Depression in Spinal Cord Injury and Traumatic Brain Injury

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Living Well and Enhancing Resilience Following Injury
Australian Psychological Society,
Rehabilitation Psychology Interest Group
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Gratitude

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• To my colleagues with whom I have had the privilege of collaborating especially: Jesse Fann, MD; Dawn Ehde, PhD; Sureyya Dikmen, PhD; Jeanne Hoffman, PhD; Nancy Temkin, PhD; Peter Esselman, MD; Kathy Bell, MD; and Jason Barber, MS
Disclosures

• No conflicts of interest
• Research funding:

![NIDILRR Logo](image1.png)

![NIH Logo](image2.png)
Overview

- Prevalence of major depressive disorder (MDD) in people with traumatic brain injury (TBI) or spinal cord injury (SCI)
- Current treatment adequacy
- Ways to improve identification of MDD
- Treatment efficacy
  - Medical
  - Psychological
  - Physical activity
- Future directions and summary
Brain Injury in Australia

• 438,300 report ABI with disability; ABI is the "main condition" for 28,700; 92% acquired ABI via accident or injury
• Primary effects: contusions, DAI
• Secondary effects: hematomas, edema, hydrocephalus, intracranial pressure, infection, hypoxia, neurotoxicity, inflammation
• Can affect mood via serotonin, norepinephrine, dopamine, acetylcholine, and GABA

Spinal Cord Injury in Australia

- Incidence: 21.0-32.3 per million
- Prevalence: estimated 10,944-19,784
- 80% male
- Age at onset: 55-64 (21%); 24-34 (19%)
- Leading causes: 42% motor vehicle crash, 40% fall, 6% water-related
- Impairments: motor/sensory, bowel and bladder, respiratory, sexual
- Common secondary conditions: pain, pneumonia, spasticity, pressure ulcers, UTI, depression

New et al., APM&R 2015; AIHW Statistics Series No. 113, 2018; SCI Facts and Figures UAB, 2010
Rates of Depression in TBI and SCI
Major Depressive Disorder (MDD)

1. Depressed mood*
2. Loss of interest/pleasure*
3. Sleep disturbance
4. Poor energy
5. Motor change agitation or slowness
6. Weight/appetite change increase/decrease
7. Impaired concentration or indecision
8. Excessive worthlessness or guilt
9. Recurrent thoughts of death or suicide

• Patient endorses at least 5 symptoms; must include at least one essential symptom (*).

“Depression” is used to refer to results from non-diagnostic questionnaires

APA, Diagnostic & Statistical Manual of Mental Disorders, 5th Edition 2015
# Rates of Major Depression

<table>
<thead>
<tr>
<th>Population</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>2-4%</td>
</tr>
<tr>
<td>One year prevalence</td>
<td>6.7%</td>
</tr>
<tr>
<td>Primary care patients</td>
<td>5-10%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10-15%</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>17-27%</td>
</tr>
<tr>
<td>Stroke</td>
<td>16-30%</td>
</tr>
</tbody>
</table>

Kessler et al., 2003, 2005; Katon & Ciechanowski, 2002; Rudisch & Nemeroff, 2003; Turner-Stokes & Hassan, 2002
Rates of MDD after TBI

N = 559

Postinjury rate is the proportion of cases ascertained with major depressive disorder for the first time after traumatic brain injury at each assessment. The values underestimate the true rates because not all participants were assessed at each time. Error bars indicate 95% confidence intervals.

Bombardier, Fann et al JAMA 2010;303(19):1938-1945
Prevalence of MDD after TBI: Meta-analysis

- 93 studies, 11,926 participants
- Overall point prevalence of MDD is 27%
- Mean prevalence of MDD appears to increase during first 5 years (21-43%) then declines to 22%
- MDD in mild TBI (16%) vs. mod-severe TBI (30%)
- Odds of developing MDD/dysthymia after TBI is 7.69 times greater than in non-injured community controls and 1.55 times greater than in medical controls

Osborn et al., Neuroscience and Biobehavioral Reviews 47 (2014) 1–15
Rates of Mood Disorder 1-5 Years after Moderate-Severe TBI in Australia*

*Major depression, dysthymia, bipolar in 161 TBI rehabilitation patients
Alway et al Psych Med 2016;46:1331-1341
Prevalence of MDD after SCI: Meta-analysis

• 19 studies, 35,676 subjects
• Included studies that used DSM criteria
• Overall prevalence is 22.2% (95% CI, 19-26%)
• Prevalence was 23.1% when three studies using self-report diagnostic methods were removed
• Rates of depression lower in studies that used DSM-IV criteria versus DSM-III or RDC
• Prevalence did not differ by proportion of men, SCI type (traumatic vs. disease), or proportion of people with tetraplegia) in the sample

Williams and Murray APM&R 2015;96:133-140
DSM-IV Psychiatric Disorders After SCI in Australia

Note: N=88; MDD=major depressive disorders, PTSD=post traumatic stress disorder, GAD=generalized anxiety disorder, AUD=alcohol use disorder, DUD=drug use disorder, MHD=mental health disorder. Risk factors for any MHD (prior history of psychiatric treatment [24 times more likely]; low education were [2 times more likely]; cognitive impairment; physical complications; anxiety) and protective factors (presence of a partner; resilience) Craig et al., APM&R 2015;96:1426-1434
Correlates and Costs of Depression
Correlates of Depression in TBI

• Greater post-concussive symptoms
• Increased aggressive behavior and anxiety
• Poorer cognition (memory, speed, executive function)
• Lower health-related QoL and greater disability
• Poorer recovery
• Poorer vocational and community integration
• Eight times more suicide attempts, 3-4 times more completed suicides

Hoge et al., 2008; Vanderploeg, 2007; Tateno et al., 2003; Jorge et al., 2004; Fann et al., 1995; Rapoport et al., 2003, 2005; Mooney et al., 2005; Kishi et al., 2001; Silver et al., 2001; Teasdale and Engberg, 2001; Lange et al, 2011; Wilk et al, 2012; Bombardier et al, 2010; Diaz et al., 2012; Lin et al., 2010; Whelan-Goodinson et al., 2008; Schiehser et al 2011
## Depression and Cognition in TBI

### TABLE 2. Major Depression Is Associated With Worse Performance on Cognitive Tasks Following Traumatic Brain Injury

<table>
<thead>
<tr>
<th>Variable</th>
<th>Major Depression (N=21)</th>
<th>No Major Depression (N=53)</th>
<th>Analysis of Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Wechsler Adult Intelligence Scale, 3rd ed.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working memory</td>
<td>22.62</td>
<td>9.09</td>
<td>30.10</td>
</tr>
<tr>
<td>Processing speed</td>
<td>14.35</td>
<td>4.57</td>
<td>18.86</td>
</tr>
<tr>
<td>Wechsler Memory Scale, 3rd ed., logical memory story 2</td>
<td>21.81</td>
<td>8.6</td>
<td>29.78</td>
</tr>
<tr>
<td>California Verbal Learning Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>44.57</td>
<td>12.8</td>
<td>57.11</td>
</tr>
<tr>
<td>Long delay free recall</td>
<td>8.05</td>
<td>4.4</td>
<td>12.19</td>
</tr>
<tr>
<td>Brief Visuospatial Memory Test total</td>
<td>20.15</td>
<td>7.1</td>
<td>24.15</td>
</tr>
<tr>
<td>Wisconsin Card Sorting Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totalb</td>
<td>3.95</td>
<td>2.2</td>
<td>5.33</td>
</tr>
<tr>
<td>Perseverative responsesc</td>
<td>31.95</td>
<td>25.4</td>
<td>15.84</td>
</tr>
</tbody>
</table>

a p<0.006 with Bonferroni correction
b N=20 for patients with major depression
c N=20 for patients with major depression; N=51 for patients without major depression
Correlates of Depression in SCI

- Longer lengths of hospital stay
- Less functional independence and mobility at discharge
- Greater occurrence of pressure sores and UTIs
- Poorer community mobility and social integration
- More days in bed, fewer days outside the home
- Greater use of paid personal care
- Greater medical expenses
- Lower Functional Independence at 1 year
- 18% higher risk of lost life expectancy

Tate et al., 1994; Elliott and Frank, 1996; Kennedy et al., 2011; Krause et al., 2011
Depression and Rehabilitation Costs

- N=1334 IRF facilities 2002-2004; 1.1M discharges
- 13% of Medicaid fee-for-service beneficiaries had mental disorders
- After adjusting for payment group and comorbidities, patients with mental disorders had higher costs
  - Mood disorder $433 (3.9% of total costs)
  - Major depression $1642 (14.9% of total costs)
  - Anxiety disorder $247 (2.3% of total costs)
- MDD should qualify for Tier 2 comorbidity in inpatient rehab prospective payment models

Dobrez, Heinemann et al Arch Phys Med Rehabil 2010;91:184-8
Beyond Incidence and Prevalence: Trajectories
Averages as Descriptors

Jung and Wickrama, 2008
Latent Class Growth Mixture Modeling

Jung and Wickrama, 2008
Depression Trajectories after SCI in European Union

Latent Class Growth Mixture Modeling (LCGMM)
Bonanno, Kennedy, et al., Rehab Psych 2012;57:236-247
Depression Trajectories after SCI in the U.S.

- Non depressed
- Mildly depressed
- Moderately Depressed

N=141; Bombardier, Adams, Arch PM&R 2016
Depression Trajectories After TBI in U.S.

N=559; Bombardier, Hoekstra et al., J Neurotrauma 2017
Clinical and Research Implications

• LCGMM identifies clinically meaningful depression subgroups
• Most people are non-depressed/resilient
• Nevertheless, under usual care conditions a significant fraction has persistent MDD
• Trajectory research may inform early intervention or prevention efforts
  – Identify and exclude from treatment trials people who are on a resilient trajectory
  – Research and clinical resources can focus on people who need attention
Current Depression Treatment Adequacy
Depression Is Under-treated After TBI

• In 559 people with TBI followed for one year:
  – 41% of those with depression received any antidepressant;
    20% received any psychotherapy; 44% received either

• In >9000 Medicare beneficiaries with TBI:
  – 42% with depression before TBI used antidepressants
  – 36% with depression after TBI used antidepressants

• Among 161 Australians with psych diagnoses after rehabilitation with no-fault compensation:
  – 31-44% received medications and 36-79% received counseling

Depression is Under-treated after SCI

• 224 outpatients with PHQ-9 > 10 from four U.S. sites
  – 29% used any antidepressant; 11% guideline level
  – 11% received psychotherapy; 6% guideline level
  – 17% received guideline level ADM or counseling

• 36 inpatients positive for a psychological disorder on MINI during inpatient rehabilitation in Sidney NSW
  – 31% on any antidepressant

• 51 inpatients with PHQ-9 ≥ 10 at four U.S. sites
  – 34% currently taking any antidepressant

Fann, Bombardier AMP&R 2011; Craig Nicholson et al APM&R 2015
Fann, Crane et al., APM&R 2013
## Depression Treatment Preferences-TBI

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>Depressed n=37</th>
<th>Non-Depressed n=108</th>
<th>Total Sample n=145</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Exercise (PE)</td>
<td>33 (89.2%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>88 (82.2%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>121 (84.0%)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Counseling/Psychotherapy (CP)</td>
<td>29 (78.4%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>69 (63.9%)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>98 (67.6%)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Alternative or Herbal (AH)*</td>
<td>25 (67.6%)</td>
<td>66 (61.1%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>91 (62.8%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Self-Help Materials (SH)</td>
<td>23 (62.2%)</td>
<td>68 (63.0%)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>91 (62.8%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Antidepressants (AD)</td>
<td>27 (73.0%)</td>
<td>42 (38.9%)</td>
<td>69 (47.6%)</td>
</tr>
<tr>
<td>Group Therapy (GT)</td>
<td>16 (43.2%)</td>
<td>47 (43.5%)</td>
<td>63 (43.4%)</td>
</tr>
</tbody>
</table>

Fann, et al., JHTR 2009; 24, 272-8
Depression Treatment Preferences-SCI

- Participants were 183 inpatients with SCI; n=50 (28%) were positive for MDD on PHQ-9
- 96% of people with SCI and depression willing to engage in some form of treatment
  - 73-61% willing to try antidepressant (PCP vs Psych)
  - 67-51% willing to try counseling (Rehab vs. MHC)
  - 75% willing to try supervised exercise
  - 47% willing to try group counseling

Fann, Crane et al. 2013 Arch PM&R
Clinical Implications

• People with depression and TBI or SCI are willing to try standard pharmacological and nonpharmacological treatments

• Nevertheless, significant under-treatment of depression persists—consistent with or worse than in primary care settings

• Routine screening for depression plus systems changes to ensure identified patients receive effective treatment for depression are needed
Improving Depression Recognition: Screening and Risk Factors
Patient Health Questionnaire - 9

- Based on DSM-IV diagnostic criteria
- Developed for use in medical populations
- Valid screening measure for MDD in medical samples
- Valid measure of depression severity
- Sensitive to change over time
- Sensitive to depression treatment
- Briefer than most other depression screening tools
- Valid over telephone

Kroenke et al., J Gen Int Med, 2001; Lowe et al., Med Care 2004
Bombardier et al, 2004; Justice et al, 2004; Katon et al, 2004; Lee et al, 2005;
Lowe et al, 2006; Ludman et al, 2004; Pinto-Meza et al, 2005; Spitzer et al,
JAMA; 1999; Watnick et al, 2005; Williams et al, 2005
## The Patient Health Questionnaire (PHQ-9)

<table>
<thead>
<tr>
<th></th>
<th>Not At all</th>
<th>Several Days</th>
<th>More Than Half the Days</th>
<th>Nearly Every Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Trouble falling asleep, staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself - or that you’re a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed. Or, the opposite - being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead or of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
## Screening for MDD in TBI

<table>
<thead>
<tr>
<th>Measure</th>
<th>Cut score</th>
<th>AUC</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHQ-9&lt;sup&gt;1&lt;/sup&gt;</td>
<td>≥ 10</td>
<td>0.97</td>
<td>.88</td>
<td>.90</td>
<td>.63</td>
<td>.97</td>
</tr>
<tr>
<td>PHQ-9&lt;sup&gt;1&lt;/sup&gt;</td>
<td>MDD Criteria</td>
<td>0.97</td>
<td>.93</td>
<td>.89</td>
<td>.63</td>
<td>.99</td>
</tr>
<tr>
<td>HADS-D&lt;sup&gt;2&lt;/sup&gt;</td>
<td>≥ 8</td>
<td>0.82</td>
<td>.62</td>
<td>.92</td>
<td>.81</td>
<td>.82</td>
</tr>
<tr>
<td>BDI&lt;sup&gt;3&lt;/sup&gt;</td>
<td>--</td>
<td>--</td>
<td>.36</td>
<td>.80</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>BDI-II&lt;sup&gt;4&lt;/sup&gt;</td>
<td>≥ 19 mTBI</td>
<td>.89</td>
<td>.87</td>
<td>.79</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>BDI-II&lt;sup&gt;4&lt;/sup&gt;</td>
<td>≥ 35 TBI</td>
<td>.89</td>
<td>.87</td>
<td>.79</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

1. Fann et al., JHTR 2005 Vol. 20, No. 6, pp. 501–511
4. Sliwinski et al., JHTR 1998;13;4:34-46
ROC: PHQ-9 vs. MDD Diagnosis in SCI

Sensitivity = 100%
Specificity = 84%
+LR = 6.10

PHQ-9 ≥ 11
Sensitivity = 100%
Specificity = 84%
+LR = 6.10

Bombardier et al, Arch PM&R 2012
Efficient Two-step Screening

1. Administer PHQ-2
   - If neither depressed mood nor loss of interest or pleasure is endorsed (43%); discontinue screening (NPV=100%)

2. If either depressed mood or anhedonia is endorsed, complete PHQ-9
   - If patient scores 11 or more, confirm diagnosis with clinical interview
# Selected Depression Risk Factors in TBI

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female)</td>
<td>✔✔</td>
</tr>
<tr>
<td>Low education</td>
<td>✔✔✔</td>
</tr>
<tr>
<td>Violent etiology</td>
<td>✔</td>
</tr>
<tr>
<td>Medicaid insurance/poor</td>
<td>✔✔</td>
</tr>
<tr>
<td>History of alcohol problems</td>
<td>✔✔✔</td>
</tr>
<tr>
<td>Cocaine/Meth intoxication</td>
<td>✔</td>
</tr>
<tr>
<td>History of depression/mental illness</td>
<td>✔✔✔</td>
</tr>
<tr>
<td>Unstable work/Unemployment</td>
<td>✔✔✔✔</td>
</tr>
<tr>
<td>Self-assessed impairment</td>
<td>✔</td>
</tr>
<tr>
<td>Functional impairment</td>
<td>✔✔</td>
</tr>
</tbody>
</table>

Bombardier et al., 2010; Dikmen et al., 2004; Gould et al., 2011; Jorge et al., 2004; Malec et al., 2007; Pagulayan et al., 2008; Schonberger et al., 2011; Seel et al., 2003; Whelan-Goodinson et al., 2009
Rate of MDD by Depression History

*P < .001; independent predictors after adjusting for all other variables

Bombardier, Fann et al JAMA 2010;303(19):1938-1945
## Pre- and Post-TBI Rates of MDD

<table>
<thead>
<tr>
<th>Author, year</th>
<th>N</th>
<th>Pre TBI MDD</th>
<th>Post TBI MDD</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hibbard, 1998</td>
<td>100</td>
<td>17%</td>
<td>61%</td>
<td>SCID over 7-year period</td>
</tr>
<tr>
<td>Whelan-Goodinson, 2009</td>
<td>100</td>
<td>17%</td>
<td>45%</td>
<td>SCID over 1-5 year periods</td>
</tr>
<tr>
<td>Ashman 2004</td>
<td>188</td>
<td>20%</td>
<td>35-21%</td>
<td>SCID over 3 mo-6 year periods</td>
</tr>
<tr>
<td>McCauley, 2001</td>
<td>115</td>
<td>7%</td>
<td>22%</td>
<td>SCID at 3 months</td>
</tr>
<tr>
<td>Jorge, 2004</td>
<td>91</td>
<td>22%</td>
<td>33%</td>
<td>Present State Exam at 3, 6, 12 mos</td>
</tr>
<tr>
<td>Bombardier, 2010</td>
<td>559</td>
<td>33%</td>
<td>53%</td>
<td>PHQ-9 at 1-6, 8, 10, 12 months</td>
</tr>
<tr>
<td>Gould, 2011</td>
<td>102</td>
<td>14%</td>
<td>29%</td>
<td>SCID at 3, 6, 12 months</td>
</tr>
<tr>
<td>Alway, 2016</td>
<td>161</td>
<td>23</td>
<td>19-30%</td>
<td>SCID at 1, 2, 3, 4, 5 years</td>
</tr>
</tbody>
</table>
Rate of MDD by Alcohol History

*P < .001; independent predictor after adjusting for all other variables

Bombardier, Fann et al JAMA 2010;303(19):1938-1945
Relationship Between Psychiatric Disorders and TBI May Be Bi-directional

Compared 1440 cases with TBI to 4320 matched controls without TBI in a large health maintenance organization. Those with prior one year history of:

- psychiatric diagnosis were 1.7 (95% CI 1.4 to 2.0) times more likely to sustain subsequent TBI
- depression were 1.4 (95% CI 1.0-2.0) times more likely to sustain subsequent TBI
- filling psychiatric medication prescription were 1.6 (95% CI 1.2 to 2.1) times more likely to sustain subsequent TBI
- utilizing psychiatric services were 1.3 (95% CI 1.0 to 1.6) times more likely to sustain subsequent TBI

Fann et al., JNNP 2002
Depression Risk Factors in SCI

- Female
- Lower education and income
- Prior history of depression (29-32%)
- History of alcohol abuse
- Less independent in ADLs
- Chronic pain
- Negative partner reactions to pain
- Maladaptive appraisal and coping
- Cognitive impairment

Stroud et al., J Pain 2006; Krause et al., APM&R 2000; Craig et al., APM&R 2015; Tetrault et al., APM&R 2014; Bombardier et al APM&R 2016; Williams et al., Rehab Psych 2014; Tirch, JSCM 1999; Kishi, Psychosomatics 2001; Kennedy et al APM&R 2011; Bonanno et al APM&R 2012; Craig et al., J Neurotrauma 2017
Clinical Implications

• PHQ-9 is a valid screen for MDD in TBI and SCI
• For many people MDD predated injury
• History of depression, substance abuse, psychosocial adversity (unemployment, impoverishment, loss of social supports) and chronic pain should increase suspicion of MDD
• Provide education and closer follow-up for those at higher risk for persistent depression
Depression Treatment Efficacy
Possible Interventions

Antidepressants

Cognitive Behavioral Therapy

Behavioral Activation

Physical Activity

Depression

Thought

Emotion

Behaviour

What we think affects how we act and feel.

What we feel affects how we think and do.

What we do affects how we think and feel.
Medical Treatment
Sertraline (Zoloft) for MDD after TBI

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ashman et al 2009 (n=52)</th>
<th>Fann, Bombardier 2017 (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sertraline</td>
<td>Placebo</td>
</tr>
<tr>
<td>HAM-D Pre</td>
<td>27.5</td>
<td>25.2</td>
</tr>
<tr>
<td>HAM-D Post</td>
<td>13.7</td>
<td>16.2</td>
</tr>
<tr>
<td>Change</td>
<td>-13.8</td>
<td>-8.9</td>
</tr>
<tr>
<td>Responders</td>
<td>59%</td>
<td>32%</td>
</tr>
<tr>
<td>MDD Post Tx</td>
<td>18%</td>
<td>37%</td>
</tr>
<tr>
<td>Trails B*</td>
<td></td>
<td>-16 s</td>
</tr>
<tr>
<td>Dropout**</td>
<td>21%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Ashman et al APM&R 2009; Fann, Bombardier JHTR 2017*p=.006; **P=.042
Depression Prevention After TBI

- Double-blind, 24 week trial of 100 mg sertraline vs. placebo in 94 patients starting within 4 weeks of TBI
- Hazards of incident depression were about 4 times greater on placebo vs. sertraline (7% vs. 25%)

Figure 2. Risk Comparison of Onset of Mood Disorder for Patients Receiving Sertraline or Placebo

Jorge et al., JAMA Psychiatry 2016;73:1041-1047
Original Investigation

Venlafaxine Extended-Release for Depression Following Spinal Cord Injury: A Randomized Clinical Trial

Jesse R. Fann, MD, MPH; Charles H. Bombardier, PhD; J. Scott Richards, PhD; Catherine S. Wilson, PsyD; Allen W. Heinemann, PhD; Ann Marie Warren, PhD; Larry Brooks, PhD; Cheryl B. McCullumsmith, MD, PhD; Nancy R. Temkin, PhD; Catherine Warms, PhD; Denise G. Tate, PhD; for the PRISMS Investigators

Sites: Washington (lead), Michigan, Alabama, Illinois, Texas, Florida

JAMA Psychiatry, 2015;72(3):247-260
PRISMS Study Design

- Two group 1:1 randomized, placebo controlled trial of venlafaxine XR vs. placebo
- Dosage titration at weeks 1, 3, 6, 8, 10
- Outcomes assessed at baseline, weeks 1, 3, 6, 8, 10, and 12
- Primary analysis: intent-to-treat, adjusted mixed-effects regression models
- **Dual primary outcomes**: Bonferroni-corrected effects on HAMD-17 and HAMD-Maier
- Secondary outcomes: pain (NRS), subjective disability (Sheehan)
PRISMS Trial Subject Flow

Total Screened 2536

Ineligible for SCID: 2259 (89%)

Eligible for SCID 277

Refused SCID / on AD's: 103 (37%)

SCID Administered 174

Did not meet tx criteria: 41 (24%)

Randomized 133

Did not meet inclusion criteria: 149 (7%)
PHQ less than 10: 1872 (83%)
Other/unknown reason: 238 (11%)

Passive refusal (third no-show): 40 (39%)
Denies depression: 16 (16%)
Does not want AD's: 10 (10%)
Other/unknown reason: 37 (36%)

Bipolar disorder or psychosis: 6 (15%)
Current substance dependency: 4 (10%)
Suicidal ideation or history: 3 (7%)
Other/unknown reason: 28 (68%)
## Effect of Venlafaxine on Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Venlafaxine XR</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HAMD-17</td>
<td>19.6 (5.5)</td>
<td>19.7 (5.4)</td>
<td>NS</td>
</tr>
<tr>
<td>12 Week HAMD-17</td>
<td>9.1 (7.1)</td>
<td>9.6 (6.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Change in HAMD-17</td>
<td>10.5</td>
<td>10.1</td>
<td>NS</td>
</tr>
<tr>
<td>% Response HAMD-17</td>
<td>59%</td>
<td>49%</td>
<td>NS</td>
</tr>
<tr>
<td>Change in HAMD Maier</td>
<td>-5.6</td>
<td>-4.8</td>
<td>.025</td>
</tr>
<tr>
<td>% Response HAMD Maier</td>
<td>46 (67%)</td>
<td>35 (56%)</td>
<td>NS</td>
</tr>
<tr>
<td>Change in Sheehan</td>
<td>-7.7</td>
<td>-3.3</td>
<td>.009</td>
</tr>
</tbody>
</table>

Fann, Bombardier et al JAMA Psychiatry 2015
Detail on Maier

1. Depressed mood
2. Feelings of guilt
3. Work and activities (interest/anhedonia)
4. Psychomotor retardation (psychic, motoric)
5. Psychomotor agitation
6. Anxiety, psychic
The Effect of Venlafaxine on SCI Pain

• Secondary analysis of pain data from PRISMS trial
  – 123 patients had at least one pain and were included
  – Participants had an average of 2.5 pains
  – Pains coded as neuropathic, nociceptive or mixed by the Spinal Cord Injury Pain Instrument*
  – SNRI hypothesized to reduce neuropathic pain

• Results
  – For neuropathic pain, 50% pain intensity response rates at 12 weeks were 29% for VFN vs. 32% for placebo (ns)
  – For nociceptive pain, 50% pain intensity response rates were 65% for VFN vs. 23% for placebo (p=.001)

*Sens=78%; spec=73%; accuracy=76% with expert physician diagnosis; Bryce et al., Spinal Cord 2014; Richards et al., APM&R 2015;96:680-9
The Effect Gabapentinoids on Depression in People with Neuropathic Pain and SCI

<table>
<thead>
<tr>
<th>Study name</th>
<th>Outcome</th>
<th>Std diff in means</th>
<th>Standard error</th>
<th>Variance</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardenas 2013</td>
<td>anxiety symptoms</td>
<td>2.029</td>
<td>0.174</td>
<td>0.030</td>
<td>1.687</td>
<td>2.371</td>
<td>11.630</td>
<td>0.000</td>
</tr>
<tr>
<td>Siddall 2006</td>
<td>anxiety symptoms</td>
<td>0.103</td>
<td>0.172</td>
<td>0.029</td>
<td>-0.233</td>
<td>0.440</td>
<td>0.602</td>
<td>0.547</td>
</tr>
<tr>
<td>Pooled anxiety symptoms</td>
<td></td>
<td>1.050</td>
<td>0.122</td>
<td>0.015</td>
<td>0.811</td>
<td>1.290</td>
<td>8.585</td>
<td>0.000</td>
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<tr>
<td>Cardenas 2013</td>
<td>depression symptoms</td>
<td>2.912</td>
<td>0.203</td>
<td>0.041</td>
<td>2.513</td>
<td>3.311</td>
<td>14.310</td>
<td>0.000</td>
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<tr>
<td>Siddall 2006</td>
<td>depression symptoms</td>
<td>0.024</td>
<td>0.172</td>
<td>0.029</td>
<td>-0.312</td>
<td>0.360</td>
<td>0.140</td>
<td>0.888</td>
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<tr>
<td>Pooled depression symptoms</td>
<td></td>
<td>1.224</td>
<td>0.131</td>
<td>0.017</td>
<td>0.967</td>
<td>1.481</td>
<td>9.330</td>
<td>0.000</td>
</tr>
<tr>
<td>Ahn 2003a</td>
<td>sleep interference</td>
<td>1.159</td>
<td>0.390</td>
<td>0.152</td>
<td>0.395</td>
<td>1.923</td>
<td>2.973</td>
<td>0.003</td>
</tr>
<tr>
<td>Ahn 2003b</td>
<td>sleep interference</td>
<td>0.662</td>
<td>0.295</td>
<td>0.087</td>
<td>0.084</td>
<td>1.241</td>
<td>2.245</td>
<td>0.025</td>
</tr>
<tr>
<td>Cardenas 2013</td>
<td>sleep interference</td>
<td>5.267</td>
<td>0.291</td>
<td>0.085</td>
<td>4.697</td>
<td>5.838</td>
<td>18.098</td>
<td>0.000</td>
</tr>
<tr>
<td>Siddall 2006</td>
<td>sleep interference</td>
<td>0.446</td>
<td>0.174</td>
<td>0.030</td>
<td>0.106</td>
<td>0.786</td>
<td>2.569</td>
<td>0.010</td>
</tr>
<tr>
<td>Pooled sleep interference</td>
<td></td>
<td>1.463</td>
<td>0.126</td>
<td>0.016</td>
<td>1.216</td>
<td>1.710</td>
<td>11.614</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Mehta et al., APM&R 2014;95:2180-6
Take Home Points

• Thus far ADMs have demonstrated modest effects beyond placebo in people with TBI and SCI
• Treating factors contributing to depression, such as pain, may reduce depression severity
• Tolerability was limited in TBI (“start low, go slow”)
• Studies were underpowered, included people with mild MDD, and had high placebo response rates, predisposing toward null findings
• ADMs may be more efficacious in people with more severe (HAMD ≥25) and persistent MDD
Behavioral and Cognitive Therapies

What we *think* affects how we act and feel.

What we *feel* affects how we think and do.

What we *do* affects how we think and feel.
Psychotherapy for Depression after TBI

• Seven (mostly CBT) studies with pre-post analysis and a control condition. Subjects were at least one year after TBI
• Pre-post effect sizes were significant in 4 studies
• Overall ES=.69 (95%CI, 0.29-1.09)
• Studies with adequate randomization did not support the efficacy of psychotherapy for depression after TBI

Stalder-Luthy et al., Arch PM&R 2013
Depression and Functioning in TBI

• Many studies have reported a relationship between poorer functioning and greater depression but the direction of the relationship has been uncertain.

• Two longitudinal studies that used cross-lagged panel designs have shown that functioning at T1 predicts depression at T2 and that depression at T1 does not predict functioning at T2.

• One implication might be that in people with TBI we should treat functioning (rehabilitation) as a way to improve depression.

Pagulayan et al., 2008; Schonberger et al., 2011
Telephone Counseling to Improve Functioning after TBI: Effect on Depression

- Reanalysis of Bell et al., Arch PM&R, 2005
- At discharge from inpatient rehabilitation 171 persons randomly assigned 1:1 to telephone counseling or usual care
- Intervention consisted of 30-45 min calls at about 2, 4, 8, 12, 20, 35 and 45 weeks after discharge
- Counselor used motivational interviewing techniques to elicit concerns, provide information and facilitate problem-solving to help with overall recovery/functioning after TBI
- Outcomes collected at one year by examiner unaware of group assignment

Bombardier et al JHTR 2009;24(4):230-238
Change in Depression Severity: 0-12 Months

BSI-D Change
Total Group

BSI-D Change
Depressed Sub-group

BSI-D, Brief Symptom Inventory-Depression; p=.02, p=.004, respectively

Bombardier et al JHTR 2009;24(4):230-238
Depression Treatment in mTBI

- 13 treatment trials found (CBT, TCA, SSRI, stimulant)
- Paucity of high quality studies
- Pre-post designs (n=8) produced an overall effect size of 1.89 (95% CI=1.20–2.58, p<0.001)
- Control group designs (n=5) produced an overall effect size of 0.46 (95% CI=-0.44–1.36, p<0.001) favoring control groups over treatment groups
- Inadequate evidence to recommend any treatment at this time

Barker-Collo et al., Brain injury 2013;32:1124-11
CBT vs. Supportive Tx for Depression in TBI

- N=77 people ~12 years post-TBI with DSM-IV “depressive disorder” randomized to 16 in-person CBT sessions (n=39) vs. 16 in-person supportive therapy (control) sessions (n=38)
- 44% dropped out; analyses--intent-to-treat
- 35% (CBT) vs. 17% (ST) no longer “depressed”
- Significant time effect (ES=.17), time X group effect was NS
- CBT group significant time effect; ST NS time trend

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Baseline total</th>
<th>N</th>
<th>Baseline completers</th>
<th>Postintervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI-II total</td>
<td>CBT</td>
<td>37</td>
<td>27.5 (8.4)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>24</td>
<td>27.3 (9.6)</td>
</tr>
<tr>
<td></td>
<td>SPT</td>
<td>37</td>
<td>24.7 (9.6)</td>
<td>24</td>
<td>25.5 (10.4)</td>
</tr>
</tbody>
</table>

Ashman et al., J Head Trauma Rehabil 2014 Vol. 29, No. 6, pp. 467–478
LIFT Study: CBT for MDD in TBI

• N=110 people ~3 years post-TBI with DSM-IV MDD randomized to: in-person CBT (n=18), tele-CBT (n=40), vs. usual care (n=42)

• 12% dropped out; analyses--intent-to treat

• There was no significant difference between combined CBT and UC groups over 16 weeks on the HAMD-17

• There was a NS trend favoring CBT on the SCL-20

• 73% (CBT) vs. 57% (UC) no longer met MDD criteria (ns)

• Those with ≥8 CBT sessions were less depressed than UC on the SCL-20 at 8 (p<.001) and 16 (p<.011) weeks

Fann, Bombardier et al., JOURNAL OF NEUROTRAUMA 2015; 32:45–57
Relationship of Cognitive, Behavioral and Physical Activity Variables to TBI Depression

• Reanalysis of data from LIFT trial—we combined groups and used regressions to explore relationships between theoretical variables and depression outcomes

• At baseline, dysfunctional attitudes and automatic thought scores were high and physical activity and pleasant experience scores were low compared to non-TBI norms

• Outcomes except dysfunctional attitudes improved

• Increase in pleasant experience was correlated with decrease in depression at 16 weeks

Bombardier, Fann et al JHTR 2017
### MBCT vs. UC for Depression IN TBI

- People ~4 years post-TBI with BDI-II ≥16; (100/105) were randomly assigned to 10 sessions of in-person MBCT (n=57) vs. usual care (n=48)
- 31% dropped out; analyses—outcome completers (n=76)
- MBCT group less depressed on BDI than controls (p=.029)

<table>
<thead>
<tr>
<th>Site 1: Ottawa, mean (SD)</th>
<th>Site 2: Thunder Bay, mean (SD)</th>
<th>Site 3: Toronto, mean (SD)</th>
<th>All sites, mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Pre</td>
<td>Post</td>
<td>N</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(7.94)</td>
<td>(7.39)</td>
<td>(2.67)</td>
<td>(7.20)</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>25.92</td>
<td>24.38</td>
<td>3</td>
</tr>
<tr>
<td>(9.48)</td>
<td>(12.07)</td>
<td>(5.86)</td>
<td>(9.02)</td>
</tr>
</tbody>
</table>

Bedard et al., J Head Trauma Rehabil 2014; 29, No. 4, pp. E13–E22
Meta-analysis of Psychosocial Treatments for Depression in SCI

- No level I studies
- Three level II randomized controlled trials
- Three level III non-randomized controlled trials
- Three level IV historical controlled trials
- Overall SMD for multimodal CBT -0.52 [-0.85, -0.19]
- Activity scheduling (behavioral activation) had the largest significant effect size -0.60 [-1.05, -0.16]

Perkes et al J Health Psychol 2013
Promising Tech Interventions

• 6 month RCT of automatic interactive voice response system delivering information on skin, depression, wellness, healthcare utilization vs, UC in MS and SCI; reduced depression in those with high baseline

• 10 week RCT of Internet based CBT vs. WLC in SCI/D with high depression, anxiety or stress; depression declined in both groups but intent-to-treat revealed the treatment group had greater increase in SWL

Houlihan et al., Spinal Cord 2013, 1–6; Migliorini et al Spinal Cord 2016, 695-701
Physical Activity
Exercise for Depression in TBI

• Systematic review of three controlled trials and six uncontrolled studies
• Quality of studies “adequate”
• Eight studies used aerobic conditioning and one study used walking
• Overall effect size 0.48 [95% CI, 0.16, 0.81]
• Effect size excluding two small studies, 0.35 [0.17, 0.52]
• There is tentative support for the notion that exercise has a small to medium effect on depression in TBI

Perry, Coetzer, Saville Neuropsych Rehab, May 13 2018
Physical Inactivity and Depression in SCI

Study

Bradley
Ditor et al.
Foreman et al.
Gioia et al.
Greenwood et al.
Guest et al.
Hicks et al. 2003
Hicks et al. 2005
Jacobs et al.
Kennedy et al.
Loy et al.
Muraki et al.
Paulsen et al.
Tasiemski et al.
Warms et al.

Correlation and 95% CI

Martin-Ginis et al Spinal Cord, 2010
Exercise for Depression in SCI

• 9 month RTC of lab-based resistance and aerobic training (n=21) vs. WLC (n=13) EX sustained good mood while mood worsened in WLC

• RCT of 12 sessions of Iyengar yoga (n=11) vs. WLC (n=12); post-treatment depression was lower in yoga group compared to WLC after controlling for baseline depression severity

• Pilot RCT of telephone counseling to increase physical activity (n=7) vs. usual care (n=8) demonstrated a large decrease in depression severity among those in the TX group relative to WLC; ES=-1.26, p=.049.

Hicks et al., Spinal Cord 2003; Curtis, Hitzig et al., J Pain Res 2017; Bombardier in preparation
Depression Management
Future Directions
Collaborative Care

• Research tends to show that screening and referral alone do not improve depression related outcomes
• In contrast, there is evidence that the collaborative care model (CCM) improves depression outcomes
• The IMPACT study used CCM to double (19% to 45%) the effectiveness of usual care for depression and it was cost effective (see http://impact-uw.org/)

Unutzer et al., JAMA 202:2836-2845
Gilbody S et al., Arch Intern Med. 2006;166(21):2314-2321;
Katon et al., Arch Gen Psychiatry. 2012;69(5):506-514
SCI CARE Treatment Model

**Physician/SCI Clinic**

**Consultants**
- Psychologist
- Physiatrist
- Psychiatrist

**Patient**

**Care Manager**

- Screen for problems
- Offer choice of Tx

- Weekly case supervision
- Treatment adjustment
- Manage treat-to-target

- Medical Tx: monitor Tx response; motivate patient to adhere
- Psychosocial Tx: Tele-CBT, physical activity counseling, hypnosis

**Feedback to MD**
- Decision support
- Care coordination
Collaborative Care Results

• 174 outpatients with chronic pain, depression or physical inactivity randomized to Usual Care (n=85) vs. Collaborative Care (n=89)

• 61% focused on pain; 31% focused on inactivity; 8% focused on depression (32% screened positive for MDD)

• Used mixed effects linear regression to measure outcomes, intent-to-treat analyses

• Primary outcome was WHOQOL-BREF

• Secondary outcomes: pain, depression, MVPA
Effect of SCI CARE on WHOQOL-BREF

- **CC**
  - QOL Baseline: 62
  - QOL 4 Months: 65
  - QOL 8 Months: 65

- **UC**
  - QOL Baseline: 63
  - QOL 4 Months: 63
  - QOL 8 Months: 63

P = .10, .08
Collaborative Care Results

• At 4 months, pain interference (AMD=-1.02, \( p<.005 \)), depression (AMD=-0.22, \( p<.05 \)), and satisfaction with care (AMD=0.39, \( p<.02 \)) improved more in CC vs. UC.

• At 8 months, pain interference (AMD=-1.25, \( p<.001 \)) and depression (AMD=-.21, \( p=.023 \)) improved more in CC vs. UC.

• At 4 months, among participants focused on improving physical activity, the WHOQOL-BREF improved more in CC vs. UC (AMD=6.22, \( p<.05 \)).
Summary

• Most people with TBI or SCI are resilient, but a significant fraction suffer from persistent mild to moderate depression.
• Depression seems to be under-treated despite patient reports of being receptive to treatment.
• Screen everyone for MDD using an efficient model: PHQ-2 → PHQ-9 → diagnostic interview.
• Have greater suspicion for depression in people with a preinjury history of depression, other mental health disorder history, substance abuse history, low education, or unsteady employment.
Summary

• Trajectory research holds hope that we will be able to individually tailor follow-up and treatment such that we avoid unnecessary treatment and deploy resources to patients most in need

• Under-treatment may be due limited evidence of treatment effectiveness and treatment resistance

• For severe depression, use multimodal treatment i.e., antidepressants and a psychosocial intervention

• TCA and SNRI antidepressants may have the added benefit of improving (nociceptive) pain in people with depression
Summary

• Several reasonable treatment choices for mild to moderate MDD; no clear winners in terms of efficacy, therefore, patient choice and risk factor profile should guide decisions

• Treatments tailored to risk factors
  – More severe MDD, prefer medications—antidepressants
  – Neuropathic pain—pregabalin, gabapentin
  – Low pleasant activities—Behavior Activation
  – Maladaptive appraisals or coping—CBT, CET, etc.
  – Sedentary lifestyle—physical activity promotion
  – Rehabilitation to help people improve functioning and return to meaningful, enjoyable roles and activities
Discussion

• What are you already doing to facilitate improved recognition and effective treatment of depression in people with TBI or SCI?
• What are some additional steps or strategies that you would like to take to improve recognition and effective treatment of depression in people with TBI or SCI?
THANK YOU

• chb@uw.edu