OBESITY AND MOOD DISORDERS

Dr. Roger S. McIntyre
Professor of Psychiatry and Pharmacology
University of Toronto
Head, Mood Disorders Psychopharmacology Unit

www.mdpu.ca
Overview

- Obesity: Phenomenon/Epiphenomenon and Off-Trajectory Promotion
- Obesity in Mood Disorders: Effect on Cognitive Function/White Matter
- Transdisciplinary treatment opportunities
Disclosures

- Stanley Medical Research Institute (SMRI)
- National Alliance for Research on Schizophrenia and Depression (NARSAD)
- National Institute of Mental Health (NIMH)
- AstraZeneca, Bristol Myers Squib, Eli Lilly, Janssen Ortho, Lundbeck, Merck, Pfizer, Shire, Sunovion, Otsuka
Obesity and Mood Disorders in the General Population


*\( p < 0.05 \)
Traditional and Emerging Risk Factors for Metabolic Syndrome in Mood Disorders

- Bipolar disorder
- Major depressive disorder

- Behavioural
- Iatrogenic
- Systems
- Anamnestic
- Psychobiology

- Obesity
- Hypertension
- Dyslipidemia
- Hyperglycemia

Integrating Environmental Experiences

Exposome

Your Exposures

Your Unique Characteristics

Disease

Centre for Disease Control and Prevention
The Effect of Early Adversity on Propensity to Mental and Medical Disorders

- All components of metabolic syndrome significantly elevated in BD adults reporting history of childhood maltreatment (N=1700)
- Waist circumference increase observed in individuals with abuse (physical/sexual) and neglect

The International Mood Disorders Collaborative Project. McIntyre RS, 2012 in press.
Odds Ratios for the Association of Metabolic Health and Obesity with Risk of Depression over 2 years follow-up (N=3851)

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Cases/ N</th>
<th>Model 1 OR (95% CI)</th>
<th>Model 2 OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy non-obese</td>
<td>160/1822</td>
<td>1.00 (Ref)</td>
<td>1.00</td>
</tr>
<tr>
<td>unhealthy non-obese</td>
<td>123/972</td>
<td>1.53 (1.16-2.03)</td>
<td>1.44 (1.08-1.92)</td>
</tr>
<tr>
<td>Healthy obese</td>
<td>41/362</td>
<td>1.31 (0.88-1.96)</td>
<td>1.38 (0.88-2.17)</td>
</tr>
<tr>
<td>unhealthy obese</td>
<td>105/695</td>
<td>1.53 (1.14-2.06)</td>
<td>1.50 (1.05-2.15)</td>
</tr>
</tbody>
</table>

Abbreviations: CES-D, Centre of Epidemiological Studies Depression; CI, Confidence interval; OR, odds ratio

Obesity Promotes Off-Trajectory Course and Outcome

Dynamic changes to:
- molecular/systems
- information processes
- psychopathology

Allostatic Load

Developmental delay

Typical/ Normal

Atypical/Mental Illness

Altered developmental trajectory

Fetal

Time (t)

Young Adult

March J, 2011
Obesity/Metabolic Syndrome/Mood Disorders Endanger Normal CNS Function

McIntyre RS et al., 2010
Overweight/obesity Has a Negative Effect on Cognitive Function in Euthymic Patients with BD

- **BMI** was negatively correlated with:
  - Attention and psychomotor processing speed as measured by the Digit Symbol Substitution Test (P<0.01)

- **Overweight/obese bipolar patients:**
  - Significantly lower score on the Verbal Fluency Test when compared to normal weight subjects (P<0.05)

Seven Risk Factor with Independent Effects on the Incidence of Alzheimer’s disease

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>PAR (%)</th>
<th>95% CI</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Education</td>
<td>19.1</td>
<td>12.3-25.6</td>
<td>1.59</td>
<td>1.35-1.86</td>
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<tr>
<td>Smoking</td>
<td>13.9</td>
<td>3.9-24.7</td>
<td>1.59</td>
<td>1.15-2.20</td>
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<tr>
<td>Physical Inactivity</td>
<td>12.7</td>
<td>3.3-24.0</td>
<td>1.82</td>
<td>1.19-2.78</td>
</tr>
<tr>
<td>Depression</td>
<td>10.6</td>
<td>6.8-14.9</td>
<td>1.90</td>
<td>1.55-2.33</td>
</tr>
<tr>
<td>Midlife Hypertension</td>
<td>5.1</td>
<td>1.4-9.9</td>
<td>1.61</td>
<td>1.16-2.24</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.4</td>
<td>1.1-4.1</td>
<td>1.39</td>
<td>1.17-1.66</td>
</tr>
<tr>
<td>Midlife Obesity</td>
<td>2.0</td>
<td>1.1-3.0</td>
<td>1.60</td>
<td>1.34-1.92</td>
</tr>
</tbody>
</table>

PAR = Population Attributable Risk: The proportion of cases of Alzheimer’s disease in the population that might be prevented if the risk factor could be removed entirely.

RR = Relative Risk
Decreased fractional anisotropy in overweight/obese bipolar patients versus normal weight bipolar patients

Subject groups

Healthy controls
N = 26

First-episode mania
N = 28

Right occipital lobe

Normal weight

Overweight and obese

*K*P*<0.05; **P*<0.01

Body Mass Index Impacts Antidepressant Response

Response to antidepressant treatment according to weight status. Mean Hamilton Depression test (HAM-D) rating scores and SEMs for 5 weeks after hospitalization (left) in normal-body mass index (BMI) and high-BMI patients and (right) in normal-BMI, overweight, and obese patients.

Metabolic Syndrome Unfavourably Influences CNS Trophic Factors

NGT=normal glucose tolerance.
IGT=impaired glucose tolerance.

Diabetes Impairs Hippocampal Neurogenesis Via Altered Metabolic/Inflammatory System


CON: control rats injected with vehicle alone; DM+N: streptozotocin-induced diabetic rats without depressive-like behaviour; DM+D: streptozotocin-induced diabetic rats with depressive-like behaviour; DM+D+AG: aminoguanidine (AG, 10 mg/kg) administrated in DM+D rats for 4 weeks

\[ a^{p<0.001} \text{ DM+N, DM+D vs CON value} ; \quad b^{p<0.001} \text{ DM+N vs DM+D} ; \quad c^{p<0.001} \text{ DM+D+AG vs DM+D value} \]

Values are means ± SD.

Role of Insulin in Normal CNS Function

- Neurotrophic
- Synaptic plasticity (Synaptogenesis)
- Neurodevelopment
- Neuroprotection
- Neuromodulatory
- Feeding and behavior

Insulin: A Critical Neuropeptide

**Intranasal Insulin**

- Delivered to CNS via extraneuronal pathway
- No effect on peripheral glucoregulatory homeostasis
- Pharmacokinetic studies indicate immediate CNS penetration
- Beneficial effect on cognitive function
Intranasal Insulin Enhances Executive Function in Bipolar Disorder

McIntyre, R. S. et al., Bipolar Disorders 2012
## Treatment Strategies For Overweight/Obesity In Patients With Mood Disorders

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Bipolar disorder</th>
<th>MDD</th>
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</thead>
<tbody>
<tr>
<td>Behavioural / diet / cognitive interventions</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line (level 3)</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line (level 3)</td>
</tr>
<tr>
<td>Metformin</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line (level 1)</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line (level 3)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line (level 2)</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line (level 3)</td>
</tr>
<tr>
<td>Modafinil</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line (level 3)</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line (level 3)</td>
</tr>
<tr>
<td>Orlistat</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line (NS)</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line (level 3)</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line (level 3)</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; line (level 3)</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; line (level 3)</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; line (level 3)</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; line (level 3)</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; line (level 3)</td>
</tr>
<tr>
<td>Amantadine</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; line (level 3)</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; line (level 3)</td>
</tr>
<tr>
<td>Naltrexone / bupropion</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Phentermine</td>
<td>NR (level 3)</td>
<td>NR (level 3)</td>
</tr>
</tbody>
</table>

Level 1: 2 randomized controlled trials (RCT) and/or meta-analysis; level 2: 1 RCT; level 3: open-label / case series. NS: not studied; NR: not recommended; MDD: major depressive disorder.

Does bariatric surgery affect psychiatric course among bipolar disorder patients?

Substance Use Disorders and Overweight/Obesity in Bipolar I Disorder: Preliminary Evidence for Competing Addictions

- Data from 36,984 individuals (> 15 years old) in the 2002 Canadian Community Health Survey

Conclusion

- Prevention and treatment of obesity may lead to prevention and/or reduction of illness burden associated with mental disorders
- Obesity as CNS toxic versus obesity as proxy of CNS toxicity
- Transdisciplinary treatment opportunities