Benzodiazepines:
What Have They Done to My Brain?

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When I was in withdrawal from benzodiazepines (actually when I was in some kind of unknown withdrawal immediately after I had quit drinking), I had no clue what was happening to me or what might be causing my extreme anxiety, panic attacks, black depression, pure terror, and inability to eat, sleep or think. I was certain that I was going insane – which only catapulted my terror into another dimension.

After a little research, I was sure that my problem was post-acute withdrawal syndrome (PAWS) from the alcohol. Several of the stories I had read in the Alcoholics Anonymous Big Book seemed to confirm that conclusion. As time went on, my symptoms got much worse. I was deteriorating mentally and emotionally. I found an addiction blog online and posted my story – also mentioning in an offhand manner that I was taking clonazepam (which I thought was actually a beneficial thing to be doing).

The answer I received in response to my post seemed ludicrous and illogical. I was told that the clonazepam was my problem – that the brain "reads" benzodiazepines the same way it "reads" alcohol. I was told that my brain was still thinking I was drinking. Of course, being a person steeped in reason, my ailing brain formed what seemed to be a very logical question: "If my brain still thinks I'm drinking, why am I in this horrid state of mental and emotional anguish? Why isn't this 'clonazepam/alcohol' making me calm and keeping me happy?" (I obviously knew nothing of benzodiazepine tolerance withdrawal at the time.)

For the next three months I refused to believe what I had been told. I was absolutely positive that the clonazepam would eventually make up for the alcohol "deficit" and I would improve and be well again. I had up-dosed and then cold-turkeyed the clonazepam several months earlier (in a mental institution) which nearly killed me. The extremely acute symptoms were beyond imagination, so I had to reinstate. I was in no hurry to try that again. In fact, it seemed like an impossible task to ever get off the clonazepam. Nevertheless, seeing no improvement whatsoever for three months after reinstating the clonazepam, I tapered from it over three months and descended into the next level of hell on earth.

In the sixth or seventh month after being off the clonazepam, I discovered a couple of the online forums for benzodiazepine withdrawal. Although I could take some comfort in knowing that I was not going crazy and that there were others enduring the same suffering, there was virtually no information regarding what exactly was going on inside

our bodies that had caused the horror story that we were each living. There was considerable discussion about supplements, other psychotropic drugs and other remedies that might lessen the suffering or even “cure” us. Eventually, I made my way to BenzoBuddies where I began to learn a little more about what had happened to me (and everyone else).

Things like tolerance withdrawal, paradoxical reaction, and post-benzodiazepine withdrawal were mentioned and discussed. Of greatest interest was the phrase “GABA receptors.” Apparently, this is where the battle for our very lives was taking place. This is where the benzodiazepines were waging a biochemical and physiological war against us. The discussion was usually very brief and was nearly always summed up with: “Our GABA receptors have been down-regulated and need to be up-regulated.” The underlying answer to up-regulation has consistently been to just distract oneself and get through time while the body heals intrinsically. (Of course, don’t take any benzodiazepines or anything else that affects GABA receptors while you are waiting.) This is very true. The body does heal intrinsically, and we should try to not be afraid while the healing is happening.

This is much easier said than done because one of the intrinsic symptoms of benzodiazepine withdrawal is fear – but not reasonable fear. This is an irrational fear that simply “exists.” If that is not enough, it is often further fueled by the unknown which spawns thoughts and questions like – “Maybe I am mentally ill. Does this really ever end? Does everyone really heal? Will I have PTSD when this is over? Am I doing this to myself?” And on and on.

To make matters worse, there are those who have been in withdrawal for many months (protracted withdrawal) with only scant improvement. They are scared – and rightly so. Others who have not been off benzodiazepines for nearly as long read the stories of those who are in protracted withdrawal and fear they will also take a long time to be well again – and rightly so.

Ever since October 2009, when I quit drinking, I have never had a clear understanding of exactly what has happened to my GABA receptors or to the receptors of anyone who has been or is in benzodiazepine withdrawal. I have read a few things posted in the forums and on Facebook groups which relate to how benzodiazepines have affected GABA receptors, but they always leave me with more questions and never really get to a place where I feel satisfied not only with the explanation but also with what might realistically be a plausible solution. In fact, maybe it’s not just a matter of “downregulation” of GABA receptors. Maybe there is more to the story.

In one of my last videos, I made the statement (with respect to the symptoms/suffering of benzodiazepine withdrawal): “Instead of fearing what it might be, face what it is.” Throughout my withdrawal experience, I had virtually no idea of “what it is.” Anything I had read was, at best, nebulous. Knowing what exactly (or at least with some reasonable degree of certainty and plausibility) was going on with my GABA receptors (and whatever else might be contributing to my suffering) would have helped to dissipate some of the fear by giving me an idea of what I was fighting. Even now that I am well, I still want to know – maybe to appease my own curiosity but also, hopefully, to help others dispel some of the misconceptions they may have concerning what benzodiazepines have done to them and what they might be able to do to help themselves (other than simply allowing their brains to heal intrinsically).

Of course, having been an environmental scientist for nearly three decades (before benzodiazepine withdrawal ended my career), at the beginning of this endeavor, I wanted to “jump right in” and start discussing plausible “solutions” without getting bogged down in the “nuts and bolts” of the problem. Unfortunately, I’m not a neuroscientist or molecular biologist, so “the slate is blank” – except for some things I recall from the many biology classes I took in college as well as information I learned as a scientist. So, I have had to “begin at the beginning.” I have been reading and studying a neuroscience textbook and various scientific papers and even posts in some of the forums and groups. I have been pondering what I’ve been reading in an effort to understand what benzodiazepines may have done to our brains or may have caused our brains to do to themselves. It has been very interesting and fascinating up to this point.

At the outset, I must acknowledge that what follows is not being presented as “an exhaustive or rigorous scientific work.” It represents some of what I have learned about the central nervous system (CNS) – primarily the GABAergic system (inhibitory neurons and synapses that produce, release and bind GABA – the system that is affected by benzodiazepines). Certainly, other “factors” play a role in how the brain reacts to the presence of benzodiazepines (including other of the many neurotransmitter/neuroreceptor systems). This discussion will initially focus on the GABAergic system and, as a matter of necessity, will include other considerations in order to surmise what may have happened to the brain as a result of benzodiazepine exposure.

For purposes of this discussion, the GABAergic system includes the neurotransmitter, GABA, and $GABA_A$ neuroreceptors (although there are also $GABA_B$ receptors).

Basic Facts About $GABA_A$ Neuroreceptors

In order to "face what it is," we first need to know "what it is." This is most easily accomplished by first having a very basic understanding of $GABA_A$ neuroreceptors – their function, what they do, how they do it and their fundamental structure. A little context is first needed so that later discussion makes sense.

The CNS is composed of approximately 100 billion nerve cells (neurons). Each neuron is composed of a dendrite (which receives electrical inputs from other neurons and does "computations") and an axon which transmits the "computations" from the dendrite to the dendrite of the next neuron via electrical pulses. The axons are essentially the "wiring" part of the brain. The neurons do not physically touch each other but rather meet at an area called a synapse. Chemicals (called neurotransmitters) cross from the end of the axons (axon terminals or presynaptic terminals) across a space (synaptic gap) to receptors located primarily on the dendrite of another neuron (also called postsynaptic terminal). There are approximately 10,000 synapses per neuron or one quadrillion synapses in the CNS. There are multiple neuroreceptors at each synapse, so there are quadrillions of neuroreceptors in the CNS.

There are many specific types of neurotransmitters and neuroreceptors in the CNS. Generally, each receptor type receives only one type of neurotransmitter. Neurotransmitters are divided into three major function classes – fast, excitatory neurotransmitters (glutamate and acetylcholine), fast, inhibitory neurotransmitters (GABA and glycine), and neuromodulators (both slow and fast). For purposes of this brief discussion, we will focus on GABA and the $GABA_A$ neuroreceptor.

Each $GABA_A$ neuroreceptor is comprised of five distinct subunits (a pentamer) with each subunit being a quaternary protein (specific folded three-dimensional structure essential for performing a specific function) composed of approximately 450 amino acids. The subunits are arranged in a circle with an ion channel in the middle.

Each of these proteins is in a "family" of proteins. There are eight families: α, β, γ, δ, ε, θ, π and ρ. Each family consists of the following number of proteins:

- α family – six proteins
- β family – three proteins
- γ family – three proteins
- δ family – one protein
- ε family – one protein
- θ family – one protein

- π family – one protein
- ρ family – three proteins

There are nineteen protein options for each subunit (although the three proteins in the ρ family are primarily expressed in the retina of the eye). Not all $GABA_A$ neuroreceptors have the same subunits or sequence of subunits. Mathematically, this means there could be extremely significant variability in the composition of $GABA_A$ neuroreceptors in the same individual. Even a single neuron can possess multiple $GABA_A$ neuroreceptors of different subunit composition. Subunit composition and sequence within the receptor are directly related to the functionality of each receptor.

The most common form of $GABA_A$ neuroreceptor is one with α_1, β_2 and γ_2 subunits. It is the receptor that is typically discussed with respect to the mechanism of action of $GABA_A$ neuroreceptors, and it is believed that benzodiazepines bind to only $GABA_A$ receptors comprised of α, β and γ subunits.

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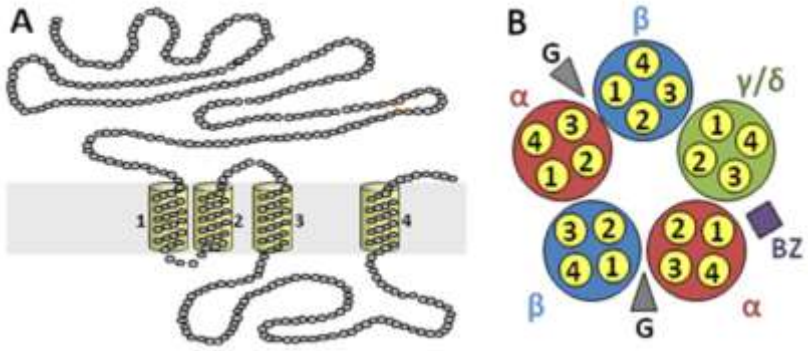
Each subunit in this form of receptor possesses a hydrophilic N-terminal domain outside the cell (the long looping structure above the four coil-like structures in diagram A below) followed by four alpha helices (the coil-like structures in diagram A) that are located within the cell membrane. The C-terminal of the protein (the short tail emanating out of the fourth coil in diagram A) is located outside the cell.

The first stage of the mechanism by which the $GABA_A$ receptor works is for GABA to bind to the two binding sites on the receptor (located on the α/β interfaces as indicated by the two gray triangles on diagram B). The conformation (molecular shape) changes, locking the GABA into the two binding sites. This is followed by additional conformational changes in the protein resulting in one or more so-called “flipped states.” More conformational changes occur that open the central channel or pore. How the binding of GABA into the binding sites results in the opening of the central channel is very unclear. The mechanism has not been explained with any certainty.



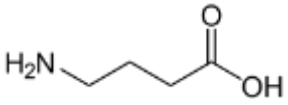
How Do Benzodiazepines "Fit In"?

Benzodiazepines are known as positive allosteric modulators (PAMs) of $GABA_A$ neuroreceptors which means that they increase the activity of $GABA_A$ neuroreceptors, i.e., enhance the ability of the central ion channel to open more frequently. They do this by binding strongly to a site on the $GABA_A$ neuroreceptor (not the same binding sites that GABA binds to). The binding of the benzodiazepine molecule to the $GABA_A$ neuroreceptor results in a change in the conformation of the receptor such that the affinity of the neuroreceptor for GABA molecules increases. As the GABA molecules lock into the two binding sites or pockets, the conformation again changes. Again, this is followed by additional conformational changes in the protein resulting in one or more so-called "flipped states." More conformational changes occur that open the central channel or pore. It is important to remember that the benzodiazepine does not bind to the GABA binding sites but rather changes the conformation of the receptor resulting in an increase in the affinity of GABA for the two GABA binding sites. In diagram B above, the benzodiazepine (BZ) binds at the interface between the α and γ/δ subunits.

Benzodiazepines are known as exogenous PAMs, meaning that they originate outside the body. Interestingly, no endogenous (originating inside the body) PAMs have been identified for the site on the $GABA_A$ neuroreceptor where benzodiazepines bind, although there is evidence that such endogenous PAMs exist. It is also thought that neurosteroids (natural metabolites synthesized from cholesterol) also bind to $GABA_A$ receptors (not at the same binding sites as benzodiazepines) and function in both an inhibitory capacity and suppressing of inhibition capacity.

A Few Words About GABA

GABA is the acronym for gamma-aminobutyric acid. It is an amino acid that is an ionotropic neurotransmitter meaning that it binds to the $GABA_A$ neuroreceptor which opens an ion channel (also called pore or gate) in the center of the receptor allowing negatively charged chloride anions from the fluid outside the neurons to pass down the channel and into the next neuron. This contributes to the negative charge or hyperpolarity inside the neuron. This has an inhibitory effect on the neuron meaning it reduces the likelihood that it will "fire" or conduct an electrical pulse from the previous neuron. Unlike the other two major amino acid ionotropic neurotransmitters (glutamate and glycine), GABA is not one of the twenty amino acids that are used in the synthesis of proteins.



Gamma-aminobutyric acid

GABA is primarily synthesized in the cytosol (watery fluid) of the presynaptic terminal (axon terminal) of neurons from which it is released – inhibitory neurons. Interestingly, GABA (the major inhibitory neurotransmitter in the brain) is synthesized from glutamate (the major excitatory neurotransmitter in the brain). This is done in one biochemical step – a decarboxylation reaction catalyzed by glutamic acid decarboxylase (GAD – a protein enzyme). After synthesis, special proteins called transporters concentrate GABA into vesicles (membrane enclosed structures) near the synaptic gap. When the cell "fires" (i.e., when an action potential is reached), the GABA molecules in the vesicles are released into the synaptic gap. This is called exocytosis.

Several things can happen to the GABA molecules after they are released. (1) They can bind to $GABA_A$ receptors on the postsynaptic terminal. (2) They can bind to autoreceptors on the presynaptic terminal (the terminal from which they were released). These receptors are usually G-protein-coupled receptors (not ionotropic receptors) that commonly inhibit neurotransmitter release from the presynaptic terminal and can also inhibit the synthesis of the neurotransmitter. (3) They can be taken up (reuptake) into the presynaptic terminal by the action of specific neurotransmitter proteins existing in the presynaptic membrane. (4) They can be taken up by astrocytes and other cells existing in the glia (area of the brain that supports, insulates and nourishes neurons) that surround the synapse. (5) They can be "directed" back to the presynaptic terminal by endocannabinoids (small lipid molecules) released from the postsynaptic terminal. This seems to be especially common when the postsynaptic membrane is very active. (6) GABA molecules can also simply diffuse into the surrounding glia of the brain.

Genetics 101 – Gene Expression

The current prevailing scientific opinion seems to be that dependence on and tolerance to benzodiazepines (or other substances that affect the GABAergic system similarly such as alcohol and z-drugs) are caused by changes or alterations in gene expression within neurons. In order to understand what this means, a brief, fundamental discussion of genetics is necessary.

The genetic material of every neuron (and every cell in the body) is DNA (deoxyribonucleic acid). DNA is contained on the chromosomes that exist in the nucleus of the neuron. The nucleus is contained in the soma or cell body of the neuron. DNA is essentially the blueprint for the whole body. It contains the assembly instructions for every part of the body. Proteins of all kinds (including shape, size, and function) are synthesized according to the instructions in the DNA. The process from the reading of the DNA to the final synthesized protein is called gene expression.

Through a process known as transcription, the information on the DNA (which never leaves the nucleus) is transcribed to another intermediary molecule called mRNA (messenger ribonucleic acid). The information (known as the transcript) is carried outside the nucleus by the mRNA into the cytoplasm of the soma (central part of the neuron). The mRNA migrates to structures in the soma called ribosomes. This is where amino acids are synthesized and sequenced into proteins by reading or translating the information on the mRNA. This is called translation. Ribosomes exist in two places in the soma – the rough endoplasmic reticulum (ER) and polyribosomes. It is believed that proteins synthesized at ribosomes of the ER are ultimately inserted into membranes of the surface of the neuron (probably as receptors) and cellular organelles. Proteins synthesized at polyribosomes are destined to be used within the cytosol, i. e., cytoplasm of the neuron (probably as enzymes). It is also thought that the proteins synthesized at the rough ER (those that will be part of the neuron membrane) are "carefully folded" in the smooth ER because they must possess specific three-dimensional structures in order to function properly.

So, if gene expression is as "cut and dry" as described here, the proteins synthesized at the ribosomes should be identical to those coded for in the DNA in the nucleus. It's not quite that simple. Through a process known as RNA splicing, the initial RNA transcript that came directly from the DNA is often altered in multiple ways resulting in mRNA molecules with different instructions that can code for different amino acids and thus produce different proteins during the translation process. In other words, the proteins coded for by the DNA are not always the ones that are synthesized at the ribosomes.

Why Have Things Gone So Awry for So Many Who Have Taken Benzodiazepines?

The answer to that question may very well also be the solution. First, based on the foregoing discussion, it would be instructive to "construct scenarios" of how the brain may react to the direct presence of benzodiazepines and to the inhibition caused by benzodiazepines. Then it may be possible to postulate why things have gone "amiss" for so many.

There are many pieces to the puzzle, and, if those pieces can be put together correctly (or even approaching correctly), the picture may become clearer even though there will undoubtedly still be some pieces missing – which may not matter with respect to a solution.

In some respects, I have the benefit of being absolutely certain that benzodiazepine withdrawal does exist simply because I have been one of its temporary prisoners and I

have read and heard many stories of others who have endured (or are enduring) benzodiazepine withdrawal. For this reason, I have been able to look at some of the available scientific information within the context of observations I have made regarding the various aspects of benzodiazepine withdrawal. Most importantly, it gives me a motivation and urgency that others who have not experienced benzodiazepine withdrawal may not have.

We have briefly discussed two basic things that appear to be involved in benzodiazepine tolerance/dependence and subsequent withdrawal. These are (1) the GABAergic system – more specifically $GABA_A$ neuroreceptors and GABA and (2) gene expression. There are dozens of other neurotransmitter systems in the brain that could be involved, at least indirectly, but the primary focus here is the GABAergic system and gene expression.

<u>The GABAergic system</u>

Exactly how the binding of GABA to a $GABA_A$ neuroreceptor results in the opening of the ion channel of the neuroreceptor is a mystery. Similarly, it is also unclear how benzodiazepines affect the GABA binding sites in the neuroreceptor resulting in its increased affinity for GABA. It is, therefore, no surprise that an understanding of what has caused some individuals to experience benzodiazepine withdrawal is equally (if not more) elusive.

A few hypothetical and/or plausible scenarios can be formulated in an attempt to determine precisely what "GABA downregulation" is and what may be its cause or causes. (At the outset, "GABA downregulation" is loosely defined as "the condition in which the GABAergic system is no longer able to provide normal neural inhibition, i. e., or being less likely to generate an action potential.")

Scenario 1 The extreme molecular conformational changes occurring in the $GABA_A$ receptors during the very frequent channel opening in the receptors (caused by benzodiazepine binding) somehow cause sufficient "stress" or "strain" in the molecular structure rendering them less functional or non-functional (perhaps by breaking hydrogen bonds in the alpha helices of the subunits). This may cause total or partial blockage of the chloride ion channel preventing movement of extracellular ions into the neuron.

Scenario 2 The brain "corrects" the elevated level of inhibition caused by the benzodiazepine by absorbing or otherwise removing $GABA_A$ receptors from neuron membranes.

Scenario 3 The brain "corrects" the elevated level of inhibition caused by the benzodiazepine by changing the protein structure of one or more of the $GABA_A$ receptor subunits so that GABA cannot bind to receptor sites or by otherwise causing total or partial blockage of the chloride ion channel preventing movement of extracellular chloride ions into the neuron.

Scenario 4 The transport of GABA away from the synaptic gap by astrocytes in glia that surround the synaptic gap is accelerated to the extent that GABA is prevented from binding to the GABA receptors. Astrocytes may also absorb the benzodiazepines in the interneuron spaces preventing it from binding to receptors.

Scenario 5 Direct enzymatic destruction of neurotransmitters (GABA) in the synaptic gap occurs preventing neurotransmitter binding.

Scenario 6 Auto receptors on the presynaptic axon terminal (typically G-protein-coupled receptors that stimulate second messenger formation) are activated producing enzymes that inhibit the release or even synthesis of GABA, thus controlling the amount of GABA released into the synaptic gap.

Scenario 7 Neurotransmitter transporter proteins in the presynaptic membrane take up the GABA from the synaptic gap and transport it back into the presynaptic axon where it is enzymatically destroyed (reuptake).

Scenario 8 Production of glutamic acid decarboxylase (GAD) – the enzyme necessary to convert glutamate to GABA – is reduced or eliminated.

<u>Alteration of gene expression</u>

With the exception of Scenario 1, all of these scenarios could conceivably result from the brain's alteration of gene expression in an effort to reduce the extreme inhibitory effect that benzodiazepines have on $GABA_A$-gated neurons. If Scenario 1 were true, one would expect the brain to repair the "damage" by synthesizing undamaged subunit proteins to replace those that were damaged. This would seem to be a rather rapid, routine process.

It has been demonstrated in laboratory studies on rats (and possibly other small mammals) that positive allosteric modulators (such as benzodiazepines, alcohol and possibly z-drugs) can create tolerance/dependence with respect to the GABAergic system. Large doses of benzodiazepines have been shown to produce

tolerance/dependence very rapidly (within a few days). The indicator that demonstrates this tolerance/dependence is a measured change in the mRNA coding for one or more of the $GABA_A$ subunits. Through RNA splicing, the brain apparently alters the mRNA transcribed from the nuclear DNA. The altered mRNA is then used to synthesize one or more proteins that differ from the proteins coded for in the DNA. This likely results in conformational changes in $GABA_A$ receptors which may cause the ion channels to open improperly or not at all (thus reducing the inhibitory effect of any GABA that is present). It could even prevent GABA molecules from binding at the binding sites on the receptors (also reducing inhibition). This is alteration of gene expression. Laboratory studies have also demonstrated that such alteration of gene expression can occur when an overabundance of GABA is present (even in the absence of benzodiazepines or other PAMs). This is evidence that Scenario 3 is a real phenomenon.

The brain could also conceivably "correct" the extreme inhibition caused by the binding of benzodiazepines by also effecting one or more of Scenarios 4 through 8. Although I did not find any studies for any of these scenarios, one or more could conceivably result from alteration of gene expression (because they all involve enzymatic action).

In a sense, the answer to the question, "Why have things gone so awry for so many who have taken benzodiazepines?," is neuroplasticity. The brain is responsible for about 20% of the body's metabolism and only weighs an average of three pounds which is, on average, 1.5% to 2.5% of one's total body weight. The neurons of the brain are constantly working – even when we are at rest. It is not hard to imagine that, when it is extremely inhibited by the effects of benzodiazepines, it interprets that inhibition as "damage" and proceeds to "correct" it as rapidly as possible. This could very well be the reason why benzodiazepines provide that extraordinary, almost incredible level of calmness for only a few weeks or less. (This was my experience and the experience of many others formerly or currently in benzodiazepine withdrawal.) The brain is simply using its neuroplasticity to compensate for what it perceives as injury. It seems to do this by altering the expression of genes in the DNA on the chromosomes in the nucleus of its neurons.

There Is Hope

If neuroplasticity has created benzodiazepine tolerance/dependence in response to extreme inhibition that the brain has interpreted as injury, then it is reasonable to not only believe, but to expect, the brain to be able to reverse that process with neuroplasticity.

If “downregulation” is the result of change in gene expression (likely from mRNA splicing), it may be reasonable to hypothesize that, if the “memory” of the mRNA splicing that has caused the change in genetic expression is “erased” (at least temporarily), the brain could “reset” or “revert” such that the mRNA once again codes from the DNA without performing the mRNA splicing that has changed the genetic expression. This would mean that the mRNA would code for the proper amino acids in the proper sequence during the protein translation process at the ribosomes. The resulting “correct” proteins (manufactured from the unaltered DNA code in the nucleus) would then be available to be used as the $GABA_A$ neuroreceptor subunits hopefully resulting in neuroreceptors that function as they did before benzodiazepine exposure. Or, if any of scenarios 4 through 8 are applicable, “correct” proteins, used as enzymes, would be available to synthesize GABA, eliminate/reduce its destruction, prevent/reduce its reabsorption/reuptake and so on.

For some reason (probably genetics), many people who have been exposed to benzodiazepines possess brains with a neuroplasticity capable of finding their way back to normalcy and health and wellness comparatively quickly. Others struggle for much longer. Perhaps there is something that could help such individuals back to wellness by reversing the alteration of gene expression – something that has not yet been discovered.

The nervous system is extremely sensitive to the balance of endogenous neurotransmitters and to exogenous psychotropic drugs (as evidenced by the negative effects caused by exposure to benzodiazepines, alcohol, antidepressants and others). Therefore, it is not likely that alteration of gene expression can be successfully addressed with another drug or drugs. (They are responsible for the problem in the first place.)

The answer may lie, at least partially, in epigenetics, the study of long-term change in gene expression not caused by changes in DNA.