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Review Article

A prescription guide for baclofen in Alcohol Use Disorder- For use by physicians and patients

Abstract

Since the discovery by Olivier Ameisen that high-dose baclofen can produce a state of indifference towards alcohol in those with Alcohol Use Disorders (AUD), the prescription of baclofen in AUD patients has exponentially increased. There are currently hundreds of thousands of patients with AUD who benefit from this treatment in France. However, the prescription of baclofen is difficult in many ways. First, the treatment, which consists in a slow progressive increase of doses, must be individually adapted, some patients needing low doses to achieve a state of indifference, while others need high or very high doses. Second, baclofen produces many adverse effects that can be very uncomfortable for patients, and may sometimes be dangerous. The third is that the patients must be strongly engaged in the management of the treatment, as they are the ones who will have to find the best way to target the moments of cravings and determine the distribution of the doses over the day to limit the occurrence of adverse effects. The doctor: patient therapeutic alliance is therefore a crucial element in the management of baclofen treatment. The present article is a guide written by both doctors and cured patients ("expert patients") for the prescription of baclofen in AUD.

Introduction

The Hypothesis of Professor Olivier Ameisen

Olivier Ameisen was a brilliant cardiologist suffering from an Alcohol Use Disorder (AUD), refractory to all alcohol dependence treatments. For him, alcohol dependence was a neurological disease: the symptoms of cravings and loss of control over drinking were due to abnormalities in brain functioning. Treating alcohol cravings with medication targeting the brain networks involved would treat the disease of alcohol dependence.

The conventional treatments for alcohol dependence could diminish but not eradicate cravings. When Ameisen looked at animal models of alcohol dependence, he found that baclofen was the only pharmaceutical agent capable of completely extinguishing cravings for alcohol. The effect of baclofen on cravings increases with increasing doses and the extinction of cravings happens at doses of around 3mg/kg. Ameisen hypothesized that the effect in rats might also happen in humans so he treated himself with similar doses of baclofen. At a dose of 270mg/day, Ameisen became "indifferent" to alcohol.

After having published a case report of his own experience

in 2005 [1], Ameisen proceeded to publish a book about baclofen treatment for AUD "The End of My Addiction" [2], first in France in 2008 then worldwide.

The Concept of Indifference

The aim of baclofen treatment is to render the patient "indifferent" to alcohol. Baclofen is the only current AUD treatment capable of producing this effect.

"Indifference" is a new concept in Addiction Medicine, described for the first time by Olivier Ameisen as "bottles of alcohol don't talk to me anymore" and is often not really understood. It is characterized by a complete eradication of obsessional thoughts about alcohol and, as a consequence, a drinking pattern that becomes effortlessly moderated to reasonable levels or to an abstinence which is freely chosen. As Ameisen described, "I am not forcing myself to remain abstinent, I just don't feel like drinking anymore". Indifferent AUD patients don't need to work at reducing their alcohol consumption. Quite simply, they no longer feel the urge to drink: their addiction has disappeared.

People with AUD who have been successfully treated with baclofen will have drinking patterns identical to non-AUD individuals. A study released on the baclofen forum internet

site baclofene.org [3], showed that about 30% of both groups chose to drink alcohol very rarely or not at all, 60% drank alcohol occasionally and the others more regularly but at safe levels (WHO criteria of less than 14 standard drinks per week in women and less than 21 drinks per week for men).

Indications and Contraindications

Baclofen is indicated for all forms of alcohol use disorder, whichever its form, abuse or dependence, occasional or continuous. Baclofen is indicated whether the aim of the patient is a complete abstinence or a simple reduction of alcohol consumption. Baclofen is also indicated in all medical illnesses resulting from chronic alcohol overconsumption, such as cirrhosis. Baclofen has no absolute contraindications except true allergy. Baclofen treatment is not recommended in patients with certain rare inherited diseases of the carbohydrate molecules, glucose and galactose or in patients with lactase deficiency or intolerance to galactose. Besides, there are a number of clinical conditions, e.g. obstructive sleep apnoea and renal insufficiency, that must be thoroughly evaluated with the patient before treatment initiation, in order to minimize the risk of adverse events and medical morbidity [4].

Information for Patients

The aim of baclofen treatment in AUD is that the patient becomes indifferent to alcohol. That means that the desire for alcohol no longer dominates thought processes. With time, thoughts about alcohol become like any other thought, passing through the patient's mind then disappearing. The aim is that ultimately, the patient will feel free of the compulsion to drink. This means it is no longer necessary to demand strict, lifelong abstinence when treating AUD.

Baclofen is an old medication which has been prescribed for over 40 years. It has been used to reduce "spasticity"—the muscle spasms which occur when muscles are partly or completely paralyzed—for example in a paraplegic patient with paralyzed legs. Because baclofen has been used to treat patients for many decades, we know a lot about baclofen's side effects and its effects in long term treatment [5], as explained later in this article. There is also information on baclofen prescribed at high doses as well as baclofen's potential effects when taken with alcohol [6]. This means that we have a good idea of what to expect with baclofen treatment.

The dose of baclofen needed to reach a state of "indifference" to alcohol is not a standard dose but is individual to each patient. The effective dose is found by assessing the patient's reactions and changes during the treatment as the dose is increased over time. The patient will be able to tell when s/he is at the right dose. It is impossible to predict in advance whether side effects will occur during treatment or what dose of baclofen will be needed to reach for effective treatment.

It's very important to stick to a steady, progressive increase in the baclofen dose to minimize the unpleasant side effects which happen when the dose is increased too rapidly.

The unpleasant side effects of baclofen are well known but

not everyone gets them. The patient may have no side effects at all or, in contrast, have multiple side effects that can be mild or severe in nature. Their evolution over time is variable but overall, they tend to improve with time. In any case, they all completely disappear if the baclofen dose is reduced or treatment is ceased.

To summarize the treatment protocol for baclofen in AUD:

Progressively increase the baclofen dose until the effective dose is reached, which will be individual for each patient. This effective dose can be defined in a few different ways: indifference to alcohol ("bottles of alcohol no longer speak to me") or the absence of craving for alcohol—the loss of the desire to drink or the disappearance of all ideas to obtain alcohol where previously this would have been an obsession.

Stay on the effective baclofen dose for a number of months in order to consolidate the positive response obtained by the treatment.

Then very slowly decrease the dose over a period of time which may last many months or many years, watching carefully for any reappearance of cravings, in which case the dose should be increased back up again.

The long-term aim is to stop the baclofen treatment which should be possible once the new pattern of cessation of uncontrolled drinking has been established for a long enough time.

Titration

The titration of baclofen involves increasing the dose slowly and progressively. There is no set way to do this. The pattern of dose increases will vary between baclofen prescribers who will have their own ways of doing the titration and will vary between individual patients: how independently they normally function, their wishes, how much they want to guide their own treatment and what other health problems they already have.

The most commonly used titration protocol for baclofen, the one that we recommend, is to increase the total daily dose of baclofen by one tablet of 10mg every three days. This is adjusted according to how the patient feels, particularly according to whether side effects appear.

The titration regime continues by continuing additions of 10mg to the total daily dose until the effective dose for that individual is reached. This is the dose at which there is a complete suppression of cravings, i.e. "indifference". The patient will recognize when the effective dose has been reached.

The titration regime is adjusted for each patient and guided by the reaction to the treatment. If the patient doesn't tolerate baclofen well, for example has side effects which are unpleasant, the increases in dose must be slowed down: by increasing the dose by 10mg only every 4–5 days, every 7 days, every 10 days or even by longer periods of time. Alternatively, the dose can be increased by 5mg (half-tablet) rather than 10mg.

If side effects are really unpleasant, further dose increases must be avoided. Either the patient can stay at the same dose at which the side effect appeared, knowing that side effects always tend to decrease with time, or the dose can be decreased back down to the previous dose at which this side effect did not occur. Once the side effect has settled, the patient can continue to increase the baclofen dose but more slowly and/or use smaller dose increases e.g. 5mg rather than 10mg.

Some patients increase their baclofen dose more rapidly than recommended, especially if they experience few or no side effects and are strongly motivated to reach their effective dose quickly. Increasing the dose rapidly will allow patients to reach their “indifference” dose faster. It also avoids patients becoming discouraged by the sometimes long period of titration needed, during which there is little positive effect on their AUD. However, overly rapid titration can also lead to patients experiencing abrupt, severe adverse effects. Therefore most prescribers recommend not to raise the baclofen dose too rapidly, even when it is well tolerated.

The doctor: patient relationship, the “therapeutic alliance”, is of critical importance in baclofen treatment. The patient needs to take an active role in treatment, under the guidance of the prescriber. The patient must inform the prescriber of what effect the baclofen treatment is having and therefore whether the dose should be increased, decreased or kept at the current level.

The effective dose varies between individuals and cannot be predicted in advance. There appears to be no correlation between the effective dose and factors such as patient weight, gender, height or how long they have suffered from an AUD. Nevertheless the effective baclofen dose seems to correlate with the severity of the alcohol dependence [7]. But overall, it is impossible to predict in advance what the effective dose will be. Each patient is unique.

The clinical trials show that the average effective dose needed is around 140–180mg/day with a wide range from 10mg/day to 500mg/day or even more [7–11]. Two patient surveys done by the Baclofen Association in August 2013 and September 2015 showed the same results, with an average dose of 170–180mg/day and the same wide dose range [3]. Importantly, it's how the patient feels which guides the rate of dose increases and decides the final dose needed for effectiveness.

With regard to drinking alcohol alongside the baclofen titration, experience shows that it is not necessary to detox before starting baclofen treatment, although we have noted that starting treatment with a detox can reduce the final baclofen dose needed. Deciding whether to start baclofen treatment with a detox or not should be discussed by the patient and doctor. If an initial detox is to be carried out, it is worth remembering that the abrupt cessation of alcohol (as for baclofen also) will lower the seizure threshold.

The prescribing doctor can suggest that the patient voluntarily moderates his/her alcohol intake during the first weeks of baclofen treatment, until the state of indifference occurs. This can also help the patient to feel more actively

involved in the treatment. In no longer seeking out social occasions for drinking, s/he comes to realize the habits and rituals around alcohol and can change them while looking to use things other than alcohol to face life's stresses.

To summarize, the titration phase aims to get the patient up to the effective dose of baclofen that induces a state of indifference towards alcohol. The upward titration of the dose requires regular adjustment of the amount and timing of the daily doses.

In this phase, the patients' feedback and the therapeutic relationship between patient and prescriber will guide the treatment.

Targeting cravings

Baclofen treatment needs to be adapted to each patient's drinking pattern i.e. targeted to the times when patients feel cravings for alcohol. There are patients who start drinking from the morning, others who start only around midday or in the afternoon and others who only drink in the evening, without feeling a desire to drink over the rest of the day. Experience has shown that it's generally not useful to take baclofen during the parts of the day in which there is no desire to drink. However this is not an absolute rule: later in this protocol, another regime will be described, that of “saturation”.

If a patient drinks each day between 6pm and 11pm but the first strong cravings start in the middle of the morning, the doses should start in the morning. It's important to ask patients who drink only in the evening if this is also the case on the weekends. If on weekends they start drinking in the morning or any time before the evening, it is the time which craving starts on the weekend that should be used to determine the timing the first dose of the day for all days of the week.

To understand why it is important to target baclofen doses to times of cravings, it helps to understand how baclofen is processed in the body. It is rapidly absorbed by the intestines and diffuses throughout the body. The maximum level of baclofen in the blood occurs between 30 minutes and 90 minutes (0.5–1.5 hour) after taking the tablets. Baclofen is passed rapidly out of the body and by 3.5 hours, only half of the baclofen taken is still in the body (the “half-life”). At a practical level, this means that the action of baclofen will start rapidly but then decrease after about 4 hours. This means that baclofen needs to be taken multiple times a day (Figure 1).

Targeting baclofen doses to achieve good craving suppression requires that doses are taken 30–60 minutes before the cravings start so that the peak blood level occurs at the same time as the cravings begin.

If the patient finds that the timed dose gives a very high blood level of baclofen which causes intolerable side effects, the usual solution is to divide up the dose into smaller doses which are spread over the hours prior to craving onset. This usually (but not always) minimizes side effects. The example below shows how the total dose can be spread into three smaller doses (Figure 2).

The "Saturation" dose regime

This regime consists of spreading the baclofen doses over the whole day to achieve a stable level in the blood all day. In some people, this will reduce undesirable side effects. This is what Olivier Ameisen did, spreading his baclofen intake over four doses, at 8am, midday, 4pm and 8pm.

Some patients chose to fractionate the baclofen doses even more over the day, for example taking small doses every 2 hours or even every hour. Each patient will adapt the dosage regime in the way that seems to be the best for reducing cravings and minimizing side effects. It can take time and multiple adjustments to find the best way to fractionate the baclofen dose over the day.

As an illustration, the diagram below shows an example with seven doses taken over the day, at 8am, 10am, 12am, 2pm, 4pm, 6pm and 8pm (Figure 3).

The maintenance phase

When the patient has reached his/her effective dose and the dose is acceptable in terms of tolerance, it is recommended to stay at this dose for 3-6 months or longer. After this period, the baclofen dose can be slowly reduced if desired.

There are no hard and fast rules as to the speed and way the doses are reduced. As a general rule, the dose reductions are

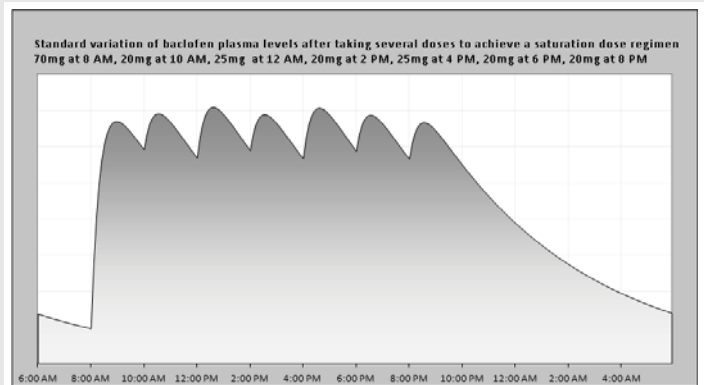


Figure 3: Standard variation of baclofen plasma levels after taking several doses to achieve a saturation dose regimen 70mg at 8 AM, 20mg at 10 AM, 25mg at 12 AM, 20mg at 2 PM, 25mg at 4 PM, 20mg at 6 PM, 20mg at 8 PM.

done in steps where the dose is reduced by 10% of the effective dose every 3-5 weeks, depending on the effect on the patient. It must be the patient who decides when s/he is ready to start reducing the dose and how rapidly this is done. The reduction is continued by slow, small steps until the minimum effective dose is reached.

One way of working out the minimum effective dose of baclofen for the maintenance phase is to reduce the dose until the desire to drink returns or the baseline amount of alcohol consumed starts to creep up. The baclofen dose must then be increased back up by 10-30mg/day (or more) until the patient returns to the previous level of comfort with alcohol in daily life. Remember, the lower the baclofen dose, the slower the reduction in dose must be in order not to miss the dose at which control over alcohol is lost.

Baclofen has not been prescribed for alcohol addiction for long enough to be able to confidently say how long baclofen treatment will be needed for. Nevertheless, our experience shows that it's possible for 20% of patients to stop baclofen treatment after a few months or years but for the others, treatment needs to be longer [7].

Our observations have shown that in 30-40% of patients who reach the state of indifference to alcohol (absence of cravings), the patient is no longer dependent on alcohol but still drinks excessively (although much less than before treatment). This may be the continuation of established drinking habits or during occasions where alcohol is normally drunk although the person is no longer craving alcohol. In these patients it is wise to suggest that s/he undertakes psychological treatment to change these behaviors that are no longer driven by craving but by habit. It can be difficult to break regular or daily drinking habits that have become entrenched over many years. The motivation to conquer an addiction requires abandoning old ways and establishing a new way of life with new habits. This process can be assisted by psychological therapy.

Experience has also shown that patients who stop all alcohol, have an indifference to alcohol which is complete and sustained and remain alcohol free over many months without effort are those who are most able to stop taking baclofen. Those who continue to drink, even at moderate levels and without any

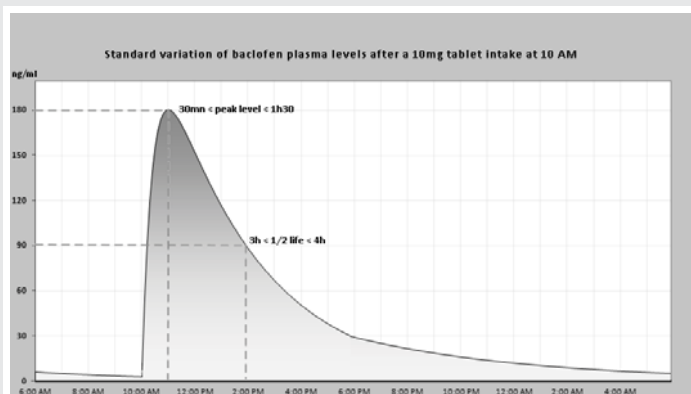


Figure 1: Standard variation of baclofen plasma levels after a 10mg tablet intake at 10 AM.

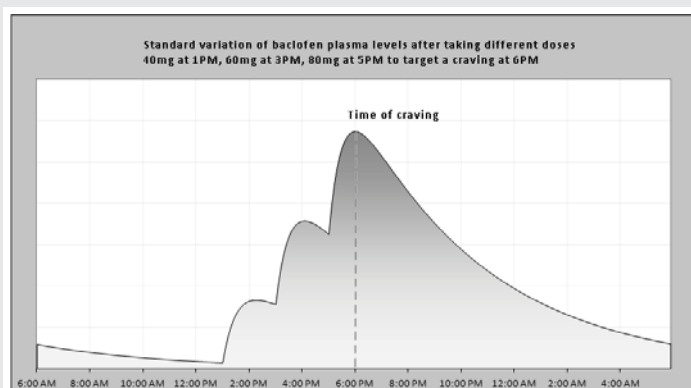


Figure 2: Standard variation of baclofen plasma levels after taking different doses 40mg at 1 PM, 60mg at 3 PM, 80mg at 5 PM to target a craving at 6 PM.

real desire for alcohol but do so by habit or with certain social occasions, will have greater difficulty in stopping baclofen. If these patients stop taking baclofen, they will continue to drink at moderate levels for a time but then tend to steadily increase their consumption and relapse back into their addiction.

The “Ameisen Test”: One of the best ways to confirm that the effective treatment dose has been reached is to ask the patient to go to the shop where s/he used to buy alcohol. If the desire to drink alcohol is ignited by the sight of wine and spirits, the baclofen dose should continue to be increased progressively. If the sight of alcohol has no more effect than looking at nappies or washing powder, the effective dose of baclofen has been reached.

Relapse into excessive or uncontrolled drinking

Baclofen is effective in 60–70% of patients [7, 9]. When patients are followed up over the medium and long term, some will relapse into excessive or uncontrolled drinking. In many cases, the problem is that adherence to the baclofen treatment regime is poor. Baclofen treatment has to be taken very regularly and on set schedules. Commonly the problem is cognitive dysfunction, which is very frequent in alcohol dependent patients, and this leads to difficulties in following a rigorous protocol or that the patient has never been organized in daily life. Another frequent situation is that the baclofen dose has been reduced too rapidly. For others, the relapse into drinking is due to stressful life events such as a relationship breakdown, job loss, increased work responsibilities, retirement, a death, a child leaving home etc. These situations require major adjustment and often increase stress and/or anxiety such that the baclofen dose needs to be increased to be effective again.

In case of relapse, as discussed above, the baclofen doses should be raised again by 10–30mg or more above the current dose. The patient will be able to feel when the new effective dose has been reached. In case of anticipated stress or social events, patients commonly learn to increase the dose/s of baclofen taken before the event or carry a few additional tablets with them which can be taken if they feel at risk of relapse during that time.

Whether there is a return of craving for alcohol or not, starting to drink again is evidence that the patient is not coping with a difficult period of time. If the baclofen treatment is still effectively controlling cravings, the patient requires help to understand the problems and overcome the difficulties. This can be done by the patient him/herself reflecting, with the help of family or friends or by seeing a psychologist.

When baclofen is restarted after a period off treatment, it is just as effective and the dose needed the second time is usually smaller than for the first time. In general, increasing the baclofen dose is easier and faster the second time, because the patient has a good understanding of the treatment.

Additional Interventions

Baclofen acts to suppress cravings and liberate the patient from his/her addiction to alcohol. Olivier Ameisen had tried

numerous treatments before trying baclofen and had been to thousands of AA meetings. In his book, *The End of my Addiction*, he clearly described that baclofen allowed him to put into practice the techniques he had learnt during his sessions of Cognitive Behavioral Therapy (CBT) and AA meetings. Baclofen gave him the freedom to reflect and re-orient his life. He was now able to use all the strategies he had learnt, which previously failed because his cravings were too intense.

Many of us have been struck by the nature of the consultations with patients on high dose baclofen treatment. Often at the start, the consultations are purely about the baclofen treatment itself, revolving entirely around side effects, dosages and the degree of craving. When the effective dose has been reached with an acceptable level of side effects, other difficulties may appear, especially in the psychological and social areas of life. Baclofen, effective as it is, does not cure loneliness, dissatisfaction with life, relationship problems or unemployment. However it does allow the person to take stock of his/her situation and face the realities of life. This can be very painful as the person confronts his/her wasted life and the associated trail of damage. In this situation, it is vital to continue to support the patient with encouragement to rebuild their social situation and psychological state, overcome isolation and find pleasure in life again. This is best done via a multidisciplinary approach. Psychological treatments such as CBT and discussion groups are valuable supports.

When group work is done with baclofen treated patients, it is important to have separate groups for patients who have chosen abstinence and those who chose to drink alcohol as the strategies discussed will be different.

If the patient has psychiatric issues such as anxiety, depression, bipolar disorder or borderline personality, of which their alcohol use is one the symptoms, their psychiatric treatment needs to continue, adapted to their situation. Baclofen can be safely used with the common psychiatric medications (benzodiazepines, sleeping pills, antidepressants and antipsychotic medications).

A unique advantage of baclofen is the mental freedom it gives patients to rethink and reconstruct their life. But when alcohol is stopped, the patient is face to face with the painful realities of life that have been blotted out by drinking. This can lead to periods of low mood or even full blown depression. Helping the patient along this personal journey is part of the therapeutic process.

The patient’s close family and friends must also change from their expectation from a goal of abstinence to an aim of reduction of drinking to safe levels. Some baclofen prescribers find it useful to systematically include the patients’ entourage (friends, family) at appointments to help them adjust to the new goals of treatment.

The Patient Forums (In France: <http://www.baclofene.fr/> and <http://www.baclofene.com/>)

Baclofen treated patients have played an important role in the history of baclofen treatment of AUD. From the early

days, patients rapidly formed groups and forums to support and accompany others who wanted to treat their AUD with baclofen. These were places where people, under the cover of anonymity, could talk freely about their experience with baclofen, the difficulties they faced during treatment and the side effects experienced. They could also discuss their addiction and receive reassurance from others, lightening the heavy burden of guilt and loneliness. The forum members knew how it felt like to be unable to resist drinking to excess and were able to respond, not with negativity and judgment but rather with understanding and encouragement.

The discussion forums are packed with a wealth of informative patient experiences. This allows people who regularly visit the forum to expand their knowledge of baclofen treatment well beyond their own experience. These “expert patients” can be invaluable to people starting baclofen treatment. The initial stages can be difficult for some patients and require almost daily follow-up which doctors don’t have the time for. The expert patients know the side effects of baclofen and have useful tips to help minimize them. They understand the importance of the timing of doses and can provide constant reassurance to the doubting or discouraged patient during the early stages of treatment.

Many patients are very grateful for the support they received from these support groups and say that “without you, I would have never succeeded”. Being part of a forum is a valuable aid in helping to succeed in winning the battle against alcohol addiction.

Warnings and Precautions

The appearance of side effects should be closely monitored in patients at high risk e.g. severe stroke or renal failure. Patients with cardiopulmonary disease and respiratory muscle weakness should be monitored. The risk of respiratory depression is increased with simultaneous use of sedative medications.

Baclofen treatment should not be stopped abruptly. If baclofen treatment needs to be stopped, a doctor should supervise the progressive reduction in dose over a number of weeks in order to avoid the symptoms of baclofen withdrawal.

Besides the previously mentioned cases of allergy or intolerance (indications and contraindications section), the following medical conditions may require alterations in baclofen treatment, so it is important to let the prescribing doctor know about these: Epilepsy, Respiratory problems, Heart failure, Stroke, Psychiatric illness, Liver Disease, Kidney Disease, Peptic Ulcers, Diabetes, problems urinating, Parkinson’s Disease.

Interactions

If a patient takes or has recently taken another medication, including those not requiring a prescription, it’s important to let his/her doctor or pharmacist know. It may be necessary to adjust the dose of baclofen if other medications are taken such as:

- Sedative medications which calm the activity of the brain such as antipsychotic medications, benzodiazepines (eg valium), sleeping tablets, sedative antihistamines (eg Phenergan), as well as opiates (morphine, oxycodone, fentanyl, methadone and Suboxone/Subutex). They may cause increased drowsiness which can increase the risks of driving and operating machinery.
- Tricyclic antidepressants which can increase muscle hypotonicity.
- Medications used to treat high blood pressure: baclofen may increase their effect on lowering blood pressure. The blood pressure should be regularly monitored and the dose of the blood pressure medications decreased if necessary.
- Levodopa used to treat Parkinson’s disease which can cause increased side effects such as confusion, agitation and hallucinations.
- Medications which can cause postural hypotension i.e. large drops in blood pressure when standing up.

Side Effects: Management and Prevention

The side effects of baclofen are frequent, of many different types and unpredictable as to when they will appear during treatment [12,13]. Many of them can be troublesome, unpleasant, sometimes very disabling in daily life although very few are serious or dangerous. What is striking and remarkable is that many patients will continue the treatment despite experiencing side effects which are potentially very troublesome.

Side effects mainly occur during the period of upward titration of the baclofen dose. In general they go away when the baclofen dose is stabilized. They are always reversible and disappear when the dose is decreased or when baclofen is stopped. However there are occasions when side effects will persist or even appear when the baclofen dose is being decreased. Others can disappear spontaneously when the dose is taken up.

Side effects can also occur when the baclofen treatment is not taken correctly. It is important to increase the baclofen in a regular and steady fashion. Changing the times the baclofen doses are taken during the day frequently or rapidly can lead to side effects appearing. It is important not to suddenly double the baclofen dose because the last dose has been missed or the patient has forgotten if the last dose has been taken or not. This will cause unpleasant side effects.

Baclofen treatment should never be stopped abruptly because of the risk of baclofen withdrawal. This can cause hallucinations, confusion or seizures. Stopping baclofen should be done over 1-4 weeks with a progressive decrease in dose eg reducing the total daily dose by 10-20mg every 2 days.

The effect of drinking alcohol while on baclofen treatment.

Experience shows that continuing to drink alcohol during

baclofen treatment will increase the risk of baclofen side effects. A survey by the Baclofen Association has shown that the side effects were present in 93% of those who were drinking as much or more alcohol as prior to baclofen treatment. In patients who were able to remain abstinent during treatment, only 63% experienced side effects from baclofen. Continuing to drink during treatment also increased the intensity of side effects. Amongst patients who did not drink during treatment, 31% did not have any side effects from baclofen treatment, and only 27% experiencing side effects which they rated as strong or unbearable. In contrast, strong or unbearable side effects happened to 64% of patients who continued to drink the same amount or more alcohol as prior to treatment (Figures 4,5).

The most common side effects

Sleepiness is the most common side effect of baclofen. Patients often describe an abrupt and almost irresistible desire to sleep rather than true sleepiness. This side effect generally starts in the early days of treatment. It tends to diminish over time but can initially be very problematic for people who work. It is important to warn people who drive to avoid doing this at the start of baclofen treatment if they experience this effect.

Fatigue is the other most commonly reported side effect. Some patients experience either fatigue or sleepiness and some have both. Fatigue is often accompanied by feelings of weakness and lack of energy. Like sleepiness, it generally diminishes with time. Fatigue is less intense when people are active such as during working hours but resumes when they are less active.

Insomnia paradoxically, some patients complain of feeling sleepy during the day but experience insomnia at night.

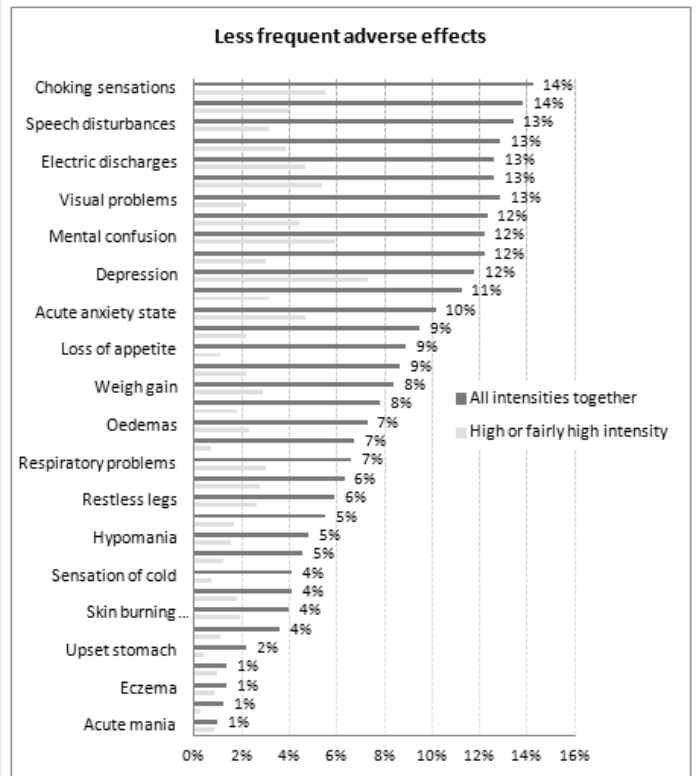


Figure 5: Less frequent adverse effects.

Adding a medication to assist sleep helps when the sleep disturbance is severe. The problems of sleep can also include restless movements or incessant “sleep talking” which can be problematic for their sleep partner. This problem does not always decrease over time. The night’s sleep can also be disturbed by dream or nightmares which are “hyper real” in that they feel more real than reality. This makes these dreams very disturbing and may lead to abundant sweating which necessitates a change of bedclothes during the night.

Nausea, vomiting and digestive problems: These common symptoms are sometimes hard to attribute to baclofen, especially at the start of treatment because they are often described in alcohol dependent patients, especially when they stop drinking. However it does appear that nausea is commonly described but is temporary.

Dizziness: This can be of variable intensity. Patients describe it as an unpleasant feeling that they will fall down. It isn’t a true vertigo. The feeling often occurs in the morning and improves over the day. When it is too unpleasant, the baclofen dose may need to be decreased temporarily.

Sexual problems increase or decrease of libido, lack of orgasm, erectile dysfunction or inability to ejaculate. Patients can be too ashamed to admit these problems so it is important to ask directly about these side effects as they will be an added source of anxiety.

Memory problems or trouble concentrating: These concern focusing attention and short-term memory e.g. can’t remember where the keys are or forget someone they met the day before. This can be very problematic in daily and professional life but disappears over time or with a decrease in dose.

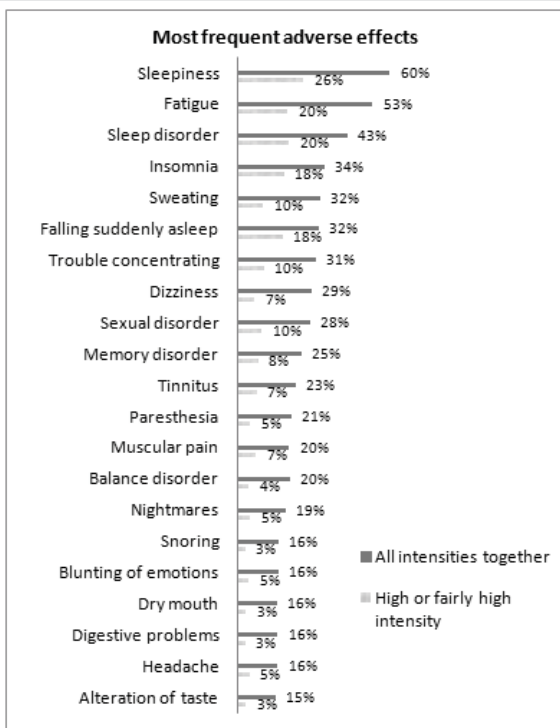


Figure 4: Most frequent adverse effects.

Sensory disorders: These are alterations in all sensory messages, including hearing, vision, touch, smell and taste. They can take the form of hallucinations (auditory and visual), parasthesias (“pins and needles”), different forms of pain (headache, muscle or joint pains), tinnitus, and sometimes sensations of electric discharges in the head or limbs. Most of these sensory alterations are transient, except tinnitus which is often enduring. These sensory disorders usually disappear when the baclofen dose is decreased.

Blunting of emotions: This is a state in which positive and negative emotions are of much less intensity than before.

Choking sensations: These are very disturbing. The persons feels like they can no longer breath normally and must consciously think to breathe or they will suffocate.

Muscle weakness: This can sometimes be problematic for some people who participate in sports while others continue to do intensive sport without any problem. Some find that this side effect improves with increased physical activity.

Less frequent side effects

Sleep Apnoea: A temporary pause in breathing during sleep. If sleep apnoea is suspected, a full sleep study should be ordered to check if sleep apnoea has been unmasked or provoked by baclofen treatment. If the patient already has known sleep apnoea, a nocturnal CPAP machine should be strongly considered before starting baclofen treatment to prevent worsening the severity of the sleep apnoea.

Depression: This is most often the apathetic type—nothing seems worth doing anymore. In rare cases, there can be suicidal ideation, possibly related to baclofen treatment. The link between suicidal ideas and baclofen is uncertain because research shows that the risk of suicide is 50-100 times greater in the alcohol dependent population, independent of any treatment modality [14]. Nevertheless, suicidal thoughts are a psychiatric emergency requiring attention and the dose of baclofen should be immediately reduced in this circumstance.

Hypomania: This is described by around 5% of patients. They don’t generally complain, rather they often enjoy it. The symptoms are increased activity, lots of energy, decreased sleep, increased self-esteem, slight euphoria and being more sociable. As long as the patient is sleeping enough and the symptoms are not too severe, there is no need to worry or treat this. In the vast majority of cases, these episodes of hypomania don’t evolve into an episode of frank mania.

Mania: This can be diagnosed when the elevation of mood is marked and represents a danger to the person. The symptoms are the same as hypomania but much more extreme. There can be delusional ideas, compulsive shopping, sexual promiscuity, a loss of social inhibitions coupled with a lack of tiredness that leads to not sleeping. This is a serious condition and requires urgent psychiatric treatment. These manic episodes can occur in patients known to have Bipolar Affective Disorder whose mood stabilizing treatment should be increased prior to starting baclofen in anticipation of the need. Much more rarely, mania

can occur in people without known Bipolar Affective Disorder, usually at high doses of baclofen or where the baclofen dose has been increased much too rapidly.

Confusional State: The gradual or abrupt onset of confusion will worry the patient’s entourage while the patient is generally not aware of it. Its occurrence may endanger the patient’s life and often requires hospitalization. The confusion will always disappear completely once the baclofen is stopped or the dose is decreased sufficiently.

Other side effects: These include oedema, excessive salivation, tremors, irritability, anxiety, paranoia, speech disturbances, incontinence and other urinary problems, nasal congestion, weight gain, weight loss, gum pain, cramps, a feeling of pressure on the chest, brisk movements while sleeping, cough, severe sensitivity to noises, a numb feeling of the skin, hair loss and dry mouth.

Management of side effects

The side effects of baclofen are linked to individual sensitivity to both the total dose of baclofen but also to how the doses are taken over the day.

There are multiple strategies that can be used to decrease side effects: slowing down the rate at which the dose is increased, reducing the dose of baclofen or changing the times at which doses are taken. It can also be helpful to add medications to treat side effects or put the patient off work when needed. These measures are also helped by basic healthy living strategies and drinking the least amount of alcohol possible. Nothing can prevent side effects at 100% but the measures described above can improve the tolerability of baclofen treatment.

In brief: If there are severe side effects, the first approach is to space out the dose increases. In general, side effects appear when the baclofen dose is increased, and they spontaneously decrease or disappear in a few days. This is why it can be helpful to space dose increases out to 7, 10 or even 15 days and recommended doing dose increases just before the weekend so that time off on the weekend can be used to adjust to the higher dose.

When these measures are not sufficient, the daily baclofen dose can be decreased by 10-20mg for enough time to let the side effects settle. The dose can then be increased again but with smaller increments e.g. 1/2 instead of 1 tablet and with dose increases spaced further apart. By doing this, a side effect which has been very troublesome will often not recur as the dose increases again.

The second approach is to adjust the timing of doses over the day. Experience shows that the time the doses are taken can be very important both in the effectiveness of treatment and in limiting side effects. A person who feels the need to drink at 6pm will take baclofen doses during the afternoon in a way that gives a maximum concentration of baclofen in the bloodstream at 6pm. Apart from being more effective, this way of taking baclofen will avoid sleepiness in the morning and

early afternoon but it can lead to more side effects being felt in the late afternoon. Other patients will strongly feel the effects of the baclofen soon after taking the tablets and realize that if they take too much baclofen at once, they feel “knocked out”. In both cases, it is helpful to fractionate the total daily dose e.g. going from three doses over the day to 4, 5 or 6 doses. It’s not always practical but can be very helpful.

Other patients who have problems when baclofen doses are taken too close together can find that spacing them out to a minimum of 3–4 hours is helpful. Less commonly, patients can find that they feel unwell or anxious if they take their doses too far apart. In this case, the doses are best spaced out evenly over the whole day so that these symptoms don’t occur.

Side effects experienced at night such as insomnia, disturbed sleep or night-time sweating are particularly affected by the timing of baclofen doses. In most patients taking the last dose of the day by 4–5pm at the latest will help this. Paradoxically, some patients get relief by taking a small dose of baclofen at bedtime. This is because amount of baclofen in the bloodstream decreases pretty rapidly after the last dose is taken: some people are sensitive to this drop and find relief in taking a small bedtime dose of baclofen.

Maintaining good lifestyle habits can also help to reduce baclofen’s side effects. This includes eating three healthy meals a day and staying hydrated with plenty of water or other non-alcoholic beverages; 1.5 to 2 liters a day or even more to compensate for the drop in liters of alcoholic drinks consumed previously. Also helpful are getting enough sleep and rest plus some gentle physical exercise such as walking or swimming. A magnesium and multivitamin supplement can also improve the tolerance of baclofen treatment in some patients.

With regard to drinking alcohol during treatment: total abstinence can be seen as an unacceptable constraint which leads many patients to refuse treatment for their alcohol dependence. Nevertheless, continuing to drink alcohol while on baclofen carries the risk of increasing the side effects of the treatment. The side effects of baclofen and alcohol are often similar in nature and so make the symptoms worse. The most dangerous combination seems to be the mix of baclofen, alcohol and benzodiazepines. It is therefore important to make patients aware of these problems and encourage them to decrease their alcohol consumption.

Overdose

The signs of an overdose of baclofen are:

- Increasing loss of consciousness up to coma.
- Weakness or hypotonicity of muscles which can last up to 72 hours and can affect the respiratory muscles.
- Other symptoms such as confusion, hallucinations, vertigo, nausea, vomiting, excessive salivation, seizures, bradycardia, hypotension and hypothermia.
- The EEG can show a burst suppression pattern and triphasic waves.

Management

There is no antidote to baclofen.

- Stop the baclofen treatment.
- Transfer immediately to hospital.
- Full supportive care which may include intubation.
- Hemodialysis can be used in cases of severe baclofen toxicity to decrease clinical manifestations and shorten the treatment time required.
- Seizures are treated with IV benzodiazepines e.g. midazolam.

Potential Mechanisms

Baclofen is a structural analogue of gamma-aminobutyric acid (GABA). It has an anti-spasticity effect by acting in the spinal cord. It slows down the transmission of reflexes/spasms by stimulating the GABA-B receptors in the spinal cord. The key role of the GABA-B receptor in the causation of addictions has been demonstrated. GABA-B receptor dysfunction has been documented in alcohol dependence, and may also be responsible for the comorbid anxiety in people with AUD and in relapse into drinking.

The GABA-B receptors are found in the reward pathway of the brain, the mesolimbic dopaminergic (MLD) pathway, on the pre-synaptic side of the dopaminergic neurons. When activated, the GABA-B receptors decrease the release of dopamine into the synapse. The GABA-B receptor agonists, like baclofen, cause a particularly marked decrease in the release of dopamine in two parts of the MLD pathway, the nucleus accumbens and ventral tegmental area. It is via these two areas that the conditioned response to different drugs (alcohol, cocaine, methamphetamine, morphine, heroin, nicotine) are diminished or suppressed. Animals treated with baclofen are rendered relatively indifferent to the effects of the addictive substance. Alternatively, GABA-B receptor agonists which attach to the pre-synaptic part of glutamatergic neurons in the limbic system can change the conditioned response to pleasant or unpleasant experiences, important in addiction.

Baclofen’s action in addictions is a combination of its anti-craving effect, i.e. a control of the compulsion to drink, with an indifference to the effects of alcohol cues and the context of drinking behavior, and an anti-anxiety effect which reduces the risk of relapse.

Conclusion: A Final Perspective

This guide has been written by both expert patients (SI, SB, JB) and physicians (RB, AS, PJ). The importance of expert patients in the management of chronic illnesses has been recognized in recent years. Expert patients are “people who have the confidence, skills, information and knowledge to play a central role in the management of life with chronic diseases” [15]. The case of baclofen treatment for alcohol dependence illustrates very clearly the importance of expert patients,

given the complex management of the illness: physicians are essential because of their knowledge about AUD and baclofen treatment, and expert patients are essential for their experience on how to manage baclofen treatment in daily life. This guide is the product of these two forms of knowledge, indispensable for the best outcome from baclofen treatment.

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