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Review Article

Gabapentin — The Popular but Controversial Anticonvulsant Drug May Be Zeroing in on the Pathophysiology of Disease

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Abstract: Originally marketed under the brand name Neurontin, the anticonvulsant drug gabapentin has become one of the most widely prescribed—and one of the most controversial—drugs in America. On the market for nearly three decades, the drug has been prescribed for everything from chronic cough to chronic pain and hot flashes to bipolar disorder; but is it the real deal, or is it just the brain-child of aggressive marketing, false advertising, and wishful thinking? This critical review will dissect gabapentin down to its molecular roots and trace its wide-ranging effects to better understand the drug and the persons who use it. It will also discuss how gabapentin (and other anticonvulsant drugs) may be doing something more profound than just treating acute symptoms. An emerging hypothesis contends that psychiatric and related function symptoms are driven by pathological hyperactivity in symptom-related circuits in the brain and that the same abnormality may, over time, be driving the development of a plethora of general medical conditions, including diabetes, high blood pressure, cardiovascular disease, autoimmune diseases, dementia, and cancer. Emerging evidence suggests that the underlying physiological abnormality—an inherent hyperexcitability of the neurological system—is very common, and clinical correlation suggests that it is inherited in a classic autosomal dominant distribution. There is also evidence that the abnormality may be reflected in one's resting vital signs, an observation that could help carriers identify the trait themselves. Gabapentin, together with other pharmacological (and non-pharmacological) interventions that reduce neuronal excitability, may, in addition to their immediate effects, have the potential to prevent the long-term erosive effects of neuronal hyperexcitability by simply turning down the stress response. Recognition of this could usher in history's greatest campaign in the fight against sickness and disease.

Keywords: Gabapentin, Anticonvulsants, Neuronal Hyperexcitability, Genetics of Psychiatric Disorders, Ionchannelopathies, Biomarkers of Disease, Preventive Health Strategies

1. Introduction

Figure 1. *Molecular structure of gabapentin.*

According to the New England Journal of Medicine, gabapentin is now one of the most popular prescription drugs in America [1]. Over the past decade, annual prescriptions for the anticonvulsant have risen steadily, more than doubling since 2009 [2, 3]. As of August, 2020, gabapentin was the 6th most commonly filled medication at pharmacies [3], with over 400 million prescriptions written between 2004 and 2018 [4]. Originally introduced in 1993 by Parke-Davis under the brand name Neurontin, gabapentin (Figure 1) has gradually found its way into the treatment of everything from chronic cough to chronic pain and hot flashes to bipolar disorder. In recent years, however, it has also found its way into the hands of drug

dealers and persons who struggle with a wide range of substance use disorders [5, 6]. Moreover, in conjunction with its illicit use, gabapentin is increasingly being found in tissue samples of persons who have died of drug overdose [5]. So that begs the question: is gabapentin a dangerous drug? Is it a medical panacea? Or is it something else?

2. History of Development

To answer these questions, let us begin by reviewing the history of gabapentin's development and what it is known to do in the body. Gabapentin was first discovered in Japan in 1970s, where it found use as a muscle relaxant and antispasmodic [7]. A few years later, it was sold to Warner-Lambert (prior to the company's acquisition of Parke-Davis), where its effectiveness as an antiepileptic drug was realized. Gabapentin received FDA approval in 1993, and approximately 15 years later, prescriptions for the drug—mainly for conditions other than its approved use—began to rise exponentially [4], with off-label prescribing reaching as high as 95%—the highest of any prescription drug in the U.S. [8]. Currently, gabapentin is FDA approved for the treatment of post-herpetic neuralgia, moderate to severe restless leg syndrome, and the adjunctive treatment of partial seizures in adults and children [7]. Gabapentin's off-label uses include generalized tonic-clonic seizures [9], neuropathic pain [10], trigeminal neuralgia [11], complex regional pain syndrome [12], diabetic neuropathy [13], postoperative analgesia [14], tension headache [15], migraine headache [15, 16], fibromyalgia [17], irritable bowel syndrome [18], treatment-resistant depression [19], bipolar disorder [20], generalized anxiety disorder [21, 22], panic disorder [23], social phobia [24], post-traumatic stress disorder [25], insomnia [25], alcohol [26, 27], opioid [28-30], cannabis [31, 32], cocaine [33, 34], and other substance use disorders [6, 35], hot flashes [36], essential tremor [37], nausea and vomiting [38], interstitial cystitis [39], overactive bladder [40], pruritus [41], chronic cough [42], and persistent hiccups [43].

3. Mechanism of Action

Gabapentin is an amino-acid derivative and structural analogue of the naturally-occurring neurotransmitter gamma-aminobutyric acid (GABA). GABA is the body's primary inhibitory neurotransmitter. When it binds to its receptor on receiving neurons, it causes chloride ion channels to open, thus reducing the excitability of the cell. Though structurally similar to GABA, gabapentin does not bind to GABA receptors, yet exerts the same physiological effect. Although several mechanisms have been proposed to explain gabapentin's anticonvulsant effects [44], the most plausible of these appears to be its selective inhibitory effect on voltage-gated calcium channels (VGCCs) [45]. These channels, among other functions, facilitate the release of neurotransmitters by conducting calcium ions into the cell.

The calcium channel consists of a complex of alpha-1, alpha-2-delta, beta, and gamma subunits in a 1:1:1:1 ratio [46]. Gabapentin is believed to inactivate the channel by acting on the alpha-2-delta subunit [47, 48]. This effect has consistently been observed in both rodent and human-based experimental models and is sufficiently robust to explain the clinical effects that have been associated with gabapentin administration [48]. Also important in understanding how gabapentin exerts its therapeutic effects is the anatomical distribution of VGCCs. VGCCs are found in the membranes of excitable cells throughout the body, including muscle cells, glandular cells, glial cells, and neurons of the central and peripheral nervous systems (Figure 2). This creates the potential for gabapentin to have a wide range of therapeutic applications.

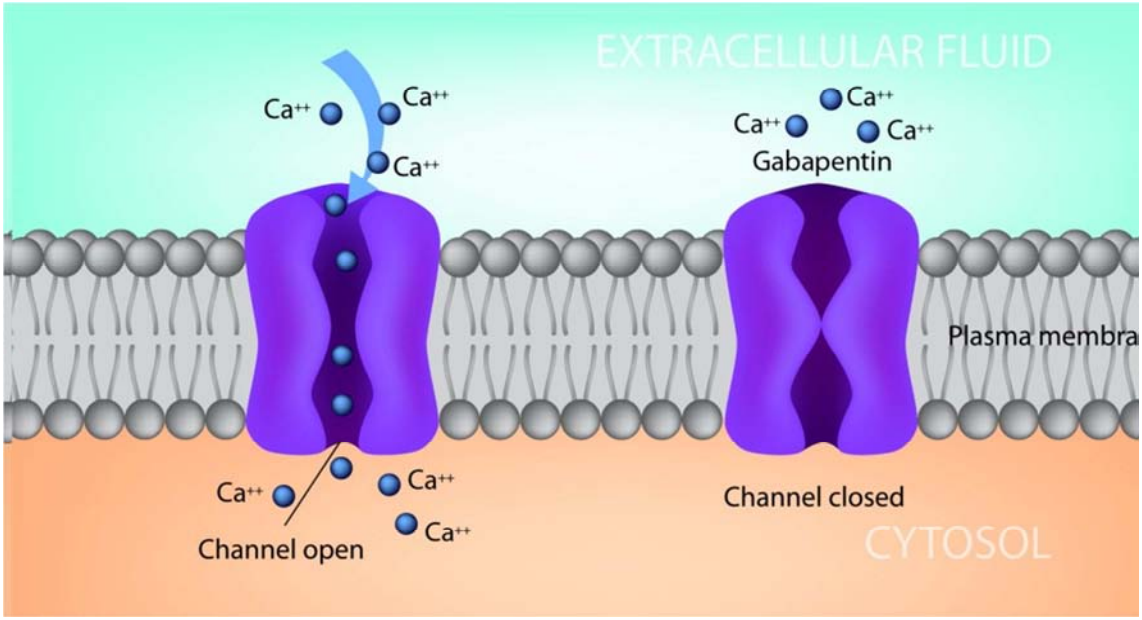

Figure 2. *Schematic illustration of the effect of gabapentin on voltage-gated calcium channels.*

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Gabapentin's putative mechanism of action in conjunction with the wide distribution of VGCCs is not the only molecular evidence that links neuroregulation to gabapentin's broad utility. Multiple gene association studies have linked ionchannelopathies to commonly-occurring psychiatric, neurologic, and general medical conditions [49-64]. One of the strongest associations involves polymorphisms of the gene CACNA1C, which codes for the alpha-1 subunit of VGCCs [51, 53-55]. Additionally, subunits of the calcium channel were downregulated in response to lithium, a drug that is known to have anticonvulsant effects [65-67]. These unlikely connections provide compelling evidence that gabapentin exerts its therapeutic effects by influencing calcium channels and highlights the importance of neuronal excitability in the pathogenesis of disease.

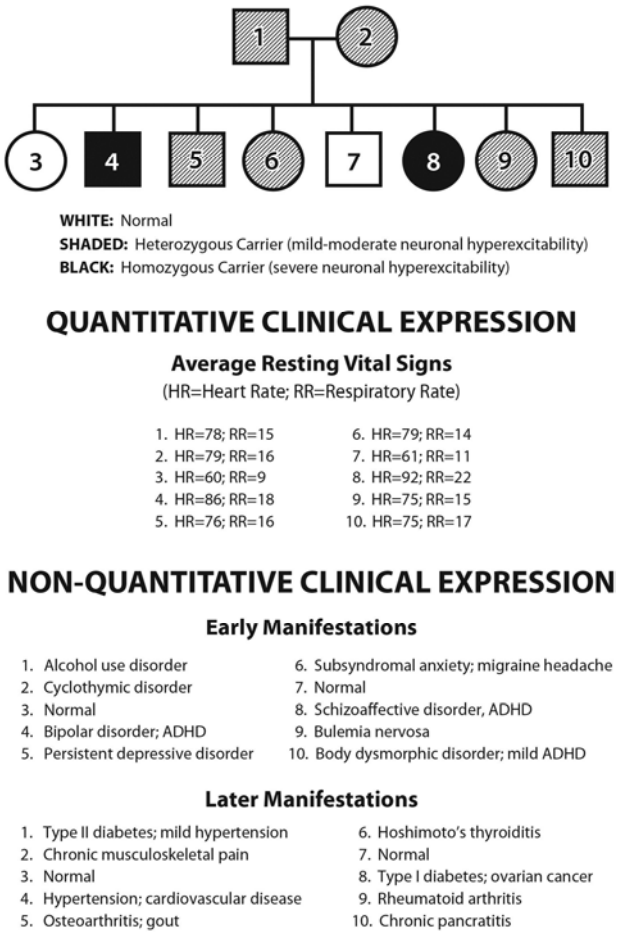

Figure 3. *Representative family pedigree illustrating the autosomal dominant inheritance pattern of the neuronal hyperexcitability trait together with resting vital signs and some of the possible early and late-onset phenotypic expressions of the trait. Note that some heterozygous carriers may have mental or emotional symptoms that are too subtle to meet formal criteria for one of the currently recognized psychiatric disorders. However, because the expression of the neuronal hyperexcitability trait is additive, descendants who inherit two alleles will typically develop more obvious symptoms and, thus, be more likely to meet formal diagnostic criteria. Homozygous carriers also tend to develop psychiatric symptoms at an earlier age than heterozygous carriers. The same tendencies are observed with the medical conditions that these individuals are prone to developing. Pedigree is based on more than three hundred consecutive family histories.*

The aforementioned associations are also corroborated by both objective and subjective clinical observations. A rapidly growing body of literature has uncovered a link between subtle elevations in resting heart and respiratory rates and the subsequent development of a wide range of general medical conditions [68]. Similarly, psychiatric disorders have been found to be associated with subtle elevations in resting respiratory rate [69]. Although less well studied in relation to resting heart rate, psychiatric disorders have long-been associated with autonomic dysregulation [70-72], and most persons with severe mental illness die of the same kinds of diseases as the general population [70, 73]; however, for unknown reasons, they die at a much earlier age [70, 73].

Although the pathophysiology of mental illness remains unclear, 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 [74], 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; and persistent firing in autonomic circuits causes persistent elevations in heart and respiratory rates [68]. Note, however, that unless the system were under stress, the vital-sign elevations (like the psychiatric symptoms) would be subtle…almost imperceptible. Indeed, the vital-sign elevations that have been linked to the development of various psychiatric and general medical conditions are not outside the normal range but rather on the upper end of normal [68]. Thus, it seems plausible that an inherent hyperexcitability of the neurological system could be driving both the vital-sign elevations and the illnesses they forecast. Also, the idea that mental disorders and physical disorders are rooted in the same physiological abnormality could help explain why persons with severe mental illness tend to die at an earlier age than the general population.

Although extensive data from family, twin, and adoption studies indicate that psychiatric disorders and their common comorbidities have a significant genetic component, individual disorders fail to show a consistent pattern of inheritance. However, if one considers the varying degrees to which the trait for neuronal hyperexcitability 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 psychiatric symptoms but on overt and soft signs of neuronal hyperexcitability, such as hyper-emotionality, mood instability, sleep abnormalities, attentional problems, functional somatic symptoms, and substance use disorders, a consistent pattern of distribution emerges; that pattern is strikingly autosomal dominant (Figure 3). The validity of this observation is supported by the additional observation that a predictable proportion of

individuals in these families seem to be resistant to developing psychiatric symptoms irrespective of how dysfunctional their family dynamics might be (Figure 3). These so-called "survivors," who appear in a classic autosomal recessive distribution, are not necessarily more mentally tough than their siblings but rather 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 individuals are also relatively resistant to physical illness suggests that among the variables that contribute to the development of disease, the trait of neuronal hyperexcitability may be the most important. Additionally, the autosomal dominant pattern of inheritance and sharp clinical distinction between those who hypothetically inherent the susceptibility genes and those who do not suggest that most of the candidate genes that have been linked to chronic mental and physical illnesses make small contributions in comparison to a few genes that make large contributions and may by themselves be enough to markedly increase one's vulnerability to developing a chronic illness. What this implies is that de-stressing the system with an anticonvulsant drug like gabapentin may have the potential to prevent the same kinds of illnesses that chronic stress tends to precipitate. This is particularly applicable to those whose neurological systems are inherently hyperexcitable and suggests that for such individuals the long-term use of an anticonvulsant, especially if combined with habits and activities that have a calming effect on the nervous system, may be protective against the development of a wide range of chronic diseases.

Considering all the adverse effects that neuronal hyperexcitability can have on health, it is not surprising that gabapentin, a drug that reduces neuronal excitability, can be beneficial for such a wide range of symptoms and conditions.

4. Safety and Utility

Gabapentin is generally well-tolerated and has excellent long-term safety in comparison to some of the other drugs in its class. The most commonly reported side effects of gabapentin are dizziness or spaciness, which occur in approximately 20% of patients but generally resolve after a few days at a steady dosage. Tiredness can also occur, but this can be avoided by limiting the dosage, and the risk of suicidal thoughts or behaviors is estimated to be around 1 in 200 cases [75]. The drug rarely causes any sexual side effects, and weight gain is reported in less than 10% of cases. Other possible side effects, reported only rarely, include nausea, muscle spasms, and peripheral edema. There is generally no need for laboratory monitoring, and gabapentin is conspicuous among anticonvulsants for its lack of clinically relevant drug interactions, an advantage that is made possible by its lack of hepatic metabolism. Gabapentin is rapidly eliminated through the kidney, having a half-life of approximately 4.8 to 8.7 hours [76].

Based on this relatively benign side effect profile and extensive clinical experience among prescribers, gabapentin had long-been considered to be relatively safe and non-addictive. In recent years, however, an exponential rise in gabapentin prescribing has become coupled with an increase in the illicit use of the drug. Gabapentin is increasingly being found at the scene of drug raids and in the toxicology reports of persons who have died of opioid overdose [4]. This has caused authorities to begin to question the safety of gabapentin. Though it is difficulty to disentangle the effects of gabapentin from the effects of opioids, alcohol, benzodiazepines, and other respiratory depressants that are commonly involved in overdose deaths, the FDA has required the manufacturers of gabapentinoids (gabapentin and its closely-related analogue pregabalin) to include new warnings about the potential of these drugs to cause respiratory depression. A few states have even gone so far as to change the status of gabapentin to a Controlled Substance (pregabalin is already Controlled), and, in an effort to help prescribers ensure that patients are not receiving duplicate prescriptions, a few other states are now requiring gabapentin dispensing information to be uploaded onto the Prescription Monitoring System. As of this writing, neither the DEA nor the CDC have issued any warnings about gabapentin, but in December, 2019, the FDA, out of an abundance of caution, warned that gabapentinoids could cause serious breathing problems in persons who have concurrent respiratory conditions or who use gabapentinoids in conjunction with other CNS depressants.

On the flip side of the controversy is the question of why the use of gabapentin is skyrocketing, not only among patients but among illicit users as well. Undoubtedly, part of the answer is that doctors are prescribing it more and more as a safer alternative to narcotic pain medication. When used alone in persons with normal breathing, gabapentin poses little risk of life-threatening respiratory depression. This is in contrast to opioids, which, even in otherwise healthy individuals, pose a risk of respiratory arrest. However, safety alone would not explain the rise in gabapentin's non-prescription use. The more likely explanation for this rise is that it actually does work for pain…and perhaps other things. One of those other things appears to be substance use disorders, particularly those involving other drugs that have anticonvulsant effects, such as alcohol and marijuana. Thus, it could be that gabapentin is acting as a safer, less addictive anticonvulsant. More commonly referred to in psychiatry as "mood stabilizers," anticonvulsants are well-known to be effective for a wide range of psychiatric disorders, from generalized anxiety to bipolar disorder [77-79]. Moreover, these disorders are known to be highly comorbid with substance use disorders [80]. Hence, in addition to relieving physical pain, gabapentin could be relieving some of the psychiatric symptoms that drive users to use addictive drugs in the first place. Gabapentin may also be a less expensive substitute for a user's drug of choice, and it may ease the withdrawal from alcohol, benzodiazepines, opioids, and other drugs that are more difficult to discontinue abruptly.

Another possible explanation for gabapentin's rising illicit use is that it purportedly makes some users "high." This has

been reported with gabapentin use alone and in combination with other drugs [81, 82]. Part of the challenge in determining the significance of this is that the word "high" means different things to different people, and only about 15% of users report experiencing this effect [81]. While it is possible that there is some yet-to-be-discovered pharmacological mechanism behind this, it is more likely that some users are equating the therapeutic effects of gabapentin (and possibly some of the side effects) with effects that they have experienced from other drugs they have used. For example, gabapentin may be reducing some of the anxiety and agitation that can accompany the use of cocaine, methamphetamine, and other psychostimulants, thereby increasing the beneficial effects or "high" that they experience from these drugs. Also, in addition to its calming effects, gabapentin is well-known to cause spaciness, dizziness, and sedation, especially at higher doses. Thus, it could be that some users equate these effects with the clouding of the sensorium, sedative effects, and mild euphoria that they experience from opioids. Interestingly, the percentage of patients who experience dizziness and sedation from gabapentin is approximately the same as the percentage of opioid users who say that they have used gabapentin "to get high" [81].

Another factor to consider is the route of administration. In addition to using larger amounts of gabapentin than would normally be prescribed by a physician, illicit users may pulverize and snort the drug [81]. Reccoppa et al. [82] provided case reports of inmates in the Florida State Department of Corrections who described achieving an altered mental state or "high" by snorting gabapentin. However, gabapentin is not the only supposedly non-addictive drug with a history of misuse in the prison system. Pierre et al. [83] described inmates in the Los Angeles County Jail who either snorted or used quetiapine intravenously to obtain its potent sedative and anxiolytic effects. Inmates across the United States refer to quetiapine as "quell," "Susie Q," or "baby heroin" [84, 85]. Like gabapentin, quetiapine calms the brain, but unlike gabapentin, it does so via its antihistaminergic and antidopaminergic effects. Other "non-addictive" medications that have developed a reputation for misuse in the correctional system include olanzapine, benztropine, trihexyphenidyl, buspirone, bupropion, and the tricyclic antidepressants [86]. Again, these drugs are purportedly misused for their sedative effects, mind-altering effects, or potential to induce a "high" [86]. When considered in the context of what illicit users say about these other widely-prescribed, non-controlled medications, it becomes more evident that gabapentin, like these other medications, may simply be a good drug in the wrong hands…or perhaps desperate hands. Statistics show that at least 50% of prison inmates have some form of mental illness [87], and so it is not surprising that they would try anything to relieve their anxiety, depression, insomnia, and other psychiatric symptoms.

Although the concerns about the illicit use of gabapentin are certainly warranted, the medical community must be careful not to allow those concerns to prevent a thorough inquiry into the physiological mechanisms by which users may be deriving symptom relief from gabapentin (and other drugs that they use). Based on the hypothesis that an inherent hyperexcitability of the neurological system is at the root of a wide range of mental, emotional, and physical conditions, any intervention that quiets the nervous system, whether it be pharmacological or non-pharmacological, addictive or non-addictive, could, hypothetically, provide symptom relief to the user.

The oldest known of these interventions is the anticonvulsant drug, alcohol. The ability to access alcohol likely predates human civilization, as the process of fermentation is completely natural. Among some of the oldest artifacts of alcohol fermentation, dated to around 7,000 BC, are jars found in a Neolithic village in Northern China that revealed traces of a mixed alcoholic beverage [88]. Similar evidence of alcohol production has been found in Iran (5,000 BC), ancient Egypt (3,150 BC) [89], and pre-Hispanic Mexico (2,000 BC). The medicinal use of alcohol was mentioned in Sumerian and Egyptian texts dating from around 2100 BC, and the Hebrew Bible recommended giving alcohol to those who were dying or depressed "to help them remember their misery no more" (Proverbs 31: 7-7). Alcoholic spirits and elixirs continued to be used medicinally since that time, and during the prohibition, prescriptions for alcohol were sought to treat a variety of ailments including excessive worry, prolonged grief, chronic pain, surgical pain, high fever, and seizure control (Figure 4). Notwithstanding its toxic and withdrawal effects, the beneficial effects of alcohol were so well-recognized that it was referred to as "the water of life." Most of alcohol's beneficial effects are thought to be mediated through its ability to quell the neurological system (i.e., its anticonvulsant effects).

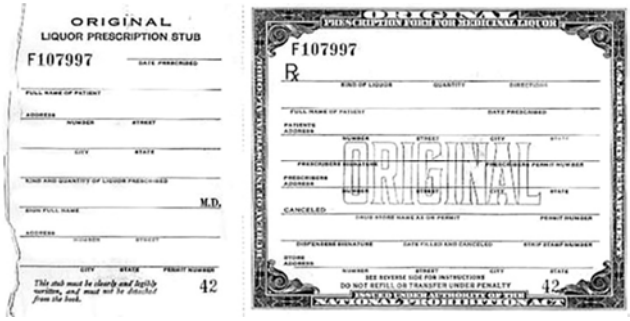

Figure 4. *Original liquor prescription stub. Courtesy of the Rex D. Davis Historical file, ATF Reference Library and Archive.*

The second oldest pharmacological intervention is cannabis. Like alcohol, constituents of the cannabis plant have powerful anticonvulsant effects, and cannabis was used medicinally since ancient times for a variety of ailments [90]. Today, so-called "medical marijuana" is steadily growing in popularity as the miracle cure for everything from migraine headaches to multiple sclerosis, and psoriasis to cancer [91]. Though most of the emphasis has been on cannabinoid receptors type 1 and 2, cannabinoids actually have low affinity for these receptors [90, 92]. Also, with the exception of Δ9-tetrahydrocannabinol, cannabinoids have antagonistic

effects at the type 1 receptor, thus predicting that they would *increase* rather than decrease neurotransmission via this receptor. This paradox has caused scientists to search for other molecular targets to explain the neuroregulatory effects of cannabinoids. What this search has found is that the primary brain-calming constituent of cannabis, cannabidiol (CBD), shows a preference for ion channels that regulate neuronal excitability. Specifically, CBD has high affinity for the transient receptor potential vanilloid (TRPV) channel, which has a high Ca^{2+} permeability and is involved in the modulation of neuronal excitability [93, 94]. When active, this channel promotes the release of the excitatory neurotransmitter glutamate and the movement of calcium ions into the cell, both of which increase the excitability of the neurological system. CBD (in contrast to Δ9-tetrahydrocannabinol, anandamide, and pro-inflammatory agents [94]) deactivates these channels, thereby reducing neuronal excitability [93]. Another ion channel with which CBD interacts is the T-type calcium channel. This channel, which normally destabilizes the neuron upon opening, is blocked by CBD, thus providing another mechanism by which CBD can reduce neuronal excitability [93]. Other molecular targets of CBD include the G-protein-coupled receptor (GPR55), two subtypes of serotonin receptors, and the Mu and Sigma opioid receptors, all of which provide additional mechanisms by which CBD can exert its neuromodulatory effects [93].

Another anticonvulsant that is being used for a wide range of health conditions is topiramate [95]. Introduced in 1996 under the brand name Topamax, topiramate reduces neuronal excitability by several mechanisms, including state-dependent inhibition of voltage-gated sodium channels, inhibition of high-voltage–activated calcium channels, inhibition of glutamate-mediated neurotransmission at α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid and kainate receptor subtypes, and enhancement of γ-aminobutyric-acid-receptor–mediated chloride flux [96]. The drug is FDA-approved for the treatment of focal and generalized seizures and for migraine headache prophylaxis [95]. However, it is also used off-label to treat obesity [97], eating disorders [98-100], bipolar disorder [101-105], rapid cycling mood disorders [106-109], schizophrenia [110, 111], obsessive-compulsive disorder [112], post-traumatic stress disorder [113], Tourette's syndrome [114], psychotropic drug-induced weight gain [95], alcohol dependence [115], cocaine addiction [116], and borderline personality disorder [117]. As with gabapentin, alcohol, and cannabis, most of the disorders for which topiramate brings symptom relief are neuropsychiatric in nature. The same is true for other anticonvulsant drugs, such as depakote, carbamazepine, oxcarbazepine, lamotrigine, tiagabine, levetiracetam, benzodiazepines, barbiturates, and the anticonvulsant-like drug lithium [77, 78]. Another broadly effective class of psychotropic drugs, the antipsychotics, likewise have brain-calming effects, but, as previously stated, they exert these effects through different mechanisms than anticonvulsant drugs. Notwithstanding the fact that some of the aforementioned drugs are either too toxic or addictive to be used therapeutically, their shared effectiveness in treating a wide range of neuropsychiatric symptoms is consistent with the hypothesis that nearly all neuropsychiatric disorders are rooted in neuronal hyperexcitability [74, 77].

Moreover, the importance of the neuronal hyperexcitability hypothesis extends beyond neuropsychiatric disorders. Epidemiological and longitudinal studies suggest that neuropsychiatric disorders are early markers of an increased vulnerability to the development of a wide range of general medical conditions, such as diabetes, high blood pressure, cardiovascular disease, autoimmune diseases, dementia, and cancer [68]. Also, as previously mentioned, the persons who are the most vulnerable to developing these conditions have an inherent elevation in their resting heart and respiratory rates [68]. This leads back to the hypothesis that the same physiological abnormality that is driving the vital-sign elevations is driving the various neuropsychiatric and general medical conditions of which they are predictive. That begs the question: if neuronal hyperexcitability were at the root of all these conditions, then why can't anticonvulsant drugs be used to treat all of them? The answer lies in the pathogenesis of disease.

5. Acute Vs. Delayed Manifestations of Neuronal Hyperexcitability

Unlike the cognitive and emotional effects of neuronal hyperexcitability, which, because they are exquisitely sensitive to neuronal excitation, occur very quickly, the erosive effects occur very slowly, generally over several decades. However, they occur more rapidly than normal because neuronal hyperexcitability can cause any system of the body to overreact. Hyperexcitable neurons can cause the skeletal muscular system to overreact, leading to chronic muscle tension [118, 119]; they can cause the digestive system to overreact, leading to irritable bowel symptoms [120]; they can cause the immune system to overreact, leading to autoimmune diseases [121, 122]; they can cause the endocrine system to overreact, leading to pathological elevations in insulin, cortisol, and catecholamines [123]; and they can cause the cardiorespiratory system to overreact [124, 125], which, besides increasing the risk heart disease and asthma [68], can drive the previously mentioned elevations in resting heart and respiratory rate [68].

Thus, over time, the excess strain on the system that is caused by untreated neuronal hyperexcitability can lead to the development of physical abnormalities that become increasingly irreversible and unresponsive to subsequent treatment with anticonvulsant drugs (more aptly called "Neuroregulators" because of their proposed mechanism of action). For example, chronic muscle tension can, over many years, lead to the development of hypertonic spasm, a chronic state of skeletal muscle hypertonicity that has been hypothesized to be at the root of most chronic musculoskeletal pain [126, 127]. Likewise, chronic hyperactivity of the immune system can eventually cause autoantibodies to

irreversibly damage various organs and tissues of the body, such as the thyroid gland, leading to thyroidopathies; the pancreas, leading to diabetes mellitus; the bowel, leading to inflammatory bowel disease; the joints, leading to rheumatoid and osteoarthritis [128]; and the nervous system, leading to multiple sclerosis and other neurodegenerative diseases.

Evidence of the ill effects of chronic neuronal hyperexcitability on heart health was first observed in the 1950s when a longitudinal study found that specific personality traits, defined as the "Type A Personality," more than doubled the risk of coronary heart disease [129]. First described by cardiologists Meyer Friedman and Ray Rosenman after an upholsterer called to their attention the peculiar fact that the chairs in their waiting rooms were worn out only on the front edge, the Type A Personality was characterized as over-ambitious, competitive, domineering, impatient, and fast-talking [129]. Also predictive of cardiac events, independently, were depression, anxiety, or both [130]. All of these are expressions of the neuronal hyperexcitability trait [68, 74], an observation that reiterates the idea that the physical abnormalities that are driven by neuronal hyperexcitability are rooted in the same physiological abnormality as the emotional and behavioral abnormalities…only their manifestation is delayed. Unlike the mental, emotional, and behavioral expressions of neuronal hyperexcitability, it takes time for the arteries to narrow, their elasticity to be lost, and the other erosive effects of neuronal hyperexcitability to occur. However, once the damage is done, it is difficult to reverse, even if the vicious cycle of stress, metabolic dysfunction, and inflammation were to be attenuated by the administration of Neuroregulators. Hence, in relation to such conditions, Neuroregulators would ideally be used prophylactically—although they could, at any time, still be of much benefit in slowing the progression of disease and preventing the strong emotional reactions that increase the risk of heart attacks and stokes acutely [131]. This is in contrast to purely psychiatric symptoms, which, being rapidly reversible, demonstrate an immediate and robust response to Neuroregulator therapy.

That is not to say that every person with hyperexcitable neurons will go on to develop a chronic medical condition. Rather, it is only to say that among those who do develop a chronic medical condition, an inherent hyperexcitability of the neurological system is likely to be antecedent to it. Consistent with this hypothesis, the total number of patient visits to mental healthcare practitioners is more than twice the number to other specialists [132] …and this despite the fact that most patients attempt to avoid the stigma of mental illness [133].

6. The Value of Early Detection

Notwithstanding the immense value of detecting the trait of neuronal hyperexcitability early in life, Neuroregulator therapy would not be the only way to prevent the early development of disease. Any psychological or physical intervention that reduces neuronal excitability could potentially reduce the risk of developing any of the wide array of psychiatric and general medical conditions that are hypothesized to be driven by the neuronal hyperexcitability trait. Some examples include psychotherapy, meditation, and spirituality, all of which reduce neuronal excitation by reducing intrapsychic tension [134-136]. Other non-pharmacological interventions include judicious stress management [134-137], maintaining an early sleep schedule [138-142], regular exercise [143-147], avoidance of caffeine and other psychostimulants, and minimization of refined sugar [148-151]. The well-established benefits of these practices bear witness to the validity of the neuronal hyperexcitability hypothesis.

7. Assessing the Risk

Figure 5. *Illustration of the abnormally intense magnetic fields that are induced as hyperexcitable neurons, like temperamental bees, over-react when stimulated. Hypothetically, only select circuits would by pathologically hyperactive at any point in time.*

The relative risk of suffering any of the psychiatric or medical consequences of neuronal hyperexcitability would hypothetically vary in relation to the degree of neuronal excitability and the degree of an individual's cumulative exposure to psychological, emotional, and physiological stress. Stressing a hyperexcitable neurological system would be like throwing stones at a beehive in which the bees (the neurons) were abnormally temperamental (Figure 5). Persons with higher levels of neuronal hyperexcitability would have more highly temperamental systems. Added to this would be the self-destructive behaviors that neuronal hyperexcitability tends to promote, such as poor dietary choices, overeating, engaging in risky behavior, mismanaging time constraints, staying up late at night, and behaving contentiously in relationships, all of which would further stress the system and further fuel the vicious cycle of stress and ill health.

8. Discussion

Gabapentin, an anticonvulsant, is rapidly becoming one of the most popular prescription drugs in America…and one of the most popular illicit drugs. Though the drug, like other non-benzodiazepine anticonvulsants, is neither a stimulant nor a depressant, its growing popularity among opioid users is raising

concerns that it could, if used in combination with opioids or other respiratory depressants, increase the risk of fatal overdose.

While these concerns are certainly warranted, the flip-side of gabapentin's skyrocketing popularity is that it could be zeroing in on the root cause of nearly all mental, emotional, and physical illnesses. From the perspective of the Neuronal Hyperexcitability Hypothesis of Psychiatric Disorders in conjunction with recent gene association studies, gabapentin is primarily treating the reversible consequences of neuronal hyperexcitability; namely, various psychiatric disorders, substance use disorders, and chronic pain disorders. Though seizure disorders can likewise be driven by neuronal hyperexcitability, they are less common and typically also involve a structural abnormality, thus reducing gabapentin's effectiveness in preventing them. Similarly, the proposed erosive effects of neuronal hyperexcitability, such as chronic musculoskeletal pain, autoimmune diseases, and circulatory diseases, involve physical changes that are relatively irreversible, thus limiting the usefulness of gabapentin (and other anticonvulsants) once extensive pathological changes have occurred. However, the increased propensity of these disorders to develop in persons with mental illness; the increased propensity that they have to develop at an earlier age in persons with more severe mental illness; and the quantitative correlation of the resting vital-sign elevations with these two expressions (i.e., higher elevations in persons with more severe mental illness) strongly suggests that the vital-sign elevations and the mental and physical illnesses of which they are predictive are all rooted in the same physiological abnormality; namely, neuronal hyperexcitability. Stated more succinctly, an inherent hyperexcitability of the neurological system amplifies the body's stress response, thereby increasing one's vulnerability to any illness that is driven by stress. This synthesis of mental and physical illnesses has enormous implications, not only for patients, who, because of the stigma of mental illness, tend to deny their psychiatric symptoms and shy away from seeking mental healthcare, but also for clinicians and payers because it reduces the need to disentangle physical illnesses from mental illnesses. Added to this are the practical benefits of having an easily assessable, objective marker of one's vulnerability to developing virtually any illness, mental or physical. The ability to detect neuronal hyperexcitability by simply measuring one's resting vital signs can allow patients to proactively take control of their health because there are a variety of medicinal (i.e., Neuroregulators) and non-medicinal (i.e., holistic) ways to reduce their level of neuronal excitability. Urgently needed are clinical studies aimed at assessing 1) the effectiveness of Neuroregulators either alone or in combination with other Neuroregulators as first-line therapy for a wide range of psychiatric and substance use disorders; 2) the accuracy of resting vital signs in predicting the development of various psychiatric and substance use disorders; 3) the effectiveness of using Neuroregulators prophylactically in teens who have upper-end-of-normal resting vital signs; 4) the effectiveness of using Neuroregulators long-term to prevent the development of various disease processes; 5) the relationship between variants of the risk gene CACNA1C and resting vital signs; and 6) the effectiveness of prophylactic Neuroregulator therapy in children who test positive for variants of CACNA1C and other risk genes for neuronal hyperexcitability.

9. Conclusion

While the use of gabapentin in combination with opioids and other respiratory depressants is understandably of concern, the rapidly expanding use of gabapentin by both prescription and non-prescription could, at the same time, be signaling the presence of a unifying mechanism in the pathogenesis of disease. Moreover, the idea that the hypothesized vulnerability trait, which could be predictive of a wide range of mental, emotional, and physical illnesses, could be identified with a simple count of breaths and heartbeats could usher in history's greatest campaign in the fight against sickness and disease.

Disclosure Statement

The author declares that this article was conceived and written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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