Advances in Treating Major Depressive Disorder

Sidney H. Kennedy, MD, FRCPC
University of Toronto, University Health Network
## Disclosures

<table>
<thead>
<tr>
<th>Category</th>
<th>Organizations</th>
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<tbody>
<tr>
<td>Advisory board or similar committee</td>
<td>AstraZeneca, Eli Lilly, Lundbeck, Lundbeck Institute, Pfizer, Servier, St. Jude Medical</td>
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<tr>
<td>Clinical trials or studies</td>
<td>Brain Cells Inc., BMS, Clera, Eli Lilly, Pfizer, Servier, St. Jude Medical</td>
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<td>Speaking engagements</td>
<td>AstraZeneca, Eli Lilly, Lundbeck, Pfizer, Servier, St. Jude Medical</td>
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<tr>
<td>Research grants</td>
<td>CIHR, Lundbeck, OBI, OMHF, OPGRS, Servier</td>
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Major Depressive Disorder: Homogeneous Treatments for a Heterogeneous Disorder

- Response rate to first line treatment is 50%
- Remission rate even after four treatments is 67%
- Many patients are treatment resistant

There are no objective biological measures on which to base diagnosis, prognosis, or treatment selection
Assessing the True Treatment Effect

- MADRS scores improved by 15.9 points in patients with a true treatment effect
- The proportion of patients who benefited from escitalopram and not from placebo was 19.5% (NNT=5)

Thase, Larsen & Kennedy, Br J Psych, 2011
# Monoamine Targets

## New and Emerging Drugs

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Mechanism of Action</th>
<th>Other Benefits and Uses</th>
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<tbody>
<tr>
<td>Desvenlafaxine</td>
<td>5HT/NE reuptake inhibition</td>
<td>Improved Tolerability</td>
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<tr>
<td>Agomelatine</td>
<td>MT1/2 agonist</td>
<td>Anhedonia/Sleep</td>
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<tr>
<td></td>
<td>5HT2C antagonist</td>
<td>Weight</td>
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<tr>
<td></td>
<td></td>
<td>Sexual Function</td>
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<tr>
<td>NERI-IV</td>
<td>Norepinephrine reuptake inhibitor</td>
<td>ADHD</td>
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<tr>
<td>Vilazodone</td>
<td>5HT reuptake inhibition</td>
<td>Positive response linked to biomarker</td>
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<tr>
<td></td>
<td>5HT1A partial agonist</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>5HT1A/5HT3/5HTT blockade</td>
<td>Favorable cognitive and sexual effects</td>
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<tr>
<td>Pramipexole,Ropinirole</td>
<td>Dopamine agonists</td>
<td>Psychomotor Retardation</td>
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<tr>
<td></td>
<td></td>
<td>Anhedonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Restless leg syndrome</td>
</tr>
</tbody>
</table>

Rizvi and Kennedy, Expert Opinion, 2012
Identification of Multiple Pathways

STRESS
Early adversity
Interpersonal conflict
Social isolation

Hypothalamus
Pituitary
CRH

NF-κB

↑ monoamines
↓ excitotoxicity
↓ trophic factors

Inflammation
↑ Pro-inflammatory cytokines
↑ Chemokines
↑ Adhesion molecules
↑ Acute phase reactants

ACTH

Adrenal gland
Cortisol

NFKB

Macrophage

Immune system

Sympathetic chain

Vagus n.

Miller et al, 2009
Progression of Research in Depression

Identification of Individual Markers
- Clinical
- Neurotransmitters
- Genetics
- Proteomics
- Neurocircuitry

Integration of clinical- and bio-markers

Personalized Treatment Selection
Symptom Dimensions as Predictors of Antidepressant Treatment Outcome

“Genome Based Therapeutic Drugs for Depression” (GENDEP) trial identified 3 factors and 6 symptom dimensions in large MDD sample

MADRS, HAMD-17, BDI

- **Observed Mood**
  - Mood
  - Anxiety
- **Cognitive**
  - Pessimism
- **Neurovegetative**
  - Sleep
  - Appetite

**Interest-Activity** dimension was a predictor of poor treatment outcome here and in STAR*D data

(Uher et al., 2009)
Anhedonia

“Neglect of those objects and pursuits which formerly proved sources of delight and instruction….”  
Haslam 1809

“Those in whom it was impossible to find the least pleasure..”  
Ribot 1896

“Inability to experience such pleasures and lacking the drive to pursue rewarding activities…”  
Rado 1956

“Sharp unreactive pervasive impairment of the capacity to experience pleasure or to respond affectively to the anticipation of pleasure”  
Klein 1974

“Loss of interest or pleasure”  
DSM-IV-TR 2000

Modified from Der-Avakian and Markou; Trends in Neurosc 2012
Definition of anhedonia has remained unchanged for the past 3 decades

Anhedonia is characterized by decreased reward processing

Cognitive psychology and behavioural neuroscience have expanded the concept of reward processing to include:

- **Anticipation** (wanting or desire)
- **Motivation** (effort)
- **Consummatory pleasure** (liking)

Sherdell et al, 2012
Der-Avakian & Markou. 2012
Adolescent Offspring of Depressed Parents: Response to Reward

One year longitudinal study of adolescents (10-18 years) at familial risk for MDD (n=197): ‘no disorder’ (n=136), ‘depressive disorder’ (n=19), ‘anxiety disorder’ (n=15), ‘externalizing disorder’ (n = 24)

Low reward seeking at baseline predicted:
- Diagnosis of MDD at 1 year follow up, independent of baseline depression symptoms
- Functional impairment (social relationships, involvement in extracurricular activities)

Rawal et al, 2012; Psychol Med
Depression and Anhedonia Neurocircuitry

Negative correlation between anhedonia ratings and right NAcc activity in MDD patients

(Hasler et al, 2008)

Anhedonia reflects a blunted DA response to rewarding stimuli particularly in mesolimbic and mesocortical tracts

(Treadway & Zald, 2011)
Agomelatine vs. Venlafaxine: Effect on Depression, Anxiety and Anhedonia

Snaith-Hamilton Pleasure Scale (SHAPS)
Hamilton Depression Rating Scale (HAM-D)
Hamilton Anxiety Rating Scale (HAM-A)

Mean Change from Baseline to Last Assessment (T3)

*P<0.01 (significant difference between groups)

Neuroinflammatory Processes

Adapted from Miller et al 2009

Soczynska et al 2012
Evidence for Inflammatory Biomarkers in MDD

- Elevations in IL-1, IL-6, CRP, TNF-α, cyclooxygenase (COX) in animal models of depression. *Maes et. al, 2009*

- Link between IL-1β, neurogenesis, stress and depression, and the potential of IL-1Ra or other cytokine antagonists as candidate antidepressants. *Koo and Duman, 2009*

- Increased expression of proinflammatory genes including COX-2 in MDD (Galecki et. al, 2010) and BD *Drexhadge et. al, 2010*

- Conflicting evidence of therapeutic benefits of COX-2 inhibitors in MDD
  - **Pro:** positive antidepressant effect *Akhondzadeh et. al, 2009; Chen et. al, 2010*
  - **Con:** increased neuroinflammation and neuroprogression *Maes, 2012*
Adjunctive Celecoxib in MDD

Akhondzadeh et al, 2009

- Cap. Fluoxetine 40 mg/day + Cap. Celecoxib 400 mg/day
- Cap. Fluoxetine 40 mg/day + Cap. Placebo

Hamilton Depression Scores vs. Trial (weeks)

n=12
n=13

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Akhondzadeh et al, 2009
Novel Therapeutic Targets: Minocycline as a Candidate Antidepressant

- Broad spectrum tetracycline antibiotic
- Anti-inflammatory and neuroprotective properties
- Effects on serotonin and dopamine transmission
- Antidepressant properties
  - Preclinical: Reduced immobility in FST
  - Clinical: As an adjunctive therapy in psychotic depression (open-label), minocycline reduced depressive and psychotic symptoms
- Ongoing trial as adjunct in bipolar depression

Soczynska et al, 2012
Subgenual Cingulate Cortex Activity Predicts Inflammation-Associated Mood Change

Inflammation (IL-6)-associated mood deterioration correlated with enhanced activity to emotional facial expressions within the sACC

Harrison et al., *Biological Psychiatry*, 2009
The Subgenual Cingulate in Depression

Normal Sadness  

MDD (Fluox resp)  

MDD (Parox resp)  

MDD (Placebo resp)

Mayberg HS et al., 1999  
Am J Psychiatry 156: 675-82

Mayberg HS et al., 2000  
Biol Psychiatry 48:830-43

Kennedy SH et al., 2003  
Am J Psychiatry 158:899-905

Mayberg HS et al., 2002  
Am J Psychiatry 159: 728-37
Altered Brain Volume and Function in Depression: Subgenual Cingulate

- 10 MRI and PET studies
  - Decreased volume in SCG and greater glucose uptake in MDD vs. HC

- 15 PET and fMRI studies
  - ↑ activation in anterior cingulate is predict good treatment response
  - ↑ activation in right amygdala, striatum, insula predict poor response

Sacher et al, 2011

Fu et al, Neurobiol Dis, 2012
Effects of CBT & Venlafaxine on Brain Metabolism

↓ Metabolism in SCG-25 with response to venlafaxine or CBT

Hyperactivity in ventral anterior cingulate predicts non-response


Konarski, Kennedy, Mayberg et al, 2009
Deep Brain Stimulation
Technique and Rationale

- Stereotactic placement of unilateral or bilateral electrodes under MRI guidance
- Electrodes are connected to a lead that is tunneled to the chest where a pulse generator (pacemaker) is implanted under the skin

- Originally developed as a technique for movement disorders
- Majority of DBS procedures in the past decade have been to suppress tremor in Parkinson’s Disease (PD)
### DBS to SCG-25 for TRD Phase II

**Effectiveness and Adverse Effects**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th># of Occurrences</th>
</tr>
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<tbody>
<tr>
<td>Wound infection</td>
<td>4</td>
</tr>
<tr>
<td>Perioperative seizure</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>5</td>
</tr>
<tr>
<td>Pain at generator site</td>
<td>1</td>
</tr>
<tr>
<td>No adverse events</td>
<td>9</td>
</tr>
</tbody>
</table>

Lozano et al., *Biol Psychiatry*, 2008

![Graph showing HAMD-17 Scores for Baseline and 12 Months](chart.png)
Deep Brain Stimulation for Treatment Resistant Depression: Follow-up after 3-6 Years

Symptom Outcomes

Functional Outcomes

Kennedy et al., Am J Psychiat 2011
Deep Brain Stimulation to SCg25 : RCT

- MDD
- HAMD>20
- Failed 4 treatments for current episode
- Stable treatment for 4+ weeks
- No significant medical illness

PET Scans (Baseline)

DBS Implantation N=40

PET Scan (12 Weeks)

DBS ON 12 weeks n=20

DBS OFF 12 weeks n=20

DBS ON 12 weeks

DBS OFF 12 weeks

Phase I

Phase II

Phase III

To Date: May 2012
- 19 patients have undergone surgery and are in follow-up
DBS RCT to SCG-25: D2 Binding

- Patient population: Patients with TRD (Target=40; 18 enrolled)

- Time points: Baseline and 3 months

- Ligand: [11C]FLB 457
  - Dopamine receptor antagonist, with high specificity for extrastriatal D2 receptors
  
  (Olsson et al, 2004; Montgomery et al, 2007)

- Double-blind preliminary analysis: 6 patients with both baseline and 3 month scans
Baseline prediction in DBS RCT
Reduction in D2 Binding at 3 Months

- Left medial frontal gyrus (BA 10/11), uncorrected at $p=.01$

MNI: -14 40 -10

Rizvi et al, data on file
Progression of Research in Depression

Identification of Individual Markers

- Clinical
- Neurotransmitters
- Genetics
- Proteomics
- Neurocircuitry

Integration of clinical- and bio-markers

Personalized Treatment Selection
Integrating clinical, imaging and molecular data to identify individualized signatures of treatment response in Major Depressive Disorder (MDD) to guide treatment selection.
### Clinical Assessment
- Extensive assessments of personality, cognitive function, life events

### Neuroimaging and Neurophysiology
- Structural and Functional (resting and challenge)
- EEG (resting and challenge)

### Molecular
- Genomics and Proteomics – dynamic markers
- Pharmacogenetics

### Informatics
- Integrated across modalities. Modelling and clustering algorithms

### Knowledge Transfer
- Integrated and “end-of-grant”
- Patients and mental health treatment providers
Iterative process to identify key features that predict treatment response in the most accurate and cost-effective manner.
CAN-BIND Protocol

Screening N=200

Baseline

W1

Esc 10 mg

W2

Esc 20 mg

W4

W6

W8

W10

W16

Responders: ≥50% drop on MADRS

Esc 20 mg

Non-Responders (Add-on)

Esc 20 mg + ARP 2-10 mg

Neuroimaging

Molecular

Clinical

Neuroimaging

Molecular

Clinical

Neuroimaging

Molecular

Clinical

Molecular

Clinical

Canadian Biomarker Integration Network for Depression
Improving Antidepressant Outcomes

- Limited value of traditional clinical subtyping to select antidepressant treatments
- Resurgence of interest in anhedonia
- Merging of clinical measures and neurocircuitry
- New therapeutic targets
- Biomarker integration as a pathway to personalized medicine?