Classification of psychotropic drugs: Problems, solutions, and more problems

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The current classification of drugs was introduced by the World Health Organization in 1976. This classification is known as the ATC system, where A refers to the anatomical site of action (e.g., the central nervous system [CNS]), T refers to the therapeutic indication (e.g., the treatment of depression), and C refers to the chemical class of the drug (e.g., selective serotonin reuptake inhibitor [SSRI]).

In the ATC classificatory system, the anatomical site of action could be the CNS (e.g., carbamazepine), the respiratory system (e.g., salbutamol), the cardiovascular system (e.g., digoxin), the gastrointestinal system (e.g., omeprazole), and so on. A problem here is that, for example, antimicrobials and antineoplastic drugs do not act on a specific anatomical system; however, they do act at a specific anatomical target, such as bacterial or neoplastic cells. Vitamins are other examples of drugs that are hard to classify with regard to an anatomical target.

For Level 1 CNS drugs, Level 2 includes analgesics, anesthetics, antiepileptics, anxiolytics, antidepressants, antipsychotics, antidepressants, mood stabilizers, hypnotics, and others. A problem here is that drugs are classified according to the original indication for which they were studied and approved. However, many drugs have many indications. For example, SSRIs have demonstrated efficacy in depression, generalized anxiety disorder, panic disorder, social anxiety disorder, posttraumatic stress disorder, obsessive-compulsive disorder (OCD), premenstrual dysphoric disorder, migraine (prophylaxis), and other conditions. Nevertheless, SSRIs are still classified as antidepressants.

Similarly, antipsychotics such as aripiprazole are effective in schizophrenia, in mania, as antidepressant augmentation treatment in major depressive disorder, as SSRI augmentation treatment in OCD, and in the treatment of delirium. Quetiapine and lurasidone are specifically effective as monotherapy for bipolar depression, and quetiapine is effective as monotherapy for generalized anxiety disorder.

Some of these are not approved indications but are indications for off-label use.

In like manner, antiepileptics such as valproate are effective in epilepsy, bipolar disorder, pain syndromes, migraine prophylaxis, aggression, anxiety, tardive movement disorders, and other labeled or off-label indications.

For Level 1 CNS drugs and Level 2 antidepressants, Level 3 includes monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), noradrenaline reuptake inhibitors, noradrenergic and selective serotonergic antidepressants, and other drugs. Here, the method of classification is a little unsystematic, for example, whereas MAOI, SSRI, and SNRI are mechanisms, TCA describes a structure. Terms such as “newer” antidepressants tell us nothing about the drugs.

CLASSIFYING ANTIPSYCHOTIC DRUGS

The problem is greater with the antipsychotic drugs. In the early decades, it was convenient to classify these drugs, based on structure, as phenothiazines, butyrophenones, diphenylbutylpiperidines, and other drugs. With subsequent drug development, many agents were synthesized that had no other member in their group. However, around the same time, a change in adverse effect profile spawned the atypical/typical distinction and usage, and afterward, the older/newer and first/second/third generation antipsychotic terminologies.

A problem here is that some of the older antipsychotics did not produce much extrapyramidal adverse effects (EPS), if at all, and were, therefore, atypical in action; thioridazine is an example. In contrast, risperidone, ziprasidone, aripiprazole, blonanserin, and many other newer antipsychotics do produce considerable dose-dependent EPS and akathisia. It would be more accurate to say that the risk of tardive dyskinesia, rather than EPS, differentiates the neuroleptics from the atypical antipsychotics.

In this context, clozapine is a very old drug, dating back to 1960 and even earlier, but belongs to the newer/atypical
group in characteristics. Furthermore, the more recent nomenclature (e.g., first vs. second generation drugs) tells us nothing about the drugs, themselves. Thus, nomenclature seems to have arisen more through invention (by authors and pharmaceutical companies) for novelty and marketing value than as a consequence of planning and science.

One possible solution for antipsychotic classification would be to base it on the mechanism, such as predominantly D2 antagonists (e.g., haloperidol), serotonin-dopamine antagonists (e.g., risperidone), dopamine-serotonin antagonists (e.g., blonanserin), and so on. In fact, such a mechanism-based nomenclature is part of a new system that has been proposed. [1,2]

WHY NOMENCLATURE IS IMPORTANT

Patients discuss their medications with other patients and with family and friends. They also read about their medications from sources that are not always reliable. Thus, a patient who receives valproate for bipolar disorder may be asked by a neighbor whether he has epilepsy; or a patient who receives quetiapine or lurasidone monotherapy for bipolar depression may ask whether he is secretly being treated for schizophrenia. Such misunderstandings can be avoided if drug nomenclature is optimized.

THE NEUROSCIENCE-BASED NOMENCLATURE

If the existing classification of psychotropic drugs falls short of the ideal, what should be the characteristics of an ideal nomenclature for psychopharmacology? Zohar et al [1,2] suggest that nomenclature should be based on current scientific knowledge; it should be update-able; it should not conflict with therapeutic indications; and it should assist clinicians in making a choice.

In 2008, a task force for psychotropic nomenclature was established. The core group represented the European College of Neuropsychopharmacology, the American College of Neuropsychopharmacology, the International College of Neuropsychopharmacology, the Asian College of Neuropsychopharmacology, and the International Union of Basic and Clinical Pharmacology. An initial proposal for a neuroscience-based nomenclature (NbN) was made in 2014 [1,2]

Currently, the NbN includes 108 drugs (comprising most but not all of the psychotropics available in the world). The NbN, outlined by Zohar et al. [1,2] describes each drug in each of the following sections: Pharmacological domains, modes of action, and additional clinical domains. Drugs can belong to more than one domain and can have more than one mode of action. The NbN is intended to be a living document and is expected to be updated annually. [2]

The pharmacological domains are based on neurotransmitter or molecular action. There are 11 domains: Acetylcholine, dopamine, GABA, glutamate, histamine, ion channel, lithium-mimetic, melatonin, norepinephrine, opioid, and serotonin.

There are ten modes of action. A drug may act as a receptor agonist, receptor partial agonist, receptor antagonist, reuptake inhibitor, reuptake inhibitor and releaser, reuptake inhibitor and receptor antagonist, an enzyme inhibitor, ion channel blocker, positive allosteric modulator (PAM), or enzyme modulator.

The additional dimensions include the following: Approved indications, efficacy and adverse effects, practical notes, and neurobiology.

APPLYING THE NEUROSCIENCE-BASED NOMENCLATURE

According to the NbN, hydroxyzine is listed as a histamine receptor antagonist; pregabalin and gabapentin are glutamate voltage-gated calcium channel blockers; buspirone is a 5HT1a receptor partial agonist; and benzodiazepines and barbiturates are GABA-PAM drugs. From a scientific perspective, such nomenclature is pleasing.

When all actions are specified, quetiapine is listed as dopamine and serotonin and alpha-2 noradrenergic receptor antagonist; included in the definition is its metabolite norquetiapine, which is a norepinephrine reuptake inhibitor. The listing of drugs such as clozapine (which has multiple sites of action) becomes even more complex.

WHERE IS THE NEUROSCIENCE-BASED NOMENCLATURE AVAILABLE?

The NbN app can be downloaded free from the links listed below.

For Android:
https://play.google.com/store/apps/details?id=il.co.inmanage.nbnomenclatureandhl=en.

For Apple:
https://itunes.apple.com/us/app/nbn-neuroscience-based-nomenclature/id927272449?mt=8.

These links are easily located through a Google search.

The NbN app allows a search by drug chemical/brand name, by indication, by mechanism of action, by former terminology, and by combinations of the above. Once a specific drug is identified, similar drugs can be easily pulled out. [2]
The NbN glossary can be downloaded from nbnomenclature.org/_static/docs/NbN_Glossary.pdf (this link can also be identified through a Google search).

LIMITATIONS

The NbN is not patient or even clinician-friendly. It merely replaces one set of shortcomings (in the old system of classification) with a new set of shortcomings. These shortcomings are listed below.

• Drugs are no longer antidepressants or antipsychotics; they are descriptions, and sometimes quite long and complicated descriptions, or even essays
• The user must understand the pharmacological concepts applied in the descriptions and the implications thereof. The average user, for example, may have difficulty in working out what a PAM does
• The descriptions so far do not include notes on receptor affinity (e.g., strong vs. weak agonists) and other aspects of binding (e.g., fast-off action), both of which can have implications for efficacy and adverse effects
• It is surprising that pharmacokinetic details find no place in the NbN, given the extent to which pharmacodynamic and clinical details are provided. One would expect, at the very least, drug metabolism and drug interaction information to be available. Unfortunately, this would make the NbN even more of a handbook on psychopharmacology than a system of classification or nomenclature
• The NbN does not include pediatric psychopharmacology in its scope, as yet
• The NbN only includes psychotropic drugs; other CNS drugs must find their own classification.

OTHER COMMENTS

• One of the most important of the weaknesses in the existing nomenclature is that, for example, drugs that are classified as antipsychotics may also be effective in anxiety, depression, OCD (as augmentation treatment), tic disorders, delirium, and other conditions. This can create confusion; for example, a patient receiving quetiapine or lurasidone for bipolar depression may ask whether his physician believes that the real diagnosis is schizophrenia. Rather than seek recourse to the NbN, it could be easier to merely explain at the time of prescription that lurasidone was originally studied as an antipsychotic, but was later found to have other benefits, such as efficacy in bipolar depression.

REFERENCES

1. Zohar J, Nutt DJ, Kupfer DJ, Moller HJ, Yamawaki S, Spedding M, et al. A proposal for an updated neuropsychopharmacological nomenclature. Eur Neuropsychopharmacol 2014;24:1005-14.
2. Zohar J, Stahl S, Moller HJ, Blier P, Kupfer D, Yamawaki S, et al. A review of the current nomenclature for psychotropic agents and an introduction to the Neuroscience-based nomenclature. Eur Neuropsychopharmacol 2015;25:2318-25.

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