IMPROVING QUALITY OF LIFE FOR PATIENTS WITH SCHIZOPHRENIA♪ ♪

Targeting Negative Symptoms and Depression♪

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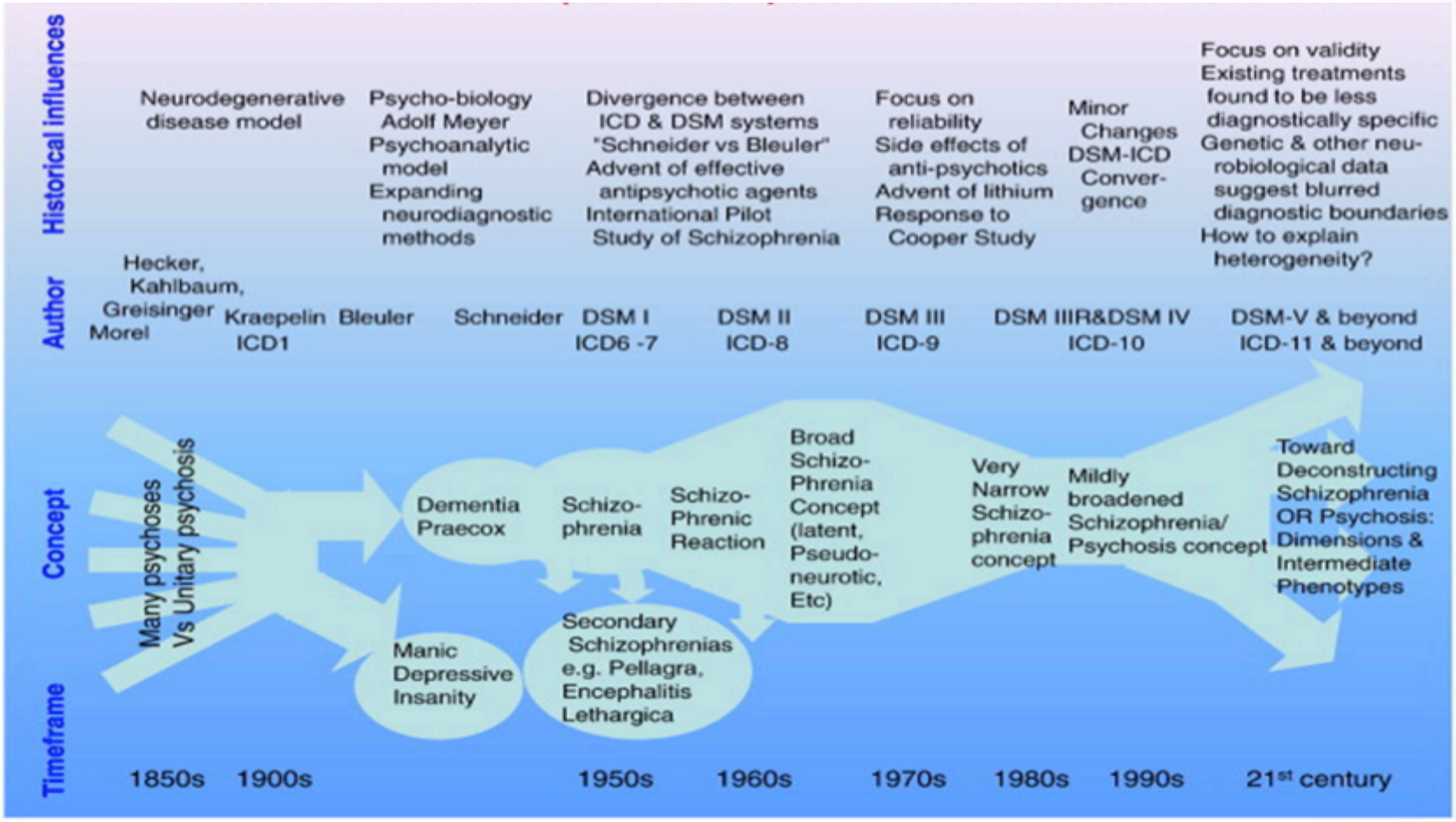
Disclosures

Honoraria from Lundbeck, Otsuka, Sunovion and Janssen Cilag Pharmaceuticals

Stocks None

Evolution of Schizophrenia

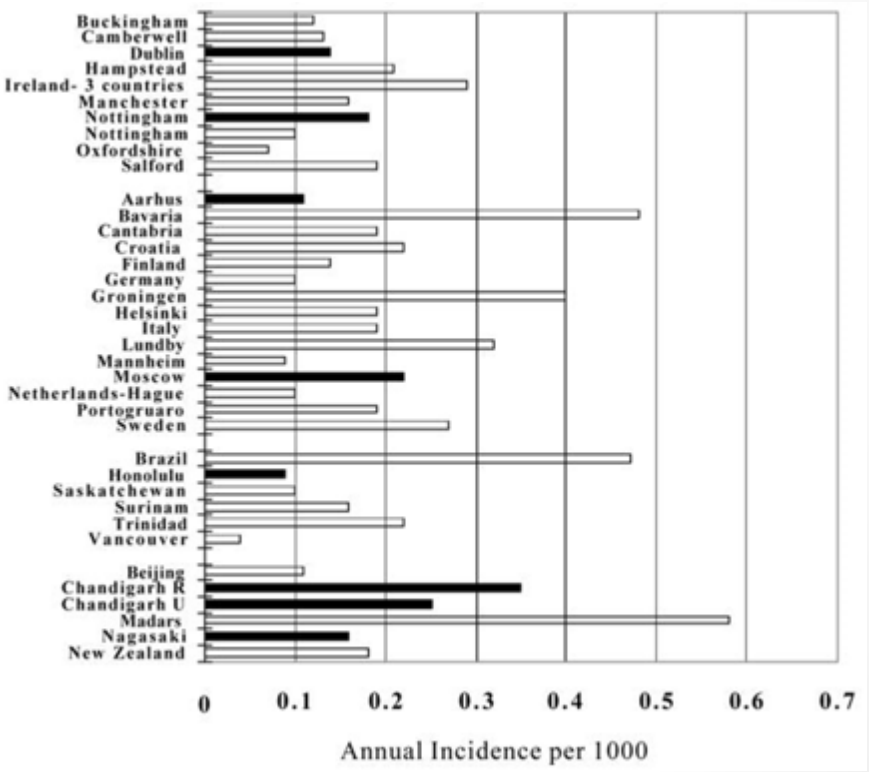


Tandon R, et al. Schizophr Res 2009; 110(1-3): 1-23;

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]



1. McGrath J et al. Epidemiol Rev 2008; 30: 67–76; 2. Messias EL, et al. Psychiatr Clin North Am 2007; 30(3): 323–338.

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.

McGrath J et al. Epidemiol Rev 2008; 30: 67–76.

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)

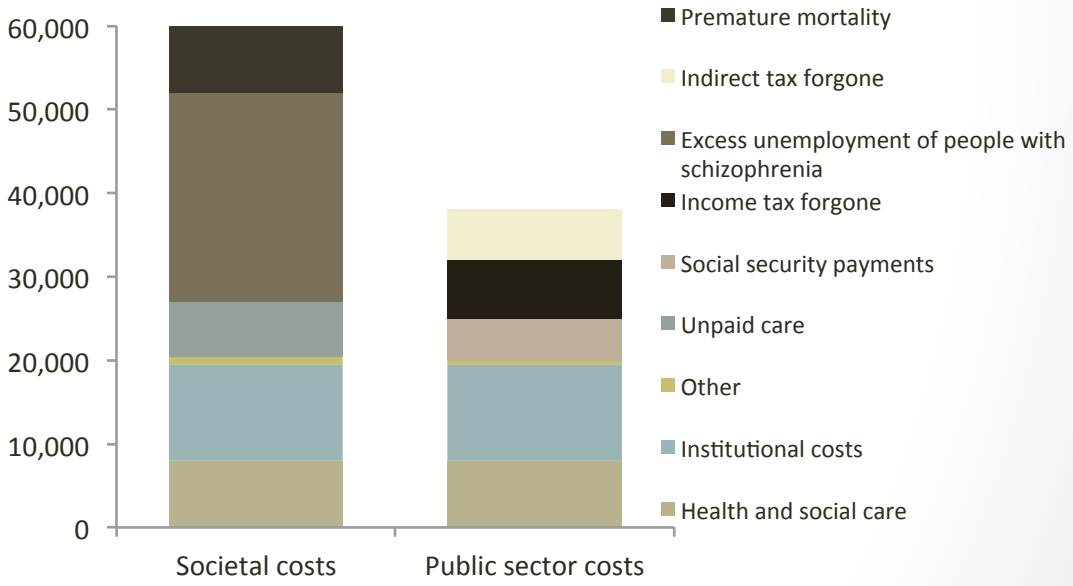
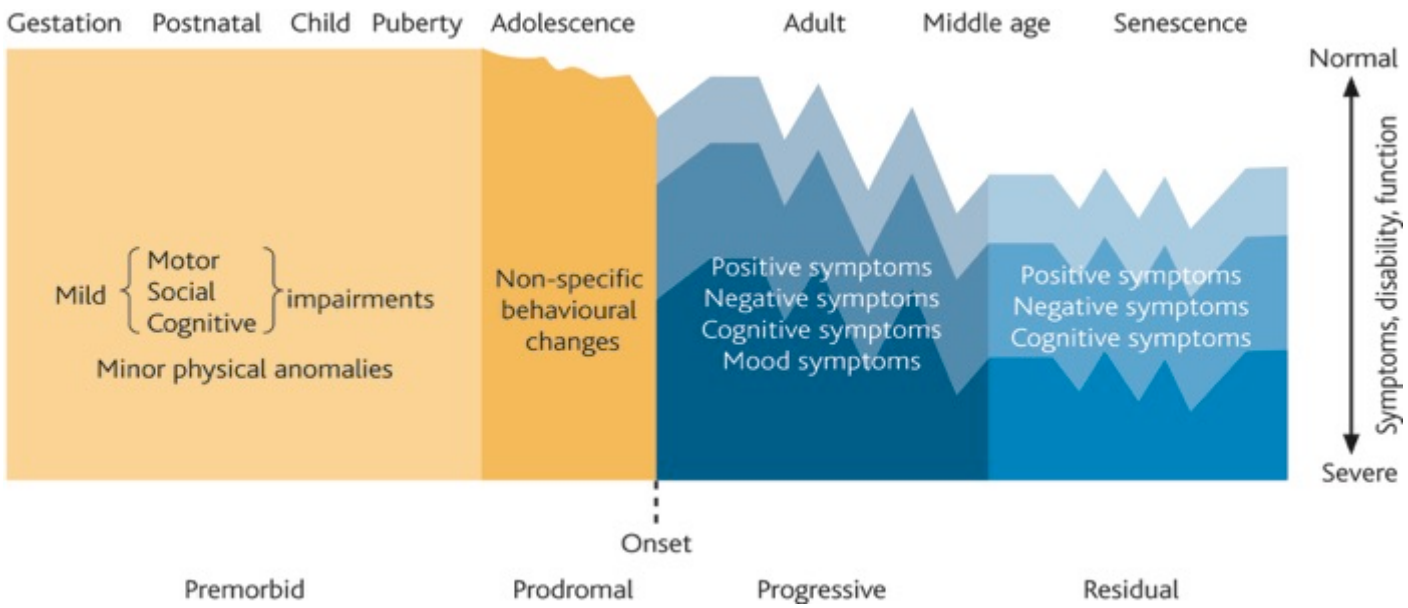


Figure adapted from: The Abandoned Illness: A report by the Schizophrenia Commission. November 2012.

For most people schizophrenia is a severe, chronic and progressive disease

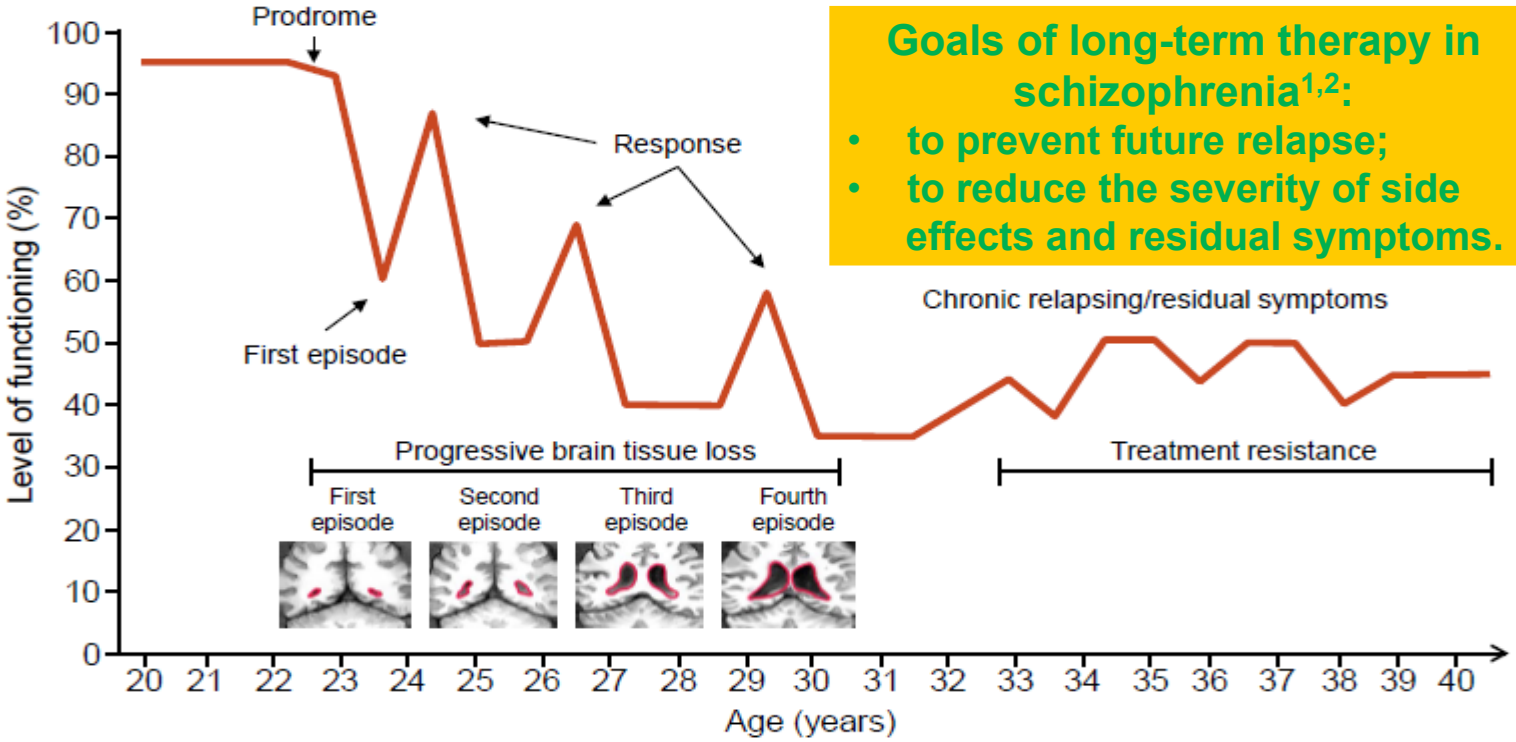
Clinical and pathophysiological course of schizophrenia[1,2]



- Some patients achieve symptomatic remission following the first episode[1]
- The majority of patients experience a fluctuating course of schizophrenia, characterised by recurring relapses, which results in functional decline and lasting neurological damage[1-3]

1. Lieberman JA. J Clin Psychiatry 2006; 67(10): e14. 2. Lieberman JA, et al. Biol Psychiatry 2001; 50(11): 884-897.
3. Lieberman JA, et al. Biol Psychiatry 2001; 49(6): 487-499.

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[1,2]:

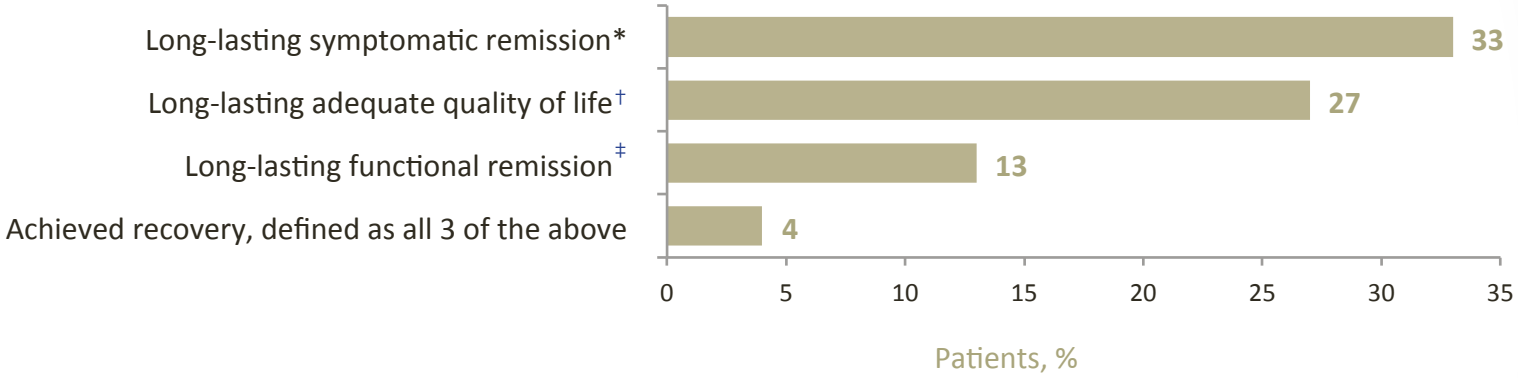
- to prevent future relapse;
- to reduce the severity of side effects and residual symptoms.

Nasrallah HA & Smeltzer DJ. In: Contemporary Diagnosis and Management of the Patient with Schizophrenia 2nd Edition. Handbooks in Health Care Co., Newton, Pennsylvania, USA, 2011

1. Lehman AF, et al; for the Work Group on Schizophrenia. *Practice guideline for the treatment of patients with schizophrenia*. 2nd Edition. 2004; 2.Falkai P, et al. *World J Biol Psychiatry.* 2006;7(1):5-40.

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:

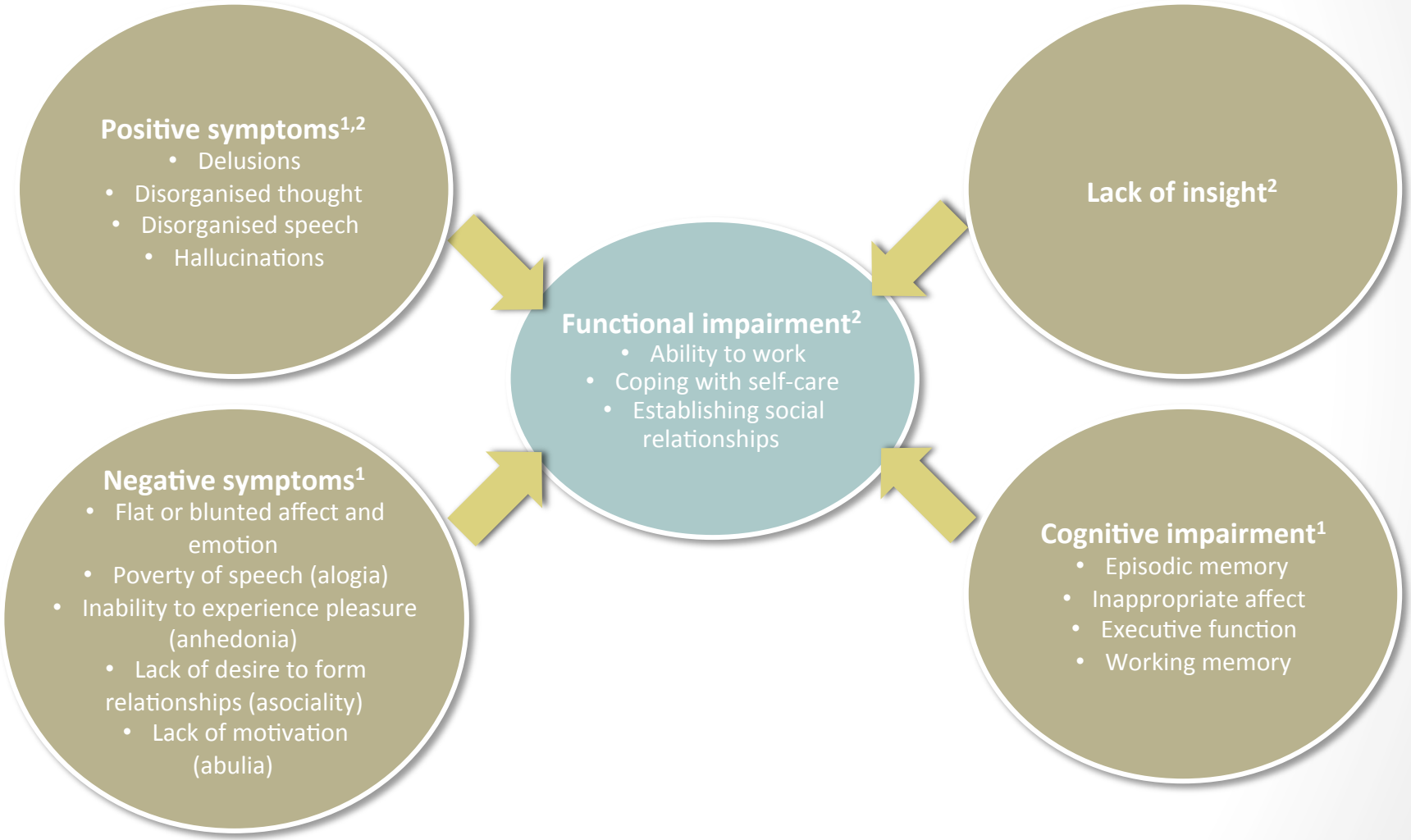


- The following factors were significantly associated with achieving recovery
  - Employment (OR 8.7, 95% CI 5.8–13.1; *P*<0.0001)
  - Independent living (OR 7.1, 95% CI 4.8–10.7; *P*<0.0001)
  - Continuous medication (OR 2.3, 95% CI 1.5–3.5; *P*=0.0003)
  - Social activity (OR 1.5, 95% CI 1.1–2.1; *P*=0.00098)

* 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.

CGI-SCH=Clinical Global Impression-Schizophrenia scale; OR=Odds ratio; SOHO=Schizophrenia Outpatients Health Outcomes; VAS=Visual analogue scale.
Novick D, et al. Schizophr Res 2009; 108(1-3): 223-230.

A variety of clusters contribute to functional impairment



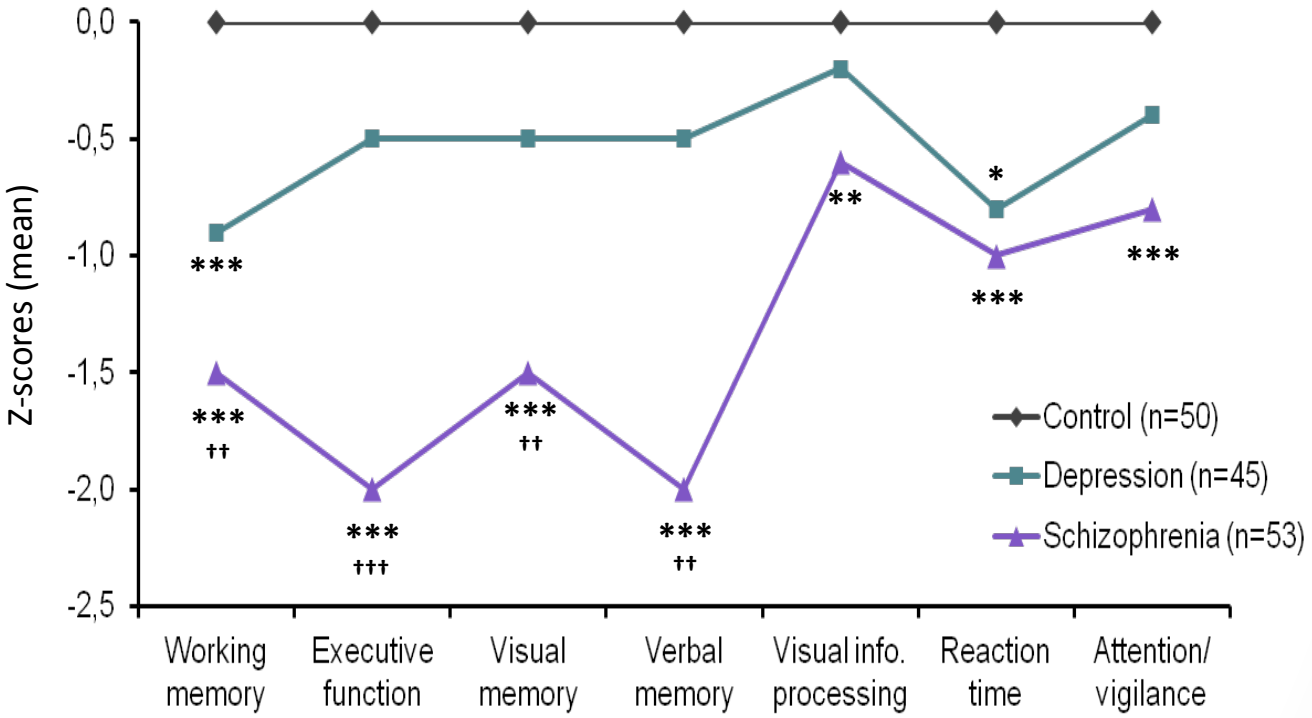
1. Tandon R, et al. Schizophr Res 2009; 110(1-3): 1-23; 2. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.

Negative Symptoms

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

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; $^{\dagger\dagger}p \leq 0.01$, $^{\dagger\dagger\dagger}p \leq 0.001$ vs patients with depression.

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

Rund BR, et al. *Acta Psychiatr Scand.* 2006;113:350-359.

Predicting Outcomes in Schizophrenia

TABLE 5. Relationships Between Cognitive Domains and Outcome Measures in 99 Subjects With First-Episode Schizophrenia Followed on Average for 7 Years

	Verbal Memory			Processing Speed and Attention		
Outcome Variable	Univariate F (df=1, 97)	p	R^2	Univariate F (df=1, 97)	p	R^2
Global psychosocial function	11.29	0.001	0.104	7.57	0.007	0.072
Relationship impairment	6.51	0.01	0.063	1.00	0.30	0.010
Recreation impairment	10.48	0.002	0.098	4.44	0.04	0.044
Work impairment	3.64	0.06	0.036	7.19	0.009	0.069

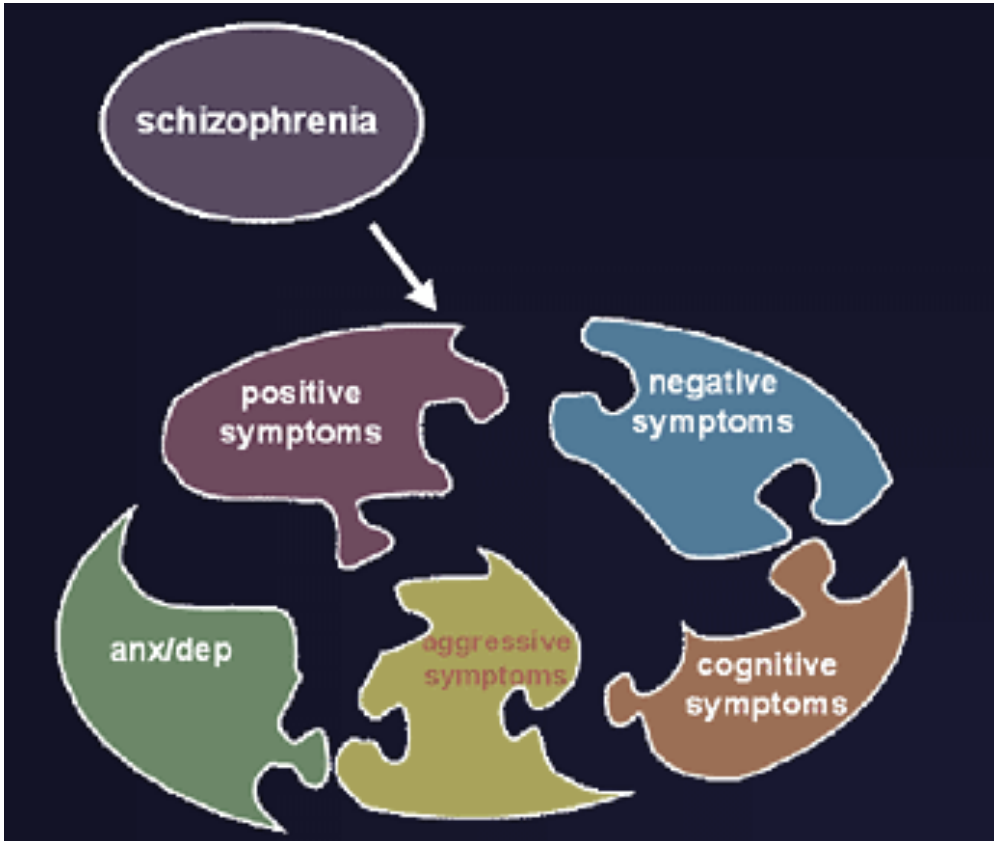
Negative symptoms and cognitive variables are not independent predictors of functioning

TABLE 6. Relationship Between Negative Symptom Severity at Intake and the Outcome Measures for 99 Subjects With First-Episode Schizophrenia Followed on Average for 7 Years

Outcome Variable	Univariate F (df=1, 97)	p	R^2
Global psychosocial function	11.95	0.0008	0.11
Relationship impairment	6.73	0.01	0.065
Recreation impairment	5.69	0.02	0.055
Work impairment	6.12	0.01	0.059

Milev P, Am J Psychiatry. 2005;162:495-506.

‘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……

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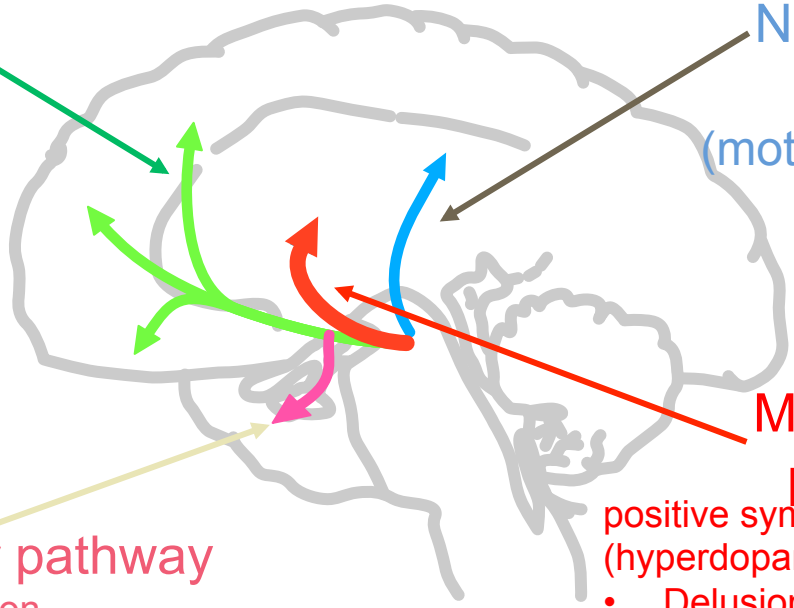
Major Dopamine Pathways & Possible Relation to Schizophrenia Symptoms



Mesocortical pathway

- negative symptoms
- cognitive dysfunction
- motivation dysfunction

Nigrostriatal pathway
(motor movement)

Mesolimbic pathway

positive symptoms (hyperdopaminergic):

- Delusions
- Hallucinations
- Disorganised thought, speech, behaviour

Tuberoinfundibular pathway
Prolactin secretion

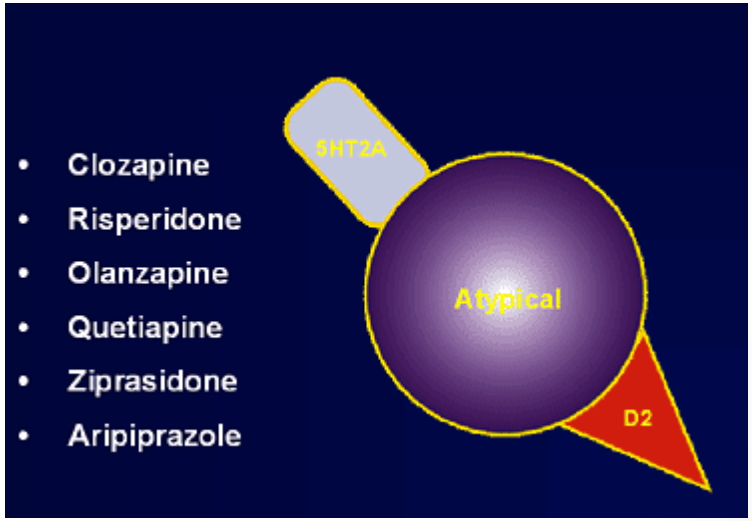
DA=Dopamine; EPS=Extrapyramidal symptoms; TD=Tardive dyskinesia.

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.
Tandon R *J Psychiatric Res* 1993;27:341-7
Stahl Essential Psychopharmacology 2000

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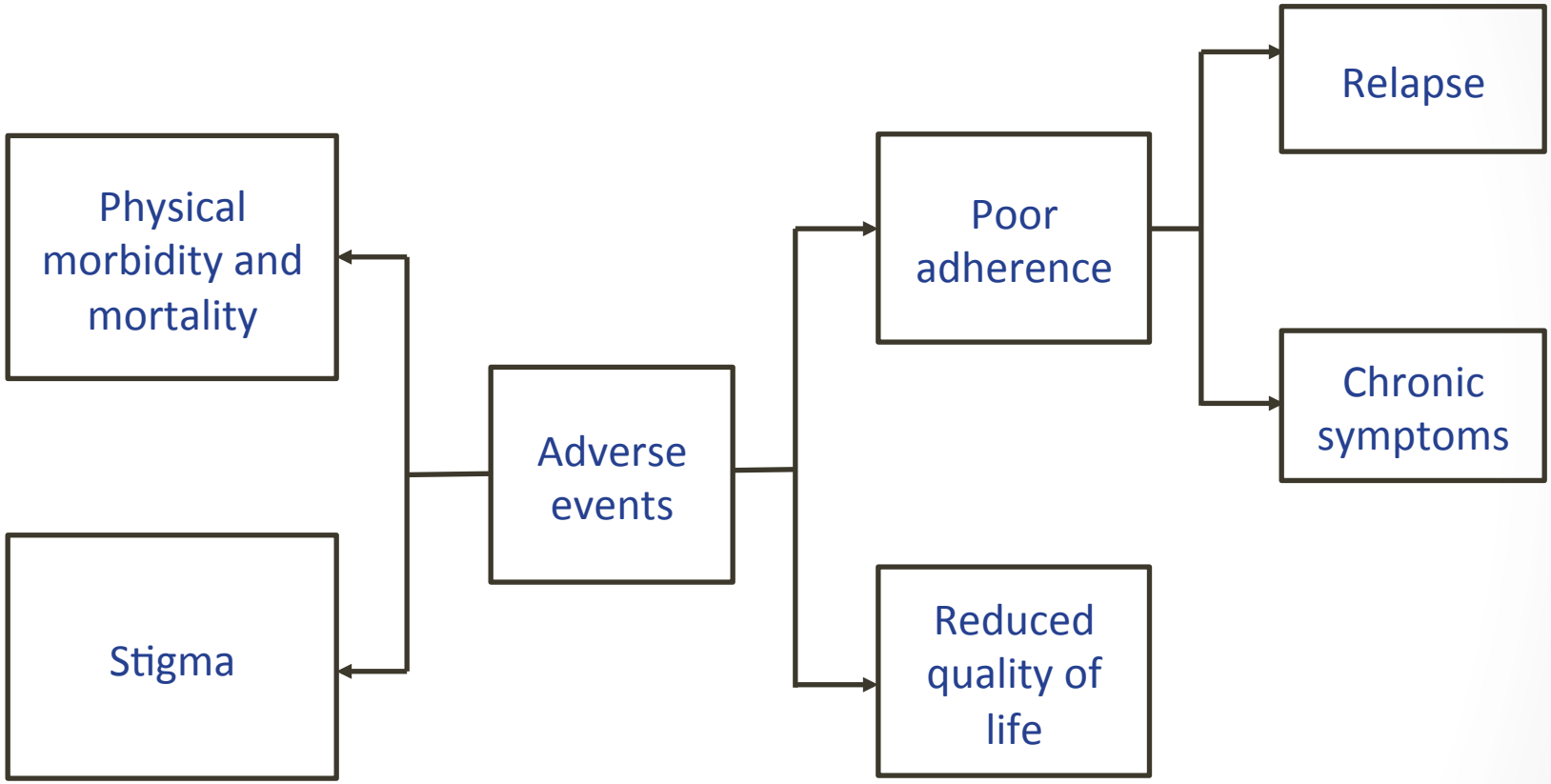
Consequences of adverse effects



Hamer S, Haddad PM. Br J Psychiatry Suppl. 2007;50:s64–70.

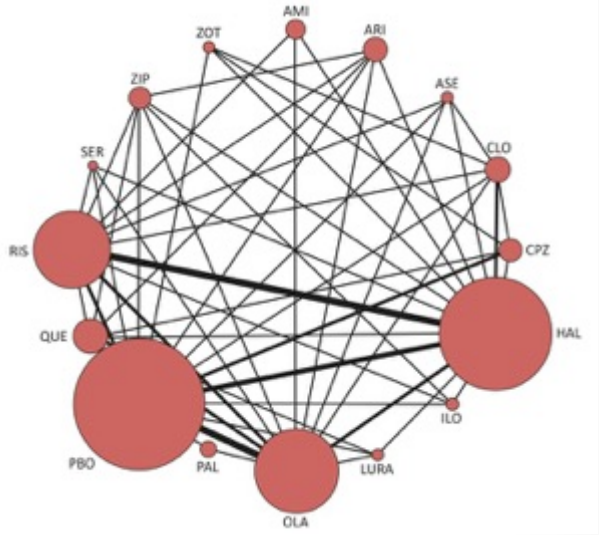
Multiple treatments meta-analysis: Leucht et al. (2013)

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



Network of comparisons for efficacy

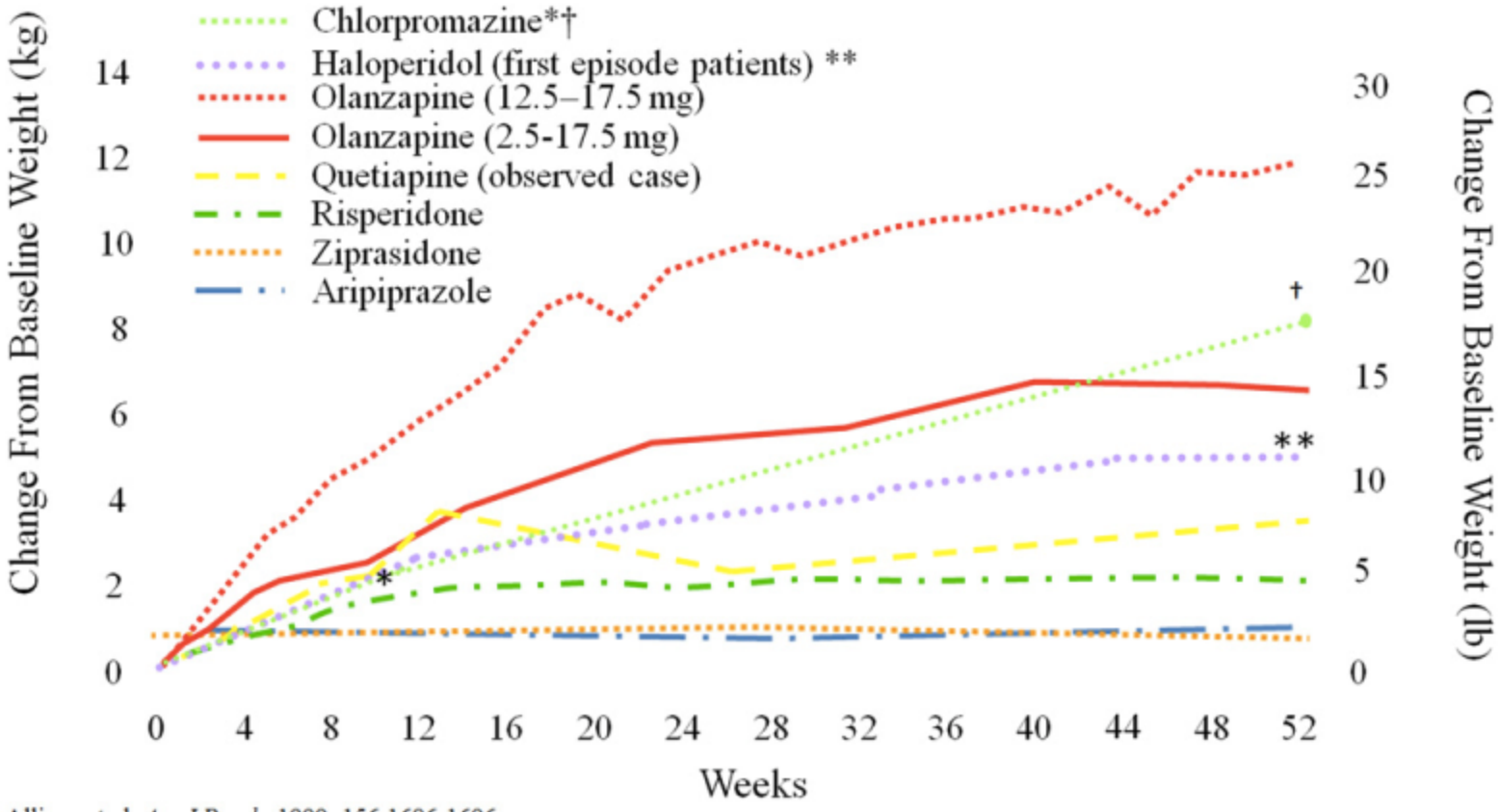
'the differences in efficacy between drugs were small'
'Antipsychotics differed substantially in side-effects'

AMI=amisulpride; ARI=aripiprazole; ASE=asenapine;** CLO=clozapine; CPZ=chlorpromazine; HAL=haloperidol; ILO=iloperidone*; LURA=lurasidone; OLA=olanzapine; PAL=paliperidone; PBO=placebo; QUE=quetiapine; RCT=randomised controlled trial; RIS=risperidone; SER=sertindole; ZIP=ziprasidone*; ZOT=zotepine.*

Leucht S, et al. Lancet. 2013;382(9896):951–62.

* Not licensed in the UK
**Not licensed in UK for schizophrenia

1-Year Weight Gain: Mean Change From Baseline Weight



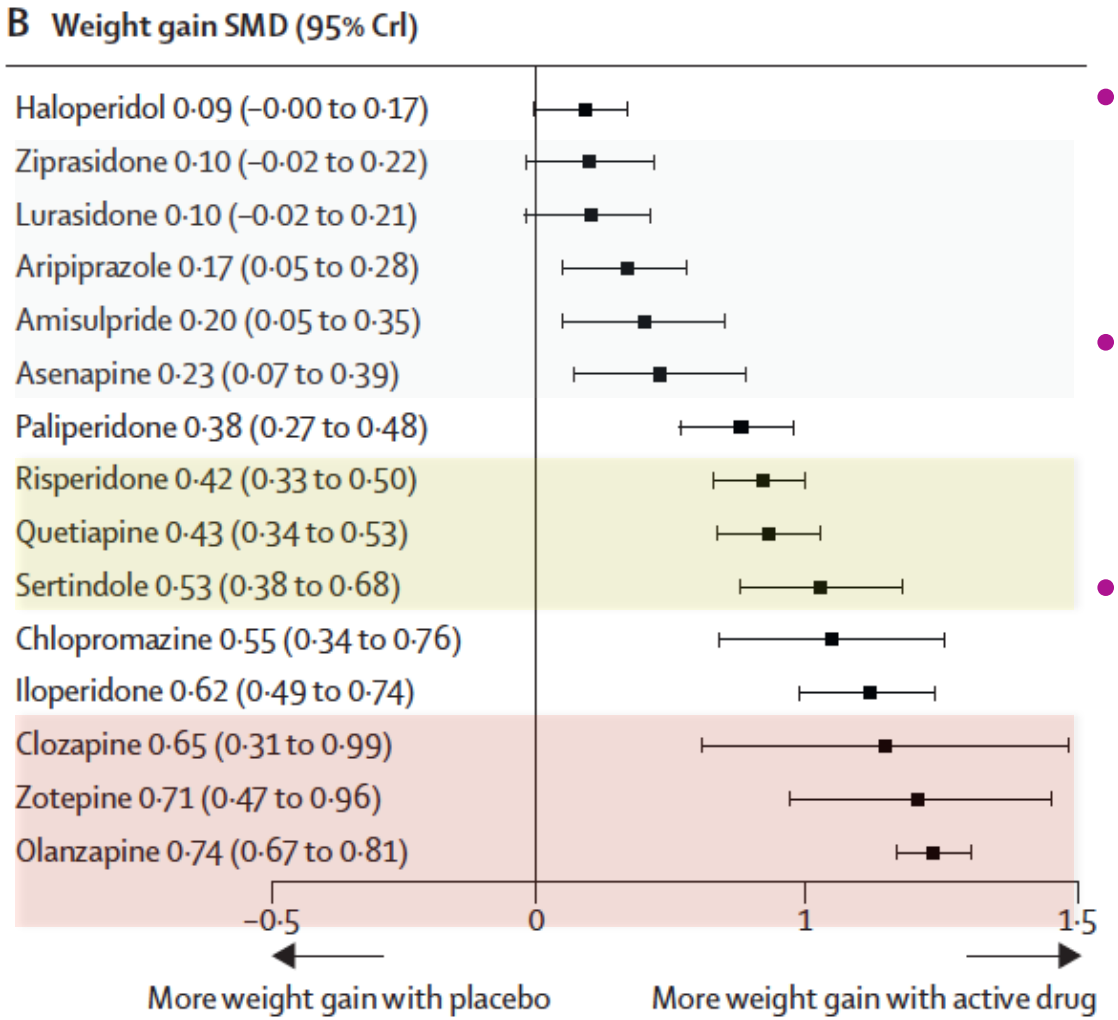
*(est 10 wks) Allison et al. *Am J Psych.* 1999; 156:1686-1696.
†(median 131 wks drug naïve) Lieberman JA, et al. *Neuropsychopharmacology*. 2003; 28:995-1003.

Nemeroff CB. *J Clin Psychiatry.* 1997;58(suppl 10):45-49; Kinon BJ, et al. *J Clin Psychiatry*. 2001;62:92-100; Brecher M, et al. American College of Neuropsychopharmacology; 2004. Poster 114; Brecher M, et al. *Neuropsychopharmacology*. 2004;29(suppl 1):S109; Geodon® [package insert]. New York, NY: Pfizer Inc; 2005. Risperdal® [package insert]. Titusville, NJ: Janssen Pharmaceutica Products, LP; 2003; Abilify® [package insert]. Princeton NJ: Bristol-Myers Squibb Company and Rockville, MD: Otsuka America Pharmaceutical, Inc.; 2005.
**Zipursky RB, et al. 2005; *British Journal of Psychiatry.* 187:537-543.

Antipsychotics & Weight Gain

Receptor	Activity	Effect/Mechanism
Dopamine-2	Antagonism	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
Histamine-1	Antagonism	Causes weight gain via increase in hypothalamic AMP-related kinase activity, which leads to increased appetite; sedative effects may lead to reduction in mobility
Muscarinic-3	Antagonism	Not directly correlated with weight gain, but causes diabetes via impairment of glucose tolerance and reduction of insulin secretion from pancreatic beta cells
Serotonin-1A	Partial agonism	May mitigate weight effects due to serotonin-2C antagonism; may decrease carbohydrate craving
Serotonin-2C	Antagonism	Causes weight gain via disinhibition of hypothalamic neuropeptide Y neurons and inhibition of pro-opiomelanocortin neurons; may also influence leptin resistance

Meta-analysis of antipsychotic drug-induced weight gain



- 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.

Leucht et al, 2013

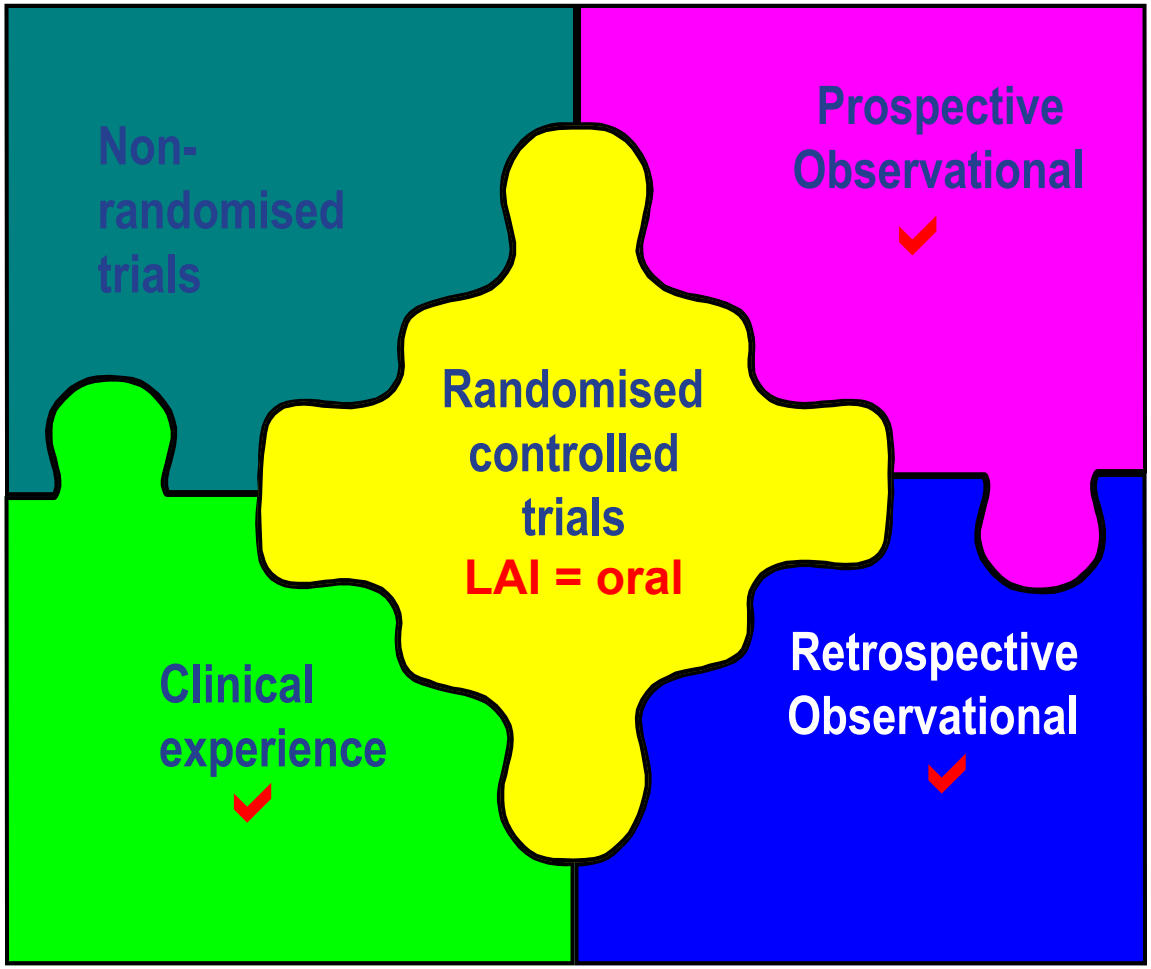
Iloperidone, sertindole, ziprasidone and zotepine are not licensed in UK.
Asenapine is not licensed for schizophrenia in UK.

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)**

Haddad et al. Patient Related Outcome Measures 2014; 5: 43-62 .

Evidence base for LAIs vs oral drugs



✔ = LAI superior to oral

Discrepancy may reflect cohort bias and altered ecology in RCTs

LAI=Long-acting injectable.

Haddad et al. Patient Related Outcome Measures 2014; 5: 43-62 .

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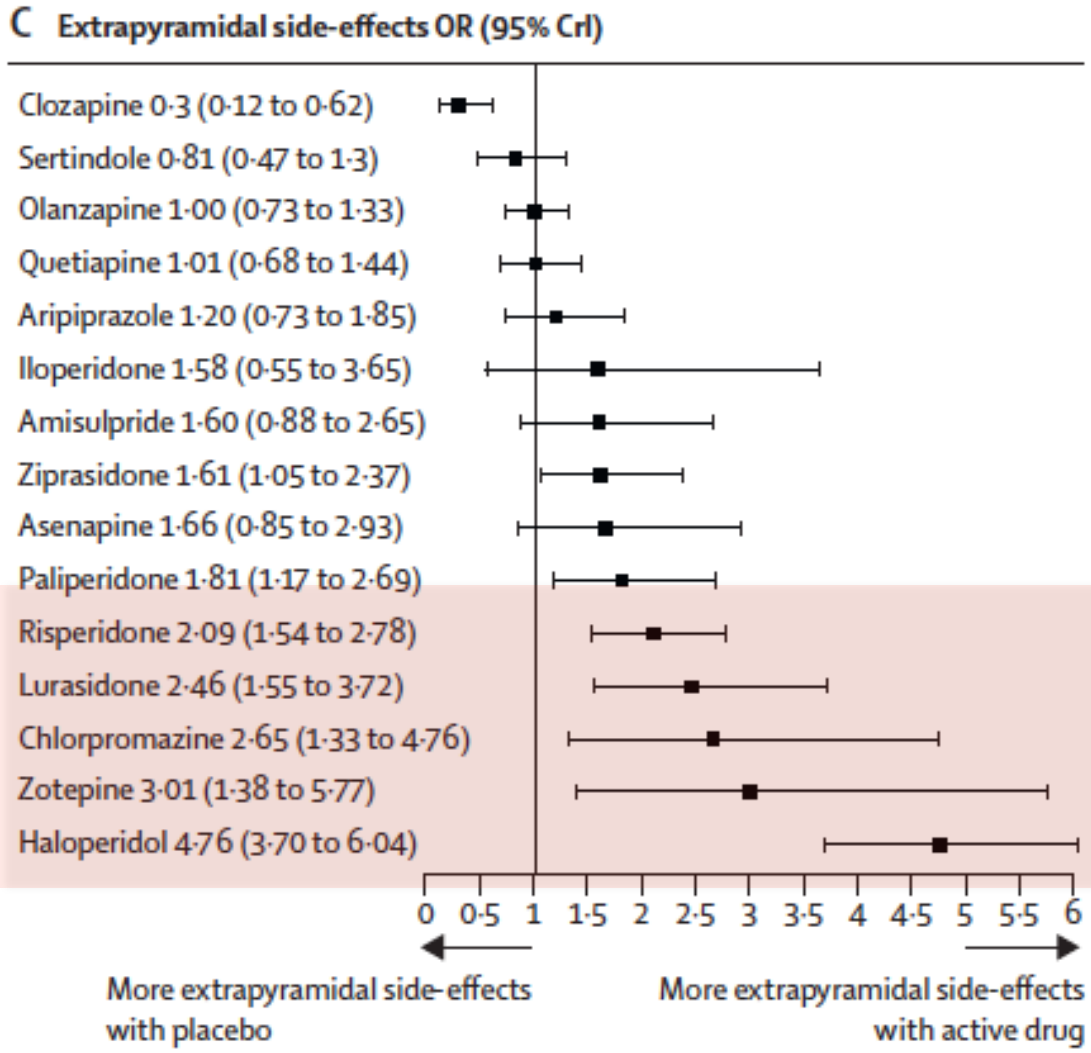
DO SOMETHING……

Meta-analysis of antipsychotic drug-induced extrapyramidal side effects



From Leucht et al, Lancet. 2013; 382 :951-62.

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

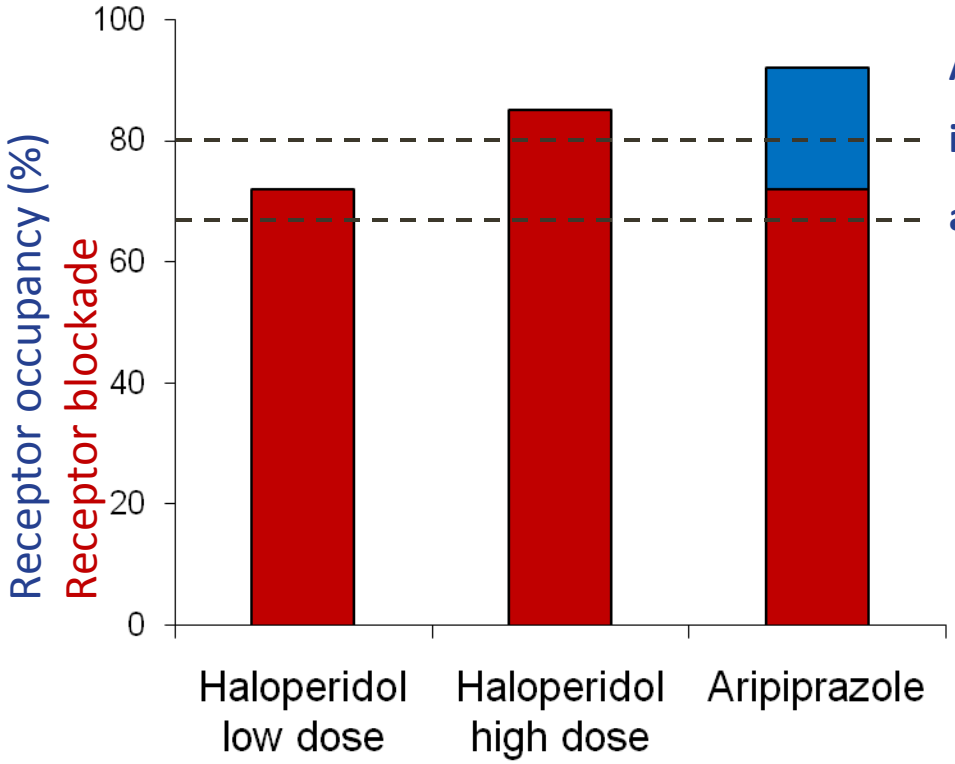
Iloperidone, sertindole, ziprasidone and zotepine are not licensed in UK.
Asenapine is not licensed for schizophrenia in UK.

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.

Reynolds (2004) J Psychopharmacol 18, 340-345

D2 partial agonism of aripiprazole and the threshold for EPS



Antagonist thresholds for:

induction of EPS

antipsychotic action

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.

Reynolds (2004) J Psychopharmacol 18, 340-345

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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.

Tandon Cur Psychiatry 2002 1:9

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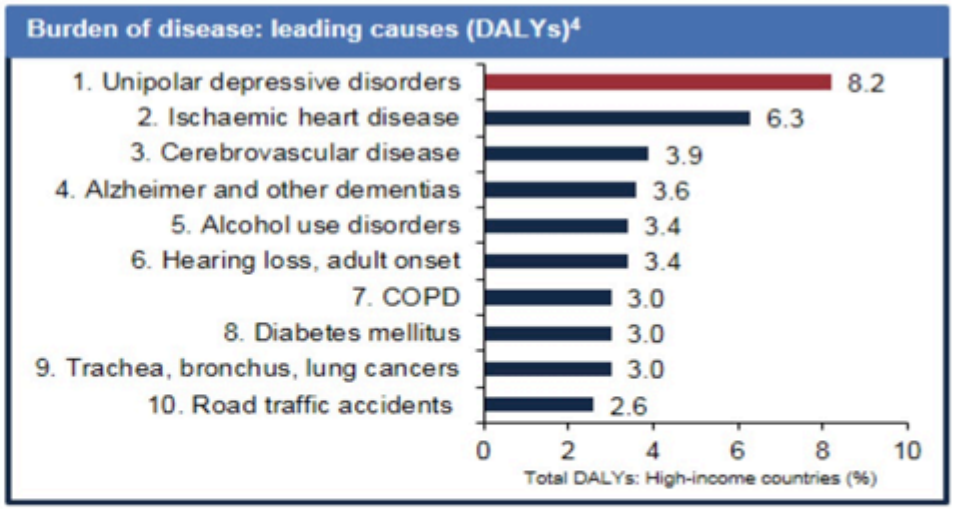
DO SOMETHING……

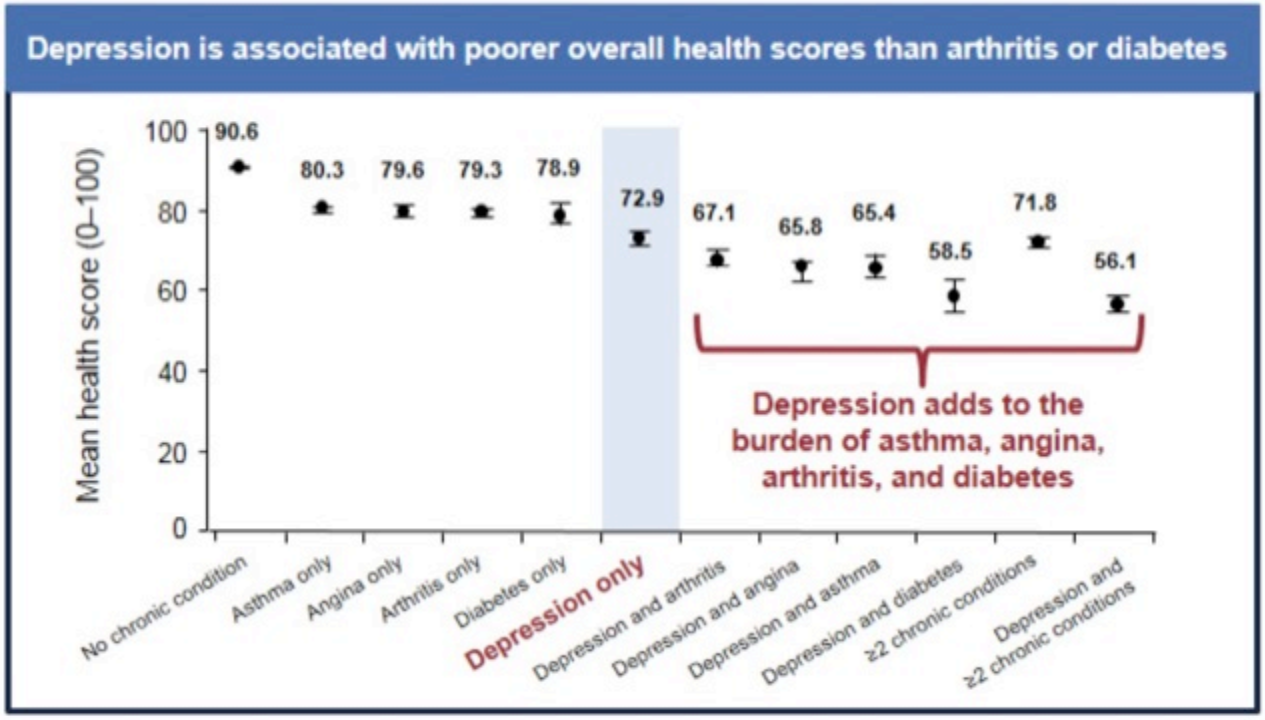
Depression is associated with significant economic costs

- Depression is the leading cause of global disease burden among mental, neurological and substance-use disorders[1]
- In England alone overall cost, including lost productivity, is estimated at £10.96 billion[2]
- The WHO predicts that depression will be the leading cause of disease burden globally by 2030[3]



1. Collins et al. Nature 2011;475:27–30
2. All-Party Parliamentary Group on wellbeing economics. 2010. Available at:http://parliamentarywellbeinggroup.org.uk/reports/
3. WHO. 2011:EB130/9
4. WHO. Global Burden of Disease 2004

Depression adds to the burden of disease for the individual



Adapted from Moussavi et al. Lancet 2007; 370: 851–858

Depression impacts on workplace productivity

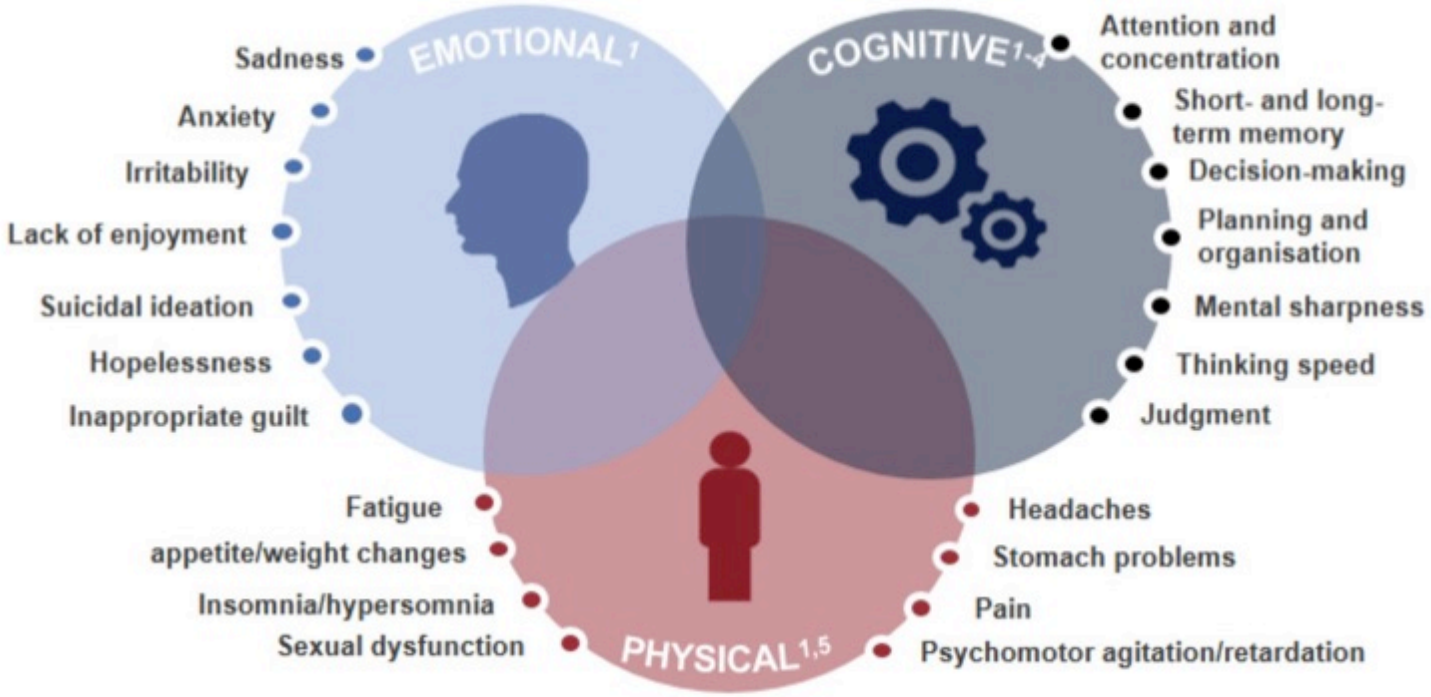
Workplace functionality

- Government-commissioned research in 2010 found that people unable to work because of depression lose **£8.97 billion** of potential earnings per year in England[1]
- In Europe, an average of **36 days** is taken off work per episode of depression[2]
- 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 work[3]

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

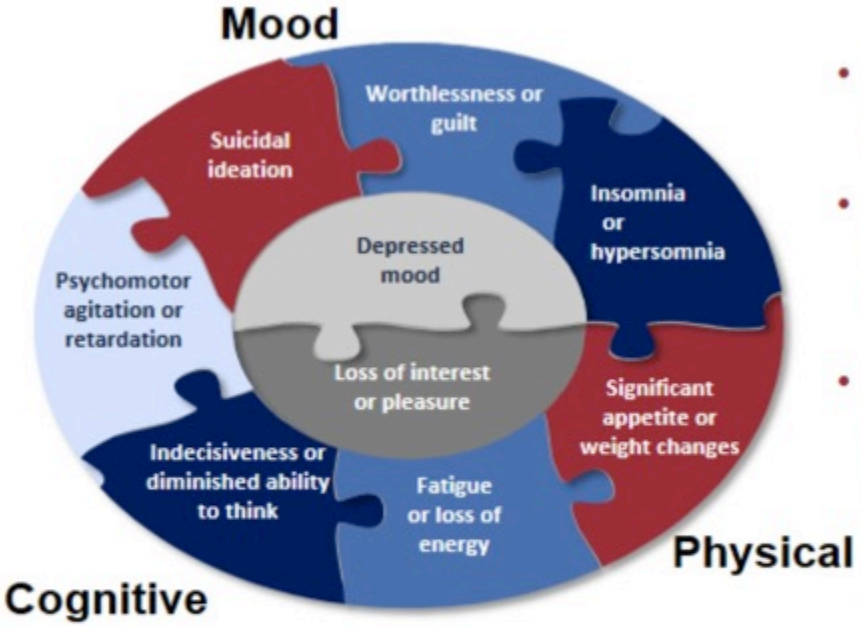
1. APPG on Wellbeing economics. 2011
2. Ipsos Healthcare. October 2012
3. Sainsbury Centre for Mental Health. 2007

Depression is clinically heterogeneous disorder



1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Health Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013
2. Marazziti D et al. Eur J Pharmacol 2010;626(1):83–86
3. Hammar A, Ardal G. Front Hum Neurosci 2009;3:26. doi: 10.3389/neuro.09.026.2009
4. Fehnel SE et al. CNS Spectr 2013;25:1–10. doi:10.1017/S1092852913000643
5. Kennedy, S.H & Razvi S. J Clin Psychopharmocol 2009;29(2):157-164

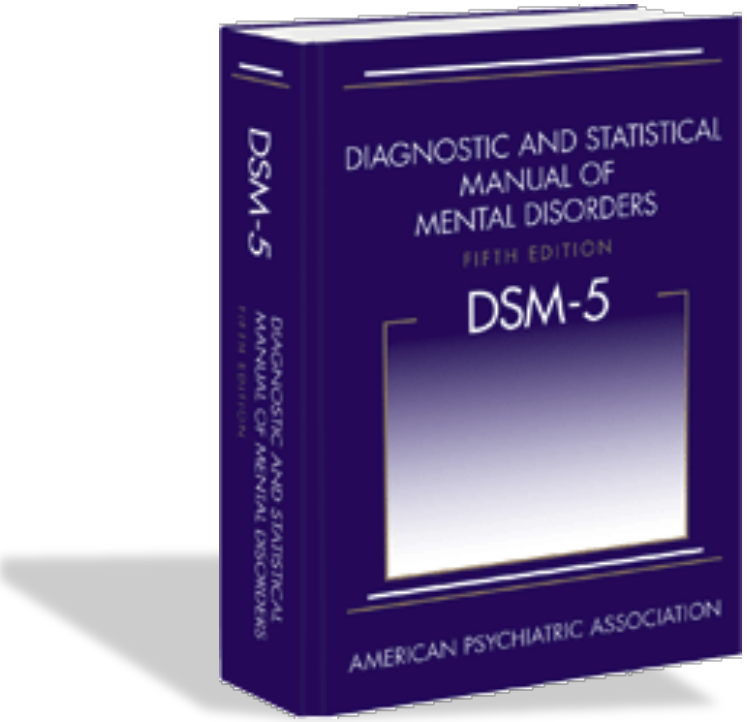
DSM-V classification: MDD symptoms



- **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

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. APA 2013

According to the DSM-5, cognitive symptoms are a criterion for a major depressive episode

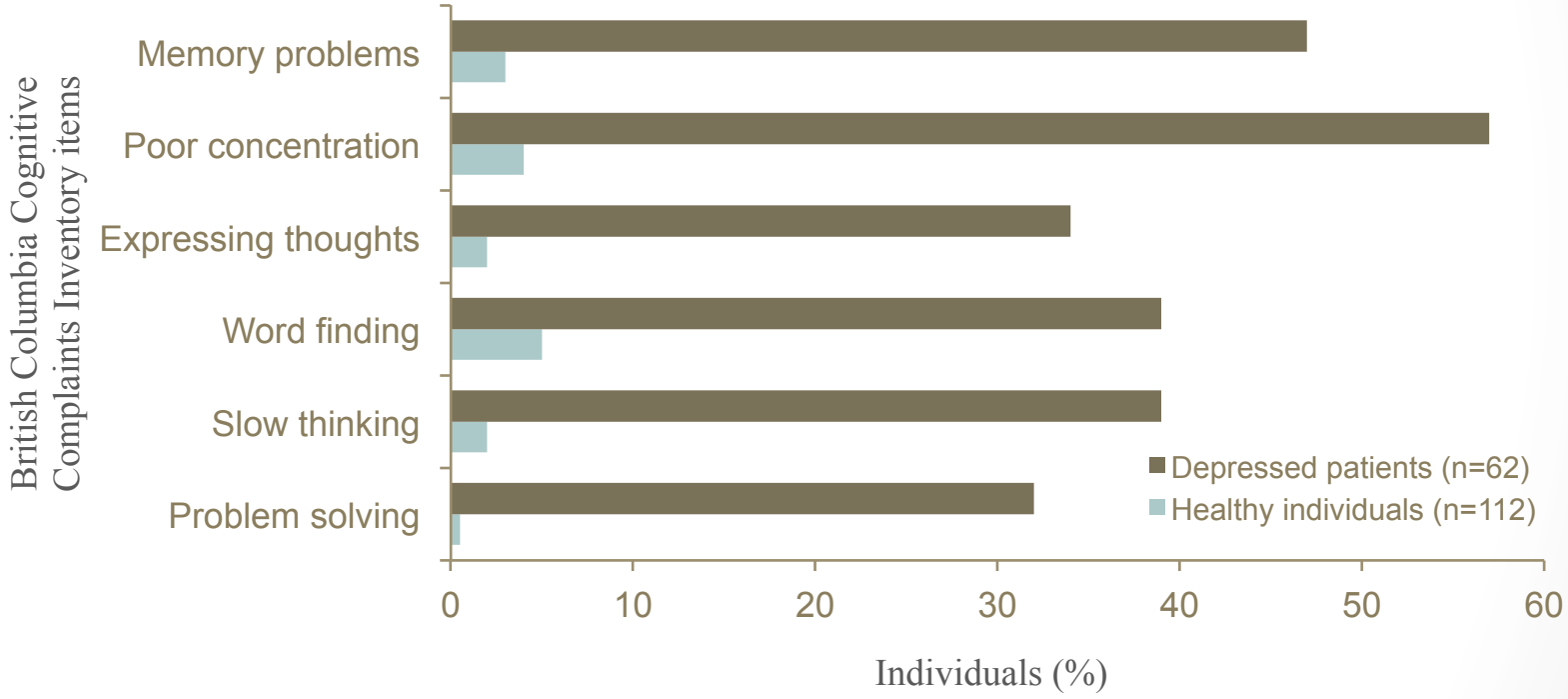


Cognitive symptoms are 1 of the 9 diagnostic criteria for depression, defined as:

"A diminished ability to think or concentrate, nearly every day (either by subjective account or observed by others)"

Cognitive complaints in depressed patients

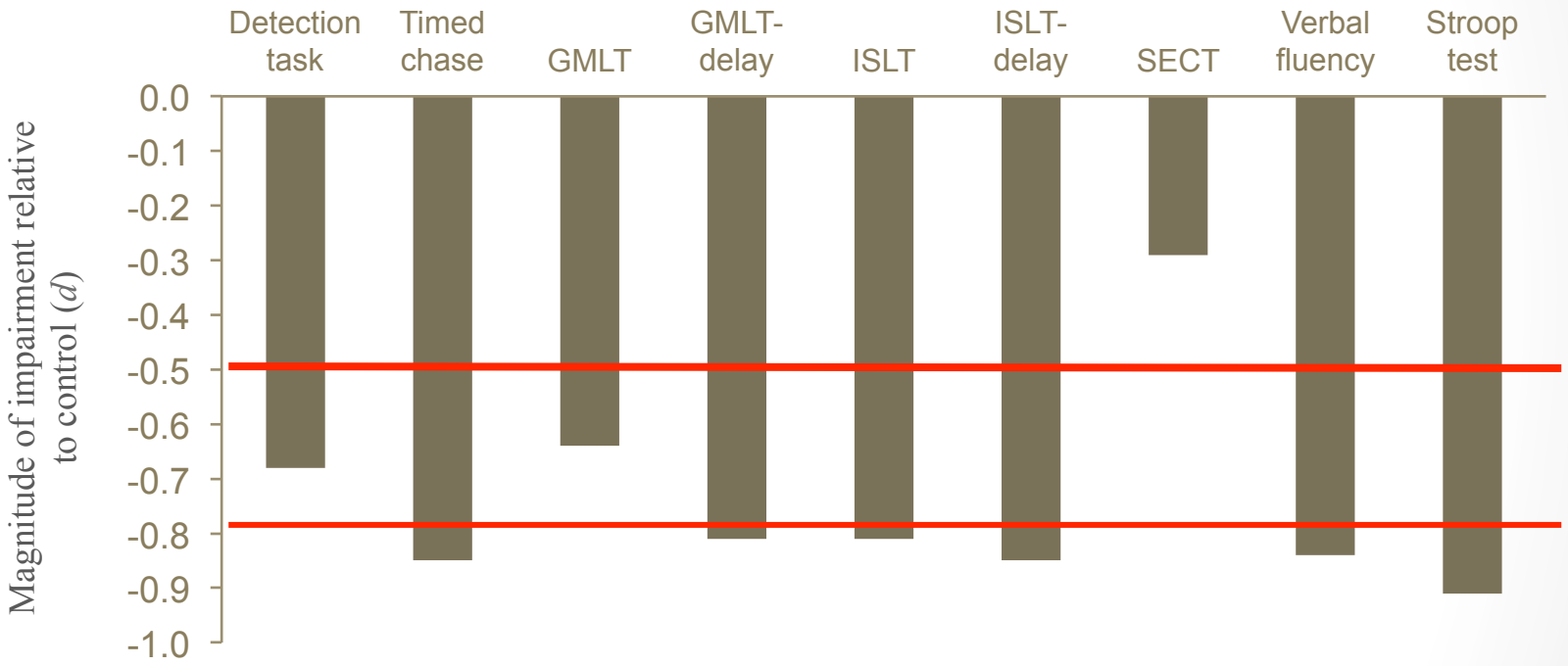
Percentage of individuals rating problems “Quite a bit” or “Very much”



- “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)

Iverson GL, Lam RW. Ann Clin Psychiatry 2013;25:135-40

Cognitive impairment in patients with depression



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

Douglas KM et al. Br J Psychiatry 2011;198:115-22

Cognitive dysfunction has functional consequences across several domains

Problems with planning

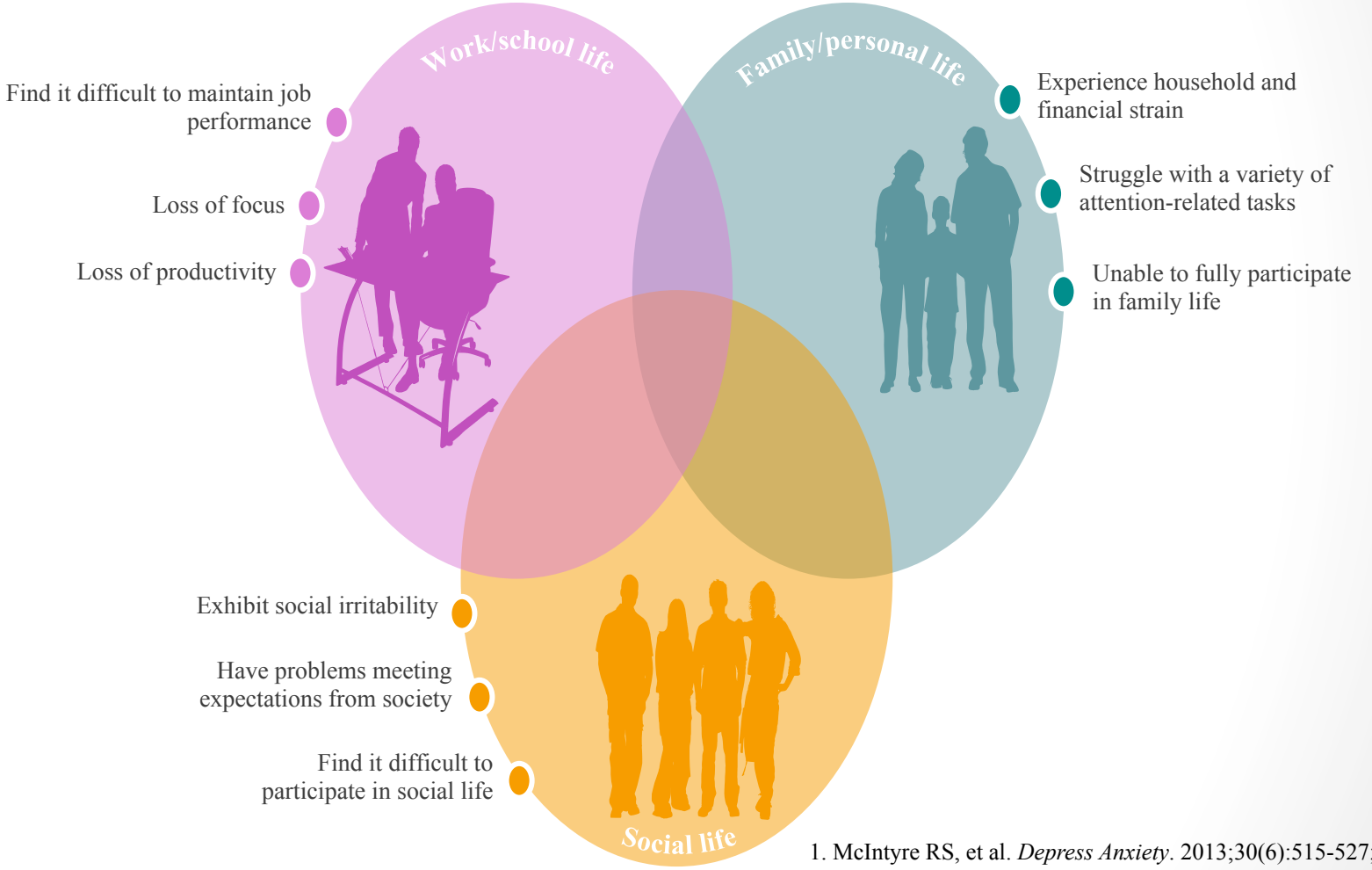
Impaired ability to concentrate

Slowness in responding

Difficulties with memory

Hammar Å, Årdal G. Front Hum Neurosci 2009;3:26;
Elliott R. Br Med Bull 2003;65:49-59

Cognitive symptoms of depression have a negative impact on many aspects of the patient's life[1,2]



1. McIntyre RS, et al. *Depress Anxiety*. 2013;30(6):515-527;
2. Hammar A, Ardal G. *Front Hum Neurosci*. 2009;3:26.

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

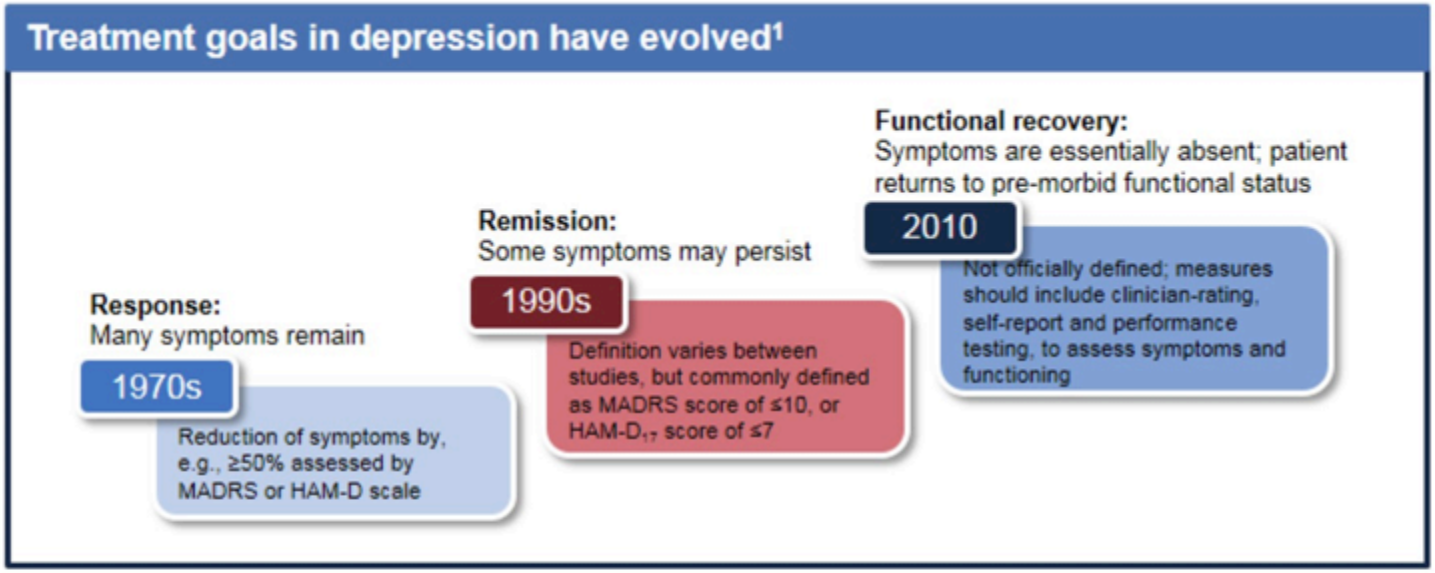
Whatever its cause, cognitive dysfunction can interfere with treatment for depression

Functional recovery: why is it important?

- The ultimate treatment goal in depression is functional recovery[1,2]
- The aim of an intervention should be the **complete relief of symptoms**,[1,2] associated with;
  - Improved functioning[3]
  - Better overall quality of life[3]
  - Lower likelihood of relapse[4]

1. Borolato B et al. CNS Neurol Disord Drug Targets 2014;13:1804-1818; 2.Stotland NL. Psychiatr Clin N Am 2012; 35: 37-49; 3.Greer TL, Kurian BT, Trivedi MH. CNS Drugs 2010; 24(4):267–284; 4.Tranter RT et al.. J Psychiatry Neurosci. 2002; 27(4): 241-7

The ultimate goal of treatment in MDD is functional recovery



- 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[2]

1. McIntyre & O'Donovan. Can J Psychiatry 2004;49(3 Suppl 1):10S–16S
2. Zimmerman et al. J Clin Psychiatry 2012;73(6):790–795

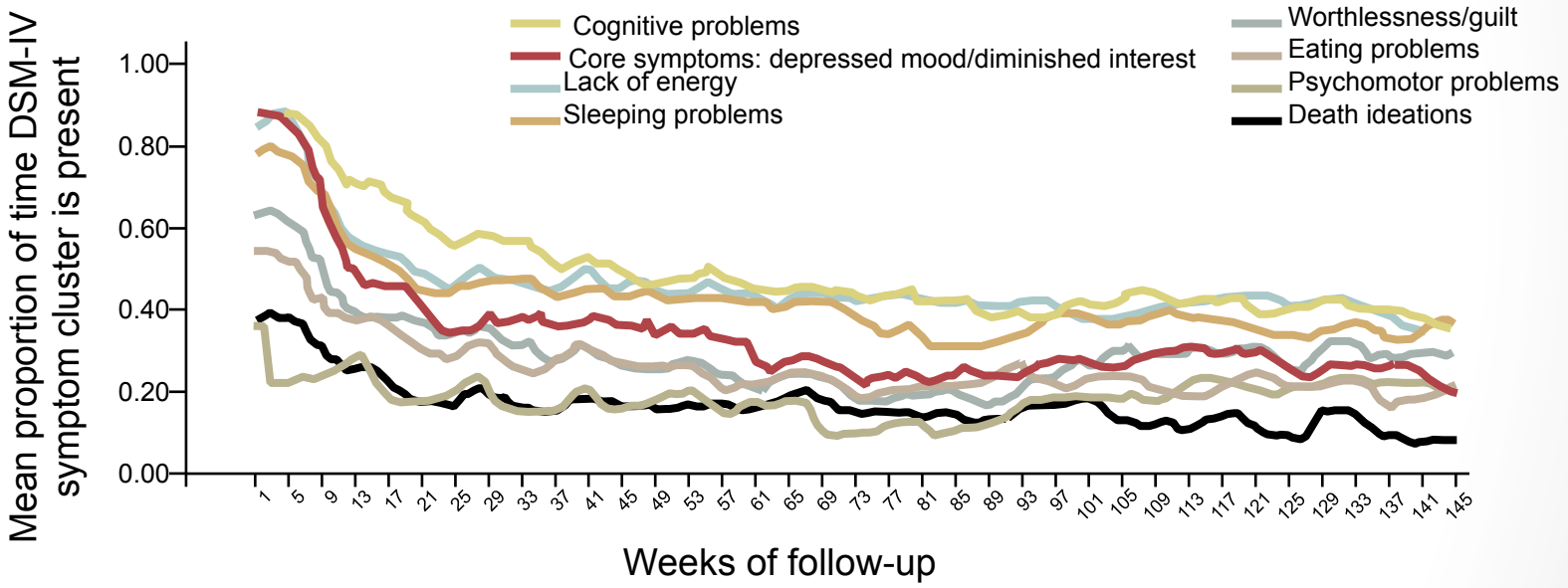
Barriers to achieving functional recovery

- 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]

1. Fournier JC et al. J Consult Clin Psychol 2009;77:775-787; 2. Kendler KS et al. Am J Psychiatry 2000;157:1243-1251; 3.Howland RH et al. Ann Clin Psychiatry 2008;20:209-218; 4. Fava M et al. Am J Psychiatry 2008;165:342-351; 5. Mulder RT. Am J Psychiatry 2002;159:359-371; 6. DeVeaugh-Geiss AM et al. Pain Medicine 2010;11:732-741; 7. Nanni V et al. Am J Psychiatry 2012;169(2):141-51; 8. Ostler K et al. Br J Psychiatry 2001;178:12-17; 9. Lamers F et al. Psychiatry Res 2011;226-231; 10. Watkins KE et al. Am J Psychiatry 2006;163:125-132;; 11. Kendler KS et al. Am J Psychiatry 2002;159:1133-1145; 12. Kendler KS et al. Am J Psychiatry 2006; 163:115-124.

Depressive symptoms persist during periods of remission and subsequent depressive episodes

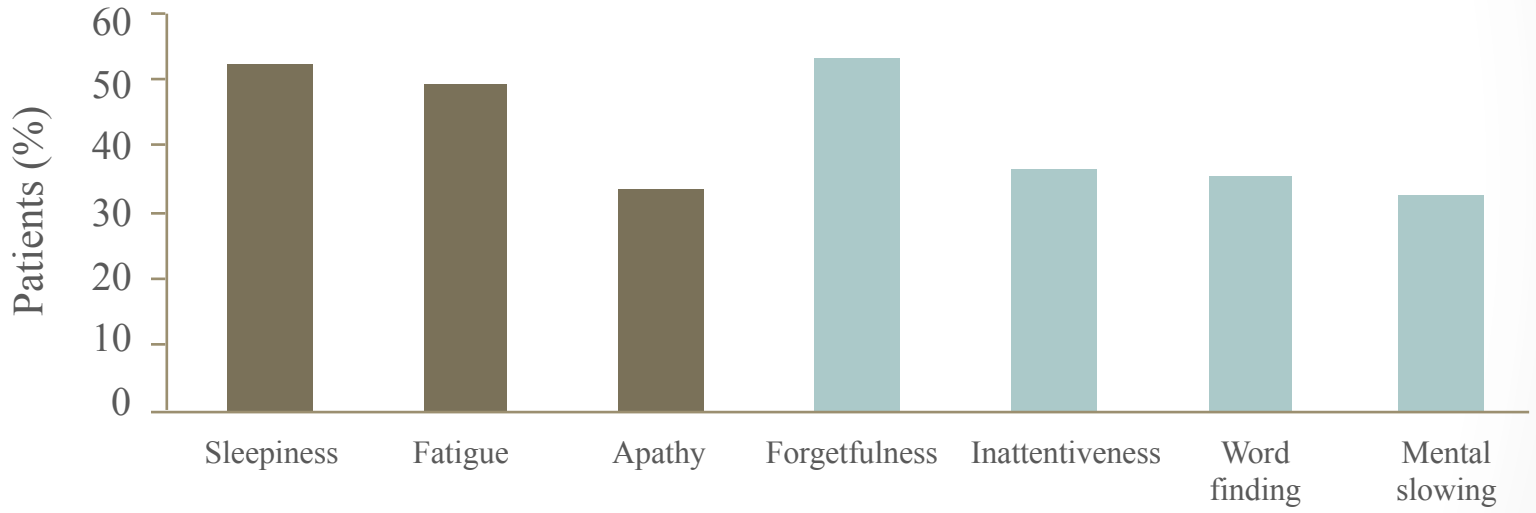
Mean proportion of time DSM-IV symptoms are present during 3-year follow-up period (n=267)



Conradi et al. Psychol Med 2011;41(6):1165–1174

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

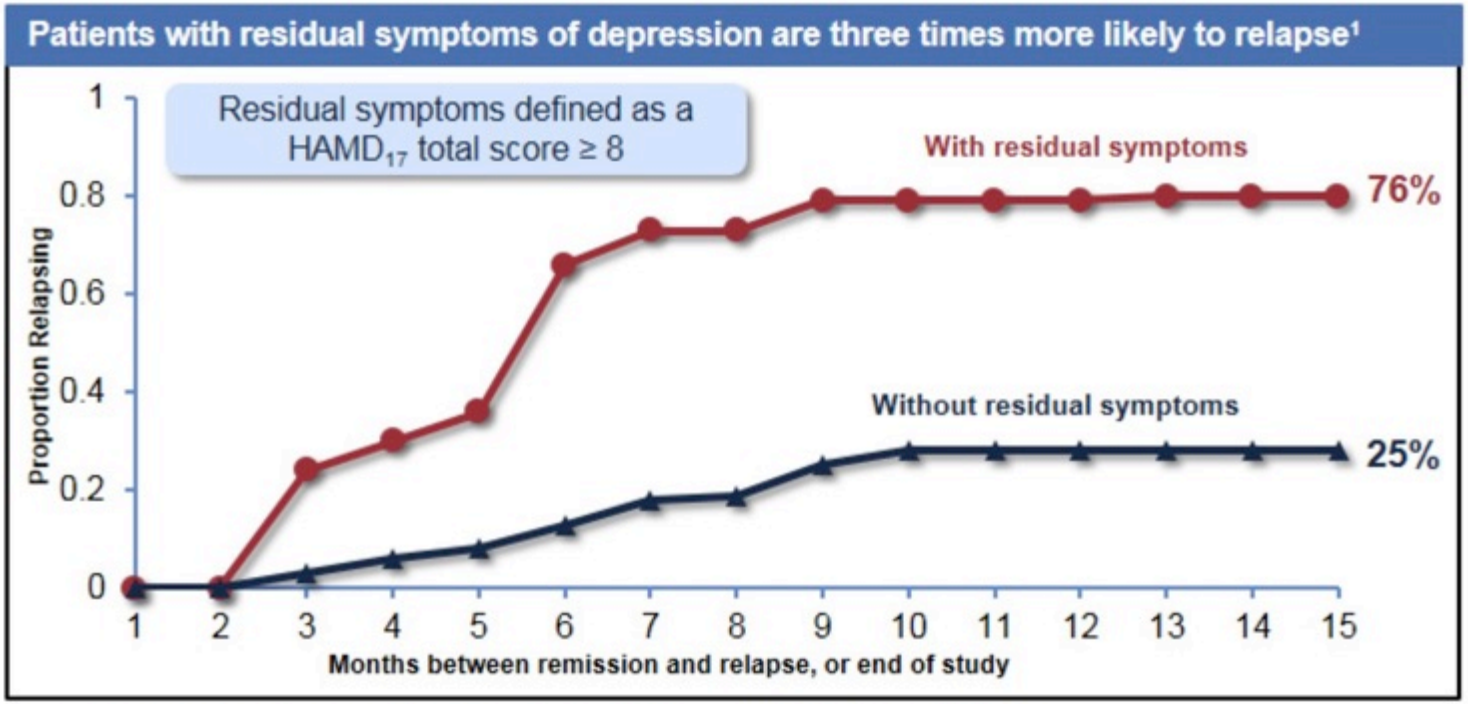


Items from the Cognitive and Physical Functioning Questionnaire

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

Fava M et al. J Clin Psychiatry 2006;67:1754-9

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

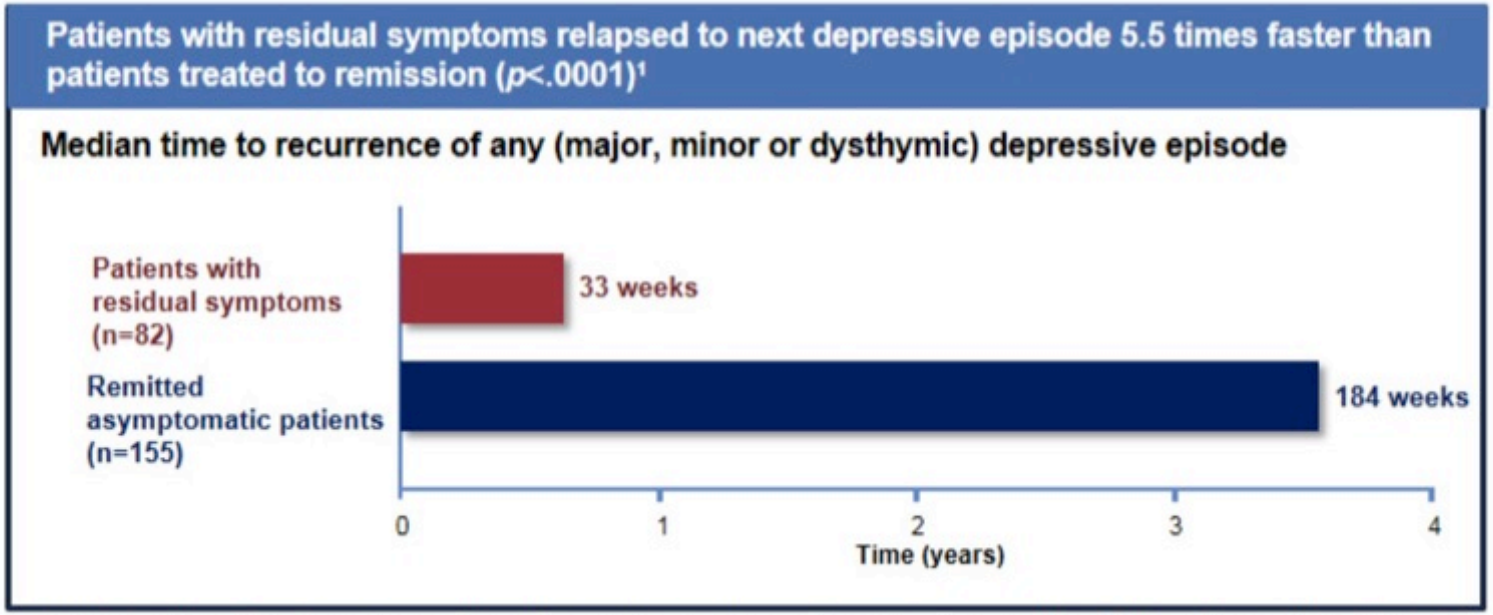


- Relapse occurred in 13/17 patients with residual symptoms, compared to 10/40 of those without residual symptoms (P<.001).
- Remission was defined as 2 consecutive months, retrospectively rated, below the Research Diagnostic Criteria (RDC) for primary unipolar major depression. Relapse was defined as a return to satisfy RDC definite major depression for ≥1 month.

1. Paykel ES et al. Psychol Med 1995; 25: 1171-1180

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 ($p<.0001$)[1]



- 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*<.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)

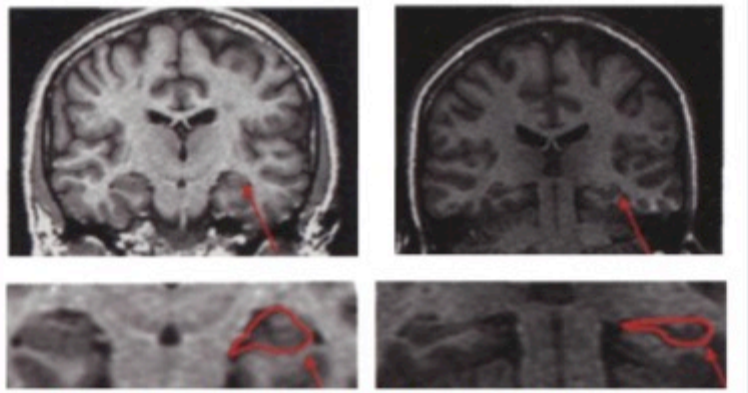
Remission was defined as asymptomatic recovery with ≥80% of well interval weeks rated asymptomatic

1. Judd LL et al. J Affect Disord 1998; 50 (2-3): 97-108

MDD is associated with hippocampal atrophy across all age groups

Age group	Observations
Adolescence[1]	Evidence of abnormalities in the hippocampus in early onset depression
Adulthood[2,3]	Findings are consistent with smaller left hippocampal volume in depression
Old age[4]	Further evidence of structural brain abnormalities in geriatric depression

Atrophy of the hippocampus in patients with depression[3]

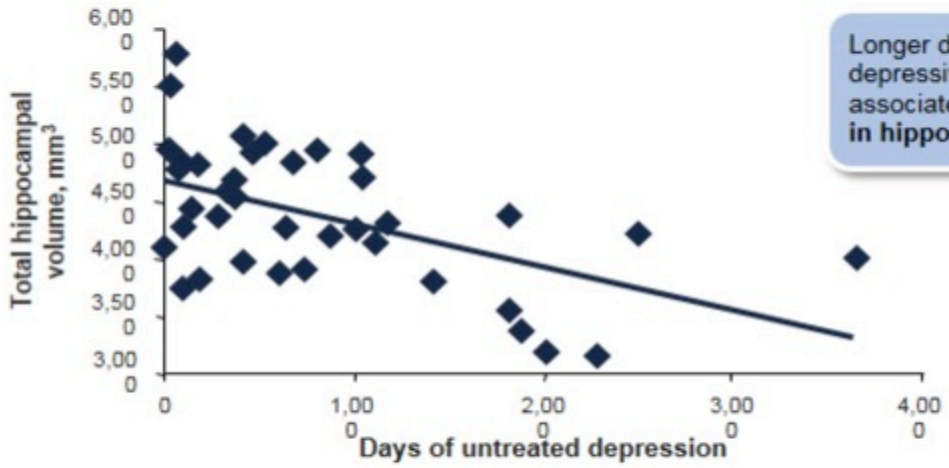


- 19% smaller volume of left hippocampus in patients with treated depression versus non-depressed control participants
- This represents a statistically significant decrease

1. MacMaster et al. BMC Med 2004;2:2
2. Bremner et al. Am J Psychiatry 2000;157(1):115–118
3. Bremner et al. CNS Spectr 2002;7(2):129–130,135–139
4. Bell-McGinty et al. Am J Psychiatry 2002;159(8):1424–1427

Hippocampal volume correlates with the duration of untreated depression

Imaging studies in depressed patients show that hippocampal volume is inversely related to the length of time the disease went untreated [1]



Antidepressants may have a neuroprotective effect during depression

1. Sheline et al. Am J Psychiatry 2003;160(8):1516–1518

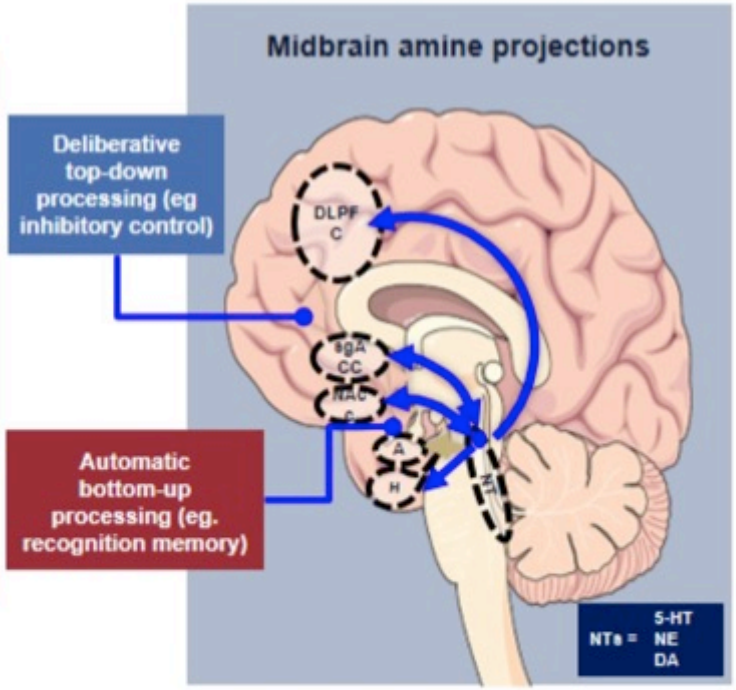
Neural correlates of cognitive impairment in depression

Key circuits of interest

Hippocampus: reduced volume and function; important for episodic memory

Prefrontal cortex: impaired connectivity and function; important for executive function, planning, and inhibition

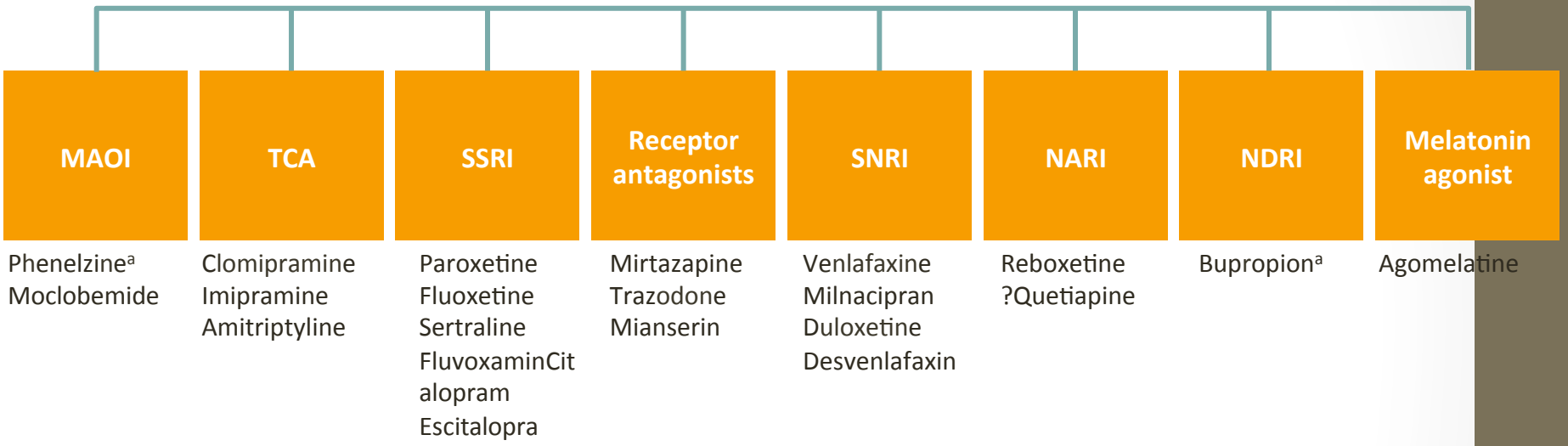
Partially overlapping circuits involved in emotional processing and regulation



A, amygdala; DA, dopamine; DLPFC, dorsolateral prefrontal cortex; H, hippocampus; NAcc, nucleus accumbens; NE, noradrenaline; NT, monoamine neurotransmitter; sgACC, subgenual anterior cingulate cortex; 5-HT, serotonin

1. Rolser JP, Sahakian BJ. CNS Spectr 2013; 18(3): 139-149

The drugs we have today



New drugs with multimodal actions

- Vilazodone[a] (USA): SSRI + 5-HT_{1A} agonist
- Vortioxetine: SSRI + effects on multiple other serotonin receptors

[a]Not licensed/available in the UK

Slattery DA et al. Fundam Clin Pharmacol 2004;18:1-21; Richelson E. Int J Neuropsychopharmacol 2013;16:1433-42

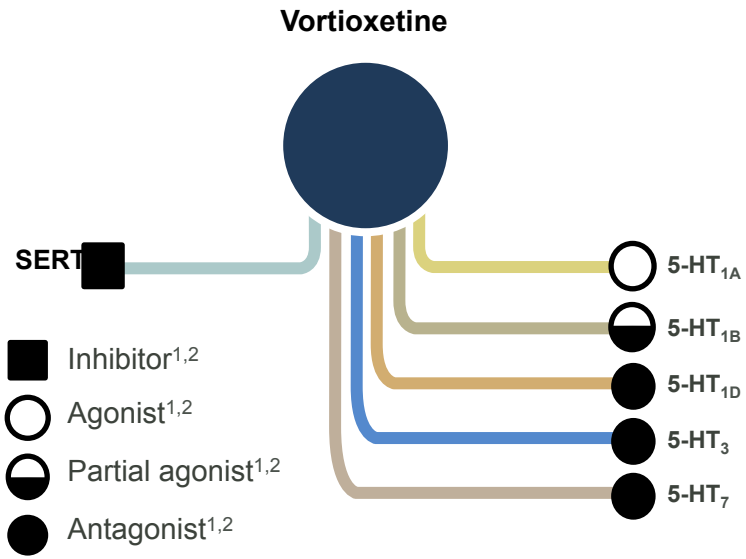
Many current treatments do not address cognitive dysfunction

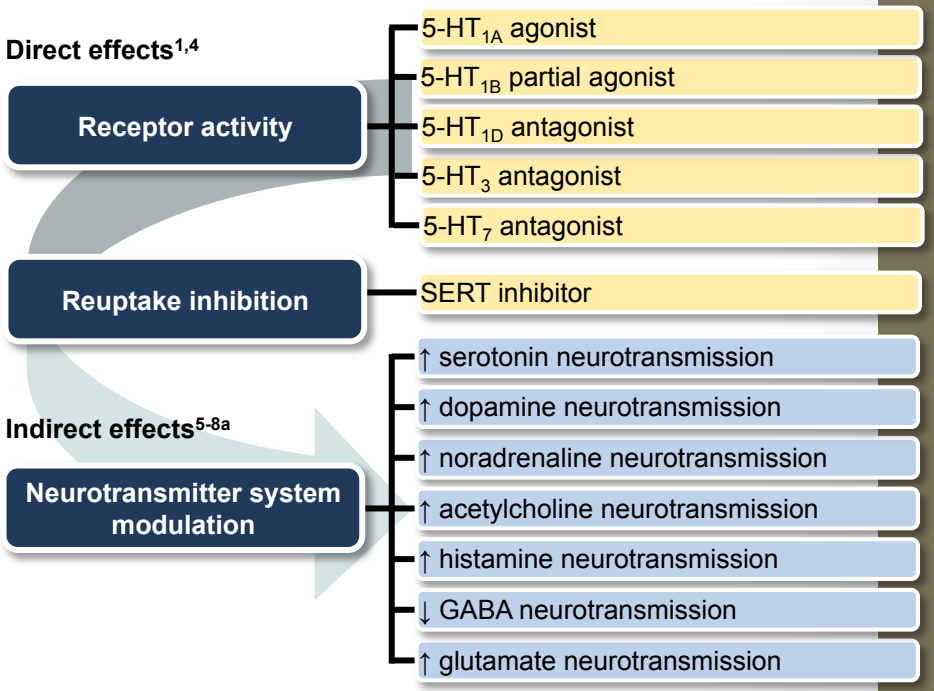
- There is emerging evidence that in some patients, the degree of cognitive deficit goes beyond that which can be accounted for by the severity of depressive symptoms[1-7]
- Many current treatments (including SSRIs and SNRIs) have limited data on cognitive dysfunction in patients with depression
- In those with partial or full resolution of depressive symptoms, cognitive impairment may persist [8,9]
- 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 [4,6-10]

1. Airaksinen E et al. Acta Psychiatr Scand 2007;115:458-465; 2. Behnken A et al. J Affect Disord 2010;122:144-148; 3. Harvey P et al. J Psychiatr Res 2004;38:567-576 ; 3. Iverson GL et al. J Affect Disord 2011;132:360-367; 4.Lee RS et al. J Affect Disord 2012;140:113-124; 5. McClintock SM et al. Neuropsychology 2010;24: 9-34 ; 6. McDermott LM, Ebmeier KP. J Affect Disord 2009;119: 1-8; 4. Reppermund S et al. Psychol Med 2009;39:603-614; 5. Weiland-Fiedler P et al. J Affect Disord 2004;82:253-238; 6.Naismith SL et al. J Clin Exp Neuropsychol 2003;25:866-877

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[1-3]



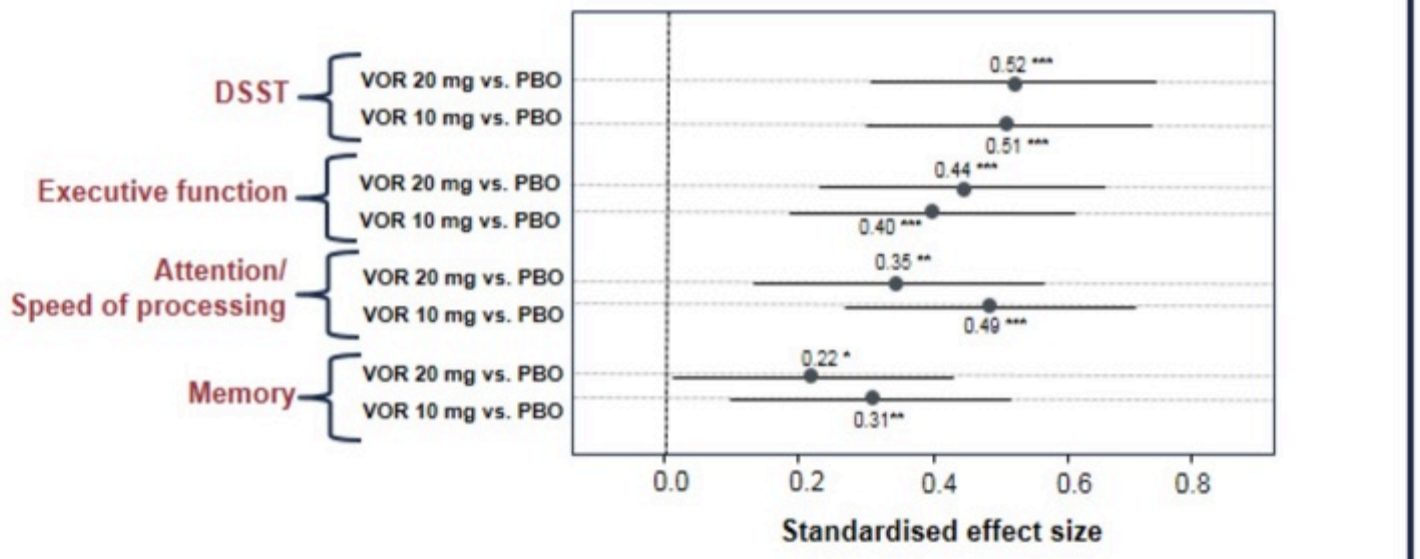


Nutt & Wilson 2015, not yet published

1. Bang-Anderson et al. 2011; 2. Mørk et al. 2012;
3. Vortioxetine SmPC; 4. Westrich et al. Poster at IFMAD 2012;
5. Mørk et al. Poster at ECNP 2011; 6. Mørk et al. Poster at SOBP 2011;
7. Pehrson et al. Poster at ECNP 2013; 8. Mørk et al. Poster at APA 2013

Vortioxetine improves cognitive performance in depression across multiple domains

Post-hoc analysis of cognitive readouts from the FOCUS study showing vortioxetine's multi-domain beneficial effect on cognitive performance at Week 8[1]



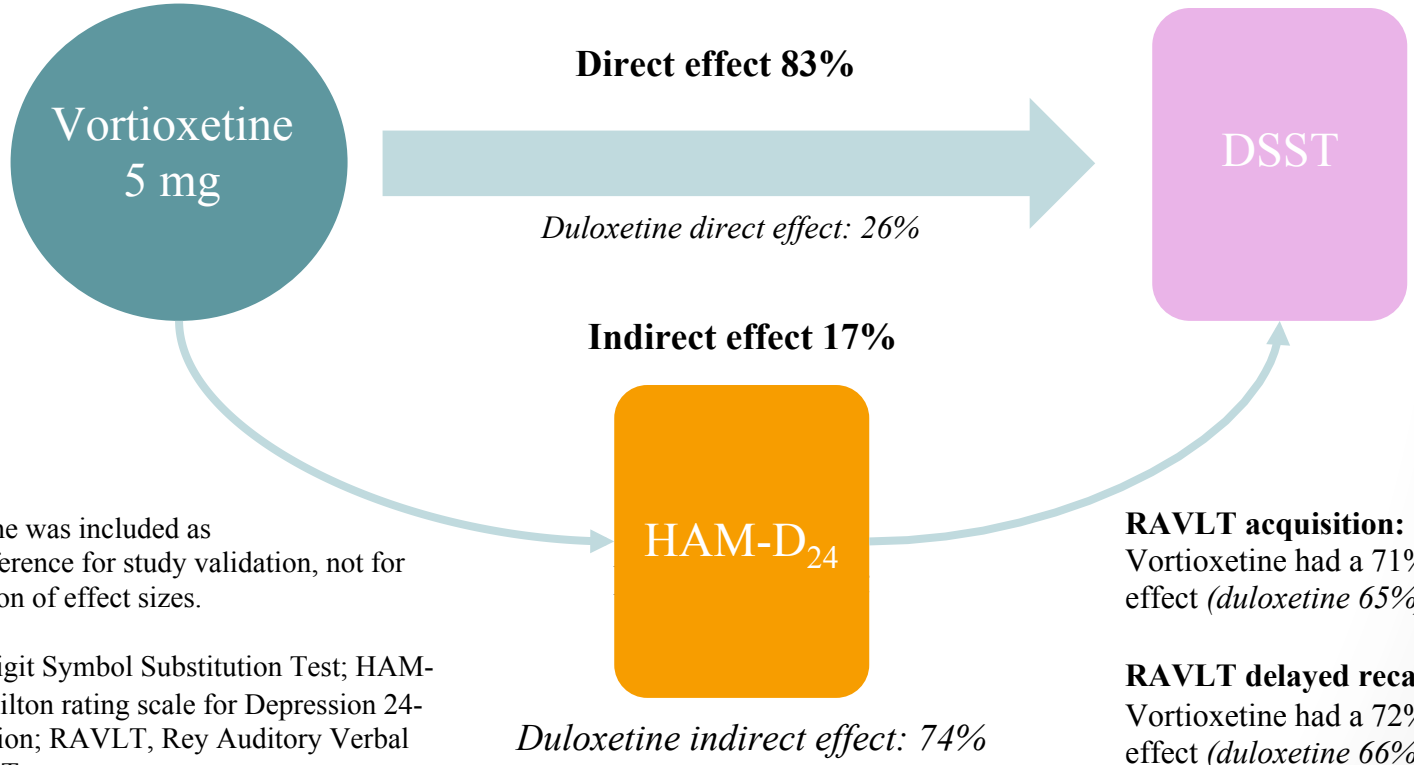
$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
Forest plot of composite Z-scores at Week 8 for the four cognitive domains derived from performance on a battery of cognitive tests (Stroop, TMTA, TMT B, SRT and RAVLT). Values are means with the 95% confidence interval for the Mixed Model for Repeated Measurements.
VOR, vortioxetine.; PBO, placebo; CRT, Choice Reaction Time test; RAVLT, Rey Auditory Verbal Learning Test; SRT; Simple Reaction Time test; TMT, Trail Making Test

1. Harrison et al. Int J Neuropsychopharmacol 2016 Advanced publication doi:doi:10.1093/ijnp/pyw054

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



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.

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

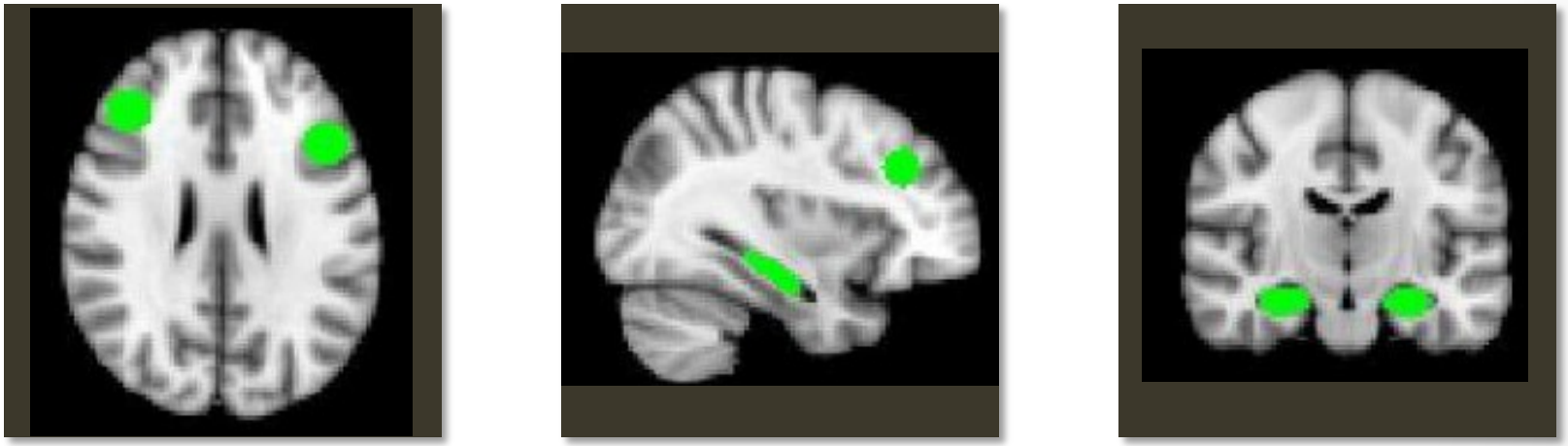
RAVLT delayed recall:
Vortioxetine had a 72% direct effect *(duloxetine 66%)*

Katona C, et al. *Int Clin Psychopharmacol*. 2012;27(4):215-223.

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 ive 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 (eg QoL, psychosocial function)
  - **needs adequate assessment and treatment for the patient to achieve functional recovery**