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Review Article

Emergent Success of GABA Modulators Links Neuronal Hyperexcitability to the Pathophysiology of Depression

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Abstract: In 2019, after it had demonstrated rapid antidepressant effects in two placebo-controlled trials, the investigational drug brexanolone received FDA approval for the treatment of postpartum depression. Less than a year later, zuranolone, an oral formulation of the same drug, achieved similar results in patients with treatment-resistant depression. Brexanolone and zuranolone are the first in a new line of investigational drugs that act by enhancing GABA neuroinhibitory currents. The significance of this pharmacodynamic effect is that it is associated with a reduction in depressive symptoms in just 2-3 days as opposed to 2-3 weeks with antidepressants. This has naturally raised many questions about the mechanism by which these drugs exert their therapeutic effects. At the same time, an emerging hypothesis contends that psychiatric symptoms are the consequence of an inability of neurons to shut off. According to the multi-circuit neuronal hyperexcitability (MCNH) hypothesis of psychiatric disorders, psychiatric symptoms develop when symptom-related circuits in the brain fire too easily and for too long. Brexanolone and zuranolone put a brake on that firing. This article will discuss the groundbreaking success of GABAergic modulation from the perspective of the MCNH hypothesis and contrast it with the pharmacodynamic effects of standard antidepressant drugs in an effort to highlight the importance of neuronal excitability in the pathophysiology of depression and showcase the utility of the MCNH hypothesis as a guide to the assessment, treatment, and prevention of a wide range of psychiatric symptoms.

Keywords: Brexanolone, Zuranolone, GABA Modulators, GABAkines, Imidazodiazepines, Neuroregulators, Neuronal Hyperexcitability, Biomarkers of Disease

1. Introduction

Mental illness is a major cause of morbidity and mortality worldwide [1]. It is a major cause of work absenteeism, substance misuse, domestic violence, homelessness, suicidality, and homicidality [2]. In addition to the psychological and emotional suffering that are caused by mental illness, affected persons are at an increased risk of developing any of a wide rage of general medical conditions, including diabetes, high blood pressure, cardiovascular disease, autoimmune disease, cancer, and dementia [3]. These illnesses have been estimated to reduce the lifespan of the mentally ill by as many as 20 years relative to the general population [2, 4].

Despite the pressing need to improve mental healthcare, the last few decades have seen relatively little improvement in treatment outcomes [5]. Consequently, intensive efforts to address the growing mental health crisis have continued on all fronts: mental health practitioners continue to explore new psychological and behavioral approaches to treating mental illness; advocacy groups continue to promote mental health awareness and explore new ways to encourage the mentally to seek treatment; and research scientists continue to pursue new molecular targets and new drugs with which to treat mental illness.

One of these new drugs and its molecular target are based on the connection between clinical depression in women and the rapid fall in progesterone that begins during the postpartum period. Metabolites of progesterone have long-been known to have neuroinhibitory effects [6], and many patients with depression seem to need something to

quiet their racing minds, calm their turbulent emotions, and improve their quality of sleep. These connections and the relative failure of neurostimulatory drugs to improve long-term outcomes in the treatment of depression have led developers to explore the potential benefits of a new approach to treating depression; namely, neuroinhibition.

This novel approach was recently introduced in the form of a synthetic analogue of one of progesterone's primary metabolites, allopregnanolone. Marketed as brexanolone (Zulresso), the drug was intravenously infused over 60 hours in a sample of women with severe postpartum depression [7]. This led to a rapid reduction of depressive symptoms, with noticeable improvement beginning in just 2-3 days as opposed to 2-3 weeks with traditional antidepressants. In March, 2019, brexanolone received FDA approval, making it the first drug to be approved for postpartum depression. In the meantime, an oral formulation of brexanolone, zuranolone (SAGE-217), was tested against placebo in 45 adults with treatment-resistant depression. The results were similar to those with brexanolone and were published in the New England Journal of Medicine as a potentially new approach to the treatment of major depressive disorder and possibly other psychiatric disorders [8, 9].

The main observation that is attracting the attention of clinicians and researchers is the rapid onset of action of these drugs. Besides raising eyebrows, their rapid therapeutic effects are raising many questions about their mechanism of action. The rapid antidepressant effects of brexanolone and zuranolone appear to be linked to their simple and direct pharmacological effects: both drugs are positive allosteric modulators of gamma-aminobutyric acid type-A (GABA-A) receptors [10]. The drugs bind to receptor sites on chloride ion channels, thereby augmenting the duration with which the naturally-occurring neurotransmitter GABA is able to increase chloride conductance into the cell. As the neuronal membrane becomes hyperpolarized, the cell's excitability decreases.

Historically, the oldest known drug to have this effect is ethyl alcohol [11]. This was followed in the modern era by barbiturates, benzodiazepines, and sedative hypnotics, an observation that highlights the utility of targeting chloride ion channels in drug development. However, after decades on the market, growing concerns about sedation, tolerance, and withdrawal with synthetic GABA modulators led to a period of dormancy in the production of this class of drugs [12]. Instead, the focus of psychotropic drug development turned to antidepressants, particularly SSRIs.

Unfortunately however, antidepressants have not panned out to be the wonder drugs that many had hoped they would be. Based on recent studies, only about one-third of patients with major depressive disorder respond to the first antidepressant they try, and even after multiple antidepressant trials, no more than two-thirds of patients have a positive response [13]. Also, among responders, approximately 50% will relapse by the end of the first year of treatment [14]. Additionally, meta-analyses of antidepressant therapy have reported only modest benefits over placebo [15], and when unpublished trial data are included, the benefits of antidepressants fall below accepted criteria for clinical significance [16]. Concomitant with these findings, the monoamine hypothesis of depression, which for more than 50 years has guided the use of antidepressants, has come under increasing scrutiny for failing to provide answers to several key questions, such as why the depletion of serotonin precursors fails to produce depressive symptoms in normal subjects [17]; why antidepressants can sometimes make depressive symptoms worse [18], and why antidepressants can sometimes have beneficial effects in disorders other than clinical depression [19].

What makes brexanolone and zuranolone different from antidepressants is that they express their effects everywhere in the brain rather than just in specific circuits (i.e., monoaminergic circuits), and what makes them different from benzodiazepines is that they modulate both synaptic and extrasynaptic GABA-A receptors rather than just synaptic GABA-A receptors [6, 10, 20]. The latter distinction may be particularly important because synaptic GABA transmission mediates phasic inhibition, whereas extrasynaptic transmission mediates tonic inhibition [21]. Some developers think this distinction may allow the new line of GABA modulators to have a lower risk of tolerance, dependence, and withdrawal than benzodiazepines [12]. It may also allow them to be more effective.

The idea that brexanolone and zuranolone exert their rapid antidepressant effects by rapidly reducing neuronal excitability is corroborated by the rapidly-occurring antidepressant effects of other drugs that rapidly reduce neuronal excitability, albeit by different mechanisms. For example, lamotrigine and oxcarbazepine rapidly reduce neuronal excitability by selectively inhibiting voltage-gated sodium channels [22, 23]; gabapentin rapidly reduces neuronal excitability by selectively inhibiting voltage-gated calcium channels [24]; and valproic acid rapidly reduces neuronal excitability through a combination of these mechanisms [25]. Also, combining these drugs with one another, as is sometimes done in the treatment of bipolar spectrum disorders, tends to have an additive benefit in reducing depressive symptoms. What's more, these drugs have benefits beyond that of reversing depression. They are also able to reduce anxiety, stabilize mood, improve sleep, and alleviate many other psychiatric symptoms irrespective of the symptom-based diagnosis [26]. The idea that they exert these therapeutic effects by reducing neuronal excitability is further corroborated by a number of other clinical observations, including: 1) that psychiatric symptoms can readily be precipitated by stress and relieved by stress-reduction; 2) that psychiatric symptoms can be precipitated by stimulant-type drugs and relieved by sedative-type drugs; and 3) that any stress on the body that increases neuronal excitability, such as an infection, a physical injury, or a drug that activates the neuroendocrine system, can precipitate psychiatric symptoms. Conversely, a relief of these factors tends to relieve psychiatric symptoms. This is critically important to recognize because most of the drugs that rapidly reduce neuronal excitability have been on the market for decades and have

demonstrated long-term effectiveness with relatively little risk of tolerance, dependence, or withdrawal. Also, being generic, these drugs are generally more affordable than brand-name drugs.

2. The Problem with Antidepressants

In contrast to anticonvulsants, antidepressants, which for decades have dominated the market in the treatment of depression, tend to lose their therapeutic effects over time [14]. Although this tendency, known technically as "tachyphylaxis," has historically been difficult to explain, an emerging hypothesis on the pathophysiology of depression and other common psychiatric disorders may help explain it. It may also help explain the paradoxical effects that antidepressants can have. According to the multi-circuit neuronal hyperexcitability (MCNH) hypothesis of psychiatric disorders, psychiatric symptoms are the consequence of pathological hyperactivity in symptom-related circuits in the brain [27]. Thus, persistent firing in anxiety circuits causes persistent feelings of anxiety; persistent firing in depressive circuits causes persistent feelings of depression; persistent firing in cognitive circuits causes ruminative and obsessive thoughts; etc... This pathological circuit-specific hyperactivity is believed to be the consequence of an inherent failure of the neurological system to self-regulate when perturbed by a psychological, emotional, or biological stressor [27-29]. Although antidepressants have the potential to correct pathological circuit-specific imbalances in the brain [30], they attempt to do so by an imprecise and poorly-controlled mechanism: they attempt to modulate the activity of specific neurotransmitters [31]. However, this runs the risk of over-correcting the balance in some circuits or under-correcting the balance in other circuits or both. It also runs the risk of creating new circuit-specific imbalances, thus explaining the paradoxical effects that antidepressants can have [30]. Moreover, even when an antidepressant is working effectively, its neurostimulatory effects [32] tend to further exacerbate the underlying problem of neuronal hyperexcitability [30]. Consequently, unless the patient's stress levels decline enough during antidepressant therapy to reduce the overall level of excitation in the brain, the antidepressant cannot be stopped without triggering a return of symptoms. And if the patient's stress levels remain high, the neurostimulatory effects of the antidepressant may eventually outstripe its neuroinhibitory effects, thus causing the medication to start losing its therapeutic effect. If the dosage of the medication is then increased (an adjustment that is often made), the patient's symptoms can either improve, remain unchanged, or worsen, depending upon how the medication adjustment affects the circuit-specific imbalances that are causing the symptoms. If symptoms improve, the reduction in symptoms can de-stress the mind enough to reduce or even end the vicious circle of mutual overestimation between the mind and the brain that keeps refueling the symptoms. If, in addition, the patient's external stressors remain low, the patient could potentially discontinue the medication without experiencing a return of symptoms—at least until his or her stress levels begin to rise again. If, as a second possible outcome of increasing the dosage, the symptom-reduction is insufficient to outweigh the added stimulatory effects of increasing the dosage, the patient's symptoms will remain unchanged. Alternatively, if the increase in dosage further exacerbates the circuit-specific imbalances that are causing the symptoms, or worse yet, it creates new circuit-specific imbalances, the patient's condition will worsen. However, as previously stated, even if the increase in medication dosage turns out to be effective in rebalancing the activity in the symptom-related circuits, it is possible that the patient's external stressors will remain too high to enable a gradual discontinuation of the medication. In such cases, the tendency for the medication to further exacerbate the underlying problem of neuronal hyperexcitability will be increased because the dosage has been increased. This is the MCNH explanation for why continued increases in antidepressant dosage can eventually lead to drug failure or, worse yet, paradoxical effects, including symptom-cycling [30, 33].

In contrast to depressed patients who have hyperexcitable neurological systems, those with *normo*excitable neurological systems are highly resistant to symptom-cycling because, as will be discussed later, *normo*excitable neurons are relatively resistant to aberrant circuit induction [34]. However, such patients, who could appropriately be described as "true" unipolar depressives, are relatively rare because the pathological circuit-specific imbalances that they develop are, hypothetically, not driven by an underlying hyperexcitability of the neurological system but by circuit-specific kindling secondary to a severe and prolonged emotional stressor [35-38]. Such severe stressors are relatively rare in comparison to the daily stressors that can cause pathological circuit-specific imbalances in persons with hyperexcitable neurological systems.

3. Practical Application of the MCNH Hypothesis

The foregoing discussion offers the first biologically-based explanation for the empirically-based recognition that patients with unipolar depressive disorders should be treated with antidepressants, whereas patients with bipolar spectrum disorders should be treated with anticonvulsants [34]. From the perspective of the MCNH hypothesis, patients with unipolar symptoms respond best to antidepressants not because their symptoms are unchanging but because they are more likely to have *normo*excitable neurological systems than patients with unstable symptoms. Likewise, patients with bipolar symptoms respond best to anticonvulsants not because their symptoms are changing but because they are more likely to have hyperexcitable neurological systems than patients with stable symptoms. This underscores the importance of determining the excitability of the neurological system in psychiatric assessment. Another reason that making this determination is so important is that patients with

hyperexcitable neurological systems would be less tolerant of the stimulatory effects of antidepressants and more responsive to the brain-calming effects of anticonvulsant drugs. The reverse would be true for patients with *normo*excitable neurological systems [34].

The MCNH hypothesis also helps explain the rapid antidepressant effects of another drug that is changing the way that depression is being treated; namely, ketamine. Very low doses of this well-known anesthetic have, like brexanolone and zuranolone, been found to reduce depression and other psychiatric symptoms within hours as opposed to weeks [39]. The proposed mechanism by which ketamine exerts its therapeutic effects is through antagonism of the excitatory neurotransmitter glutamate [40]. Again, what this demonstrates is that calming the brain, irrespective of the mechanism by which it is achieved, tends to relieve psychiatric symptoms. It also demonstrates the utility of the MCNH hypothesis as a comprehensive, pathophysiologically-based explanation for the development of psychiatric symptoms. Supplementing the current symptom-based approach to psychiatric care with a pathophysiologically-based approach is of critical importance both because symptom-based approaches are relatively unreliable and because they do not identify a clear biological target for treatment.

That leads to the question: what causes the neurological system to be hyperexcitable in the first place?

Strikingly, the top candidate genes for the major psychiatric disorders—disorders that together express all of the most common psychiatric symptoms—involve ionchannelopathies [41-44]. Specifically, the protein products of the candidate genes fail to adequately regulate the firing of neurons, thus increasing the excitability of the neurological system. What this means is that descendants who inherit the neuronal hyperexcitability trait would be at increased risk of developing psychiatric symptoms from the time that their brains were formed in the womb. The validity of this is supported by the primacy of stress as a precipitant of psychiatric symptomatology. Although symptoms do, in most cases, first manifest during adolescence and early adulthood [45], the detailed histories of affected persons reveal that symptoms are more stress-related than age-related. That is to say, they typically begin when the affected person's stress levels first begin to rise appreciably, irrespective of the person's age. Likewise, they typically begin to remit when stress levels begin to decline. In addition, there tends to be a time-lag between the onset of a precipitating stressor and the onset of symptoms. According to the mind-brain hypothesis of the cognitive-emotional system [46], this delay is the time needed for mental stimulation of the brain to induce enough kindling to precipitate symptoms [35, 36]. First observed by Graham Goddard in his experiments on rats, kindling describes the natural tendency for neurons to become increasingly responsive when stimulated repeatedly [37]. This adaptive process, which under normal physiological conditions is more aptly described as "primed burst potentiation" [47], is the MCNH explanation for why stress, if severe enough for long enough, can drive the development of psychiatric symptoms even in persons with *normo*excitable neurons. In essence, kindling itself can increase the excitability of the symptom-related neurons and circuits [38]. Hypothetically, the reason that psychiatric symptoms most commonly first manifest during adolescence and early adulthood is that for most persons the transition from childhood to adulthood is the first time in life that stress levels begin to rise appreciably and persist for an extended period of time.

That leads to another question: why aren't anticonvulsants more widely used in the treatment of psychiatric disorders?

The simple answer is that, short of a biologically-based explanation for the development of psychiatric symptoms, psychiatric disorders always have been and continue to be symptom-based. The problem with this diagnostic system is that symptoms are relatively non-specific, hence the high degree of symptom-overlap between psychiatric diagnoses. However, the gap between different diagnoses is closing with the growing recognition that a wide range of mood disorders form a continuum from "pure" unipolar depression to classic bipolar disorder [48]. Although the adoption of this so-called "bipolar spectrum" has been a giant step forward in psychiatry, it is still symptom-based. Hence, it could be improved if the spectrum could be redefined in terms of pathophysiology.

According to the MCNH hypothesis, depression, anxiety, insomnia, and other common psychiatric symptoms, irrespective of which psychiatric disorder they are identified with, are different expressions of a core biological abnormality. That abnormality is a hyperexcitability of the neurological system. Simply put, neurological systems that are inherently hyperexcitable lack the self-regulatory capacity to prevent various thoughts and emotions from becoming abnormally intense and persistent [27]. However, based on extensive clinical observations, the degree of neuronal excitability appears to vary between affected individuals and even between affected siblings in the same families [34]. Those with more severe symptoms are thought to have higher levels of neuronal hyperexcitability than those with less severe symptoms, and, due to the increased risk of aberrant circuit induction that they have, those with more severe symptoms are thought to have a greater propensity to cycle than those with less severe symptoms [34]. When placed on a continuum, the neuronal excitability spectrum roughly equates to the bipolar spectrum introduced by Akiskal [48]. However, the neuronal excitability spectrum has three important advantages. First, it is less subjective than the bipolar spectrum; second, it explains a broader range of psychopathology than the bipolar spectrum; and third, it illuminates a core biological target for treatment.

At one end of the neuronal excitability spectrum are those persons who have very calm brains, and at the other end are those who have very excitable brains. Those with very calm brains tend to be peaceful, easy-going, and flexible; whereas, those with very excitable brains tend to be uptight, moody, and rigid. Because psychiatric symptoms are, by definition, pathological reverberations of normal thoughts and emotions, persons with *hypo*excitable neurological systems would, as

previously stated, be relatively resistant to developing psychiatric symptoms. Also as previously stated, such persons would, even if they did develop symptoms, be relatively resistant to symptom-cycling, thus explaining why "true" unipolar depression is on this end of the neuronal excitability spectrum. Also, because such persons are so emotionally nonreactive, some could be described as emotionally insensitive—not that they really are insensitive—but they might appear to be insensitive because they are so emotionally nonreactive. Hypothetically, this group would include those who, if they really were callous and insensitive, might meet criteria for primary psychopathy [34]. Their lack of emotionality and tendency to intellectualize could help explain why primary psychopaths have been stereotyped as "cool and calculated." The low excitability of their neurological systems could also be what makes them so resistant to pharmacological intervention. Antidepressants would be of little use to them because such persons would be relatively resistant to developing the pathological circuit-specific imbalances that are hypothesized to underlie clinical depression, and anticonvulsants would be of little use to them because their neurological systems are not hyperexcitable. When such persons do feel depressed or anxious, their emotions would more likely reflect loneliness, emptiness, or fear than pathologically-elevated activity in symptom-related circuits in the brain. In sharp contrast to those with very *hypo*excitable neurological systems, those with very *hyper*excitable neurological systems would be hyper-reactive, moody, and dramatic. Alternatively, such persons, in an effort to defend against their exquisite emotional sensitivity, could be shy, introverted, or withdrawn. In either case, their neurological systems would be so excitable that they would likely be symptomatic even under conditions that most persons would consider to be very low-stress. In parallel to the small subgroup of persons with *hypo*excitable neurological systems that might be described as primary psychopaths, a similar subgroup of persons with *hyper*excitable neurological systems might, if they were likewise callousness and insensitive, be described as "secondary psychopaths" [34]. Note, however, that not all persons with hyperexcitable neurological systems would have classic bipolar symptoms. The explanation for this relates to the pathophysiology of symptom-cycling.

Although the biological mechanism that underlies symptom-cycling is still unknown, a hyperexcitability of the neurological system offers an anatomically and electrophysiologically sound explanation for this common phenomenon [34, 36]. The dense packing and extensive interconnectedness of neurons in the brain create the potential for the flow of electrical activity to deviate from its intended path. Hypothetically, hyperactive feeder circuits could, through their collateral connections to other neurons, aberrantly fuel activity in relatively *hypo*active receiver circuits while themselves quieting down due to synaptic fatigue [49]. This, in turn, could cause a concomitant shift in attention, cognition, and emotion that would progressively feed the bipolar switch. Persons with more neuron-to-neuron connections would tend to cycle more rapidly, and persons with fewer neuron-to-neuron connections would tend to cycle less rapidly. Rapid-cyclers would tend to have more subtle changes in mood and other symptoms because they would not remain in any specific cognitive-emotional state long enough for that state to be clearly recognized. The opposite would be true for non-rapid cyclers. However, because of all the emotional chaos that they live with, all such persons would have a tendency to feel depressed on an existential basis, if not on a neurological one. This conceptualization would help explain the high frequency with which bipolar spectrum disorders are misdiagnosed as unipolar depressive disorders. It would also help explain the relatively low incidence of classic bipolar disorder in patients with autism spectrum disorders [50], a diagnostic group that is thought to have a triad of neuronal hyperexcitability, too many neurons, and too many neuron-to-neuron connections [51, 52]. In fact, this triad of abnormalities could be what causes them to have so much difficulty handling and processing sensory input. It could also be what allows some of them to develop such extraordinary though narrowly-focused intellectual skills.

Based on the contention that persons with the highest levels of neuronal excitability would be the most vulnerable to stress and, thus, most likely to develop psychiatric symptoms, it is remarkable that the sales of antidepressants outnumber the sales of anticonvulsants by nearly ten-to-one [53-56]. The most likely explanation for this is that bipolar spectrum disorders continue to be misdiagnosed as unipolar disorders [57-59]. Although the frequency of this error has been declining over past few decades, it is still highly prevalent as suggested by the relatively little progress that has made in improving long-term treatment outcomes for most psychiatric disorders [5]. As long as bipolar spectrum patients continue to be treated with antidepressants and other stimulatory-type drugs, treatment outcomes, for the reasons previously discussed, are not likely to improve very much. It is the recognition of this, albeit through a different line of reasoning, that is leading research scientists to return to developing brain-calming drugs in the treatment of mental illness [12]. The development of brexanolone and zuranolone has placed SAGE pharmaceuticals at the forefront of this movement. By targeting the GABAergic system, brexanolone and zuranolone represent a clear shift from stimulating the brain to quieting the brain in the treatment of depression and possibly other psychiatric disorders [60, 61].

In a sense, the shift from stimulating to calming the brain began with the introduction of SSRIs, as serotonergic agents have fewer stimulating effects than the catecholaminergic drugs that preceded them. However, SSRIs do have neurostimulatory effects, most notably on cortical neurons [32]. Their potential to stimulate the brain is demonstrated by the fact that, as previously discussed, their therapeutic effects tend to fade over time. It is also demonstrated by their propensity to have paradoxical effects, including bipolar switching [18]. In contrast, non-benzodiazepine anticonvulsants, non-stimulating antipsychotics, and other brain-calming drugs rarely have these paradoxical effects.

They are also less likely to lose their beneficial effects over time [62].

However, a point of concern about calming the brain through positive allosteric modulation of GABA-A receptors is the tenancy for this mechanism to be associated with tolerance, dependence, and withdrawal. Based on existing evidence with progesterone and its metabolites, and the loss of progesterone's sedating effects during pregnancy [6], this would likely pertain to brexanolone and zuranolone. In what may be an effort to circumvent this problem, brexanolone and zuranolone are being promoted as short-term, as-needed treatments for postpartum depression and clinical depression, respectively. Although this is a substantial departure from the customary approach to psychiatric pharmacotherapy, the idea of using these drugs as brief, on-demand therapies does have some attractive aspects. First, most psychiatric patients would prefer a short course of medication over a long course of medication. Hence, the idea of an as-needed antidepressant is likely to attract many patients who would otherwise opt out of taking a psychotropic drug. Second, by rapidly quieting the brain, brexanolone and zuranolone could act as fire extinguishers that help break the vicious circle of mutual overstimulation between the mind and the brain that causes psychiatric symptoms to perpetuate. A natural consequence of this effect would be a reduction in the patient's perceived level of stress, thereby providing another mechanism through which symptoms could be alleviated and prevented from recurring.

Still, there are several potential concerns about this strategy. First, a short course of medication might not quiet the brain enough to break the vicious circle that causes psychiatric symptoms to perpetuate. Second, even if a short course of medication were enough to put the fire out, the fire would be likely to restart unless the patient's stress level declined appreciably. Third, the co-administration of a GABA modulator with an antidepressant, an approach that is actively being studied as of the time of this writing, could confound the ability to determine the cause of any side effects or counter-therapeutic effects that may occur as the medication dosages are being adjusted. Fourth, psychiatric symptoms can be difficult to distinguish from normal responses to cognitive-emotional stressors; hence, patients would be at risk for either using the medication too often or not often enough. If they were to use it too often, the development of tolerance could cause it to gradually lose its effect; were they not to use it often enough, they could wind up needing to take more medication for a longer period of time because they allowed the fire in their brains to gather too much pace before they attempted to put it out. Fifth, even after completing a successful course of pharmacotherapy, patients may have low-level exacerbations of their symptoms as their stress levels fluctuate over time. Some patients may notice these symptoms, others may not. And even if significant others were to notice the symptoms and express their concerns, some patients may refuse to acknowledge those concerns, especially if they are experiencing manic-like symptoms or there are tensions in their relationships with concerned others. Alternatively, some patients may be aware of their residual symptoms and, thus, request continuous medication refills, especially if the medication had been working well and their symptoms are recurring shortly after reaching the end of their prescriptions. Sixth, short courses of pharmacotherapy could lead patients to think that mental illness is a condition that, like a cold or flu, could be briefly treated and completely cured. In reality, however, mental illness is the symptomatic expression of a biological vulnerability to stress; hence, symptoms are likely to return whenever triggering stressors return. This underscores the importance of proper education about mental illness and encouraging patients to incorporate the healthy lifestyle habits that can combine with medication to help keep symptoms at bay or even eliminate the need for medication altogether.

As the first comprehensive neurophysiological hypothesis of psychiatric disorders, the MCNH hypothesis makes this kind of analysis possible and has the capability of empowering both providers and patients with the ability to make properly informed decisions about psychiatric care and illness prevention. It specifies the cause of mental illness, the ways it can be treated, and the ways it can be prevented. By calling attention to the importance of calming the brain, it incentivizes the use of natural interventions to calm the brain, such as stress reduction, establishment of an early sleep schedule, moderate exercise, avoiding caffeine and other psychostimulants, minimizing refined sugar, and enjoying a relaxing hobby. It also calls attention to the many other medical interventions that have brain-calming effects, most notably generic anticonvulsants drugs, such as gabapentin, oxcarbazepine, lamotrigine, valproic acid, carbamazepine, topiramate, tiagabine, levetiracetam, and the anticonvulsant-like drug lithium. These drugs, which could more aptly be called "neuroregulators" because of their proposed mechanism of action [26], would also include antipsychotic drugs, especially those that lack any significant neurostimulatory effects. Concerningly, however, neuroregulators, especially anticonvulsant neuroregulators, are grossly underutilized in psychiatry due to the continued misdiagnosis of bipolar spectrum disorders as unipolar depressive disorders [57-59]. Moreover, even when neuroregulators are utilized appropriately, they are commonly used sub-optimally due to the failure to recognize neuronal hyperexcitability as the core biological abnormality in mental illness.

From the perspective of the MCNH hypothesis, the most biologically accurate way to treat mental illness would be to identify the neuronal hyperexcitability trait and then focus efforts on therapeutically modifying the trait. That would mean starting treatment with a neuroregulator and then combining neuroregulators with one another in an approach that could be called "focused neuroregulation" [63]. This is in distinction to combining neuroregulators with antidepressants, psychostimulants, and other drugs that have pharmacologically conflicting and potentially counteracting effects. Moreover, based on the premise that focused neuroregulation would be addressing the core abnormality in mental illness, it would tend to be effective in reducing all

psychiatric symptoms irrespective of the symptom-based diagnosis.

Recognizing neuronal hyperexcitability as the core abnormality in mental illness also opens the door to a first in psychiatric medicine; namely, mental illness prevention. This is based on the idea that the neuronal hyperexcitability trait can be identified through simple vital-sign measurements. Over the past decade, a burgeoning number of studies have found that upper-end-of-normal resting vital signs are associated with a variety of mental illnesses. For example, in a longitudinal study involving more than one million men in Sweden, Latvala et al. [64] found that subtle elevations in resting heart rate were predictive of the later development of generalized anxiety disorder, obsessive-compulsive disorder, and schizophrenia. Similarly, Blom et al. [65] found that adolescent girls with emotional disorders had increased resting respiratory rates in comparison to healthy controls. Notably, these associations also involve a wide range of chronic physical illnesses, including diabetes [66, 67], high blood pressure [68, 69], cardiovascular disease [70, 71], cerebrovascular disease [72, 73], cancer [74, 75], dementia [80], and all-cause mortality [76-80]. The subtle vital-sign elevations with which these illnesses are associated are thought to be the consequence of a tonic elevation in basal neurological activity in those persons who inherit the genes for neuronal hyperexcitability [81]. This is the MCNH explanation for why the lifespan of persons with severe mental illness tends to be much shorter than the general population [4, 81].

In the past, educating those at risk for mental illness would have been challenging due to the inability to determine which members of affected families were actually carriers of the neuronal hyperexcitability trait. However, the recognition that resting vital signs can be used to identify the trait before symptoms even begin has the potential to change all that [34]. Also, helping those at risk to see that upper-end-of-normal resting vital signs are markers not of a psychological problem or character defect but of a biological abnormality that underlies a wide range of chronic health conditions, including mentally and emotionally-distressing symptoms, offers the first hope of completely destigmatizing mental illness while at the same time illuminating a clear biological target for treatment. What's more, the idea that possible carriers of the neuronal hyperexcitability trait could screen themselves through a simple, objective measure of the body's most basic functions could circumvent the barrier of shame that might otherwise prevent them from identifying and seeking to modify the neuronal hyperexcitability trait prophylactically.

4. Discussion

The purpose of this review was to connect an emerging new approach to the treatment of depression with an emerging new hypothesis on the pathophysiology of psychiatric disorders. By highlighting the benefits of calming the brain, the groundbreaking success of brexanolone and zuranolone is ushering in a new era in the treatment of mental illness. It is also attesting to the validity of the MCNH hypothesis, the first to integrate brain circuitry, brain physiology, mind-brain dynamics, and molecular genetics to form a comprehensive psychophysiological explanation for the development of psychiatric symptoms. The practical significance of linking mental illness to neuronal excitability is that it calls attention to the importance of calming the brain in the treating these conditions. It also calls attention to other molecular mechanisms through which the neuronal hyperexcitability trait can be therapeutically modified and to other drugs that can rapidly reduce neuronal excitability, such as the generic anticonvulsants listed earlier. Working through channels other than those of chloride ions, these drugs have already proven themselves to be fast-acting, safe, and effective in long-term use. However, they have been sorely underutilized in psychiatry due to the failure to recognize neuronal hyperexcitability as the core biological abnormality in mental illness. Lacking this biological target for treatment, clinicians tend to limit the use of anticonvulsants to the treatment of bipolar spectrum disorders. The problem with this symptom-based approach is that bipolar spectrum disorders are commonly misdiagnosed as unipolar depressive disorders and treated with antidepressants. Even when a bipolar patient is properly diagnosed and treated with an anticonvulsant drug, a failed or suboptimal response typically triggers a switch to, or addition of, a drug from a different class. In the absence of a clear biological target at which to direct treatment, clinicians have no choice but to rethink their diagnosis and continue to chase after symptoms when treatment fails or is only partially effective. The recognition of neuronal hyperexcitability as the core abnormality in mental illness circumvents this problem. Although the possibility of misdiagnosing a unipolar depressive disorder as a bipolar spectrum disorder does exist, the risk is exceedingly low because the incidence of "true" unipolar depression is exceedingly low [34]. From the perspective of the MCNH hypothesis, anticonvulsant-drug failures could more aptly be viewed as reminders that, due to patient-specific factors, no single drug is effective for every patient with the same biological abnormality. Hence, several different anticonvulsants may need to be tried or combined with one another before an adequate therapeutic response can be attained. It is also noteworthy that unlike with drugs that modulate the activity of specific neurotransmitter systems, anticonvulsants can be safely combined with one another because they tend to reduce the excitability of the neurological system as a whole. This re-emphasizes the value of continuing to develop new anticonvulsant drugs, such as the new line of GABA modulators, despite the availability of several existing drugs that have demonstrated the ability to reduce neuronal excitability.

Then again, it should be apparent from the foregoing discussion that drug availability is only half of the battle in the treatment of mental illness. The other half of the battle is to accurately identify the biological target for treatment. Both of these challenges are overcome by the MCNH hypothesis. Beyond these benefits, the MCNH hypothesis illuminates the core biological abnormality in virtually all chronic diseases

because, as previously mentioned, all such diseases appear to be rooted in the same abnormality—an inherent hyperexcitability of the neurological system [81].

In addition to all of these benefits, focusing treatment on therapeutically modifying the neuronal hyperexcitability trait opens the door to a first in psychiatry; namely, mental illness prevention. This is made possible by the observation that upper-end-of-normal resting vital signs mark the presence of the neuronal hyperexcitability trait even in the absence of overt psychiatric symptomatology [64]. Recognizing this, affected persons could potentially be offered education about the mental and physical health risks associated with chronic untreated neuronal hyperexcitability. Additionally, those with the highest levels of neuronal hyperexcitability, a determination that could be estimated from the degree of the resting vital-sign elevations and the severity of past psychiatric symptoms, if previously experienced [34], could be offered prophylactic neuroregulator therapy.

5. Study Limitations and Directions for Future Research

Although this review is based on decades of longitudinal clinical observations and the latest scientific studies, some of the tenets are speculative, and carefully designed clinical trials will need to be performed before the proposed strategies can be codified and translated into clinical practice. For example, the idea that neuronal hyperexcitability is the core biological abnormality in mental illness will need to be tested through controlled studies that combine neuroregulators with one another rather than combining them with antidepressants, psychostimulants, and other drugs that have pharmacologically conflicting and potentially counteracting effects. Also, the beneficial effects of anticonvulsant therapy on resting heart and respiratory-rate measurements will need to be studied more formally and with larger sample-sizes before recommendations for practice can be made. In addition, all-member family studies will be needed to verify the hypothesis that those family members who grow up mentally and emotionally healthy and, thus, would be presumed to have *normo*excitable neurons actually have significantly lower resting vital signs than their affected siblings. In conjunction with this, comparator studies will be needed to determine the short and long-term health benefits of anticonvulsant prophylaxis in those family members who have upper-end-of-normal resting vital signs and also to confirm that anticonvulsant prophylaxis significantly lowers their resting vital signs while they are still asymptomatic.

6. Conclusion

Since antiquity, the pathophysiology of mental illness has been an enigma. However, the emergence of a new strategy in the treatment of depression and possibly other psychiatric disorders in parallel with a new hypothesis on the pathophysiology of psychiatric disorders has highlighted neuronal hyperexcitability as the core biological abnormality in these disorders. In addition to offering a neurophysiological explanation for the rapid antidepressant effects of brexanolone and zuranolone, the MCNH hypothesis calls attention to the continued misdiagnosis of bipolar spectrum disorders as unipolar depressive disorders and offers a more accurate means by which to determine which patients should be treated with antidepressants and which should be treated with anticonvulsants. In so-doing, it also calls attention to the gross underutilization and suboptimal utilization of an entire class of relatively safe, inexpensive, and non-addictive drugs—drugs that have consistently demonstrated long-term effectiveness in reducing neuronal excitability. In addition, the recognition that the neuronal hyperexcitability trait also appears to underlie the development of a wide range of chronic physical illnesses could completely change the way that mental illness is perceived. It could transform the perception of mental illness as a sign of character weakness to a new "fifth" vital sign: the subjective marker of a physiological abnormality that underlies a wide range of chronic health conditions, including but not limited to mental and emotional conditions [82]. Beyond these advantages, focusing efforts on identifying the neuronal hyperexcitability trait could save clinician time and reduce diagnostic error because it would shift the emphasis on symptoms to an emphasis on identifying the biological abnormality that underlies the symptoms. It would also open the door to a whole new world in mental healthcare; namely, mental illness prevention. This would be made possible by the observation that the neuronal hyperexcitability trait exerts its effects on resting vital signs even in the absence of overt psychiatric symptomatology. Through these potentially groundbreaking advances, the MCNH hypothesis, in conjunction with resting vital-sign measurements and emerging data on the psychotherapeutic potential of calming the brain, could completely destigmatize mental illness, bring an end to the mental health crisis, and usher in a new era of preventive healthcare.

Competing Interests

The author declares that he has no competing interests.

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