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Use of Sodium Gamma-Hydroxybutyrate (GHB) in Alcoholic Heroin Addicts and Polydrug-Abusers

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Summary

Sodium gamma-hydroxybutyrate (GHB) is one of the most effective options available for the treatment of hard-core alcoholism in maintenance programmes that aim to achieve relapse prevention and rehabilitation. Polysubstance abuse and multiple addiction have become quite common in alcoholic youths and former heroin addicts receiving inadequate or no specific treatment. In approaching these categories, GHB is usually neglected, on the basis of the idea that its abuse potential must be amplified in abuse-prone individuals. However, the normalizing effects of anticraving treatment on the behaviour of heroin addicts may make GHB a suitable remedy for the heroin-alcohol polyabuse picture. The same cannot be said of cocaine abusers, due to the lack of anticraving treatments possessing major, reliable effectiveness. After reviewing the data in the literature on the use of GHB in alcoholics and other kinds of abusers, we describe 13 cases of alcohol-abusing heroin addicts, in which GHB proved to possess some effectiveness, even if there were major limitations regarding compliance and completeness of response.

Key Words: GHB, Polyabuse, Abuse Liability, Alcohol-Abusing, Heroin Addicts, Methadone, Buprenorphine.

Use of GHB in alcohol dependence

Safety and efficacy

Sodium gamma-hydroxybutyrate (GHB) is a natural compound which can be found as a metabolite in human nervous tissues; it binds to specific receptorial sites in the brain. It exerts its action by modulating other systems too, or by affecting multiple-ligand receptorial sites^(29, 48, 50). At different dose levels, GHB's effects may be primarily anaesthetic or euphoric. At lower dosages it increases dopamine release, which is consistent with its documented anticraving properties, and its valuable impact on abuse liability and on the psychotic symptoms produced by overdosing^(10, 21, 23). The onset of its effects is rapid; its half-life is so short as to require dose-refraction at least into thirds during the course of the day in therapeutic regimens, or using greater refraction (with fractions at intervals as short as three hours, corresponding to 8 fractions a day) – a procedure which results in more stable effects^(5, 15, 30, 43).

After failing to show antipsychotic properties in schizophrenic patients in two preliminary evaluations^(27, 47), GHB proved effective against alcohol withdrawal and alcohol addiction⁽⁴⁴⁾. In these therapeutic settings, GHB was safe and well tolerated⁽⁵⁾. As for the treatment of alcohol withdrawal, it is preferable to other agents because of its shorter half-life, which allows repeated administration free of the risks of late overdosing by accumulation. Its binding rate to plasma proteins is negligible, it is eliminated almost completely without producing metabolites, and it does not affect the liver metabolic system^(5, 43).

In the meantime, reports about its abuse, its use as a date rape drug, and its recreational use outside therapeutic settings raised major concerns about the spread of GHB treatment. Hence, most of its therapeutic potential has been neglected in the attempt to avoid misuse. The outcome is that GHB, despite being one of the few effective drugs for the treatment of alcoholism, is rarely resorted to, and then mainly through inclusion in short-term schedules⁽²²⁾.

GHB has proved to be superior to placebo, benzodiazepines and clomethiazole in the management of alcohol withdrawal^(9, 18). When compared to flunitrazepam, GHB showed it was more effective against autonomic symptoms (lower rate of adjunct clonidine administration), though less effective against psychotic symptoms related to the transient increase of dopaminergic transmission (higher rate of adjunct haloperidol administration). GHB is as effective as diazepam over the whole range of alcohol withdrawal, and it allows a quicker resolution of psychic symptoms^(1, 26, 41).

Research has proved that GHB is effective in reducing alcohol use by addicted subjects during periods of variable length (3-12 months). On methodological grounds, the effectiveness of GHB may be questioned, because of the absence of randomized controlled trials. However, due to the lack of widely available, mainly effective medications for the average alcoholic, the behavioural effects of GHB must necessarily be compared to the spontaneous course of alcoholism when left untreated. Moreover, participants in GHB studies were selected either on the basis of documented resistance

to other available treatments or on the grounds of a severe grade of alcoholism.

In a multicentre study on 179 patients, complete response (sobriety) was achieved in 78% of the sample, the relapse rate being as high as 69.3% within a 6 month follow-up, and 78.6% in a 12 month follow-up after treatment discontinuation ⁽³⁾. In a 12-month study on treatment-resistant alcoholics, the retention rate was as high as 60%, with a 10% rate of complete response and a further 15% rate of partial response (comprising a reduction in drinking amounts and/or frequency). Interestingly, partial response was not associated with a worse outcome with respect to complete response. The possibility of achieving a complete response seems to be related to lower baseline consumption amounts.

Responsiveness to GHB seems to vary through time: in two separate studies, Addolorato and colleagues ^(3,4) reported a momentous response rate of 78.1% at 6 months and of 67.8% among two-month survivors. In the 12-month study by Maremmani and colleagues, complete response was less frequent, and less likely in the long-term, though it must be noted that the subjects enrolled in this inquiry were all resistant to other treatments. Moreover these authors regard retention in treatment (60%) as a parameter of effectiveness on addictive behaviour, though clearly not on consumption levels. Lastly, these authors have proved that equivalent results can be achieved with more severely ill subjects, regardless of sobriety, in terms of psychosocial adjustment and improvement ⁽³³⁾. The short-term retention rate with GHB is higher: in the study by Maremmani and colleagues, none patients had dropped out by the end of the first month ⁽³³⁾, while Addolorato and colleagues report a survival rate above two thirds at two months and of about two thirds at three months, in two separate samples ⁽³⁾. The reduction recorded in the retention rate in moving from the shorter to the longer term should not be interpreted as a tendency for GHB to lose its apparent effectiveness; in reality, the long-term values simply yield a more realistic picture in reflecting GHB's therapeutic impact on a chronic relapsing disease such as alcoholism.

As is true of the general stereotype of addiction, in alcoholism too withdrawal and short-term compliance are quite likely to be accomplished for a variety of reasons; they represent non-specific behavioural features which can be observed during the early phase of treatment without possessing any therapeutic meaning. The longer the length of observation, the easier it becomes to recognize a behavioural change or a gradually changing trend induced by ongoing treatment, so allowing discrimination from a transient phase of apparent remission.

Given its short half-life, GHB should be administered in refracted or repeated doses. Repeated dosing is needed in the management of withdrawal, to maintain symptoms suppression through time by the replacement of eliminated GHB with further oral amounts. In maintenance regimens, dosages are refracted: in this case, repeated dosing is meant to provide the brain with a tonic, stable, stimulation. The difference is that higher single doses produce stronger but quickly fading effects, which are phasic in nature, while lower doses that are administered more frequently, but with equal cumulative daily amounts, have a weaker but steadier effect, with a narrow concentration gap

and a lower liability to abuse. On clinical grounds, a six-fraction schedule turned out to allow a higher retention rate than less frequent administrations of equal cumulative amounts⁽³⁰⁾. In another study⁽⁴⁾ the transition from a three- to a five-fraction schedule (with equal daily doses of 50 mg/day) appeared to permit a major improvement in treatment response; of 37 patients retained at two months with partial response, over two thirds achieved and maintained sobriety during the following two months, after being shifted to the five-fraction schedule. Despite the large size of the sample (n= 154), no definitive statement can be made as to whether that improvement can be attributed to the change in schedule or to an increase in the short-term response to GHB through time for partial responders.

In conclusion, on one hand it is advisable to increase the refraction ratio rather than increasing single dosages. On the other, it is not yet possible to achieve stable high levels of GHB in the blood by using high rates of refraction, that is, high levels of GHB tonic stimulation. A slow-release form of GHB would overcome this problem by allowing the use of GHB to produce slow-acting, long-lasting effects along a dose-response curve, as happens in the case of methadone. In this case, it would be possible to increase dosages up to the level required to neutralize severe alcohol craving.

Withdrawal and abuse liability

As might be expected, prolonged GHB administration leads to the development of tolerance, and heightens susceptibility to abrupt discontinuation in the form of rebound symptoms of variable severity. The reasons for such variability, though, are still unclear. In the short term, for instance, it is quite unlikely that one will develop withdrawal from GHB, even after taking it as a substitution treatment for alcohol withdrawal⁽¹⁷⁾; as far as the medium to long term is concerned, no cases of GHB withdrawal were reported in a group of narcoleptic patients to whom it had been administered at doses of 3 to 9 g/day⁽⁵¹⁾. It therefore seems that GHB withdrawal is more typical of subjects taking high GHB dosages outside any therapeutic setting, as a recreational drug, or when patients abuse prescribed GHB^(8, 12, 20, 39, 46). Moreover, it may be that withdrawal develops accidentally in subjects who abruptly discontinue prescribed GHB without seeking medical advice: it is, however, improbable that alcoholics who take GHB for therapeutic purposes, when dropping out of programmes or showing unresponsiveness to GHB, will fail to react by increasing alcohol consumption, so avoiding any rebound. Apart from this, subjects compliant with therapeutic protocols will have their GHB gradually tapered, so no withdrawal can be expected.

GHB withdrawal does stick to the general model of depressant withdrawal^(8, 12). It is characterized by a very quick onset (1 to 3 hours after latest dose), an escalation to a delirium state which develops more rapidly than with other depressants, and a gradual extinction in times similar to those encountered with alcohol or short-acting withdrawal from benzodiazepine. Psychic symptoms are more prominent than somatic ones⁽⁴⁹⁾. Diazepam treatment is quite effective^(2, 3).

GHB is traded illegally as a recreational drug with pleasurable narcotic and euphoric effects. In particular, it is employed as a sex-enhancing drug, and in some cases it is

administered to unsuspecting victims in order to make them prone to sexual intercourse and induce retrograde amnesia (a feature of date rape drugs), as happens with other substances, such as flunitrazepam.

In a laboratory setting, GHB has euphoric effects at dosages of 30 mg/kg but not at 15 mg/kg ⁽⁴⁵⁾. In a clinical sample of alcoholics receiving 50 mg/kg /die three times a day, abuse occurred in 10% of patients over a six-month exposure period ⁽³⁾. A trend towards abuse may develop in the long term, and be forerun by a period of balance. It is advisable to keep single doses low, so that the subject does not become conscious of the effects of GHB, because if he or she does, this usually acts as a predictor of subsequent abuse due to positive reinforcement. GHB abuse should be defined with reference to how subjects handle their GHB; some subjects, for instance, report taking GHB in order to avoid resorting to alcohol, and may ask for increasing dosages in order to achieve better control of their alcohol craving. Such patients are not GHB abusers, nor are those who keep on drinking alcohol although they are taking GHB. GHB abusers are those who run out of prescribed GHB due to a self-determined increase in dosages, and usually take larger dosages less often than prescribed (for example, taking their whole daily dose in one single administration), because this reveals a specific craving for GHB. An overdose of GHB, below the coma level, may induce sedation, simple confusion or psychotic confusion (delirium) ^(24,40). Chronic abusers are expected to develop intoxication symptoms similar to those induced by alcohol or benzodiazepines ⁽¹⁶⁾.

Treatment of alcoholic heroin addicts

GHB and heroin abuse

GHB has proved to be effective in blocking opiate withdrawal in subjects tolerant to heroin or methadone ^(17, 19): the onset of action is rapid and the effects of GHB can be maintained by repeated administration.

During the period of observation, subjects stopped using opiates, as proved by negative urinalyses and negative naloxone challenges at the end of treatment ^(17, 19). The mechanism of interaction between GHB and the opioid system is unclear, but it does not seem to be directly mediated by opioidergic receptors ^(13,45). In a small sample of heroin addicts rendered tolerant to stable methadone doses, single doses of GHB caused no toxic effects ⁽⁴⁵⁾.

On these grounds, GHB has been used, in short-term or even rapid detoxification programmes, in subjects tolerant to heroin, for whom methadone or buprenorphine would have been more reasonable therapeutic options. Episodes of malpractice have happened too, GHB being employed to favour the accomplishment of medically supervised detoxification from therapeutic methadone. The liability of GHB to abuse, when it is administered as an anticraving agent to populations of methadone-maintained heroin addicts, has not yet been measured. If slow-release GHB became available, research in this field would be more viable and the use of GHB would become safer.

GHB in the treatment of alcoholic heroin addicts

GHB may be effective in treating alcoholic heroin addicts because of its opioid agonist action, and there are no scientific foundations for regarding alcohol-abusing heroin addicts as unfit for this kind of treatment. The concurrent use of GHB and methadone is feasible and safe^(32,35). However, unlike methadone, GHB induces craving in certain patients; moreover, addicts in general are a population at risk, with a high incidence of impulsive and reckless subjects, so that it might be imprudent to expose addicted patients to a potential drug of abuse such as GHB. In any case, it should be remembered that, on behavioural grounds, heroin addicts successfully maintained on methadone can be viewed as radically different from untreated heroin addicts. Treatment responders do, in fact, display normalized behaviour, not only as far as opiate use is concerned, but also in terms of impulsiveness associated with ongoing abuse of other substances: the behavioural stereotype of methadone-maintained subjects does not include proneness to substance abuse.

In alcoholics with high levels of impulsiveness, habitual binge-drinking is incompatible with GHB prescription, due to the risk of toxic synergy. By contrast, in heroin-using heroin addicts or alcohol-abusing methadone-maintained subjects, binge drinking is less likely; methadone treatment, even when ineffective in preventing or treating alcohol abuse, may modify the drinking pattern, and bring binge drinking to extinction. Paradoxically, some precautions, which are needed for pure alcoholics, may be inappropriate for heroin-addicted alcoholics.

Table 1 displays data on GHB treatment administered to heroin alcoholics at the Vincent P. Dole Dual Diagnosis Team of the Department of Psychiatry of the University of Pisa.

It should be borne in mind that the following precautions should be taken when exposing methadone-maintained heroin addicts to GHB:

- administration to be supervised by a significant one;
- controlled availability of the drug, so as to prevent overdosing;
- the use of lower single doses, given that heroin addicts are able to discriminate GHB when it is administered at higher single doses⁽⁴⁵⁾;
- assessment of subjective effects, in line with the rule according to which a stable, peakless effect is associated with a low likelihood of abuse;
- GHB to be started separately from methadone, only after tolerance to opiates has become high or stable, and the patient has recently been abstinent from heroin;
- methadone treatment is preliminary to GHB treatment; only subjects who have stopped using heroin should be started on GHB.

GHB use in polyabuse patterns

GHB is one of the few effective agents against chronic alcohol craving^(3,4,30,33). It may be employed as maintenance therapy, and does allow the achievement of satisfactory

Table 1. Pharmacological interactions and dosages in methadone-maintained alcoholics heroin addicts in the experience of the Vincent P. Dole Dual Diagnosis Team.			
	Dosages (mg/daily)		
	Min	Mean	Max
Methadone (stabilization)	60	150	380
GHB	1750	4725	5250
Clonazepam	2	5	9
Trimipramine	50	70	100
<i>Maremmani et al, Heroin Addict Rel Clin Probl, 2003 (Revised)</i>			

levels of social adjustment in formerly impaired alcoholics, even when sobriety is not attained. Its mechanism of action seems to comprise pro-dopaminergic and gabaergic properties^(29, 48, 50). Due to its pro-dopaminergic action, GHB may turn out to be helpful both to polydrug abusers and polyaddicts, who are becoming increasingly frequent in the population of treatment-seeking alcoholics.

On the other hand, polyabusers, due to their high level of impulsiveness, are not sufficiently reliable to be admitted to a structured treatment programme, both on decisional and behavioural grounds. Despite this limitation, one reasonable strategy is to target cravings one by one, starting with the most destabilizing substance and/or the most effective treatment regimen, and setting up a “Chinese box” sequence. After putting up shutters against the first source of destabilization, a second treatment regimen may be added, so that the second treatment may count on a greater level of baseline compliance. The effectiveness of some agents, even when hampered by a low level of compliance, may still be a usable resource.

In the literature it is still controversial whether GHB can be used for subjects who have abused or are abusing other substances apart from alcohol, with special reference to narcotics. On the other hand, alcohol is seldom the only abused substance in young drinkers, and polysubstance dependence is far from rare.

Polyabusers may resort to alcohol secondarily, without being addicted to it, in order to handle intoxication from their substance of choice by enhancing its pleasurable effects or producing a pleasurable mixture. However, secondary abuse may turn into actual addiction, regardless of which substance was abused first; some alcohol polyabusers may thus end up as alcoholics or polyaddicts. The selection of polyabusing subjects for GHB treatment should account for differential diagnosis between alcohol abuse and addiction, rather than the chronological sequence of abuse. Also, the criteria for exclusion should include some behavioural trends or mental states which imply poor compliance and impulsiveness.

Cocaine

As long as cocaine consumption is out of control, and unless craving has been kept under control for some time, cocaine abusers should be regarded as unsuitable for GHB prescription. In fact, polyabuse pictures often feature cocaine as the main cause of global impulsiveness and unreliability, and no treatment option has proved of major efficacy against cocaine abuse in terms of compliance and the suppression of craving.

Heroin and Morphine (fast-acting opiates)

It must, however, be added that GHB use is conceivable in an alcoholic heroin addict, once satisfactory behavioural stability has been achieved by means of agonist treatment.

In subjects who are given stable dosages of an opiate agonist, the addition of GHB does not produce unfavourable reactions⁽⁴⁵⁾. In the Vincent P. Dole Dual Diagnosis Team Methadone Maintenance Treatment Programme, a group of stabilized patients on an average methadone dose of 150 mg/day (range 60-380 mg/day), reduced alcohol consumption after being started on GHB at an average dosage of 4.725 g/day (range 1.75-5.25 g/day)^(32, 35).

In heroin addicts, alcohol dependence can develop before heroin addiction or together with it^(7, 11, 28, 37); alternatively, it may mark a later-stage transition from a more expensive, illegal drug to a cheaper, legal one, across a common opioidergic bridge. Some heroin addicts, incorrectly treated in short-term or agonist-free programmes, may resort to alcohol in order to stay detached from a heroin environment. Lastly, treatment with ineffective methadone dosages (known as 'undermedication') favours alcohol consumption and abuse during the programme^(31, 34, 36, 42). Eventually, some heroin addicts belonging to the previous categories will end up becoming actual alcoholics through a secondary form of alcohol abuse. Others may stay detached from alcohol, avoiding addiction at all stages, simply through the (re)introduction or dose-adjustment of agonist treatment^(6, 28, 37, 38). In other words, GHB may be administered to heroin addicts whose alcohol abuse fails to respond to effective dosages of methadone during a maintenance programme.

GHB may be administered to heroin addicts, regardless of whether alcoholism is primary or secondary to heroin addiction in a chronological sense, after ascertaining that alcohol abuse is not an indirect expression of an unbalanced craving for opiates (masked heroinism). It would be useful to compare a maintenance regime at blocking dosages (100 mg/day) to a combined regimen of methadone and GHB, in order to clarify the interconnection between cravings for heroin and alcohol in this particular population of alcohol abusers.

Moreover, GHB may be used to treat recently detoxified heroin addicts who have recently experienced an intensifying craving for alcohol, so as to prevent its evolution towards secondary alcohol abuse.

Lastly, GHB may be resorted to in the case of abstinent heroin addicts who do not clearly need agonist treatment to be restored, but show an increasing trend towards drink.

Benzodiazepines

Concurrent alcohol and benzodiazepine abuse may develop in two ways: benzodiazepines may either act as a replacement for alcohol episodically or cyclically, or be combined with it after specific craving drives, which signify an autonomously developed benzodiazepine addiction. Independent benzodiazepine addiction should be challenged with induction and stabilization with clonazepam at blocking dosages. In the programme run by the Vincent P. Dole Dual Diagnosis Team, a subgroup of alcoholic heroin addicts was successfully treated with a combination of clonazepam (average dose 5 mg/day, range 5-9 mg/day) and GHB (average dose 4.725 g/day, range 1.75-5.25 g/day). As to the possible synergic effect of benzodiazepines and GHB, the induction of GABA-A tolerance by higher clonazepam dosages allows patients a higher level of safety, since it provides protection against intermittent GABA-A stimulation with abused depressants.

Principles for the safe and effective use of GHB

GHB's metabolic profile is the main limitation to the feasibility of maintenance treatment. In fact, its short half-life requires a certain level of compliance for effective dosages to be reached and maintained by regular self-administration. Addicts usually show poor compliance; in the specific case of heroin addicts, this problem can be partly overcome by tying the patient to the treatment setting through his or her acquired tolerance to agonist medications. On the other hand, a long-acting formulation of GHB would be unsafe in the early phase of treatment, due to potentially unfavourable interactions with alcohol, just as in the case of long-acting disulfiram. On one hand, the short latency of action of GHB is useful in the rapid buffering of alcohol withdrawal, but, on the other, it functions as the basis for GHB's abuse liability, together with its pro-dopaminergic action.

In order to minimize the risk of abuse, one must choose subjects for whom GHB treatment looms as feasible, and, secondly, select those at low risk of abuse behaviours. Whenever possible, GHB should be handed over to a third person (a significant one), whose duty is supervise its administration at prescribed doses and at regular intervals. Subjects should not handle large amounts of GHB, especially when self-administering it; limited supplies should be made available at regular intervals. It is advisable to divide daily dosages, right from the start, into four to six small fractions^(5, 14, 30, 43), so as to assess a patient's compliance and avoid the narcotic effects that would be elicited by large single doses.

Apart from justified concerns about side-effects and possible interactions with other abused substances, the aim of this strategy is to avoid GHB being discriminated by the brain as a source of euphoria. In particular, subjects who have already experienced opiate-induced euphoria are likely to discriminate GHB when it is administered at higher single doses, even when the cumulative daily amounts of exposure are equal⁽⁴⁵⁾.

Once treatment has started, the persistence of drinking behaviours – though these

will probably occur at lower levels – is not a reason for terminating treatment. In fact, this kind of benefit constitutes a partial response to GHB (reduction in drinking frequency and/or amounts) and it resembles the outcome that constitutes a complete response (sobriety) ⁽³³⁾.

Alcohol use during GHB treatment cannot be regarded as GHB misuse, just as heroin use during methadone treatment cannot be classified as methadone misuse. Subjects taking lower GHB doses may try to achieve greater control over their craving by increasing their GHB doses autonomously. These behaviours should not be mistaken for GHB abuse, either; GHB abuse consists of the consumption of higher GHB doses in order to elicit euphoric effects.

GHB may be combined with other effective treatments for alcohol abuse. After some time disulfiram can be added to a GHB regime, in order to proceed step by step towards complete sobriety after partial control over drinking has been achieved. In psychotic subjects, who are sensitive to GHB's dopaminergic effects, this combination is potentially harmful. A GHB-naltrexone combination is theoretically feasible, since doses of GHB do not seem to act directly via opioid receptors ^(13,45).

Case reports

Cases 1-8 have been described by Maremmani and Pacini ⁽³⁴⁾ and cases 9-13 by Lamanna and Maremmani ⁽²⁵⁾.

Case 1

G.C: male, 34 years, married, with a 6-year-old daughter. He works as a salesman for a wine factory; his work requires him to travel frequently and he lives with his family in a small town. His family of origin belongs to an intermediate-income class with an average cultural level; both of his parents have white-collar jobs. His only brother is an alcoholic who keeps sober for long periods of time (the latest period lasted two years), has repeatedly tried disulfiram treatment, but relapsed after discontinuing the self-administration of the drug more than once, reaching levels of intoxication which required hospitalization.

The patient applied for cocaine abuse treatment. Information gathered by the clinical interview led to a diagnosis of alcohol addiction, opiate addiction and cocaine addiction. He first tried alcohol at the age of 14, he first abused it at 16, and started drinking regularly at 18 (six 33 cl beers and 6 high-grade alcoholic drinks). Regular consumption proceeded for the following 16 years with two intervals of sobriety, one within a therapeutic community for heroin addicts, the other determined in a spontaneous way because of alcohol-related health concerns. On two occasions the patient went into a drink-induced coma, and on two other occasions he had car accidents while driving under the influence of drink; he suffered several minor traumas due to alcoholic intoxication. The patient first tried heroin at the age of 23 and became a regular user

within the following two years. At the age of 27 he spent some time in a therapeutic community, but he relapsed into alcohol abuse shortly after being discharged; he was soon drinking as much as before, and after two months relapsed into heroin abuse, too. Binge-drinking became very frequent (over three times a week). Approximately one year before entering our programme the patient suffered from acute alcoholic hepatitis; on that occasion he was also diagnosed as HCV-infected: as a reaction, the patient stopped using alcohol and minimized heroin use by resorting to cocaine, but soon become addicted to that. At the time of our first evaluation, he has been addicted to cocaine for 6 months, to opiates for 180 months and to alcohol for 292 months. He had never undergone specific treatment programmes for any of his addictions.

He was initially started on buprenorphine combined with a dopaminergic drug (ropinirole 0.75 g/day) in order to overcome cocaine craving, within a clinical trial. Opiate and cocaine use dwindled to extinction. After 4 months, the patient increased his drinking and dropped out of the programme, soon to relapse into heroin and cocaine use as well. Accompanied by his family, he applied for re-entry into treatment and was started back on the same regimen, adding GHB at a 2.625 g/day dose. Although control over cocaine and opiate abuse was satisfactory, compliance with treatment was limited to buprenorphine (8 mg/day): the patient discontinued ropinirole after a few weeks, and stopped taking GHB on a regular basis, with two periods of total discontinuation. Alcohol abuse increase every time GHB was discontinued. After buprenorphine dosage was stepped up to 12 mg/day, alcohol abuse evolved according to a different pattern, free from binge-drinking episodes. At that point the patient began working and had a good relationship with his significant ones.

After two years of treatment, a depressive episode set in, followed by a hypomanic phase, during which the patient intensified his drinking habits and experienced a bout of opiate craving. Buprenorphine was autonomously discontinued for one week in order to allow heroin use, but the patient promptly applied for treatment; in line with medical advice, he was transferred to a methadone programme, receiving 60 mg/day in the induction period. During the first two weeks, as he was still hypomanic, he continued his use of opiates and turned dysphoric as soon as an opioid blockade was established, but soon after reaching a dose of 100 mg/day, his craving was extinguished and his mood normalized. Meanwhile, GHB was reintroduced (this was the third attempt), this time under his wife's supervision, at 2.625 g/day. To date, the patient has taken GHB regularly for eight weeks, with a stable reduction of drinking amounts. Symptoms of muscular contractions and speech during sleep were reported, but were probably due to the antidepressant the patient had started taking on his own initiative (citalopram), and stopped after it was discontinued. EEG and NMR were negative, as well as general blood tests. No symptoms of alcohol withdrawal were recorded. Opiate use is again almost down to zero (with only two episodes in the last two weeks). Cocaine use was not ongoing this time, and did not restart; the patient is currently taking 0.50 mg/day of ropinirole.

Case 2

LM: female, 40 years old, divorced. She used to run a little shop together with her sister but got into debt and went bankrupt. Lately, she has found a job as a clerk. Her family belongs to the working class. Her twin sister is a heroin addict, but was successfully treated in a methadone maintenance programme at an average dose (100 mg/day). Her former husband is a habitual drinker.

The patient first tried heroin while staying abroad, at the age of 23, during a hypomanic phase. She started using heroin regularly after two weeks and continued for some months, but she eventually stopped after her return to Italy. Meanwhile, she had started drinking occasionally, and some episodes of intoxication occurred; in the next few years, she kept on drinking without any regular pattern. Four years ago, while facing financial and family problems, she reported an intensification of alcohol use, and started drinking regularly, beginning early each morning. Moreover, her use of heroin resumed, and she started using illegal methadone at a 10 mg daily dose, on a regular basis, since it was cheaper than heroin and lasted longer, bringing stable mood elation, talkativeness, increased physical energy, and an optimistic attitude. These effects are identical with those reported by her sister when using heroin. Alcohol use has increased up to the present, with frequent episodes of intoxication, along with benzodiazepine polyabuse. One episode of coma and a car accident due to depressant intoxication have been reported. The patient applied for alcohol abuse treatment, following her sister's advice. She was diagnosed as suffering from Bipolar II disorder, against the background of a cyclothymic temperament, and a histrionic-borderline personality mode. She was started on GHB, but was not compliant (she skipped doses, and missed taking GHB for whole days). After eight weeks, symptoms of depressant intoxication were still significant and episodes of intoxication still occurred. At this time she was hospitalized for coma due to acute jugular thrombosis, whose origin is still unknown. After discharge she kept on drinking, with severe symptoms of intoxication, and was soon hospitalized in a psychiatric ward. Although her urinalyses revealed recent consumption of alcohol, benzodiazepines and methadone, and her blood tests revealed high levels of benzodiazepines, the patient vehemently denied taking anything but alcohol, and kept up her denials even when confronted with the evidence of drug blisters found in her bag. Some days later, she admitted using these substances, but still minimized the amounts. Two weeks after discharge, she still had poor insight, claiming she had drastically improved her control over alcohol craving, but agreed to enter a methadone maintenance programme. Dosage was increased up to 30 mg/day and combined with gabapentin at a dose of 1200 mg/day. She refused to try GHB again, claiming she was intolerant to it. Methadone was further increased to 100 mg/day and was effective in suppressing benzodiazepine use and binge-drinking. Alcohol consumption remained stable, with at most five high-grade drinks a day. A depressive episode occurred six months later during treatment and was challenged by fluoxetine, but she got over it within 10 days after fluoxetine initiation. The patient tapered her methadone to 60 mg/day against medical advice and increased her drinking; she then accepted the introduction

of GHB as an alternative to increasing methadone again. When taking GHB 3.5 g/day she did not display symptoms of intolerance or alcohol withdrawal. Alcohol use fell to two drinks a day within a week and remained stable over the following eight weeks. The patient has kept working since, but she is still in conflict with family members over her personality features. Her somatic condition is currently of some concern; it comprises hardening of the hepatic portal venous system, a duodenal tumour with an unspecified grade of malignancy, and anaemia due to iron deficiency.

Case 3

BN: female, 35 years old. She is married with a 12-year-old daughter, who is being fostered by her mother's parents, as ordered in a trial sentence. She used to work in her family's factory, but was unable to continue, due to her addictive disease. Her husband is a heroin addict, and they live together in a small town. The socioeconomic status of both families of origin is good. Alcohol does not run in her family at all. The patient applied for treatment together with her husband; they had been referred to the centre by both their families in order to achieve detoxification from heroin. Alcohol intoxication was evident in both, and more severe for her; she denies serious drinking habits, and only admits to taking one drink a day. She first used heroin at the age of 20, and became a regular user at 26, always snorting it. Some months before our evaluation, husband and wife travelled to Switzerland on their own, in order to attempt self-managed detoxification from heroin, and came back two months later. Although they stayed heroin-free, he had resorted to heavy alcohol use, and she had intensified her drinking habits in such a way as to become chronically intoxicated. The patient reported first using alcohol at 20 years, when she became a regular drinker, increasing her consumption to about 7 drinks a day by 26. She never stopped drinking while using heroin, and, after detoxification from heroin, reached a daily intake of 14 drinks. She had never undergone any treatment for either addictive disorder. Methadone was started and increased up to 70 mg/day, more gradually than on average in order to reduce the risk of a combined overdose in the period when the patient's tolerance of opiates was still low. Afterwards, she was induced into GHB treatment at a 3.5 g. At this first attempt, compliance was poor; she discontinued GHB after three weeks, only to restart a week later, though not on a regular basis. Opiate use was over, while alcohol abuse persisted, and increased during the GHB-free week. After psychoeducational sessions, the patient agreed to try GHB again, reducing alcohol use to 3 drinks a day. In the meantime, she was able to go back to work, which had not happened, despite a stable heroin-free condition, in the previous six months of treatment. Later on, she autonomously discontinued GHB and relapsed into heavier alcohol use, which required further psychoeducational work. Her insight has always been poor, but was to some extent improved by regular psychoeducational sessions. In reporting the recent course of her drinking, she was eager to minimize. She denied that she has ever drunk large amounts, and claimed that she is currently drinking "definitely less" than before, but gave no details, and concluded

that her drinking habits are no different from anyone else's.

Case 4

L.M.: male, 37 years old, married to the woman described in case 3. He is the younger of two brothers; he used to work in his family's factory as a departmental director, but stopped because of drug-related problems. His family belongs to an upper socioeconomic class. No case of alcohol abuse has been reported among relatives. He started using heroin at 18 years old (two years before his wife-to-be, to whom she was already engaged at the time), and became a regular user at 27 (one year later than his wife), always snorting it. Alcohol use was insignificant before their attempt to achieve detoxification from heroin, some months before our evaluation. He was started on methadone and stabilized at 70 mg/day within 12 weeks (see case 3). Due to persistent daily alcohol use, GHB was added at a dose of 3.5 g. The patient took GHB regularly for the first two months and became detached from alcohol quite rapidly, discontinuing alcohol altogether some time later. He has so far experienced no relapse into heroin or alcohol use. No GHB withdrawal symptoms have been reported.

Case 5

D.G., female, 39 years old, a widow. She was born the second of four siblings, studied as an interpreter in foreign languages and used to work in that capacity until drug-related problems caused interference. She has lived in various different towns, moving in response to the requirements of her job. She is now living with her family of origin, due to financial difficulties. Her mother suffers from an obsessive-compulsive disorder, her father is an alcoholic and her sister a heroin addict.

She first used heroin at the age of 15; she became addicted during the first year of use and started injecting it. At the age of 18 she spent a period in a therapeutic community, relapsing after discharge. In the following months, she was hospitalized in order to undergo detoxification and short-term naltrexone administration. None of this treatment, despite high expectations, ever provided a stable resolution of the disease. She first enrolled in a methadone maintenance programme in 1992, and stopped using heroin for a year. She eventually negotiated programme termination with her case managers, and became heroin-free and highly functional for three years, but eventually relapsed into heroin use and applied for treatment in the same programme, with satisfactory results. Treatment again achieved results thanks to methadone tapering, but after a time opiate use was resumed, becoming regular again after three years, when the patient applied for treatment for the third time; on this occasion the benefit was complete and rapidly accomplished.

Alcohol use began quite early (when she was 13 years old), and became regular while heroin use was still occasional (at 15). The patient's alcohol consumption pattern has been regular, and does not show a single period of sobriety, the highest amounts recorded

being 1.5 litres of beer a day, without binge-drinking episodes. In 1997, when she was about to relapse into heroin use, she was hospitalized due to acute liver failure caused by alcohol intoxication combined with chronic HCV infection. She stayed abstinent for two months after discharge, while she was following a methadone maintenance treatment programme at a 40 mg/day dose and taking GHB at 3.5 g. Treatment with GHB was tapered on medical advice (which seems to have been unreasonable, considering her clinical therapeutic history); she remained abstinent from heroin during methadone treatment, but relapsed heavily into alcohol use.

Case 6

R.S.: male, 44 years old, an only son, never married; he lives with his family in a town, and finds temporary employment as a blue-collar worker. His family belongs to the working class. He first tried alcohol when he was 18, and became a regular drinker at 25. Amounts are usually as high as one bottle of wine a day, but he might drink twice or three times as much during weekends, and he drinks excessively during evenings and nights with friends. He had been drinking for ten years without periods of sobriety, and following a stable pattern, when he started on heroin at the age of 33. Heroin addiction took less than a year to set in, and a year later he applied for short-term methadone treatment, which was followed by an immediate relapse. During an outpatient treatment programme he rapidly stopped heroin use, at a dosage of only 60 mg/day (far below the average of our sample), but alcohol use persisted, even if with lower amounts and fewer binge episodes. In that period the patient's condition improved. GHB was introduced after two years of successful methadone maintenance; at that point the patient accepted the proposal that his alcoholism should be treated in a specific way. At a GHB dose of 3.5 g/day, alcohol showed a fall of 20% at two weeks, and of 50% at four weeks. Compliance with regular GHB treatment was targeted during repeated brief psychoeducational sessions, which were started at the patient's request after he had stopped GHB for one week and immediately relapsed into heavy drinking. The reintroduction of GHB was effective, and alcohol consumption has stayed as low as 30% of baseline and 15% of the lifetime maximum.

Case 7

M.G.: female, 36 years; her only son lives with her former partner. She is homeless and trades sex for hospitality and drugs. She started using substance in her late adolescence as a polyabuser (cocaine, alcohol, heroin and depressants), and was admitted to emergency departments several times when suffering from intoxication or withdrawal from depressants. She was once hospitalized in a psychiatric ward in order to stop her abuse practices, and was started on methadone, up to a 130 mg/day stabilization dosage. Abuse was minimized until 1995, when a team of case managers convinced the patient she should stop taking methadone in order to be regarded as a reliable mother

and be allowed to have a stable relationship with her son. She was advised to enter a therapeutic community and have her methadone tapered there, where she could start meeting her son. After five months she left the community, leaving her son to the social workers, and relapsing into polyabuse. Her social situation radically deteriorated until the next treatment period, starting in 1999 (methadone maintenance at 150 mg/day). Regrettably, that second attempt failed to control alcohol abuse, so that rehabilitation was not as satisfactory as it had been the previous time. After three years, her dosage was as low as 40 mg/day, but alcohol abuse had not intensified with respect to the 150 mg/day phase, and the patient agreed to add GHB 3.5 g/day in order to be able to benefit from social facilities, since she had to meet the requirement of sobriety to receive support from Social Services. Drinking was minimized within one month, but her case managers paradoxically suggested she should discontinue GHB in order to complete her treatment, and she relapsed within a week, reaching previous levels of abuse. She is now receiving treatment for the third time at another centre, and has achieved a significant reduction in her alcohol craving, but her compliance is unstable and she swings between periods of light drinking when receiving GHB treatment and periods of heavy drinking after GHB discontinuation. Her psychosocial situation has not improved significantly, and she has continued to trade sex for a place to stay.

Case 8

A.D.: female, 22 years old, lives with her family (three brothers and her parents) in a small town. Her family is well off, and owns a little factory; her brother is a university student, while she found a blue-collar job after leaving high school. She applied for alcohol abuse treatment on her mother's insistent advice. Symptoms of affective instability are relevant, although the patient shows a degree of concern about recurrent anxiety (panic attacks) and social phobia, which she has tried to counteract by alcohol use. She has used a variety of substances from the age of 18 (cannabis, alcohol, MDMA and amphetamines), including heroin, but she took heroin only over a three-month period, when she was 20. She decided to stop using heroin as soon as she experienced withdrawal symptoms, without needing any medication, but then switched to cocaine first, and alcohol later, showing a binge pattern. Binges used to take place twice a week with friends, but became a daily event in the last period before consultation. Initially, amounts of consumption were as high as 1.5 litres of beer and 10 high-grade drinks; later on, she started drinking a further 0.5 litres of beer before seeing friends, and regularly became drunk, with promiscuous sexual behaviour during the nights and multiple car accidents in the mornings. The patient also abused cocaine and prescribed benzodiazepines, though irregularly, while heroin use was sporadic (two episodes in 4 months). Cocaine was consumed at the end of alcohol binges, while benzodiazepines were resorted to in the mornings in order to control agoraphobia and allow her to reach her place of work. The patient was given a prescription of gabapentin (1600 mg/day), paroxetine 20 mg/day and GHB, up to 3.5 g/day. At two weeks she had managed to

reduce her drinking by 50%, with a lower frequency of binges; at eight weeks, alcohol use had fallen to 10% of its earlier levels, and no binges had occurred recently. Blood tests were normal. On two occasions, however, the patient took low doses of benzodiazepines in the morning, stealing them from her mother's closet, after being denied a medical prescription. After four month's abstinence from alcohol and benzodiazepines, the patient suddenly took 12.25 g of GHB all at once in the morning, and was treated for CNS depressant intoxication; this was certainly the first episode of GHB abuse, since GHB had been always administered by her mother before she seized it that morning, and GHB is not easy to find on the Italian black market. The patient reported taking GHB on an impulse, without any precise expectation, but in a state of excitement about trying the effect, and definitely without any suicidal intention. GHB was not confirmed, and she was given a prescription of valproic acid and carbamazepine. Despite staying abstinent from alcoholics, the patient relapsed into daily heroin use by injection for two weeks; as a result, she was started on buprenorphine in combination with valproic acid only. After reaching 8 mg of buprenorphine, the patient has stayed abstinent from both alcohol and opiates for six months, and substance use has remained limited to cannabis, showing an irregular pattern.

Case 9

S.D.: 40 years old, male, never married, suffering from a Bipolar Disorder, type I. Metadone stabilization dosage was 210 mg/day and GHB was employed at 10.5 g/day. The patient was initially hospitalized in a Prison Hospital for mentally ill detainees, and was recognized as suffering from a severe psychiatric disturbance complicated by polydrug abuse. At the time of our first evaluation, he was receiving heavy doses of traditional benzodiazepines and neuroleptics, which did not influence his cravings and self-destructive impulsiveness.

Despite methadone maintenance at 210 mg/day, the patient's craving for alcohol and sedatives stayed high: despite his refusal to increase methadone, GHB was combined with significant improvement. The patient became more accessible to dialogue, stopped self-destructive behaviours and showed less frequent and severe mood swings; this made possible the tapering of his neuroleptic medications, while maintaining his mood stabilizers and traditional psychotropic medications.

Case 10

C.C., 35 years, female, black, never married, suffering from bipolar disorder of type II and HIV+. In her history, alcohol use was primary with respect to heroin use, but she had become addicted to both substances. Methadone and GHB treatments were started together, maximum dosages being 60 mg/day of methadone and 7 g/day of GHB. and her condition improved radically, with the extinction both of craving and addictive behaviours. Moreover, the state of her infections was found to have improved, too,

and the course towards AIDS has been arrested so far.

Case 11

S.R.: 43 years old, male, married, suffering from Bipolar Disorder of type II. He had been in treatment with methadone for a long time at a 100 mg/day stabilization dosage, but had displayed alcohol abuse practices of increasing frequency and severity throughout the previous months, despite staying abstinent from opiates, as before. After the induction of GHB at 40 mg/day, satisfactory remission was achieved.

Case 12

S.N.: 39 years old, male, never married, suffering from Bipolar Disorder, type II, and Panic Disorder. He had a longstanding history of severe heroin addiction, which was brought to an end by methadone maintenance treatment at a maximum dosage of 160 mg/day. One year ago, the patient went through stressful life events, with a resumption of panic symptoms and generalized anxiety, which he tried to control by increasing his consumption of alcohol and benzodiazepines. Since the patient was reluctant to increase his methadone dosage, GHB was proposed and introduced up to a 5.25 g/day dosage. His consumption of alcohol and benzodiazepines fell drastically, and has so far stayed below the level of intoxication.

Case 13

N.G.: 42 years, male, living with his partner, suffering from Bipolar Disorder, type I, and HIV+. He had started methadone treatment after many years of heroin addiction, and had become stably heroin-free and rehabilitated at a dose of 80 mg/day. Periods of alcohol intoxication were, however, recurrent, and he had been hospitalized more than once with symptoms of liver failure. During the last hospitalization period, GHB was introduced at a 5.25 g/day dosage. Alcohol abuse has been under control ever since.

Conclusions

Sodium gamma-hydroxybutyrate (GHB) may be resorted to as means of alcohol abuse control even in polyabusers. Precautions must, however, be taken to counteract the higher level of impulsivity in such populations, because the substance polyabuse tends to raise GHB's potential for abuse. GHB may be used in heroin addicts who have already been stabilized on methadone treatment, due to the anti-impulsive effect of methadone maintenance and the minimization of secondary alcohol and depressant abuse with adequate methadone dosages. Cocaine users should not be given prescriptions of GHB in an outpatient setting; cocaine craving should, in fact, be targeted first, so as to increase compliance up to the minimum required to allow adherence to a main-

tenance, fractioned-dose GHB programme. The availability of a slow-acting, longer half-life GHB would change its pharmacokinetic profile into one more suitable for the healing of craving-related brain pathways. Its abuse potential would be minimized as a result, and its use could then be extended to impulsive individuals, as happens with methadone or buprenorphine.

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Received November 27, 2006 - Accepted January 5, 2007