Activation and Recovery after Acute Brain Injury

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Disclosures

None
Disclaimers

I am a neurointensivist, not an inpatient physiatrist or an outpatient neurologist.

Focus is on “recovery”, not rehabilitation, on patients with “periconsciousness”, in “prerehabilitation”.

Question is how to “activate” patients after acute brain injury, how to transform them from passive to active participants in care.

Emphasis is on mechanism of and evidence for agents to “activate” consciousness.

Effects of physical/occupational/speech therapy, electrical stimulation (SS, RMNS, DBS, TMS, etc) are beyond my scope.

Terminology is contrived but I hope neither misleading nor incorrect. Problem is important.
Recovery

TBI: After severe TBI with VS x4 wks, 50% regained consciousness by 1 y (Levin 1991).

Cardiac arrest: After cardiac arrest with TTM, 47% achieved CPC 1-2 by 6 mos (Nielsen 2013).

Large hemispheric ischemic stroke: In <60 y with early hemicraniectomy for large hemispheric ischemic stroke, 43% achieved mRS 0-3 by 1 y (Vahedi 2007).

SAH: After Hunt and Hess 5 SAH, 20% achieved mRS 0-3 by 1 y (Witsch 2016).

ICH: After ICH Score 4 ICH, 16% achieved mRS 0-3 by 90 d (Morgenstern 2015).

CPC cerebral performance score, mRS modified Rankin score, ICH intracerebral hemorrhage, SAH subarachnoid hemorrhage, TBI traumatic brain injury, TTM targeted temperature management, VS vegetative state
Objectives

Distinguish disorders of consciousness.

Describe the monoaminergic, glutamatergic, cholinergic, and GABAergic pathways that regulate consciousness.

Understand the special potential for activation in diffuse brain injury and focal brainstem injury.

Understand the evidence for monoaminergic activation.

Recognize the benefit of serotonergic agents after recovery of consciousness.

State the paradoxical effect of zolpidem as a GABAergic activator.

Learn a practical approach to trials of activation after acute brain injury.
Road to Recovery
**Disorders of Consciousness: ASPEN working group** (Giacino 2002)

<table>
<thead>
<tr>
<th></th>
<th>consciousness</th>
<th>sleep/wake</th>
<th>motor</th>
<th>auditory</th>
<th>visual</th>
<th>communication</th>
<th>emotion</th>
</tr>
</thead>
<tbody>
<tr>
<td>coma</td>
<td>-</td>
<td>-</td>
<td>reflex/posture only</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>vegetative state</td>
<td>-</td>
<td>+*</td>
<td>postures or withdraws to pain, occasional nonpurposeful movement</td>
<td>startle, brief orienting</td>
<td>startle, brief fixation</td>
<td>-</td>
<td>-, reflexive smiling or crying</td>
</tr>
<tr>
<td>minimally conscious state</td>
<td>partial</td>
<td>+*</td>
<td>localizes to pain, reaches for objects, holds or touches in a manner that accommodates size and shape, automatisms</td>
<td>localizes, inconsistent commands</td>
<td>sustained fixation, sustained pursuit</td>
<td>contingent vocalization, inconsistent but intelligible verbalization or gesture</td>
<td>contingent smiling or crying</td>
</tr>
<tr>
<td>locked-in syndrome</td>
<td>full</td>
<td>+</td>
<td>quadriplegic</td>
<td>+</td>
<td>+</td>
<td>aphoncic/anarthric, vertical eye movement, blinking</td>
<td>+</td>
</tr>
</tbody>
</table>

*Apparent sleep/wake cycles, but not true sleep or wakefulness by EEG*
Motor-Cognitive Continuum (Schiff 2010)
Consciousness

Monoaminergic, glutamatergic, and cholinergic nuclei in brainstem activate cortex either directly or through intralaminar thalamus or basal forebrain.

Cortex regulates thalamus through GABAergic striatopallidal feedback.

Adapted from Parvizi and Damasio 2003, Schiff 2010
Coma: Focal (Parvizi and Damasio 2003)
Coma: Diffuse (Wang 2008)
Activation

An activator is a medication that manipulates neurotransmitters to improve arousal. This effect has the potential to hasten recovery, foster plasticity, or enable rehabilitation.

Potential is highest for conditions in which the anatomy of consciousness is impaired, namely focal brainstem injury or diffuse cortical/subcortical injury.

Potential is lowest in lateralized lesions or electroencephalographic disorders.
Activation: Pitfalls

Small, often uncontrolled studies

Various pathology (TBI, stroke, ICH),
  severity of injury (severe-mild TBI),
  time from injury (days-years),
  duration of treatment (1 dose-6 mos),
  dosing,
  outcomes (GOS-E, HVLT, CANTAB-(RVIP A0), COWAT, WAIS III, TMT, NFI, BDI-II,
  DSLS, CGIC, WMS II, PASAT, subjective experience, staff observation)

Numerous agents

ICH intracerebral hemorrhage, TBI traumatic brain injury

<table>
<thead>
<tr>
<th>Drug</th>
<th>Studies</th>
<th>Subjects</th>
<th>Methodology</th>
<th>Positive</th>
<th>Negative</th>
<th>Equivocal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>22</td>
<td>471</td>
<td>DBRC (3)</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DBXR (12)</td>
<td>7</td>
<td>4</td>
<td>1</td>
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<td></td>
<td></td>
<td></td>
<td>SBRC (1)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CS (6)</td>
<td>5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>1</td>
<td>51</td>
<td>DBXR</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Dextroamphetamine</td>
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<td>17</td>
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<td>1</td>
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</table>

CS cohort/case/observational series, DBRC double blind randomized control, DBXR double blind randomized crossover, SBR single blind randomized control

<table>
<thead>
<tr>
<th>Drug</th>
<th>Studies</th>
<th>Subjects</th>
<th>Methodology</th>
<th>Positive</th>
<th>Negative</th>
<th>Equivocal</th>
</tr>
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<tbody>
<tr>
<td>Amantadine*</td>
<td>9</td>
<td>472</td>
<td>DBRC (2)</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DBXR (2)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CS (5)</td>
<td>3</td>
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<td>1</td>
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<tr>
<td>Bromocriptine</td>
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<td>75</td>
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<td>0</td>
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<td></td>
<td></td>
<td></td>
<td>CS (2)</td>
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<td>Levodopa</td>
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</table>

*Non-competitive NMDA receptor antagonist, indirect dopamine agonist, as well as possible anticholinergic effects

CS cohort/case/observational series, DBRC double blind randomized control, DBXR double blind randomized crossover
# Serotonergic (Mead 2012)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Studies</th>
<th>Subjects</th>
<th>Methodology</th>
<th>Positive</th>
<th>Negative</th>
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<tr>
<td>Fluoxetine</td>
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<td>826</td>
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<tr>
<td>Citalopram</td>
<td>3</td>
<td>179</td>
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<td>0</td>
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<tr>
<td>Sertraline</td>
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<td>130</td>
<td>DBRC</td>
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</table>

DBRC double blind randomized control
## Cholinergic (Poole and Agrawal 2008)

<table>
<thead>
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<th>Drug</th>
<th>Studies</th>
<th>Subjects</th>
<th>Methodology</th>
<th>Positive</th>
<th>Negative</th>
<th>Equivocal</th>
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<td>389</td>
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<td>1</td>
<td>0</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>OL (9)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>XD (2)</td>
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<td></td>
<td></td>
<td></td>
<td>CS (2)</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CS (2)</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CDP Choline</td>
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<td>129</td>
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<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CS (1)</td>
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<td>1</td>
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<tr>
<td>Physostigmine(+/- Lecithin)</td>
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<td>56</td>
<td>DBXR (2)</td>
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<td>0</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CS (4)</td>
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<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

CS cohort/case/observational series, DBRC double blind randomized control, DBXR double blind randomized crossover, OL open label, XD crossover
GABAergic/Unknown  (Cossu 2014, Saccucci 2016)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Studies</th>
<th>Subjects</th>
<th>Methodology</th>
<th>Positive</th>
<th>Negative</th>
<th>Equivocal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolpidem</td>
<td>5</td>
<td>162</td>
<td>DBXR (2)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CS (3)</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Modafinil</td>
<td>1</td>
<td>53</td>
<td>DBXR (1)</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

CS case/cohort/observational series, DBXR double blind randomized crossover

NMDA, AMPA antagonists (not agonists) failed in large trials of stroke (ischemic and hemorrhagic, 6317 patients, 10 RCT) and TBI (7 RCT, 760 patients).

Hope was to block early glutamatergic excitotoxicity.

Highlights danger of too early intervention.

Not explored for activation or rehabilitation.

TBI traumatic brain injury
Common Activation Practices (Whyte 2005)

Longitudinal observational cohort of 124 patients with VS or MCS 4-16 wks after TBI

Only amantadine was associated with greater recovery (and dantrolene was associated with lesser recovery).

Of 85 patients on amantadine, 26 were conscious before amantadine, 36 recovered consciousness in 0-2 wks, and 23 remained unconscious.

MCS minimally conscious state, VS vegetative state, TBI traumatic brain injury

<table>
<thead>
<tr>
<th>Medication</th>
<th>Exposed &lt;28 d</th>
<th>% Exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-blockers*</td>
<td>53</td>
<td>43</td>
</tr>
<tr>
<td>Anticonvulsants*</td>
<td>49</td>
<td>40</td>
</tr>
<tr>
<td>Amantadine*</td>
<td>47</td>
<td>38</td>
</tr>
<tr>
<td>Serotonergics*</td>
<td>39</td>
<td>31</td>
</tr>
<tr>
<td>Trazodone*</td>
<td>35</td>
<td>28</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>Carbamazepine*</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Dantrolene*</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Baclofen</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Clonidine</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>

* Reached screening cut off
A subgroup analysis of 53 patients with data 2 wks before and 2 wks after amantadine showed significant improvement.
Amantadine (Giacino 2012)

DBRC, 184 patients, 4-6 wks after severe TBI, DRS >11 and inability to follow commands consistently and engage in functional communication

Amantadine v placebo x 4 wks, then 2 wks washout
100 mg q12h for wk 0-2,
then 150 mg q12h if Δ DRS/wk <=2 for wk 3,
then 200 mg q12h if Δ DRS/wk <=2 for wk 4,
then 3 d taper and washout for wk 4-6

Primary outcome Δ DRS/wk from wk 0-4 (effect)

Secondary outcome Δ DRS/wk from wk 4-6 (durability)

DBRT double blind randomized control, DRS disability rating score, TBI traumatic brain injury
**Amantadine** (Giacino 2012)

In wk 0-4 recovery was faster with amantadine (0.24 $\Delta$ DRS/wk, $p=0.007$).

From wk 4-6 recovery converged.

No difference in serious adverse events.

The effect of amantadine continuation beyond 4 wks is unknown.

DRS disability rating score
Methylphenidate  (Moein 2006)

DBRC, 40 severe TBI, 40 moderate TBI

Randomized to methylphenidate 0.3 mg/kg q12h on hospital day 2 until discharge.

In severe TBI, methylphenidate was associated with reduced ICU and hospital LOS by 23% (p=0.06 for ICU, p=0.029 for hospital). In moderate TBI, methylphenidate was reduced ICU LOS by 26% (p=0.05) but not hospital LOS.

No subsequent studies
Fluoxetine: FLAME (Chollet 2011)

DBRC, 118 patients, 5-10 d after stroke, FMMS <55

Excluded NIHSS >20, depression

Fluoxetine 20 mg v placebo x3 mos

Primary outcome Δ FMMS

Secondary outcome Δ mRS

DBRC double blind randomized control, FMMS Fugl-Meyer motor scale, mRS modified Rankin score, NIHSS National Institute of Health stroke scale
Fluoxetine: FLAME (Chollet 2011)
Zolpidem (Clauss 2000)

Selective GABA-α1 agonist concentrated in GPi

First case report in 2000 in South African Medical Journal. Patient was in VS 3 y after TBI. Given zolpidem 10 mg to treat agitation. 30 min later, he greeted mother and answered questions. Peak effect was at 1 h and lasted 4 h before return to VS.

Effect of zolpidem demonstrated on SPECT

GPi globus pallidus interna, VS vegetative state
Zolpidem  (Whyte 2014)

DBXR, 84 patients, 4 mo of DRS >11 after acute brain injury, zolpidem naive

Randomized to single dose of zolpidem or placebo 10 mg

4 definite responders

Response lasted 1-2 h, sometimes ended with somnolence

Responders could not be distinguished from non-responders by history, imaging

Adverse events were more common with zolpidem
Zolpidem  (Whyte 2014)

TABLE 3  Adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Zolpidem Phase 1</th>
<th>Zolpidem Phase 2</th>
<th>Placebo Phase 1</th>
<th>Placebo Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staring spell</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Fever</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Shaking/jerking/</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>restless movements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distressed expression</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Reduced arousal</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Coughing</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Shallow respiration</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tracheostomy tube</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>clogging/dislodgement</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Screaming</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>“Spitting up”</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Total</td>
<td>18</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

*Fisher’s exact test, $P = 0.014$.  
$^bX^2, P < 0.01.$
Activation: What to Do?

Every acute brain injury is different.

No single activator will help all patients.

What to do?
1. Practical
2. Scientific
Activation: a Practical Approach

Consider activation in patients with impairments of consciousness after diffuse cortical/subcortical injury or focal brainstem injury. Then try different agents in post-acute brain injury phase (minimum 2 wks).

Among monoaminergics, use amantadine before methylphenidate. Start amantadine 100 mg bid. Increase weekly to 200 mg bid if tolerated x4 wks.
   If amantadine helps, consider risks and benefits of continuation.
   If amantadine does not help, stop amantadine and start methylphenidate 0.3 mg/kg bid.
      Increase weekly to 0.6 mg/kg bid if tolerated x4 wks.
      If methylphenidate helps, consider risks and benefits of continuation.
Consider trials of zolpidem 10 mg each week.
   If zolpidem helps, may use up to zolpidem 10 mg tid.

In patients with improvements in arousal, consider fluoxetine 20 mg to supplement rehabilitation (> recovery).
Study individual patients to isolate mechanism of impaired consciousness.

Structural: MRI, DTI

Functional: FDG-PET, fMRI, qEEG

Molecular? 123I-Ioflupane PET, PHNO PET for dopamine, 11C-MRB PET for noradrenaline

Based on results, choose and test best agent(s).
Activation: Long-Term Recovery Unit

Referrals by families nationwide for patients with VS/MCS

Admission to Rockefeller University Hospital for prolonged video, EEG, telemetry, oximetry, and pupillometry, as well as periodic PET, MR

Trials of activators for effect
Activation: Zolpidem  (Williams 2013)

3 patients, MCS, 1 TBI, 1 HIE, 1 ICH, known zolpidem response
Activation: Zolpidem (Williams 2013)

Before/after wmv
Conclusions

In vegetative state, a patient is unconscious with the appearance of sleep-wake cycles. In minimally conscious state, a patient displays inconsistent but discernible evidence of consciousness, including stimulus localization, sustained fixation/pursuit, command following, and ineffective communication. In locked in syndrome, a patient has intact consciousness with absent motor function.

Monoaminergic, glutamatergic, and cholinergic pathways stimulate arousal through the ascending reticular activating system, thalamus, and basal forebrain. GABAergic pathways regulate consciousness through corticostriatopallidal feedback to the thalamus.

Activation has the greatest potential to induce consciousness in patients with focal brainstem injury or diffuse brain injury.
Conclusions

Amantadine and methylphenidate have the best evidence for monoaminergic activation.

Fluoxetine may augment rehabilitation after recovery of consciousness.

In select patients, zolpidem may cause a dramatic, transient activation and return to consciousness.

In stuporous or comatose patients 2 wks after acute brain injury, consider trials of activation. Begin with amantadine for 1 mo and if ineffective methylphenidate. Perform trials of zolpidem weekly. Start fluoxetine if arousal is improved.


References


References


