Antidepressant drugs

Prof. Nicoletta Brunello
Department of Life Sciences
University of Modena and Reggio Emilia
Depression is a disease of the entire body

Depression not only affects your brain and behavior—it affects your entire body.

National Institute of Mental Health
# Depression

## Leading causes of disability-adjusted life years (DALYs) in all ages

<table>
<thead>
<tr>
<th></th>
<th>2001</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lower respiratory infections</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>2</td>
<td>Perinatal conditions</td>
<td>Unipolar depressive disorder</td>
</tr>
<tr>
<td>3</td>
<td>HIV/AIDS</td>
<td>Road traffic accidents</td>
</tr>
<tr>
<td>4</td>
<td>Unipolar depressive disorder</td>
<td>Cerebrovascular pathologies</td>
</tr>
<tr>
<td>5</td>
<td>Diarrhoeal disease</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
</tbody>
</table>

Major depression is a common illness that severely limits psychosocial functioning and diminishes quality of life. In 2008, WHO ranked major depression as the third cause of burden of disease worldwide and projected that the disease will rank first by 2030. In practice, its detection, diagnosis, and management often pose challenges for clinicians because of its various presentations, unpredictable course and prognosis, and variable response to treatment.

Despite this, unravelling the neurobiological basis of the etiology of depression is still a challenge.
Key symptoms of Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 for major depressive disorder

- Depressed mood
- Anhedonia
- Feelings of worthlessness or guilt
- Suicidal ideation, plan, or attempt
- Fatigue or loss of energy
- Sleep ↓ or ↑
- Weight or appetite ↓ or ↑
- Ability to think or concentrate, or indecisiveness
- Psychomotor retardation or agitation

Symptoms of depression (2 weeks)

Cumulative functional impairment

Fundamental symptoms
Emotional symptoms
Neurovegetative symptoms
Neurocognitive symptoms
Evolution of antidepressant drugs


MAO inhibitors

MAO-I

TCA

Serendipity

phenelzine

tranylcypromine
Evolution of antidepressant drugs


MAO inhibitors
- phenelzine
- tranylcypromine

Tricyclic antidepressants
- imipramine
- amitriptyline
- clomipramine
Tricyclic antidepressants

- Dizziness
- Orthostatic hypotension
- Ejaculatory problems
- Weight gain
- Drowsiness
- Dizziness

Dry mouth, constipation, urinary retention, blurred vision, tachicardia, cognitive disturbances

- Membrane stabilization: A-V conduction, ventricular arrhythmias
- Complex effects: tremor, reduction seizure threshold, (mioclonus, epilepsy) manic switch

ANTIDEPRESSIVE EFFECT
Evolution of antidepressant drugs


Monoamine hypothesis of depression

• Depletion of catecholamines results in induction of depression
• Inhibition of neurotransmitter reuptake or degradation improves symptoms of depression
• Depression might be caused by a deficiency of monoaminergic neurotransmitters
  • serotonin
  • noradrenaline
  • dopamine

Serendipity

• Depression might be caused by a deficiency of monoaminergic neurotransmitters
Monoamine hypothesis of depression

normal

depressed

treated

Presynaptic

Postsynaptic

• IMAO
• TCA
• SSRI
• NARI
• SNRI
Key areas of the brain implicated in depression

- Hippocampus
- Amygdala
- Orbitofrontal Cortex
- Prefrontal Cortex
- Anterior Cingulate Cortex
Serotonin (5-HT) and Norepinephrine (NE) Pathways in the Human Brain
Evolution of antidepressant drugs


Serendipity

MAO-I

TCA

Refinement

SSRI

Fluoxetine

Citalopram

Paroxetine

Fluvoxamine

Sertraline
Mechanism of action of SSRI

Advantages of SSRI

- low acute toxicity
- no reaction with diet component
- lack of collateral cardiovascular effect
Pharmacodynamic and pharmacokinetic profile of SSRI

- **Fluoxetine** (SRI)
  - CYP2D6
  - CYP3A4
  - NRI
  - 5HT₂

- **Citalopram** (SRI)
  - H-1

- **Sertraline** (SRI)
  - DRI
  - Sigma

- **Paroxetine** (SRI)
  - CYP2D6
  - M-ACh
  - NRI
  - NOS

- **Escitalopram** (SRI)
  - CYP1A2
  - CYP3A4

- **Fluvoxamine** (SRI)
  - Sigma
## SSRI: SIDE EFFECTS

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Fluvoxamine (%)</th>
<th>Fluoxetine (%)</th>
<th>Sertraline (%)</th>
<th>Paroxetine (%)</th>
<th>Citalopram (%)</th>
<th>Escitalopram (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>26</td>
<td>11</td>
<td>14.3</td>
<td>16.4</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>4</td>
<td>3.5</td>
<td>7</td>
<td>6</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>4</td>
<td>5.3</td>
<td>8.4</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Anejaculation</td>
<td>7</td>
<td>1.9</td>
<td>13.3</td>
<td>12.9</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>14</td>
<td>5.9</td>
<td>7.5</td>
<td>14.3</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Weight gain</td>
<td>&lt; 1</td>
<td>7</td>
<td>5</td>
<td>25</td>
<td>&lt; 5</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

Evolution of antidepressant drugs

- **1950**
  - MAO-I
- **1960**
  - MAO-I
  - TCA
- **1970**
  - MAO-I
  - TCA
- **1980**
  - MAO-I
  - TCA
  - SSRI
- **1990**
  - MAO-I
  - TCA
  - SSRI
  - venlafaxine
  - mirtazapine
- **2000**
  - MAO-I
  - TCA
  - SSRI
  - venlafaxine
  - mirtazapine
  - escitalopram
  - duloxetine
- **2010**
  - MAO-I
  - TCA
  - SSRI
  - venlafaxine
  - mirtazapine
- **2015**
  - MAO-I
  - TCA
  - SSRI
  - venlafaxine
  - mirtazapine
- **2019**
  - MAO-I
  - TCA
  - SSRI
  - venlafaxine
  - mirtazapine

**Serendipity** vs **Refinement**
Noradrenaline and serotonin re-uptake inhibitors (SNRI)

Desvenlafaxine (Pristiq)
Duloxetine (Cymbalta, Xeristar)
Milnacipran (Ixel)
Venlafaxine (Efexor, Zarelis)

**SELECTIVITY - :**
- low doses mainly on serotonin transmission
- moderate doses on both systems
- high doses even on dopamine transmission

**SIDE EFFECTS** of SNRI are partly similar to those of SSRI (nausea, gastrointestinal discomfort) and partly typically noradrenergic (tachycardia, increased blood pressure, weight gain and increased appetite)
Noradrenergic and Specific Serotonergic Antidepressant Antagonism

**mirtazapine**

- **5HT**$_{2A}$ antagonism = no sexual disturbances
- **5HT**$_{3}$ antagonism = antiemetic effect
- **5HT**$_{2C}$ + H1 antagonism = sedation and weight gain
Interaction of other antidepressants with CYP450

- Venlafaxina (NRI, SRI)
  - CYP2D6: ++

- Duloxetina (NRI, SRI)
  - CYP2D6: +

- Mirtazapina (α2, 5-HT3)
  - CYP2D6: +

- Trazodone (H1, α-1, 5-HT2A, 5-HT2c, 5-HT3)
  - DARI

- Bupropione (NRI)
  - CYP2D6: ++
| CYP 1A2 | Caffeina, teofillina, aminofillina, paracetamolo, fenacetina, clozapina, propranololo, R-warfarin, imipramina, triciclici | 0 | + | ++ | ++ | 0 | 0 |
| CYP 2C9 | Ibupofene, naprossene, fenitoina, S-warfarin, tolbutamide | 0 | ++ | ++ | ++ | 0 | 0 |
| CYP 2C19 | S-mefenitoina, omeprazolo, propranololo, diazepam, citalopram, triciclici | 0 | ++ | ++ | ++ | 0 | 0 |
| CYP 2D6 | Codeina, destrometorfano, triciclici, captopril, flecaainde, encainide, tioridazina, perfenazina, clozapina, risperidone, aloperidolo, propranololo, timololo, metoprololo, paroxetina, fluoxetina | +/+ | +++++ | + | +++++ | + | 0/+ |
| CYP 3A4 | Cisapride, terfenadina, astemizolo, pimozide, loratadina, ciclosporina, triciclici, nefazodone, sertralina, zolpidem, corticosteroidi, eritromicina, carbamazepina, lidocaina, chinidina, triazolam, midazolam, alprazolam | + | + | + | ++ | 0 | 0 |

0 = absent  ++ = weak  +++ = mild  ++++ = moderate  ++++= high
Evolution of antidepressant drugs


**Serendipity**

MAO-I

TCA

**Refinement**

SSRI

venlafaxine
mirtazapine
reboxetine

agomelatine

escitalopram
duloxetine
Evolution of antidepressant drugs


MAO-I
TCA

SSRI

venlafaxine
mirtazapine
reboxetine

agomelatine

escitalopram
duloxetine

..Tailoring

Serendipity

Refinement

vortioxetine
ADVERSE EFFECTS LINKED WITH PHARMACOLOGICAL PROFILE

Traditional Antidepressants

5-HT reuptake inhibition

5-HT agonism

NE reuptake inhibition

α1 antagonism

α2 antagonism

H1 antagonism

Ach antagonism

DA reuptake inhibition

Psychomotor activation

Psychosis

Sexual dysfunction

Activating side effects

Nausea

GI disturbances

Activating effects

Dry mouth - Urinary retention - Activating effects - Tremor-CV troubles

Dizziness

Reflex tachycardia

Urinary retention

Memory dysfunction

Postural hypotension

Priapism

Blurred vision

Dry mouth

Constipation

Sinus tachycardia

Urinary retention

Memory dysfunction

Postural hypotension

Priapism

Blurred vision

Dry mouth

Constipation

Sinus tachycardia

Urinary retention

Memory dysfunction
Acute effect of antidepressant drugs

- TCA, SSRIs, SNRIs, NRIs, NDRIs
- Reuptake
- Presynaptic receptors
- MAOI, RIMA
- NT Catabolism
- $\alpha_2$ antagonists
- Increased synaptic concentration of neurotransmitters
Limits of monoamine hypothesis

- Dietary monoamines depletion does not induce depression in healthy individuals
- Primary drug action is much faster than therapeutic effect
- Studies of drug-receptor interaction (binding assay) “down regulation” of 5-HT2 and β NA receptors induced by chronic treatment with antidepressants

hypothesis of dysregulation of receptor-mediated functions
Dysregulation of receptor-mediated functions

- Amount of neurotransmitter
- Receptor sensitivity
- Clinical effect
Evolution of hypotheses on pathophysiology/ pharmacotherapy of mood disorders

- **Monoaminergic hypothesis (1960-70s)**
  Depression is caused by a decreased availability of monoaminergic neurotransmitters. Antidepressants boost monoamine levels.

- **Monoaminergic receptor hypothesis (1980s)**
  Depression is caused by abnormalities in monoamines receptors. Chronic antidepressants alter sensitization state of receptors.

- **Hypothesis of signaling adaptation (1990s)**
  Chronic antidepressants induce adaptive changes in post-receptor signaling cascades, and in gene expression.

- **Hypothesis of neuroplasticity (2000s)**
  Chronic antidepressants change neuroplasticity, cellular resilience and synaptic plasticity.
Antidepressant mechanism
A cascade of neuroplasticity events

Regulation of neurotransmitters availability

Regulation of neurotransmitter receptors expression/function

Regulation of intracellular signaling cascades

Control of gene expression

Neuroplasticity, Cellular resilience, Neurogenesis

Synaptic plasticity

Target genes

Control of gene expression
NEUROTROPHIC HYPOTHESIS OF DEPRESSION
NEUROTROPHIC HYPOTHESIS OF DEPRESSION

Normal state

Depressed state

Treated state

BDNF
Monoamines
Glutamate
Other signals

BDNF
Monoamines
Glutamate
Other signals

BDNF
Monoamines
Glutamate
Other signals

Glucocorticoids
Deficits of neuronal plasticity associated with major depression

Reduced volume and functional activity of selected cerebral structures

Hippocampus
Prefrontal, frontal and temporal cortex

Reduced number of glial cells in prefrontal cortex

Stress can exert major effects on brain function through the modulation of mechanisms impinging on neuronal plasticity
Increase of glutamate release

Altered expression and function of neuroplastic markers as well as proteins involved in cell-cell communication and neuronal resiliency

Neurotrophic factors (BDNF)
Cerebral atrophy and major depression

* Significant inverse relationship between total hippocampal volume and the length of time depression went untreated.


“Childhood trauma associated with smaller hippocampal volume in women with major depression”  

“Amygdala and hippocampus volumes in pediatric major depression”  
Neurotrophic hypothesis of depression

- Atrophy of selected brain structures can be associated with depression.
- These changes may represent the consequence of genetic dysfunction and/or the result of adverse life experiences (stress).
- Structural and functional impairment is the consequence of altered expression and function of proteins involved in synaptic plasticity and cellular resiliency.
- Chronic administration of antidepressants induces \( \uparrow \) BDNF in hippocampus.
- Time course of response for antidepressants corresponds to delay of trophic factor synthesis (much more than to receptor modifications).
- The neurotrophin BDNF appears to be a key element in this context and a potential target for long-term pharmacological intervention.
Future drugs: direct action on BDNF?

Advantages:
- Direct action on plasticity

Limits:
- Lack of small agonist molecules
- Different and/or opposite effect of BDNF in other neuronal circuits

Post-mortem data from depressed humans show that depression is associated with a decrease in the amount of BDNF in the hippocampus and an increase (of similar magnitude) in the NAc, an example of the regional specificity of depression-related neuroplastic changes.
Linking conventional antidepressants to reductions in NMDA receptor function: a framework for the development of novel therapies.
Evolution of antidepressant drugs


MAO-I
TCA

Serendipity

Refinement

venlafaxine
mirtazapine
reboxetine

SSRI
escitalopram
duloxetine

agomelatine

..Tailoring

vortioxetine
esketamine
PROPOSED MECHANISMS OF ACTION OF KETAMINE AS ANTIDEPRESSANT
PROPOSED MECHANISMS OF ACTION OF KETAMINE AS ANTIDEPRESSANT

Fast de-suppression of BDNF protein translation and downstream neurotrophic signaling
Pharmacotherapy of major depressive disorder: antidepressant actions at the synapse

Presynaptic neuron
- eg. raphe nucleus, locus coeruleus
- S-HTT
- α2-adrenergic R
- NAT
- DAT
- MAO
- α1-adrenergic
- α2-adrenergic R

Postsynaptic neuron
- eg. hippocampus
- S-HT_T, R
- S-HT_T, R
- S-HT_T, R
- S-HT_T, R
- α1-adrenergic
- α2-adrenergic R
- H1 R
- Muscarinic acetylcholine R
- Ca^{2+}-dependent or MAPK cascades
- Cell signalling
- CREB
- PKA
- ProBDNF
- mBDNF
- Cytoplasm
- Nucleus

Neurotransmission

Neural network remodelling

Transporters
- S-HT
- NA
- DA
- Medication

Receptors
- Presynaptic
  - S-HT_{1A}
  - S-HT_{1B}
  - S-HT_{2A}
- Postsynaptic
  - S-HT_{1A}
  - S-HT_{1B}
  - α2
  - H1
  - M1

Other key actions
- Agomelatine
- Amitriptyline
- Bupropion
- Clomipramine
- Desvenlafaxine
- Duloxetine
- Escitalopram
- Fluoxetine
- Fluvoxamine
- Levomilnacipran
- Mianserin
- Milnacipran
- Mirtazapine
- Moebelamide
- Nortriptyline
- Paroxetine
- Phenelzine
- Reboxetine
- Sertraline
- Tranylcypromine
- Trazodone
- Trimepramine
- Venlafaxine
- Vildazodone
- Vortioxetine

- TCAs
- SSRIs
- α2-adrenergic receptor antagonists
- α2-adrenergic agonists
- H1 antagonists
- MAO inhibitors
- NNRIs
- SNRIs

Neurogenesis
- Maturation
- Transport of mBDNF to dendrites and axons
- TrkB R
- Neural progenitor

Blood vessel
- Endothelial cell
- MDR-Pgp
- Serotonin
- Noradrenaline
- Dopamine
- Acetylcholine
- Histamine
- mBDNF