Safety  Tolerability  Efficacy  Payment  Simplicity (STEPS)

Full Functional Recovery = Efficacy + Tolerability – (Residual + Comorbidities)

Residual symptoms = Cognitive dysfunction
Comorbidities = Pain, Migraine, Anxiety

→ Multimodal antidepressants
Vortioxetine: a new « multimodal » antidepressant (Leiser et al., Br. J. Pharmacol., 2013)
Hypoactivity of the prefrontal cortex in patients with MDD and cognitive dysfunction
Blocking mGlu2 receptors to improve cognition in MDD

Glutamate

mGlu2

mGlu2 → 5-HT$_{2A}$

Glutamate mGlu2 LSD Ketanserine
NAMs Psylocibin

$G_{i/o}$

AC

cAMP

ATP

$5-HT_{2A}$
Development of mGlu2/3 NAMs to improve cognitive dysfunction associated with major depression (Goeldner et al., Neuropharmacol., 2013)
NMDA receptor blockade by ketamine: rapid and efficient antidepressant effect but potential cognitive dysfunction and psychotomimetic effects associated with chronic treatment.

5-HT3 receptor blockade: the key for a cell-specific inhibition of cortical and hippocampal GABAergic interneurons.

Overall effects of vortioxetine:
Reduced GABA transmission
Increased glutamate transmission
Vortioxetine enhances the activity of pyramidal neurons in the mPFC by blocking 5-HT₃ receptors in interneurons

Riga et al., Neuropharmacol., 108, 2016
Vortioxetine enhances neurotransmitter release
(Mork et al., 2012)

\[ \uparrow 5-HT_{1A/1B} = \uparrow DA, \text{Ach} \quad \text{mPFC} \]

\[ \downarrow 5-HT_3 = \downarrow DA, \uparrow \text{ACh} \quad \text{mPFC} \]
MDD patients: failure of hippocampal activation during the encoding phase in non-emotional memory task (Bremner et al., 2004) and during impaired recollection performance in subjects with repeated episodes of MDD (Milne et al., 2012)
Vortioxetine antagonizes synaptic inhibition caused by 5-HT in hippocampal CA1 pyramidal neurons (Dale et al., J. Psychopharmacol. 28, 2014)
Hippocampal LTP: activity-dependent synaptic plasticity and learning and memory

Collingridge et al., Nat Rev Neurosci 2005
Depolarization-dependent activation of NMDA receptors
(Kerchner and Nicoll, Nat. Rev. Neurosci., 2012)
Vortioxetine enhances LTP in hippocampal slices and corrects stress-induced LTP impairment in vivo
Comorbidity between depression and chronic pain

Pain Matrix
Perception
Emotion
Cognition
Behavior
Top-down 5-HT becomes hyperalgesic in chronic pain (Ossipov et al., J. Clin. Inv., 2010; Zhang et al., Nat. Med. 2011)

**Hyperalgesic in chronic pain**
(5-HT₃, 5-HT₂B)
Clinical profile of vortioxetine based on the multimodal MoA

Efficacy (↓ SERT, ↓ 5-HT3)

Effect on cognitive symptoms (↓ 5-HT3, ↑ ACh rel.)

Excellent PK and tolerability profile

Lack of psychotomimetic effects (↓ 5-HT3)

Anxyolitic effect (↑ 5-HT1A)
(Pae et al. J. Psych. Res., 2015; Baldwin et al., JAD, 2016)

Predicted analgesic effect (↓ 5-HT3)
Safety, Tolerability, Efficacy, Payment, Simplicity (STEPS)

**Full Functional Recovery** = Efficacy + Tolerability – (Residual + Comorbidities)
Residual symptoms = Cognitive dysfunction

Neurodegenerative disorders, MS, chronic pain
QoL = Efficacy + Tolerability + Adequate control of psychiatric comorbidities

Multimodal antidepressants
FFR = Efficacy + Tolerability – (Residual + Comorbidities)

No effect on cQT (safety)
Favorable profile of tolerability
No sexual dysfunction
No increase in body weight

Long elimination $t_{1/2}$
Preferential metabolism by CYP2D6
No CYP inhibition
No CYP induction
Vortioxetina

<table>
<thead>
<tr>
<th></th>
<th>5-HT1a</th>
<th>5-HT1b</th>
<th>5-HT1d</th>
<th>5-HT2c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erezione</td>
<td>↓↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Eiaculazione</td>
<td></td>
<td>Accelerata</td>
<td>Ritardata</td>
<td>?</td>
</tr>
<tr>
<td>Peso corporeo</td>
<td>↑</td>
<td>↓</td>
<td></td>
<td>↓</td>
</tr>
</tbody>
</table>
Vortioxetine does not inhibit any major CYP isoform
Spina and Santoro, Riv. Psich., 2015

Table 1. Inhibitory effect of newer antidepressants on cytochrome P450 (CYP) enzymes

<table>
<thead>
<tr>
<th></th>
<th>CYP1A2</th>
<th>CYP2C9</th>
<th>CYP2C19</th>
<th>CYP2D6</th>
<th>CYP3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0/+</td>
<td>0</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>+</td>
<td>++</td>
<td>+/+</td>
<td>+++</td>
<td>+/+</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Sertraline</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+/+</td>
<td>+</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bupropion</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Agomelatine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0/+</td>
<td>0</td>
</tr>
<tr>
<td><strong>Vortioxetine</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

0= minimal or no inhibition; + = mild inhibition; ++ = moderate inhibition; +++ = potent inhibition
Modified from Spina and de Leon25.
Safety  Tolerability  Efficacy  Payment  Simplicity
(STEPS)

Full Functional Recovery = Efficacy + Tolerability – (Residual + Comorbidities)
Residual symptoms = Cognitive dysfunction

Neurodegenerative disorders, MS, chronic pain
QoL = Efficacy + Tolerability + Adequate control of psychiatric comorbidities

↓
Multimodal antidepressants
Network oscillations and cognitive functions

Ulhhaas and Singer, Nat. Rev Neurosci. 2010
5-HT\textsubscript{3} Receptors are localized on calretinin-positive GABAergic interneurons in the hippocampus

Dale et al., CNS Spectrum, 2016

<table>
<thead>
<tr>
<th></th>
<th>Gpe/Gpi</th>
<th>STN</th>
<th>Striatum</th>
<th>SNpc/SNpr</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT_{1A}</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>5-HT_{1B}</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>5-HT_{3}</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>5-HT_{7}</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Activation of 5-HT$_{1A}$ receptors attenuates the potentiation of haloperidol-induced bradykinesia by fluoxetine (Shimizu et al., 2013)
Activation of 5-HT$_{1A}$ receptors improves motor fluctuations and LIDs in rodents and primates (Bibbiani et al., Neurology, 2001)
5-HT3 receptor blockade attenuates haloperidol-induced bradykinesia and catalepsy (Ohnu et al., Neuropharmacol., 2011)
The TCR-calcineurin-NFAT-IL2 pathway in T cell activation
5-HT3 receptor blockade prevents T cell activation by targeting the calcineurin pathway (De La Vega et al., Biochem. Pharmacol., 2005)
Anti-inflammatory and immune suppressive activity of 5-HT$_3$ receptor antagonists
(Fakhfouri et al., Drug Disc. Today, 2012)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Setting investigated</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tropisetron</td>
<td>INS-1 cell line</td>
<td>↑Insulin release</td>
</tr>
<tr>
<td>Granisetron</td>
<td>Experimental IBD</td>
<td>↓Colonic levels of TNF-α, IL-1β, IL-6 and MDA, ↓colonic MPO activity, ↓histologic and macroscopic damage score</td>
</tr>
<tr>
<td>Tropisetron</td>
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</tr>
<tr>
<td>Tropisetron, Ondansetron</td>
<td>SEB- or PMA + lo-stimulated human T cells</td>
<td>↓T cell activation</td>
</tr>
<tr>
<td>Tropisetron</td>
<td>SEB-stimulated human T cells</td>
<td>↓IL-2</td>
</tr>
<tr>
<td>Tropisetron, Ondansetron</td>
<td>PMA + lo-stimulated Jurkat T cell line</td>
<td>Inhibition of NFAT, AP-1 and NF-κB transcriptional activity</td>
</tr>
<tr>
<td>Ondansetron, Tropisetron</td>
<td>Human airway</td>
<td>Blockade of 5-HT-induced contraction</td>
</tr>
<tr>
<td>Tropisetron</td>
<td>Cerebellar granule neurons</td>
<td>Inhibition of calcineurin activity</td>
</tr>
<tr>
<td>Tropisetron, Ondansetron</td>
<td>LPS-stimulated human monocytes</td>
<td>↓TNF-α and IL-1β release</td>
</tr>
<tr>
<td>Tropisetron</td>
<td>Serotonin-stimulated macrophage-like synovial cells</td>
<td>↓PGE$_2$</td>
</tr>
<tr>
<td>Tropisetron</td>
<td>Osteoarthritis, rheumatoid arthritis</td>
<td>↓Joint swelling and pain</td>
</tr>
<tr>
<td>Granisetron</td>
<td>TMJ arthritis</td>
<td>↓Movement pain</td>
</tr>
<tr>
<td>Tropisetron</td>
<td>Experimental embolic stroke</td>
<td>↓Brain edema and infarct volume, ↓cortical TNF-α and MPO</td>
</tr>
<tr>
<td>Tropisetron</td>
<td>Experimental sepsis</td>
<td>↓IL-6 and noradrenaline</td>
</tr>
</tbody>
</table>
Clinical profile of vortioxetine based on the multimodal MoA

Efficacy (↓ SERT, ↓ 5-HT3)

Effect on cognitive symptoms (↓ 5-HT3, ↑ ACh rel.)

Excellent PK and tolerability profile

Lack of psychotomimetic effects (↓ 5-HT3)

Anxyolitic effect (↑ 5-HT1A)

(Pae et al. J. Psych. Res., 2015; Baldwin et al., JAD, 2016)
Alzheimer’s disease: \( \uparrow \text{ACh release} \)

Parkinson’s disease: \( \uparrow 5-HT_{1A} \downarrow 5-HT_3 \)

L-DOPA-induced dyskinesias: \( \uparrow 5-HT_{1A} \)

Multiple Sclerosis: \( \downarrow 5-HT_3 \)

Neuropathic pain/Migraine: \( \downarrow 5-HT_3 \)

but….. PD interaction with triptans (\( \downarrow 5-HT_{1D} \))
Bioactivation of tamoxifen by CYP2D6 avoid combination with vortioxetine

Fluoxetine
Paroxetine
Duloxetine
Inhibition of 5-HT synthesis in the RVM causes analgesia in chronic pain (Wei, et al., J. Neurosci. 30, 2010)

Serotonergic pathways descending from the RVM are hyperalgesic in chronic pain
Safety  Tolerability  Efficacy  Payment  Simplicity 
(STEPS)

Full Functional Recovery = 
Efficacy + Tolerability – (Residual + Comorbidities)

Residual symptoms = Cognitive dysfunction
Comorbidities = Pain, Migraine, Anxiety

Multimodal antidepressants
Metabolizzatori rapidi
CYP2D6*1/CYP2D6*2

Metabolizzatori lenti (3-5% caucasici)
CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6

Metabolizzatori intermedi
CYP2D6*10, CYP2D6*17, CYP2D6*41

Metabolizzatori ultrarapidi (ca. 3-4% caucasici)
CYP2D6*1 o 2xN (15-20% Etiopi, Algerini)

Inibitori CYP2D6 da evitare:
Chinidina, Celecoxib, Amiodarone, Terbinafina,
Paroxetina, Fluoxetina, Bupropione, Duloxetina,
Aloperidolo, Levomepromazina
Epigenetic suppression of inhibitory interneurons hyperactivates 5-HT raphe neurons in neuropathic pain (Zhang et al., Nat. Med. 2011)
Metabolism of vortioxetine by cytochrome-P450
New frontiers in the treatment of depression

Treating drug-resistant patients

Shortening the temporal latency

Improving cognitive symptoms

Activation of cortical and hippocampal pyramidal neurons via a cell-specific inhibition of GABAergic interneurons
Defective cortical activation during the execution of an executive task in depressed patients (Elliot, Trends Cogn. Sci., 1998)
Vortioxetine promotes earlier changes in dendrite morphology with respect to fluoxetine in the hippocampus (Chen et al., Eur. Neuropsychopharmac., 2016)
Le regioni della pain matrix (soprattutto giro del cingolo, corteccia insulare, amigdala): crocevia tra dolore cronico e patologie psichiatriche (ansia, depressione)
CYP2D6 has a major role in vortioxetine metabolism
5-HTTLPR polymorphism: S/S = low; L/L = high

+ rs25531 SNP

$L_A/L_A = high$ expression

S/S = low expression

$L_G/L_G = low$ expression
Functional anatomy of the dorsal raphe nucleus
(Jasinska et al., TINS 2012)
Rapid desensitization of 5-HT1A receptors and recovery of DRN neuron firing rate following vortioxetine (Betry et al., 2013)
Perspective: To study the temporal latency of vortioxetine in S/S, S/L, and L/L patients.
Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study


Cortical layer V

Deep cortical layers

Brainstem

NMDAR

Glutamate release

5-HT2A

Psilocin/
LSD/DMT

PSL

BDNF

AMPA

Psilocin/
LSD/DMT

5-HT neuron

QIDS score

Baseline
1 week
2 weeks
3 weeks
5 weeks
3 months

Hedges' g
3.1
p=0.002

Hedges' g
3.2
p=0.002

Hedges' g
3.2
p=0.002

Hedges' g
2.7
p=0.003

Hedges' g
2.0
p=0.003

Psilocybin

LSD
Autoimmune-induced NMDA receptor dysfunction: conceptual and psychiatric practice implications

Table 1  Characteristic clinical manifestations of anti-NMDAR encephalitis and phencyclidine intoxication.

<table>
<thead>
<tr>
<th>Phencyclidine effects</th>
<th>Anti-NMDAR encephalitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive symptoms</td>
<td>Non-specific viral-like symptoms</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>Positive symptoms</td>
</tr>
<tr>
<td>Perceptual alterations</td>
<td>Negative symptoms (e.g. apathy, lack of emotion)</td>
</tr>
<tr>
<td>Cognitive deficits</td>
<td>Perceptual alterations</td>
</tr>
<tr>
<td>Rigidity, focal dystonia</td>
<td>Cognitive deficits</td>
</tr>
<tr>
<td>Coarse tremor and twitching</td>
<td>Catatonia, dystonic features</td>
</tr>
<tr>
<td>Facial grimacing, circumoral face twitching, lip smacking and chewing</td>
<td>Oroolingual dyskinesias</td>
</tr>
<tr>
<td>Oculogyric crisis, opisthotonus</td>
<td>Seizures</td>
</tr>
<tr>
<td>Hypertension and tachycardia</td>
<td>Autonomic instability</td>
</tr>
<tr>
<td>Altered consciousness</td>
<td>Altered consciousness</td>
</tr>
</tbody>
</table>
Potent 5-HT3-R blocking activity of vortioxetine

vortioxetine $\rightarrow$ 5-HT3 $\rightarrow$ Na$^+$/Ca$^{2+}$
Vortioxetine enhances gamma oscillations (Leiser et al., Br. J. Pharmacol., 2014)
Multimodalità: azione farmacologica attraverso almeno 2 meccanismi d’azione differenti

SSRI

1 meccanismo d’azione (inibizione reuptake)

SNRI

2 bersagli farmacologici, ma 1 modalità d’azione (inibizione reuptake)

Agomelatina

3 bersagli farmacologici

1 modalità d’azione (attività recettoriale)

Vilazodone

2 bersagli farmacologici

2 modalità d’azione

(attività recettoriale + inibizione del reuptake)

Vortioxetina

6 bersagli farmacologici

2 modalità d’azione

(attività recettoriale + Inibizione del reuptake)

Inhibitore reuptake  ○ Agonista  ● Agonista parziale  ● Antagonista