Beyond the antidepressant label: Neuroscience-based Nomenclature

Pierre Blier, MD, Ph.D
Professor, Psychiatry and Cellular & Molecular Medicine
University of Ottawa
Endowed Chair and Director
Mood Disorders Research
The Royal Institute of Mental Health Research
Canada Research Chair, Psychopharmacology
Disclosures

Investigator-initiated grants, and/or scientific presentations, and/or advisory boards, and/or scientific expertise in litigation cases

- Allergan
- BMS/Otsuka
- CIHR (Canadian Gov.)
- Eli Lilly
- Forest/Activis
- Johnson & Johnson
- Lundbeck
- Meda-Valeant
- Merck
- NIMH
- Ontario Brain Institute
- Pfizer
- Servier
- Shire
- Sunovion
- Takeda

None for the Neuroscience-based Nomenclature Task Force
Plan of the presentation

- To further illustrate that the current classification (nomenclature) is illogical and confusing because it uses names based upon the initial licensed clinical action
- Demystify the overuse of “antidepressants” based on faulty nomenclature
- Provide examples of medications used for depression based on mechanisms of action
- Look at a future of drug development with and without NbN
The necessity of introducing the Neuroscience-based Nomenclature

- Anti-epileptics have been used in bipolar disorder
- Antidepressants are first-line medications for anxiety disorders and for obsessive compulsive disorder
- The anti-hypertensive medication clonidine is FDA-approved for attention deficit disorder
- Atypical antipsychotics are used in unipolar and/or bipolar depression
- Two anesthetic agents are in development for treatment-resistant depression
The necessity of introducing the Neuroscience-based Nomenclature

- Using the indication-based denominations is confusing for patients, regardless of their diagnosis
- Physicians have to dedicate a significant proportion of their interview time to explain the rationale of their pharmacological intervention(s)
- Many of our patients have cognitive deficits and may not grasp the importance of our explanations
- Many return home confused...
The necessity of introducing the Neuroscience-based Nomenclature

- They often delay or may not even fill their prescription because they will have to see their, perhaps-not-so-friendly neighborhood, pharmacy staff
- Compliance, possibly already impaired by cognitive deficits, may be hindered
- Suboptimal and inadequate treatment duration will occur, often leading to relapse and/or recurrence
Efficacy/Tolerability/Compliance

Euthymia
Symptoms
Syndrome
Treatment phases

Increased severity

Time

Minimum Amount of Recommended Treatment

30% stop medicine

Response

Acute
(6 to 12 wk)

Continuation
(4 to 9 mo)

Maintenance
(≥1 yr)

Relapse

Remission Relapse

Recurrence

≈70% of patients no longer on medication

≈50% stop medicine

30% stop medicine


*Clinical Practice Guideline No. 5: Depression in Primary Care, Vol. 2*. Agency for Health Care Policy and Research; 2000.


The beta-blocker propranolol (Inderal®) can be used:

- To treat high blood pressure
- To decrease supraventricular tachycardia
- To prevent migraine headaches
- To treat essential tremors
- To decrease performance anxiety
- To cheat in shooting contests…
A semi-consensus in Psychiatry?

- Selective serotonin reuptake inhibitors not always referred to as “antidepressants”
- Patients with anxiety disorders usually do not require as much education concerning their prescription
- Patients with OCD commonly know that SSRIs are first-line medications for their condition
Unintended consequences of inadequate classification for psychotropics

- Increasing stigma

- Strengthening the anti-psychiatry movement...

- Putting under the same umbrella “antidepressants, anxiolytics, antipsychotics,” and other drugs can create the perception of an over-consumption of psychotropic agents
Use of “antidepressants” in various countries

Defined daily dose per 1,000 people per day

Prevalence of psychiatric disorders for potential use of “antidepressants”

Table 2  Prevalence of mental disorders according to the MINI\textsuperscript{a}

<table>
<thead>
<tr>
<th>Disorder (prevalence period)</th>
<th>$n = 3345$</th>
<th>Unweighted prevalence</th>
<th>Weighted prevalence</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depressive episode (current)</td>
<td>157</td>
<td>4.7</td>
<td>4.4</td>
<td>3.4–5.5</td>
</tr>
<tr>
<td>Dysthymia (2 years)</td>
<td>20</td>
<td>0.6</td>
<td>0.4</td>
<td>0.1–0.7</td>
</tr>
<tr>
<td>Panic disorder (current)</td>
<td>39</td>
<td>1.2</td>
<td>1.3</td>
<td>0.7–1.9</td>
</tr>
<tr>
<td>Agoraphobia (1 month)</td>
<td>175</td>
<td>5.2</td>
<td>4.6</td>
<td>3.5–5.6</td>
</tr>
<tr>
<td>Social phobia (1 month)</td>
<td>77</td>
<td>2.3</td>
<td>2.2</td>
<td>1.4–2.9</td>
</tr>
<tr>
<td>Generalized anxiety disorder (6 months)</td>
<td>145</td>
<td>4.3</td>
<td>4.2</td>
<td>3.2–5.2</td>
</tr>
<tr>
<td>Panic disorder with agoraphobia</td>
<td>45</td>
<td>1.4</td>
<td>1.2</td>
<td>0.7–1.8</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Diagnoses were considered valid if they were associated with “a lot” of interference with life.

# Use of “antidepressants” in medical issues

<table>
<thead>
<tr>
<th>Reason</th>
<th>TCAs %</th>
<th>SSRIs %</th>
<th>Venlafaxine %</th>
<th>Other %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>33.3</td>
<td>67.1</td>
<td>70.7</td>
<td>73.2</td>
</tr>
<tr>
<td>Anxiety</td>
<td>16.7</td>
<td>8.4</td>
<td>8.5</td>
<td>19.5</td>
</tr>
<tr>
<td>Stress</td>
<td>0.0</td>
<td>2.1</td>
<td>6.1</td>
<td>9.8</td>
</tr>
<tr>
<td>Sleep</td>
<td>43.3</td>
<td>17.5</td>
<td>23.2</td>
<td>53.7</td>
</tr>
<tr>
<td>Low energy</td>
<td>0.0</td>
<td>1.4</td>
<td>1.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Migraine headaches</td>
<td>23.3</td>
<td>6.3</td>
<td>8.5</td>
<td>7.3</td>
</tr>
<tr>
<td>Pain management</td>
<td>33.3</td>
<td>12.6</td>
<td>9.8</td>
<td>36.6</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>26.7</td>
<td>0.7</td>
<td>4.9</td>
<td>4.9</td>
</tr>
</tbody>
</table>

*Table 3  Reported reasons for AD use*¹

¹Among subjects who reported using 1 or more ADs. Subjects were allowed to report more than one reason for use, hence, some percentages add up to > 100%.

---

Unintended consequences of inadequate classification for psychotropics (contd)

- Before evaluating the overuse/underuse of medication(s):
  - We must know the prevalence of a condition
  - We must know the reason why a medication is used
  - We should know if more than one medication is used in the same patient for the same purpose (i.e. for combination or combination)
Evolution of treatments for depression

“Antidepressants”

- **1950s**: Uptake blockers
  - Tricyclic antidepressants
- **1960s**: MAOIs
  - Phenelzine
- **1970s**: 5-HT/NE receptor drugs
  - Norepinephrine (NE) selective
  - Serotonin (5-HT) selective
  - RIMAs
  - Mianserin
  - Mirtazapine (NaSSa)
- **1980s**: SSRIs
  - Bupropion
- **1990s**: SNRI/s NSRIs
  - Agomelatine
  - Vilazodone
- **2000s**: Vortioxetine, lurasidone; adjuncts: aripiprazole, brexpiprazole
- **2010s**: Licensed treatments:
  - Depression
  - Anxiety
  - OTHERS…
Functional connectivity

5-HT for NE neurons

5-HT2A for NE neurons

5-HT2C for DA neurons
What are these new terms?

**Unimodal**
1 mode of action (reuptake inhibition)

**Multifunctional**
2 pharmacological targets but 1 mode of action (reuptake inhibition)

**Multifunctional**
3 pharmacological targets but 1 mode of action (receptor activity)

SSRI

Multifunctional
3 pharmacological targets but 1 mode of action (receptor activity)

SNRI

Multifunctional
2 pharmacological targets but 1 mode of action (reuptake inhibition)

Aripip.

D2 agonism
5-HT$_{1A}$ agonism
5-HT$_{2A/2C}$ antagonism

SERT

Dose-dep.

NET
What is multimodal?

**Vilazodone**
- 2 pharmacological targets
- 2 modes of action (receptor activity + reuptake inhibition)

**Vilazodone**
- SERT (SSRI)
- 5-HT$_{1A}$ (Buspirone +)

**Quetiapine**
- Multimodal
- 4 targets and 2 modes of action (receptor activity + reuptake inhibition)

**Quetiapine**
- NET
- 5-HT$_{1A}$ (+)
- 5-HT$_{2A/2C}$ (-)
- $\alpha_2$ (-)
Vilazodone

LOCUS COERULEUS

RAPHE

5-HT

POSTSYNAPTIC NEURON

5-HT

5-HT

5-HT1A

NE

α₁

α₂

β₁

5-HT

α₂

α₁

α₂

α₂

(+)

(-)
The SSRI/5-HT$_{1A}$ agonist still inhibits rat 5-HT neuronal firing in the absence of serotonin through the 5-HT$_{1A}$ receptor

What is multimodal?

Multimodal
6 pharmacological targets and
2 modes of action
(receptor activity + reuptake inhibition)
The serotonin (5-HT) system:

Serotonin Syndrome:
- Increased heart rate & blood pressure
- Myoclonus, increased CPK
- Hyperthermia
- Abdominal cramps/diarrhea
- Increased tendon reflexes (+ve Babinski)
- Agitation and/or Confusion
- Death

Courtesy of Steve Szabo, MD, PhD
Amitriptyline (Elavil®) is also a multimodal agent

1) is a potent histamine 1 receptor antagonist
2) is a potent serotonin (5-HT)\textsubscript{2A} receptor antagonist
3) Is a potent 5-HT\textsubscript{2C} receptor antagonist

1) can inhibit 5-HT reuptake
2) can inhibit NE reuptake
<table>
<thead>
<tr>
<th>Class</th>
<th>serotonin multimodal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of action</td>
<td>serotonin &amp; norepinephrine reuptake inhibitor; serotonin antagonist</td>
</tr>
</tbody>
</table>

**Domain 1: Indications**
- major depressive disorder;
- chronic pain

**Domain 2: Efficacy**
- improves symptoms of depression & anxiety; reduces chronic pain in low d.

**Side effects**
- dry mouth, blurry vision, urinary hesitancy, constipation, orthostatic hypotension, toxic (potentially lethal) in overdosage

**Practical notes:** at low doses (~50 mg) is primarily a H1 and 5-HT$_{2A}$ antagonist; mainly metabolized by CYP 2D6; ¼ doses to be in used in slow and higher doses in ultra rapid metabolizers
The Curious Case of Benjamin Button
Ketamine/Esketamine

- Ketamine is a dissociative anesthetic agent at 2 mg/kg, iv, given in a bolus
- It has been in clinical practice for over 40 years
- It does not depress breathing or cardiovascular parameters
- It is the most used anesthetic worldwide
- It is commonly used in pediatric ER for transient anesthesia
- And yes…some people have put it on street as a recreational drug!
Rapid but transient therapeutic effect of low-dose slow infusion of ketamine in MDD

Zarate et al, Arch Gen Psychiat 2006

Murrough et al, Am J Psychiat 2013

* Placebo
○ Ketamine

0 5 10 15 20 25 30
21-item HDRS Score

-60 min 40 min 80 min 110 min 230 min Day 1 Day 2 Day 3 Day 7

Murrough et al, Am J Psychiat 2013

Red: Ketamine (N=47)
Orange: Midazolam (N=25)

Day 1 Day 2 Day 3 Day 7

Response Rate (%)
In absence of NbN, what would ketamine and related agents be called?

Ongoing research also indicate a therapeutic effect in OCD, PTSD, and robustly decreases anxiety.

Ketamine is short-acting NMDA antagonist, a norepinephrine reuptake inhibitor, a serotonin reuptake inhibitor, a μ-opiod agonist, a σ-receptor ligand, and it increases AMPA receptor responsiveness.

To be continued…
Conclusions

- NbN will help decrease stigma
- Improved compliance will improve outcome it will promote site-directed rational pharmacotherapy
- It will reduce irrational polypharmacy
- This classification better justifies our use of various medications to treat syndromes and/or symptom domains
- NbN allows to categorize novel agents and avoid confusion among scientists, clinicians, patients, and hopefully in the future regulatory agencies