Benzodiazepines:
If I Were My Brain, What Would I Do?

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Much has been written (especially in benzodiazepine withdrawal forums and groups) concerning not only what causes benzodiazepine withdrawal but also what can be done to relieve, or even end, the withdrawal and all the extreme mental, emotional and physical symptoms that it entails. Invariably, the offending culprit is “downregulation of GABA receptors,” and the path to ending withdrawal is to allow the GABA receptors to “upregulate” in their own time and in their own way.

For some individuals who have discontinued benzodiazepines, it seems that downregulation never happens, because they have no apparent withdrawal. For others, upregulation (after discontinuation of the drug) happens relatively rapidly as evidenced by a rather short period of withdrawal before returning to wellness. Sadly, there is a very significant group of individuals who languish in the pure agony of withdrawal for many months with seemingly no end in sight.

So, why is there such variability in the ability of individuals to “heal” after discontinuation of benzodiazepines? More specifically, why does it take so long for some to be well again? Is there anything that can speed the healing process for such individuals?

In order to at least hypothetically answer these questions in some logical manner, it is necessary to have a “starting point” from which to begin. This would require knowing what it is that those in benzodiazepine withdrawal are healing from (the “damage”) and the cause of that “damage.” As previously stated, the “damage” is typically referenced as “downregulation of GABA receptors.” In the April 19, 2016 “companion” paper to this one (Benzodiazepines: What Have They Done to My Brain?), I have loosely defined downregulation as “the condition in which the GABAergic system is no longer able to provide normal neural inhibition, i. e., it is less likely to generate an action potential.”

The seemingly apparent cause (at least in part) is alteration of gene expression. (Of course, the assumption is that the benzodiazepines affect the brain in such a way that it alters gene expression resulting in a “downregulated” GABAergic system and an individual often suffering intensely for a prolonged period of time. In that regard, benzodiazepines are the cause of the cause [alteration of gene expression].)

In a Nutshell

Alteration of gene expression and what has led to that alteration (as they apply to downregulation of the GABAergic system) are explained at a rather fundamental, but hopefully sufficient, level in the April 19, 2016 companion paper. An even shorter version of that explanation follows:

- Benzodiazepines bind to the $GABA_A$ receptor resulting in enhanced binding of GABA to other binding sites on the receptor.
- In response to the GABA binding, the central channel or pore of the receptor opens in a manner that allows the influx of chloride anions into the neuron reducing the action potential of the neuron, i.e., decreasing the likelihood that the neuron will fire, or, conversely, increasing the likelihood of neural inhibition.
- In response to this enhanced inhibition, the brain, somewhere between reading the code on the DNA and synthesizing the proteins (structural proteins and enzymes) from that code, effectively alters the code (probably through mRNA splicing). This alteration results in one or more structural proteins that comprise the $GABA_A$ receptors that differ from the structural proteins coded for in the DNA. This alteration also likely occurs for synthesis of one or more enzymes that play key roles in the GABAergic system. The overall effect of these gene expression alterations is significant reduction of neural inhibition.
- The end result is a brain that is either deficient in its inhibitory capacity or excessive in its excitability or both. This creates enormous problems for the one in whom the brain resides.

Why Would the Brain Do This?

It is the brain's job to ensure that everything "goes as planned" in the body. The brain is the communication and computation center or system of the body and its ultimate responsibility is to keep the body alive and functioning as well as possible. In that regard, it never gets a "break." Even during sleep, it has to ensure that we continue to breathe and that all our organ systems are functioning as necessary. It is not interested in rest for rest's sake. It allows rest so that it can continue to "think and do" in order to live. It has not been created nor has it evolved to stay at rest and simply "enjoy" itself. It has a job to do, and that's its priority.

If left to its own devices, it may very well "ignore" the GABAergic system (and other inhibitory neurotransmitter systems) and simply "be active." Obviously, it would burn out rapidly (death of neurons caused by uncontrolled excitotoxicity) without the rest provided by the inhibitory systems. Too much inhibition is undesirable, but no inhibition is also unacceptable.

Certainly, the GABAergic system exists in order to put the “brakes” on when rest (and all that rest entails) is needed to keep the excitatory neurotransmitter systems from “overdoing it” and harming or even killing the body. Clearly, there is a very “fine line” with respect to the balance between neural excitation and inhibition in the brain relative to how well the body functions.

Interestingly, there is evidence that endogenous positive allosteric modulators (PAMs) that bind to the same sites as benzodiazepines do exist. These naturally occurring PAMs have not been identified (but could be related to neurosteroids). This is a rather amazing paradox. Those binding sites were not created or did not evolve to one day be occupied by benzodiazepines. These are apparently very “sensitive” binding sites that serve a very special purpose and, perhaps, should not be disturbed or “used” negligently or without regard for what the brain might do in response to such intrusion. (One would logically assume that these binding sites play a key role in maintaining the balance between neural excitation and inhibition.)

It would appear that, since the brain is being “forced” to significantly increase its inhibition (something it innately doesn’t want to do) due to the presence of benzodiazepines, it decides to do an “end run” by altering the instructions it gets from its DNA. The altered instructions often result in unchecked excessive reduction of inhibition or an increase in excitation or a combination of both.

Why Doesn’t the Brain “Reverse” This Process Once the Benzodiazepines Are Discontinued?

It would seem that the brain should easily be able to reverse the changes that it has made to the GABAergic system just as quickly as it initially made those changes (certainly within a few weeks). For some individuals, the reversal is made very rapidly. For many, it is not.

The answer for this disparity typically is that “we are all different.” This is quite true. Genetically, there are no two of us identical. But is there a specific genetic aspect that can be examined or considered (at least in a hypothetical way) in an effort to possibly discover how it might be influenced or otherwise affected in hopes of reversing the process more rapidly for everyone?

In order for the brain to “reverse” the effects of what benzodiazepines (or possibly any other anthropogenic psychotropic chemical agent) have done to it, it must get its instructions to do so from somewhere. It has already altered the instructions from its DNA to deal with the excessive neural inhibition. In a sense, it has “gone rogue.” It is

freelancing. It has nowhere to go for instruction that would instruct it to go back to its instruction book (its DNA) and use those instructions without altering them first. Perhaps, the brain is quite satisfied with what it is doing. It is in "overdrive." It is in a hyper-excitable, extremely active state. It is constantly thinking and obsessing and looking for answers. Never mind that the obsessive thoughts and all that go with them are excruciatingly painful and usually quite useless. In a very real sense, the brain has forgotten that it is supposed to read its DNA and transcribe it without changing it. It doesn't "know" that is the answer to its self-imposed agony because nothing is telling it so. All it "remembers" is that it must alter the code from its DNA – even though the original reason for that alteration is no longer valid, i. e., the benzodiazepines are long gone.

For the person experiencing this "neural state of confusion," it "feels" like the brain is "fighting" itself – almost like there are two brains. One seems to be intentionally torturing the other. The brain is constantly looking for a solution to ending the anguish, yet it is the brain that is causing it – and it knows it. But it doesn't know how to stop it. Could it be that it has simply forgotten something very fundamental – how to read its own DNA without altering its code?

Interestingly, many individuals in benzodiazepine withdrawal lament that they no longer recall who they were in their past (even before taking benzodiazepines) or whom they have become (other than someone suffering interminably). They often feel as though they have lost their identity and have a strong sense of disconnection to anything or anyone – even themselves. There is an extreme fear that this "new entity" is now who they are and who they will be for the rest of their days. It is as though the "real" them has wondered off and left an empty shell. It feels very much like living in a vacuum of nothingness, knowing there is a place to return to but having no idea how to get there.

Even more interestingly, many who have endured benzodiazepine withdrawal and who have returned to wellness are once again able to remember life events prior to the use of benzodiazepines and the ensuing withdrawal from them. They remember "who they were." I have often described the lifting of all the mental/emotional symptoms of withdrawal (depression, anxiety, fear, panic, loss of cognition, feeling of disconnectedness, and many more) as "looking into the distance and seeing you return to yourself." And, strangely, you recognize yourself immediately – almost as if you were never gone.

I have always viewed this in a figurative way. But, could there actually be a literal neurologic/neurochemical basis for it? Biologically, in many ways, our DNA defines us. In essence, it is "who we are" here on earth. Is it possible that the alteration of gene

expression (initially caused by the extreme inhibition which has been caused by benzodiazepine exposure) has literally "separated us from ourselves," i.e., has forced us to react to life without being able to access and use the code in our DNA? Is the brain actually "translating" that "separation" into something we can consciously detect or feel? Is it "signaling" to us that it knows what is wrong but can't resolve it? Of course, there is no objective way to know, but it does beg the next question.

Is There Anything That Could Help the Brain Remember From Whence It Has Come?
Let us suppose that the brain has, in fact, forgotten how to get back to its instruction book (its DNA) without altering the instructions written in the book. For some, the task occurs rather rapidly and easily. For others, it takes many months, and for some who are currently in the midst of seemingly interminable benzodiazepine withdrawal, the task seems impossible no matter how hard their brain keeps seeking the solution.

For these individuals, what sources of help are available that may possibly give hope for now and resolution in the future? Although we all heal intrinsically, "waiting" for those GABA receptors to "upregulate" seems like an exercise in futility. Is there anything else that may help "turn the tide"?

Over the years that I have been involved in the world of benzodiazepine withdrawal, individuals (including myself) have tried many different things to end their withdrawal or to minimize the intensity of the symptoms of benzodiazepine withdrawal while waiting for their GABA receptors to upregulate. These have all fallen into two basic categories: psychotherapy and treatment by ingesting either other psychotropic drugs and/or various supplements.

Generally, psychotherapy has failed for those in withdrawal – although a few have reported positive results. I went to group therapy and also individual therapy for about two years with, if anything, harmful effects. I usually left those sessions feeling much worse and more hopeless. Therapy certainly did nothing to reverse any alteration of gene expression.

Similarly, other drugs and supplements were relatively ineffective and often made matters much worse. I found some relief of a few symptoms at times but generally felt worse with every drug or supplement I tried. The mere fact that my plight had been caused by the haphazard prescribing of a psychotropic drug with little to no scientific basis for it is evidence that adding more drugs could easily result in additional misery and problems. This is true of literally thousands of others fighting withdrawal.

Early in my withdrawal experience, when I was extremely desperate and suicidal, I did try one other form of therapy. At the time, I was in the psychiatric hospital suffering with severely acute withdrawal from an extremely fast taper from four milligrams of clonazepam. One evening one of the nurses told me that I was in a "funk" and needed something to get me out of it. She thought she knew just the thing to do it.

My Experience with ECT (Electroconvulsive Therapy)

When the nurse had mentioned ECT to me, I actually didn't know what she meant. I had always heard it referred to as "shock treatment." I believe it was the next day that my psychiatrist explained it to me. Of course, the first thing that came to my mind was the movie, *One Flew Over the Cuckoo's Nest*. Even so, my desperation was so great that I pushed that to the side of my thoughts. I was out of places to turn, and I was incredibly ill. Earlier in the week, the nurse who distributed the night meds told me that I should not be in that place and I should not be taking the drugs. In my head, I knew he was right. I recall that, at the time, I stood there and wondered how I had gotten so far from myself and where "myself" was. I had lost myself. I could not even respond to the nurse in any intelligible way. How had I ended up in a mental institution? What had happened to my brain?

That Thursday evening I found myself sitting alone in a small community room watching a short video of ECT actually being performed on a patient. I watched them placing the monitoring leads, blood pressure cuff, oxygen sensor, and oxygen mask as well as the injections of anesthetic and muscle relaxant. That was not disturbing in the least. I watched them place the electrodes on the patient's skull and apply the current. This resulted in what appeared to be rather benign "quivering" of the body that was not particularly upsetting and didn't appear to be painful. I just felt a bit surreal imagining me being that person.

The following afternoon I was wheeled to another wing of the hospital to get my first treatment. I was taken into a large room with bays where about a dozen people were in hospital beds awaiting ECT treatment. An IV was started on me, and my blood pressure and pulse were monitored electronically. I was obsessed with my blood pressure and heart rate, and didn't spend much mental energy on thoughts of the treatment itself until it was my turn. At that point, I tried to focus on the names of my wife and kids and my home address in an effort to remember them because I had been told that memory is sometimes affected by ECT.

I was wheeled over to a "nook" area right outside the ECT room (which was actually a huge former surgical suite) to await my turn. I was very frightened (probably more as a result of my severely acute withdrawal condition) and fully expected to die. I was taken

into the suite where there were three or four people. Monitoring leads were placed on several areas of my body, and a black cuff was placed just above one of my ankles. The anesthetic and muscle relaxant were injected into my IV, and an oxygen mask was placed over my mouth and nose.

My eyes opened as I was being wheeled back to my area of the bay. I was a bit groggy and disoriented but immediately turned my thoughts to the names of my family members and my home address. I didn't feel any better, but I didn't feel any worse either.

I had three more treatments the following week that were very similar with only one exception. For some reason, immediately after treatment as I was being wheeled back to the bay area, I had a lot of mucous and woke up gasping for air. No one was alarmed, so I guess it was a common occurrence. I had heard others who had returned from treatment also gasping similarly while I was waiting for my treatments.

I had a total of four treatments. It was hard to say if I had any sort of memory loss because my memory was already very bad from the benzodiazepine withdrawal I was in. Other than the gasping for air, the procedures were uneventful and without pain. There was no flailing of arms or legs, no arching of the back, no grimacing in physical anguish. My ECT reality would have made for a very lackluster movie.

This is not to say that there were not any "improper" aspects of my ECT experience. There was one, and it was quite large.

I had still been taking about one milligram of clonazepam when ECT was recommended as a treatment option for me. Even in my clouded state, I remember being told that benzodiazepines interfere with ECT (probably because benzodiazepines have anti-seizure properties). In order to ensure that benzodiazepines would not interfere with my treatment, I was switched from clonazepam to lorazepam (which has a shorter half-life – approximately 12 to 18 hours compared to 20 to 30 hours). I was also required to do a"mini-withdrawal" for 24 hours prior to each ECT treatment, meaning that the lorazepam was withheld every other day for 24 hours. (That created even more horrendous withdrawal suffering.)

In retrospect, the ECT could not have possibly had any beneficial effect. The half-life of lorazepam was still sufficiently long so that there was plenty of it remaining in my body to continue to affect my GABAergic system and interfere with the ECT. My experience was doomed to failure from the start, but I did not know that at the time.

Could ECT Be an Effective Treatment for Benzodiazepine Withdrawal?

Before discussing this question, it should be understood that this "search" for something that could "reverse" (or, at least, positively affect) benzodiazepine withdrawal is not an advocacy for psychiatry, as it is currently practiced. Certainly, the state of psychiatry is in need of significant modification. This does not mean that the existing "tools" must be abandoned as long as they are used appropriately and with great care for the patient's health and well-being.

Could ECT be effective in righting a wrong – one that has largely been caused by the drugs of psychiatry (in this case benzodiazepines)? I honestly don't know, but there are some aspects about it that lead me to believe that it would be worth a try if I were in benzodiazepine withdrawal. (I actually did submit to ECT treatment even though it had no way of helping me at the time. Such was the magnitude of my desperation.)

The immediate goal of ECT is rather simple – to induce a seizure. It is believed that this somehow affects both the GABAergic system and, to some degree, one's memory. (My memory was already extremely poor, as is the memory of many who have taken benzodiazepines, so I was more interested in simply "feeling well" again.)

In benzodiazepine withdrawal (and even during ongoing exposure to benzodiazepines), the GABAergic system is clearly adversely affected through a mechanism of alteration of gene expression. To what extent this is true is largely unknown, but there are many ways the brain could reduce neural inhibition by making modifications to the GABAergic system.

Is it possible that, through the alteration of gene expression, the brain has altered its "internal memory" to the extent that it no longer directly uses the unaltered genetic code from the DNA that applies to the GABAergic system? Could ECT somehow affect the brain's "internal memory" such that it "forgets" the "signaling" that has caused it to alter the genetic code via mRNA splicing (or some other means)? If so, it would seem that it would then freely be able to revert to reading its genetic code (the portion that applies to the GABAergic system) and no longer find it necessary to alter it.

There really are no black and white answers to these questions, but they are worthy of answers. "What if" ECT could help to reverse the effects of benzodiazepines or otherwise restore the GABAergic system? What if one day those suffering interminably through benzodiazepine withdrawal could "snap out of it" – almost miraculously?

"Tis a consummation devoutly to be wished."