IMPROVING QUALITY OF LIFE FOR PATIENTS WITH SCHIZOPHRENIA

Targeting Negative Symptoms and Depression

Dr Andreas Papadopoulos
Locum Consultant Psychiatrist AWP NHS Trust
Honorary Senior Lecturer University of Bristol
Member of the SW Division RCPsych Executive Committee
info@drandreasp.co.uk
Disclosures

Honoraria from Lundbeck, Otsuka, Sunovion and Janssen Cilag Pharmaceuticals

Stocks None
Evolution of Schizophrenia

Epidemiology of schizophrenia

- Median lifetime morbid risk of schizophrenia 7.2 per 1,000 population\(^1\)
- Incidence rate varies 5-10 fold
- More common in males: 1.4:1\(^1\)
- Earlier age of onset in males\(^2\)

Incidence of schizophrenia in selected studies published after 1985 (dark bars = WHO studies)\(^2\)

---

Mortality

• People with schizophrenia have a shorter life span than the rest of the population
• Median SMR = 2.6
• Contributors for all-cause mortality include:
  - Suicide
  - Cardiovascular disease
• SMR rising in recent decades
• Lifestyle and adverse effects of medication are both likely to contribute

SMR=Standardised mortality ratio. 
Economic burden of schizophrenia in England

Cost to society:
£11.8 billion (£60,000 per individual with schizophrenia) per year

Cost to the public sector:
£7.2 billion (£36,000 per individual with schizophrenia) per year

- One-third of societal costs are direct expenditure on health and social care (institutions and community)
- More than half is a result of the lost productivity of people (through unemployment and premature death)
- Remaining costs are informal care costs (incurred by families and carers)

Annual costs of schizophrenia to society and the public sector (£ per person with schizophrenia, 2010/11 prices)

Figure adapted from: The Abandoned Illness: A report by the Schizophrenia Commission. November 2012.
For most people schizophrenia is a severe, chronic and progressive disease

Clinical and pathophysiological course of schizophrenia¹ ²

- Some patients achieve symptomatic remission following the first episode¹
- The majority of patients experience a fluctuating course of schizophrenia, characterised by recurring relapses, which results in functional decline and lasting neurological damage¹ ³

The deteriorating course, brain tissue loss, and treatment resistance with repetitive relapses following the first episode in schizophrenia

Goals of long-term therapy in schizophrenia\textsuperscript{1,2}:  
• to prevent future relapse;  
• to reduce the severity of side effects and residual symptoms.


Some patients with schizophrenia may achieve functional recovery with effective treatment

- In a 3-year prospective observational study (SOHO), adults with schizophrenia (n=6,642) achieved:

  - Long-lasting symptomatic remission*: 33
  - Long-lasting adequate quality of life†: 27
  - Long-lasting functional remission‡: 13

  Achieved recovery, defined as all 3 of the above

- The following factors were significantly associated with achieving recovery:
  - Employment (OR 8.7, 95% CI 5.8–13.1; \( P<0.0001 \))
  - Independent living (OR 7.1, 95% CI 4.8–10.7; \( P<0.0001 \))
  - Continuous medication (OR 2.3, 95% CI 1.5–3.5; \( P=0.0003 \))
  - Social activity (OR 1.5, 95% CI 1.1–2.1; \( P=0.00098 \))

* Defined as <4 in the CGI-SCH positive, negative, cognitive, and overall severity score, plus no inpatient admission for ≥24 months.
† Defined as achieving an EQ-5D VAS score of ≥70 for ≥24 months.
‡ Defined as employed/student, plus independent living, plus active social interactions for ≥24 months.

A variety of clusters contribute to functional impairment

**Positive symptoms**¹,²
- Delusions
- Disorganised thought
- Disorganised speech
- Hallucinations

**Negative symptoms**¹
- Flat or blunted affect and emotion
- Poverty of speech (alogia)
- Inability to experience pleasure (anhedonia)
- Lack of desire to form relationships (asociality)
- Lack of motivation (abulia)

**Cognitive impairment**¹
- Episodic memory
- Inappropriate affect
- Executive function
- Working memory

**Lack of insight**²

**Functional impairment**²
- Ability to work
- Coping with self-care
- Establishing social relationships

## Negative Symptoms

<table>
<thead>
<tr>
<th>Affective</th>
<th>Communication</th>
<th>Conational</th>
<th>Relational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blunted affect—including deficits in facial expression, eye contact,</td>
<td>Poverty of speech and poverty of content of speech.</td>
<td>Lack of drive or goal-directed behavior.</td>
<td>Interest in social activities and</td>
</tr>
<tr>
<td>gestures, and voice pattern.</td>
<td>Alogia</td>
<td>Avolition.</td>
<td>relationships is reduced (asociality).</td>
</tr>
<tr>
<td>In mild form, gestures may seem artificial or mechanical, and the</td>
<td>Mutism</td>
<td>Personal grooming may be poor.</td>
<td>Interpersonal relations may be of</td>
</tr>
<tr>
<td>voice is stilted or lacks normal inflection. Little spontaneous movement,</td>
<td>Vague and generalized.</td>
<td>Physical activity may be limited.</td>
<td>little interest.</td>
</tr>
<tr>
<td>speak in a monotone, and gaze blankly in no particular direction.</td>
<td>Increased latency. or in the midst of</td>
<td>Patients typically have great difficulty following a</td>
<td>Friendships become rare and shallow,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>work schedule or hospital ward routine.</td>
<td>with little sharing of intimacy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contacts with family are neglected.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sexual interest declines.</td>
</tr>
</tbody>
</table>
Cognitive Deficits in Patients with Schizophrenia and Depression

Neurocognitive test scores in patients with depression (mean HAM-D 22.4, n=45), schizophrenia (mean PANSS 75.6, n=53) and control subjects (n=50)

*\(p \leq 0.05\), **\(p \leq 0.01\), ***\(p \leq 0.001\) vs control; ††\(p \leq 0.01\), †††\(p \leq 0.001\) vs patients with depression.

HAM-D, Hamilton Rating Scale for Depression; PANSS, Positive and Negative Symptom Scale.

Predicting Outcomes in Schizophrenia

Negative symptoms and cognitive variables are not independent predictors of functioning

‘Holistic’ approach

Stahl Essential Psychopharmacology 2000
Assessing severity

**Standardised Tools:**

- Brief Psychiatric Rating Scale (BPRS)
- Positive and Negative Symptom Scale (PANSS)
- Scale for the Assessment of Negative Symptoms
- Schedule for the Deficit Syndrome (SDS)
Assessing severity

Interview - difficult to fully assess or differentiate between 1ary and 2ary:

• In a patient on antipsychotic treatment who is experiencing psychotic symptoms (e.g., persecutory delusions), depressive symptoms, and prominent negative symptoms, the clinician can only guess whether the negative symptoms are primary or secondary.

• In a patient who is socially withdrawn and delusional, withdrawal may be secondary to delusions or may represent a primary negative symptom.

• In a patient on typical antipsychotics, a flat affect may be caused by antipsychotic-induced EPS or it may be a primary negative symptom.

• A disorganized patient with schizophrenia and depression is often unable to convey his or her feelings coherently, so that negative symptoms secondary to affective disturbance may often be mistaken as primary.

• Consider whether symptoms are specific to the presumed aetiology, such as guilt and sadness in depression or cogwheeling and tremor in EPS.

• Treat empirically, and monitor whether negative symptoms improve. If they improve with antidepressant treatment, for example, then depression was the presumable cause. If they improve with anticholinergics, they were presumably secondary to EPS.
Treatment

**PRINCIPLES**

1. Treat positive symptoms  
2. Ensure compliance  
3. Treat EPSEs  
4. Psychosocial interventions  
5. Treat Depression if present

DO SOMETHING......
Treatment

**PRINCIPLES**

1. Treat positive symptoms
2. Ensure compliance
3. Treat EPSEs
4. Psychosocial interventions
5. Treat Depression if present

DO SOMETHING......
Major Dopamine Pathways & Possible Relation to Schizophrenia Symptoms

- **Mesocortical pathway**
  - negative symptoms
  - cognitive dysfunction
  - motivation dysfunction

- **Nigrostriatal pathway** (motor movement)

- **Mesolimbic pathway**

- **Tuberoinfundibular pathway**
  - Prolactin secretion

- **Positive symptoms (hyperdopaminergic):**
  - Delusions
  - Hallucinations
  - Disorganised thought, speech, behaviour

DA=Dopamine; EPS=Extrapyramidal symptoms; TD=Tardive dyskinesia.

Adapted from Lieberman et al. CNS Drugs 2004;18:251-267
Treat Positive Symptoms

Typical vs Atypical Antipsychotics

• No real difference in efficacy on positive symptoms

• Atypical antipsychotics improve negative symptoms by about 25%, compared with 10 to 15% improvement with typical antipsychotics.

Kane J Arch Gen Psychiatry 1988;45(9):789-96.
Stahl Essential Psychopharmacology 2000
Treatment

PRINCIPLES

1. Treat positive symptoms
2. Ensure compliance
3. Treat EPSEs
4. Treat Depression if present
5. Psychosocial interventions

DO SOMETHING......
Consequences of adverse effects

- Physical morbidity and mortality
- Adverse events
- Poor adherence
- Reduced quality of life
- Stigma
- Relapse
- Chronic symptoms

Hamer S, Haddad PM. Br J Psychiatry Suppl. 2007;50:s64–70.
Multiple treatments meta-analysis: Leucht et al. (2013)

Aim
• Create hierarchy for 15 antipsychotic drugs and placebo
• Efficacy and major side-effects
• Direct and indirect comparisons

Data set
• 212 RCTs
• Acute schizophrenia
• 43,049 participants
• Mean illness duration: 12 years
• Mean age: 38 years

‘the differences in efficacy between drugs were small’
‘Antipsychotics differed substantially in side-effects’
1-Year Weight Gain: Mean Change From Baseline Weight


## Antipsychotics & Weight Gain

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Activity</th>
<th>Effect/Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine-2</td>
<td>Antagonism</td>
<td>Causes weight gain via decrease in limbic dopaminergic activity, possibly increasing reward-seeking behaviors such as food intake; can also contribute to weight gain via disinhibition of prolactin release from the hypothalamus</td>
</tr>
<tr>
<td>Histamine-1</td>
<td>Antagonism</td>
<td>Causes weight gain via increase in hypothalamic AMP-related kinase activity, which leads to increased appetite; sedative effects may lead to reduction in mobility</td>
</tr>
<tr>
<td>Muscarinic-3</td>
<td>Antagonism</td>
<td>Not directly correlated with weight gain, but causes diabetes via impairment of glucose tolerance and reduction of insulin secretion from pancreatic beta cells</td>
</tr>
<tr>
<td>Serotonin-1A</td>
<td>Partial agonism</td>
<td>May mitigate weight effects due to serotonin-2C antagonism; may decrease carbohydrate craving</td>
</tr>
<tr>
<td>Serotonin-2C</td>
<td>Antagonism</td>
<td>Causes weight gain via disinhibition of hypothalamic neuropeptide Y neurons and inhibition of pro-opiomelanocortin neurons; may also influence leptin resistance</td>
</tr>
</tbody>
</table>
Meta-analysis of antipsychotic drug-induced weight gain

<table>
<thead>
<tr>
<th>Drug</th>
<th>SMD (95% CI)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>0.09 (-0.00 to 0.17)</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>0.10 (-0.02 to 0.22)</td>
<td></td>
</tr>
<tr>
<td>Lurasidone</td>
<td>0.10 (-0.02 to 0.21)</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>0.17 (0.05 to 0.28)</td>
<td></td>
</tr>
<tr>
<td>Amisulpride</td>
<td>0.20 (0.05 to 0.35)</td>
<td></td>
</tr>
<tr>
<td>Asenapine</td>
<td>0.23 (0.07 to 0.39)</td>
<td></td>
</tr>
<tr>
<td>Paliperidone</td>
<td>0.38 (0.27 to 0.48)</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.42 (0.33 to 0.50)</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>0.43 (0.34 to 0.53)</td>
<td></td>
</tr>
<tr>
<td>Sertindole</td>
<td>0.53 (0.38 to 0.68)</td>
<td></td>
</tr>
<tr>
<td>Chlomipramine</td>
<td>0.55 (0.34 to 0.76)</td>
<td></td>
</tr>
<tr>
<td>Iloperidone</td>
<td>0.62 (0.49 to 0.74)</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>0.65 (0.31 to 0.99)</td>
<td></td>
</tr>
<tr>
<td>Zotepine</td>
<td>0.71 (0.47 to 0.96)</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>0.74 (0.67 to 0.81)</td>
<td></td>
</tr>
</tbody>
</table>

- Olanzapine has greater weight gain than all other antipsychotics (except zotepine).
- Only haloperidol, lurasidone and ziprasidone do not differ significantly from placebo.
- Apart from the wide range of relative weight gain reported for clozapine, three non-overlapping groups of antipsychotic drugs can be distinguished.

Iloperidone, sertindole, ziprasidone and zotepine are not licensed in UK.
Asenapine is not licensed for schizophrenia in UK.

Leucht et al, 2013
Improving adherence

- **Patient-specific** and may require several approaches
  - Understand the patient’s knowledge, beliefs and concerns about their illness and medication and any potential barriers to medication-taking

- **Simple pragmatic strategies**
  - Shared decision making
  - Simplify medication regimens
  - Managing side effects

- **Psycho-education** and other psychosocial interventions

- **Reminders** and adherence aids
  - Daily compartmentalised pill boxes, electronic reminders, real-time monitoring

- **Financial incentives**

- **Service based interventions**

- **Long-acting injections (LAIs)**

Evidence base for LAIs vs oral drugs

Non-randomised trials

Prospective Observational

Randomised controlled trials

LAI = oral

Retrospective Observational

Discrepancy may reflect cohort bias and altered ecology in RCTs

LAI=Long-acting injectable.
Treatment

PRINCIPLES

1. Treat positive symptoms
2. Ensure compliance
3. Treat EPSEs
4. Psychosocial interventions
5. Treat Depression if present

DO SOMETHING......
Meta-analysis of antipsychotic drug-induced extrapyramidal side effects

- Risperidone, paliperidone, chlorpromazine and haloperidol *inter alia* induce significantly more EPS than placebo.
- Clozapine uniquely induces fewer EPS than placebo.

Iloperidone, sertindole, ziprasidone and zotepine are not licensed in UK. Asenapine is not licensed for schizophrenia in UK.

Receptor mechanisms: minimising EPSEs

- Of currently available antipsychotic drugs, only quetiapine, clozapine and aripiprazole are free of a dose-dependent emergence of EPS.

- For clozapine and quetiapine, this may be due to:
  - Weak and displaceable antagonist affinity for the D2 receptor.

- For aripiprazole:
  - Partial D2 receptor agonist activity.

D2 partial agonism of aripiprazole and the threshold for EPS

Haloperidol is a full antagonist and will block agonist effects of dopamine at the D2 receptor.

Aripiprazole is a partial agonist and will partially stimulate and partially block the receptor.

Treatment

PRINCIPLES

1. Treat positive symptoms
2. Ensure compliance
3. Treat EPSEs
4. **Psychosocial interventions**
5. Treat Depression if present

DO SOMETHING......
Psychosocial Interventions

... builds on relationships between the patient and others and may involve:

- social skills training (living skills, communication, conflict resolution, vocational skills, etc.)
- vocational rehabilitation, and
- psychotherapy.

**Activity-oriented therapies** appear to be significantly more effective than verbal therapies.

**Goals of psychosocial therapy:**
- set realistic expectations for the patient
- stay active in treatment in the face of a protracted illness
- create a benign and supportive environment for the patient and caregivers

In early studies of social skills training, patients and their families described enhanced social adjustment, and hospitalization rates improved. More recent studies have confirmed improved social adjustment and relapse rates but suggest that overall symptom improvement is modest.
Treatment

PRINCIPLES

1. Treat positive symptoms
2. Ensure compliance
3. Treat EPSEs
4. Psychosocial interventions
5. Treat Depression if present

DO SOMETHING......
Depression is associated with significant economic costs

- Depression is the leading cause of global disease burden among mental, neurological and substance-use disorders.
- In England alone overall cost, including lost productivity, is estimated at £10.96 billion.
- The WHO predicts that depression will be the leading cause of disease burden globally by 2030.

---

3. WHO. 2011:EB130/9
4. WHO. Global Burden of Disease 2004
Depression adds to the burden of disease for the individual
Depression impacts on workplace productivity

**Workplace functionality**

- Government-commissioned research in 2010 found that people unable to work because of depression lose £8.97 billion of potential earnings per year in England¹.

- In Europe, an average of 36 days is taken off work per episode of depression².

- UK estimates suggest that 1.5 times as much working time is lost through presenteeism* as absenteeism for mental health conditions, accounting for £15 billion/year in reduced productivity at work³.

*Presenteeism = working despite illness or injury etc, resulting in lower productivity

---

¹ APPG on Wellbeing economics. 2011
² Ipsos Healthcare. October 2012
³ Sainsbury Centre for Mental Health. 2007
Depression is clinically heterogeneous disorder

DSM-V classification: MDD symptoms

- 5 or more of these symptoms must be present for at least 2 weeks
- At least one of these must be depressed mood or loss of interest or pleasure
- Diagnostic symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
According to the DSM-5, cognitive symptoms are a criterion for a major depressive episode.

Cognitive symptoms are 1 of the 9 diagnostic criteria for depression, defined as:

“A diminished ability to think or concentrate, nearly every day (either by subjective account or observed by others)”
Cognitive complaints in depressed patients

Percentage of individuals rating problems “Quite a bit” or “Very much”

- “Moderate” cognitive complaints found in 27% of depressed patients (2% of control individuals)
- “Severe” cognitive complaints found in 13% of depressed patients (none in control individuals)
Cognitive impairment in patients with depression

Magnitude of impairment relative to control ($d$)

Detection task
Timed chase
GMLT
GMLT-delay
ISLT
ISLT-delay
SECT
Verbal fluency
Stroop test

GMLT, Groton Maze Learning Test; ISLT, International Shopping List Task; SECT, Social Emotional Cognition Test; $d$, Cohen’s $d$ effect size

Cognitive dysfunction has functional consequences across several domains

- Problems with planning
- Impaired ability to concentrate
- Slowness in responding
- Difficulties with memory

Hammar Å, Årdal G. Front Hum Neurosci 2009;3:26;
Cognitive symptoms of depression have a negative impact on many aspects of the patient’s life\textsuperscript{1,2}

Cognitive dysfunction interferes with treatment

- Medication adherence
- Psychotherapy response
  - All psychotherapy is, at least in part, learning-dependent
  - Exposure therapy is explicitly learning-dependent
  - Impairments in attention, memory and executive function impair response to cognitive behavioural therapy
- Psycho-education
  - Treatment recommendations are more difficult for patients who are inattentive and memory impaired

Whatever its cause, cognitive dysfunction can interfere with treatment for depression
Functional recovery: why is it important?

- The ultimate treatment goal in depression is functional recovery\textsuperscript{1,2}.
- The aim of an intervention should be the complete relief of symptoms,\textsuperscript{1,2} associated with:
  - Improved functioning\textsuperscript{3}
  - Better overall quality of life\textsuperscript{3}
  - Lower likelihood of relapse\textsuperscript{4}

The ultimate goal of treatment in MDD is functional recovery.

- **Response:** Many symptoms remain.
  - **1970s:** Reduction of symptoms by, e.g., ≥50% assessed by MADRS or HAM-D scale.
  - **1990s:** Definition varies between studies, but commonly defined as MADRS score of ≤10, or HAM-D score of ≤7.

- **Remission:** Some symptoms may persist.

- **2010:** Functional recovery: Symptoms are essentially absent; patient returns to pre-morbid functional status.
  - Not officially defined; measures should include clinician-rating, self-report and performance testing, to assess symptoms and functioning.

- Approximately half of those depressed patients who achieve ‘remission’, as defined by commonly applied rating scales (MADRS and HAM-D), do not consider themselves to be in remission.

References:
Barriers to achieving functional recovery

- Chronicity\(^1\) and number of lifetime episodes\(^1,2\)
- Length of current episode\(^3\)
- Co-morbidity (e.g. anxiety,\(^3,4\) personality disorder\(^5\))
- Painful symptoms\(^6\)
- Childhood maltreatment\(^7\)
- Attending a practice with a high Jarman underprivileged area score\(^8\)
- Neuroticism\(^5,9\)
- Substance misuse\(^10\)
- Stressful life events\(^2,11-12\)

Depressive symptoms persist during periods of remission and subsequent depressive episodes

Mean proportion of time DSM-IV symptoms are present during 3-year follow-up period (n=267)

Non-functional recovery: Subjective cognitive symptoms after treatment

Proportion of patients (n=117) in full or partial remission after 3 months of treatment reporting cognitive and physical impairment

Items from the Cognitive and Physical Functioning Questionnaire

- Cognitive dysfunction ranged from 30–50% of patients
- Symptoms may have been residual, adverse events or a combination

Patients with residual symptoms relapse earlier and at a faster rate than patients that have achieved remission.
Residual symptoms can lead to faster relapse

Patients with residual symptoms relapsed to next depressive episode 5.5 times faster than patients treated to remission ($p < 0.001$).\(^1\)

<table>
<thead>
<tr>
<th>Median time to recurrence of any (major, minor or dysthymic) depressive episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with residual symptoms ($n=82$)</td>
</tr>
<tr>
<td>Remitted asymptomatic patients ($n=155$)</td>
</tr>
</tbody>
</table>

- Patients with residual symptoms relapsed to next major depressive episode more than 3 times faster than patients treated to remission (68 vs 231 weeks, respectively; $P < 0.0001$).
- Overall, patients with residual symptoms were 368% more likely to relapse during recovery than patients treated to remission (OR, 3.68; 95% CI, 2.64–5.12).

Remission was defined as asymptomatic recovery with ≥80% of well interval weeks rated asymptomatic.
MDD is associated with hippocampal atrophy across all age groups

<table>
<thead>
<tr>
<th>Age group</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescence</td>
<td>Evidence of abnormalities in the hippocampus in early onset depression</td>
</tr>
<tr>
<td>Adulthood</td>
<td>Findings are consistent with smaller left hippocampal volume in depression</td>
</tr>
<tr>
<td>Old age</td>
<td>Further evidence of structural brain abnormalities in geriatric depression</td>
</tr>
</tbody>
</table>

- 19% smaller volume of left hippocampus in patients with treated depression versus non-depressed control participants
- This represents a statistically significant decrease

Hippocampal volume correlates with the duration of untreated depression
Neural correlates of cognitive impairment in depression
The drugs we have today

- **MAOI**: Phenelzine, Moclobemide
- **TCA**: Clomipramine, Imipramine, Amitriptyline
- **SSRI**: Paroxetine, Fluoxetine, Sertraline, Fluvoxamine, Citralopram, Escitalopram
- **Receptor antagonists**: Mirtazapine, Trazodone, Mianserin
- **SNRI**: Venlafaxine, Milnacipran, Duloxetine, Desvenlafaxin
- **NARI**: Reboxetine, ?Quetiapine
- **NDRI**: Bupropion
- **Melatonin agonist**: Agomelatine

New drugs with multimodal actions
- **Vilazodon** (USA): SSRI + 5-HT$_1$A agonist
- **Vortioxetine**: SSRI + effects on multiple other serotonin receptors

*Not licensed/available in the UK

Many current treatments do not address cognitive dysfunction.

- There is emerging evidence that in some patients, the degree of cognitive deficit goes beyond that which can be accounted for by the severity of depressive symptoms.

- Many current treatments (including SSRIs and SNRIs) have limited data on cognitive dysfunction in patients with depression.

- In those with partial or full resolution of depressive symptoms, cognitive impairment may persist.

- Evidence is accumulating to support the view that, in subgroups of patients, cognitive deficits constitute a dimension of depression that is independent of, and dissociable from, depressive symptomatology.

References:
Vortioxetine is a multimodal antidepressant with a distinct pharmacological profile

Vortioxetine has a multimodal action that combines receptor activity and reuptake inhibition, leading to modulation of neurotransmission in several systems\textsuperscript{1-3}

\textbf{Direct effects}\textsuperscript{1,4}
- 5-HT\textsubscript{1A} agonist
- 5-HT\textsubscript{1B} partial agonist
- 5-HT\textsubscript{1D} antagonist
- 5-HT\textsubscript{3} antagonist
- 5-HT\textsubscript{7} antagonist

\textbf{Reuptake inhibition}
- SERT inhibitor

\textbf{Indirect effects}\textsuperscript{5-8a}
- ↑ serotonin neurotransmission
- ↑ dopamine neurotransmission
- ↑ noradrenaline neurotransmission
- ↑ acetylcholine neurotransmission
- ↑ histamine neurotransmission
- ↓ GABA neurotransmission
- ↑ glutamate neurotransmission

\textit{Nutt & Wilson 2015, not yet published}

Vortioxetine improves cognitive performance in depression across multiple domains
Vortioxetine related effects on cognition are mainly direct

Direct effect on DSST, RAVLT acquisition and RAVLT delayed recall in patients ≥65 years

Path analysis: Direct effect of vortioxetine on DSST

- Direct effect 83%
- Indirect effect 17%

DSST

Vortioxetine 5 mg

Duloxetine direct effect: 26%

HAM-D_{24}

Duloxetine indirect effect: 74%

RAVLT acquisition: Vortioxetine had a 71% direct effect (duloxetine 65%)

RAVLT delayed recall: Vortioxetine had a 72% direct effect (duloxetine 66%)

Duloxetine was included as active reference for study validation, not for comparison of effect sizes.

DSST, Digit Symbol Substitution Test; HAM-D_{24}, Hamilton rating scale for Depression 24-item version; RAVLT, Rey Auditory Verbal Learning Test.
Vortioxetine on cognition and BOLD fMRI signals in remitted patients and control individuals

Regions of interest

• Target regions of the brain that have previously been shown to have altered activity in depression

BOLD fMRI, blood-oxygen-level dependent functional magnetic resonance imaging

Courtesy of GM Goodwin
Summary

- Negative Symptoms in Schizophrenia are associated with Cognitive Dysfunction and these symptoms are included in the diagnostic criteria for both Schizophrenia and Depression, and are common both at presentation and during remission.

- Negative and cognitive dysfunction have important functional consequences for patients.

- Cognitive dysfunction is:
  - Prevalent
  - Pervasive
  - Persistent
  - Progressive
  - Pertinent to patient-reported outcomes (e.g., QoL, psychosocial function)

- Needs adequate assessment and treatment for the patient to achieve functional recovery.