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A proposal for an updated neuropsychopharmacological nomenclature

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Abstract
Current psychopharmacological nomenclature remains wedded in an earlier period of scientific understanding, failing to reflect contemporary developments and knowledge, does not aid clinicians in selecting the best medication for a given patient, and tends to confuse patients by prescribing a drug that does not reflect their identified diagnosis (e.g. prescribe "antipsychotics" to depression). Four major colleges of Neuropsychopharmacology (ECNP, ACNP, Asian CNP, and CINP) proposed a new template comprising a multi-axial pharmacologically-driven nomenclature tested by four surveys. The template has five axes: 1—class (primary pharmacological target and relevant mechanism); 2—family (reflecting the relevant neurotransmitter and mechanism); 3—neurobiological activities; 4—efficacy and major side effects; and 5—approved indications. The results of the surveys suggest that the clinicians found the available indication-based nomenclature system dissatisfactory, non-intuitive, confusing, and doubt-inducing for them and the patients. The proposed five-axis template seeks to upend current usage by placing pharmacology rather than indication as the primary axes, with the proposed nomenclature relating primarily to Axis 1—the class, and usage of the other axes would largely

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depend upon the extent to which the clinician seeks to deepen the scientific and clinical base of his involvement. A significant proportion of the participants in the four surveys were in favour of the proposed system, a similar number wanted to consider the idea further, and only a small proportion (8.6%) were against it. The proposed five-axis pharmacology based nomenclature template is a system which might refresh and reflect the current scientific concepts of neuropsychopharmacology.

1. Introduction

Ideally, pharmacological nomenclature should embody contemporary scientific knowledge, help the clinician in making an informed decision, and enhance patient adherence to the treatment plan. Unfortunately, current psychiatric drug classification (Figure 1) fails to serve any of these purposes. First, it does not reflect the advances in our knowledge. Thus, for example, the terms "antidepressant" and "antipsychotic" were coined in the early 1950s in line with their clinical use during that period—long before the relevant neuroscience information was understood. The anachronistic "antipsychotic" was even extended to "second generation antipsychotics"—a term that, despite its potential marketing appeal, has no relation to current neuropsychological knowledge either of the psychotropic's relevant modes of action or its potential clinical efficacy.

The class to which a drug belongs reflects neither its relevant neurotransmitter nor its mechanism of action and consequently does not guide the clinician as to the full spectrum of disorders it can be used to treat. The nomenclature employed by our colleagues in hypertension, in contrast, identifies the drug's principal mode of action (see Table 1), thus guiding them towards a combination of medications that address different mechanisms when seeking to augment the response to the treatment.

Finally, the current nomenclature is also confusing to the patients, as some of the "antipsychotics" are used to treat both depression (e.g., quetiapine, olanzapine, etc.) (Bauer et al., 2009; Thase et al., 2007; Berman et al., 2007) and anxiety disorders (e.g., olanzapine and quetiapine) (Komossa et al., 2010; Zohar and Allgulander, 2011), thus liable to cause patients to become confused: "Why I am being prescribed an 'antipsychotic' when I am suffering from depression or anxiety". "Is my situation that bad, Doctor? Am I in danger of becoming psychotic?" Under such circumstances, it is not difficult to understand that adherence to the course of medication prescribed may be seriously compromised.

The term "antidepressant" fares little better. Many antidepressants are also employed as "anti-anxiety" medications when the patient is not depressed (Zohar et al., 1987). This is again likely to be confusing and/or worrisome for the patient: "Why am I given antidepressants if I am not depressed?"

The present contributors also contend that, just as updates are constantly sought with respect to diagnosis (DSM III, IV, 5, ICD 9, 10, 11, etc.), similar adjustments to pharmacology nomenclature should be sought.

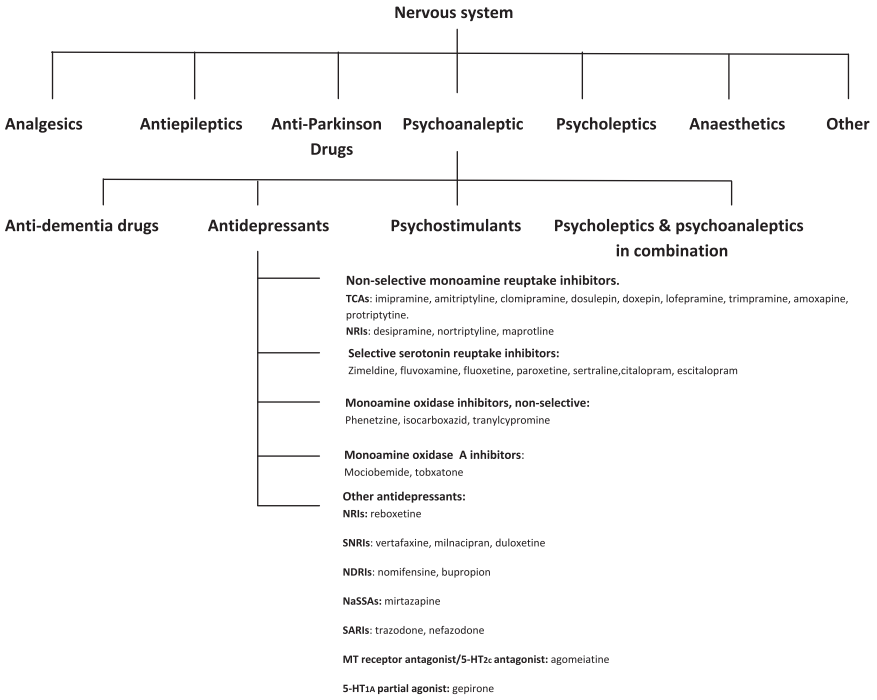

Figure 1 Current antidepressant nomenclature under the WHO system.

Table 1 Classes of medication in the treatment of hypertension.

Class name	General characteristics
Diuretics	Reduce excess sodium and water, thereby controlling blood pressure.
Beta-blockers	Reduce heart rate and heart workload, and its blood output.
ACE (angiotensin-converting enzyme) inhibitors	Reduce production of angiotensin, thereby facilitating the relaxation and dilation of blood vessels, in turn lowering blood pressure.
Angiotensin II receptor blockers	Block the effects of angiotensin, a peptide hormone that stimulates arterial constriction.
Calcium channel blockers	Prevents calcium from entering the smooth muscle cells of the heart and arteries, thereby relaxing and dilating constricted blood vessels.
Alpha blockers	Reduce resistance of the arteries, thus relaxing the muscle tone of the vascular walls.
Alpha-2 receptor agonists	Decrease activity of the sympathetic (adrenaline-producing) region of the involuntary nervous system.
Central agonists	Help decrease constriction of blood vessels.
Peripheral adrenergic inhibitors	Reduce blood pressure by blocking neurotransmitter receptors in the brain.
Blood vessel dilators/ vasodilators	Cause the muscles in the walls of the blood vessels (especially the arterioles) to relax, allowing the vessel to dilate.

In December 2008, four major organizations with a direct psychiatric pharmacological brief—the European College of Neuropsychopharmacology (ECNP), the American College of Neuropsychopharmacology (ACNP), the Collegium Internationale de Neuropsychopharmacologie (CINP), and the Asian College of Neuropsychopharmacology (AsCNP)—determined that the time had come to meet the nomenclature challenge. In collaboration with the International Union of Basic and Clinical Pharmacology (IUPHAR), they established a taskforce with the mission of updating and formulating pharmacological nomenclature relevant to brain disorders. Although the goal was to produce a template according to which existing compounds could be reclassified and new compounds introduced, it was acknowledged that, in the case of novel medications, the formation of a new class might be justified. A multi-axial, pharmacologically-driven nomenclature was subsequently developed, with regard to which four field tests were conducted. The following section presents the multi-axial template and the results of the field tests.

2. Experimental procedures

2.1. Developing the multi-axial template

Following a series of meetings between representatives of the four organizations (JZ and DJN for ECNP; DJK for ACNP; SMS and HJM for CINP; SY for AsCNP; and MS for IUPHAR) and consultation with colleagues and pharmaceutical company representatives, the following multi-axial template was developed (Table 2).

Axis 1 identifies the primary pharmacological target and the mechanism. Axis 2 lists its family, reflecting the primary neurotransmitter and relevant mechanism. Axis 3 relates to the drug's known neurobiological activities, including its neurotransmitter effects, brain circuits, and physiological effects (in both humans and animals). Axis 4 details the clinical observations, including the drug's major known efficacy and side effects. Axis 5 includes only current approved indications. Additionally, as an end-note of some tables (when appropriate) another feature coined "Committee Note" will be added. The Committee Note will include information about potential new indication and other 'clinical pearls'.

2.2. Testing the multi-axial template

Four field tests designed to examine the potential acceptance and efficacy of the proposed system were conducted. The first was carried out in September 2011 in Paris at the annual ECNP meeting. This trial included 371 respondents: 286 (77%) psychiatrists, 22 (6%) brain researchers, 19 (5%) pharmacologists, 7 (2%) psychologists, and 41 (11%) "other". Responses were obtained via feedback from a keypad system that allowed each of the 371 participants to express his/her opinion anonymously, free of group or peer pressure.

The second survey was conducted in Prague at the annual EPA meeting (March 2012). On this occasion there were 80 respondents, including 59 (74.2%) psychiatrists, 7 (9.1%) brain researchers, 2 (3%) psychologists/neurologists, and 11 (13.6%) "other". Here, too, responses were obtained via feedback using a keypad system.

The third survey was conducted in February 2012 via an internet questionnaire and included 455 participants: 252 (55.4%) psychiatrists, 24 (5.3%) psychologists, 8 (1.8%) pharmacologists, 3 (0.7%) neurologists, 2 (0.4%) brain researchers, and 166 (36.5%) "other".

The fourth survey was conducted in October 2012 at the ECNP's Twenty-Fifth Annual Congress in Vienna. 326 delegates participated, of whom 245 (75.1%) were psychiatrists, 22 (6.7%) brain researchers, 6 (1.8%) psychologists, 2 (0.6%) neurologists, and 32 (9.8%) "other".

The surveys conducted at the three Congresses (ECNP Paris and Vienna and EPA in Prague) were based on questions asked during a session dedicated to the nomenclature initiative. For the fourth survey, US practitioners were directed via one of the author's (SMS) website to an e-survey site, where they were asked to respond to the questions presented in the same order as at the Congresses. In total, responses were received from 1232 participants: 842 (68%) psychiatrists, 53 (4.3%) brain researchers, 45 (3.7%) pharmacologists, 37 (3%) psychologists, 7 (0.6%) neurologists, and 250 (20.3%) "other".

The questions asked are presented in Table 3 and relate to four areas:

1) Relevant characteristics (Questions 1–2).
2) Current practice and knowledge (Questions 3–6).
3) Feedback regarding nomenclature dilemmas (Questions 11–17).
4) Response to the proposed nomenclature following the proposal of the multi-axial concepts (Questions 18–22).

Table 2 Proposed template for a multi-axial psychopharmacological nomenclature.

Axis 1	**Class (primary pharmacological target)**		
	Relevant mechanism		
Axis 2	**Family (primary neurotransmitter(s) and relevant mechanism)**		
Axis 3	**Neurobiological activities**		
		Animal	Human
	Neurotransmitter effects		
	Brain circuits		
	Physiological		
Axis 4	**Efficacy and major side effects**		
Axis 5	**Indications**		

Committee Note:

Table 3 Questions used in the field tests of the proposed multi-axial nomenclature template.

	Question	Response options
1	How many patients do you see yearly?	- More than 10 - Less than 10 - I don't see any patients
2	Are you a	- Psychiatrist - Neurologist - Psychologist - Brain researcher - Other
3	Have you heard of WHO categories of drug classes?	- Yes - No
4	What class are antidepressants listed as in WHO system?	- Analeptic - Antidepressant - Psychoanaleptic - Psychostimulant - Thymoleptic
5	Does the current classification of antidepressant drugs into SSRIs, SNRIs etc. affect your prescribing practice? Do you consider the different classes to have significant and so clinically relevant differences?	- Yes - No - Don't know
6	Which factor do you think of first when you are deciding which antidepressant to use?	- Pharmacology - Pharmacokinetics - Cost - Adverse effects
7	If SSRI = Selective serotonin reuptake inhibitor, what should SNRI mean?	- Selective noradrenaline reuptake inhibitor - Serotonin non-selective reuptake inhibitor - Serotonin noradrenaline reuptake inhibitor
8	NaSSAs are	- Noradrenaline and serotonin receptor antagonists - Noradrenaline antihistamine and serotonin selective antagonists - Noradrenaline and selective serotonin receptor antagonists - Noradrenaline and serotonin specific antidepressant - Noradrenaline and selective serotonin antagonists
9	What is psycholeptic?	- Title of the latest song from Lady Gaga - The official term for an antipsychotic by FDA - The official term for an antipsychotic by WHO - The official term for an antipsychotic by FDA and WHO
10	Which organisations adopt each other's terminology for antipsychotics?	- WHO - APA

Table 3 (*continued*)

Question	Response options
	- FDA - EMA - USP - ACNP/ECNP/CINP - AsCNP - All of the above - None of the above
11 Which term do you prefer for the new antipsychotics?	- Second-generation antipsychotic - Atypical antipsychotic - Serotonin dopamine agonist - Other
12 Given that some antipsychotics are also approved as antimanics and as antidepressants, do you think your preferred term for the new antipsychotics is:	- Adequate/acceptable - Confusing/inadequate
13 How should the new antipsychotics be classified?	- By clinical use (i.e., antipsychotic, mood stabilizer, antidepressant) even if one drug is in more than one class - By their principal shared mechanism of action - By their functional neurobiological effect - By their symptom improvement profile - If possible, all the above
14 What would you prefer for drugs with multiple targets of action?	- Multifunctional - Multimodal - Mixed action - Dirty - Rich pharmacology
15 For agents that improve psychosis but also have other clinical actions, should we use	- A pharmacological term, such as serotonin dopamine antagonist, or 5HT2C antagonist, etc. - A clinical term such as antipsychotic, antimanic, antidepressant - Other
16 If more than one term applies to a single molecule, such as 'serotonin dopamine antagonist, plus serotonin 1A partial agonist', or 'antipsychotic/antimanic/antidepressant', to include one molecule in several classes or to give one molecule more than one name would be	- Helpful, agree that this should be done - Confusing, disagree that any agent should be classified in more than one way - Don't know
17 How should a drug that improves just negative symptoms of schizophrenia but does not block D2 receptors be categorized?	- As an antipsychotic - As a negative symptoms antipsychotic - By its pharmacologic action (e.g., glycine reuptake inhibitor, etc.) - Something else
18 What should we call vilazodone (Viibryd), the new antidepressant with serotonin reuptake blocking and serotonin 1A partial agonist properties?	- SSRI - Antidepressant - Serotonin partial agonist reuptake inhibitor (SPARI) - Something else
19 What should we call a selective glycine reuptake inhibitor that has evidence of efficacy in schizophrenia?	- Negative symptoms antipsychotic - Antipsychotic - Selective glycine reuptake inhibitor (SGRI) - Glycine reuptake inhibitor (GRI) - Glycine type 1 reuptake inhibitor - Something else
20 What should we call agomelatine (Valdoxan), the new antidepressant with melatonin 1 and 2 agonist, 5HT2C antagonist properties that increase dopamine and norepinephrine in the prefrontal cortex?	- Melatonergic antidepressant - Melatonergic agonist, 5HT2C antagonist - Melatonergic NDDI (norepinephrine and dopamine disinhibitor) - Something else
21 What should we call Lu21004, the agent with preliminary evidence of antidepressant action with 6 actions: serotonin reuptake inhibition, 5-HT_{1A} partial agonism, and 5-HT_3, 5-HT_7,	- SSRI - Antidepressant - Multifunctional neurotransmitter enhancer

Table 3 (*continued*)

	Question	Response options
	and 5-$HT_{1B/D}$ antagonism that increases 5 neurotransmitters: serotonin, norepinephrine, dopamine, acetylcholine, and histamine?	- Multimodal neurotransmitter enhancer - Something else
22	What are your first thoughts on the multi-axial nomenclature of psychotropics?	- Fully support - Not yet sure - Disagree

3. Results

A total of 1232 participated in the four surveys. Due to technical limitations, some questions were not posed in all four surveys. This is noted below when reporting the results of the relevant questions. For the entire sample, 842 (68.3%) respondents were psychiatrists, the remainder being neurologists (n=7, 0.6%), psychologists (n=37, 3.0%), pharmacologists (n=45, 3.7%), brain researchers (n=53, 4.3%), or "others" (n=250, 20.3%). The majority of the respondents (993, 80.6%) saw patients on a regular basis, some (238, 19.3%) not seeing any or only a few a year.

The EPA and ECNP Vienna surveys also asked participants about prescribing practices (n=406): 252 prescribed medication to over 70% of their patients (62.1% of all respondents or 80.7% of those who saw patients). A summary of the respondents' background characteristics is presented in Table 4.

When asked about their practice and knowledge of the current nomenclature system, 772 (62.7%) respondents had not heard of the WHO drug-class categories, only 368 (29.9%) were aware that the WHO categorizes antidepressants as "thymoleptics". 1043 (84.7%) acknowledged that the classifications of SSRI and SNRI affected their prescription choice. The majority (64%) claimed that pharmacology formed the principal factor in deciding which antidepressant to prescribe, the second most prevalent consideration being adverse events (24.8%). When asked to speculate what SNRI should stand for based on SSRI as standing for "Selective Serotonin Reuptake Inhibitor", 826 (67.0%) contended that the present title—Serotonin-Noradrenaline Reuptake Inhibitor—is the obvious choice. 356 (28.9%) conceded that, based on the precedent set by SSRI, SNRI should actually stand for "Selective Noradrenaline Reuptake Inhibitor". Confusion was especially pronounced regarding NaSSA, with responses more or less equally distributed across the options. Only 21.3% correctly chose "noradrenergic and specific serotonergic antidepressants".[2] 680 respondents[3] (59.0%) maintained that official WHO term for an antipsychotic is psycholeptic (the correct answer). 94 (8.2%) thought the term was an FDA formulation, 319 (27.7%) believing the two bodies to be jointly responsible for the terminology. 521 (56.5%) respondents thought that one or more of the psychiatric and drug agencies adopt one another's terminology for antipsychotics, less than half (506, 43.9%) were aware that they do not.

With respect to feedback regarding nomenclature dilemmas, respondents were divided as to whether the new antipsychotics should be called second-generation antipsychotics (23.5%), atypical antipsychotics (31.6%), serotonin dopamine antagonists (29.9%), or another term (15.1%). In light of the frequent use of some "antipsychotics" as "anti-manics" and "antidepressants", 826 (71.7%) agreed that the terminology was inadequate or confusing. 398 (34.5%) respondents preferred a classification of antipsychotics based on the specific drug's principal shared mechanism of action vs. 427 (37.1%) who preferred a classification based on several characteristics—their clinical use, functional neurobiological effect, and symptom-improvement profile—if and when possible.

The floor feedback regarding drugs with multiple targets of action was split between multifunctional (26.3%), multimodal (42.8%), and mixed action (25.3%).[4] With respect to agents that mitigate psychotic symptoms along with other clinical actions, the highest preference was for a pharmacologically-driven (51.9%) rather than a clinical-based term (24.8%) or other option (20.6%). When a single molecule can be defined by more than one name, respondents felt that placing it in more than one class or giving it more than one name would be helpful (74.3%). Finally, 797 (64.7%) of the participants felt that a drug that mitigate negative symptoms in schizophrenia but does not block D2 receptors should be categorized primarily by its pharmacological action.

Response to the proposed multi-axial nomenclature was tested by taking specific drugs as examples. Participants were first asked about vilazodone (Viibryd), a new antidepressant with serotonin reuptake blocking and serotonin 1A partial agonist properties (Table 5).[5] The consensus was that this agent should be classified under the "serotonin partial agonist reuptake inhibitor" (SPARI) family (73.4%) rather than SSRI (3.7%), antidepressant (8.5%), or 'something else' (14.3%). When asked what name they would choose for a selective glycine reuptake inhibitor evidencing efficacy in the treatment of schizophrenia (Table 6),[3] the majority (58.3%) preferred the term "selective glycine reuptake inhibitor" (SGRI) over "negative symptoms antipsychotic" (5.0%), antipsychotic (3.8%), glycine reuptake inhibitor (18.7%), glycine type 1 reuptake inhibitor (10.5%), or 'something else' (3.2%).

The preferred term for agomelatine (Valdoxan)—an antidepressant with melatonin 1 and 2 agonist and 5HT2C antagonist properties that increases dopamine levels in the

[2]This question was not asked at the ECNP survey in Vienna.

[3]Not including the EPA survey.

[4]This question was not asked at the ECNP survey in Vienna. N=906.

[5]Participants were not asked about this compound at the EPA survey. N=1152.

Table 4 Summary of the survey respondents' background characteristics.

Characteristic	Response	ECNP Paris 2011 (n=371)	EPA Prague 2012 (n=80)	US Web Survey 2012 (n=455)	ECNP Vienna 2012 (n=326)	Total (n=1232)
Profession	Psychiatrist	77%	74.2%	55%	75.1%	68.3%
	Neurologist	0%	3.0%	0.7%	0.6%	0.6%
	Psychologist	2%		5.3%	1.8%	3.0%
	Pharmacologist	5%	0.0%	1.8%	5.5%	3.7%
	Brain researcher	6%	9.1%	0.4%	6.7%	4.3%
	Other	11%	13.6%	36.5%	9.8%	20.3%
Patients seen per year	More than 10	72%	61.5%	92.3%	78.8%	80.6%
	Less than 10	8%	14.3%	4.2%	21.2%	10.5%
	Don't see patients at all	20%	24.3%	3.5%	(Option not given)	8.8%

Table 5 vilazodone. *Multi-axial psychopharmacological nomenclature for vilazodone.*

Axis 1	**Class** serotonin **Relevant mechanism:** reuptake inhibitor and receptor antagonist		
Axis 2	**Family** serotonin reuptake inhibitor and 5-HT1A partial agonist		
Axis 3	**Neurobiological activity**		
		Animal	Human
	Neurotransmitter effects	Increases extracellular levels of 5-HT in frontal cortex and hippocampus; No effect on norepinephrine levels	
	Brain circuits	Preferential activation of cell body 5-HT_{1A} autoreceptors than postsynaptic 5-HT_{1A} receptors	Binds to 5-HT reuptake sites; Binds preferentially to cell body 5-HT_{1A} autoreceptors than postsynaptic 5-HT_{1A} receptors
	Physiological	Does not produce a 5-HT syndrome but attenuates it when triggered by a potent 5-HT_{1A} agonist	Marked REM suppression, slow wave sleep increased
Axis 4	**Efficacy and major side effects** Anxiety symptoms; May produce significant nausea upon treatment initiation; discontinuation syndrome		
Axis 5	**Approved indications** Major depressive disorders (USA) Committee notes Gradually decrease upon discontinuation		

Committee Note: Gradually decrease upon discontinuation.

prefrontal cortex and norepinephrine in the prefrontal cortex and hippocampus (Table 7)—was melatonergic agonist and 5HT2C antagonist (47.1%), melatonergic antidepressant gaining a 17.8% vote, melatonergic NDDI (norepinephrine and dopamine disinhibitor) a 28.1% vote, and 'something else' a 7.5% vote.[6] Finally, respondents were asked about vortioxetine (Lu AA21004), an investigational antidepressant thought to work through a combination of two complementary mechanisms of actions—receptor activity modulation and reuptake inhibition. In vitro studies indicate that vortioxetine is a 5-HT_3, 5-HT_7, and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist, and inhibitor of the 5-HT transporter (Bang-Andersen et al., 2011; Westrich et al., 2012). In vivo preclinical studies have demonstrated that vortioxetine enhances the levels of 5 neurotransmitters: serotonin, noradrenaline, dopamine, acetylcholine, and histamine in specific areas of the brain (Mørk et al., 2012) (Table 8).[7] The majority preferred the term "multimodal neurotransmitter enhancer" (58.9%) over SSRI (5.2%), antidepressant (5.3%), multifunctional neurotransmitter enhancer (25.2%), or 'something else' (9.5%).

3.1. Response to the multi-axial nomenclature

Overall, the response to the multi-axial nomenclature proposal presented at the meetings was that the current nomenclature clearly needs to be updated. When asked

[6]This compound was not adduced at the EPA or the ECNP Vienna surveys.

[7]Participants were not asked about this compound at the EPA survey.

Table 6 bitopertin. *Multi-axial psychopharmacological nomenclature for bitopertin.*

Axis 1	**Class** glycine **Relevant mechanism:** reuptake inhibitor		
Axis 2	**Family** Selective glycine reuptake type 1 (Glyt1) inhibitor		
Axis 3	**Neurobiological activity**		
		Animal	Human
	Neurotransmitter effects	Increased synaptic and CSF glycine level (1,2) (Alberati et al., 2012)	Increased CSF glycine levels (Pizzagalli et al., 2012)
	Brain circuits	Decreases DA release from the mid-brain to the striatum (1). Enhances working memory in the prefrontal cortex in primates (3) (Borroni et al., 2011)	Unknown
	Physiological	Social withdrawal in (ongoing) rodent studies. Enhancement of NMDA receptor Dependent LTP rat hippocampus slice.	
Axis 4	**efficacy and major side effects** negative symptoms of schizophrenia—especially social and emotional withdrawal in patients with persistent, predominant negative symptoms—when used adjunctively with antipsychotic therapy.		
Axis 5	**approved indications**		

Committee Note: In Phase III, for schizophrenia for both indications: negative symptoms and sub-optimally controlled increases the concentration of glycine in the synaptic cleft by blocking its reuptake through the GlyT1, glutamate action is enhanced at the NMDA receptor—glycine being a co-agonist at this site.

their opinion regarding the proposed multi-axial system, a significant proportion (45.2%) was in favour, a similar number (46.1%) wanting more time to consider the idea. Only a small proportion (8.6%) disagreed.

4. Discussion

The multi-axial proposal for a new neuropsychopharmacological nomenclature is based on a five-axis template that attempts to embody and reflect contemporary neuroscience knowledge and insights. The new concepts in this nomenclature may help the clinician in making informed therapeutic decisions, as well as providing more logical messages to patients regarding the scientific rationale of their treatment.

One of the intentions of the proposed nomenclature is to harness contemporary knowledge in neuroscience to the service of therapeutic decisions i.e. augmentation, combination etc. Although it is not intended to promote off-table use of psychotropic it provides better tools to examine more sophisticated use of our pharmacological armamentarium in personalized-based approach, base of the domain prism, which is imbedded in the proposed template.

In order for it to be utilized, the five-axis template should be applied to both existing medications and new drugs. Once in place, continued use will establish it as a clear, helpful, and intuitive classification system for psychotropic medications.

The results of the four surveys demonstrate the inherent limitations of the available indication-based nomenclature for clinicians. This has resulted in referral to drugs by the first indication awarded—despite its other subsequently-approved usages (e.g., "antidepressants" used to treat anxiety disorders and OCD or "antipsychotics" prescribed for treatment-resistant depression, tic disorders, and some anxiety disorders). Such a practice is not only non-intuitive, confusing, and doubt-inducing for the prescribing clinicians but also causes confusion and thus non-adherence in patients who find it difficult to accept that the medication they have been prescribed belongs to a class designed to treat a different disorder.

Perhaps not coincidentally, this attempt to update psychiatric drug nomenclature accompanies and complements another evolution in psychiatry. Recently, efforts have been invested in identifying endophenotypes of psychiatric diseases—i.e., cognitive and biological markers not readily measurable at a clinical level that are specific to, and indicative of, the disorder (Insel et al., 2010). Here, too, the focus lies on the underlying pathology (endophenotype) rather than the surface symptoms (phenotype).

The current proposal has its weaknesses which include lack of sufficient knowledge of actual mechanism of action of drugs used in psychiatry and how their pharmacological mechanism relates to clinical action. This is true specifically for Axis 1 and 2. However, the suggested nomenclature does reflect the contemporary knowledge as well as the progress in neuroscience since the present classification has been made.

Another weakness is that the proposed nomenclature might be viewed as complicated and cumbersome and hence it may prove insufficiently practical and challenging in gaining clinical acceptance. The four surveys go some way to addressing this issue. Despite the limitations of the system used—a keypad system on three occasions and e-voting in one case—the overall majority of the responders (many of whom see patients and prescribe medication on a regular basis) supported the proposed nomenclature. This endorsement appears to derive from two sources: (a) a clear dissatisfaction with the current system; and (b) an evident

Table 7 Name: agomelatine. *Multi-axial psychopharmacological nomenclature for agomelatine*

Axis 1	**Class** melatonin serotonin **Relevant mechanism**: receptor agonist and antagonist		
Axis 2	**Family** melatonin type 1 and type 2 receptor agonist serotonin 5-HT2C receptor antagonist		
Axis 3	**Neurobiological activity**		
		Animal	Human
	Neurotransmitter effects	Increases extracellular dopamine (DA) and norepinephrine (NE) in the rat prefrontal cortex and hippocampus; no effect on DA in the nucleus accumbens	Unknown
	Brain circuits	Modifies suprachiasmatic nucleus function; increases DA activity in the mesolimbic and mesocortical pathways	Prefrontal cortex, hippocampus, amygdala (fMRI)
	Physiological	Increases DA transmission to the dorsal raphe 5-HT neurons; increases 5-HT firing and 5-HT_{1A} transmission in the hippocampus; reverses the decrease of neurogenesis produced by prenatal stress; resynchronisation of circadian rhythms; increased neuroplasticity	Phase advance of circadian rhythms. No change in sleep architecture, in particular no increase in slow wave sleep as expected with 5HT2 antagonists.
Axis 4	**efficacy and major side effects** anxiety symptoms; rare cases of transient elevation of hepatic enzymes; Little effect on sexual function		
Axis 5	**approved indications** Major depressive disorder		

Committee Note: Rare cases of hepatic failure. A synergy between melatonergic agonist and 5HT2C antagonist actions is believed to exist. GAD indication under regulatory review.

Table 8 vortioxetine. *Multi-axial psychopharmacological nomenclature for vortioxetine*

Axis 1	**Class** serotonin **Relevant mechanism**: reuptake inhibitor, receptor antagonist and partial agonist		
Axis 2	**Family** Multimodel drug: Serotonin reuptake inhibitor, 5-$HT_{3,}$ 5-HT_7, 5-HT_{1D} receptor antagonist, 5-HT_{1A} and 1B receptor partial agonist		
Axis 3	**Neurobiological activity**		
		Animal	Human
	Neurotransmitter effects	Increases 5-HT NA, DA, and ACh in ventral hippocampus and prefrontal cortex Histamine in medial prefrontal cortex 5-HT in nucleus accumbens	Occupies SERT in raphe nucleus (PET)
	Brain circuits	Increases cortical neurotransmitter activity via disinhibition of the raphe nucleus and peripheral 5-HT receptors	
	Physiological		Suppresses REM sleep
Axis 4	**efficacy and major side effects** Improves cognitive dysfunction in depression		
Axis 5	**approved indications** Major depressive disorders		

desire to harness pharmacological insights to the prescription process.

A major task for a proposed nomenclature is to see how it integrates with (rather than replaces) current accepted systems such as the European Drug Index (EDI) and the Anatomical, Therapeutic Chemical (ATC) classification. The proposed nomenclature is actually in line with ATC as it includes a therapeutics component (Axis 4 and 5) and a

chemical component (Axis 1, 2 and 3). Furthermore, being more elaborate, the five-axis template adds useful information for the clinicians.

The change—and the challenge—posed by the new nomenclature is that of turning the current nomenclature upside down; the indications driving the existing nomenclature dropping to Axis 5 and pharmacology being placed at the top of the list. While the five-axis system is convoluted and unwieldy, routine use might be based primarily on Axis 1 (the class). Moving to other axes is optional—dependent to a large extent on how far the clinician wishes to pursue the specific clinical situation facing him. However, the choice of psychotropic drug ideally should encompass the data presented in all axes yet with careful references to Axis 5 (approved indication).

5. Conclusion

The need to update the current classification in order to reflect the contemporary knowledge in neuropsychopharmacology is clear to researchers and clinicians alike. A five axises system which focuses on pharmacology rather than indication is proposed.

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Conflict of interest

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