A New Nomenclature for Psychotropic Drugs

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Introduction: Current classifications of psychotropic drugs, developed in the 1960s, are based on beliefs about clinical effectiveness. This article evaluates the scientific validity of current drug terms and possible alternative classifications.

Methods: A historical, conceptual, and empirical review of the psychopharmacology literature is provided. Consistency of classification is examined by 3 major categories: chemical structure, pharmacodynamic mechanism, and clinical efficacy.

Results: Current drug terms based on clinical effectiveness are not valid scientifically, either claiming efficacy which is disproven or ignoring other areas of clinical efficacy. Hence, clinical efficacy is not a consistent and scientifically valid way of classifying psychotropic drugs. Chemical structures are also heterogeneous for drugs with similar clinical efficacy. The most consistent way to define drug classes is pharmacodynamic mechanism. Specific drug groups identified are: *monoamine agonists* ("antidepressants" and "stimulants"), *dopamine blockers* ("antipsychotics"), *second messenger modifiers* ("mood stabilizers), and *gabaergic agonists* ("anxiolytics" or "hypnotics").

Conclusions: Consistent with a recent proposal of psychopharmacology organizations, this article proposes a new nomenclature based mainly on biological pharmacodynamic mechanisms. Specific terms that are scientifically valid and clinically practical are suggested. It is hoped that this new language would allow for more meaningful and accurate communication between clinicians and patients.

Key Words: psychopharmacology, classification, nomenclature, drug classes, biological mechanisms, clinical indications

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The great debate about how to classify psychiatric diagnoses, as in the recent DSM-5 revision (Diagnostic and Statistical Manual—fifth edition), has included attention to practical implications of diagnosis.[1] Because a DSM diagnosis implies treatment, often with medications, controversy about diagnoses is often a proxy for attitudes toward medications.[2]

Yet, despite millions spent on DSM revisions, little effort has been given to how we should classify the psychotropic drugs.

Currently terms—like "antidepressants," "antipsychotics," "anxiolytics," "stimulants"—are vague, broad, and antiquarian, with practical effects: how we name drugs influences how we use them.[3] Some suggested problems with our current nomenclature are summarized in Table 1.

The current nomenclature is based on clinical terms codified by a special committee of the World Health Organization in 1967.[4] Despite an explosion of neuroscience research,[5] no effort was made to revise this World Health Organization schema until the last few years, when a nomenclature task force was created by 4 neuropsychopharmacology groups (European College of Neuropsychopharmacology [ECNP], American College of Neurospychopharmacology [ACNP], Collegium Internationale Neuropsychopharmacologicum, and the Asian College of Neuropsychopharmacology). In the interests of brevity, and reflective of its main panelists, this joint group will be referred to as the ECNP/ACNP group hereafter. That task force proposed a radical change in classification of psychiatric drugs which involves an emphasis on biological mechanism.[6]

The proposal presented in this article was written without any knowledge of the ECNP/ACNP task force proceedings and is independent of, consistent with, and simpler than the ECNP/ACNP schema.

METHODS

A historical, conceptual, and empirical review of the scientific literature was performed to determine and elucidate the distinguishing features of psychotropic drug classes. Nomenclature was assessed by seeking a classifying feature that is most consistent for a drug class, specifying as many agents in that class as possible, and not being present for as many agents in other drug classes as possible. Classifying features examined, based on previous attempts at drug classification[4] and standard approaches in pharmacology,[7] were chemical structure, clinical efficacy, and pharmacodynamic mechanisms.

RESULTS

As shown in Table 2, in standard and common clinical usage,[8] there are 5 major drug classes in the traditional psychopharmacology nomenclature: antidepressants, antipsychotics, mood stabilizers, sedative-anxiolytics, and stimulants. Their classic corresponding diagnoses are major depressive disorder (MDD), schizophrenia, bipolar disorder, anxiety disorders, and attention deficit hyperactivity disorder (ADHD). Each common class is examined below.

As a general rule, the primary indications for the drug classes are accompanied by a good deal of evidence of efficacy for secondary indications. All but one (anxiolytic sedatives) have relatively consistent pharmacodynamic mechanisms (the pharmacodynamic discussion in this article is limited to receptor binding or direct and indirect effects on neurotransmitter availability or direct second messenger effects). All but one (amphetamines and amphetamine-like agents) have very inconsistent chemical structures. The results of this analysis suggest that pharmacodynamic mechanism is the most consistent method by which to classify psychotropic drugs. In Tables 3 to 4, an alternative nomenclature based mainly on pharmacodynamic mechanisms is suggested. These mechanisms apply to all drugs in each class, although subclasses and specific agents may differ from each other in other actions.

Antidepressants

It is a little known fact that the earliest clinical observation in the 1950s with the first antidepressants was not that they treated depression, but that they caused mania in patients putatively diagnosed with schizophrenia (which often reflected misdiagnosed manic-depressive illness). Geigy tested imipramine first in

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TABLE 1. Problems With the Current Psychopharmacology Nomenclature

1. Based on clinical terms ("antidepressant") that are not directly related to diagnoses (different types of depression exist)
2. Therapeutically, nonspecific (antidepressants are anxiolytic; antipsychotics are antimanic)
3. Sometimes too narrow (antipsychotics can work for non-psychotic conditions; antidepressants can work for non-depressive conditions)
4. Sometimes too broad (antidepressants are ineffective for some depressive conditions)
5. Sometimes defined by the pharmaceutical industry (origin of the term "mood stabilizer")
6. Can be associated with stigma ("antipsychotic")
7. May mislead patients ("mood stabilizer" can imply not being allowed to have a range of moods)
8. May bias research ("mood stabilizers" may not be seen as "antidepressants" worthy of study for depressive conditions)

hospitalized patients with schizophrenia and noticed they became frankly manic. Four decades later, Dr. Alan Broadhurst of Geigy, who was involved in those initial observations, recounted what happened in an oral history: "Some patients began to deteriorate with increasing agitation and a few went into frank hypomania. One gentleman, in such a state, managed to obtain a bicycle and rode in his nightshirt to a nearby village, singing merrily, much to the alarm of the inhabitants. This was not very good PR either for the hospital or for Geigy….[It was} so exciting that a drug should produce mood changes like this. We were simply at a loss to explain it….we began to wonder if the flattened affect of schizophrenia was somehow elevated by the drug to hypomania, might a similar elevation of mood be possible in patients with depression." (pp 116–117).[9] Hence, the term "mood elevator" was used as well as "psychic energizer".[10] Eventually, the clinical investigator, Dr Frank Ayd, propounded the term "antidepressant" in an analogy to "antibiotics".[11] Although specific antibiotics can be ineffective in specific infections, at least some antibiotics are effective for most bacterial infections. In contrast, the efficacy of "antidepressants" as a class has been disproven in bipolar depression, both acutely[12] and in maintenance.[13] The "antidepressant" class is also disproven as effective in MDD with mild baseline depressive severity, based on a meta-analysis of all extant published and unpublished Food and Drug Administration (FDA) data.[14,15] About one half of all antidepressant randomized clinical trials of acute MDD have been negative.[16] Antidepressants also have limited benefit in depressive conditions of medical etiology, such as cancer,[17] although they help post-stroke depression.[18] In contrast to the varied efficacy of antidepressants in depressive syndromes, as reviewed above, "antidepressants" appear more consistently effective in reducing anxiety conditions, like panic attacks and generalized anxiety.[19,20] In other words, these agents are more consistently "anxiolytic" than "antidepressant."

In summary, the scientific rationale for the term antidepressant, based on efficacy in depressive syndromes, is weak.

Turning to chemical structures and pharmacodynamic mechanisms, as 2 other nomenclature groupings, there is more consistency to the latter. The chemical structures of antidepressants vary. The only subgroup defined by its chemical structure is the tricyclic antidepressant class (which also includes some "tetracyclics" as well, with similar pharmacology). However, drugs which are not strongly antidepressant in effect, such as chlorpromazine and carbamazepine, share the same tricyclic structure.[7]

TABLE 2. Traditional Psychopharmacology Nomenclature

	Antidepressants	Antipsychotics	Mood Stabilizers	Anxiolytics/Hypnotics	Stimulants
Main indication	Major depression	Mania, acute psychoses	Bipolar disorder	Anxiety disorders. insomnia	Attention disorders
Efficacy in main corresponding diagnosis	Moderate	Marked	Unproved	Marked	Marked
Secondary diagnoses treated	Anxiety diagnoses	Mania, unipolar or bipolar depression	Major depression	Mania, depression	MDD, sexual dysfunction, obesity
Efficacy in secondary diagnoses	Marked	Moderate to marked	Unproved	Marked	Marked
Consistent chemical structure	No	No	No	Mostly (benzodiazepines)	Mostly amphetamine-like
Consistent pharmacodynamic mechanism	Mostly (increased monoamine activity)	Mostly (dopamine blockade)	Mostly second messenger changes	Mostly GABA agonism	Mostly dopamine agonists
Historical basis	1950s hypomania in psychotic patients	1950s benefit in mania & schizophrenia	1950s amphetamine + barbiturate for depression/anxiety	1960s benzodiazepine effects	1930s treatment of depression

TABLE 3. Proposed Psychopharmacology Nomenclature

Criteria	Monoamine Agonists	Dopamine Blockers	Second Messenger Modifiers	GABAergic Agonists	Other
Clinical efficacy	Depression and anxiety syndromes and ADHD	Psychosis and mania	Prevention recurrences of depressive or manic episodes	Anxiety or insomnia	Anxiety or insomnia
Actions	Increase activity of dopamine, norepinephrine, or serotonin	Block dopamine receptors	Affect second messenger systems extensively	Stimulate GABA receptors and/or open chloride ion channels	Antihistamines, adrenergic antagonists, melatonin agonists

In contrast, all antidepressants increase monoaminergic activity in some way (which can vary, like reuptake inhibition or direct receptor agonism). Hence, the term monoamine agonists would consistently describe almost all antidepressants (Table 3). Further subgrouping based on specific monoamines affected could then be made if desired (Table 4).

Stimulants

These drugs were originally used to treat depressive syndromes (amphetamines were the main "antidepressant" class from the 1930s until the 1960s), not ADHD. Other uses include enhancement of sexual drive and weight loss. These varied clinical effects are not captured by the vague clinical terminology of "stimulants."

Turning to chemical structure and pharmacodynamics mechanisms, again the latter is more consistent. These agents do not all share the same amphetamine chemical structure (although many do), but they all share a dopaminergic enhancing effect, with differences in degree, amphetamines being most robust, and bupropion and modafinil milder. Hence, the pharmacodynamic

TABLE 4. A New Proposed Nomenclature for Psychotropic Drugs

Subclass	Specific Agents
Monoamine agonists (formerly "antidepressants" and "stimulants")	
MAOIs	phenelzine, tranylcypromine, ixocarboxazid, selegiline
SRIs	citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine*, trazodone, venlafaxine*, vilazodone
NRIs	atomoxetine, desipramine
SNRIs	amitriptyline, clomipramine, nortritypline, desvenlafaxine, duloxetine, imipramine, milnacipran, *l*-milnacipran, sibutramine, venlafaxine*
SDRIs	sertraline
Serotonin/norepinephrine potentiator	mirtazapine
Serotonin partial agonist	buspirone
Dopamine agonists	*d*-amphetamine
	mixed amphetamines
	Lisdexamfetamine
	d-methylphenidate
	R,S-methylphenidate
	modafinil
	buropion
Gabaergic agonists and other classes (formerly "anxiolytic" or "sedating" agents)	
Gabaergic agonists	benzodiazepines (diazepam, lorazepam, alprazolam, clonazepam, among others), gabapentin, zolpidem, zaleplon, zoplicone, eszopiclone
Other	Antihistamines: diphenydramine, hydroxyzine, doxepin**
	Adrenergic antagonists: propanolol, clonidine
	Melatonin agonists: ramelteon
Dopamine blockers (formerly "antipsychotics")	
Dopamine antagonists*	chlorpromazine, haloperidol, perphenazine, thiothixene, thioridazine, trifluoperazine
Dopamine/serotonin antagonists	asenapine, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, lurasidone, paliperidone, quetiapine, risperidone
Dopamine partial agonists	aripiprazole, ziprasidone
Second messenger modifiers (formerly "mood stabilizers")	
Direct second messenger modifiers	Lithium, Valproate, Carbamazepine
Other	Glutamate blocker: Lamotrigine

*These agents are pure SRIs at low dose, but have NRI activity added at usual doses; ** at low dose.

SNRI indicates serotonin-norepinephrine reuptake inhibitors; DRI, dopamine reuptake inhibitor; MAOIs, monoamine oxidase inhibitors; SDRIs, serotonin-dopamine reuptake inhibitors.

mechanism of being "dopamine agonists" seems most parsimoniously consistent to pick out this drug class from others (Table 3). Again, they can have other effects as well, such as noradrenergic effects with methylphenidate and bupropion. However, they all share the dopamine agonistic mechanism.

It is noteworthy that pure norepinephrine reuptake inhibitors (NRIs), such as desipramine or atomoxetine, show benefit for ADHD, but are not viewed clinically as "stimulants" because they do not exercise immediate energy-increasing effects and have delayed cognition-enhancing effects, in contrast to dopamine agonists, such as amphetamines.[8]

Antipsychotics

These agents originally were called "major tranquilizers," because of their overall agitation-reducing effects,[21] then "neuroleptic" ("nervous system-seizing"),[22] for their neurological side effects. Preferring a positive than negative phrase, the term antipsychotic, first introduced by the Canadian psychiatrist Heinz Lehmann in the 1960s,[3] gained increasing usage. Lehmann was aware that the term was based on limited evidence: "In 1956, when I was addressing the Canadian Medical Association, I introduced the term 'antipsychotic' apologetically, and more as a metaphor than a designation."[3] Time has proven Lehmann more correct than he knew: these agents work for psychotic symptoms, they also benefit nonpsychotic mania and sometimes nonpsychotic depressive states.[23] The term neuroleptic is more consistent clinically because all agents in this class have at least some extrapyramidal side effects.[24] However, using side effects for class names would be expected to produce negative attitudes toward those agents.

Turning to chemical structure and pharmacodynamic mechanisms, again these agents vary widely in pharmacological structure; early drugs were phenothiazines in structure, but others (like haloperidol) were butyrophenones, and still other (such as clozapine and olanzapine) dibenzodiazepines[7]; other complex structures also exist.

Once again, biological mechanisms are the most consistent shared characteristic in this class. They are all, without exception, "dopamine blockers," which may be the best defining term for the class (Table 4). Most block dopamine receptors quite potently,[7] a few (quetiapine and clozapine) moderately.[25] Other effects, like serotonin-2 receptor blockade, can identify subgroups, like the so-called atypical antipsychotics of recent decades. Given that these "atypical" dopamine/serotonin blockers are used much more frequently than the original ("typical") class, it would seem odd to call "atypical" what is now standard and typical. More importantly, some differences exist in biological mechanism among specific agents in the dopamine/serotonin blockers. Specifically, aripiprazole has some dopamine agonism and ziprasidone has notable SRI-NRI–like effects.[7]

Mood Stabilizers

In the 1950s this term was used for the combination of dextroamphetamine (a "stimulant") and phenobarbital (a sedative barbiturate).[11] The term was not developed specifically for treating manic or depressive episodes, as in current usage. Because lithium was the only agent used and approved for manic-depressive illness in the 1960s to the 1980s, there was no need for a class term. When carbamazepine began to be used for bipolar illness in the 1980s, and then valproate received an FDA indication for mania in the 1990s, it appears that that Abbott Laboratories (makers of Depakote) co-opted the old "mood stabilizer" term.[26,27] Since then, multiple "antipsychotics" have received FDA indications for mania and/or maintenance treatment of bipolar illness, leading to increasingly confusing terminology: "antipsychotics," it is said, are also "mood stabilizers." The validity of the scientific evidence supporting maintenance efficacy of antipsychotics in bipolar illness has been questioned.[28]

One could insist on the use of "mood stabilizer" only for agents which have preventive, prophylactic efficacy in bipolar disorder,[29] but clinicians seem inclined to interpret the term linguistically, as an agent which "stabilizes" the mood in between mania and depression, that is, which *acutely* improves manic and depressive episodes, a usage which is not scientifically well founded.[30]

Regarding chemical structures, there is great variability, ranging from a single ion (lithium), to a simple carbohydrate structure (valproate), a tricyclic structure (carbamazepine), and a complex molecule (lamotrigine, a dichlorophenyl-triazine-diamine).[7]

Again, though not absolute, pharmacodynamic mechanisms are the most consistent feature of this class: it is now clear that lithium has powerful second messenger intracellular effects, which exert neuroplastic long-term changes in the brain.[31] Valproate and carbamazepine also have some second messenger effects, though not as extensive as lithium (affecting protein kinase C for valproate, and cyclic adenosine monophosphate activity for carbamazepine).[32] Thus, a preliminary nomenclature for those 3 agents could be defined as "second messenger modifiers," because these agents all appear to modify second messenger pathways without much activity in synaptic neurotransmitters and their receptors (lithium has mild serotonergic effects and valproate mild gabaergic effects, but their second messenger properties are much more extensive).[32]

Lamotrigine, which is a glutamate receptor antagonist [7], does not have known second messenger effects, which are unstudied. Hence, the proposed nomenclature lists lamotrigine in its own class as a glutamate blocker (Table 4).

Anxiolytics/Hypnotics

These drugs were termed tranquilizers, for their general calming effect, then "minor tranquilizers" to distinguish their mild effects from "major tranquilizers" (antipsychotics).[21] Benzodiazepines and barbiturates were the first anxiolytics, developed in the 1930s and 1940s (and preceded for a century by bromides, which they replaced).[21] They have been followed in recent years by nonbenzodiazepine hypnotics (like zolpidem and zaleplon). The SRIs are also widely used for anxiolytic effects, and trazodone and quetiapine for hypnotic effects.

Again, a simple clinical classification is insufficient because other drug classes, such as monoamine agonists and dopamine blockers, also can have sedating or anxiolytic effects. Also, there is no pharmacological structural consistency among these agents.

There is more heterogeneity to pharmacodynamic mechanism here than in previous drug classes, but it is still the case that most of these anxiolytic/hypnotic agents are "gabaergic agonists," which may provide the most parsimonious class label (Table 4). Other drugs with similar clinical benefits can be defined by their separate biological mechanisms: antihistamines, melatonin agonists, and adrenergic blockers (Table 4).

DISCUSSION

In this review, the most consistent defining feature of drug classes was pharmacodynamic mechanism, not clinical effects, as in current usage. This discussion will address potential criticisms and then relate this new nomenclature to the recent ECNP/ACNP task force proposal.

Critiques

It can be said that knowledge of pharmacodynamic mechanisms is weak: drugs within a class vary, and direct relation to clinical efficacy is not proven (and perhaps even theoretically unprovable). One could challenge the monoamine agonism consistently found in "antidepressants," and point to the huge literature on immunomodulating effects, neuropeptide system effects, substance P, and cortisol-releasing factor. The proposed nomenclature does not claim that the selected pharmacodynamic mechanisms are the proven causes of clinical efficacy, but rather that the selected pharmacodynamic mechanisms are simply present to a consistent degree.

There is accepted precedent for this proposal. The monoamine oxidase inhibitor drug class has always been defined by its pharmacodynamic mechanism. The class has efficacy proven for many depressive conditions (though not bipolar depression), many anxiety conditions, and some other uses (early Parkinson disease for selegiline). The proposal here is to generalize from the monoamine oxidase inhibitor nomenclature to all drug classes and use pharmacodynamic mechanism for classification more generally.

Another critique could be that some mechanisms, such as dopamine receptor blockade, are not scientifically valid because the "dopamine-excess hypothesis" of schizophrenia remains unvalidated.[33] However, classifying a drug class by dopamine blockade need not imply the "pharmacocentric" assumption that drug mechanism reflects the pathophysiology of disease.[34] The key classification question is not whether the biological mechanism is central to the illness it treats, but rather whether it defines the class consistently and coherently.

The ECNP/ACNP Proposal

The proposal presented here was independent of the ECNP/ACNP task force recommendations, which came to a similar conclusion.[6] That work is consistent with, and supportive of, the basic ideas in this article. The main critique made here of the ECNP/ACNP proposal is that it is too complex and extensive for clinical purposes and instead is more applicable to research purposes. Further, it is noteworthy that the ECNP/ACNP proposal does not include any reference to redefining "mood stabilizers" as "second messenger modifiers," as proposed in this article.

In the ECNP/ACNP nomenclature, 5 axes are proposed: axis 1 "Class (primary pharmacological target), Relevant mechanism"; axis 2 "Family (primary neurotransmitter(s) and relevant mechanism); axis 3 "Neurobiological activities"; axis 4 "Efficacy and major side effects"; axis 5 "Indications".

This 5-axis system is complex and involves many assumptions that are scientifically difficult to defend. For instance, we often do not know the primary "relevant mechanism" of a drug for a clinical effect; some drugs have multiple mechanisms, and some have unknown mechanisms. The reintroduction of "efficacy" and "indications" shares the many flaws of our current clinically based nomenclature: what level of clinical evidence will be required for claims of efficacy and indications? What if uses are off-label?

An example is provided in the ECNP/ACNP proposal with the medication vilazodone. It would be given the following nomenclature: axis 1—class: serotonin, relevant mechanism: reuptake inhibitor and receptor antagonist. Axis 2—family: serotonin reuptake inhibitor and 5HT1A partial agonist. Axis 3—neurobiological activity: increases extracellular levels of 5HT in frontal cortex and hippocampus, preferential activation of cell body 5HT1A autoreceptors, attenuates 5HT syndrome. Axis 4—efficacy and major side effects: anxiety symptoms; may produce significant nausea, discontinuation syndrome. Axis 5—approved indications: MDD.

The proposal in this article would simply list vilazodone as a monoamine agonist. Further identification could be made as its main mechanism being another SRI. More detailed elaborations about partial serotonin agonism could be explained if needed, but clinicians would have a basic understanding of what this drug does if they understood that it was a monoamine agonist which was a SRI. Its clinical uses could then be explored not only for depressive conditions but also for anxiety symptoms and other standard serotonergic uses.

A final point is that it has been suggested by members of the ECNP/ACNP task force that the new nomenclature should be tied to DSM categories. This is a questionable suggestion given that DSM categories can be criticized based on limited scientific validity in many cases.[35] Just as we need our drug classification to be more scientifically solid, links should be made to a diagnostic classification that is more scientifically solid than the DSM system (as suggested by, but not limited to, the NIMH RDoC approach).[36]

Clinical Implications

An important clinical utility to this change in drug nomenclature would be to allow for more helpful discussions between clinicians and patients. For instance, patients are confused if a clinician does not want to give an "antidepressant" for bipolar depression; if it is an antidepressant, it should work, they reason. They are confused if clinicians recommend an antipsychotic for nonpsychotic unipolar depression; I am just depressed, not psychotic, they reason. They think "mood stabilizers" will keep them from having normal mood states. All these misconceptions, based on linguistic usage, will disappear with the new nomenclature. Instead, clinicians can name the drugs biologically briefly, as we now do with SRIs, and then turn to other evidence to describe why those drugs may or may not work for certain clinical symptoms. Further, some talk of biological mechanisms might help explain some common side effects, such as the Parkinsonian effects of dopamine blockers. In all these cases, the new nomenclature would allow for more meaningful and accurate communication between clinicians and patients.

The culture is already suffused with these terms: most patients have heard of serotonin and dopamine. A small amount of further education can define the meaning of "monoamines" and "second messengers." This kind of biological discussion can be fruitful in helping patients understand the basics about their illnesses. Clinicians will also benefit from paying more attention to biological differences and similarities among drugs that may have clinical relevance to efficacy or side effects.

One may ask how such a change in language would affect other players, like the pharmaceutical or insurance industries. It may be that it will be harder for pharmaceutical companies to engage in sometimes misleading marketing (these "antipsychotics" are also "antidepressants"). This proposal could force pharmaceutical companies to use more neutral language in their advertising, at least in how they refer to drug classes. It is difficult to know how insurance companies would react, but one would hope that neutral drug terms would also force them to rely on clinical research studies, and not linguistic usage, for making payment decisions.

CONCLUSIONS

After decades of neuroscientific advance, a more scientific classification is possible based on biological mechanisms of pharmacodynamic action. A proposal for such a drug classification, consistent with, but more clinically useful than, the recent ECNP/ACNP proposal, is provided. In summary, the proposed new nomenclature is more scientifically valid than our current

clinical usage and would allow for more meaningful and accurate communication between clinicians and patients.

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In the past 36 months, Dr. Ghaemi has had a research grant from Takeda Pharmaceuticals and has provided research consultation to Sunovion Pharmaceuticals. Neither he nor his family holds equity positions in pharmaceutical corporations.

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