CNS Drug Development: Lessons Learned Part 2. Symptoms, Not Syndromes as Targets Consistent with the NIMH Research Domain Approach

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This column is the second in a series exploring lessons for psychiatric drug development that can be learned from the development of 6 central nervous system drugs with novel mechanisms of action over the past 25 years. Part 1 presented a brief overview of the neuroscience that supported the development of each of these drugs, including the rationale for selecting their targets and indications. This column reviews specific principles involved in the development of these 6 drugs that have important implications for the future of psychiatric drug development. These include focusing on efficacy for a specific symptom or behavior rather than a broad syndrome, choosing a target in the brain with a specific behavioral output that is conserved from lower mammalian to human brains, and measuring outcomes based on behavioral phenomena that can be readily measured in an unambiguous parametric way. It is hoped that the Research Domain Criteria initiative of the National Institute of Health will promote research advances consistent with this model. (*Journal of Psychiatric Practice* **2015;21:60–66**)

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In writing the history of a disease, every philosophical hypothesis whatsoever that has previously occupied the mind of the author, should lie in abeyance. This being done, the clear and natural phenomena of the disease should be noted—these, and these only. They should be noted accurately, and in all their minuteness; in imitation of the exquisite industry of those painters who represent in their portraits the smallest moles and the faintest spots. No man can state the errors that have been occasioned by these physiological hypotheses. Writers, whose minds have taken a false color under their influence, have saddled diseases with phenomena which existed in their own brains only; but which would have been clear and visible to the whole world had the assumed hypothesis been true. Add to this, that if by chance some symptom really coincides accurately with their hypothesis, and occur in the disease whereof they would describe the character, they magnify it beyond all measure and moderation; they make it all and in all; the molehill becomes a mountain; whilst, if it fail to tally with said hypothesis, they pass it over either in perfect silence or with only an incidental mention, unless, by means of some philosophical subtlety, they can enlist it in their service, or else, by fair means or foul, accommodate it in some way or other to their doctrines.

Dr. Thomas Sydenham, 1763[1]

This column is the second in a series reviewing the lessons that can be learned from the development of the 6 central nervous system (CNS) drugs with novel mechanisms of action that have been approved over the past 2 decades: ondansetron, aprepitant, ramelteon, varenicline, lorcaserin, and suvorexant. In the first column in this series, I reviewed the neuroscience that supported the development of each drug, including the rationale for selecting a) the target, which in each case was a receptor for a specific neurotransmitter, and b) the indication, which was based on an understanding of the role that that target played in a specific neural

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circuit in the brain. The indications were chemotherapy-induced nausea and vomiting for ondansetron and aprepitant, smoking cessation for varenicline, weight loss for lorcaserin, and insomnia for suvorexant and ramelteon.

Two important lessons can be learned from the development of these drugs: 1) to pick a target for drug discovery based on a knowledge of the appropriate circuitry in the brain, and 2) to pick a single symptom or behavior that is mediated by that target in that brain circuit. Ideally, the target, the circuit, and the behavior should be conserved from lower mammalian species to man, so that the results of animal studies will be readily translatable to the eventual indication in humans.

In reading the first column in this series, some readers may have questioned its relevance since these drugs are CNS active but they are not psychiatric medications. I would counter this concern with 3 points: First, the organ of relevance to psychiatry is the brain and, thus, drugs that work via a mechanism and circuit in the brain are relevant to psychiatry. Second, smoking, weight gain, and insomnia are directly relevant to psychiatry because each of these problems is overrepresented in patients with accepted psychiatric disorders. Third, the lessons learned from the development of these six drugs have important implications for overcoming the problems that have led most large pharmaceutical companies to abandon drug development in psychiatry, as discussed in the following sections.

Efficacy based on the treatment of a symptom or behavior rather than a syndrome

Ondansetron and aprepitant treat nausea (a symptom) and vomiting (a behavior). Ramelteon and suvorexant treat insomnia (both a symptom and a behavior). Varenicline aids with smoking cessation (a behavior). Lorcaserin aids with weight loss by decreasing feeding (a behavior).

Such symptoms and behaviors are the output of brain function in single discreet pathways. In contrast, syndromes are man-made constructs that are often based on multiple different pathways that would likely be less amenable to treatment by an agent with a single mechanism of action, unless that mechanism had broad effects on brain function, such as is the case with benzodiazepines, which potentiate the inhibitory action of gamma-aminobutyric acid (GABA) in multiple systems in the brain. Effects on such a ubiquitous neurotransmitter can produce multiple different effects, only some of which may be desirable. For example, benzodiazepines can have anti-anxiety effects but they can also impair memory and coordination and can potentiate the effects of other sedative agents, including alcohol.

Efficacy based on a specific target in a specific circuit with a specific behavioral output

Ondansetron and aprepitant work by antagonizing the effect of serotonin in the chemotactic trigger zone. Ramelteon and suvorexant act on two different targets in the circuit that mediates sleep versus wakefulness. Varenicline works on the alpha-4, beta 2 receptor in the reward circuit. Lorcaserin blocks the 5-HT_{2C} receptor in the circuit that regulates feeding behavior.

The fact that these circuits are conserved from lower mammalian to human brains means that animal models are directly translatable to man, which is not the case for animal models of syndromic diagnoses such as major depression or schizophrenia. For this reason, there is a substantial leap of faith from the animal models that are used to screen for antidepressants and antipsychotics to clinical trials in patients with those conditions. In fact, the validity of those animal models is generally based on the effects of the drugs rather than being independently validated, which leads to circularity and to the discovery of drugs with the same mechanisms of action.

When considered on the basis of brain circuitry, the problem with the animal models for antipsychotics and antidepressants becomes readily apparent. For example, a common animal model for psychotic illness is to make the animal (usually rats or mice) hyperactive, even to the point of stereotypic movements, through administration of large doses of amphetamine and then to test the ability of the investigational drug to block that behavior. This model is based on overactivity of dopamine in the extrapyramidal motor system and selects for drugs that are dopamine-2 antagonists in this system. Hence, drugs that produce positive results in this model cause extrapyramidal side effects. In contrast, the validity of the animal models for nausea/vomiting, obesity, smoking, and sleep is based on the same behavior and circuitry in the animal and in man.

Table 1. Six central nervous system drugs with novel mechanisms of action developed in the past 25 years

Generic name	*Brand name*	*Outcome to be evaluated*
Ondansetron	Zofran	nausea and vomiting
Aprepitant	Emend	nausea and vomiting
Ramelteon	Rozerem	insomnia
Varenicline	Chantix	smoking cessation
Lorcaserin	Belviq	weight loss
Suvorexant	Belsomra	insomnia

The measure of efficacy is a behavioral phenomenon that is readily measured in an unambiguous parametric way

As shown in Table 1, the efficacy of these drugs is measured based on a dichotomous outcome (eg, the person vomited or not, or the person is smoking or not) or on a readily assessed parametrically measured variable (eg, amount of weight loss, number of cigarettes smoked, number of hours slept). Sleeping can also be measured using polysomnography to determine electrophysiologically the amount of time spent in the various phases of sleep to determine how physiologically normal the sleep was.

These outcomes are in marked contrast to results obtained from the rating scale instruments that are used to assess the efficacy of antidepressants and antipsychotics (eg, the Hamilton Depression Rating Scale [HDRS] for major depression and the Positive and Negative Syndrome Scale [PANSS] for schizophrenia). These scales are administered by researchers and thus reflect a researcher's subjective opinion of the subjective report of a patient. They are nonparametric and rate multiple symptoms that most likely represent dysfunction in multiple different circuits.

The problems with such scales will be obvious to most readers. Consider the PANSS, which rates a patient's symptoms across three domains: positive, negative, and general psychopathology. The scale assesses 7 positive symptoms, 7 negative symptoms, and 16 general psychopathology symptoms for a total of 30 items. Each symptom is rated on a scale from 1, which represents normal, to 7, which reflects a patient with a symptom that is among the most severe the rater has ever encountered. Thus, an individual who is judged to be normal scores a 30 and an individual whose symptoms are considered extreme on every item rates a 210.

Nevertheless, the total PANSS score does not necessarily reflect the clinical severity of the disorder. A PANSS score of 90 is almost double a score of 48; yet an individual with a score of 48 may be much more of a clinical concern that a patient with a score of 90. This statement is illustrated by the following example: patient A scores a 3 (mildly ill) on each of the 30 items, yielding a score of 90, whereas patient B scores normal on 27 of the 30 items but scores a 7 on three items: hallucinations, delusions, and hostility, yielding a score of 48. However, patient B is likely to be hospitalized for his or her psychosis, whereas patient A will most likely be treated as an ambulatory outpatient. Another example even more strongly highlights the potential problems with such rating scales. Patient C scores 2 (defined as the upper range of normal) on every item, resulting in a score of 60; thus, this patient has not scored above the upper limit of normal on any item yet has a higher total score than patient A. In addition, the scores on these scales likely represent a composite of symptoms that are mediated by dysfunction in multiple different circuits in the brain.

So what is the problem?

Most of the major pharmaceutical companies have abandoned, at least for the foreseeable future, the development of new psychiatric medications. Even when these companies were active in this area, they had failed to develop an antidepressant or antipsychotic with a novel mechanism of action in more than 50 years. While new molecules have been developed as antidepressants and antipsychotics during this period, each has had the same mechanism(s) of action as previous drugs in these categories. All currently approved antidepressants and antipsychotics work by affecting the neurotransmission of biogenic amines (eg, dopamine, norepinephrine, or serotonin) either by blocking their receptors or their transporter proteins. That is likely why most patients have a comparable response to these drugs in terms of efficacy. Although a few patients may respond uniquely well to one but not to the rest of these drugs, these patients are exceptions, probably due to

inter-individual variability (most likely genetic) in either the target of the drugs or their pharmacokinetics, a topic that is beyond the scope of this series.

Of note, clozapine is an exception to the statement that all antipsychotic medications have overlapping efficacy. Clozapine was, in fact, approved because it was shown to be efficacious in patients with schizophrenia whose illnesses were unresponsive to other low and high potency antipsychotics.[2] That fact led many pharmaceutical companies to try to dissect pharmacologically what made clozapine unique. Considerable efforts and money were expended on this search in the 1980s and 1990s, but to no avail. Further discussion of this topic is also beyond the scope of this column.

Over the past few decades, attempts have continued to develop antidepressants and antipsychotics with novel mechanisms of action, but, to date, these attempts have been unsuccessful despite full-fledged development efforts. Examples include the failed attempts to develop antidepressants that work via substance P and antipsychotics that worked via glutamate metabotropic receptor antagonists. Several other mechanisms have also been explored, but each has failed to meet the criteria outlined at the beginning of this column.

So what is the solution?

In the rest of this column, I will focus on selecting appropriate indications. In the third column of this series, I will discuss advances being made in understanding the circuitry of the brain, which hold promise for identifying circuits of interest and targets within those circuits.

The field of psychiatry and the U.S. Food and Drug Administration (FDA) need to recognize a fundamental truth: ***symptoms and behaviors are the output of brain function, whereas syndromes are man-made constructions.*** I mention the FDA because drugs must be approved for a specific indication and the FDA has traditionally used syndromic diagnoses as the basis for approval for psychiatric medications and has discouraged the use of symptoms as an indication.

However, some recent evidence indicates that this situation may be changing. For example, risperidone has been approved for the treatment of agitation in individuals with autism. Another example is the distinction between primary and secondary insomnia made in both the DSM-IV and by the FDA, with primary insomnia a condition in which the only problem was insomnia with no other known etiology, whereas secondary insomnia involved another putative cause, which could be caffeinism but also major depression, a syndromic diagnosis in which one of the symptoms may be insomnia. However, when understood from the standpoint of brain circuitry, the pathophysiology may be exactly the same in so-called primary insomnia and insomnia secondary to major depression.

The syndromic approach to psychiatric diagnoses arguably reached its zenith with the Washington University Research Criteria (WURC) (commonly referred to as the "Feighner Criteria"),[3] and it has been on a downhill trajectory, admittedly solely from a research perspective, ever since. The WURC were created to foster research and increase understanding of the problems that affect patients with such illnesses. For this reason, the approach underlying the WURC was to create discrete syndromic clusters with minimal overlap between each syndromic cluster. The underlying concept was that discrete clusters would more likely represent fundamentally distinct groups in terms of etiology and pathophysiology, following the adage of "dividing nature at its joints." Parenthetically, I was a resident at Washington University during what was arguably the "golden age" of this syndromic diagnostic approach before the advent of the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III).[4]

Although DSM-III and its later editions, DSM-IV[5] and DSM-5,[6] were conceptual descendants of the WURC, they were created principally to serve a billing purpose rather than to foster research. The author acknowledges that each edition of the DSM, from DSM-III to DSM-5, begins with a statement that its goals are to facilitate clinical diagnosis and communication and enhance research. Yet his opinion is that the primary goal is understandably to provide a mechanism to permit billing for needed services rather than to promote research. Otherwise, a model more like the WURC would have been used.

If viewed from a research perspective, it is easy to say, as some authors have, that the creators of the DSM-III, -IV, and -5 took a good idea (ie, the WURC) to a logical but absurd outcome. While the WURC had 14 diagnostic categories, that number ballooned to over 200 in the DSM-III and has increased further in subsequent iterations. Only a small number of cat-

egories were included in the WURC, not because the developers thought that all patients would fit into one of these categories, but because they wanted each category to be as discrete as possible so that it might be more "pure" in terms of etiology and/or pathophysiology. In fact, the developers of the WURC themselves reported that about a third of patients would not fit into one of their 14 categories. The problem for most of these patients was not that they did not meet criteria for *any one* category but that they met criteria for *too many* categories. Those patients were classified as suffering from an undiagnosed psychiatric disorder.

While the WURC approach of having a large number of undiagnosed patients was fine from a research perspective, it was not practical from the perspective of clinical practice because practitioners have to have a diagnosis to bill for care, which explains why the number of diagnoses ballooned in DSM-III and its descendants. Although DSM-III through DSM-5 have been criticized for being unscientific, it is important to remember that their purpose was not principally to advance science but rather to serve the needs of the practitioner.[7] The real problem was that the FDA, and hence the pharmaceutical companies which understandably followed the regulators' lead, began using the DSM-III and its subsequent iterations as a basis for establishing indications for the approval of new drugs.

This is not a new observation. Although I have spent the majority of my career in clinical psychopharmacology, I have periodically written on the problems of using the current plethora (albeit from a research rather than a bill coding perspective) of psychiatric syndromic diagnoses as indications for new drug development. I published the first such article in 1982,[8] and I have continued to publish on this theme periodically up to this present column.[9–12] The themes of these articles included attempts in the late 1980s to create categories for further drug approval without a scientific or empirical rationale,[8] the substantial overlap in diagnostic criteria,[9] and the failure to include biomarkers as part of diagnostic criteria.[10] Perhaps, the most comprehensive of these articles, published in 1990, proposed two concepts that were somewhat novel at the time: 1) establishing a multi-site network for clinical research with a core facility as a resource for the sites within the network, and 2) adding dimensional approaches that would cut across syndromic boundaries and potentially be more biologically relevant to brain function than man-made syndromes.[10] Both of these approaches have subsequently been taken up by the National Institute of Mental Health (NIMH), at least temporarily.[13–15]

The concept of a network of sites tied to a core facility to promote research aimed at a better understand of the pathophysiology and pathoetiology of psychiatric illness was original with the author. However, he based this approach on the model developed by the National Cancer Institute (NCI) which had been quite successful at that time and has continued to yield great success in terms of advancing the understanding and treatment of cancer. As with the NCI, the proposal is to have a network of psychiatric sites (not restrictive but inclusive) coupled to a core facility or facilities. The sites would work-up and treat patients in accordance with a constantly evolving protocol, the development of which would be driven by empirical results. The core facility would maintain a research database that would allow tracking of participants to facilitate follow-up studies. It would also have laboratory facilities to store biological samples from participants for the study of the basic etiology of the illnesses and to develop biomarkers to guide diagnosis and treatment. While the NCI sites had the advantage of storing cancer tissue, the psychiatric sites would need to rely on genetic and biochemical assays of blood and other samples, as suggested by emerging hypotheses.

This concept was realized for a limited period by the large clinical trials established by the NIMH: the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study,[13] the Clinical Antipsychotic Treatment Intervention Effectiveness (CATIE) trial,[14] and the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD).[15] Each of these trials incorporated many of the features described in my 1990 article, but unfortunately they were time-limited and did not continue once the leadership that had established them left the NIMH. I believe that such a program should be a core feature of the NIMH plan going forward, given the success that the NCI has achieved with this approach.

In addition to the efforts of the NIMH, another such network has been developed, the National Network of Depression Centers (NNDC) (www.nndc.org). The NNDC currently has 21 sites and is also based on the model developed by the NCI. The founding site is at the University of Michigan under the direction of

John Greden, M.D. While such private efforts are laudable, in my opinion, such networks need to be a) inclusive and b) long-term. The second goal would seem most likely to be reliably assured by an NIMH programmatic initative rather than a private effort such as the NNDC or projects funded by a time-limited NIMH grant such as the STAR*D. Otherwise, such efforts are likely to be fragmentary, as was the case with the STAR*D and other NIMH grants from that period discussed above.

The dimensional approach proposed in my 1990 article is now in the ascendancy, as illustrated by the NIMH's Research Domain Criteria (RDoC) initiative, which implements Strategy 1.4 of the 2008 NIMH Strategic Plan to "develop, for research purposes, new ways of classifying mental disorders based on behavioral dimensions and neurobiological measures."[16] The NIMH has recently been advocating the use of the RDoC to advance science and hopefully the understanding of the pathophysiology and etiology of psychiatric illnesses. As stated on the project's website for the project,

> RDoC attempts to bring the power of modern research approaches in genetics, neuroscience, and behavioral science to the problems of mental illness, studied independently from the classification systems by which patients are currently grouped….The heart of RDoC is a matrix of functional dimensions, grouped into broad domains such as cognition and reward-related systems, examined across units of analysis ranging from genetics and circuit activity to psychology and behavior. Emphasis is placed upon the developmental trajectories through which these functions evolve over time, and the interaction of neurodevelopment with the environment. RDoC research starts with basic mechanisms and studies dysfunctions in these systems as a way to understand homogeneous symptom sets that cut across multiple disorders, rather than starting with clinical symptoms and working backwards.[16]

There are currently 5 Domains in the RDoC matrix, with these domains, constructs, and sub-constructs defined as follows (summarized from the workshops on each domain):

Negative Valence Systems: Systems primarily responsible for responses to aversive situations or context, such as fear, anxiety, and loss.

Positive Valence Systems: Systems primarily responsible for responses to positive motivational situations or contexts, such as reward seeking, consummatory behavior, and reward/habit learning.

Cognitive Systems: Systems responsible for various cognitive processes.

Systems for Social Processes: Systems that mediate responses to interpersonal settings of various types, including perception and interpretation of others' actions.

Arousal/Regulatory Systems: Systems responsible for generating activation of neural systems as appropriate for various contexts, and providing appropriate homeostatic regulation of such systems as energy balance and sleep.

These domains are similar to the three dimension I proposed in my 1990 article: (a) passivity to aggression, (b) introversion to extroversion, and (c) intellectual quotient.

As I will discuss in the next column in this series, these domains may better map to the sensory-emotional-cognitive-motor circuits being discovered in the human brain than more complex and disparate syndromic constructs, and thus they may be more appropriate targets for therapeutic intervention.

During the DSM-5 process, experts in the field of personality disorders expended considerable effort trying to introduce a dimensional framework for the personality disorders. While the DSM-5 Task Force supported this effort, the Board of the American Psychiatric Association did not (John Oldham, personal communication). However, this concept did make it into Section III of DSM-5 as an Alternative Model and a chapter currently in press focuses on the parallels between this new model and the RDoC domains.[17] Personality traits like symptoms may be more directly mapped to specific brain function than are multi-symptomatic syndromic diagnoses such as major depression. Dogs, for example, are bred as much for their temperament as their body habitus.

Conclusion

Six CNS drugs with novel mechanisms of action were developed in the last 25 years, all of which targeted single symptoms or behaviors rather than complex

syndromic constructs such as major depression. The DSM-5 and earlier versions of the DSM have an important role in allowing clinicians to bill for treatment but they have not proven helpful in attempts to develop compounds with novel mechanisms of action. Symptoms and/or behaviors may be more suitable targets for therapeutic development because they may be more readily mapped to specific brain circuits. The RDoC initiative of the NIMH will not replace but will hopefully complement the DSM-5, by facilitating research into brain mechanisms relevant to the fundamental rather than the descriptive nature of psychiatric disorders. In the next column in this series, I will review advances being made in our understanding of the neural circuits that underlie higher brain functions and are relevant to psychiatry.

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