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Research Article

Anticonvulsants: The Psychotropic and Medically Protective Drugs of the Future

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Abstract: After more than a century of scientific study and philosophical debate, the neurobiology of psychiatric disorders is still unclear. However, an emerging hypothesis contends that psychiatric and related functional symptoms are rooted in an inherent hyperexcitability of the neurological system. Particularly under the influence of stress, too many neurons fire for too long, resulting in circuit-specific psychiatric symptoms such as anxiety, depression, irritability, insomnia, inattention, and obsessional thinking as well as various physical symptoms that have no identifiable organic cause, such as migraine headache, fibromyalgia, irritable bowel, and chronic pain. Based on this hypothesis, anticonvulsant drugs, which could more aptly be called "Neuroregulators" because of their proposed mechanism of action, should have emerged as the drugs of choice for most of these disorders. Yet the use of anticonvulsants, at least for psychiatric disorders, dwindles in comparison to antidepressants, antipsychotics, psychostimulants, and sedative hypnotics. This article addresses the dearth of anticonvulsant drug use and the hypothetical reasons that several other classes of drugs continue to be used ahead of anticonvulsants despite the expanding base of evidence in support of the neuronal hyperexcitability hypothesis. The article will also propose new ways that anticonvulsants could be used to optimize their effectiveness for the wide range of disorders they should be able to treat, and it will discuss the means by which anticonvulsants could, in theory, be used prophylactically to prevent the development of an equally wide range of general medical conditions, including diabetes, high blood pressure, cardiovascular disease, autoimmune disease, dementia, and cancer.

Keywords: Anticonvulsants, Bipolar Spectrum Disorders, Neuronal Hyperexcitability, Ionchannelopathies, Preventive Medicine

1. Introduction

After more than a century of scientific study and philosophical debate, the neurobiology of psychiatric disorders remains unclear. However, an emerging hypothesis contends that psychiatric and related functional symptoms are rooted in an inherent hyperexcitability of the neurological system [1, 2]. Particularly under the influence of stress, too many neurons fire for too long, resulting in circuit-specific psychiatric symptoms such as anxiety, depression, irritability, insomnia, inattention, and obsessional thinking as well as various physical symptoms that have no identifiable organic cause [1]. Based on this hypothesis, anticonvulsants should have emerged as the drugs of choice for most psychiatric and related functional disorders. Yet the use of anticonvulsants dwindles in comparison to antidepressants, antipsychotics, psychostimulants, and sedative hypnotics. That raises the obvious question: is the Multi-Circuit Neuronal Hyperexcitability (MCNH) Hypothesis of Psychiatric Disorders incomplete, or are other classes of psychotropic drugs being used more heavily because of diagnostic confusion and a flaw in the current (symptom-based) approach to treating psychiatric disorders? This article will address this question and, based on the MCNH hypothesis, discuss a more rational, physiologically-based approach to the treatment of psychiatric and functionally-related disorders. It

will also discuss how this treatment approach could, unlike symptom-based pharmacotherapy, be prophylactic against the development of a wide range of general medical conditions, including diabetes, high blood pressure, cardiovascular disease, autoimmune disease, dementia, and cancer.

2. History of Anticonvulsant Use

Historically, anticonvulsant drugs were among the first to be used for a wide range of ailments. The oldest of these was alcohol, with archeological evidence of a methodological fermenting process dating back to around 7,000 BC [3] and evidence of alcohol's medicinal use mentioned in Sumerian, Egyptian, and Hebrew texts (Proverbs 31: 7-7). The second oldest medicinal remedy was the cannabis plant, which is now well-known to have powerful anticonvulsant effects [4-6]. This was followed by the opium poppy, which, like cannabis, has sedative and analgesic effects. Heading into the modern era, anticonvulsants and other brain-calming drugs continued to be used medicinally, beginning with bromine, an anticonvulsant that Sir Charles Locock's used for "hysterical epilepsy" [7], followed in succession with the use of barbiturates, benzodiazepines, and antipsychotic drugs, all of which 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 1950s, when the antituberculin drugs isoniazid and iproniazid were serendipitously discovered to have antidepressant effects [8, 9]. Notably, these effects were very different than the quieting effects of the drugs that had been used before them. An Associated Press release from Staten Island's Seaview Hospital, where the antidepressant effect was first discovered (Figure 1), captured a telling scene: patients dancing in celebratory mood; hence the term "anti-depressant" [10]. Some of these patients, who had been under quarantine for tuberculosis, were suddenly feeling so good emotionally that they wanted to leave the sanatorium against the directive of the hospital staff. Subsequently, word about the dramatic mood-elevating effects of antidepressants began to spread rapidly, thus catapulting them in popularity over the brain-calming drugs that preceded them. The race to develop new and improved antidepressants has continued ever since.

3. The Logic Behind Antidepressants

For more than 50 years, the therapeutic rationale behind antidepressants, known as the "monoamine hypothesis of depression," is that they improve mood by boosting the activity of monoamine neurotransmitters [11]. Still, this fails to explain how abnormalities in serotonin, norepinephrine, and dopamine signaling translate into a depressed mood. Today, more than a half century later, that question remains unanswered.

Figure 1. *Staten Island's Seaview Hospital, where the first clinical trials to assess the efficacy of iproniazid (the precursor of modern-day antidepressants) took place. In the 1950's, this large sanitarium was one of the busiest in the United States. Courtesy of Wikipedia.*

4. A New Hypothesis

However, an emerging hypothesis may be changing that. According to the MCNH hypothesis of psychiatric disorders, psychiatric symptoms, including depressive symptoms, are the consequence of abnormally elevated and persistent firing in symptom-related circuits in the brain [1]. Thus, just as abnormally elevated and persistent firing in specific motor circuits would cause the related muscles to become spastic, abnormally elevated and persistent firing in anxiety circuits would cause persistent feelings of anxiety; abnormally elevated and persistent firing in depressive circuits would cause persistent feelings of depression; abnormally elevated and persistent firing in pleasure circuits would cause persistent feelings of euphoria, and so on. Based on this hypothesis, depressive and other psychiatric symptoms would resolve when the abnormally elevated firing was brought under control…or at least balanced by firing in competing circuits [1, 12-15]. Thus, from the perspective of the MCNH hypothesis, antidepressants combat depression by decreasing neurotransmission in depressive circuitry, increasing neurotransmission in the reward circuitry, or both.

5. The Problem with Antidepressants

The problem with antidepressants, however, is that the excitatory and inhibitory effects that they exert on circuit-specific firing is unpredictable; too much of one effect or not enough of the other can cause an over-correction of symptoms, as in antidepressant-induced mania, or a worsening of symptoms, as in paradoxical depression [1].

Also, the stimulatory effects of antidepressants, including serotonin reuptake inhibitors (SSRIs) [16], can increase the overall level of excitation in the brain. As this occurs, it can increase the risk that specific circuits will become abnormally hyperactive either spontaneously or in conjunction with willful cognitions and emotions. It can also increase the risk of aberrant circuit induction because highly active circuits are more likely to fuel activity in circuits that would normally be

less active [17]. This is the MCNH explanation for manic-depressive switching [1, 17]. The other problem with antidepressants is that they go everywhere in the brain. Consequently, they tend to change the excitation/inhibition balance in various circuits indiscriminately. While this can sometimes lead to a therapeutic elevation in mood, it can also lead to a worsening of symptoms or the emergence of new symptoms, such as anxiety, irritability, or insomnia [18-22].

Then again, even when an antidepressant has a normalizing effect on mood, the persistent change that it causes in circuit-specific neurotransmission can reduce a patient's flexibility in cognitive-emotional processing. For example, if a patient were to have an experience that would normally cause grief, the antidepressant might prevent him or her from experiencing that grief in a normal way. Some patients describe this as a "numbing" or "blunting" of their emotions [23]. While this effect might be desirable for some, it should not be the goal of pharmacotherapy. The goal of pharmacotherapy (or any biological therapy) should be to re-establish normal brain function. Whatever psychologically-induced emotions (as opposed to neurologically-induced emotions) a patient experiences provide valuable feedback in relation to that individual's actions and attitude. Hence, any drug that interferes with or distorts these emotions should be considered counter-therapeutic. Yet another problem with antidepressants is that their chronic stimulatory effects can eventually make the brain so hyperactive that their inhibitory effects lose the ability to counterbalance their stimulatory effects. This can result in a loss of therapeutic effect (as demonstrated by a 50% relapse rate by the end of the first year of treatment [24]) and can potentially leave the patient in a more compromised state than before the medication was started [25-28].

6. The Benefits of Anticonvulsants

In contrast to antidepressants, anticonvulsants reduce neuronal excitability. Through this simple mechanism, they tend to correct circuit-specific imbalances, and they tend to correct them everywhere in the brain because they go everywhere in the brain. They also correct them quickly because of their direct mechanism of action: anticonvulsants reduce excitation in the brain by modulating ion channels and/or the activity of gamma-amino-butyric acid [29]. Consequently, anticonvulsants, which could more aptly be called "Neuroregulators" because they regulate the firing of neurons [30], have the potential to quickly and indiscriminately reduce psychiatric symptoms while at the same time minimizing the risk of sudden and unexpected changes in symptomatology; hence their categorization in psychiatry as "mood-stabilizers" (Figure 2). Also, because anticonvulsants are devoid of stimulatory effects, their therapeutic effects tend to persist, providing long-term protection against symptom recurrences.

In the same way that they can reduce psychiatric symptoms, anticonvulsants can reduce the functional physical symptoms that are often associated with psychiatric symptoms. For example, by reducing neurological activity to and from nerves, blood vessels, and muscles in the head and neck, anticonvulsants can reduce migraine headaches [31, 32], tension headaches [33], temporal-mandibular joint pain [34], tinnitus [35], and burning mouth syndrome [36]. By reducing neurological activity to and from the digestive tract, anticonvulsants can reduce digestive sensitivity and irritable bowel symptoms [37, 38]. By reducing the neurological activity to and from the skin, fascia, and other connective tissues, anticonvulsants can reduce symptoms of diabetic neuropathy [39, 40], trigeminal neuralgia [40] post-herpetic neuralgia [40], fibromyalgia [41-44], and other acute or chronic pain syndromes [45].

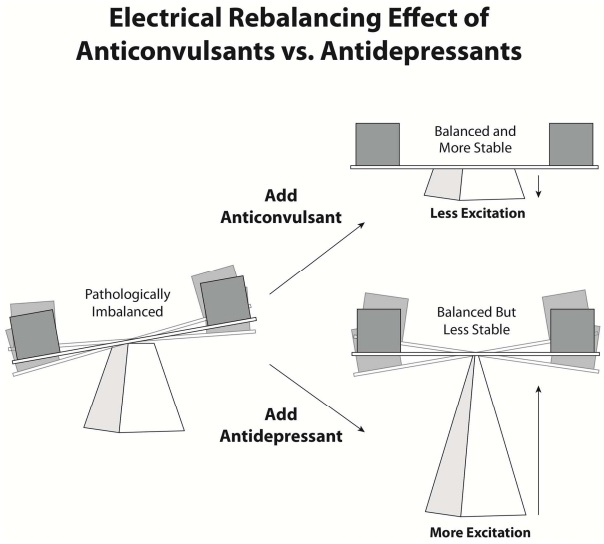

Figure 2. *Comparative illustration of the electrical rebalancing effect of anticonvulsants vs. antidepressants. Note that in the process of correcting a circuit-specific imbalance, anticonvulsants REDUCE the overall level of electrical activity in the brain (symbolized by the reduced height of the top pyramid), thereby increasing the stability of the system. This is in contrast to antidepressants, which, in the process of correcting a circuit-specific imbalance, INCREASE the overall level of electrical activity in the brain (symbolized by the increased height of the bottom pyramid), thereby reducing the stability of the system. The degree to which an antidepressant destabilizes the system would depend upon the balance between its neurostimulatory and neuroinhibitory effects, thus explaining why SSRIs tend to be less destabilizing than tricyclic antidepressants.*

Although anticonvulsants are known to be at least partially effective for all of the aforementioned conditions (as well as many others) [46], two questions remain. First, why are anticonvulsants not even more effective than they are? Second, why are anticonvulsants not more widely prescribed than they are?

Hypothetically, the answer to the first question lies in the failure of clinicians to combine anticonvulsants when one or another of them is insufficient to fully control symptoms. According to the MCNH hypothesis, the pathological circuit-specific hyperactivity that drives psychiatric and related functional systems is rooted in a genetically-based hyperexcitability of the neurological system [1]. Genetic studies suggest that the protein products of risk genes that have been linked to psychiatric and related physical symptoms

fail to adequately regulate the firing of neurons [47-60]. Anticonvulsants can potentially compensate for this abnormality by regulating the neurons themselves. Unfortunately, however, they are not always able to do this adequately. Part of the problem might be that in some individuals, a specific anticonvulsant is unable to recognize the binding sites of its intended receptors. Another part of the problem might be that in some individuals, a specific anticonvulsant fails to effect the receptors that are involved with symptom-related ionchannelopathies or other excitatory effects. Still another part of the problem might be that in some individuals, a specific anticonvulsant inhibits as many (or more) "feel good" circuits as "feel bad" circuits, thus negating its positive effects or even making symptoms worse. It is also possible (though unlikely because there are far more excitatory neurons in the brain than inhibitory neurons [61]) that a specific anticonvulsant would inhibit more inhibitory neurons than excitatory neurons, thereby increasing rather than decreasing the level of excitation in the brain. Although all of these potential barriers are possible, all would be relatively rare because anticonvulsants tend to reduce rather than increase circuit-specific imbalances. Indeed, clinical experience has shown that anticonvulsants rarely cause paradoxical effects [62]. On the other hand, the intrapsychic tension caused by psychosocial stressors, unhealthy attitudes, and dysfunctional coping mechanisms tends to increase circuit-specific imbalances, and it is possible that in some individuals the level of intrapsychic tension is so high that anticonvulsants, even when used in combination with other Neuroregulators, could not possibly stop the flood of excitatory activity that the intrapsychic tension, like a steady wind fanning the flames of a smoldering fire, induces in the hyperexcitable brain.

Notwithstanding the potential barriers to effective Neuroregulator therapy, there is much that can be done to improve the therapeutic success of these drugs. The most basic of these is to start using them more often…and more appropriately. This speaks to the second of the two questions posed earlier. Despite the availability of several safe, non-addictive, generic anticonvulsants, these highly versatile drugs are still the least commonly used of all psychopharmacological agents. The following are possible reasons for this.

First, the effects of neuregulators are not as impressive as those of antidepressants and psychostimulants. It should be remembered, however, that central to the robust mood-elevating effects of stimulant-type drugs is their ability, by altering the activity of specific neurotransmitters, to drive persistent (and unnatural) changes in circuit-specific firing [25]. Though this may be better than leaving a patient in a chronic state of depression, it can prevent the subtle shifts in mood that would normally be driven by daily life experiences. Recall that antidepressants can also cause emotional extremes, paradoxical effects, and the emergence of new symptoms. The various unnatural effects that antidepressants can have tend to be misinterpreted, minimized, or even ignored in drug studies, as the primary aim of such studies is to measure the mood-elevating effects of antidepressants.

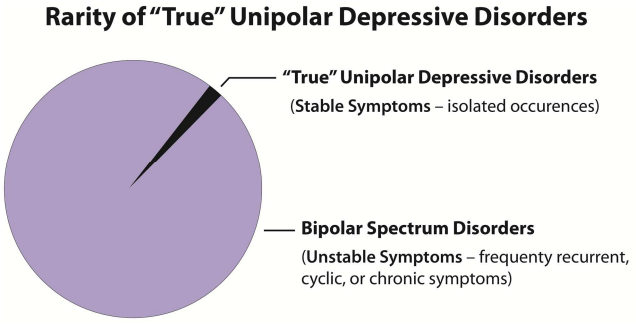

Figure 3. *Pie chart estimating the proportion of psychiatric patients with cyclic or persistent symptomatology (i.e., bipolar spectrum disorders) in comparison to those with stable and isolated or episodically-occurring symptoms (i.e., true unipolar symptoms). Relative proportions are based on the hypothesis that moderate stress, which is encountered by most persons on a frequent basis, is typically enough to precipitate symptoms in persons whose neurological systems are hyperexcitable, thus causing them to have frequently recurring or chronic symptoms (as in bipolar spectrum disorders). In contrast, severe and persistent stress, which is encountered relatively infrequently, is required to precipitate symptoms in persons whose neurological systems are normoexcitable and, therefore, relatively resistant to developing pathological circuit-specific imbalances or aberrant circuit induction (as in true unipolar disorders). Because their neurological systems are normoexcitable, these patients also tend to be more tolerant of antidepressants than those with unstable or persistent symptoms [1, 17].*

The second reason that anticonvulsants are underutilized in psychiatry is diagnostic confusion. Although several anticonvulsants are FDA-approved for the treatment of bipolar disorder, and the evidence base guides their use as first-line therapy for cyclic mood disorders [63, 64], these disorders are commonly misdiagnosed as either unipolar depression or recurrent depression [65-68]. Studies have repeatedly found that patients with bipolar disorder can wait 10 years or more before receiving a proper diagnosis [65, 66]. Moreover, given that bipolar disorder is the easiest to diagnose of all the disorders in the bipolar spectrum, the diagnostic delay in patients with a more subtle cycling of symptoms, as described by bipolar II disorder, cyclothymic disorder, and cyclic depression, is undoubtedly much longer. What's more, some of these patients do not even experience mood symptoms; instead, they experience waves of anxiety, irritability, energy, or sleep disturbance. Such patients are probably never correctly diagnosed (Figure 3). What's more, some of these patients do not even experience mood symptoms; instead, they experience waves of anxiety, irritability, energy, or sleep disturbance. Such patients are probably never correctly diagnosed (Figure 3). Finally, and adding yet another layer of complexity, is the potential need to try a different anticonvulsant if one is ineffective. Like most other classes of drugs, no single anticonvulsant is effective for every patient. Consequently, the failure of a select anticonvulsant to reduce symptoms could easily be interpreted as a misdiagnosis and, therefore, dissuade the clinician from trying a different anticonvulsant. Thus, even though the evidence base informs the use of anticonvulsants as first-line therapy for disorders in the bipolar spectrum, they are, due to

diagnostic confusion, used much less frequently than guided by the evidence. This is a matter of grave concern because, as indicated by their Black Box warnings, antidepressants can make unstable symptoms worse or even life-threatening.

The third reason that anticonvulsants are underutilized in psychiatry is a failure to recognize the underlying biological abnormality. Short of a clear understanding of the pathophysiology of depression and other psychiatric disorders, treatment continues to be symptom-based rather than pathology-based. Consequently, medications are matched to diagnosis, and multiple medications, typically from different classes, are routinely combined in the hopes of relieving all of the patient's symptoms. Rarely are medications from the same class combined, as this could throw the neurological system further out of balance. From this perspective, it would be counterintuitive to think that combining different anticonvulsants could be more effective than combining drugs from different classes. However, anticonvulsants are uniquely suited to be combined with one another because, rather than accentuating the neurological imbalances that cause symptoms to develop, they tend bring the system back into balance [1, 17, 30].

The fourth reason that anticonvulsants are underutilized in psychiatry is that the term "anticonvulsant" does not, either to the patient or to the clinician, sound as safe or as appropriate for psychiatric use as the term "antidepressant." Similarly, the labeling of benzodiazepines (a specific class of anticonvulsants with addictive potential) as "anxiolytics" rather than "anticonvulsants" tends to prevent clinicians from recognizing the potential anxiolytic effects of other (non-addictive) anticonvulsants, such as gabapentin, oxcarbazepine, lamotrigine, topiramate, tiagabine, and levitiracetam. Likewise, the labeling of non-benzodiazepine anticonvulsants as "mood stabilizers" rather than "Neuroregulators" or some other more inclusive, more functionally-appropriate term tends to prevent clinicians from recognizing their usefulness in treating cyclic anxiety, cyclic irritability, cyclic insomnia, and other common, but subsyndromal, manifestations of bipolarity [69-71].

The fifth reason that anticonvulsants are underutilized in psychiatry is inappropriate dosing. Because anticonvulsants are so seldom used in comparison to other classes of psychotropic drugs, clinicians have comparatively little experience titrating them (Figure 4) [72-75]. This, together with the lack of a clearly-defined biological target for treatment, increases the risk of drug failure, either because of under-dosing, which can prevent the medication from adequately modulating its intended receptors, or over-dosing, which can result in intolerable side effects or even paradoxical effects.

The sixth reason that anticonvulsants are underutilized in psychiatry is the fear of causing suicidal thoughts and behaviors. Though antidepressants, through their risk of paradoxical effects [76], are nearly 10 times more likely to cause suicidal thoughts and behaviors than anticonvulsants [62, 77], they are much closer to the standard of care, and so some clinicians may feel that, in the event of an adverse reaction, their risk of liability would be lower when prescribing an antidepressant than when prescribing an anticonvulsant.

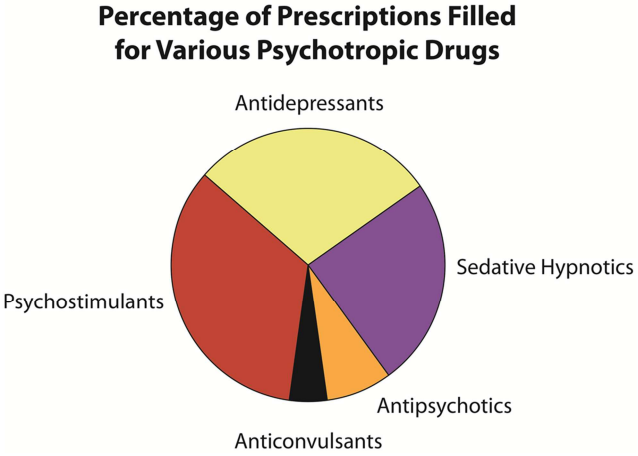

Figure 4. *Relative proportion of prescriptions written from the 5 classes of psychotropic drugs (psychostimulants, antidepressants, antipsychotics, sedative hypnotics, and anticonvulsants). Estimates exclude anticonvulsant use for seizure disorders.*

The seventh reason that anticonvulsants are underutilized in psychiatry is marketing. Whereas antidepressant manufacturers are fully focused on the mental health field, anticonvulsant manufacturers are more heavily focused on neurological applications for their drugs. Hence, the marketing of antidepressants to psychiatrists far exceeds the marketing of anticonvulsants. In addition, with the psychiatric population far outnumbering the epilepsy population [78], the number of new antidepressants currently in development far exceeds the number of new anticonvulsants. This makes it a kind of winner-takes-all for antidepressants.

Thus, the relatively sparse use of anticonvulsants in psychiatry is not necessarily reflective of their therapeutic potential. Moreover, in addition to the large burden of psychiatric morbidity and mortality that anticonvulsants could potentially prevent, there is emerging evidence that early diagnosis and treatment with anticonvulsants could help prevent the development of a wide range of general medical conditions, including diabetes, high blood pressure, cardiovascular disease, autoimmune diseases, dementia, and cancer [79]. By reducing neuronal excitability, anticonvulsants de-stress the neurological system, and so any illness that can be precipitated by stress [80] can hypothetically be prevented by treatment anticonvulsants, particularly if they are used during periods of high stress. Although a similar de-stressing effect can be achieved with antidepressants, the effect tends to be offset by their stimulating effects. Also, as previously discussed, their stimulating effects tend to cause them to lose their therapeutic effects over time.

7. Discussion

Though anticonvulsants and other brain-calming drugs have, throughout history, been the most widely used remedies with or without a prescription, newer anticonvulsants, though

much safer than those of the past, are the least prescribed psychotropic drugs. Perhaps for this reason, there has been little progress in psychiatry since the 1950s, when antidepressants began to replace benzodiazepines and other brain-calming medications for a wide variety of conditions.

Although the monoamine hypothesis has guided the use of antidepressants for more than 50 years, the hypothesis has several limitations. First, it fails to explain why at least 30% of depression sufferers fail to respond to more than one trial of antidepressants [81], and even among responders, approximately 50% relapse by the end of the first year of treatment [24]. Second, it fails to explain why the experimental depletion of monamine precursors is mood-neutral in healthy subjects [82]. Third, it fails to explain why antidepressants sometimes cause a paradoxical worsening of symptoms [18]. Fourth, it fails to explain why depression can undergo rapid shifts in severity and polarity in some patients [17]. Taken together, these limitations of the monoamine hypothesis suggest that the biochemical changes that have been associated with depression are not primary but rather secondary to a more fundamental abnormality.

In recent years, the association between psychiatric disorders and elevated cytokine levels had led some researchers to believe that inflammation might be at the root of mental illness. However, anti-inflammatory drugs fail to completely eliminate psychiatric symptoms, and they appear to be more helpful in those patients who have higher levels of pre-treatment inflammation [83, 84]. As with antidepressants, these observations are more consistent with a secondary effect than a causal effect.

Another burgeoning area of interest has been stress hormones and disruptions of the hypothalamic-pituitary axis, as many patients with depression have been found to have elevated cortisol levels. However, most patients with clinical depression have no evidence of hypothalamic-pituitary dysfunction [85], and attempts to modulate this neuroendocrine system pharmacologically have met with limited therapeutic success [86].

The most recent area of interest has centered on the excitatory neurotransmitter glutamate. Several lines of evidence have linked major depressive disorder to a dysregulation of glutamate signaling [87], and a single dose of the glutamate receptor antagonist ketamine has been observed to produce rapid antidepressant effects in patients with treatment-resistant depression [88]. However, the drug is short-acting, and questions remain about the sustainability of its therapeutic effects over time. Also, recognizing that the intravenous route of administration has practical limitations, researchers have begun looking easier ways to administer the drug. Small-scale preliminary data have demonstrated that the therapeutic effects of oral administration are similar to those of intravenous administration; however, the therapeutic effects of oral administration were delayed by weeks rather than minutes [89]. Also, nearly 50% of patients did not respond, and about 23% demonstrated a worsening of their depressive symptoms [90]. Intranasal administration has also been studied and has yielded benefits similar to intravenous administration, though the magnitude of the effect may be less [91]. Notwithstanding its therapeutic effects in some patients, ketamine is short-acting, and so the potential adverse effects of ongoing dosing, such as cognitive impairment, tolerance, and withdrawal, are of significant concern [92].

From the perspective of the MCNH hypothesis, ketamine reduces depressive symptoms by reducing excitation in the brain (i.e., by blocking glutamate, the most abundant excitatory neurotransmitter in the nervous system). However, the ketamine hypothesis of depression, like the monoamine hypothesis, fails to explain why glutamate, dopamine, serotonin, and other neurotransmitter systems become dysregulated in the first place. According to the MCNH hypothesis, the dysregulation of these systems, along with the dysregulation of metabolic, immunologic, and autonomic functions that are associated psychiatric disorders, are rooted in an inherent hyperexcitability of the neurological system. Because this abnormality is diffuse, it is best treated with drugs that affect the neurological system diffusely; namely, anticonvulsants. The other advantage of anticonvulsant drugs over other medical interventions is that most of the newer anticonvulsants are relatively safe in long-term use. This is an important advantage because neuronal hyperexcitability, being a constitutional abnormality, typically requires ongoing dosing.

Throughout history, anticonvulsants and other brain-calming drugs have been the mainstay of psychiatric treatment. This is in spite of the fact that the molecular target for these drugs had not yet been identified. However, an emerging hypothesis—one that illuminates a clear biological target for the treatment of psychiatric and related functional disorders—is pointing back to the value of anticonvulsants. Also, while not necessarily advocating the first-line use of antidepressants, anti-inflammatories, or antiglutaminergic drugs, the MCNH hypothesis provides a comprehensive psychophysiological explanation for how these and many other psychotropic drugs exert their therapeutic effects [1]. It also explains how non-pharmacological interventions, such as stress-reduction, meditation, exercise, psychotherapy, and various other non-pharmacological interventions exert their therapeutic effects [46].

Finally, in conceptualizing nearly all psychiatric and related functional disorders as different manifestations of a shared physiological abnormality, the MCNH hypothesis eliminates the problem of diagnostic confusion. This is of profound importance because the symptom-based treatment of psychiatric disorders has not only led to the overprescribing and stacking of medications (many of which have conflictual effects), but it has also drawn prescribing practices away from what are hypothesized to be the safest, fastest-acting, and most continuously effective medications available. What is needed now are clinical studies to either disprove the MCNH hypothesis or transform the field of psychiatry into a biologically-precise, pathologically-based medical specialty that is on-par with other medical specialties and, thus, equally worthy of patient trust.

8. Conclusion

Despite enormous strides in neuroscience and the continual synthesis of new antidepressants, antipsychotics, and psychostimulants, the field of psychiatry, hampered by the continued practice of symptom-based treatment, remains at a virtual standstill. Urgently needed is a reconceptualization of psychopathology, one that looks beyond the symptoms to the root of the problem and focuses treatment on correcting that problem. This is what the MCNH hypothesis of psychiatric disorders offers. By targeting the underlying neurophysiological abnormality, the barriers created by diagnostic ambiguity are removed, and the floodgates for a more judicious use of medications, particularly anticonvulsants, are opened. Moreover, because the MCNH hypothesis unifies mental health and physical health, it reduces the stigma of mental illness, thereby helping to overcome barriers that have historically prevented patients from seeking mental health care. This has enormous implications because, in addition to reducing and preventing psychiatric symptomatology, early treatment with anticonvulsants can potentially reduce the risk of developing any of a wide range of general medical conditions. Kraepelin, Freud, and other pioneers in psychiatry predicted that the underpinnings of psychopathology would one day be revealed through neuroscience. That day may have arrived, and the tools to implement the new paradigm may already be available.

Disclosure Statement

The author declares that he has no competing interests.

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