

Depression, Dementia and Drug Development

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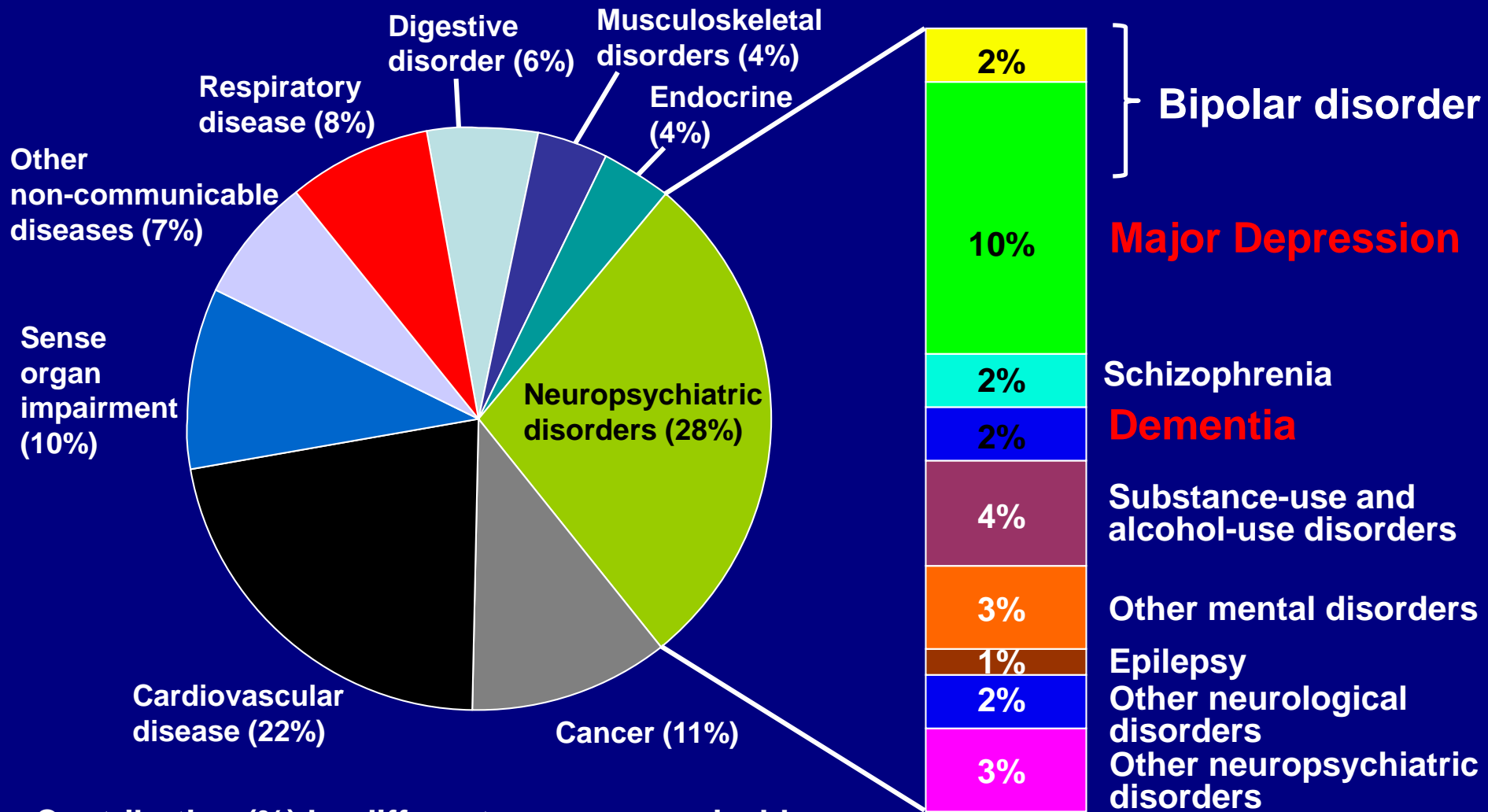
**Institute of Psychiatry,
Psychology & Neuroscience**

KING'S
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LONDON

Disclosures

- Employed by King's College London; Honorary Consultant Maudsley and Bethlem Hospitals (NHS).
- Paid lectures and advisory boards for all major pharmaceutical companies with drugs used in affective and related disorders.
- No share holdings in pharmaceutical companies or related companies.
- Lead Investigator for Embolden Study (AZ), BCI Neuroplasticity Study, and Aripiprazole Mania Study; Investigator-initiated studies from AZ, Eli Lilly and Company, Lundbeck, Wyeth.
- Grant funding (past and present): NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); NIHR (UK).
- NIHR Therapeutics Cluster Lead; Chair of Special Committee for Psychopharmacology RCPsych; President of International Society for Affective Disorders; President Elect of the BAP

The Disease Burden of Psychiatric Disorders



Contribution (%) by different non-communicable diseases to disability-adjusted life-years worldwide in 2005

Prince et al 2007

Pharmacotherapies for Mood Disorders

| 1940 | 1950 | 1960 | 1970 | 1980 | 1990 | 2000 | 2010 | ?????? |
|------|------|------|------|------|------|------|------|--------|
|------|------|------|------|------|------|------|------|--------|

Electro-
Convulsive
Therapy

Lithium

Anti-depressants

MAOIs
MARIs

Second
generation anti-
depressants

SSRIs, SNRIs, NARIs,
RIMAs and NASSA

Anticonvulsants

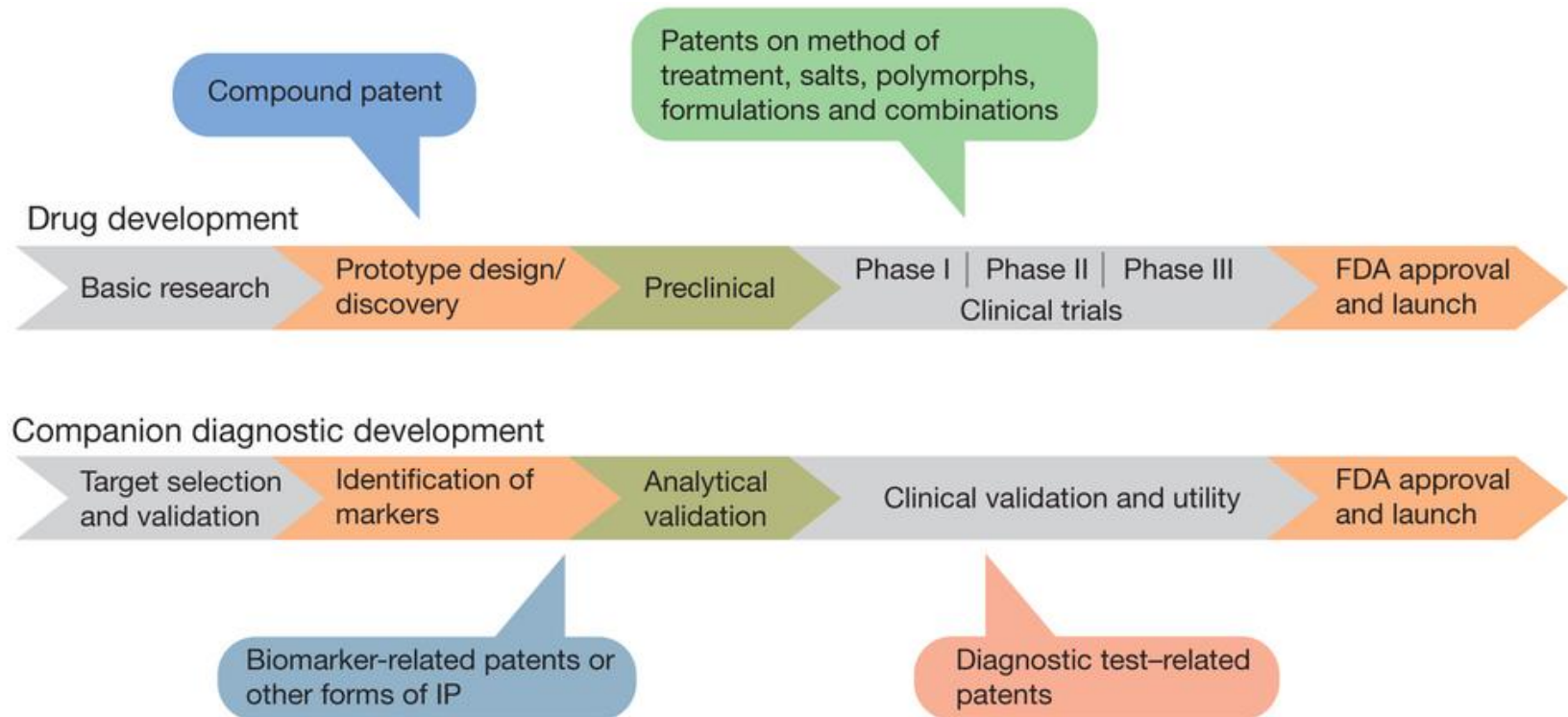
Carbamazepine
Valproate

Lamotrigine

Next-
generation
antipsychotics

Quetiapine
Olanzapine
Clozapine
Asenapine
Aripiprazole

Drug Development Pathway



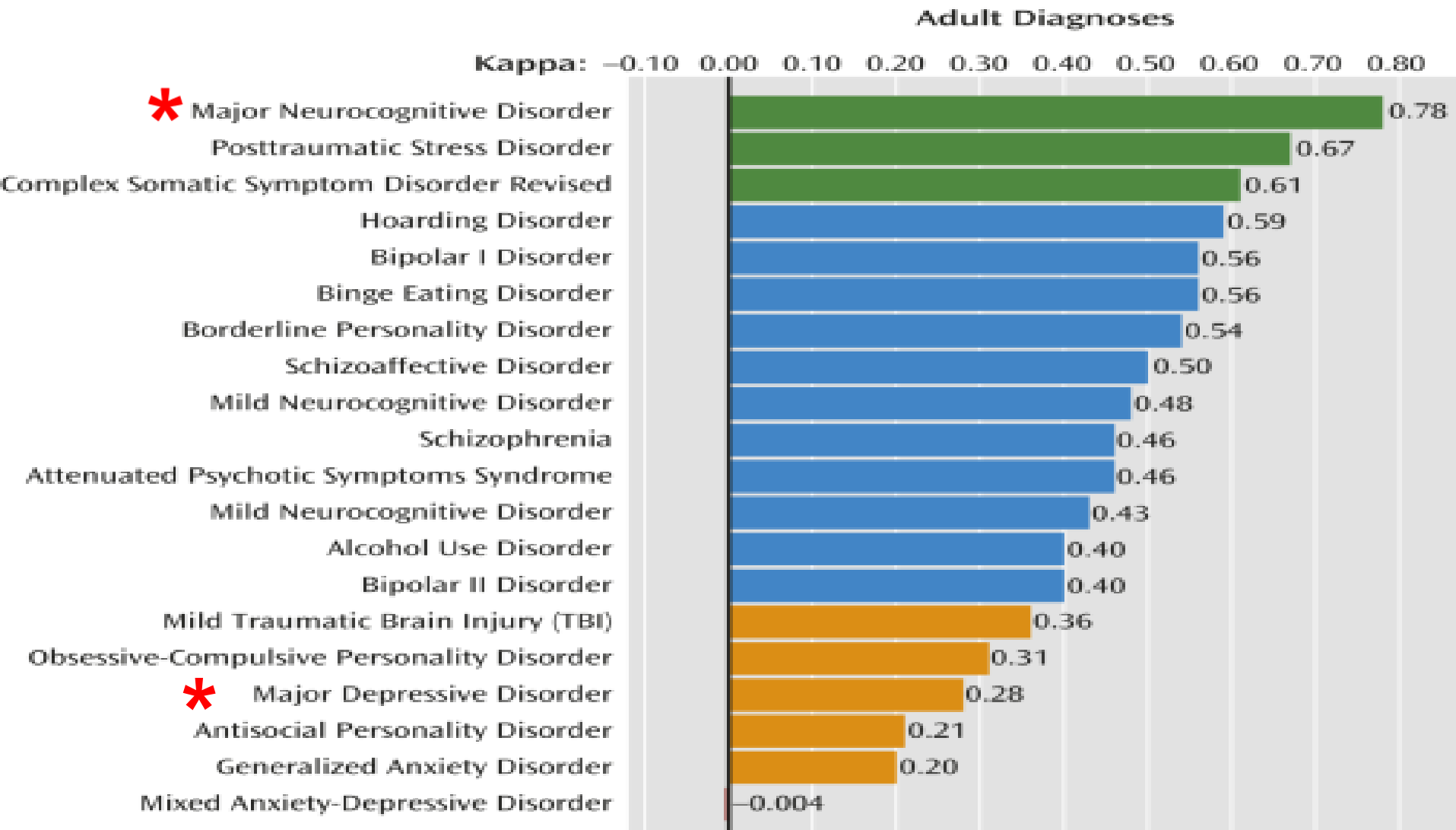
Drug Development Pathway

| Phase I | Phase II | Phase III | Phase IV |
|--------------------------------------------|-----------------------------|-----------------------------------------|---------------------------------------------------------|
| 20-80 participants | 100-300 participants | 1,000-3,000 participants | Thousands of participants |
| Up to several months | Up to (2) years | One (1) - Four (4) years | One (1) year + |
| Studies the safety of medication/treatment | Studies the efficacy | Studies the safety, efficacy and dosing | Studies the long-term effectiveness; cost effectiveness |
| 70% success rate | 33% success rate | 25-30% success rate | 70-90% success rate |

New Blooms and Old Thorns

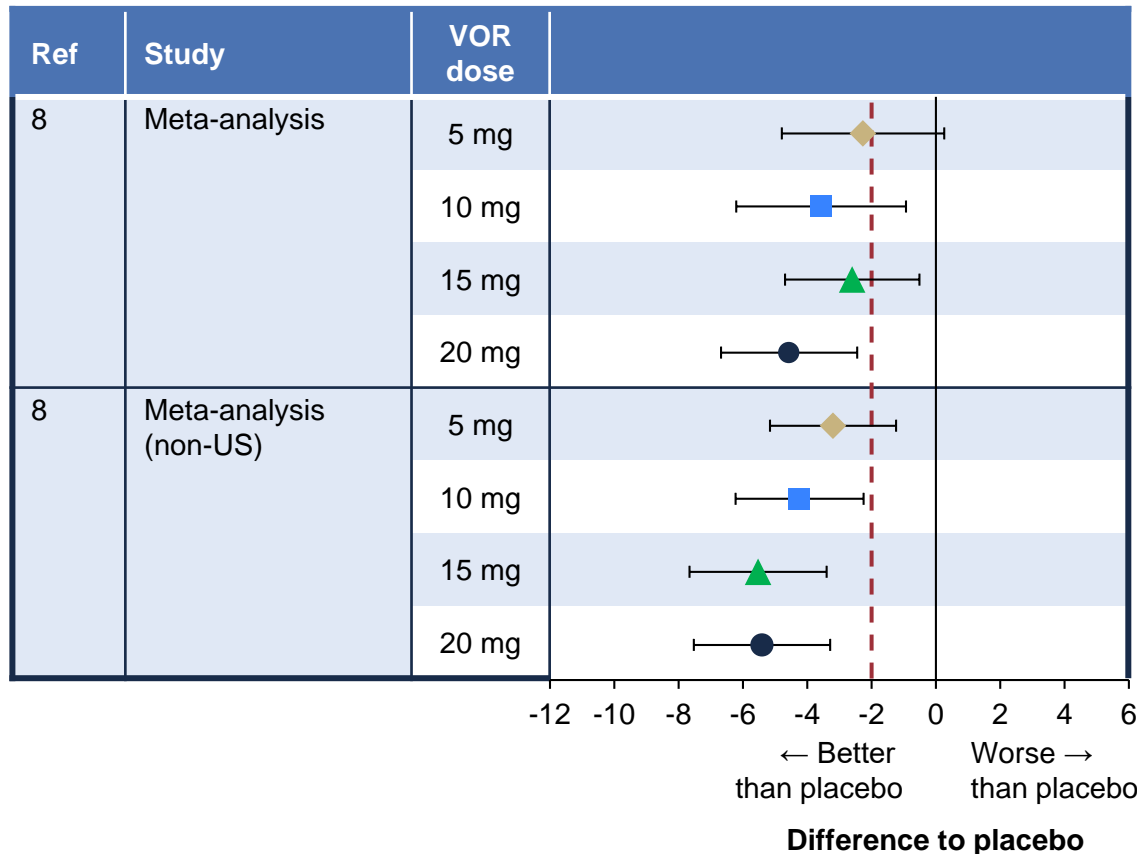
Am J Psychiatry. 2013;170(1):1-5.

Interrater Reliability of Diagnoses From the Initial DSM-5 Field Trials



Vortioxetine is effective for the short-term treatment of major depressive disorder

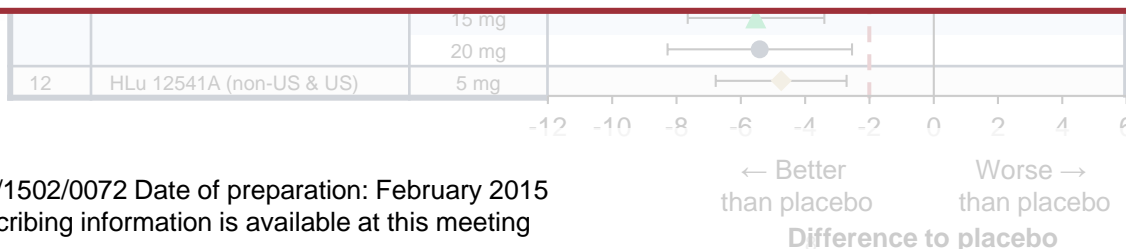
Change from baseline in MADRS total score at Week 6/8 (FAS, MMRM)¹¹⁻¹²



Meta-analyses of the results of 11^a short-term studies show:

- The superiority of vortioxetine compared with placebo at doses of 5, 10 and 20 mg
- A dose response across the therapeutic range of 5 to 20 mg/day vortioxetine

^aHLu 12541A in elderly patients (≥65 yrs)¹² not included



6. Jacobsen et al. 2015;
7. McIntyre et al. 2014;
8. Vortioxetine EPAR. 2013;
9. Jain et al. 2013;
10. Mahableshwarkar et al. 2013;
11. Mahableshwarkar et al. 2015;
12. Katona et al. 2012

5 Types of Biomarkers

Proof of
Mechanism

Proof of
Principle

Proof of
Concept

Predictive
Biomarkers

Safety
Biomarkers

Proof of Mechanism

- Does the drug bind to the intended target?
- Does the drug produce the expected pharmacological effect?

Proof of Principle

- Does the drug have a pharmacological impact on the disease studied?

Proof of Concept

- Does the drug produce a clinically meaningful change on disease?

Predictive Biomarkers

- Do we know which patients are more likely to respond? Can we pre-select patients who are most likely to respond?

Safety Biomarkers

- Can we detect early signs of expected toxicity?

Proof of Concept

- Does the drug produce a clinically meaningful change on disease?

Predictive Biomarkers

- **Do we know which patients are more likely to respond? Can we pre-select patients who are most likely to respond?**

Safety Biomarkers

- Can we detect early signs of expected toxicity?

BNC210.006 Study Design IoPPN

Research Design

- 1. Randomized, placebo-controlled, four way crossover design in which each subject received each drug dose on separate occasions, with each occasion separated by at least 5 days to allow for washout. The drug doses were placebo, lorazepam 1.5mg, BNC210 low dose (300mg), BNC210 high dose (2000mg).**

Subjects

- 1. We recruited 24 subjects (21 female) who met diagnostic criteria for Generalized Anxiety.**

Baseline characteristics

Age : 23,3±6,2 (18-49) years

BMI : 23,7±3,1 (18,7-28,6)

Spielberger Trait Anxiety : 54,6±7,6 (37-68)

HAM-A: 18,4±9 (3-37)

mild:12; mild-moderate:7; moderate-severe:6; severe :2

MADRS : 9,3±3,9 (2-16)

Five factors questionnaire (OCEAN)

Openness : 43,2 ± 7,7

Conscientiousness : 46,7 ± 10,3

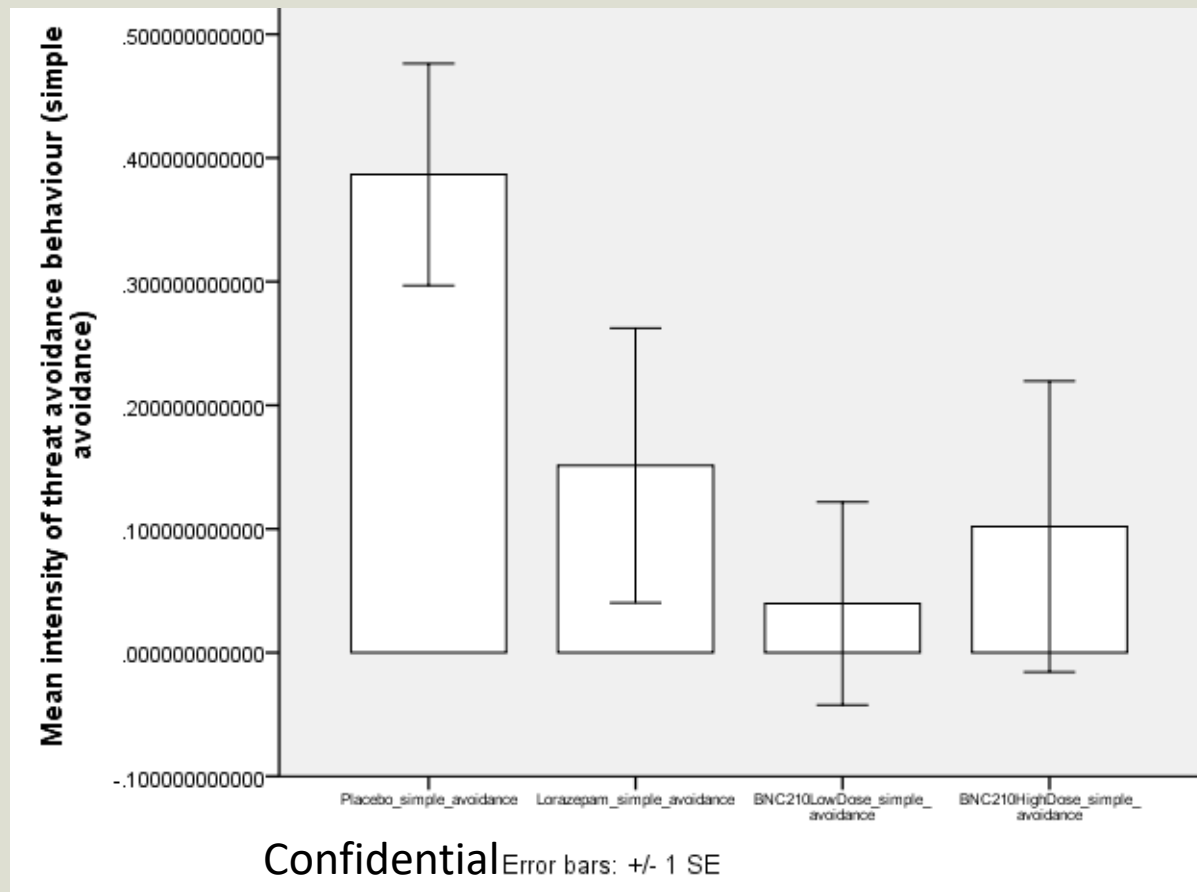
Extraversion : -5,9 ± 12,3

Agreeableness : 41,7±6,8

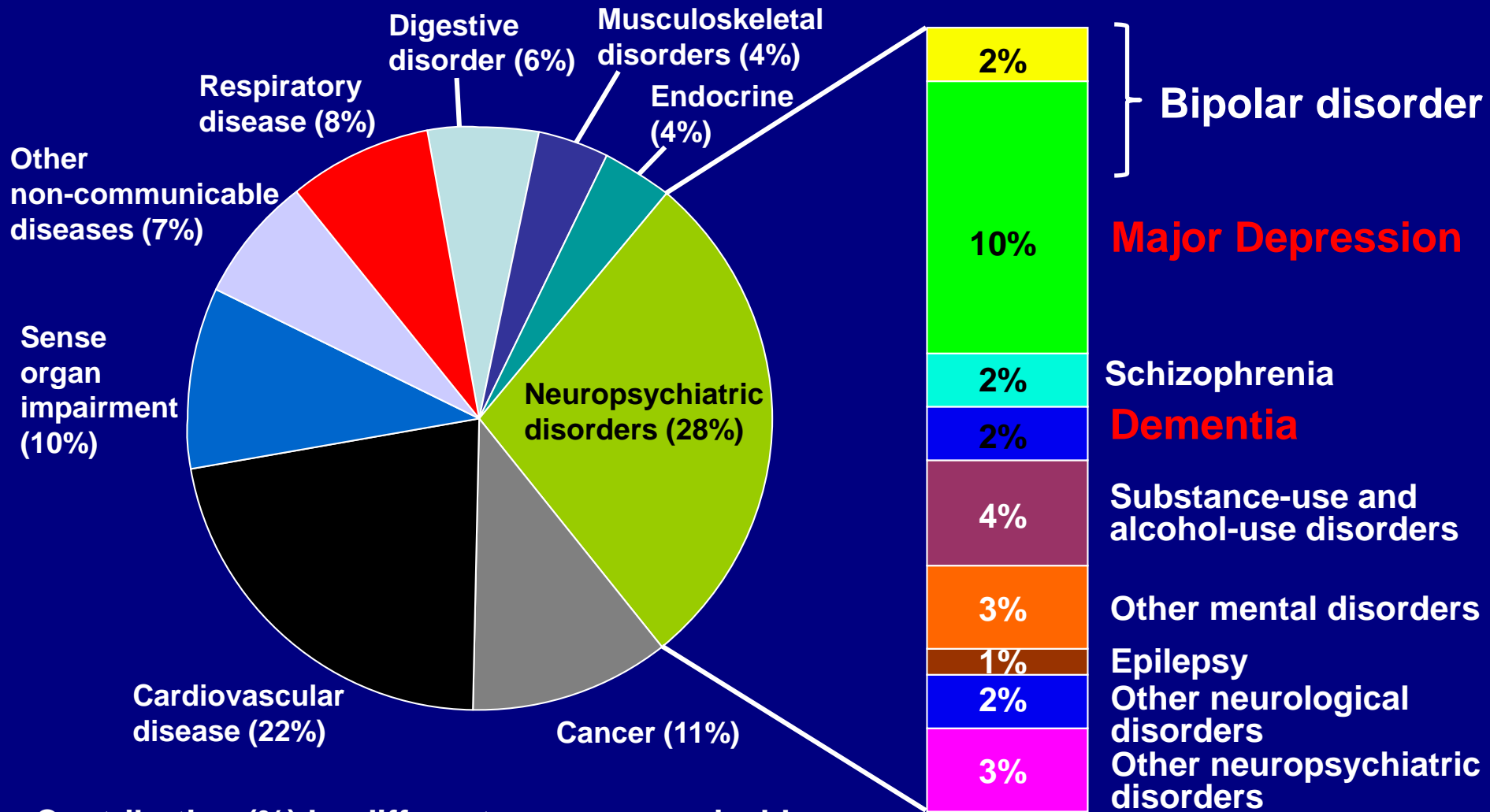
Neuroticism : 52,3±7,0

Significant separation from placebo occurred in the case of both the low and high dose of BNC210

Lorazepam showed a similar direction of effect but it failed to separate significantly from placebo ($F = 2.072$, $p = .165$). Note: $n = 21$ (females only).



The Disease Burden of Psychiatric Disorders



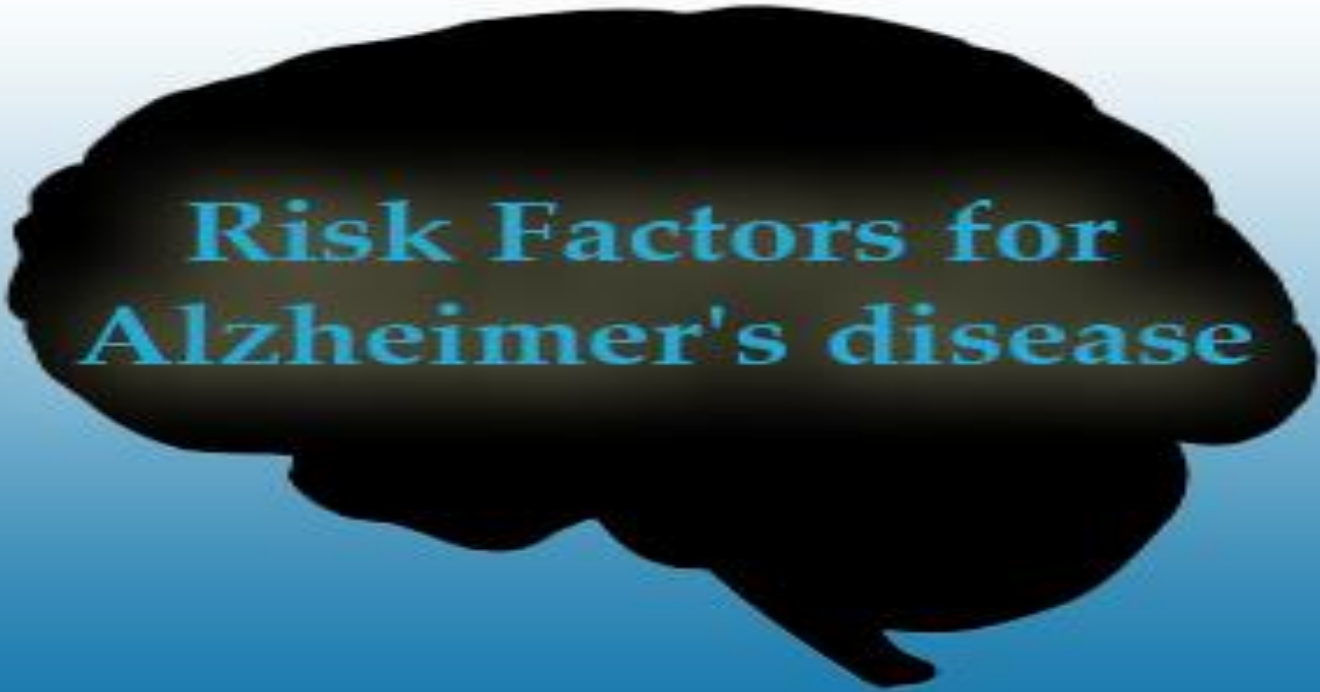
Contribution (%) by different non-communicable diseases to disability-adjusted life-years worldwide in 2005

Prince et al 2007

How is depression different in the elderly compared to other age groups?



- Depression in the elderly is often unrecognized
- Depression increases risk of cardiac disease, increases risk of death following a heart attack, and increases likelihood of death following any disease
- Depression reduces elderly person's ability to rehabilitate
- Depression increases risk of suicide
 - Rate in people ages 80-84 is 2 x as much as rest of population
- Advancing age often accompanied with loss



Risk Factors for Alzheimer's disease

Summary of risk factors for Alzheimer's³⁻¹¹

Increases risk

Type 2 diabetes

Heavy smoking

Depression

Better hygiene

Decreases risk

Higher levels of education

Being a cancer survivor

Receiving chemotherapy treatment for cancer

Breast-feeding

Depression and Dementia



Table 1

The Association Between Previous History of Depression and the Risk of Developing Dementia

| Time of Depressive Symptoms | Odds Ratio of Developing Dementia | 95% Confidence Interval |
|--------------------------------------------|-----------------------------------|-------------------------|
| One year prior to dementia onset | 4.6 | 2.9 to 7.3 |
| One to 25 years prior to dementia onset | 1.4 | 1.0 to 1.9 |
| More than 25 years prior to dementia onset | 1.7 | 1.0 to 2.8 |
| Any prior history of depression | 1.9 | 1.1 to 3.2 |

Source: Boustani M (2004); data from Green et al. (2003) and Jorm (2001).

Table 2

Common neuropsychological deficits in late-life depression and clinical correlates

Information processing speed

Slow to respond or initiate behavior; incomplete grasp of complex information (because of a lag in processing)

Attention and concentration

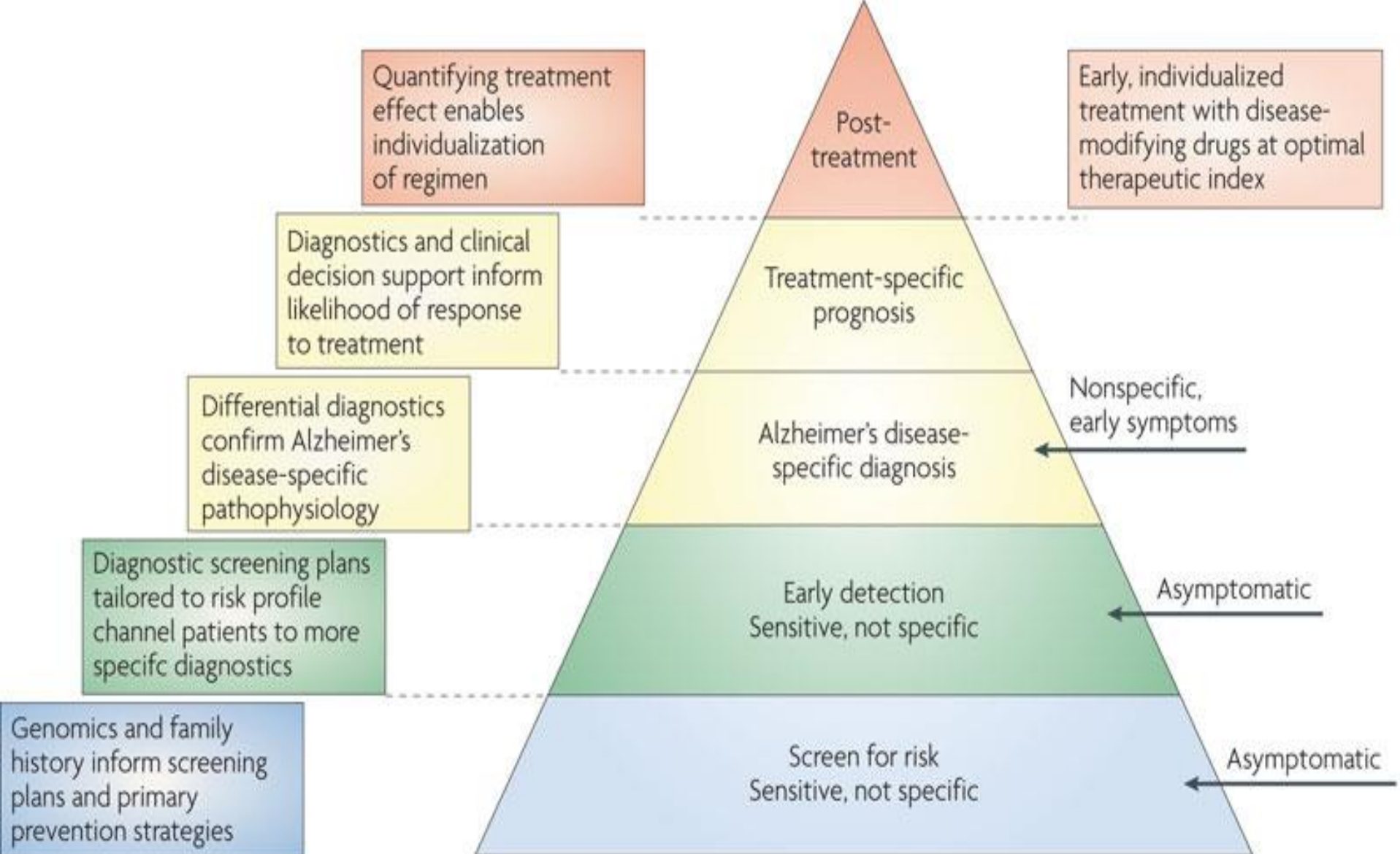
Absentmindedness for daily activities, events, and appointments; tasks left incomplete; decreased attentiveness for reading or conversation, which can also disrupt memory

Executive functions

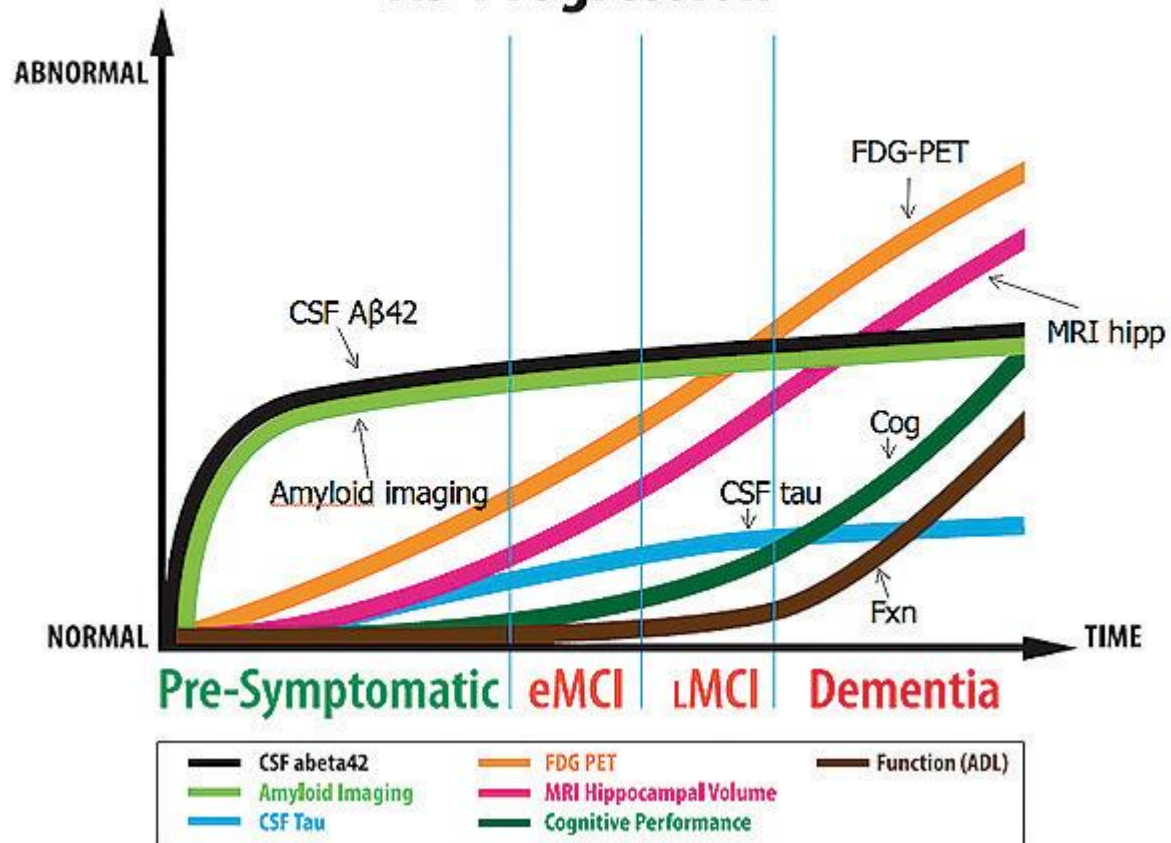
Difficulty with calculating, sequencing, multitasking, and other novel problem solving; inflexible behavior or thinking; perseverative or ruminative thinking; decline in organization and planning; indecisiveness, decreased initiation of behavior

Memory

Forgetfulness and absentmindedness, but should improve with prompts, cues, or explicit memory aids



AD Progression

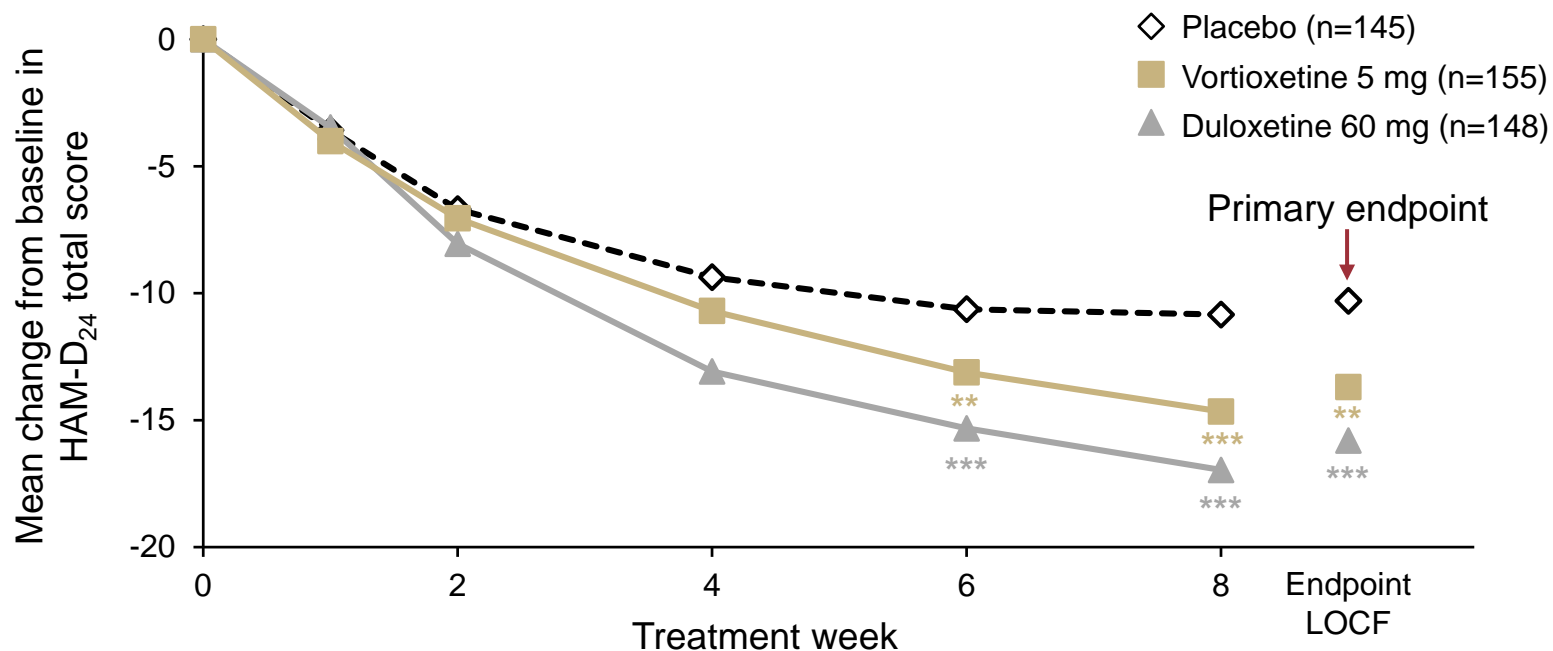


| Spheres | Biomarkers |
|--------------------|-----------------------------------------------------------------|
| Biochemical | CSF Blood-based |
| Neuroanatomical | CT scan MRI scan |
| Metabolic | PET scan SPECT scan |
| Genetic | APP PSEN1 PSEN2 APOE4 |
| Neuropsychological | Episodic memory Other—attention, executive functioning, etc. |

APP, Gene for amyloid precursor protein; APOE4, Apolipoprotein E4 allele; CSF, Cerebrospinal fluid; CT, Computed tomography; MRI, Magnetic resonance imaging; PET, Positron emission tomography; PSEN1 and PSEN 2, Preseniline gene 1 and 2; SPECT, Single photon emission computed tomography

Vortioxetine is effective in elderly patients with depression

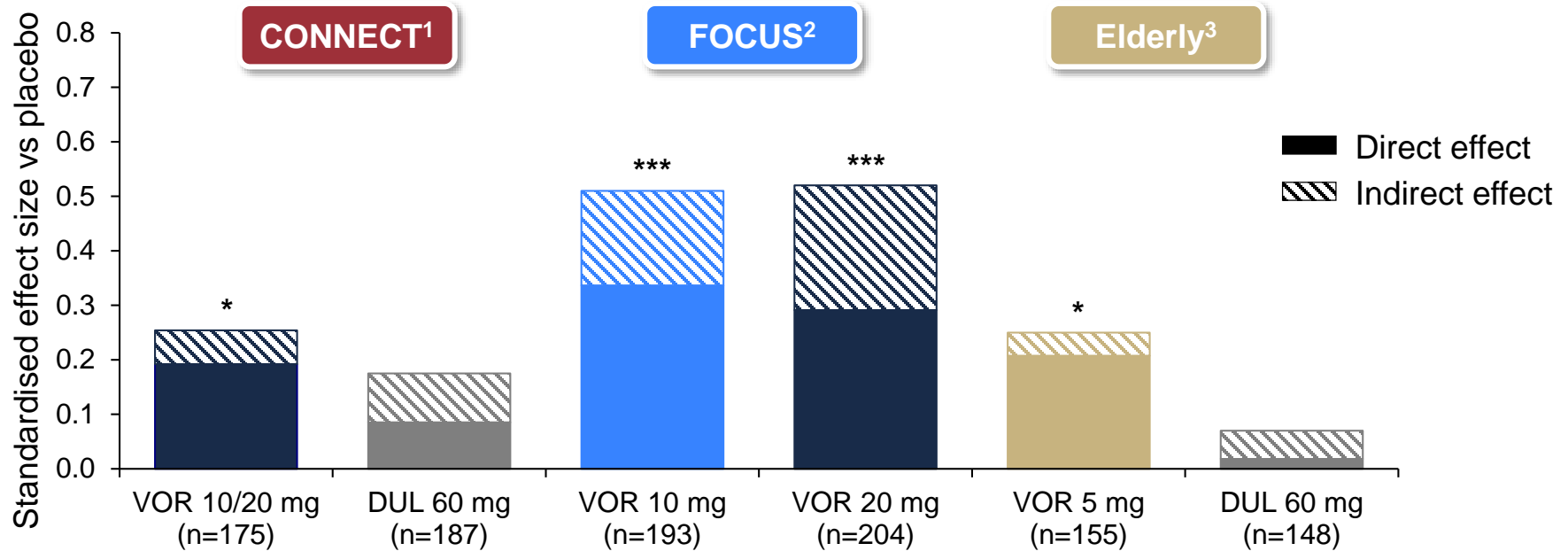
8-week placebo-controlled study in patients aged ≥ 65 years Mean change from baseline in HAM-D₂₄ score by visit (FAS, MMRM; endpoint LOCF)



p<0.01, *p<0.001 vs placebo; nominal p values for MMRM; duloxetine was included as active reference for study validation, not for comparison of effect sizes

Vortioxetine mediated an improvement in cognitive performance in depression in three clinical trials

DSST – Replication: Number of correct symbols, change from baseline at Week 8 (FAS, ANCOVA, LOCF, path analysis)



*p<0.05, ***p<0.001 vs placebo; path analysis mediated via MADRS total score; duloxetine was included as active reference in the CONNECT and Elderly studies for study validation, not for comparison of effect sizes; DSST scores were assessed as a predefined primary outcome of CONNECT, secondary outcome of FOCUS, and exploratory outcome of the Elderly study, with path analyses performed *post hoc*

UK/VOR/1502/0072 Date of preparation: February 2015
Full prescribing information is available at this meeting

1. Mahableshwarkar et al. Neuropsychopharmacology 2015;40(8):2025–2037;
2. McIntyre et al. Int J Neuropsychopharmacol 2014;17(10):1557–1567;
3. Katona et al. Int Clin Psychopharmacol 2012;27(4):215–223

Conclusions

- There is a great need for more efficacious and better tolerated treatments for neuropsychiatric disorders;
- The drug development process may be enhanced with use of biomarkers;
- Late Onset Depression is a particular risk factor for Dementia;
- The LOD group (enriched for biomarkers) provides an opportunity to study effects of new drugs.

Thank you for your Attention!



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