American Journal of Psychiatry and Neuroscience
2022; 10(3): 111-124
http://www.sciencepublishinggroup.com/j/ajpn
doi: 10.11648/j.ajpn.20221003.15
ISSN: 2330-4243 (Print); ISSN: 2330-426X (Online)

Suicide: A New Hypothesis on the Pathogenesis of Disease, Method of Screening, and Means of Prevention

Michael Raymond Binder

Department of Psychiatry, NorthShore University HealthSystem, Highland Park Hospital, Highland Park, USA

Email address:
mbinder@drmichaelbinder.com

To cite this article:
Michael Raymond Binder. Suicide: A New Hypothesis on the Pathogenesis of Disease, Method of Screening, and Means of Prevention. *American Journal of Psychiatry and Neuroscience*. Vol. 10, No. 3, 2022, pp. 111-124. doi: 10.11648/j.ajpn.20221003.15

Received: August 2, 2022; **Accepted**: August 17, 2022; **Published**: August 29, 2022

Abstract: Suicide has become a global epidemic. Every 40 seconds, another person completes the act, and for every person who successfully commits suicide, there are many more who attempt to take their lives. Although many factors are known to increase the risk of suicide, there continues to be a lack of clarity about why some persons decide to end their lives and, equally disturbing, a lack of predictability about when they decide to end their lives. However, an emerging hypothesis contends that a subtle but highly prevalent neurophysiological abnormality is at the root of nearly all psychopathology, including suicidal thinking and behavior. According to the multi-circuit neuronal hyperexcitability hypothesis of psychiatric disorders, an inherent hyperexcitability of the neurological system causes normal thoughts and emotions to become abnormally amplified and persistent. 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... In addition to offering a biologically-based explanation for the development of psychiatric symptomatology, the severe emotional distress, loss of behavioral control, and waxing and waning of symptoms that this neurophysiological abnormality can create from an early age offers a highly plausible explanation for why an affected person might eventually attempt suicide and why the timing of that decision is so difficult to predict. This article will trace the epidemic of suicide to its molecular roots and propose a simple, objective way to assess one's vulnerability to suicide and an equally simple way to reduce that vulnerability before it is too late.

Keywords: Suicide, Neuronal Hyperexcitability, Psychobiology of Stress, Biomarkers of Disease, Preventive Medicine, Anticonvulsants, Mood Stabilizers, Neuroregulators

1. Introduction

Perhaps no tragedy is as psychologically and emotionally disturbing to both the victims and their loved ones as suicide. For the victims, suicide actualizes an unnatural and untimely death, and for loved ones, the irreversibility and often unexpectedness of the tragedy can cause emotional wounds that never completely heal. Yet suicide has become a global epidemic. According to the World Health Organization, roughly 800 million people die by suicide each year, which equates to roughly one suicide every 40 seconds [1]. In the United States, suicide is a leading cause of death in adolescents and young adults, and despite numerous public and private efforts to reduce these figures, the death toll over the last decade has risen by more than 30% [2]. What's more, these statistics are just the tip of the iceberg. For every person who successfully commits suicide, there are many more who attempt to take their lives. This review will trace the act of suicide to its molecular roots and propose an evidence-based, objective way to determine which persons are at risk for becoming suicidal, treat the underlying abnormality, and prevent this lethal symptom before the worst of tragedies occurs.

2. Why Do People Commit Suicide

The possible motives for suicide are as numerous as there are individual psyches and individual circumstances. However, nearly all motives boil down to one or a combination of two fundamental motives: 1) the desire to relieve emotional pain; and 2) the desire to relieve physical pain. Moreover, recognizing that both emotional and physical

pain translate to the experience of suffering, nearly all psychological motives for suicide, whether conscious or unconscious, planned or unplanned, can be reduced to a single motive: the desire to relieve suffering.

Curiously, however, the desire to take one's own life does not appear to be linked to the normal experience of suffering. Rather, it appears to be linked primarily to suffering in the context of mental illness. Psychological autopsies have found that approximately 90% of all suicide victims have a documented history of mental illness [3, 4]. And given that approximately half of all persons who struggle with suicidal thoughts never receive treatment [5], it is conceivable that virtually all persons who commit suicide struggle with some form of mental illness. The validity of this is supported by a meticulously thorough study of suicide that was conducted in the 1950s. During a 1-year period beginning in May, 1956, a complete autopsy, which included medical, psychiatric, and social service exchange records, was performed on 134 individuals who had been confirmed by the county coroner to have died by suicide [6]. Of the 119 cases in which relatives and friends as well as others in the community who knew the victims, such as coworkers, bartenders, nurses, attorneys, and clergy, were available for detailed interviews, 94% were determined, by two psychiatrists who reviewed all of the victims' records independently, to have had some form of mental illness. In comparison, 4% were found to have had a terminal medical illness but no definite mental illness. Thus, at least in the urban area in which this study was conducted, suicide had occurred almost exclusively in persons who were deemed to have been mentally ill.

3. In Search of the Vulnerability Factor

Although suicide is clearly linked to mental illness, not all forms of mental illness carry the same risk of suicide. For example, those diagnosed with a mood disorder have a 6% risk of suicide [7]; those diagnosed with an anxiety disorder have a 3% risk [8]; those diagnosed with schizophrenia have a 4% risk [7]; those diagnosed with alcoholism have a 7% risk [7]; and those diagnosed with borderline personality disorder have a 10% risk [9]. However, all of these numbers vary by less than 10%, and all represent a significantly increased risk of suicide relative to the general population. Also, there is a large degree of diagnostic overlap between psychiatric disorders, with each sharing many features of the others. This suggests that nearly all forms of mental illness share some factor that makes those affected vulnerable to suicide. Moreover, that factor must either cause suffering or at least worsen the person's degree of suffering because, as previously discussed, nearly all motives for suicide can be reduced to the desire to relieve suffering. Another important clue to what the vulnerability factor might be is the well-established link between stress and mental illness, and the equally well-established link between stress and suicidality [10-12]. This shared link, taken together with the link between suffering and suicide, suggests that whatever the factor is that makes one vulnerable to suicide has 3 characteristics: 1) it precipitates psychiatric symptoms; 2) it is exacerbated by stress; and 3) it increases one's degree of suffering.

During the last century, numerous efforts have been made to identify the vulnerability factor in mental illness. Whereas it was once thought that the vulnerability factor might be rooted in the mind, it has become increasingly clear that it must be rooted in the brain [13]. Although no specific factor has been fully embraced by the medical community, the leading hypotheses pertaining to the neurobiology of mental illness are the monoamine hypothesis [14], the glutamate hypothesis [15], the immune hypothesis [16], the central sensitivity hypothesis [17], the endocrine hypothesis [18], the GABAergic hypothesis [19], the mitochondrial hypothesis [20], the neurotrophic hypothesis [21], and the gut-brain hypothesis [22]. Although each of these hypotheses helps explain some aspect of the neuropathology related to mental illness, none of them explain how stress actually causes the biochemical and structural changes that are observed in the brains of the mentally ill, nor do any of them explain how the identified abnormalities actually translate into psychiatric symptomatology.

However, an emerging hypothesis contends that psychiatric symptoms are driven by 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… [23]. The relevance of this to psychopathology in general and suicide in particular is that an abnormal increase in the intensity and persistence of various thoughts and emotions is precisely what distinguishes psychiatric symptoms from normal thoughts and emotions. It could also be what distinguishes the suffering of the mentally ill from the normal experience of suffering.

Yet, the MCNH hypothesis still falls short of explaining: 1) how stress drives pathological hyperactivity in specific neurons and circuits; and 2) how that pathological hyperactivity actually translates into the experience of psychiatric symptoms. To answer these questions, the relationship between the mind and the brain must be re-examined. The prevailing view is that thoughts and emotions are purely manifestations of complex brain function. It is thought that because neural signaling induces magnetic fields, those magnetic fields are the only source of human thoughts and emotions [24, 25]. However, this reductionist view would reduce human beings to mindless automatons whose thoughts, feelings, and actions were dictated by the whims of biological processes and neurological reflexes. Such a simplistic view would also fail to explain where the will comes from, where the attentional element comes from, and, in a broader sense, who the person is that is experiencing the effects of the neurological activity.

Still, some would argue that the brain, together with the

rest of the body, is the person. However, neither the brain nor the body have perceptual ability. This is clearly demonstrated by the clinical effects of a severe spinal cord injury. For example, in a "complete" injury of the spinal cord at the level of the neck, none of the neurological activity that would be activated by sensory receptors in the person's arms, legs, or anywhere else in the body below the point of injury would be perceived. The neurological system would be active, but the person would not be able to perceive it. If, however, the ascending neurological input were to somehow traverse the point of injury in the neck and reach the head, the person would be able to perceive it. This implies that the perceptual element must be somewhere in the head. However, the perceptual element could not be part of the brain because the brain, both structurally and functionally, is part of the neurological system, and as illustrated by the example, the activity of the neurological system cannot be perceived without the perceptual element. The only logical conclusion is that perception must be a function of the mind, which is in the head of the person [26].

Additionally, it is self-evident that the mind is capable of exerting effort. It takes mental effort to concentrate; it takes mental effort to push one's self physically; it takes mental effort to tolerate pain; and it takes mental effort to grapple with intrapsychic conflict. Effort involves energy, and energy induces magnetic fields. At the same time, neurological processes induce magnetic fields as neurons depolarize and repolarize. Hence, the mind and the brain are naturally poised to communicate in the same language; namely, electromagnetic energy. In accordance with Faraday's Law [27], mentally-induced magnetic fields could stimulate the production of action potentials [28], and action potentials could induce the production of magnetic fields [25].

That this two-way dialogue between the mind and the brain actually occurs has now been demonstrated experimentally. Recording from single neurons in patients implanted with intracranial electrodes for clinical reasons, Cerf et al. [29] found that willful thoughts and intentions readily stimulated specific neurons when subjects were asked to perform specific mental tasks. Conversely, Penfield [30], in his seminal work on brain mapping, found that stimulating different parts of the human brain with an electrical probe triggered different thoughts and emotions. Importantly, this bidirectional influence between the mind and the brain could help explain why psychiatric symptoms tend to develop under the influence of mental and emotional stress. The mind, when under stress, could overstimulate specific neurons and circuits, thus causing them to become hyperactive. The hyperactive neurons and circuits could, in turn, reactivate the associated thoughts and emotions. This would result in a vicious circle of mutual overstimulation between the mind and the brain that could, over time, cause the associated magnetic fields to become abnormally intense and abnormally persistent. As the electromagnetic dialogue between the mind and the brain continued to ramp up, so too would the intensity of the mental and emotional stress. Normally, this process would be modulated by neurological self-regulatory mechanisms. However, those mechanisms would be partially compromised in carriers of the neuronal hyperexcitability trait, thus placing them at risk for pathological reactions to stress. This would implicate neuronal hyperexcitability in the pathogenesis of both mental illness and suicidal behavior.

The idea that a hyperexcitability of the neurological system is the vulnerability factor that predisposes a person to both mental illness and suicidality is corroborated by the subjective and objective markers of mental illness.

4. Subjective Markers of Mental Illness

Detailed clinical observations indicate that most persons with mental illness, irrespective of their illness-type or state of remission, have busy minds and unstable moods. For example, most report having more thoughts per unit time than persons without mental illness. They also tend to experience stronger and more turbulent emotions than persons without mental illness. Interestingly, however, some of these individuals report that they also have times when their minds are empty or that they feel emotionless [31]. Although healthy individuals likewise report some variability in their mental and emotional activity, the differences between the active state and the inactive state are not as dramatic as in persons with mental illness. Also, because so many random thoughts pop into the minds of the mentally ill and because so many strong emotions wash over them, they have a tendency to act on them without taking the time to think them through in conjunction with the slower functioning brain [26]. Consequently, they tend to be distractible and impulsive.

Another distinguishing feature of persons with mental illness is their tendency to overreact to psychosocial stressors, and their corresponding difficulty settling down after the stressors resolve [32, 33]. Whereas a normal person might take five or ten minutes to recover from a cognitive-emotional stressor, a person with mental illness might take hours or even days to recover. Their slowness to recover appears to be the consequence of the brain's inability to self-regulate [34, 35], which then keeps the mind engaged in the psychophysiological dynamic that was triggered by the stressor [26]. Note that the delay in recovery also increases the risk that they will behave in a way that will add fuel to the fire or that they will become overwhelmed if they are hit with another stressor before they fully recover from the previous stressor [23]. In addition to these problems, persons with mental illness tend to be plagued by insomnia, a problem that they generally attribute to the inability of their minds to shut off.

In addition to their psychological and emotional struggles, persons with mental illness tend to suffer from various physical ailments that have no identifiable organic basis. Some examples of these so-called "functional" physical symptoms include migraine headaches, fibromyalgia, irritable bowel, and chronic pain [17]. Note that all of these effects—the tendency to ruminate, the instability of mood,

the tendency to be impulsive, the tendency to overreact to stress, the slowness to recover from stress, the trouble sleeping, and the unexplained physical symptoms—are ones that increase the risk of suicide.

5. Objective Markers of Mental Illness

Over the past decade, an explosion of new research has identified a correlation between resting vital-sign measurements and the later development of various psychiatric disorders and general medical conditions [36]. For example, in a longitudinal study involving more than one million men in Sweden, Latvala et al. [37] 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. [38] found that adolescent girls with emotional disorders had increased resting respiratory rates in comparison to healthy controls. The general medical conditions with which upper-end-of-normal resting vital signs have been associated include diabetes [39, 40], high blood pressure [41, 42], cardiovascular disease [43, 44], cerebrovascular disease [45, 46], cancer [47, 48], dementia [49], and all-cause mortality [50-53]. Notably, these are the same illnesses that shorten the lives of the mentally ill [54].

The link between upper-end-of-normal resting vital signs, mental illness, and chronic physical illness is thought to be a chronic hyperactivation of the autonomic nervous system as well as other systems of the body, including the cognitive-emotional system, the hypothalamic-pituitary-adrenal system, the immunologic system, and the metabolic system—all consequent to an inherent hyperexcitability of the neurological system [36]. Hypothetically, the reason that psychiatric and functional physical symptoms tend to precede the development of diagnosable medical conditions is that the cognitive-emotional system is more expressive of neuronal excitation than other organs and systems of the body. The physical consequences tend to be delayed because they express the gradual erosive effects of neuronal hyperexcitability [55, 56]. Based on the foregoing observations, which are rapidly being replicated, it has been hypothesized 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 [36].

What makes these findings so pertinent to the study of suicide is that they could be paving the way to suicide prevention. If neuronal hyperexcitability is in fact the vulnerability trait in mental illness, focusing efforts on reducing the excitability of the neurological system could lead to a rapid resolution of psychiatric symptoms, including suicidal ideation. Also, if the neuronal hyperexcitability trait could be detected before symptoms begin, it could allow high-risk individuals to be educated about the trait and potentially offered preventive strategies, including prophylactic pharmacotherapy.

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 [57-60]. 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 implies 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 symptoms. Although symptoms do, in most cases, first manifest during adolescence and early adulthood [61], the detailed histories of affected persons reveal that symptoms are much more stress-related than age-related. That is to say, they typically first manifest 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, this delay is the time required for mental stimulation of the brain to induce enough kindling to precipitate symptoms [62, 63]. First observed by Graham Goddard in his experiments on rats [64], kindling describes the natural tendency for neurons to become increasingly responsive when stimulated repeatedly. This adaptive process, which under normal physiological conditions is more aptly described as "primed burst potentiation" [65], 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 [66]. Hypothetically, the reason that psychiatric symptoms typically 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.

6. How Influential Is the Neuronal Hyperexcitability Trait

An analysis of the pedigrees of affected families illustrates the relative degree of influence of the neuronal hyperexcitability trait. Though mental illness is known to have a strong genetic component, family, twin, and adoption studies have failed to demonstrate a clear pattern of distribution for any of the common psychiatric disorders. However, if one considers the varying degrees to which the neuronal hyperexcitability trait can be expressed and the diversity of forms that its expression can take, one could not reasonably expect the same symptomatology to be passed from one generation to the next even if the same gene variants were inherited. If, with this in mind, we go back and reconstruct family pedigrees based not on specific

constellations of symptoms but on overt as well as soft signs of neuronal hyperexcitability, such as hyperthymic temperament, cognitive rigidity, mood instability, sleep abnormalities, attentional problems, functional somatic symptoms, and misuse of illicit drugs, a consistent pattern of distribution emerges: that pattern is strikingly autosomal dominant [23]. It is also additive, as a predictable proportion of the children in those families in which both parents are symptomatic are more severely symptomatic than their siblings [23]. The validity of this observation is supported by the additional observation that a predictable proportion of the siblings of affected children seem to be resistant to developing psychiatric symptoms irrespective of how dysfunctional their family dynamics might be. These so-called "survivors," who appear in a classic autosomal recessive distribution, are not necessarily more mentally tough than their affected siblings but more neurologically stable presumably because they did not inherit one of the gene variants that have been linked to neuronal hyperexcitability. Moreover, the fact that these siblings are also relatively resistant to physical illness suggests that among the variables that contribute to the development of chronic disease, the trait of neuronal hyperexcitability may be the most important [55].

7. Suicide Prevention

7.1. Target the Underlying Biological Abnormality

Based on the contention that an inherent hyperexcitability of the neurological system is at the root of both mental illness and a wide range of general medical conditions, one would expect that any intervention that had a calming effect on the brain would help reduce and possibly even prevent the development of these conditions. The growing movement toward complementary and alternative medicine is bearing witness to this [67, 68]. It is becoming increasingly clear that stress-reduction, maintaining an early sleep schedule, exercising regularly, avoiding caffeine and other psychostimulants, and minimizing refined sugar, all of which have a calming effect on the brain, can both reduce and help prevent sicknesses of the mind and body [69]. In fact, these practices have a rich tradition that dates back to antiquity [70]. And, historically, when medicinal remedies were used, they most commonly consisted of preparations that had nerve-calming effects, such as alcoholic elixirs, cannabis powders, opium extracts, valerian, chamomile, and other emotionally and physically-soothing compounds [71-74]. These remedies were used to treat a variety of health conditions, including eczema, colic, rheumatism, menstrual cramps, anxiety, depression, insomnia, pain, and various inflammatory conditions. Heading into the modern era, the anticonvulsant potassium bromide was used to treat "hysterical epilepsy" [75], followed in turn by the use of barbiturates, antipsychotics, and benzodiazepines, all of which, like the compounds that preceded them, had calming effects on the nervous system. Thus, for a wide variety of health conditions, particularly mental and emotional conditions, 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 [76]. This was followed by the introduction of methamphetamine in the 1940s, which in turn was followed by the introduction of antidepressants in the 1950s [77, 78].

However, treatment outcomes for mental illness have not improved very much since the introduction of psychostimulants and antidepressants [79]. This despite the increasing trend toward combining antipsychotic and other sedative-type drugs, which have brain-calming effects, with antidepressants and psychostimulants, which have brain-stimulating effects. From the perspective of the MCNH hypothesis, the brain-calming effects of antipsychotics and other sedatives, and the brain-stimulating effects of antidepressants and psychostimulants, tend to cancel each other out [80, 81], thus resulting in the current trend toward polypharmacy without any significant improvement in treatment outcomes [82].

What is urgently needed is a more accurate understanding of what causes psychiatric symptoms to begin with, as this would allow treatment to target the underlying abnormality rather than chasing after symptoms with drugs that have multiple, conflicting, and sometimes paradoxical effects. The MCNH hypothesis, in conjunction with a more functionally-specific understanding of mind-brain dynamics, provides an answer to this urgent question and, for the first time, illuminates a clear biological target for the treatment of a wide range of psychiatric symptoms, including suicidal behavior [83].

7.2. What a Biological Approach to Suicide Prevention Would Look Like

Upon completion of a thorough safety assessment, the diagnostic assessment of suicidal patients would be based on more than current and past psychiatric symptomatology; it would include an effort to determine the excitability of the neurological system [84]. One of the many advantages of assessing this core physiological parameter is that it would transcend the changeableness and lack of specificity of symptoms. It would also reduce the need to distinguish one psychiatric diagnosis from another [84]. This could spare a great deal of clinician time and patient confusion considering the high degree of overlap in the current diagnostic system. Also, not all patients present with classic psychiatric symptomatology. In fact, a relatively high proportion of patients unconsciously "convert" their mental and emotional pain into physical symptoms and present to their primary care physicians [85]. This markedly reduces the chances that the real problem will be identified. Other sufferers present with functional physical symptoms, such as migraine headaches, fibromyalgia, or irritable bowel, which again reduces the chances that the underlying abnormality will be addressed. Still other sufferers, due to the stigma of mental

illness, flatly refuse to accept a psychiatric diagnosis or even entertain the possibility that a psychiatric disorder could underlie their symptoms. There are also many patients who, being appointed for a routine physical examination, find it easy to avoid disclosing any symptoms though some might be grappling with a serious mental health issue.

In all of these cases, the availability of an objective mental health screening tool, such as resting vital-sign measurements, could be indispensable in identifying which patients need to be screened more carefully for mental illness. It could also help distinguish which asymptomatic patients are truly at increased risk for mental illness from those who merely have a family history of mental illness. The importance of improving mental illness surveillance and circumventing the many barriers posed by symptom-based diagnostic systems is underscored by the fact that nearly 40% of persons who attempt suicide make some type of healthcare visit within one week of the attempt; more than 50% within one month of the attempt; and more than 70% within one year of the attempt [86].

In addition to offering the first objective mental health screening tool, the MCNH hypothesis introduces a new, pathophysiologically-based diagnostic term. In recognition of its genetic mode of transmission, its emotional manifestations, and its effects on the autonomic nervous system, the presence of the neuronal hyperexcitability trait could aptly be expressed by the non-stigmatizing acronym FLASH (familial limbic autonomic system hyperexcitability) [36]. The acronym fittingly recapitulates the fundamental abnormality that it describes; namely, flash-like emotional and behavioral responses due to a hyperexcitability of the neurological system.

What would distinguish FLASH storms from seizure activity is that in FLASH the involved neurons would be fewer in number, circuit-specific, and synchronous rather than hypersynchronous in their activity [63]. Moreover, because neuronal hyperexcitability is a trait rather than a syndrome, and because the trait is also thought to underlie a wide range of general medical conditions, the use of the term "FLASH syndrome" would not necessarily specify the presence of psychiatric symptomatology as opposed to other signs and symptoms that are thought to be rooted in neuronal hyperexcitability, such as essential hypertension, chronic pain, and functional physical symptoms [32, 56]. This would help prevent it from becoming stigmatized while at the same time broadening its applicability.

Returning to the question of what a pathophysiologically-based approach to suicide prevention would look like, a diagnosis of FLASH syndrome would naturally inform the application of brain-calming techniques and interventions. Ideally, the first action steps would be to educate the patient about the underlying neurophysiological abnormality followed by efforts to encourage the healthy lifestyle habits that were discussed previously. Interestingly, this recommendation aligns with a new set of clinical practice guidelines in psychiatry. For the first time, the Royal Australian and New Zealand College of Psychiatrists has recommended attention to diet, regular exercise, and sleep hygiene as "non-negotiable first steps" in the treatment of major depressive disorder [69]. Unfortunately, however, persons with higher levels of neuronal excitability or, if stress levels are also high, even moderately-elevated levels of neuronal excitability, are typically too symptomatic to implement these natural brain-calming interventions. Also, natural interventions take time to habituate, and even when they are practiced regularly, they are not nearly as effective as medication can be. Consequently, most patients will fair best from one or a combination of brain-calming drugs, at least until their stress levels decline enough to allow their neurological activity to return to baseline [87]. Early and aggressive pharmacotherapy, particularly for persons with higher levels of neuronal excitability, can be like extinguishing a small fire before it spreads through the whole house. Also, once the fire is out, continued pharmacotherapy can prevent small fires from restarting. This, in turn, can facilitate the implementation of the aforementioned lifestyle changes and help ensure that those changes are transformed into habits so as to keep symptoms at bay and possibly reduce or even discontinue medication. It can also help prevent the secondary psychological problems that commonly result from chronic, untreated neuronal hyperexcitability.

Although this strategy builds upon long-held historical practices, the idea of quieting the nervous system was, at the turn of the twentieth century, superseded by psychotherapy and, more recently, antidepressant therapy in the hope that these modalities would revolutionize the treatment of mental illness. The problem is that psychotherapy targets the mind, not the brain, and the monoamine hypothesis of depression, upon which the use of antidepressant drugs is based, does not address the core biological abnormality in mental illness [88, 89]. Although antidepressants do have the potential to reduce psychiatric symptomatology, they do so by an imprecise and poorly-controlled mechanism. By modulating the activity of specific neurotransmitters (i.e., dopamine, norepinephrine, and serotonin), they unwittingly attempt to rebalance the electrical activity in specific neural circuits [14]. 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 [83]. In contrast, anticonvulsants, which could more aptly be called "neuroregulators" because of their proposed mechanism of action [90], correct circuit-specific imbalances by reducing the neuronal excitability that is driving the imbalances [23]. The historical effectiveness of anticonvulsants and other brain-calming drugs, and the emerging success of zuranolone (SAGE-217), a novel neuroregulator that is rapidly reducing symptoms in a growing list of psychiatric disorders [91, 92], bear witness to this effect. And although anticonvulsants are well-known to be effective in the broad diagnostic category known as "bipolar spectrum disorder" [31, 93], such patients are almost always misdiagnosed with a unipolar depressive disorder

[94-96]. This assertion is supported by the fact that the sales of antidepressants out-stripe the sales of anticonvulsants by nearly ten-to-one [97-100]. It is also supported by the observation that nearly all patients with symptom instability, irrespective of their primary psychiatric diagnosis, exhibit a rapid and sustained response to various combinations of anticonvulsant drugs [87]. Moreover, this response is typically so robust that it usually allows bipolar spectrum patients to discontinue any psychotropic drugs they may have been taking prior to adding anticonvulsants. Conversely, attempting to treat bipolar spectrum patients with antidepressants or psychostimulants alone may temporarily quell some of their symptoms, but over time their stimulatory effects tend to offset their therapeutic effects because they further exacerbate the underlying problem of neuronal hyperexcitability. In patients with "true" unipolar depression, antidepressants can have a more robust effect than anticonvulsants; however, such patients are relatively rare because the 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 [62-64, 66]. Such high-level stressors are relatively rare in comparison to the daily stressors that can cause circuit-specific imbalances in persons with hyperexcitable neurological systems.

7.3. Psychotherapy

Because psychotherapy targets the mind rather than the brain, it is unable to reduce psychiatric symptoms directly. However, to the extent that it can reduce intrapsychic tension, psychotherapy can reduce mental stimulation of the brain, thereby reducing psychiatric symptoms indirectly. Psychotherapy sessions can also provide a transient sense of relief as the emotional support and positive thoughts of the therapist draw the patient away from refueling the specific circuit loops that are associated with his or her distress. Then again, there are several factors that can potentially offset some of the benefits of psychotherapy. First, everything that is discussed in therapy is processed by the mind in conjunction with the corresponding neural circuitry. Hence, if the brain is hyperexcitable, the content will be subject to neuropsychological distortion. In other words, hyperexcitable neural circuits can distort what the mind is processing through the brain [26]. Consequently, there is a risk that the therapy can become centered on thoughts and emotions that are related more to aberrant discharges from the brain than to the external stressors that led to the treatment. Also, some of these thoughts and emotions can actually increase intrapsychic tension, thus *increasing* rather than decreasing the neurological activity that is fueling the symptoms. Hypothetically, the reason that Freudian psychotherapy primarily targeted neurotic-range psychopathology was that neuroses, which according to the MCNH hypothesis are driven by mild-to-moderate levels of neuronal hyperexcitability [84], would have been less subject to neuropsychological distortion than more severe forms of psychopathology, which would have been driven by higher levels of neuronal excitability [101]. With less electrical congestion in their brains, 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 they attempted to work through mentally and emotionally challenging issues.

Another limitation of psychotherapy is that it fails to correct the biological abnormality that increases one's vulnerability to developing psychiatric symptoms in the first place. Consequently, most of the benefits of psychotherapy are short-lived, although some of them, through learning, neuroplastic changes, and, ultimately, changes in attitude, can be more enduring, thus helping patients to handle future stressors without allowing them to stress their minds and, indirectly, their brains as much. Nonetheless, recognizing the potential limitations of psychotherapy in patients with moderate psychopathology, and the potential risks of psychotherapy in patients with severe psychopathology, prudence dictates that the excitability of the neurological system be reduced concomitant to initiating psychotherapy in the former group, and prior to initiating psychotherapy in the latter group, particularly when employing confrontational, exploratory, and other intensive forms of psychotherapy. This is particularly important to consider when treating patients who are acutely or chronically suicidal or psychotic or both.

7.4. Ancillary Support Services

The historical failure to identify the root cause of mental illness and the growing number of genes that appear to be linked to various psychiatric disorders has led many experts to believe that mental illness is the consequence of a complex interplay between genetic, developmental, and psychosocial factors. This, in turn, has refueled efforts to develop a more comprehensive array of intervention and support services for persons who suffer from mental illness, particularly those who are suicidal [102]. Nonetheless, the effectiveness of these services is likely to remain limited due to the many treatment barriers that continue to be created by the stigma of mental illness and the practical difficulty that affected persons have with utilizing such services consistently. Recognizing neuronal hyperexcitability as the core biological abnormality in mental illness could change all that. It could overcome the stigma of mental illness; it could give suicidal persons their lives back by focusing treatment on reducing the excitability of their neurological systems; and, as will be discussed next, it could even allow at-risk persons to avoid mental illness altogether.

7.5. Prevent the Development of Psychiatric Symptoms

Even greater than the continued challenge of treating the mentally ill would be the challenge of offering illness prevention strategies to those who see themselves as healthy but are actually at increased risk of becoming mental ill. Yet recognizing the tremendous toll that developing psychiatric

symptoms, particularly when they include suicidal thoughts and behaviors, can take on one's self-esteem, one's relationships, and one's daily functioning, and being equally cognizant of the long-term health risks associated with untreated neuronal hyperexcitability, developing a method of preventing symptoms before they even begin could have incalculable benefits. Such an intervention would require the ability to do three things: 1) identify at-risk individuals prior to the onset of symptoms; 2) offer an effective prophylactic strategy without causing shame; and 3) determine the effectiveness of the prophylactic strategy even in the absence of symptoms. Hypothetically, resting vital-sign measurements could make all of that possible.

7.5.1. Identify at-Risk Individuals Prior to the Onset of Symptoms

As previously discussed, the neuronal hyperexcitability trait appears to follow a classic autosomal dominant distribution. In recognition of this, one could not assume that every child in an affected family would be at increased risk of developing mental illness. Hence, there would need to be some way of distinguishing those children who were at increased risk from those who were not at increased risk. Based on the premise that neuronal hyperexcitabilty drives a subtle elevation in resting heart and respiratory rates, simply measuring an individual's resting vital signs would offer an objective way to make that distinction. It would also be a highly practical method both because of its simplicity and because asymptomatic young persons would be unlikely to have any of the factors that could confound the validity of resting vital-sign measurements, such as substance misuse, cardiorespiratory disease, and cardiorespiratory medications.

7.5.2. Offer an Effective Prophylactic Strategy Without Causing Shame

For those who were determined to be at increased risk, the first prophylactic intervention would be to provide education about the neuronal hyperexcitability trait. This would include a discussion about the origin of the trait, the effects of cognitive-emotional stress on the trait, and the effects of diet and lifestyle on the trait. It would also include an explanation that the trait is extremely common, affecting an estimated 40% of the population [84], and that nearly all psychiatric symptoms are caused by the trait [23, 32, 103]. This includes anxiety, depression, mood swings, racing thoughts, obsessions, compulsions, low self-esteem, social anxiety, panic attacks, post-traumatic stress, inattention, insomnia, psychotic symptoms, functional physical symptoms, substance misuse, and suicidal ideation [32]. It would also include a discussion about the ways that various illicit drugs can affect the neuronal hyperexcitability trait. For example, it would explain that alcohol, shortly after being consumed, tends to reduce neuronal excitability, thereby tending to reduce anxiety, normalize mood, and improve sleep. Conversely, the withdrawal phase has the opposite effects. Likewise, it would explain that some of the cannabinoids in marijuana, such as cannabidiol (CBD) and cannabidivarin (CBDV), reduce neuronal excitability and, thus, are both pharmacologically and clinically therapeutic [104]. This is in contrast to tetrahydrocannabinol (THC), which is pharmacologically counter-therapeutic though it might confer some short-lasting pleasurable effects. This is important for users to understand because it is counterintuitive to think that a substance, which in its so-called "low-potency" form (i.e., low THC content) has both pharmacologically and clinically therapeutic effects, might, in its "high-potency" form (i.e., high THC content), actually have pharmacologically counter-therapeutic effects. Yet another important point to convey would be that neuronal hyperexcitability tends to accentuate the "high" from cocaine and other psychostimulants, thus making them even more addictive than they already are.

In the past, educating high-risk youth in these areas would have been challenging due to a lack of objective evidence that any given individual had an increased risk of mental illness. However, the growing recognition that the core abnormality in mental illness can be identified using resting vital-sign measurements—measurements that can be made using an ordinary smartphone or wearable device—has opened the door to allowing at-risk individuals to perform the assessment themselves. This could incentivize them to take control of their health. It could also open the door to prophylactic anticonvulsant therapy, an intervention that, by normalizing brain function, could not only help prevent the development of psychiatric symptoms but could also improve an affected person's day-to-day functioning and reduce his or her risk of developing any of a wide range of chronic diseases.

7.5.3. Determine the Effectiveness of the Prophylactic Strategy Even in the Absence of Symptoms

In the absence of overt psychiatric symptoms, it would normally be difficult to determine the effectiveness of mental illness prophylactic strategies. However, because natural interventions, such as stress-reduction, establishment of an early sleep schedule, and regular exercise, tend to cause a gradual fall in resting vital-sign measurements, whereas effective anticonvulsant prophylaxis tends to cause an immediate fall in these measurements, it would theoretically be possible to determine the differential contributions of these two types of intervention.

8. Discussion

Suicide prevention continues to be one of the world's greatest health challenges, and decoding the pathophysiology of suicidal thoughts and behaviors is critical to meeting that challenge. What makes suicide so difficult to understand is that mental and emotional suffering are never, in ordinary experience, severe enough to warrant inflicting lethal harm to one's self. However, the MCNH hypothesis, in conjunction with a mind-brain duality of the cognitive-emotional system, sheds light on the mystery of suicide by postulating that a pathological hyperexcitability of the neurological system can, in some cases, turn up the affected person's cognitive-emotional volume to such an extent that the associated

suffering becomes too difficult to bear. Also, because neuronal hyperexcitability is, in most cases, a trait rather than a state abnormality, most suicide victims had likely been grappling with their symptoms for much of their lives. Hence, the decision to commit suicide is likely not, in most cases, driven by a single episode of intense emotional suffering but rather a repeating pattern of intense suffering [6]. The same would apply to suffering caused by chronic physical pain, as this too is hypothetically driven by an underlying hyperexcitability of the neurological system [32, 105, 106].

Although some suicidal persons never allow anyone to know what kind of mental and emotional torment they go through, the idea that they suffer chronically is corroborated by the fact that the symptoms of mental illness typically begin early in life and, correspondingly, the risk of suicide steadily increases with age [107]. That suicidal persons suffer chronically is also corroborated by the loss of hope that they express through the act of suicide and the many warning signs that they typically give as they approach the point of no longer being able to bear their suffering. Yet because the symptoms of neuronal hyperexcitability tend to abate during low-stress periods and because the locus of hyperactivity in the hyperexcitable brain typically does not remain focal but rather roams around the brain like a wandering tornado [23], suicidal persons can become euthymic or even hyperthymic for variable and sometimes lengthy periods of time. They can also experience an abnormal quieting of their minds and emotions for variable periods of time because hyperactive circuits compete for dominance [108]. These reprieves could help them keep their suicidal thoughts private until they begin to lose the hope that the inner anguish that they repeatedly experience will one day come to an end. Even when they do begin to lose hope, they may continue to experience intermittent emotional reprieves because of the dynamic nature of the electrical disturbance in their brains. For example, it is not uncommon for a suicidal patient to present to a hospital emergency department only to reassure attending staff, upon formal evaluation, that he or she is no longer suicidal. Although such changes in clinical status could, in some cases, be attributable to the intervention itself, there are many cases in which such a patient becomes suicidal again shortly after returning home or even before leaving the emergency department. This seeming ambivalence can cause family and friends to become decreasingly alarmed about the sufferer's talk of suicide while the sufferer actually becomes increasingly close to reaching his or her limit. Even more concerning, the decreasing alarm of loved ones could escalate the sufferer's suicidality either because of a perceived loss of support or, conversely, because it reduces the sufferer's concern that he or she will be missed. It is also important to recognize that, at the neurological level, the pathological hyperactivity in the neural circuits that are associated with suicidal ideation can cause the affected person to feel compelled to act on his or her thoughts and emotions in much the same way that a person with obsessive-compulsive disorder can feel compelled to act on his or her obsessions [23]. That's because the thoughts and emotions are fueled, at least in part, by the brain. This can be very frightening to the sufferer, particularly if he or she has no willful intentions to be self-harm. It can also be quite confusing to those who are trying to help because it is counterintuitive to think that a person who is seriously contemplating suicide is genuinely reaching out for help. Equally confusing is the observation that the person's mental and emotional state can rapidly change as the locus of hyperactivity surreptitiously roams from one set of circuits to another [23]. These changes, which can sometimes be dramatic, could help explain why the act of suicide is so difficult to predict, even for the sufferer, and why some persons commit suicide even at a very early age.

Although the pathophysiology of symptom-cycling is still unknown, a hyperexcitability of the neurological system offers an anatomically and electrophysiologically sound explanation for this phenomenon [63, 84]. 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 can, through their collateral connections to other neurons, aberrantly fuel activity in relatively *hypo*active receiver circuits while themselves quieting down due to synaptic fatigue [109]. This, in turn, can cause a concomitant shift in attention, cognition, and emotion that then progressively feeds the bipolar switch. The frequency with which symptoms cycle would depend upon the degree of connectedness of the neurological system, the degree of neuronal excitability, and the overall level of excitation in the brain [84]. It would also depend upon the cognitive-emotional state of the individual because thoughts and emotions stimulate the associated neurons and circuits. However, based upon the erratic cognitive, emotional, and behavioral patterns of bipolar spectrum patients, who are thought to constitute the vast majority of psychiatric patients [31, 93], it appears that the relatively large magnetic fields that are induced by pathological circuit-specific hyperactivity generally overpower the relatively weak magnetic fields that are induced by willful mental intentions [28]. Thus, when the locus of hyperactivity involves cognitive circuits, it can cause the mind to overthink things, ruminate about things, and repeatedly check things irrespective of the willful intentions of the individual. It can cause the mind to be distractible, and, if the mind is bombarded with more thoughts than the brain can process psychophysiologically before the mind decides to act on them, it can cause behavior to be impulsive. It can also cause perceptual abnormalities, such as auditory and visual hallucinations, if, for example, the locus of hyperactivity migrates to circuits that would normally be activated by sensory input from the eyes, ears, and other sensory organs. When the locus of hyperactivity involves limbic circuits, it can cause the affected person to experience various emotional states, such as anxiety, depression, irritability, euphoria, or various mixtures of these depending upon which specific circuits are pathologically hyperactive at any point in time [23]. Notice that all of these phenomena—racing thoughts, mood swings, impulsivity, and psychotic

symptoms—are elements that increase the risk of suicide. Thus, in addition to offering a phenomenological basis for the tight link between mental illness and suicidal behavior, the MCNH hypothesis offers an electrophysiological basis for the tight link between the two.

The validity of this conceptualization is supported by the findings of the Robins study, in which nearly half of the suicide victims were diagnosed with manic-depressive disorder, and more than a quarter with alcohol dependence [6]. According to the MCNH hypothesis, manic-depressive disorder, better known today as "bipolar disorder," is rooted in very high levels of neuronal hyperexcitability and, as alluded to earlier, substance misuse nearly always represents an effort to self-medicate the symptoms of neuronal hyperexcitability. Unsurprisingly, the chief of these substances is alcohol, which was once used medicinally on account of its potent anticonvulsant effects (i.e., its ability to reduce neuronal excitability). The idea that the heavy alcohol users in the study were self-medicating their hyperexcitable neurological systems is corroborated by the observation that they tended to utilize fewer medical services than non-users, particularly in the weeks prior to their suicide [6]. Another observation that is consistent with the MCNH hypothesis is that none of the victims in the study were deemed to have neurotic-range or other less severe forms of psychopathology that would be associated with lower levels of neuronal excitability [84]. Also, the lack of any unipolar depressives among the suicide victims is consistent with the idea that "true" unipolar depression is relatively rare and that the close link between suicide and unipolar depression that has been reported in less thorough studies likely reflects a continued misdiagnosis of bipolar depression as unipolar depression [94-96]. Had the Robins study not been so carefully conducted, the researchers would likely have made this same diagnostic error because all of the manic-depressive victims in the study had reportedly taken their lives during the depressive phase of the illness [6].

While depression is the symptom-type that is the most closely associated with suicidal thoughts and behaviors, it is the biological basis of suicide and the electrophysiology of neuronal hyperexcitability that makes the act so difficult to predict. This underscores the importance of understanding the psychobiology of psychiatric symptoms in general and suicidal behavior in particular. With the recognition that psychiatric symptoms are driven by an underlying hyperexcitability of the neurological system, the current paradigm of assessing and diagnosing patients based on symptoms alone could be enhanced by a new paradigm in which the focus of the assessment is to identify the biological abnormality that underlies the symptoms. In addition to circumventing the diagnostic errors that are associated with symptom-based assessments, the MCNH hypothesis illuminates a definitive biological target for treatment. Hypothetically, suicidality and a wide range of other psychiatric symptoms could quickly be reduced or even eliminated by simply reducing the excitability of the neurological system. This is in contrast to the imprecise and unpredictable process of chasing after specific symptoms with drugs that have multiple, conflicting, and sometimes paradoxical effects [82].

Yet another advantage of applying the MCNH hypothesis to psychiatric practice is that it could circumvent the many barriers to treatment that continue to be perpetuated by the shame of having a mental illness. As previously discussed, the presence of the neuronal hyperexcitability trait can aptly be expressed by the non-stigmatizing but fittingly-descriptive acronym, FLASH [36]. This, taken together with the ability to target the core abnormality in psychiatric disorders, can potentially remove the three biggest barriers to progress in mental healthcare; namely, stigma, diagnostic ambiguity, and lack of a clear biological target for treatment. Moreover, because the trait of neuronal hyperexcitability is also thought to underlie a wide range of general medical conditions, the use of the term "FLASH syndrome" would not necessarily specify the presence of psychiatric symptomatology. This would help prevent it from becoming stigmatized while at the same time broadening its applicability to the wide range of other chronic health conditions that it is thought to underlie.

9. Study Limitations and Directions for Future Research

Although this review is based on extensive, longitudinal clinical observations and the latest scientific evidence from around the world, some of the ideas have yet to be proven experimentally, and so further analysis and discussion will be needed before the proposed strategies can be codified and translated into clinical practice. Specifically, the idea that neuronal hyperexcitability is the core abnormality in mental illness will need to be better 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-sign measurements 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.

10. Conclusion

Despite continued efforts to increase suicide awareness

and access to care, there has been relatively little progress in decreasing suicide rates. This is likely due in-part to the continued stigma of mental illness, and in-part to the continued inability to identify the underlying cause of mental illness. The MCNH hypothesis, in conjunction with resting vital-sign measurements, offers the first non-stigmatizing way to identify what is hypothesized to be the core abnormality in mental illness and treat that abnormality so as to rapidly reduce psychiatric symptoms, including suicidal thoughts and behaviors. By simply measuring the patient's resting vital signs, the trait of neuronal hyperexcitability can be identified and therapeutically modified through a combination of natural and pharmacological interventions. Helping patients understand that upper-end-of-normal resting vital signs are markers not of a mental problem but of a biological abnormality that underlies a wide range of chronic health conditions, including but not limited to mental and emotional conditions, offers the first hope of completely destigmatizing mental illness while at the same time illuminating a broadly effective target for treatment. In addition, focusing efforts on identifying the neuronal hyperexcitability trait would 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 drives a subtle elevation in resting vital signs even in the absence of overt psychiatric symptomatology. What's more, the idea that possible carriers of the trait could screen themselves through a simple, objective measure of the body's basic functions could circumvent the barrier of shame that might otherwise prevent them from identifying and seeking to modify the trait prophylactically. Through these potentially groundbreaking advances, the MCNH hypothesis, in conjunction with resting vital-sign measurements, offers an unprecedented opportunity to restore hope, save lives, and bring an end to the mental health crisis.

Conflicts of Interest

The author declares that he has no competing interests.

References

[1] World Health Organization (2018). Global Health Estimates 2016: Deaths by cause, age, sex, by country and by region, 2000-2016. World Health Organization, Geneva.

[2] Garnett, MF, Curtin SC, Stone DM. Sc. D. NCHS Data Brief No. 433, March 2022.

[3] Brådvik L. Suicide Risk and Mental Disorders. Int J Environ Res Public Health 2018; 15 (9): 2028.

[4] Arsenault-Lapierre G, Kim C, Turecki G. Psychiatric diagnoses in 3275 suicides: a meta-analysis. BMC Psychiatry 2004; 4: 37.

[5] Schreiber J, Culpepper L. Suicidal ideation and behavior in adults. www.uptodate.com 2022.

[6] Robins E, Murphy GE, Wilkinson RH Jr, Gassner S, Kayes J. Some clinical considerations in the prevention of suicide based on a study of 134 successful suicides. Am J Public Health Nations Health 1959; 49 (7): 888-899.

[7] Inskip HM, Harris EC, Barraclough B. Lifetime risk of suicide for affective disorder, alcoholism and schizophrenia. Br J Psychiatry 1998; 172: 35-37.

[8] Kanwar A, Malik S, Prokop LJ, Sim LA, Feldstein D, Wang Z, Murad MH. The association between anxiety disorders and suicidal behaviors: a systematic review and meta-analysis. Depress Anxiety 2013; (10): 917-929.

[9] McGirr A, Paris J, Lesage A, Renaud J, Turecki G. Risk factors for suicide completion in borderline personality disorder: a case-control study of cluster B comorbidity and impulsive aggression. J Clin Psychiatry 2007; 68 (5): 721-729.

[10] Stewart JG, Shields GS, Esposito EC, et al. Life stress and suicide in adolescents. J Abnorm Child Psychol 2019; 47 (10): 1707-1722.

[11] O'Connor RC, Nock MK. The psychology of suicidal behaviour. Lancet Psychiatry 2014; 1 (1): 73-85.

[12] Liu RT, Miller I. Life events and suicidal ideation and behavior: a systematic review. Clin Psychol Rev 2014; 34 (3): 181-192.

[13] Insel T, Cuthbert B, Garvey M, et al. Research Domain Criteria (RDoC): Toward a new classification framework for research on mental disorders. American Journal of Psychiatry 2010.

[14] Ressler KJ, Nemeroff CB. Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. Depress Anxiety. 2000; 12 (Suppl 1): 2-19.

[15] Newport DJ, Carpenter LL, McDonald WM, et al. APA Council of Research Task Force on Novel Biomarkers and Treatments. Ketamine and other NMDA antagonists: Early clinical trials and possible mechanisms in depression. Am J Psychiatry 2015; 172 (10): 950-966.

[16] Pariante CM. Increased inflammation in depression: A little in all, or a lot in a few? Am J Psychiatry 2021; 178: 1077-1079.

[17] Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum 2007; 36 (6): 339-356.

[18] Chávez-Castillo M, Núñez V, Nava M, et al. Depression as a neuroendocrine disorder: Emerging neuropsychopharmacological approaches beyond monoamines. Advances in Pharmacological and Pharmaceutical Sciences 2019; 2019.

[19] Hasler G, van der Veen JW, Tumonis T, et al. Reduced prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. Arch Gen Psychiatry 2007; 64 (2): 193-200.

[20] Allen J, Romay-Tallon R, Brymer KJ, et al. Mitochondria and mood: Mitochondrial dysfunction as a key player in the manifestation of depression. Front Neurosci 2018; (12): 386.

[21] Liu B, Liu J, Wang M, Zhang Y, Li L. From serotonin to neuroplasticity: evolvement of theories for major depressive disorder. Front Cell Neurosci 2017; 11: 305.

[22] Evrensel A, Ceylan ME. The Gut-brain axis: The missing link in depression. Clin Psychopharmacol Neurosci 2015; 13 (3): 239-244.

[23] Binder MR. The multi-circuit neuronal hyperexcitability hypothesis of psychiatric disorders. AJCEM 2019; 7 (1): 12-30.

[24] Pockett S. The electromagnetic field theory of consciousness: A testable hypothesis about the characteristics of conscious as opposed to non-conscious fields. Journal of Consciousness Studies 2012; 19 (11-12): 191-223.

[25] McFadden J. Synchronous firing and its influence on the brain's electromagnetic field: Evidence for an electromagnetic theory of consciousness. JCS 2002; 9 (4): 23–50.

[26] Binder MR. Mind-brain dynamics in the pathophysiology of psychiatric disorders. AJPN 2022; 10 (2): 48-62.

[27] Forbes N, Mahon B. Faraday, Maxwell, and the electromagnetic field: How two men revolutionized physics. Prometheus Books, New York, 2014.

[28] Anastassiou CA, Perin R, Markram H, Koch C. Ephaptic coupling of cortical neurons. Nat Neurosci 2011; 14 (2): 217-223.

[29] Cerf M, Thiruvengadam N, Mormann F, et al. On-line, voluntary control of human temporal lobe neurons. Nature 2010; 467: 1104-1108.

[30] Penfield W. Epilepsy and surgical therapy. Archives of Neurology and Psychiatry 1936; 36 (3): 449-484.

[31] Lara DR, Akiskal HS. Toward an integrative model of the spectrum of mood, behavioral and personality disorders based on fear and anger traits: II. Implications for neurobiology, genetics and psychopharmacological treatment. Journal of Affective Disorders 2006; 94 (1-3): 89-103.

[32] Binder MR. Neuronal hyperexcitability: significance, cause, and diversity of clinical expression. AJCEM 2021; 9 (5): 163-173.

[33] Dell'Ossoa L, Strattab P, Conversanoa C, et al. Lifetime mania is related to post-traumatic stress symptoms in high school students exposed to the 2009 L'Aquila earthquake. Comprehensive Psychiatry 2014; 55: 357-362.

[34] Johnstone T, van Reekum CM, Urry HL, Kalin NH, Davidson, RJ. Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. J. Neuroscience 2007; 27 (33): 8877-8884.

[35] Leuchter AF, Cook IA, Hunter AM, Cai C, Horvath S. Resting-state quantitative electroencephalography reveals increased neurophysiologic connectivity in depression. PLoS One 2012; 7 (2): 1-13. e32508.

[36] Binder MR. FLASH syndrome: tapping into the root of chronic illness. AJCEM 2020; 8 (6): 101-109.

[37] Latvala A, Kuja-Halkola R, Rick C, et al. Association of resting heart rate and blood pressure in late adolescence with subsequent mental disorders: A longitudinal population study of more than 1 million men in Sweden. JAMA Psychiatry 2016; 73 (12): 1268-1275.

[38] Blom EH, Serlachius E, Chesney MA, Olsson EMG. Adolescent girls with emotional disorders have a lower end-tidal CO_2 and increased respiratory rate compared with healthy controls. Psychophysiology 2014; 51 (5): 412-418.

[39] Lee DH, de Rezende LFM, Hu FB, Jeon JY, Giovannucci EL. Resting heart rate and risk of type 2 diabetes: A prospective cohort study and meta-analysis. Diabetes Metab Res Rev 2019; 35 (2): e3095.

[40] Aune D, o'Hartaigh B, Vatten LJ. Resting heart rate and the risk of type 2 diabetes: A systematic review and dose-response meta-analysis of cohort studies. Nutr Metab Cardiovasc Dis 2015; 25 (6): 526-534.

[41] Colangelo LA, Yano Y, Jacobs Jr DR, Lloyd-Jones DM. Association of resting heart rate with blood pressure and incident hypertension over 30 years in black and white adults: The CARDIA study. Hypertension 2020; 76 (3): 692-698.

[42] Shi Y, Zhou W, Liu S, et al. Resting heart rate and the risk of hypertension and heart failure: A dose-response meta-analysis of prospective studies. J Hypertens 2018; 36 (5): 995-1004.

[43] Cooney MT, Vartiainen E, Laatikainen T, et al. Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. Am Heart J 2010; 159 (4): 612-619.

[44] Khan H, Kunutsor S, Kalogeropoulos AP, et al. Resting heart rate and risk of incident heart failure: three prospective cohort studies and a systematic meta-analysis. J Am Heart Assoc 2015; 4 (1): e001364.

[45] Yu J, Dai L, Zhao Q. Association of cumulative exposure to resting heart rate with risk of stroke in general population: The Kailuan cohort study. Journal of Stroke and Cardiovascular Diseases 2017; (26): 11: 2501-2509.

[46] Huang Y-Q, Shen G, Huang J-Y, Zhang B, Feng Y-Q. A nonlinear association between resting heart rate and ischemic stroke among community elderly hypertensive patients. Postgrad Med 2020; 132 (2): 215-219.

[47] Anker MS, Ebner N, Hildebrandt B, et al. Resting heart rate is an independent predictor of death in patients with colorectal, pancreatic, and non-small cell lung cancer: results of a prospective cardiovascular long-term study. European Journal of Heart Failure 2016; 18 (12).

[48] Park J, Kim JH, Park Y. Resting heart rate is an independent predictor of advanced colorectal adenoma recurrence. PLoS One 2018; 13 (3): e0193753.

[49] Burke SL. Resting heart rate moderates the relationship between neuropsychiatric symptoms, MCI, and Alzheimer's disease. Innov Aging 2019; 3 (suppl 1): S641.

[50] Aune D, Sen A, o'Hartaigh B, et al. Resting heart rate and the risk of cardiovascular disease, total cancer, and all-cause mortality - A systematic review and dose-response meta-analysis of prospective studies. Nutr Metab Cardiovasc Dis 2017; 27 (6): 504-517.

[51] Zhang D, Shen X, Qi X. Resting heart rate and all-cause and cardiovascular mortality in the general population: a meta-analysis. CMAJ 2016; 188 (3): E53-E63.

[52] Baumert M, Linz D, Stone K, et al. Mean nocturnal respiratory rate predicts cardiovascular and all-cause mortality in community-dwelling older men and women. European Respiratory Journal 2019; DOI: 10.1183/13993003.02175-2018.

[53] Jouven X, Empana J-P, Schwartz PJ, et al. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med 2005; 352: 1951-1958.

[54] Erlangsen A, Andersen PK, Toender A, et al. Cause-specific life-years lost in people with mental disorders: a nationwide, register-based cohort study. The Lancet 2017; 4 (12): 937-945.

[55] Binder MR. Neuronal hyperexcitability: The elusive but modifiable instigator of disease. AJCEM 2022; 10 (1): 1-7.

[56] Binder MR. Gabapentin—the popular but controversial anticonvulsant drug may be zeroing in on the pathophysiology of disease. AJCEM 2021; 9 (4): 122-134.

[57] Ferreira MAR, O'Donovan MC, Sklar P. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. Nat Genet 2008; 40 (9): 1056-1058.

[58] Yuan A, Yi Z, Wang Q, et al. ANK3 as a risk gene for schizophrenia: new data in Han Chinese and meta analysis. Am J Med Genet B Neuropsychiatr Genet 2012; 159B (8): 997-1005.

[59] Green EK, Grozeva D, Jones I, et al., Wellcome Trust Case Control Consortium, Holmans, PA, Owen, MJ, O'Donovan, MC, Craddock N. The bipolar disorder risk allele at CACNA1C also confers risk of recurrent major depression and of schizophrenia. Mol Psychiatry 2010; 15 (10): 1016-1022.

[60] Lopez AY, Wang X, Xu M, et al. Ankyrin-G isoform imbalance and interneuronopathy link epilepsy and bipolar disorder. Mol Psychiatry 2017; 22 (10): 1464–1472.

[61] Kessler RC, Amminger GP, Aguilar-Gaxiola S, et al. Age of onset of mental disorders: A review of recent literature. Curr Opin Psychiatry 2007; 20 (4): 359-364.

[62] Post RM. Kindling and sensitization as models for affective episode recurrence, cyclicity, and tolerance phenomena. Neuroscience & Biobehavioral Reviews 2007; 31 (6): 858-873.

[63] Binder MR. Electrophysiology of seizure disorders may hold key to the pathophysiology of psychiatric disorders. AJCEM 2019; 7 (5): 103-110.

[64] Goddard GV. Development of epileptic seizures through brain stimulation at low intensity. Nature 1967; 214: 1020-1021.

[65] Rose GM, Diamond DM, Pang K, Dunwiddie TV. Primed burst potentiation: lasting synaptic plasticity invoked by physiologically patterned stimulation. In: Haas HL, Buzsàki G. (eds) Synaptic plasticity in the hippocampus. Springer, Berlin, Heidelberg, 1988.

[66] Wada JA, Sato M, Corcoran ME. Persistent seizure susceptibility and recurrent spontaneous seizures in kindled cats. Epilepsia 1974; 15 (4): 465-478.

[67] Jonas WB, Eisenberg D, Hufford D, Crawford C. The evolution of complementary and alternative medicine (CAM) in the USA over the last 20 years. Complementary Medicine Research 2013; 20: 65-72.

[68] Lakhan SE, Vieira KF. Nutritional therapies for mental disorders. Nutr J 2008; 7: 2.

[69] Malhi GS, Bell E, Bassett D, et al. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry 2021; 55 (1): 7-117.

[70] Ahonen M. Ancient philosophers on mental illness. History of Psychiatry 2018; 30 (1): 3-18.

[71] McGovern PE, Zhang J, Tang J, et al. Fermented beverages of pre-and proto-historic China. PNAS 2004; 101 (51): 17593-17598.

[72] Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin. British Journal of Pharmacology 2008; 153 (2): 199–215.

[73] Srivastava JK, Shankar E, Gupta S. Chamomile: A herbal medicine of the past with bright future. Mol Med Report 2010; 3 (6): 895-901.

[74] Petrovska B. Historical review of medicinal plants 'usage. Pharmacognosy Reviews 2012: 6 (11): 1-5.

[75] Pearce JMS. Bromide, the first effective antiepileptic agent. Journal of Neurology, Neurosurgery & Psychiatry 2001; 72 (3).

[76] Ciccarone D. Stimulant abuse: pharmacology, cocaine, methamphetamine, treatment, attempts at pharmacotherapy. Prim Care 2011; 38 (1): 41-58.

[77] Hillhouse TM, Porter JH. A brief history of the development of antidepressant drugs: from monoamines to glutamate. Exp Clin Psychopharmacol 2015; 23 (1): 1-21.

[78] Ramachandraih CT, Subramanyam N, Bar KJ, Baker G, Yeragani VK. Antidepressants: from MAOIs to SSRIs and more. Indian Journal of Psychiatry 2011; 53 (2): 180-182.

[79] Insel TR, Wang PS, The STAR*D Trial: Revealing the need for better treatments. Psychiatric Services 2009. https://doi.org/10.1176/ps.2009.60.11.1466.

[80] Khedr EM, Elserogy Y, Fawzy M. Effect of psychotropic drugs on cortical excitability of patients with major depressive disorders: A transcranial magnetic stimulation study. Psychiatry Research 2020; 291: 113287.

[81] Cooper DC, Moore SJ, Staff NP, Spruston N. Psychostimulant-induced plasticity of intrinsic neuronal excitability in ventral subiculum. J Neurosci 2003; 23 (30): 9937-9946.

[82] Kukreja S, Kalra G, Shah N, Shrivastava A. Polypharmacy in psychiatry: A review. Mens Sana Monogr 2013; 11: 82-99.

[83] Binder MR. Anticonvulsants: The psychotropic and medically protective drugs of the future. AJCEM 2021; 9 (5): 180-188.

[84] Binder MR. The neuronal excitability spectrum: A new paradigm in the diagnosis, treatment, and prevention of mental illness and its relation to chronic disease. AJCEM; 2021; 9 (6); 187-203.

[85] deGruy III F. Mental health care in the primary care setting. National Academies Press, Washington, D. C., 1996.

[86] Ahmedani BK, Stewart C, Simon GE, et al. Racial/ethnic differences in health care visits made before suicide attempt across the United States. Medical Care 2015; 53 (5): 430.

[87] Binder MR. Neuronal Hyperexcitability: the elusive link between social dysfunction and biological dysfunction. WJPH 2022; In Press.

[88] Heninger GR, Delgado PL, Charney DS. The revised monoamine theory of depression: a modulatory role for monoamines, based on new findings from monoamine depletion experiments in humans. Pharmacopsychiatry 1996; 29 (1): 2-11.

[89] Binder MR. New hypothesis unifies previous theories of psychopathology and identifies core biological abnormality in psychiatric disorders. AJCEM 2022; 10 (1): 23-37.

[90] Binder MR. Introducing the term "Neuroregulator" in psychiatry. AJCEM 2019; 7 (3): 66-70.

[91] Gunduz-Bruce, Silber C, Kaul I, et al. Trial of SAGE-217 in patients with major depressive disorder. N Engl J Med 2019; 381: 903-911.

[92] Walkery A, Leader LD, Cooke E, VandenBerg A. Review of allopregnanolone agonist therapy for the treatment of depressive disorders. Drug Des Devel Ther 2021; 15: 3017-3026.

[93] Akiskal HS. The bipolar spectrum: new concepts in classification and diagnosis. In: Grinspoon L, editor. Psychiatry Update; The American Psychiatric Association Annual Review. Vol. 2. Washington DC: American Psychiatric Press 1983, pp. 271–292.

[94] Lubloy A, Kereszturi JL, Nemeth A, Mihalicza P. Exploring factors of diagnostic delay for patients with bipolar disorder: a population-based cohort study. BMC Psychiatry 2020; 20 (75).

[95] Dagani J, Signorini G, Nielssen O, et al. Meta-Analysis of the interval between the onset and management of bipolar disorder. The Canadian Journal of Psychiatry 2016; 64 (4).

[96] Hirschfeld R, Lewis L, and Vornik L. Perceptions and impact of bipolar disorder: how far have we really come? Results of the National Depressive and Manic-Depressive Association 2000 survey of individuals with bipolar disorder. J Clin Psychiatry 2003; 64 (2): 161-174.

[97] Sultan RS, Correll CU, Schoenbaum M, et al. National patterns of commonly prescribed psychotropic medications to young people. J Child Adolesc Psychopharmacol 2018; 28 (3): 158-165.

[98] Brody DJ, Gu Q. Antidepressant use among adults: United States, 2015-2018. National Center for Health Statistics. NCHS Data Brief No. 377, September 2020.

[99] Chong Y, Fryar CD, Gu Q. Prescription sleep aid use among adults: United States, 2005–2010. NCHS Data Brief. 127, August, 2013.

[100] Cascade E, Kalali AH, Weisler RH. Varying uses of anticonvulsant medications. Psychiatry (Edgmont) 2008; 5 (6): 31-33.

[101] Varvin S. Which patients should avoid psychoanalysis, and which professionals should avoid psychoanalytic training?: A critical evaluation. Scandinavian Psychoanalytic Review 2014; 26 (26): 109-122.

[102] Liu NH, Daumit GL, Dua T, et al. Excess mortality in persons with severe mental disorders: a multilevel intervention framework and priorities for clinical practice, policy and research agendas. World Psychiatry 2017; 16 (1): 30-40.

[103] Grunze HCR. The effectiveness of anticonvulsants in psychiatric disorders. Dialogues Clin Neurosci. 2008; 10 (1): 77-89.

[104] Perucca E. Cannabinoids in the treatment of epilepsy: Hard evidence at last? J Epilepsy Res 2017; 7 (2): 61-76.

[105] Fleming KC, Volcheck MM. Central sensitization syndrome and the initial evaluation of a patient with fibromyalgia: a review. Rambam Maimonides Med J 2015; 6 (2): e0020.

[106] Aurora SK, Wilkinson F. The brain is hyperexcitable in migraine. Cephalalgia 2007; 27 (12) 1442-1453.

[107] Ritchie H, Roser M, Ortiz-Ospina E. Suicide. Our World in Data 2015. https://ourworldindata.org/suicide.

[108] Hargreave E. (2006). The neuroplasticity phenomenon of kindling. http://hargreaves.swong.webfactional.com/kindle.htm. (Accessed 5/19/18).

[109] Henkel AW, Welzel O, Groemer T W, et al. Fluoxetine prevents stimulation-dependent fatigue of synaptic vesicle exocytosis in hippocampal neurons. Journal of Neurochemistry 2010; 114 (3): 697-705.