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Dihydrocodeine for the Treatment of Alcohol Dependence

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Summary

Objective: In most cases, alcohol dependence shows a profile similar to that of many chronic diseases, but no effective basic treatment comparable to that adopted with the other illnesses has been established up to now. In particular, patients with repeated relapses, despite a broad range of therapeutic approaches, and patients who are unable to attain what is essentially a state of abstinence from alcohol, continued to need a basic medication. **Methods:** Convinced by a few specialized colleagues who reported successful treatments of alcohol addicts with Dihydrocodeine (DHC) and by a first own patient of ours who showed a complete reduction of his severe alcohol craving when given Codeine-based pain medication, we went on to treat as many as 77 (M/F: 55/22) heavily alcohol-addicted patients with DHC, beginning in 1997. Right from the start, the data were documented meticulously. We present a retrospective analysis of this documentation here. **Results:** The patients had a history of a total of 1060 medically assisted detoxifications and specialized therapies. The 4 year-retention rate was 26.1%, including 6.5% of treatments that had a successful outcome. In our 12-step scale on clinical impressions, we noticed a significant improvement from a mean of 3.5 to 6.7. The demand for medically assisted detoxifications in patients who had at most 2 years left was reduced by 63%. Mean GGT improved from 201.1 U/l at baseline to 57 U/l after 4 years. The MCV value also showed a significant improvement. Mean GGT of patients with additional chronic hepatitis C improved from 198.3 U/l at baseline to 86.4 U/l after 1 year. **Conclusions:** Our data are preliminary, and these are practice-generated results, which are far from reflecting the whole potential of this new approach. Between 10 and 20% of these patients recorded no good effects from DHC. In around half of the patients the treatment was abandoned for several reasons, in some cases because of the anxiety caused by the pioneering nature of this non-established therapy: a treatment with partly overcautious dosages. But in about 25% of the patients, DHC was an almost perfect medication, sometimes even crucially better than all previous approaches, even in absolutely desperate cases. A lot of regular studies are needed, comparing different substances, settings, dosages and clarifying the cause and pathomechanism of the effects. This should be done because it seems that we are standing at a gateway leading into immense new opportunities. In the long run the breakthrough will be a question of the right mixture of scientific investigation, well-structured implementation with sufficient control, but also, and this may be most important factor, enough trust in our patients and the prescribing doctors. On a long-term basis there will be no success without a structure that supports and reassures, but also represents, this trust.

Key Words: Dihydrocodeine - Alcohol Dependence

1. Background

Basic treatments have been developed for most diseases with a chronic or polyleptic character, e.g. asthma, hypertension, diabetes, rheumatic disease, migraine, especially if they are associated with too many or too severe exacerbations. Dependence on alcohol shows a similar profile in most cases, but, to date, no effective basic treatment has been established. The need is extremely evident, mainly for patients with no working abstinence and repeated relapses, despite all the therapeutic approaches implemented, and for patients who are unable to achieve an urgently needed abstinence from alcohol.

Basic treatment means basic medication. In alcohol dependence, the aim of that medication should be a reduction of craving, relapses and alcohol-related problems. The first hope was to achieve this by using substances without any potential addiction-inducing capacity. The practical relevance of such substances remained limited. The number of prescriptions of the most prescribed substance in Germany, Acamprosate, is so low (0.7 Mio DDD 2006, [21]) that it does not reach 1% [11] of these addicted patients or 5% of the appropriate patients [12], and most of those who take it report no effect. The effect of the opioid antagonist Naltrexone does not seem crucially stronger, though the substance is more frequently prescribed in

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the Scandinavian countries. The role of Disulfirame has remained absolutely marginal for decades.

The failure of the antagonistic or addiction-avoiding substances probably offers a crucial hint about how to treat patients. Why are addictive substances used? If we ask patients themselves, they answer: 'As tranquillizers, to blot out bad things in the brain, sometimes to overcome displeasing self-consciousness'. This implies that they have unpleasant, inhibiting perceptions, in some cases uninterruptedly, in others sporadically. They describe it as a grave handicap, which is often hard or impossible to bear. No wonder, then, that the craving repeatedly turns out to be stronger than willpower.

From this point of view, it is clear enough that what many of them need is an agonist that is strong enough to bring some of the positive effects of alcohol. This is not as easy as in the case of opiate addicts, where we know the opiate receptors. Heroin, for instance, can be replaced by other substances acting at the opiate receptors, like Methadone, Codeine, Morphine and Buprenorphine.

For alcohol, too, a replacement is needed, because it is too toxic and too hard to control. But nothing is known about alcohol receptors. What kinds of agonists are able to give some of the positive effects of alcohol without the associated dangers? In this case, too, we get important hints from our patients. Some try a switch to or a completion with benzodiazepines; this is very questionable, because of a more dominant, negative impact on psychic resilience and, in most cases, no good therapeutic control over the real dosage is possible.

Possibly related to this, but clearly showing an improvement, are the first encouraging results obtained with Gamma-Hydroxybutyrate (GHB), a GABA (B) receptor agonist, so far mainly documented in Italian studies [1, 2, 3,7, 8, 22, 23,24,26]. GHB is effective in reducing alcohol intake and in maintaining abstinence, partly better than Naltrexone or Disulfirame. Some results were not much better than with the antagonistic substances, and considering their marginal clinical role, this is only the beginning of a new way forward. Critical experiences due to dangerous or fatal poisoning with GHB have been reported, for instance from Spain [14] and Sweden [20].

Another substance with a similar agonism is Baclofen. In this case too Italians have demonstrated that severely alcohol-dependent patients can be treated very effectively with this agonist [4, 5].

In Germany, Clomethiazole is the standard medication for the treatment and prevention of alcohol withdrawal syndrome. It is also widely used as an agonist substance for long-term treatment, but almost only by non-specialized physicians without a therapeutic concept. A lot of life-threatening emergency events with combined Alcohol-Clomethiazole poisonings led to official declarations that Clomethiazole is obsolete for outpatient treatment [9].

Some alcohol-dependent patients report the good ef-

fects of amphetamines, and that they need more alcohol if they have no access to these substances.

What about the opioids? Heroin addicts often report that they stopped drinking too much alcohol when they switched to heroin. This substance acting at the opiate receptors was obviously able to displace alcohol. Did it happen because of a greater potential for exhilaration? In any case, a connection between alcohol and opiate receptors has been scientifically known for many years. Publications, in particular by Fröhlich and Gianoulakis [13, 15, 16, 17], have proved this clearly. The partial efficacy of treatment with opiate antagonists [28] also demonstrates this connection. Caputo et al., once again an Italian group, published results suggesting a possible effect of short-term Methadone administration in reducing alcohol consumption in a population of non-alcoholic heroin-addicted patients in 2002 [6]. On the other hand, many Methadone maintenance patients have alcohol-related problems, and their physicians are often unsure how to overcome them. In individual cases, raising the dosage of the opioid to very high levels (Methadone for instance, to 400 mg daily) was extremely successful, giving us another hint that opioids can help to overcome alcohol addiction.

For our specific procedure, we have learnt both from colleagues and patients. 2 pioneering German doctors, originally specialized in maintenance treatment for opiate addicts, reported and published their first convincing experiences in treating alcohol-dependent patients with Dihydrocodeine (DHC) [18, 10]. This idea was first made public as early as 1929 [19], but was then forgotten for decades. Our personal scepticism was crucially minimized when one desperate patient, permanently suffering from strong craving and repeated relapses, reported to us in 1997 that the intake of 3 analgesic tablets each containing 30mg Codeine had strongly reduced his craving. Very cautiously, and with his comprehensive written consent, we started to treat him with DHC systematically.

2. Methods

Since then, we have treated 77 (M/F: 55/22) heavily alcohol-addicted patients with DHC. The whole prescribed medication, its dosage, all further relapses, detoxifications, laboratory results and the general impression, were continuously documented right from the start. We now present the retrospective analysis of this documentation.

3. Results

The medical history of these patients was impressive: 922 previous medically assisted detoxifications, 679 of them in a hospital; additionally, 138 therapies in specialized addiction clinics. Mean age of the patients was 46.0 y, mean duration of ostentatious alcohol consumption 22.1 y. In 93.2% the indication was an inability to live with or

without alcohol, in 33.8% there were urgent somatic and in 29.7% urgent social reasons. 15 patients had a history of sporadic or dependent use of opiates, which had been overcome for 9.4 years on average.

DHC has to be normally taken q.i.d.. Starting dosage in most cases was 120 mg (4 x 30mg) daily. The mean dosage was raised to 287 mg daily after 21 months and

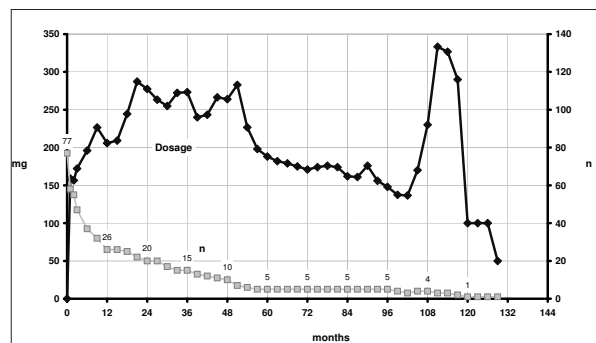


Figure 1. Average daily dosage DHC, showing that it was possible to control and to reduce the dosage over years. In some patients, the reduction was postponed in favour of the optimal dosage for a sustained stabilization, after a few years (peak of the dosage at the right).

then slowly reduced, reaching 137 mg after 100 months (DHC-base). In the last few years, we have tended to use slightly higher dosages (Figure 1).

Of 46 patients, included until 12/03, 9 (19.6%) were

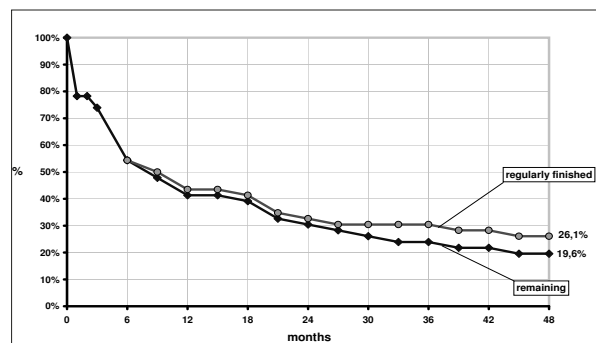


Figure 2. Patients remaining on DHC treatment and patients who had regularly finished the treatment without further relapse – insertion until 2003.

still on treatment 4 years later. 3 had successfully finished the treatment without further relapses (4 year-retention rate among all patients was 26.1%) (Figure 2).

The actual status of the 77 was: 18 remaining on treatment (23%), 6 had finished with sustained success (8%), 53 were no longer being treated, and had been unsuccessful (69%, including 14 (18%) who left the treatment within the first month). In our 12-step scale on clinical impressions, we noticed a statistically significant improvement from mean 3.5 to 6.7. Patients remaining

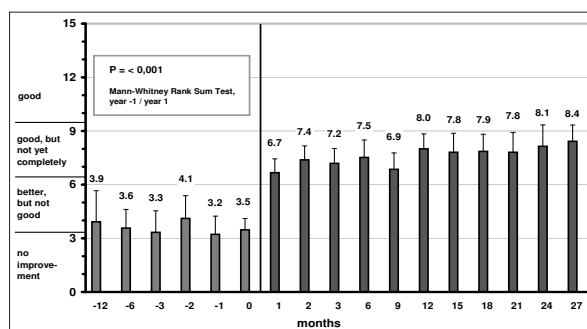


Figure 3. Clinical impression - average of all patients who remained > 2y (n = 21)

>2 years (n = 21) had an improvement from 3.5 to 8.1 at the end of the 2 years (Figure 3).

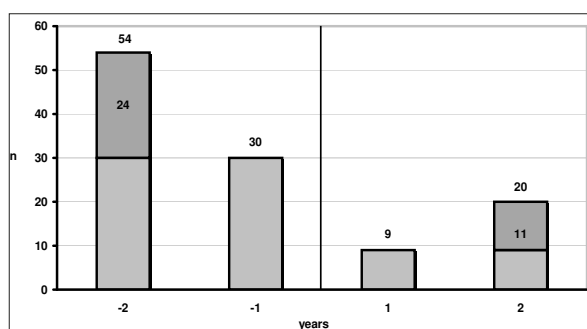


Figure 4: Medically assisted detoxifications – patients with documented 2 years before and after start of the DHC treatment (54 - 20 = -63%!).

These patients had needed 54 medically assisted detoxifications during the 2 previous years and 20 during the first 2 years after starting on DHC (Figure 4).

The no-relapse/relapse-ratio since the last consultation

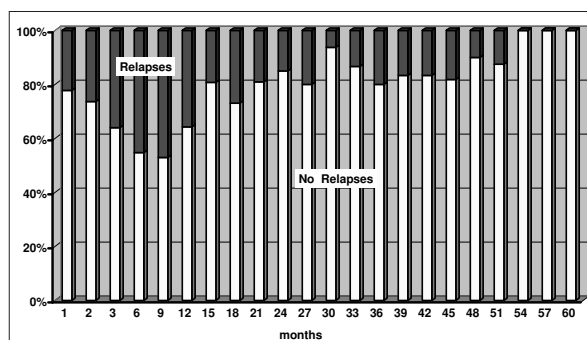


Figure 5. No-relapse/relapse-ratio since the last consultation of all patients

of all patients fell to 1.13 at month 9 but then rose to 7 after 4 years and reached 100% no relapse level by the 5th year (Figure 5).

Mean GGT of all patients improved from 201.1 U/l at baseline to 79.2 U/l after 1 year (or 216.6 in all patients, including more than one year before, to 79.2 U/l, $p=0.05$) and to 57 U/l after 4 years (n then only 6, p therefore only 0.093, Figure 6).

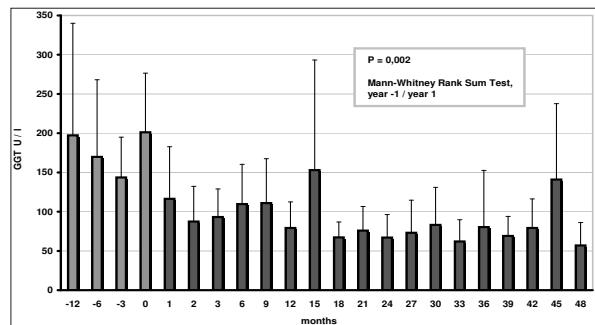


Figure 6. GGT values with 95% confidence intervals during the last year before and the first 4 years on DHC treatment

The MCV value also showed an improvement from 96.6 fl at baseline to 93.6 fl after 1 year ($p = 0,148$), but the difference in the mean values of these two groups was not great enough to reject the possibility that the difference was due to random sampling variability. Taking all the measurements recorded for months 0, -3, -6 and -12 together and comparing them with all the measurements for months 3, 6, 9 and 12, the difference was clearly significant ($p=0,004$). Mean GGT of patients with additional chronic hepatitis C ($n = 8$) improved from 198.3 U/l at baseline to 86.4 U/l after 1 year ($p = 0,063$) (Figure 7).

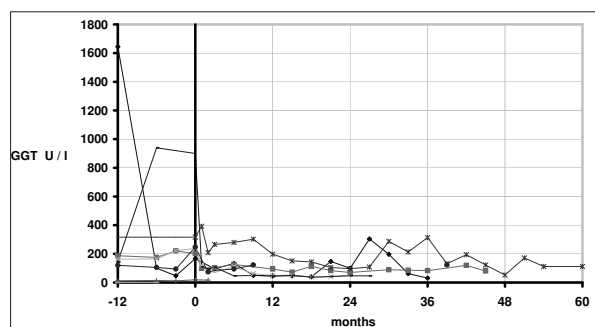


Figure 7. GGT values of the patients with simultaneous chronic hepatitis C

4. Discussion

Most of our patients were in a desperate stage of the addiction disease. The extremely high number of previous detoxifications and treatment attempts go to indicate the high and ineffective therapeutic costs of those patients and the therapeutic helplessness. Obviously, these patients

are suffering from a chronic disease with repeated exacerbations/relapses; there may be additional disorders, too, such as permanent craving, handicapping and often destroying their life.

There can be no doubt: all the attempts made with agonists, the general success of maintenance therapies for opiate addicts and the widespread ineffectiveness of abstinence-based, or treatments that aim to achieve abstinence, indicate that this chronic disease has to be treated in the same way as other chronic diseases – with effective basic medication. It must be a substance, or a combination of substances, able to give patients at least some of the effects of alcohol, in many cases. The experts have to find out and perform studies on which substance is the best, generally and individually, and what the best setting is for this kind of treatment.

All these substances, in principle, have to face four central problems:

1. Addiction;
2. Danger in case of abuse;
3. The black market;
4. Uncontrolled prescriptions from doctors who have no therapeutic concept.

On item 1: Our patients have a chronic disease with an addiction or a craving for substances that have an addictive potential. One of their central problems is their denial of the addiction and its chronic character, together with the continuing failure of their attempts to escape the addiction. What they need is to finally accept the chronic character of the disease and their addiction. The addiction has then to be treated in the best possible way, with settings and substances that allow the subject to live as well and as free of danger as possible. Of course, there is no universal solution applicable to all patients. The treatment has to be as individually differentiated as in other chronic diseases, especially in mental disorders. Practical experience and evidence from scientific trials have to be animatedly connected. Addiction itself is widely acceptable, if all this can be guaranteed, and in many cases it is much better than an unsuccessful attempt to live without any addiction.

On item 2: The tendency to abuse agonistic substances is always strong; as a result, none of these substances can be considered innocuous. But when they are used regularly, many of these substances are relatively harmless and well tolerated. It is therefore our responsibility to do everything possible to ensure that their use shows a high degree of reliability. This is a central issue for an intelligent infrastructure, as it comprises both the single treatment and the whole logistical network that covers an entire region, with all its regulations and rules. We have experienced very different conditions deriving from the regulations of earlier periods, and are therefore sure that it is possible to find very intelligent solutions that guarantee a satisfactory quality of this treatment without exorbitant bureaucracy, restrictive regulations and dramatic disadvantages for our patients.

The side effects, as well as the acute and the chronic toxicity of each substance, must be taken seriously. Consideration of these factors and their consequences have to be well-balanced. Unduly lax handling and excessively restrictive administration are both able to do a lot of harm, and this is a crucial objection that can be made against any form of use of agonistic medications. But a very reliable and effective middle course is possible. We are able to report this very encouraging experience.

Good infrastructure of specialized centres and practices, a good level of cooperation well with less specialized physicians, cooperation with all interdisciplinary partners, as well as with patients' relatives and other contact people, are all necessary. Financial incentives can help to build up this infrastructure. Central details include: support features, specialists, support centres, handouts, quality circles, meetings, training and retraining offers, and control over the quality of support. All this should not be restrictive or frightening, but bring encouragement and a sense of support.

On the plane of individual treatment, a few basic medical rules for addicts are helpful and crucial:

- regular, thorough, empathy-based dialogues before and during therapy,
- an interdisciplinary approach,
- written dosage regulations, along with advice to take doses on schedule and never as needed,
- strict bookkeeping of consumption (my personal recommendation),
- prescription and rationing of the substitutes, counted out for a limited period of time only,
- blood and/or urinary parameters, to be checked as random samples.

This is not the place to explain this in greater detail. A summary is essential: what has been shown is that a much more qualified and humane treatment can be provided by adopting an intelligent regimen of this type, instead of lots of restrictive regulations laden with mistrust. It will never be possible to exclude the danger of fatal abuse one hundred per cent, but we can minimize this risk crucially. We must weigh this residual risk against all the other risks of otherwise insufficient or missed treatments.

On item 3: this again concerns the black market. The existence of this market is a question of infrastructure, and all the dangers that originate there pose the challenge of getting sufficient information: there are many additional aspects, like trust and mistrust, contact and support, or discrimination and persecution. In the long run, and possibly for ever, black markets for agonistic substances are a widespread reality. People consume what are, at least potentially, very dangerous substances without there being any advice, control or therapeutic concept. This is a high, real mortal danger. We can never absolutely avoid prescribed medications being circulated in any black market, but we can do a lot to minimize the percentage and the associated risks. We must never

disregard those risks. But we have to see that, if we are too worried about this, we will miss crucial chances to improve the treatment of addicted patients. The danger deriving from too much anxiety and avoiding all possible risks, may, on all overall basis, be higher than the real risks arising from abused substances on the black market. What is needed is a cooperative, pragmatic consideration of all aspects.

On item 4: we have to minimize uncontrolled prescriptions from doctors who have no therapeutic concept. For the same reasons. These prescriptions induce and perpetuate individual abuse and give an incentive to the black market. It is no solution to prohibit nearly all prescriptions, by limiting them to only a few physicians or centres. These restrictive concepts are implemented in most countries. They are based on mistrust, while trying to ensure the best possible quality. This is not the place to discuss this thoroughly. But we can point out that we have had a much better experience by applying a much less restrictive system, based on much more trust, support and pragmatic evaluation. We are able to solve this problem in a very satisfactory way, but we have to work on it. It does not happen automatically. And it is clear that new therapeutic concepts are a question of having an appropriate infrastructure both for individual treatment and for whole regions.

DHC has a special history in Germany, touching on all these problems. For many years, it was the most prescribed substitute for opiate addicts, while the prescription of Methadone was strongly restricted until 1998. The prescription of DHC was neither forbidden nor really allowed; it was left unregulated. There was no research, nor coordinated evaluation: the psychiatric experts railed against it, and doctors who prescribed it had to fear major difficulties in case of any bad event. By contrast, addicts said: 'I need it, it helps me', and many stories of impressive success were reported in circles of prescribing doctors, mainly GPs. Thus many prescribed it, but many of them partly on the basis of hearsay, without integration in any quality circle, and without regulation, because they were absolutely left alone. As a result, many prescriptions were made out without observing the basic rules of medicine for addicts mentioned above.

Treatment of opiate addicts with DHC became more widespread without rules, standards or controls. More and more deaths occurred, in each case connected with disastrous mismanagement, showing the central importance of proper management and the dangers of using this substance without a responsible structure. The best way to have optimized the situation would have been to install support centres and promote the foundation of quality circles. But there was too much resistance in society. Therefore an opposite course was implemented, against the advice of experienced doctors and despite some good published data [21,29]: DHC was then almost forbidden; it was only allowed in rare emergency cases if no other admitted substitute would be tolerated.

Doctors were forced to switch these patients over from DHC to Methadone. This was an interesting experience, because many patients reported: 'It's not the same'. Most patients preferred Methadone, but their doctors recognized increased alcohol-related problems. This was never properly evaluated well, but was a development often reported by practitioners. It should also be mentioned that the new, much more restrictive rules changed our therapeutic relationship with patients in a fundamental way. Crucial components of a good treatment ('good' always comprises 'based on trust') as well as of projects for the development of a flourishing addiction medicine were lost.

Codeine and DHC remained widely forbidden. They were almost never prescribed any more, and now have an unproven, bad reputation. In other countries without this special history, the development took a quite different direction. In Scotland, for instance, Robertson et al. were able to publish a study in 2006 that compared DHC with Methadone, concluding that these two substances have a similar level of effectiveness and are safe to use in treating opiate addiction [27].

The special nature of events in Germany has given it an inappropriate background for the introduction of DHC as a basic medication for alcohol-dependent patients. For this very reason we have to be especially cautious. Any future attempt would mean starting from scratch.

In addition, we have to deal with several fundamental objections that DHC treatments can only:

- Worsen the situation by making alcohol dependent opiate addicts, too; patients would then have two addictions, which is worse than having only one. We never observed this in any case. Where the effects of DHC were insufficient and there were new relapses with alcohol, we had to take one of two decisions: either to increase the DHC dosage, because it appeared to be the right way to go, or to leave the DHC treatment by tapering the dosage. Both options were easily applicable in most of these cases.
- Worsen the situation, because mixed intoxications with opioids and alcohol are more dangerous than those with alcohol alone. This is a question of having an adequate therapeutic concept and order. In our management of cases, we never saw a really dangerous mixed intoxication.
- Worsen the situation, because opiate addiction is not better than alcohol dependence. This is an old misunderstanding. Switching from alcohol to opiates brings a crucial improvement to the situation of most patients: alcohol is the cause of severe acute and long-term toxicity. Opiates do indeed bring a dangerous acute toxicity in the case of serious overdoses (which were responsible for the cases of death described above), but nearly no long-term toxicity at all. Alcohol is almost uncontrollable. Medically prescribed opiates

are perfectly controllable – a crucial difference and improvement.

- Worsen the situation, because the degree of dependence is greater: withdrawal from opioids is more difficult than from alcohol. This objection is based on the illusion that the way to stop an addiction as quickly as possible is by withdrawal. The concept of basic therapies must be long-term, with the aim of achieving sustained stability, and this is normally achievable not by withdrawal but by a very gradual reduction in the dosage of the medication up to abstinence. For some patients, it is certainly better to keep them on adequate medication for the rest of their lives.

All these objections go to show that many questions need to be clarified. Anxiety-based restrictions are a handicap on the implementation of new developments. They are often misunderstood as being able to replace the development of a good infrastructure. Our results provide only a first hint. Ordinary trials for more evaluation and basic knowledge (by comparing different substances, settings, dosages and clearing the cause and path mechanism of the effects) are needed as a first step, then the development of a good standard guaranteed by specialized doctors; in addition to these criteria, there should be no barriers against the inclusion of normal practitioners. Quite the contrary: we need to avoid the outcome that GPs leave this field to a few experts, or that they ever get the feeling of being left alone. Our attention should at last turn to a good and encouraging support system able to ensure a good practical standard; it should not be focused on a lot of rules and discouraging laws.

Our treatments cannot yet represent an optimized standard. The setting and the whole logistical framework have not been developed yet. Patients realize that many other experts react sceptically. Any explanation that includes reservations makes them anxious. 10 - 20% of the patients had no good effect from DHC. Lastly, our dosage was cautious, possibly too cautious for several for our patients. Due to the extremely pioneering character of the treatment, we avoided giving higher dosages, for fear of inducing a double addiction in the long run. In reality, we did not observe this development in any single case. The predominant improvement in most cases and the almost perfect result in a quarter of our patients showed that there is now a new way to improve the situation, even in absolutely desperate cases.

Our results, meanwhile, covering more than 10 years, indicate long-term perspectives. There can be no question about it: the all-or-none law is no longer valid in the treatment of alcohol dependency. It's always a lucky situation to achieve a doubt-free, stable abstinence from alcohol. But, then again, it's absolutely expedient to treat all the patients who are desperate because of recurrent relapses despite all interventions, including ours. Some of the patients reported that the DHC-based therapy was a much better solution for them than all the previous

abstinence-based therapies, and they were sorry they had not had this opportunity much earlier.

A few patients were suffering from a concomitant attention deficit disorder. For a short time, they were simultaneously being treated by our psychiatrists with methyl-amphetamines, and some of them showed a second crucial improvement. This experience is still at too early a stage for a regular publication, but the first impression is very clear: another helpful way forward is now available.

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Contributors

The authors contributed equally to this work.

Conflict of Interest

The authors have no relevant conflict of interest to report in relation to the present study.

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