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A Precision Medicine Approach to the Treatment of Psychiatric Disorders

Michael Raymond Binder, M.D.

Abstract- Due to a lack of clarity about the pathophysiology of psychiatric disorders, short and long-term treatment outcomes continue to be very inconsistent, and the prescribing of multiple medications that can have unpredictable, conflicting, and sometimes paradoxical effects continues to be more the rule than the exception in modern psychiatric practice. Dosing is also an issue, as standard doses of psychotropic drugs are often too high, thus causing some patients to incur unnecessary side effects, which in turn can lead to poor compliance or even discontinuation of treatment. Worse yet, these negative outcomes can cause disappointed patients to dissuade other would-be patients from seeking treatment. Recognizing these concerns and the fact that most persons with mental illness never seek treatment to begin with, the need for greater precision and fewer side effects in the prescribing of psychotropic drugs cannot be overstated. Based on an emerging hypothesis on the pathophysiology of psychiatric disorders, this article will discuss a promising new approach to psychopharmacotherapy that has the potential to simplify drug selection, reduce dosing requirements, and minimize side effects. By targeting the core physiological abnormality in psychiatric disorders, the use of medications that have unpredictable, conflicting, and sometimes paradoxical effects can be minimized, and the lowest doses of the most appropriate drugs can be used to achieve faster, more consistent, and more enduring therapeutic effects in a group of disorders that are now considered to be a public health crisis.

Keywords: neuronal hyperexcitability, psychotropic drugs, antidepressants, antipsychotics, psychostimulants, anticonvulsants, mood stabilizers, neuroregulators, mental health, medication side effects, mental health crisis, preventive medicine.

I. INTRODUCTION

Due to a lack of clarity about the pathophysiology of psychiatric disorders, treatment outcomes in psychiatry continue to be very inconsistent [1, 2], and the prescribing of multiple medications that can have unpredictable, conflicting, and sometimes paradoxical effects has become more the rule than the exception [3]. Many patients are also confused about their diagnosis and how it relates to their treatment. Of equal concern is the fact that most patients who need psychiatric care fail to seek care. Based on data from the Mental Health Million project [4], which polled the English-speaking population of 10 countries, 58% of those questioned did not seek help for clinically

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apparent mental health issues. In the United Kingdom, only 50% sought help, and in the United States, only 45% sought help. The possible reasons for these low numbers include limited access to care, insufficient financial resources, failure to recognize one's need for care, lack of confidence in the benefits of care, the stigma of mental illness, and fear of taking psychotropic drugs [5]. This last reason—fear of taking psychotropic drugs—usually centers around concerns that such drugs could cause a change in personality, a worsening of symptoms, debilitating side effects, or social stigma. Therefore, with all of these concerns looming in the mind of the patient, it is incumbent upon clinicians to clearly explain what pathological process they are treating when they prescribe psychotropic medication. Clinicians should also strive to minimize both the number of medications and the side effects of those medications. However, the problem that clinicians face is that the underlying cause of most psychiatric disorders remains unclear. Consequently, they can neither visualize what they are treating nor can they properly explain to patients what they are treating.

This article will discuss a promising new approach to psychopharmacotherapy that, based on new insights into the pathophysiology of psychiatric disorders, has the potential to guide better patient education about treatment, improve the quality of treatment, and minimize the side effects of treatment. By targeting the core physiological abnormality in psychiatric disorders, the use of drugs that have unpredictable, conflicting, and sometimes paradoxical effects can be replaced by drugs that, being directed squarely at the biological target, can achieve faster, more consistent, and more enduring therapeutic effects.

II. BACKGROUND OF PSYCHOTROPIC DRUG SELECTION

Historically and still today, the medical treatment of psychiatric disorders is primarily symptom-based rather than pathology-based. This is the unfortunate consequence of a lack of consensus on the pathophysiology of psychiatric disorders. Although many behavioral health experts believe that most of the common psychiatric disorders, such as generalized anxiety disorder, major depressive disorder, bipolar disorder, and schizophrenia, are rooted in a shared biological abnormality [6-9], there are still many who

believe that each psychiatric syndrome has its own unique biological underpinnings [10]. The need to better understand these disorders has become imperative, as the effectiveness of treatment is lagging far behind the escalating mental health crisis. Thus far, the only psychiatric disorder for which there has been a consensus opinion is clinical depression, for which the monoamine hypothesis has guided the use of antidepressants for more than fifty years [11]. Over the past decade, however, even this hypothesis has been called into question because of its failure to explain several important observations. First, it fails to explain how antidepressants can be effective in the treatment of psychiatric disorders other than clinical depression [12]; second, it fails to explain why a depletion of serotonin precursors does not produce depression symptoms in healthy subjects [13]; third, it fails to explain why antidepressants can sometimes cause a paradoxical worsening or cycling of symptoms [14-18]; and fourth, it fails to explain how the putative abnormalities in monoamine transmission actually translate into depressive symptomatology [19].

However, an emerging hypothesis offers answers to these questions and supersedes the monoamine hypothesis by providing the first neuropsychiatric explanation for a wide range of psychiatric disorders and related clinical observations. According to the multi-circuit neuronal hyperexcitability (MCNH) hypothesis, psychiatric symptoms, irrespective of their symptom-based diagnosis, are caused by pathological hyperactivity in the associated neuronal circuits [20]. Thus, for example, pathological hyperactivity in anxiety circuits causes elevated and persistent feelings of anxiety; pathological hyperactivity in depressive circuits causes elevated and persistent feelings of depression; and pathological hyperactivity in cognitive circuits causes racing thoughts and obsessive thinking [20]. The most common cause of this hyperactivity is thought to be cognitive-emotional stress, as tension in the mind, like stones being thrown at a beehive, has an agitating effect on the brain. According to the MCNH hypothesis, this agitating effect is abnormally amplified when the neurons of the brain, like irritable bees, are inherently hyperexcitable [19]. This would not only explain many observations that the monoamine hypothesis does not [11, 21], but it would also incorporate the effects of brain structure [22], brain physiology [19, 20], brain circuitry [20, 23], and mind-brain dynamics [19] to explain virtually every phenomenon that has been observed clinically in psychology and psychiatry [22-27]. It would also explain why there is so much overlap between symptom-based psychiatric diagnoses [22], and why the same medications can often be used to treat multiple psychiatric syndromes [28, 29].

III. TOWARD A PATHOLOGY-BASED APPROACH TO TREATMENT

What the MCNH hypothesis suggests is that a wide range of psychiatric disorders, including generalized anxiety disorder, major depressive disorder, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder, attention deficit hyperactivity disorder, and schizophrenia, could be treated by simply reducing the excitability of the neurological system. Although the use of anticonvulsants had traditionally been relegated to the treatment of bipolar disorder [30, 31], the added ability of these drugs to treat a wide range of psychiatric disorders is illustrated by three significant advances in psychiatry: 1) the establishment of bipolar spectrum disorders as a dimensional diagnosis [7, 8]; 2) the recognition that anticonvulsants are the drugs of choice for all disorders in the bipolar spectrum [32]; and 3) the rapid antidepressant effects of ketamine [33, 34] and zuranolone [35-37], both of which have potent brain-calming effects. Still, that raises the question of why it has taken so long to recognize the broad applicability of anticonvulsants.

The answer lies in the flood of excitement that was created when the antidepressant effect was serendipitously discovered in the 1950s. An Associated Press release from Staten Island's Seaview Hospital, where the mood-elevating effect of anti-tuberculin drugs was first recognized, captured a telling scene: patients dancing in celebratory mood [38]. Some of the patients, who were still in quarantine for tuberculosis, were feeling so good emotionally that they wanted to leave the hospital against medical advice. In other words, the antidepressant effect of isoniazid was not just normalizing mood; it was elevating mood to the point of affecting judgement. Nonetheless, the impressiveness of the effect and subsequent acceptance of the monoamine hypothesis as a neurochemical explanation for the effect caused it to be heralded as a medical breakthrough. Subsequently, clinicians became strongly entrained to prescribe antidepressants for almost any patient who presented with depressive symptomatology.

However, consistent with the idea that antidepressants were causing a subtle, mood-related distortion of judgment, their use was also found to increase the risk of switching from depression to mania in some patients [15-18]. Based on evidence that this risk was greatest in patients with bipolar disorder [14-18], concerted efforts were made to distinguish bipolar disorder from unipolar depression [7, 39-41]. The problem is that these two disorders can be indistinguishable, at least until the first manic phase of bipolar disorder occurs. Even then, the diagnosis can be delayed because mania itself often evades detection. The difficulty of making an accurate diagnosis is illustrated by the fact that the average patient with bipolar disorder is misdiagnosed with unipolar

depression for years or even decades before the correct diagnosis is made [42-44]. The risk of misdiagnosis is even greater for those with milder forms of bipolar disorder, such as bipolar II disorder, cyclothymic disorder, and cyclic depression, and it is conceivable that many such patients are never correctly diagnosed. This is a matter of grave concern because, in addition to causing bipolar switching, antidepressants can worsen the course of disorders in the spectrum, sometimes with disastrous consequences [14, 40].

Fortuitously, the challenge of distinguishing bipolar spectrum disorders from unipolar depression can be circumvented by applying the MCNH hypothesis because the hypothesis is pathology-based rather than symptom-based. Treatment is aimed at reducing the excitability of the neurological system rather than specific symptoms. By addressing the root cause of psychiatric symptoms, all of the symptoms, including symptom-cycling, can be reduced simultaneously. According to the MCNH hypothesis, symptom-cycling is the consequence of aberrant circuit induction, a kind of neurological short-circuiting that occurs when pathologically hyperactive feeder circuits stimulate activity in circuits that would normally be less active [20, 22, 23]. Persons with inherently hyperexcitable neurological systems have a tendency to cycle both because their neuronal circuits have a propensity to become pathologically hyperactive and because their relatively hypoactive receiver circuits are themselves hyperexcitable. Also, because the frequency with which symptoms cycle would depend upon the total number of neuron-to-neuron connections, the MCNH hypothesis would predict that those patients with the most neurons would be the most rapid cyclers, whereas those with the least neurons would be the least rapid cyclers [22]. Patients with an intermediate number of neurons could experience cycles within cycles [22, 45, 46]. It is also possible that some cognitive-emotional states, such as intense grief, could keep the locus of hyperactivity stuck in one specific firing pattern, thus tending to prevent symptoms from cycling [19, 22]. Thus, using the MCNH hypothesis, it would not be the frequency of cycling nor even the presence of cycling that would guide medication selection but, rather, the excitability of the neurological system.

IV. HOW TO IDENTIFY THE NEURONAL HYPEREXCITABILITY TRAIT INDEPENDENT OF PSYCHIATRIC SYMPTOMATOLOGY

Although the ability to identify the neuronal hyperexcitability trait independent of psychiatric symptomatology had previously been lacking, an explosion of recent studies has identified an association between resting vital-sign measurements and the later development of various psychiatric conditions. In a longitudinal study involving more than one million men in

Sweden, Latvala et al. [47] found that subtle elevations in resting heart rate (RHR) were predictive of the later development of generalized anxiety disorder, obsessive-compulsive disorder, and schizophrenia. Similarly, Blom et al. [48] found that adolescent girls with various emotional disorders had increased resting respiratory rates (RRR) in comparison to healthy controls. Persons with higher resting heart and respiratory rates have also been found to be at increased risk of developing a wide range of chronic medical conditions, including diabetes [49-52], high blood pressure [53-55], cardiovascular disease [56-61], cancer [62-64], dementia [65], and all-cause mortality [62, 66]. The subtle vital-sign elevations with which these disease processes are associated are thought to be the consequence of a tonic elevation in basal neurological activity in persons who inherit the genes for neuronal hyperexcitability [25]. In other words, neuronal hyperexcitability could be at the root of a wide range of chronic medical conditions in addition to various psychiatric conditions. Hypothetically, the reason that psychiatric symptoms tend to precede the development of diagnosable physical abnormalities is that the cognitive-emotional system is more expressive of neuronal excitation than other organs and systems of the body [67]. The physical consequences tend to be delayed because they express the gradual erosive effects of neuronal hyperexcitability, which can take years or even decades to occur [25, 68, 69]. The fundamental mechanism by which neuronal hyperexcitability is thought to drive these erosive effects is the same as that by which it is thought to drive the elevated vital signs: hyper-activation of the sympathetic nervous system [25]. Chronic sympathetic dominance, which maintains the body in a catabolic state, accelerates the aging process and increases one's vulnerability to every disease process that chronic stress can drive. It has been estimated that, in the absence of any significant cardiorespiratory disease, confounding medications, or substances of abuse, an RHR above 75 beats/min or an RRR above 15 breaths/min is indicative of the neuronal hyperexcitability trait [22, 25]. In addition to providing an objective method of identifying the neuronal hyperexcitability trait, the association between resting vital signs and chronic illness could help explain why the lifespan of persons with severe mental illness tends to be so much shorter than the general population [25, 68, 69]. It also suggests that, in addition to reducing psychiatric symptoms, reducing the excitability of the neurological system could help postpone or even prevent the development of a wide range of chronic diseases. This idea is supported by the anecdotal observation that effective treatment with anticonvulsants frequently lowers resting heart and respiratory rate measurements quite significantly.

In addition to simplifying diagnostics and guiding treatment, the MCNH hypothesis predicts that the vast majority of persons who struggle with

psychiatric symptoms have relatively high levels of neuronal excitability. This follows from the fact relatively minor stressors, which would be sufficient to precipitate psychiatric symptoms in persons with higher levels of neuronal excitability, are experienced much more often than the unusually high stressors that would be necessary to precipitate psychiatric symptoms in persons with lower levels of neuronal excitability [70]. Persons with higher levels of neuronal excitability would be more sensitive to stress both because their hyperexcitable neurons would abnormally amplify stress and because, over time, their hyperexcitable neurons would accelerate stress-induced kindling [19, 22]. Persons with higher levels of neuronal excitability would also be more likely to experience symptom-cycling because highly excitable neurons would have a greater propensity to facilitate aberrant circuit induction [23]. Treatment with antidepressants would further increase this risk because antidepressants (including SSRIs) have stimulatory effects on the brain [71, 72]. Hypothetically, this is what places such patients, who could be categorized as “bipolar spectrum,” at elevated risk for bipolar switching when treated with antidepressants. The more appropriate drugs for such patients would be anticonvulsants. Yet, because the symptom-cycling in such patients is often subclinical [42-44], and because neuronal hyperexcitability also tends to cause symptoms of ADHD [22], the vast majority of such patients are treated with antidepressants and psychostimulants. What creates even more confusion is that these drugs do tend to reduce symptoms, at least until the kindling that they fuel increases the overall level of excitation in the brain enough to offset their therapeutic effects [72, 73]. Until now, the failure to recognize this and the continued treatment of symptoms rather than neuropathology in psychiatric patients has resulted in the over-prescribing of antidepressants, psychostimulants, and other psychotropic drugs in lieu of anticonvulsants [28]. That is not to say that antidepressants are never helpful but only to say that they are more appropriate for the minority of patients who do not have hyperexcitable neurons. Such patients, who could be categorized as “true” unipolar depressives because of their relative resistance to symptom-cycling would, for the same reason, be unlikely to cycle even when treated with stimulating antidepressants. This is the MCNH explanation for why treatment with antidepressants has generally been found to be safer in patients with unipolar depression [74] than bipolar spectrum disorder [32, 75, 76]. However, considering the rarity of true unipolar depression in comparison to the high frequency with which antidepressants are prescribed [22, 77], the MCNH hypothesis also points to the weakness of symptoms alone as a guide to psychiatric pharmacotherapy.

Clearly, the idea of treating nearly all of the common psychiatric disorders by reducing the excitability of the neurological system would simplify drug selection because it would highlight a biological target for which the treatment is evident. Thus, rather than chasing after specific symptoms with different classes of medication, such as anxiety symptoms with benzodiazepines, depressive symptoms with antidepressants, and psychotic symptoms with antipsychotics, a single non-benzodiazepine anticonvulsant or combination of anticonvulsants could be used to reduce all of these symptoms simultaneously. Note that in addition to simplifying drug selection and reducing medication load, this approach, which could be called “focused neuroregulation [78],” would circumvent the problem of ambiguous and overlapping diagnoses. Additionally, by reducing the total number of medications prescribed and replacing many brand-name drugs with generic ones, focused neuroregulation has the potential to reduce the side effect burden, medication costs, and conflicting effects that combining drugs from different classes can create. It also has the potential to simplify drug titration because anticonvulsants, which, based on their putative mechanism of action, could more aptly be called “neuroregulators” [79], exert their therapeutic effects in minutes rather than weeks. That means a patient could be started on a neuroregulator at an extremely low dosage and then titrated upward every one-to-two days rather than one-to-two weeks, as would be necessary with an antidepressant. It also means that any drug that was ineffective could be replaced much faster than when a drug takes several weeks to take effect. Moreover, because neuroregulators work to normalize brain function rather than modulate the activity of specific neuronal circuits, they can be combined with one another with relatively little risk of destabilizing mood, hence the term “mood stabilizer” [80-84].

V. MEDICATION DOSING

The overprescribing of psychotropic drugs is not the only problem that begs to be addressed in modern clinical practice. The other is the dosing of psychotropic drugs. There are numerous factors that contribute to determining the optimal dosage of a medication for an individual patient. These include absorption and distribution, mechanism of action, receptor affinity, and metabolism and excretion. Although absorption and distribution are commonly assumed to be the most important of these, the actual contribution that each factor makes is highly specific to the individual. That underscores the importance of tailoring to the patient the quantity of drug prescribed.

a) *Absorption and Distribution*

Regardless of the quantity of a drug one ingests, the drug remains outside the body until it is absorbed through the intestinal wall. This absorption process can be affected by many factors, including drug solubility, intestinal membrane permeability, digestive enzyme activity, and food intake [85]. Drug absorption can also be affected by a person's emotional state, as stress tends to reduce intestinal absorption [86]. Furthermore, once in the bloodstream, the drug must cross the blood-brain barrier (BBB) before it can bind to its target receptors in the brain. Passage through the BBB can be affected by several factors, including the chemical properties of the drug, whether or not the drug is bound to plasma proteins, and the electrical charge of the drug [87]. While most small lipophilic drugs may cross the BBB by simple diffusion, others may pass through aqueous channels or require either mediated diffusion or active transport. Additionally, only free (non-protein-bound) molecules are available to cross the BBB via transendothelial diffusion, and fat-soluble drugs may be absorbed into fatty tissue, thus reducing their bioavailability. Together, all of these time-dependent factors contribute to the 20-40-minute delay in the onset of action of most medications. Obviously, the route of administration is also important, as absorption can be facilitated by direct inhalation of a drug, chewing and sublingual holding of a drug, or injection of a drug subcutaneously, intramuscularly, or intravenously. Thus, numerous factors can affect the speed and extent to which a drug actually reaches its target receptors.

b) *Mechanism of Action*

Because the number of different pathological processes that can occur in the human body far outnumber the assortment of ways that those processes can be expressed clinically, many different pathological processes can precipitate the same signs and symptoms. This highlights the importance of fit between drug selection and pathological process in determining the dosage requirements of a particular drug. The more that a drug's pharmacological effects can correct, offset, or compensate for the abnormality that is driving the patient's symptoms, the more efficiently the drug will work and, thus, the less of the drug that will be needed to express its therapeutic effects.

c) *Receptor Affinity*

In order for most drugs to exert their therapeutic effects, the molecules of the drug, like keys fitting into locks, must bind to and activate their target receptors. Although most receptors within a species are very similar in size and shape, there are also minor differences, just as there are in one's head-size, hand-size, and foot-size. This can affect the ability of specific drugs to bind to and activate their target receptors. The better the fit between the drug and the receptor, the more likely the drug is to exert its therapeutic effects.

Also, the greater the drug's affinity for the receptor, the less of the drug that will be needed to maintain its therapeutic effect. However, a drug can also cause side effects if it binds to off-target receptors. This underscores the importance of finding the sweet spot when dosing psychotropic drugs.

d) *Metabolism and Excretion*

Immediately after a drug enters the bloodstream, the processes of distribution, metabolism, and excretion begin. Hence, dosing requirements can depend highly on fat solubility, liver enzyme activity, and glomerular filtration rates. Total blood volume and body weight also contribute to dosing requirements; however, these two factors generally pale in comparison to the many other factors that affect the dosing requirements of a drug.

VI. THE NEED FOR INDIVIDUALIZED DOSING

With all of the aforementioned factors influencing the dosage of a drug that is needed to achieve a therapeutic effect and, conversely, unwanted side effects, there is clearly a need for individualized dosing of any drug that is prescribed. Yet most prescribers simply initiate treatment at the "recommended" starting dose or lowest available dosing strength. Clearly, however, this fails to align with the complexity and unpredictability of patient-specific factors. Then again, even if a prescriber were to take into consideration all of the aforementioned factors, there would still be no reliable way to determine how those factors come together to predict the therapeutic dose (and side effect dose) of a given drug for a given individual.

In recent years, however, various new pharmacogenomic tests have been developed to help clinicians determine which medications would be best tolerated by which patients. The problem is that these tests, though genetically-based, fail to incorporate the many other factors besides drug metabolism that influence the dosing requirements of a particular drug for a particular patient. Dosing requirements would also depend upon the degree of fit between the drug's primary mechanism of action and the type of pathology that is being treated. This has been particularly problematic in psychiatry due to the lack of clarity about what pathological process is being treated and the continued reliance on symptoms rather than pathology as a guide to pharmacotherapy. This reiterates the importance of replacing the current (symptom-based) approach to psychiatric diagnosis and treatment with a pathology-based approach.

VII. TOWARD IMPROVING THE PRECISION OF PSYCHOTROPIC DRUG DOSING

With so many variables affecting dosing requirements, the safest and most accurate way to titrate psychotropic drugs, like most other drugs, is to start low and go slow. Another helpful practice is to consider a patient's ethnic background, as some ethnic groups, such as Asians, tend to be slow metabolizers of some drugs [88, 89]. Still, the problem with a gradual titration is that it can delay clinical improvement by weeks or even months because antidepressants, which in psychiatry are the most commonly prescribed drugs, take several weeks to exert their therapeutic effects. This is in-part what drove the development of the new pharmacogenomic tests. It was thought that by coordinating drug selection to a patient's enzyme activity, antidepressant therapy could be initiated at doses closer to the therapeutic dose without significantly increasing the risk of medication side effects. However, as previously discussed, the many other factors that influence dosing requirements besides metabolism can cause the genomic testing results to be misleading. Therefore, it is also important to review the patient's experience with other medications that may have been tried, particularly those in the same class as the proposed medications. This can be very helpful because an individual's sensitivity to medication tends to generalize across drug classes and across medications within a given class. Yet another dosage guide, and one that is seldom utilized, is the history of drug sensitivities in the patient's parents, siblings, and other blood relatives. If high drug sensitivity is found to run in a patient's family, the clinician should allow the patient to fractionate the lowest available dosage of any newly-prescribed medication. If the starting dose is found to be well-tolerated, the patient can simply take a little more of the medication. An added benefit of this conservative approach is that the unlikelihood of side effects gives the patient a little more time to overcome any apprehension about starting a new psychotropic drug. It is far better for a patient to become impatient with a new drug than to become frightened of it due to initial side effects. These simple precautionary measures can, in some cases, make the difference between a successful outcome with a drug and an outcome that leaves the patient unwilling to take any more of the drug or, worse yet, any other psychotropic drug.

Another cautionary note with regard to drug dosing is the use of serum levels. Although obtaining a blood level can be helpful in some cases, blood levels should not be used as a substitute for close clinical monitoring during dosage titration. That's because blood levels do not take into account the possibility that a particular patient may be highly responsive to a drug, thus allowing lower-than-average blood levels to achieve an adequate therapeutic effect. In many cases, these

lower blood levels can prevent the occurrence of side effects without compromising effectiveness because most drugs exert their optimal therapeutic effects at a dosage just below their side effect dosage. Where blood levels are most useful is in the monitoring of patients who, for the various reasons described earlier, require unusually high doses of a particular medication in order to achieve a therapeutic effect. In such cases, obtaining a blood level can be used to justify the need for higher dosing and can also be used to substantiate any suspicions of medication non-compliance or drug diversion. Unfortunately, far too many patients are allowed to bear unnecessary side effects simply because the prescriber felt the need to maintain the serum level within the "therapeutic range."

VIII. DISCUSSION

The goal of this article was to address the problems of diagnostic confusion, psychotropic drug overprescribing, and side-effect burden due to a lack of precision in the treatment of psychiatric disorders. All of these problems could potentially be minimized by applying an emerging hypothesis that contends that psychiatric symptoms are the consequence of cognitive-emotional stress superimposed upon a pathological hyperexcitability of the neurological system. Fortunately, targeting this problem with neuroregulators yields rapid results, thus allowing the medications to be started at comfortably low doses and rapidly titrated to clinical improvement. In so-doing, the risk of side effects is minimized without substantially extending the time to therapeutic effect. Also, by remaining focused on the biological target, focused neuroregulation streamlines treatment, thus circumventing the need to use combinations of drugs that, being directed at symptoms rather than neuropathology, may have competing or even paradoxical effects. Anecdotally, focused neuroregulation has yielded far more improvement, in far less time, and with far less side effects than standard antidepressant therapy in a wide range of psychiatric disorders, including the majority of patients who would, based on current nosology, be diagnosed with major depressive disorder or dysthymia. Moreover, in nearly all of these patients, some of whom have been observed for more than two decades, the initial benefits have been maintained without any need of further dosage adjustment.

Although anticonvulsant neuroregulators are also used to treat epilepsy, the dosage of these drugs can usually be lower when treating psychiatric disorders because the target abnormality, namely neuronal hyperexcitability, is entirely reversible. This is in contrast to seizure disorders, in which the excitability of the neurological system might need to be brought to subnormal levels in order to compensate for the structural abnormality that may be lowering the seizure

threshold. Thus, for example, while the average dosage of oxcarbazepine needed to prevent seizures typically ranges between 600mg and 1200mg per day, the average dosage needed to prevent psychiatric symptoms typically ranges between 150mg and 600mg per day. In fact, some psychiatric patients have been observed to respond to oxcarbazepine doses as low as 50-100mg per day. The same phenomenology has been observed with other anticonvulsants, such as gabapentin, depakote, lamotrigine, and topiramate [90]. Of course, lower dosing is also easier when treating psychiatric disorders because, unlike when treating seizure disorders, the therapeutic effect is observable almost immediately. What's more, anticonvulsant stacking, which is commonly employed in neurology, is not only effective in psychiatry but is apt to be even more effective than in neurology because the target abnormality is entirely reversible. Indeed, it has been said that the potential benefits of anticonvulsants in the treatment of psychiatric disorders may overshadow those that have been observed in the treatment of seizure disorders [91]. Long-term, anticonvulsants may even be protective against the development of various disease states [67, 68].

IX. DIRECTIONS FOR FUTURE RESEARCH

Urgently needed are clinical studies comparing the benefits of focused neuroregulation to standard treatment for a variety of psychiatric disorders. Such studies should also compare the number of different medications needed to control symptoms, the side effect burden of those medications, and the duration of effect of those medications. They should also compare the effect of those medications on resting heart and respiratory rate measurements. If these studies yield promising results, longer-term prospective studies could be performed to assess the potential for early treatment with neuroregulators to delay or even prevent the development of various chronic diseases.

X. CONCLUSION

The well-recognized problems of diagnostic ambiguity, polypharmacy, and side-effect burden in the treatment of psychiatric disorders has the potential to be solved by shifting the treatment of these disorders from a symptom-based approach to a pathology-based approach. Guided by the MCNH hypothesis, neuroregulators could be started at comfortably low doses and then titrated rapidly to clinical improvement. Because neuroregulators work to normalize brain function, they can also be combined with one another just as they are in the treatment of epilepsy. Moreover, because neuronal hyperexcitability tends to dysregulate virtually every system of the body, treatment with neuroregulators could be as medically protective as it is psychiatrically beneficial. With less than half of all

persons who need psychiatric care actually seeking care, and many of those who do seek care shying away from psychotropic medication, the need for better education about what abnormality is being treated and a more targeted approach that uses fewer medications, at lower doses, and with fewer side effects is evident. All of these needs could potentially be met by targeting what is hypothesized to be the underlying driver of mental illness. By seizing this long-awaited opportunity, we can strive toward a future in which behavioral healthcare, like other fields of medicine, is aimed at specific pathological processes, thus streamlining care, speeding recovery, and helping to overcome the long-held stigma of mental illness.

Conflicts of Interest

The author declares that he has no competing interests.

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