporting system such as DAWN. It is interesting that the DAWN ME system, which incorporates a sample of over 100 ME offices from almost all of the major metropolitan areas in the US (SAMHSA, 1999b), does not identify some of the same deaths uncovered by the DEA. Determining why this is so may offer a unique opportunity to assess the validity of the DAWN system.

Evidence for an increasing problem with GHB abuse also comes from the reports of the National Institute on Drug Abuse Community Epidemiology Work Group (CEWG). The CEWG is a nationwide network of epidemiologists and drug abuse researchers that meets regularly to discuss emerging substance abuse problems. This group relies on the data from the national surveys mentioned above as well as information available from the Arrestee Drug Abuse Monitoring program of the National Institute of Justice, information on seizures, drug prices, etc. from the DEA and the Uniform Crime Reports of the Federal Bureau of Investigation. In addition, qualitative data are obtained from street ethnographers, treatment specialists, and other community-based experts. As early as the 1995 report (Community Epidemiology Work Group, 1996), localized evidence of GHB abuse began to appear, identified along with much more prevalent drugs such as ketamine, MDMA and flunitrazepam, as a new 'club drug'. In each subsequent yearly report of the CEWG, increasing attention has been paid to the problem of GHB abuse. The June 1999 full report (Community Epidemiology Work Group, 1999a) and the December 1999 advance report (Community Epidemiology Work Group, 2000) describe increasing nationwide abuse of GHB in dance clubs and raves, and describe some mortalities associated with this practice. Use of the GHB precursors, GBL and 1,4-butanediol, is also described.

Perhaps the largest source of public concern over GHB abuse comes from media reports which have focused public attention on the issue. There have been many widely publicized cases of GHB abuse problems. Not surprisingly, media accounts have focused on the date rape phenomenon, with some very tragic stories of young women who have been raped or murdered. For example, a recent case in Detroit, Michigan (Detroit Free Press, 2000) resulted in convictions of three young men for involuntary manslaughter and one for related offenses in a case where a 15-year old girl was apparently given GHB without her knowledge and died the next day. Her companion was also rendered comatose, but recovered. Cases such as these, as well as stories on GHB shown on popular television shows, widely publicized warnings from public health officials, the establishment of a 'club drug' Internet site by NIDA (http://clubdrugs.org) and other factors have lead to widespread public attention to the problem in the US.

It is not clear to what extent the problem with GHB abuse is confined primarily to the US. Case reports and warnings have appeared from Europe, Africa and Australia (e.g. George, 1996; Thomas et al., 1997; Williams et al., 1998; Hunderup and Jorgensen, 1999), but we are not aware of any published quantitative data on the abuse of GHB outside the US. There is an international component of the CEWG, which brings together drug abuse epidemiologists from around the world. Perusal of their most recent report (Community Epidemiology Work Group, 1999b) reveals very little attention being paid to GHB, although there was a mention of it in the report from South Africa. It is beyond the scope of this review to undertake a systematic review of international reports of GHB abuse, so we can only conjecture about the worldwide impact of this problem. From the published literature and the sources of information available on the Internet, the GHB abuse problem appears to be of much less public health concern outside the US. Whether the US is a harbinger of things to come in other areas is not yet known.

In summary, there are clear indications from various national reporting systems designed to identify new drug abuse problems that there has been an emergence of a problem with GHB abuse in the US beginning no later than 1994 or 1995. Quantitative data on the prevalence in the population is not available and the nature of the data from such systems as DAWN, the CEWG and reports of the DEA cannot place GHB abuse into quantitative perspective with other substance abuse problems. Clearly, the DAWN system, which does show a large increase in GHB mentions, still shows it to be far down on the list in terms of mentions relative to nearly all other well-recognized drugs of abuse. Together with a dramatic upsurge of public attention, which parallels these qualitative indicators of the GHB problem, it is clear that a greater understanding of this drug and the scientific information available on it is needed by drug abuse professionals.

8. Regulatory status in the US

Until fairly recently, GHB was not a controlled substance anywhere in the US, and, as described earlier, was sold legitimately until 1990 when the FDA banned its sale to consumers. As of February 2000, at least 28 states had enacted regulations to control GHB or its chemical precursors. Although the legal definitions for schedules of controlled substances differ from state to state, they generally follow that of the US Controlled Substances Act in which compounds with abuse liability but without approved medical use are placed in Schedule I. Drugs with approved uses are then placed in Schedules II through V in generally descending order of abuse liability and/or public health concern. The medical use status of GHB is unclear at this point. We reviewed earlier some of the medical indications for which GHB has been used and that it is under active development at this time as a prescription drug treatment for narcolepsy. Yet, it does not currently have FDA approval for commercial use outside of its Treatment Investigational New Drug status approved by the FDA in 1998 which allows its use in clinical trials. Without a clear resolution of whether GHB has medical uses or not, states differed in how they controlled it. Some states have taken the position that, without FDA approval for commercial sale, there is no 'valid medical use' and placed it in Schedule I. Other states have relied on the Greenspoon decision (United States Court of Appeals for the First Circuit Court, 1987) which stated that 'valid medical use' was not legally determined by FDA approval but rather by virtue of medical practice. These states have placed GHB in Schedules II through IV. Other states have waited for a federal decision on the matter.

Throughout much of the 1990's, federal regulatory authorities have also been uncertain how to regulate GHB under the Controlled Substances Act, considering both its uncertain status as a medical treatment and conflicting information about its abuse potential. In late 1999, the US Congress took steps to resolve the issue by passing legislation to control GHB. Enactment of this bill in February, 2000 directed the US Attorney General to use her emergency scheduling authority to make GHB a Schedule I substance but to treat GHB products being studied under FDA-approved protocols as Schedule III substances. This legislation also mandates that Schedule III designation will apply to any FDA-approved New Drug Application for GHB-containing products, although it does specify some additional reporting requirements for them. This situation is somewhat analogous to the current federal control

status of tetrahydrocannabinol, where the chemical is controlled in Schedule I, but the FDA-approved formulation in sesame oil (Marinol®) is in Schedule III.

Since possession or sale of analogues of controlled substances can often be prosecuted under federal or state controlled substances statutes, the control of GHB will have an impact on the availability of GBL, 1,4-butanediol, tetrahydrofuran and other GHB precursors as well. These compounds are chemically related to GHB (Fig. 1), although whether they are GHB analogues as defined legally depends on the statutory definition of analogue and a court's interpretation of it. GBL is a liquid used commercially in the manufacture of paint, beer, plastics and textiles and in the synthesis of many other chemicals. It is also used as a solvent and as a constituent of some paint removers and drying oils. Other GHB precursors have widespread commercial use as well. Because GBL was being sold over the Internet for internal use and in 'chemistry kits' where GHB was the chemical result, the FDA asked companies that manufactured products containing GBL to recall them voluntarily. The success of this is unclear, but Internet sites we checked that were selling GBL are no longer doing so.

The same federal legislation that provided for the control of GHB made GBL a list I chemical as defined by the Chemical Diversion and Trafficking Act of 1988 of compounds that are used in the manufacture of a controlled substances. This places reporting requirements on users of GBL but does not preclude that it could be designated as a controlled substance analogue to GHB. The regulatory status of 1,4-butanediol, tetrahydrofuran and other precursors of GHB is not specifically addressed by this legislation, but these compounds too could potentially be designated as controlled substance analogues for purposes of prosecution.

It will be important to assess the impact of these regulatory changes on the GHB abuse situation in the US. It will also be important to assess what effect these new restrictions have on research and development with this compound in order to arrive at a balanced evaluation of the impact of these new regulations. These regulatory changes should result in reduced availability of illicit GHB, but as with other controlled substances, an illegal distribution system and diversion of medical products may emerge. Because narcolepsy affects relatively few people, a national distribution mechanism that bypasses local pharmacies is being considered for Xyrem® which should help insure that diversion is prevented or minimized. It is possible that GHB will become no easier to obtain than abused depressant drugs, such as the barbiturates, nonbarbiturate sedatives and benzodiazepines. As discussed below, scientific research has not established that GHB has the same intrinsic abuse potential as these better known drugs. Thus, another possible outcome of a reduced availability of GHB is that its abuse and misuse will decrease dramatically as potential users switch to abused depressants with greater abuse potential. Of course, it is possible that GHB has found a niche among substance abusers for which classical abused depressant drugs cannot serve as replacements, and illicit use will continue.

9. Summary and conclusions concerning abuse potential

GHB presents several unique characteristics which must be considered when evaluating its overall abuse potential relative to known drugs of abuse. For one, GHB is a natural constituent of the human body. Although high doses of exogenously administered GHB can reasonably be expected to produce effects that would not occur under normal physiological conditions, the difference from normal may be one of degree and not a qualitative difference. Secondly, GHB is not pharmacologically equivalent to any existing controlled substances. Although it shares some effects with abused depressant drugs, clear differences from these drugs have been shown. GHB has a unique cellular site of action in the brain that is not a receptor for any other drugs except various GHB analogs, an antagonist and several benzamide neuroleptics (Maitre et al., 1990; Hechler et al., 1993; Maitre et al., 1994). GHB does not interact directly with known sites of action of any abused drug, including any known modulatory sites on the $GABA_A$ receptor. The preclinical pharmacological profile of GHB also differs from classical depressant drugs. Although it can produce depressant effects, it also has excitatory effects at high doses and can be a convulsant in some species.

Behavioral pharmacology studies with GHB also provide evidence for differences between GHB and classic sedative/hypnotic drugs. Drug discrimination studies are particularly relevant because they probably reflect properties of drugs that are directly relevant to their abuse, namely the nature of the acute intoxicating effects. Drug discrimination studies with GHB fail to consistently show cross-substitution with abused depressant drugs such as the benzodiazepines and barbiturates (Winter, 1981; Woolverton et al., 1999). Similar results are obtained in various species, including nonhuman primates, and with different routes of administration, including oral administration. On occasion some partial cross-substitution is observed with GHB and various $GABA_A$ agonists (Winter, 1981; Lobina et al., 1999). However, to place these results in perspective it is important to recognize that nonabused medications with anticonvulsant or depressant effects such as muscimol, baclofen, gabapentin and valproic acid also can show partial cross substitution with abused depressant

drugs (e.g. Grech and Balster, 1993, 1994). There is evidence for some cross-substitution with ethanol, but only over a very narrow dose range and this effect has not been demonstrated consistently (Colombo et al., 1995c; Metcalf et al., 1999). Stronger evidence for cross substitution has been reported between GHB and the $GABA_B$ agonist baclofen (Lobina et al., 1999), a nonabused drug, particularly at high doses. In addition, drug discrimination studies in animals have also shown that GHB does not have discriminative stimulus effects similar to those of heroin, morphine, pentobarbital, triazolam, cocaine, *d*-amphetamine, PCP or LSD (Winter, 1981; Beardsley et al., 1996; Woolverton et al., 1999) supporting the view that GHB has a unique profile of psychoactive effects.

Self-administration studies of GHB show evidence for only weak and inconsistent reinforcing effects. In the studies in rhesus monkeys using a substitution procedure, self-administration rates for GHB were well below those seen with the positive controls used in these studies, PCP and methohexital, and much more similar to those obtained with vehicle tests (Beardsley et al., 1996; Woolverton et al., 1999). Authors of both studies concluded that GHB had, at most, weak reinforcing effects suggesting that it has low abuse potential. Similar testing procedures in monkeys readily demonstrate the reinforcing effects of barbiturates and typically show reinforcing effects of benzodiazepines as well (Griffiths and Weert, 1997). Rodent studies have been more suggestive of reinforcing effects of GHB. There is one study showing a conditioned place preference with GHB (Martellotta et al., 1997), but this procedure has only rarely been used in abuse potential assessment. Both oral and i.v. self-administration have been shown in rodents, but results were variable and difficult to interpret conclusively as reflecting centrally-mediated reinforcing effects (Colombo et al., 1995a, 1998; Martellotta et al., 1998b).

Repeated administration of GHB can result in tolerance development, although there is some evidence that it is more difficult to produce tolerance with GHB than with ethanol (Colombo et al., 1995d). Many drugs produce tolerance, so this fact alone has little relationship to abuse potential. There are studies showing cross-tolerance with ethanol (Fadda et al., 1989; Colombo et al., 1995d). The significance of this for abuse is unclear, although it could support a conclusion that GHB and alcohol share some common mechanisms of action. On the other hand, cross-tolerance of GHB with baclofen and muscimol has also been reported (Gianutsos and Moore, 1978; Gianutsos and Sudzak, 1984). There have been no reports of physical dependence development with repeated GHB administration in animals, however, this has never been the primary focus of any controlled preclinical studies. In humans, several cases of dependence, based on the emergence of clinical symptoms subsequent to GHB cessation, have been reported following extended administration of extremely high doses (Friedman et al., 1996; Galloway et al., 1997; Addolorato et al., 1999b). There are a few studies showing that GHB can attenuate withdrawal signs in animals and humans dependent on ethanol (Gallimberti et al., 1989; Fadda et al., 1989) as well as alleviate craving in humans (Gallimberti et al., 1989, 1992; Addolorato et al., 1996). This may be due to a true cross-dependence with ethanol or to a physiological attenuation of specific withdrawal signs. Taken together, preclinical studies of tolerance and dependence could be used to support a finding that GHB has some physical dependence potential but it does not appear to be as easily induced as with classical sedative hypnotic drugs. In those instances where dependence was noted, the withdrawal signs and symptoms did not appear as severe as those seen with barbiturates, alcohol or even benzodiazepines (Sellers, 1988; Saitz and O'Malley, 1997). They have been viewed as not life threatening and typically present as insomnia and anxiety. Even when GHB was given to chronic alcoholics to treat their addiction to alcohol, withdrawal from GHB was uneventful. It could be predicted that it would be difficult to produce primary physical dependence with GHB because its short duration of action would require many multiple daily administrations to maintain the elevated levels in the body probably necessary to induce dependence.

The reports of actual abuse also clearly show that GHB has some abuse potential. The scope of abuse in humans is difficult to evaluate since none of the traditional survey instruments provide information on its prevalence. The DAWN system is clearly showing a dramatic rise in GHB mentions, but the actual numbers are low relative to other common drugs of abuse. Perhaps because GHB has been so readily available and is inexpensive on the street, life styles dominated by securing and using GHB are not commonly reported. The lack of routine analytical methods for identifying GHB in tissues and fluids has also contributed to our uncertainty. Appropriate scheduling of GHB based on the scientific evidence combined with vigorous enforcement of the laws related to GHB manufacture and use as well as improved control of distribution of its precursors should reduce the public health problem posed by the drug. It is possible, with reduced availability resulting from new regulations, that the rapid rise in GHB use will be followed by an equally rapid decline in use. The rapidly changing status of GHB should also provide opportunities to conduct research on the effectiveness of these public health measures.

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