Depression, Dementia and Drug Development

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BRC Translational Therapeutics

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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.

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• 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

- Neuropsychiatric disorders (28%)
  - Schizophrenia (2%)
  - Bipolar disorder (10%)
  - Major Depression (2%)
  - Dementia (2%)
  - Substance-use and alcohol-use disorders (4%)
  - Other mental disorders (3%)
  - Epilepsy (1%)
  - Other neurological disorders (2%)
  - Other neuropsychiatric disorders (3%)

- Cardiovascular disease (22%)
  - Other non-communicable diseases (7%)
  - Respiratory disease (8%)
  - Digestive disorder (6%)
  - Musculoskeletal disorders (4%)
  - Endocrine (4%)
  - Sense organ impairment (10%)

Prince et al 2007
# Pharmacotherapies for Mood Disorders

|------|------|------|------|------|------|------|------|------|---------|

**Electro-Convulsive Therapy**

**Lithium**
- **Anti-depressants**
  - MAOIs
  - MARIs

**Second generation anti-depressants**
- SSRIs, SNRIs, NARIs, RIMAs and NASSA
  - Carbamazepine
  - Valproate
  - Lamotrigine

**Next-generation antipsychotics**
- Quetiapine
- Olanzapine
- Clozapine
- Asenapine
- Aripiprazole
Drug Development Pathway

Drug development

- Basic research
- Prototype design/discovery
- Preclinical
- Phase I | Phase II | Phase III Clinical trials
- FDA approval and launch

Companion diagnostic development

- Target selection and validation
- Identification of markers
- Analytical validation
- Clinical validation and utility
- FDA approval and launch

- Compound patent
- Patents on method of treatment, salts, polymorphs, formulations and combinations
- Biomarker-related patents or other forms of IP
- Diagnostic test-related patents
Drug Development Pathway

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Phase IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-80 participants</td>
<td>100-300 participants</td>
<td>1,000-3,000 participants</td>
<td>Thousands of participants</td>
</tr>
<tr>
<td></td>
<td>Up to several months</td>
<td>Up to (2) years</td>
<td>One (1) year +</td>
</tr>
<tr>
<td></td>
<td>70% success rate</td>
<td>Studies the efficacy</td>
<td>Studies the long-term effectiveness;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33% success rate</td>
<td>cost effectiveness</td>
</tr>
<tr>
<td></td>
<td>Studies the safety of medication/treatment</td>
<td></td>
<td>70-90% success rate</td>
</tr>
</tbody>
</table>
New Blooms and Old Thorns
Interrater Reliability of Diagnoses From the Initial DSM-5 Field Trials

![Bar chart showing the interrater reliability of diagnoses from the Initial DSM-5 Field Trials. The diagnoses are ranked by Kappa values, indicating the level of agreement between raters. Major Neurocognitive Disorder has the highest Kappa value of 0.78, followed by Posttraumatic Stress Disorder (0.67). Other diagnoses with notable Kappa values include Complex Somatic Symptom Disorder Revised (0.61), Hoarding Disorder (0.59), Bipolar I Disorder (0.56), Binge Eating Disorder (0.56), Borderline Personality Disorder (0.54), Schizoaffective Disorder (0.50), Mild Neurocognitive Disorder (0.48), Schizophrenia (0.46), Attenuated Psychotic Symptoms Syndrome (0.46), Mild Neurocognitive Disorder (0.43), Alcohol Use Disorder (0.40), Bipolar II Disorder (0.40), Mild Traumatic Brain Injury (TBI) (0.36), Obsessive-Compulsive Personality Disorder (0.31), Major Depressive Disorder (0.28), Antisocial Personality Disorder (0.21), Generalized Anxiety Disorder (0.20), and Mixed Anxiety-Depressive Disorder (0.004).]
Vortioxetine is effective for the short-term treatment of major depressive disorder

Meta-analyses of the results of 11\textsuperscript{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

\textsuperscript{a}HLu 12541A in elderly patients (≥65 yrs)\textsuperscript{12} not included

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Full prescribing information is available at this meeting
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?
Does the drug produce a clinically meaningful change on disease?

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

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?
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.
## Summary of risk factors for Alzheimer's disease\(^3-11\)

<table>
<thead>
<tr>
<th>Increases risk</th>
<th>Decreases risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes</td>
<td>Higher levels of education</td>
</tr>
<tr>
<td>Heavy smoking</td>
<td>Being a cancer survivor</td>
</tr>
<tr>
<td>Depression</td>
<td>Receiving chemotherapy treatment for cancer</td>
</tr>
<tr>
<td>Better hygiene</td>
<td>Breast-feeding</td>
</tr>
</tbody>
</table>

\[^3-11\]: References for the risk factors.
Depression and Dementia

Table 1

<table>
<thead>
<tr>
<th>Time of Depressive Symptoms</th>
<th>Odds Ratio of Developing Dementia</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>One year prior to dementia onset</td>
<td>4.6</td>
<td>2.9 to 7.3</td>
</tr>
<tr>
<td>One to 25 years prior to dementia onset</td>
<td>1.4</td>
<td>1.0 to 1.9</td>
</tr>
<tr>
<td>More than 25 years prior to dementia onset</td>
<td>1.7</td>
<td>1.0 to 2.8</td>
</tr>
<tr>
<td>Any prior history of depression</td>
<td>1.9</td>
<td>1.1 to 3.2</td>
</tr>
</tbody>
</table>

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

- CSF Aβ42
- Amyloid imaging
- CSF tau
- FDG-PET
- MRI hippocampal volume
- Cognitive performance

Pre-Symptomatic | eMCI | lMCI | Dementia

Function (ADL)

CSF abeta42
Amyloid Imaging
CSF Tau
<table>
<thead>
<tr>
<th>Spheres</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical</td>
<td>CSF</td>
</tr>
<tr>
<td></td>
<td>Blood-based</td>
</tr>
<tr>
<td>Neuroanatomical</td>
<td>CT scan</td>
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<tr>
<td></td>
<td>MRI scan</td>
</tr>
<tr>
<td>Metabolic</td>
<td>PET scan</td>
</tr>
<tr>
<td></td>
<td>SPECT scan</td>
</tr>
<tr>
<td>Genetic</td>
<td>APP</td>
</tr>
<tr>
<td></td>
<td>PSEN1</td>
</tr>
<tr>
<td></td>
<td>PSEN2</td>
</tr>
<tr>
<td></td>
<td>APOE4</td>
</tr>
<tr>
<td>Neuropsychological</td>
<td>Episodic memory</td>
</tr>
<tr>
<td></td>
<td>Other—attention, executive functioning, etc.</td>
</tr>
</tbody>
</table>

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, Presenilin 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-D_{24} 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

**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

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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


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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!
CONTACT DETAILS

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