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Review Article

Focused Neuroregulation in the Treatment and Prevention of Mental and Physical Illness

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Abstract: Despite the enormous strides that have been made in neuroscience, the pathophysiology of psychiatric disorders remains unclear. Consequently, various forms of psychotherapy, pharmacotherapy, and neuromodulatory therapy continue to be applied without a clear understanding of what pathological process is being treated. However, an emerging hypothesis contends that psychiatric symptoms are the consequence of pathological hyperactivity in symptom-related circuits in the brain. According to the Multi-Circuit Neuronal Hyperexcitability (MCNH) Hypothesis of Psychiatric Disorders, 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 caused by an inherent failure of the neurological system to self-regulate when perturbed by a psychological, emotional, or biological stressor. Based on this hypothesis, it would not be unreasonable to think that psychiatric symptoms, irrespective of which disorder was being treated, would respond favorably to any natural or medicinal intervention that reduces the excitability of the neurological system. Although the use of brain-calming drugs in psychiatry is not new, what is new is the idea of focusing their use on correcting a specific physiological abnormality that is believed to underlie the symptoms. This technique, which could be called "Focused Neuroregulation," would differ from standard pharmacotherapy in that if one anticonvulsant failed to alleviate or only partially alleviated symptoms, another anticonvulsant would be substituted or added rather than turning to an off-target class of drugs. This approach is clinically valid because each anticonvulsant is structurally different, and there are multiple mechanisms (and receptors) through which the excitability of the neurological system can be therapeutically regulated. Also, anticonvulsants, unlike other classes of psychotropic drugs, tend to bring the system back into balance; hence the term "mood stabilizers." Yet another benefit of Focused Neuroregulation is that it could help prevent or slow the progression of the many chronic health conditions that have been linked to an inherent hyperexcitability of the neurological system. In recognition of these potential benefits, and in an effort to avoid the many problems that are associated with the symptom-based treatment of psychiatric and related functional symptoms, the aim of this article is to incentivize the study of a more targeted approach to the treatment of mental illness and the prevention of chronic disease.

Keywords: Neuronal Excitability, Neuronal Hyperexcitability, Pathophysiology of Psychiatric Disorders, Biomarkers of Disease, Fifth Vital Sign, Anticonvulsants, Neuroregulators, Preventive Medicine

1. Introduction

Despite the enormous strides that have been made in neuroscience, the pathophysiology of psychiatric disorders remains unclear. Consequently, various forms of psychotherapy, pharmacotherapy, and neuromodulatory therapy continue to be applied without a clear understanding of what pathological process is being treated. However, an emerging hypothesis contends that psychiatric symptoms are the consequence of pathological hyperactivity in symptom-related circuits in the brain. According to the Multi-Circuit Neuronal Hyperexcitability (MCNH) Hypothesis of Psychiatric Disorders, 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… [1]. This pathological circuit-specific hyperactivity is believed to be caused by an inherent failure of the neurological system to self-regulate when perturbed by a psychological, emotional, or biological stressor [1]. Although the MCNH hypothesis has yet to be validated through rigorous scientific experimentation, there is biological, observational, pharmacological, neuropsychiatric, behavioral, medical, psychophysiological, experimental, radiological, genetic, and explanatory evidence that nearly all psychiatric disorders and their functional comorbidities are rooted in this single, shared, neurophysiological abnormality [1]. Based on this multidisciplinary body of evidence, it would not be unreasonable to think that psychiatric symptoms, irrespective of which disorder was being treated, would respond favorably to any natural or medical intervention that reduces the excitability of the neurological system. Although the use of brain-calming drugs in psychiatry is not new, what is new is the idea of focusing their use on a specific physiological abnormality regardless of the nature of the patient's psychiatric symptoms. This technique, which could be called "Focused Neuroregulation," would differ from standard pharmacotherapy in that if one anticonvulsant (or other brain-calming drug), which could more aptly be called "Neuroregulators" because of their proposed pharmacological effect [2], failed to alleviate symptoms or only partially alleviated symptoms, another Neuroregulator would be substituted or added rather than turning to an off-target class of drugs. Another potential benefit of focused Neuroregulation is that it could help prevent or slow the progression of the many chronic health conditions that have been linked to an inherent hyperexcitability of the neurological system [3]. In recognition of these potential benefits, this article will discuss the practicality, safety, and potential advantages of Focused Neuroregulation as a means of treating and preventing chronic disease.

2. Brief History of Psychotropic Drug Use

Historically, the first drugs to be used for mental and emotional ailments were anticonvulsants. The oldest of these is alcohol, with archeological evidence of a methodological fermentation process dating back to around 7,000 BC [4] and references to alcohol's medicinal use found in Sumerian, Egyptian [5], and Hebrew texts. The second oldest medicinal remedy is cannabis, which is now well-known to have powerful anticonvulsant effects [6-8]. This was followed by the opium poppy, another drug that, like alcohol and cannabis, has brain-calming effects. Heading into the modern era, bromine, another anticonvulsant drug, was used to treat "hysterical epilepsy" [9]. This was followed by the use of barbiturates, benzodiazepines, and antipsychotic drugs, all of which, like the compounds that were used before them, have brain-calming effects. Thus, particularly for mental and emotional illnesses, quieting the nervous system had been the mainstay of medicinal treatment throughout most of recorded history.

The first exception to this did not appear until the 1920s, when the stimulant-type drug amphetamine was found to improve attention, elevate mood, and decrease appetite [10]. This was followed by the introduction of methamphetamine in the 1940s, which in turn was followed by the introduction of antidepressants in the 1950s [11, 12]. An Associated Press release from Staten Island's Seaview Hospital, where the antidepressant effect was first observed, captured a telling scene: patients dancing in celebratory mood; hence the term "anti-depressant" [13]. Some of these patients were suddenly feeling so good emotionally that they wanted to leave the tuberculosis sanatorium despite still being under quarantine. Subsequently, word about the dramatic mood-elevating effects of antidepressants began to spread, thus catapulting the new drugs in popularity over the brain-calming drugs that preceded them. Today, the race to develop new and improved antidepressants continues, and although psychostimulants have, due to their large-scale misuse and diversion, been federally controlled since 1970, the number of prescriptions written for the drugs now rivals that for antidepressants [14, 15] (Figure 1).

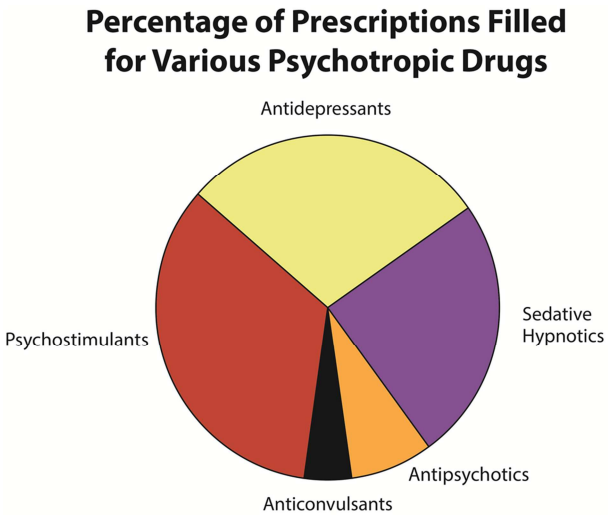

Figure 1. *Pie chart illustrating the sales of antidepressants and psychostimulants relative to other psychotropic drugs.*

3. The Problem with Antidepressants and Psychostimulants

What is concerning about the large number of prescriptions written for antidepressants and psychostimulants is that they activate parts of the brain [16, 17]. According to the MCNH hypothesis of psychiatric disorders, this activating effect adds to the underlying problem of neuronal hyperexcitability [18], thus explaining why these drugs have a propensity to cause anxiety, irritability, insomnia, and manic-depressive cycling [18-21]. In addition to these complications, antidepressants

and psychostimulants drive a compensatory reduction in receptor function, thus helping to explain why their abrupt discontinuation tends to precipitate withdrawal symptoms. Nonetheless, studies have found that the use of stimulant-type drugs does not increase the long-term risk of substance misuse [22]. However, the hypothetical reason for this is that substance misuse is not so much a consequence of drug exposure but of a continual quest to self-regulate the hyperexcitable brain.

Another concern about the large-scale prescribing of antidepressants and psychostimulants is that of polypharmacy. Due to a lack of clarity about the underlying cause of psychiatric disorders, mental health care continues to be symptom-based rather than pathology-based. Consequently, patients are frequently prescribed drugs from multiple classes, some of which have conflicting pharmacological effects. In addition, the stacking of psychotropic drugs increases the risk of side effects, toxic effects, and withdrawal effects. It also increases expense, particularly because psychiatric disorders tend to be chronic in nature.

All of this reiterates the need for a pathophysiologically-based guide by which to prescribe psychotropic drugs. According to the MCNH hypothesis of psychiatric disorders, psychiatric symptoms, irrespective of which diagnostic category they are assigned to, are driven by a pathological elevation in the activity of the related brain circuits [23-25]. Hence, it follows that quieting those circuits would reduce the associated symptoms. This is the basis upon which natural interventions, such as stress reduction, proper rest, moderate exercise, avoidance of psychostimulants, and minimization of refined sugar, are thought to improve both mental and physical well-being [3]. Unwittingly, it is also the basis upon which sedative-type drugs had been the mainstay of psychiatric treatment until the discovery of stimulant-type drugs.

Irrespective of their potential for paradoxical and withdrawal effects, antidepressants and psychostimulants continue to be the mainstay of psychotropic drug therapy. This seems to be a carryover of the excitement that was created by the discovery of the antidepressant effect and the subsequent introduction of serotonin reuptake inhibitors (SSRIs) in the 1980s. The popularity of psychostimulants likely stems from the overlap of their pharmacological effects with those of antidepressants and the high co-morbidity between mood disorders and attentional disorders. In a sense, the excitement about antidepressants and psychostimulants is warranted because they do help some patients. The problem is that they alter receptor function, and they manipulate the activity of various cognitive and emotional circuits in unpredictable ways.

The MCNH explanation for the broad utility of antidepressants is that, by modulating neurotransmission, they have the potential to partially or, in some cases, fully correct the circuit-specific balances that cause psychiatric symptoms. The problem is that they also have the potential to accentuate pre-existing circuit-specific imbalances or even create new ones. In addition, the neurostimulatory effects of antidepressants [26], including SSRIs [16], increase the risk of aberrant circuit induction. Aberrant circuit induction is the hypothetical process by which collateral connections between circuit loops allow the flow of circuit-specific activity to deviate from its intended path [18, 21]. This neural "short-circuiting" is the MCNH explanation for the manic-depressive switching that can occur in association with antidepressant therapy. Importantly, this risk increases as the excitability of the neurological system increases [18], thus explaining why patients who fall into the bipolar spectrum (i.e., those with hyperexcitable neurological systems), are at an increased risk of antidepressant-induced paradoxical effects [18]. This is a matter of grave concern because the MCNH hypothesis, which contends that mild-to moderate stressors can be enough to drive patients with hyperexcitable neurons into treatment, would predict that the vast majority of patients who present for psychiatric evaluation have hyperexcitable neurons [18]. It would also mean that only the small minority of patients who have normoexcitable neurons would be relatively resistant to antidepressant-induced paradoxical effects [18]. This could help explain why the response rate to antidepressant therapy is so disappointingly low. A similar problem tends to occur with psychostimulants; by increasing the activity of dopamine and norepinephrine, psychostimulants tend to increase the level of excitation in the brain. Although this effect tends to be masked clinically by their ability to enhance cortical [27] and thalamic [28] neuromodulatory function, the overall effect, particularly at higher doses, is to increase neuronal excitability. This effect, together with the downregulation of dopaminergic and adrenergic receptors, increases the risk of tolerance, dependence, and withdrawal.

4. Safer and More Effective Treatment

4.1. Overcoming Diagnostic Confusion

Undoubtedly, the importance of distinguishing bipolar spectrum patients, who would most appropriately be treated with anticonvulsant drugs, from unipolar depressive patients, who would most appropriately be treated with antidepressant drugs [18], was under-appreciated in the early days of antidepressant-prescribing. Consequently, the robust antidepressant effects that some patients experienced were assumed to be reproducible in any patient who presented with symptoms of depression. To a large extent, that perception still exists. Also, there continues to be considerable debate about how best to distinguish bipolar spectrum disorders from unipolar depressive disorders. This diagnostic challenge is created by the fact that there is so much symptom-overlap between the two disorder-types and because, in their early stages, bipolar disorders and unipolar disorders commonly share all of the same symptoms. The ability to solve this diagnostic dilemma objectively is one of the many benefits of the MCNH hypothesis. By recognizing neuronal hyperexcitability as the core neurophysiological abnormality in psychiatric disorders, the distinction between bipolar

spectrum disorders and unipolar disorders can be made based on resting vital-sign measurements. A rapidly growing body of evidence suggests that a resting heart rate above 75 beats/min or a resting respiratory rate above 15 breaths/min is indicative of the neuronal hyperexcitability trait [3].

4.2. Tailoring Treatment

Still, diagnostic ambiguity is not the only barrier to the appropriate use of antidepressant and anticonvulsant drugs. Short of a comprehensive understanding of what biological abnormality psychotropic drugs are treating, a patient's failure to respond to an anticonvulsant can lead the clinician to second-guess his or her diagnosis of a bipolar spectrum disorder and switch to an antidepressant. Perhaps due to the popularity of antidepressants and the logical connection between depressive symptoms and the term "anti-depressant," most clinicians today would do just that—switch the patient to an antidepressant. Some might even prescribe a psychostimulant, especially because there is so much pharmacological overlap between antidepressants and psychostimulants and because attentional disorders are highly co-morbid with mood disorders. Also, because most clinically-depressed patients appear to need something to stimulate their systems, it is counterintuitive to think that what they really need is something to calm their systems [20]. This is demonstrated by the highly disproportionate number of prescriptions that are written for antidepressants and psychostimulants in comparison to anticonvulsant and antipsychotic drugs (Figure 1).

Yet another barrier to the judicious use of antidepressants and anticonvulsants is the failure to combine anticonvulsants when a single agent is only partially effective. Again, owing to the lack of a clearly-defined biological target for treatment, the tendency is to address any residual symptoms by adding a drug that is matched to the symptoms rather than staying focused on the underlying physiological abnormality. The problem with this approach is that it strays from the root of the problem. Based on the MCNH hypothesis, the more prudent approach would be to add another anticonvulsant. This approach, which could be called "Focused Neuroregulation," is clinically valid because each anticonvulsant is structurally different, and there are multiple mechanisms (and receptors) through which the neurological system can be therapeutically regulated.

Moreover, anticonvulsants are uniquely suited to be combined with one another because, rather than accentuating the neurological imbalances that hypothetically cause psychiatric symptoms to develop, they tend bring the system back into balance; hence the term "mood stabilizer." By addressing what is believed to be the root cause of most psychiatric disorders, focused neuroregulation holds the promise of better outcomes with fewer drugs.

The final barrier to the successful use of anticonvulsants, and perhaps the easiest to overlook, is that of dosing and titration. Although anticonvulsant drugs exert their pharmacological effects in less than one hour, their therapeutic effects are highly dependent on accurate dosing. Too low of a dose won't work, and too high of a dose can cause intolerable side effects. This problem is further complicated by the fact that the recommended dosing of anticonvulsants is based primarily on experience with seizure disorders. However, seizure disorders, though being more likely to occur in persons with hyperexcitable neurons, are typically not caused by neuronal hyperexcitability alone. In most cases, another abnormality is present, thus permitting the hypersynchronous neuronal firing that distinguishes a seizure disorder from a psychiatric disorder [21]. Hence, for most patients with seizure disorders, anticonvulsants have to quiet the brain enough to overcome this other abnormality. Psychiatrists are faced with the lesser challenge of solely having to quiet the brain. For them, any reduction in neuronal excitability could be enough to reduce the patient's symptoms. Fittingly, it has been said that anticonvulsants may be more effective for psychiatric disorders than for seizure disorders [29]. This idea is supported by the observation that anticonvulsant dosing for psychiatric disorders is generally lower than for seizure disorders. A failure to recognize this can cause psychiatric patients to incur unnecessarily severe side effects…and possibly to reject the treatment altogether. Hypothetically, it could even cause them to experience a paradoxical worsening of symptoms if too many "feel good" circuits are inhibited.

5. Psychotherapy

Although numerous studies have demonstrated the benefits of psychotherapy either alone or in combination with pharmacotherapy, there is less data regarding which forms of psychotherapy and which medication combinations are best for which patients. This is partly due to the large heterogeneity in the way that psychotherapy is practiced and partly due to a lack of objective criteria by which to distinguish one psychiatric disorder from another. The other confounding factor is the lack of clarity about the mechanism by which different forms of psychotherapy and different medications reduce psychiatric symptomatology.

The MCNH hypothesis, in conjunction with resting vital-sign measurements, circumvents these problems because it identifies, for the first time, the precise mechanism by which psychotherapy and pharmacotherapy exert their complementary therapeutic effects. According to the MCNH hypothesis, psychiatric symptoms are the consequence of pathological hyperactivity in symptom-related circuits in the brain. One of the chief causes of this hyperactivity is a vicious cycle of mutual overstimulation between the mind and the brain; the more stressed the mind becomes, the more hyperactive the associated neurons and circuits become, and the more hyperactive the associated neurons and circuits become, the more stressed the mind becomes [30]. Therefore, to the extent that psychotherapy is able to reduce intrapsychic tension, it is able to reduce psychiatric symptoms.

However, what can sometimes hinder psychotherapy is the propensity for neuronal hyperexcitability, which, according to the MCNH hypothesis, is the underlying driver of nearly all psychopathology, to distort cognitions and emotions. In other

words, the patient can potentially present for discussion thoughts and emotions that are related more to aberrant discharges in the brain than to what is truly driving the intrapsychic tension. What's more, some of these thoughts and emotions can further increase intrapsychic tension; hence, discussing them in psychotherapy can wind up adding to rather than detracting from the underlying problem. Hypothetically, the reason that Freudian psychotherapy primarily targeted neurotic-range psychopathology was that neuroses [31], which, according to the MCNH hypothesis, are driven by mild-to-moderate levels of neuronal hyperexcitability, would have been less subject to neuropsychological distortion than more severe forms of psychopathology, which are driven by higher levels of neuronal excitability [18]. Patients with neuroses would also have had better processing ability and more room for tolerating the transient increases in neuronal activity that would have been stimulated as the patient attempted to work through mentally and emotionally challenging issues. This underscores the importance of determining a patient's level of neuronal excitability in the process of formulating a treatment plan.

6. The Value of Resting Vital-Sign Measurements

Beyond helping to identify the neuronal hyperexcitability trait, resting vital-sign measurements could allow clinicians to objectively determine the degree of neuronal hyperexcitability because resting heart and respiratory rates tend to correlate with the basal level of neuronal excitability [18]. This information could then be used to formulate a more appropriate treatment plan. Patients with low-to-moderate levels of neuronal hyperexcitability, which would drive neurotic-range symptomatology, could potentially be treated with psychotherapy and other non-medical interventions, such as stress-reduction, regular exercise, and mindfulness meditation. In patients with higher levels of neuronal hyperexcitability, the aforementioned interventions, though potentially helpful in calming the brain, would in most cases be neither adequate nor consistently doable. Thus, for such patients, the MCNH hypothesis would guide pharmacotherapy as the first-line intervention. By rapidly reducing neuronal activity, anticonvulsants and other brain-calming drugs would rapidly reduce the thoughts and emotions that are driven more by pathologically-elevated neurological activity than by unresolved mental and emotional conflicts. By reducing this neurological "spam," the patient's perceived level of stress would rapidly diminish, and the vicious cycle of mutual overstimulation between the mind and the brain that had been fueling the psychiatric symptoms would begin to resolve. This, in turn, would allow the patient to begin to resume goal-directed activity, including natural interventions. It would also help focus psychotherapy (if still needed) on the real issues while at the same time reducing the risk of psychotherapy-induced regression.

However, efforts to reduce neuronal excitability should not be limited to those with higher levels of neuronal hyperexcitability. In patients with mild-to-moderate levels of neuronal hyperexcitability, pharmacotherapy aimed at reducing neuronal excitability can allow the patient to rapidly regain perspective and, in most cases, reduce the need for psychotherapy. What's more, because neuronal hyperexcitabilty is an inherited trait, anticonvulsant therapy can potentially bring an affected patient to a higher level of functioning than before the inciting stressor began. It could also reduce the risk of relapse because the underlying vulnerability trait has been therapeutically modified. This does not necessarily apply to antidepressant therapy because antidepressants, though having the potential to correct circuit-specific imbalances, do not necessary decrease neuronal excitability [20]. In fact, some antidepressants, particularly those with prominent dopaminergic and noradrenergic effects, increase neuronal excitability [32-36]. Thus, the MCNH hypothesis in conjunction with resting vital-sign measurements can be used to more accurately guide treatment.

7. Neuronal Hyperexcitability and Physical Health

7.1. Potential Benefits

The potential benefits of applying the MCNH hypothesis in conjunction with resting vital-sign measurements are not limited to mental healthcare. There is growing evidence that neuronal excitability, as measured by resting vital signs [3], also reflects on the body's ability to handle biological stressors [37, 38]. Thus, resting vital-sign measurements can potentially prognosticate the body's ability to fight infection, tolerate surgery, and, generally speaking, recover from illness. The MCNH explanation for this assertion is that an underlying hyperexcitability of the neurological system tends to dysregulate the metabolic system, the immunologic system, the digestive system, the neuromuscular system, and other systems of the body. The higher the level of neuronal excitability, the greater the disruption. Hence, higher resting vital-sign measurements would be prognostic of an increased vulnerability to illness and an increased risk of complications during the recovery process. This idea is supported by a range of clinical observations. For example, the risk of diabetic ketoacidosis, a potentially life-threatening complication of a serious illness, such as a systemic infection, a severe injury, or a cardiovascular event, is ten times higher in patients with schizophrenia than in the general population [39]. According to the MCNH hypothesis, patients with schizophrenia have some of the highest levels of neuronal excitability and, thus, some of the highest resting vital-sign measurements [18]. Similarly, patients with personality disorders, who likewise have some of the highest levels of neuronal excitability [18], were found to require more general medical consultations, longer hospital stays, and higher numbers of prescriptions than the general population [40]. Yet another example comes

from observations related to the recent outbreak of SARS-Co-V-2. Several studies found that COVID-19 patients with a history of mental illness had more complicated recoveries and higher rates of mortality than those without a history of mental illness [41, 42]. Again, based on the MCNH hypothesis, such patients would have had upper-end-of-normal resting vital signs [3, 18, 43].

7.2. Streamlining Treatment

In addition to being able to forecast illness-susceptibility and the risk of medical and psychiatric complications during the course of treatment, resting vital-sign measurements in conjunction with the MCNH hypothesis could help circumvent the many barriers posed to psychiatric assessment in medically-ill patients suspected of having psychiatric comorbidity. These barriers include: 1) the substantial delays in seeking psychiatric consultation that are caused by the insidious onset of psychiatric symptoms; 2) the attribution bias that commonly influences members of the healthcare team when psychiatric comorbidity is suspected; 3) the challenge of obtaining an accurate psychiatric history in medically-ill patients; 4) the tendency for psychiatric symptoms to fluctuate in severity over time; 5) the distortion of psychiatric symptoms that occurs as a result of many patients, due to the stigma of mental illness, repressing, minimizing, or "converting" their psychiatric symptoms into less distressing and more socially acceptable expressions; 6) the diagnostic ambiguity created by the extensive symptom-overlap between psychiatric disorders; 7) the lack of clarity about what biological abnormality is driving the symptoms when psychiatric comorbidity is identified; and 8) the decision of some patients to flatly refuse psychiatric consultation.

Adding yet another layer of complexity to the psychiatric assessment of medically ill patients is the extensive overlap between psychologically-driven physical symptoms, neuropsychiatrically-driven physical symptoms, and medically-driven physical symptoms. For example, poor appetite and weight loss in a cancer patient could be caused by discouragement, clinical depression, progression of disease, or some combination of these factors. The same could be said of persistent pain following surgery or a loss of motivation following a crippling physical injury. Psychiatric assessments also tend to be resource-intensive due to the time required to obtained sensitive information from patients and their family members.

All of these barriers to timely, accurate, and effective psychiatric intervention could be circumvented by simply glancing at the patient's resting vital signs. Unless there are confounding factors, such as treatment with beta blockers, a cardiac pacemaker, a significant respiratory illness, or some other factor that would alter the normal functioning of the cardiorespiratory system, a resting heart rate above 75 beats/min or a resting respiratory rate above 15 breaths/min would, according to the MCNH hypothesis, suggest that an inherent hyperexcitability of the neurological system was contributing to the patient's clinical picture [18]. In other words, a constitutional propensity for the neurological system to overreact to stress would be complicating the assessment, management, and recovery of the patient. The identification of neuronal hyperexcitability would also illuminate the biological target for treatment without having to distinguish, based on clinically grounds, which component of the patient's symptoms was functional, and which was organic.

Because the neurological system is the hub of nearly all bodily functions, the symptoms related to neuronal hyperexcitability could include a lack of motivation, poor appetite, low energy, persistent pain, a distortion of pain, immunological dysregulation, abnormal blood sugars, elevated or unstable blood pressures, or some other mental, emotional, or physical symptom that is deemed to be complicating the patient's recovery. The idea that all of these signs and symptoms are rooted in a shared vulnerability trait could help explain why disentangling psychological, psychiatric, and medical contributors to disease has traditionally been so difficult. However, by simply identifying and treating any underlying hyperexcitability of the neurological system, the need to distinguish one contributor of disease from another is eliminated.

7.3. Unifying Functional and Physical Disorders

The beauty of this conceptualization is that it replaces the age-old dichotomy between mental illness and physical illness with a new synthesis of disease. It posits that psychiatric symptoms are not manifestations of a separate pathological process but rather subjective markers of a vulnerability trait that is at the root of nearly all chronic illnesses, whether mental or physical [3], and the many barriers to recovery that have heretofore been hard to define [44]. It tramples down the stigma of mental illness by reconceptualizing psychiatric symptoms (along with the perception of pain) as a "fifth" vital sign that, like other vital signs, can give clinicians a better picture of what is going on in the body.

In summary, the MCNH hypothesis posits that the inherited trait of neuronal hyperexcitability is the ubiquitous instigator of disease and that there are two ways to identify its presence: 1) psychiatric and functional physical symptoms; and 2) upper-end-of-normal resting vital signs. The value of resting vital-sign measurements is that, for the reasons previously discussed, neuronal hyperexcitability does not always manifest as identifiable psychiatric symptomatology [18]. Conversely, resting vital-signs may not, due to the presence of cardiopulmonary confounders, always be reliable barometers of neuronal excitability. However, using this combination of objective and subjective vital signs could, without ambiguity, guide the need to reduce the excitability of the neurological system in treatment-resistant and poorly-progressing patients. Then again, the mere fact that a patient is not progressing or has frequently recurring symptoms should alert the clinician to the possibility of an underlying hyperexcitability of the neurological system. Simply treating such patients with an effective Neuroregulator (or combination of Neuroregulators) could lead to a more rapid resolution of both physical and psychiatric symptoms and a better response to the primary

treatment. Hypothetically, it could also reduce the risk of recurrence, especially if applied with a recommendation to make healthy lifestyle changes.

7.4. How to Therapeutically Modify the Vulnerability Trait

As discussed earlier, the most effective natural ways to reduce neuronal excitability include stress reduction, establishment of an early sleep schedule, regular exercise, avoidance of caffeine and other psychostimulants, and minimization of refined sugar. Particularly for some patients, this would also include attention to gut health, optimization of vitamin D levels, and avoidance of specific foods and environmental allergens. However, for those with very hyperexcitable neurological systems and those who are under the additional strain of a severe psychological or biological stressor, these efforts alone, though helpful, would not likely be adequate to control symptoms. That is where the use of Neuroregulators becomes indispensable. Anticonvulsant Neuroregulators have an immediate and powerful calming effect on the brain. Among the safest and most effective of these are gabapentin, oxcarbazepine, lamotrigine, lithium, depakote, topiramate, levetiracetam, and tiagabine. In addition to being fast-acting, these drugs are non-addictive, consistently effective, and relatively inexpensive, thus making them practical for both short and long-term use. Sometimes necessary, though less preferred due to their greater risk of side-effects, are the first and second generation antipsychotic Neuroregulators [2]. Though second generation antipsychotics generally have fewer side effects than first generation antipsychotics, they still tend to have more side effects than anticonvulsant Neuroregulators. They also tend to be more expensive.

No less important than identifying the need for Neuroregulators is the need to dose them correctly. As previously discussed, this is complicated by the difference in dosing requirements when anticonvulsants are used to treat psychiatric disorders as opposed to seizure disorders. However, as in epilepsy, there is often added benefit to combining anticonvulsants when attempting to reduce neuronal excitability, as there are many mechanisms (and receptors) though which the excitability of the neurological system can be reduced.

Last and perhaps most significant because it opens the door to a whole new world of preventive medicine is the prospect of identifying the trait of neuronal hyperexcitability prior to the onset of any clinically-recognizable mental or physical symptoms. Although the prophylactic use of Neuroregulators would seem to preclude the ability to assess their effectiveness in reducing neuronal excitability, a reduction in resting vital signs may prove to be a reliable way to assess this. Hypothetically, the greater the reduction in resting heart rate, respiratory rate, and blood pressure, the greater the protective effect the medication is likely to have. The ability to detect neuronal hyperexcitability through simple vital-sign measurements together with a non-threatening, non-stigmatizing, logically-sound explanation for the prophylactic use of Neuroregulators, could usher in history's greatest campaign in the fight against sickness and disease.

8. Discussion

Although anticonvulsants and other brain-calming substances had been the mainstay of psychiatric treatment throughout much of recorded history, the discovery of the antidepressant effect began to change the pharmacotherapy of mental illness to the point where the use of antidepressants and psychostimulants has largely overtaken the use of anticonvulsants and other brain-calming drugs [14, 15]. The biggest reason for this appears to be the strong connection between the diagnosis of clinical depression and antidepressant therapy. However, there continues to be considerable debate about how best to distinguish unipolar depressive disorders, which are most appropriately treated with antidepressants, from bipolar disorders, which are most appropriately treated with anticonvulsants. What's more, the monoamine hypothesis, which for more than fifty years has guided the use of antidepressants in the treatment of depression, is increasingly coming under attack for being too simplistic to explain how psychiatric symptoms arise [45]. Meanwhile, the actual response rate to antidepressants is so low that mental health researchers have started looking for new molecular targets for which to taylor drugs in the treatment of mood disorders, anxiety disorders, and other common psychiatric disorders.

One such target is the ion channels of neurons throughout the nervous system. There is increasing evidence that targeting ionchannelopathies with anticonvulsant drugs may be the final frontier of psychopharmacology [20]. It is also one that, unsurprisingly, would circle back to the long history of anticonvulsant use in the management of mental and emotional disorders. That is exactly what the MCNH hypothesis calls for: the use of anticonvulsant drugs to therapeutically modify what appears to be the fundamental abnormality in nearly all psychiatric disorders; namely, an inherent hyperexcitability of the neurological system. In addition to providing the first comprehensive neurophysiological hypothesis of psychiatric disorders, the MCNH hypothesis, in conjunction with resting vital-sign measurements, provides the first objective method of distinguishing "true" unipolar depressive disorders from bipolar spectrum disorders, thereby simplifying diagnostics and guiding treatment based on biology rather than symptomatology. It also paves the way for an entirely new avenue of prevention because there is rapidly growing evidence that the neuronal hyperexcitability trait is at the root not only of a wide range of psychiatric disorders but also of any illness, mental or physical, that can be precipitated or exacerbated by stress. Therefore, in lowering the risk of psychiatric symptoms, the prophylactic use of neuregulators could also be lowering the risk of diabetes, hypertension, heart disease, autoimmune disease, cancer, dementia, and a wide range of other chronic illnesses. This broadly beneficial effect, which could hypothetically be accomplished through neuroregulation, would unify the field of psychiatry with all

other branches of medicine and provide a biologically-precise, non-stigmatizing, user-friendly term with which to describe the means by which the underlying neurophysiological abnormality could be therapeutically modified; namely, "neuroregulation."

In addition, by recognizing neuronal hyperexcitability as the underlying driver of nearly all disease processes, the MCNH hypothesis, in conjunction with resting vital-sign measurements, could be used to identify and therapeutically modify the underlying driver of those processes without having to distinguish functional symptoms from physical symptoms or use socially-stigmatizing terms like "schizophrenia," "bipolar disorder," and "borderline personality disorder." Instead, it would inform the use of the more pathophysiologically-appropriate term "FLASH Syndrome" [3]. FLASH is an acronym that stands for Familial Limbic Autonomic System Hyperexcitability. It describes what is hypothesized to be the fundamental abnormality in psychiatric disorders; namely, an inherent hyperexcitability of the neurological system that over-activates the limbic and autonomic nervous systems, thus elevating the affected person's temperament, vital signs, and emotional responses to any form of stress, be it psychological, emotional, or biological. In so-doing, neuronal hyperexcitability also tends to dysregulate the endocrine, the immunologic, the metabolic, the muscular, and other systems of the body that are critical to maintaining homeostasis. In recognition of its pervasive effects on physiological function, FLASH syndrome would not be specific to mental illness but would be applicable to any pathological process that could be triggered or exacerbated by stress. Such broad applicability would naturally work to prevent the term from becoming stigmatized and dispel the many myths and erroneous assumptions that, throughout the ages, have been held about mental illness.

The appropriate treatment for FLASH syndrome would be to calm the neurological system. This could be accomplished through one or a combination of medicinal and non-medicinal interventions. In persons with mild-to-moderate neuronal hyperexcitability, non-medicinal interventions, such as stress reduction, establishment of an early sleep schedule, regular exercise, and, in patients with significant psychosocial stressors, psychotherapy, might be adequate to relieve symptoms. In persons with higher levels of neuronal excitability, medicinal therapy with one or a combination of anticonvulsant drugs might be necessarily. Although it might, from a pharmacological perspective, sound odd to use anticonvulsants to facilitate healing and prevent disease, it is entirely consistent with the aforementioned natural health-maintenance interventions in that both are hypothesized to exert their therapeutic effects by calming the nervous system. And although it might also sound redundant to target the same physiological abnormality with multiple drugs from the same class (i.e., by combining anticonvulsants) one must recognize that a single anticonvulsant, even when taken in conjunction with multiple non-medicinal interventions, might not be adequate to compensate for the underlying gene abnormality. It is this oversight that I believe is at least partly responsible for the delay in recognizing the profound benefits of anticonvulsant therapy. Be that as it may, the identification of a shared vulnerability trait in these disorders has exposed a clear biological target for treatment, thus making it possible to stay focused on correcting the underlying abnormality rather than continuing to chase after individual symptoms with drugs that have varied and sometimes contradictory pharmacological effects.

9. Recommendations for Future Research

Urgently needed are clinical studies aimed at assessing the utility of identifying the neuronal hyperexcitability trait through resting vital-sign measurements and compensating for it with one or a combination of natural and pharmacological interventions. Also recommended are studies aimed at examining the validity of using resting vital-sign measurements to predict the psychiatric and medically-beneficial effects of Neuroregulators in complex medical cases and the medically-protective effects of Neuroregulators in vulnerable but asymptomatic individuals.

10. Conclusion

Although the MCNH hypothesis has yet to be verified through rigorous scientific experimentation, the logic, simplicity, and explanatory power of the hypothesis, together with the long-recognized benefits of brain-calming drugs in the management of many mental and physical ailments, bear witness to its validity. Many of the greatest scientists and thinkers throughout history have said that the beauty and simplicity of a hypothesis is greater evidence of truth than scientific experimentation. "Beauty brings with itself evidence that enlightens without mediation," wrote Hans Von Balthasar, one of history's most renowned philosophers. By shedding light on the physiological abnormality that underlies a wide range of mental and physical illnesses, the MCNH hypothesis provides, for the first time, a specific biological target for treating psychiatric disorders and of preventing a plethora of chronic physical illnesses. This, together with identifying an objective means by which to identify the vulnerability trait, has the potential to replace cumbersome diagnostic systems, streamline treatment, and ultimately prevent many psychiatric and medical illnesses from ever beginning. With the biological target now visible, mental health clinicians would be able, through Focused Neuroregulation, to use anticonvulsants and other brain-calming medications to pluck up psychiatric symptoms by their molecular roots. They would also be able to team up with primary care practitioners to use them prophylactically against the development of a wide range of psychiatric and general medical conditions. Moreover, because the newer anticonvulsants are some of the safest and least expensive drugs on the market, the idea of using them long-term would be as practically feasible as it is sensible.

Conflicts of Interest

The author declares that he has no competing interests.

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