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COMMENTARY

A new nomenclature for classifying psychotropic drugs

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The Neuroscience-based Nomenclature (NbN) for psychotropic drugs was developed as an alternative to the current Anatomical Therapeutic Chemical (ATC) indication-based classification in order to provide more precise designations for this drug class. The ATC nomenclature for psychotherapeutics is limited in that it fails to specify either pharmacological domains or mechanism of action and also does not describe all the potential uses of a particular agent. The disconnect between the drug classification and its clinical use is not very useful for scientific purposes and is confusing for patients and caregivers, often leading to a misunderstanding of the intended effects of the prescribed medication and, most importantly, to low treatment adherence. The NbN classifies psychopharmacological agents on the basis of contemporary scientific information on their pharmacology and mechanisms of action so as to provide physicians clear alternatives when selecting or altering therapeutic regimens. The classification of each psychotropic drug includes four additional dimensions: approved indications; efficacy and side effects; practical note; neurobiology. By emphasizing the pharmacology and the molecular mechanism of action, NbN provides a vehicle for clinicians and basic scientists to improve the understanding and clinical use of this important drug class.

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Tables of Links

TARGETS	
GPCRs [2]	**Transporters** [3]
D_2 receptor	NET
5-HT_2 receptor	
5-HT_{1A} receptor	
NE α2 receptor	

LIGANDS	
Amisulpride	Desipramine
Aripiprazole	Olanzapine
Brexpiprazole	Quetiapine
Cariprazine	

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2, 3].

The Neuroscience-based Nomenclature (NbN) for psychotropic drugs was developed as an alternative to the current Anatomical Therapeutic Chemical (ATC) indication-based classification in an attempt to provide more precise designations for this drug class. Several journals, including *European Neuropsychopharmacology, Biological Psychiatry, Neuropsychopharmacology, CNS Spectrums*, *European Psychiatry, Clinical Psychopharmacology and Neuroscience*, *International Journal of Neuropsychopharmacology* and *The World Journal of Biological Psychiatry* have adopted NbN as the nomenclature of choice for psychotherapeutics in their publications.

The ATC nomenclature for psychotherapeutics is limited in that it fails to specify pharmacological domains or mechanisms of action and also does not indicate all potential uses of a particular agent. Under the ATC classification, 'antidepressants' may be prescribed for anxiety disorders and 'second generation antipsychotics' are used for treating depressed patients with no signs or symptoms of psychosis. This disconnect between the drug classification and its clinical use is confusing for patients and caregivers, often leading to misunderstandings regarding therapeutic aims [4, 5]. Moreover, the ATC-based indications are of little value in providing clinicians with the pharmacological information needed to make the most informed decisions regarding patient care. For example, the term 'second generation antipsychotic' includes five medications with five different pharmacodynamic profiles: D_2 receptor antagonists (e.g. amisulpride); D_2/5-HT_2 receptor antagonists (e.g. olanzapine); D_2/5HT_{1A} partial agonists (e.g. aripiprazole, brexpiprazole); D_2/5HT_2/NEα_2 receptor antagonists (e.g. clozapine); and D_2/5HT_2 receptor antagonist/NE reuptake inhibitors (e.g. quetiapine). In addition, the ATC nomenclature system fails to take into consideration other important aspects of the mechanisms of action of psychotherapeutics. Thus, at present the antipsychotics aripiprazole and olanzapine are included in the same category even though there are data indicating that the former differs from the latter in its 'functional selectivity' on the D_2 receptor-related signalling pathway [6]. Other important mechanistic differences between these agents are gaining more clinical relevance with recently-approved antipsychotics like cariprazine and brexpiprazole.

Given the limitations of the ATC classification system, the European College of Neuropsychopharmacology (ECNP), the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the International College of Neuropsychopharmacology (CINP) and the International Union of Basic and Clinical Pharmacology (IUPHAR) established a joint task force to design a more precise and descriptive nomenclature for psychotherapeutics. The NbN system (website: http://nbnomenclature.org) is the result of this effort [4, 7]. The aim of the undertaking was to design a system that classifies psychopharmacological agents on the basis of contemporary scientific information on their pharmacology and mechanisms of action to provide physicians with clearer alternatives than the ATC system when selecting or altering therapeutic regimens. It was also felt important that the nomenclature system be sufficiently flexible to accommodate the discovery of new agents with different pharmacological profiles and different mechanisms of action. The NbN system includes four additional dimensions beyond basic pharmacology:

1. **Approved indications**: These are based on the recommendations of major regulatory agencies (e.g. Food and Drug Administration, European Medicines Agency, etc.).
2. **Efficacy and side effects**: This highlights other potential, but not yet formally approved, indications for which there is authoritative evidence of efficacy. In addition, the most common or life-threatening side-effects are indicated.
3. **Practical note**: A summary of the most relevant clinical information as determined by the task force.
4. **Neurobiology**: This dimension, which includes preclinical and clinical data, highlights preclinical findings of particular value to physicians.

Currently, 108 psychotherapeutics representing a broad range of agents and indications have been classified according to the NbN guidelines. For example, desipramine is described as follows: (1) norepinephrine reuptake inhibitor; (2) approved for the treatment of major depressive disorder; (3) a CYP2D6 substrate with antidepressant efficacy that displays side effects expected of an agent that interacts with multiple neurotransmitter receptors; and (4) interacts with a host of secondary targets with multiple effects on brain chemistry and signalling. The drug target or receptor

nomenclature will follow the IUPHAR/BPS nomenclature available on www.guidetopharmacology.org or the Concise Guide to Pharmacology [8].

According to the ATC classification, psychotropic drugs are generally considered to belong only to one of five classes: antipsychotics, antidepressants, anxiolytics, hypnotics, and mood stabilizers. However, these classes fail to account for different recently approved psychotropic agents. For example, quetiapine can be placed in any of four different ATC categories (antipsychotics, antidepressants, hypnotics, and mood stabilizers). Thus it is often prescribed at doses of 100 mg or less as a bedtime sedative, at doses of 150–300 mg day^{-1} as a treatment for major depression (alone or in combination with another antidepressant), at 300–600 mg day^{-1} for bipolar disorder, and with doses above 600 mg day^{-1} for schizophrenia. Using the NbN classification, quetiapine is described in the axis 1 'name' as a receptor antagonist (D2, 5-HT2) and reuptake inhibitor (NET) (metabolite), which succinctly explains its broad clinical profile. Studies indicate that drug compliance improves in neuropsychiatric patients when they have a better understanding of their condition and of the mechanism of action of the therapeutic agent. As designed, the NbN will help patients better understand the dimensional approach currently used by psychiatrists when deciding on a drug regimen. Given the information provided by the NbN system, the dimensional approach will emerge following discussions between the patient and the physician concerning the mechanism of action of psychotherapeutics and how they affect the pathophysiology of the disorder.

The NbN will be particularly useful for describing psychotropic drugs in the literature, such as reporting the results of clinical trials. The molecular mechanism of action, as specified in the NbN system, can provide the scientific rationale for undertaking a study instead of having to rely solely on the ATC-based indication that is often based mainly on existing empirical findings. For example, the new classification will help explain why quetiapine, acting as a norepinephrine reuptake inhibitor, has been studied in bipolar depression and approved for the treatment of this condition independent of its antipsychotic actions which are due to D2 and 5HT2 receptor blockade. The same approach can be applied with aripiprazole when considering its clinical efficacy at low doses in treatment-resistant depression (TRD) by virtue of its being a partial dopamine D2 receptor agonist and its ability to interfere with certain molecular pathways thought to be impaired in TRD. A glossary is available to assist in classifying psychotropics according to the NbN system (http://nbnomenclature.org/_inc/layout/save_pdf.inc.php?file=NbN_Glossary.pdf&action=download_pdf).

It is recognized that there are challenges to adopting any new classification system beyond abandoning the established nomenclature. One of these challenges is that medications are often grouped according to their presumed mechanisms of clinical action. However, this is based on the premise that the mechanism of action for the intended clinical effect is known, which is not always the case (e.g. lithium). Moreover, most psychotropic drugs are fully effective only after chronic administration, with information slowly emerging about the molecular pathways and systems that may be involved in the delayed response.

To ease the transition to NbN, some journals have adopted its use in stages. In the first stage authors are required to define a term, such as antipsychotics, using NbN criteria when the word first appears in the text. Furthermore, to make publications searchable by NbN, the new nomenclature defining the drugs mentioned in the report should be added to the keywords section of the manuscript. To this end, journals are encouraged to add an NbN subcategory to the keyword search. The new keyword will include ten pharmacological domains and the ten modes of action which are currently the basis of NbN. By emphasizing the pharmacology and the molecular mechanism of action, NbN provides a vehicle for clinicians and basic scientists to improve communication with patients and scientific colleagues, and to enhance the understanding and use of this important drug class.

Competing Interests

There are no competing interests to declare.

References

1 Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SP, *et al*. The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucl Acids Res 2016; 44: D1054–68.

2 Alexander SPH, Davenport AP, Kelly E, Marrion N, Peters JA, Benson HE, *et al*. The Concise Guide to PHARMACOLOGY 2015/16: G protein coupled receptors. Br J Pharmacol 2015; 172: 5744–869.

3 Alexander SPH, Kelly E, Marrion N, Peters JA, Benson HE, Faccenda E, *et al*. The Concise Guide to PHARMACOLOGY 2015/16: Transporters. Br J Pharmacol 2015; 172: 6110–202.

4 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.

5 WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2015. Oslo.

6 Boyd KN, Mailman RB. Dopamine receptor signaling and current and future antipsychotic drugs. Handb Exp Pharmacol 2012; 212: 53–86.

7 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.

8 Alexander SPH, Kelly E, Marrion N, Peters JA, Benson HE, Faccenda E, *et al*. The Concise Guide to PHARMACOLOGY 2015/16: Overview. Br J Pharmacol 2015; 172: 5729–43.