Redux Dementia: Behavioural and Psychological Symptoms in Neurocognitive Disorders

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Learning Objectives

- List the indications for initiating pharmacological treatment for behavioural and psychological symptoms of dementia (BPSD), and know some algorithms for treating BPSD.
- Outline the process for withdrawing pharmacological treatment for behavioural and psychological symptoms of dementia (BPSD), particularly antipsychotics.
- Describe the major side effects of the major psychototropic classes of medications used to treat BPSD, including "black box" warnings.
Disclosure for Dr. Chan

- Relationships with commercial interests: None

- Including:
  - Grants/Research Support
  - Speakers Bureau/Honoraria
  - Consulting Fees
  - Investments or Shares

- There will be discussion of off-label uses of psychotropic medications
Mitigating Potential Bias

- Use of generic names for medications
- Review of various classes of pharmacological agents, and not focusing just a one class
BPSD? NPS? BPSNCD??

- **DSM 5:**
  - “Major Neurocognitive Disorder” = Dementia
  - “Minor Neurocognitive Disorder” = Mild Cognitive Impairment = MCI

- **BPSD = NPS (Neuropsychiatric Symptoms)?**
  - Multiple domains, may be concurrent and overlapping
  - Can occur at any stage of the disease
BPSD: Domains on NPI (Neuropsychiatric Inventory)

- Anxiety
- Dysphoria, Irritability
- Aggression, Agitation
- Psychosis
- Euphoria, Disinhibition
- Apathy
- Aberrant Motor
BPSD Clusters

Apathy
- lack of initiative

Psychosis
- delusion, hallucination

Aggression/Agitation
- verbal, physical

Affective
- dysphoria, elation
- irritability, anxiety

Hyperactivity
- pacing, restlessness, disinhibition
Case #1

- 93 yo man, resides in extended care home. Advanced dementia, urinary incontinence. Generally seems pleasant to engage with some periods of calling out at times in the day. Poor historian. Strikes out during care, requiring multiple staff members to assist. Aggression led to staff injury so transported to hospital to rule out delirium...
Differential Diagnosis

- **Delirium**
  - Acute change, fluctuation. CAM to screen
- **Major Depression**
  - Difficult to diagnose in advanced dementia
- **Pain (Flo et al. Drugs and Aging 2014)**
  - Under-detected
  - Verbal vs. non-verbal cues
**Bowels**: when was the patient’s last bowel movement

**Bladder**: when did they last urinate? Any urinary symptoms?

**Beverage**: are they hungry or thirsty? Have they been offered preferred beverages or food?

**Bottom (to Top)**: Visual survey for obvious precipitants of distress and agitation

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*4 B’s of discomfort in older adults with dementia. Harris, BMJ 2011*
• Stepwise protocol for treatment of pain over 8 weeks in LTC residents with moderate-severe Dementia can:
  ■ Improve agitation
  ■ Improve mood
  ■ Improve apathy
  ■ Improve night-time behaviours
  ■ Improve appetite

But NOT irritability or ADL’s
Husebo’s Stepwise Protocol

Stepwise protocol initiated if pain identified:

1. Acetaminophen
2. Oral morphine (up to 20mg/day)
3. Transdermal buprenorphine
4. Pregabalin

Alternative approach??
<table>
<thead>
<tr>
<th>Sublingual Narcotic</th>
<th>Fentanyl</th>
<th>Sufentanil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equivalent Dose</td>
<td>50-100 mcg</td>
<td>10 mcg</td>
</tr>
<tr>
<td>Dose for incident pain</td>
<td>10-50 mcg sl. Do not swallow for 5 min after a dose</td>
<td>5-25 mcg (max 50 mcg) sl. Do not swallow for 2 min after</td>
</tr>
<tr>
<td>Onset of action</td>
<td>5-15 minutes. Peaks at 20 minutes.</td>
<td>2-3 minutes</td>
</tr>
<tr>
<td>When to administer</td>
<td>10 minutes prior</td>
<td>3-5 minutes prior</td>
</tr>
<tr>
<td>Duration</td>
<td>30-45 minutes</td>
<td>10-25 minutes</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Watch resp rate q 5-10 minutes for 30 minutes</td>
<td>Watch resp rate q 5-10 minutes for 30 minutes</td>
</tr>
</tbody>
</table>
BPSD: Pain

- Sleep
- Dysphoria
- Appetite
- Aggression, Agitation, Anxiety
- Pain
- Apathy

Apathy, Sleep, Appetite, Dysphoria, Pain, Aggression, Agitation, Anxiety
Case #2-part 1

- 78 yo woman from residential intermediate care home, noticed to have acute change in behaviour and mobility over a month. Known history of dementia. Not on psychototropic medications usually, but getting Zopiclone lately. Shares a room. Refusing medications, calling out at times, sleeping poorly at night and so napping a lot in the day. Falling frequently. Maybe visually hallucinating. Now comes to hospital after a fall.
Management of BPSD

- Non-pharmacological
  - Needs Driven Model

- Pharmacological
<table>
<thead>
<tr>
<th>Usually Not Respond to Medications</th>
<th>Can Be Responsive to Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple Wandering</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Inappropriate urination/defecation</td>
<td>Sadness, crying, sleep complaints and other depressive symptoms</td>
</tr>
<tr>
<td>Inappropriate dressing/undressing</td>
<td>Withdrawal and apathy</td>
</tr>
<tr>
<td>Disruptive repetitive activities (perseveration) or vocalizations</td>
<td>Elation, pressured speech and hyperactivity (manic-like)</td>
</tr>
<tr>
<td>Tugging at lapbelts</td>
<td>Persistent and distressing delusions or hallucinations</td>
</tr>
<tr>
<td>Hiding / hoarding</td>
<td>Physical aggression or persistent verbal aggression</td>
</tr>
<tr>
<td></td>
<td>Sexually inappropriate behaviour</td>
</tr>
<tr>
<td></td>
<td>Sleep disturbance</td>
</tr>
</tbody>
</table>
Pharmacotherapy for BPSD

- **Atypical Antipsychotics (AP’s)**
  - Risperidone, Olanzapine, Quetiapine
  - Clozapine, Ziprasidone, Aripiprazole
- **Typical Antipsychotics**
- **Antidepressants**
- **Cholinesterase inhibitors (AchEI’s)**
- **Memantine**
- **Anticonvulsants**
- **Benzodiazepines**
Pharmacotherapy for BPSD

- Atypical Antipsychotics (AP’s)
  - Risperidone, Olanzapine, Quetiapine
  - Clozapine, Ziprasidone, Aripiprazole
- Typical Antipsychotics
- Antidepressants: SSRI’s
- Cholinesterase inhibitors (AchEI’s)
- Memantine
- Anticonvulsants
- Benzodiazepines
Antidepressants for agitation and psychosis in Dementia. Seitz et al. 2013, Cochrane Database; Barak 2011

- 9-10 RCT’s
- Comparator to placebo or antipsychotic
- Citalopram, escitalopram, sertraline, trazadone
- Sig effect over placebo, comparable effect to antipsychotic
SSRI’s Side effects

- Interaction with Warfarin, Digoxin, Statins, β-Blockers and Calcium channel blockers via cytochrome P450 system
- Hyponatremia (SIADH) particularly in the elderly
- Risk of falls, fractures, and osteoporosis
- Risk of GI bleed doubled (Andrade, J. Clin. Psychiatry 2010), esp. with NSAID’s, anticoagulants
- FDA warning (2011): ↑QTc for Citalopram >40mg/d
- Health Canada (2012): For elderly, max dose 20 mg/d Citalopram and 10 mg/d Escitalopram.

Baseline Na level, Na within 4 weeks
Monitor carefully INR’s if on warfarin, etc.
Consider baseline ECG
Pharmacotherapy for BPSD

- Atypical Antipsychotics (AP’s)
  - Risperidone, Olanzapine, Quetiapine
  - Clozapine, Ziprasidone, Aripiprazole
- Typical Antipsychotics
- Antidepressants
- Cholinesterase inhibitors (ChEI’s)
- Memantine
- Anticonvulsants
- Benzodiazepines
BPSD Clusters: AchEI’s, Memantine

Gauthier et al. Int. J. Psychogeriatrics, 2010

NPI

Includes 10 behavioral areas:

1. Delusions - Memantine
2. Hallucinations
3. Agitation/Aggression - Memantine
4. Depression - AchEIs
5. Anxiety - AchEIs
6. Elation/Euphoria
7. Apathy/Indifference - AchEIs
8. Disinhibition
9. Irritability - Memantine
10. Aberrant motor behavior

May also include 2 neurovegetative areas:

11. Sleep and Nighttime Behavior Disorders
12. Appetite and Eating Disorders
Monitoring with ChEI’s and Memantine

- ECG at baseline highly suggested
- Can be safely combined with other psychotropics
- Monitor for unexplained falls, syncope
- Discontinue if bradycardic (memantine, ChEI’s) or significant conduction abnormality (ChEI’s)
Pharmacotherapy for BPSD

- Atypical Antipsychotics (AP’s)
  - Risperidone, Olanzapine, Quetiapine
  - Clozapine, Ziprasidone, Aripiprazole
- Typical Antipsychotics
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- Cholinesterase inhibitors (AchEI’s)
- Memantine
- Anticonvulsants
- Benzodiazepines
Antipsychotics are indicated when:

- there is a *significant risk of harm* to the patient or others or
- when agitation or aggressive symptoms are
  - persistent,
  - recurrent, or
  - severe enough

*to cause significant suffering and distress, or significant interference with care*

Salzman et al 2008; CCMHS 2006; GPAC 2008; Lyketsos et al 2006
Examples of Commonly Used Antipsychotic Dosages for the Elderly

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting Dose (mg)</th>
<th>Dosing Frequency</th>
<th>Incremental Dose (mg)</th>
<th>Average Total Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>quetiapine</td>
<td>12.5</td>
<td>bid/tid/hs (if XR)</td>
<td>12.5-25</td>
<td>150</td>
</tr>
<tr>
<td>risperidone</td>
<td>0.25</td>
<td>od/bid</td>
<td>0.25</td>
<td>1</td>
</tr>
<tr>
<td>olanzapine</td>
<td>1.25</td>
<td>od (hs)/bid</td>
<td>1.2-2.5</td>
<td>5</td>
</tr>
<tr>
<td>loxapine</td>
<td>2.5</td>
<td>bid/tid</td>
<td>2.5-5</td>
<td>25</td>
</tr>
<tr>
<td>haloperidol</td>
<td>0.25</td>
<td>od/bid</td>
<td>0.25-0.5</td>
<td>2</td>
</tr>
<tr>
<td>aripiprazole</td>
<td>0.5</td>
<td>od</td>
<td>0.5-1</td>
<td>2-10</td>
</tr>
</tbody>
</table>

Avoid Risperidone, Olanzapine and Loxapine in Lewy Body Dementia (LBD) or Parkinson's Disease Dementia (PDD). Haloperidol contraindicated.
Canadian Coalition for Senior’s Mental Health (www.ccsmh.ca)

CPG’s published in 2006, update 2014

“Assessment and Treatment of Mental Health Issues in Long-Term Care Homes”
Antipsychotics for BPSD

- We recommend that risperidone, olanzapine and aripiprazole be used for severe agitation, aggression and psychosis associated with dementia where there is risk of harm to the patient and/or others. The potential benefit of all antipsychotics must be weighed against the significant risks, such as cerebrovascular adverse events and mortality. (Grade 2A)

- There is insufficient evidence to recommend for or against the use of quetiapine in the management of severe agitation, aggression and psychosis associated with dementia. (Grade 2B)
Atypical Antipsychotics: Mortality Risk (Black Box Warning)

- Mortality risk
  - Odds Ratio = 1.7 times
    (FDA April 2005)
    - 17 studies: 5106 pts, 4.5% vs 2.6% placebo
  - Odds Ratio = 1.54 times
    (Schneider JAMA 2005;294:15)
    - 15 studies: 3353 pts, 3.5% vs 2.3% placebo
“15 randomised placebo-controlled trials of atypical antipsychotics provides robust evidence for an increased risk of CVAEs, with a pooled relative risk of 2.57 (95% CI 1.41-4.66)”

Base rate is less than 5%
After initial management with Loxapine 15 mg/d and supplemented with Methotrimeprazine, she develops a gait disturbance and begins to lean to the right when upright.
Risks for EPS in Elderly on Antipsychotic Treatment

- Aging (pharmacodynamic drop off of D$_2$ receptors)
- Pharmacokinetic: slow metabolizers; aging
- Underlying Neurocognitive Condition
  - Lewy Body Dementia
  - Parkinson’s Disease with or w/o Dementia
  - Parkinson’s plus syndromes
  - Vascular Parkinsonism
  - Advanced AD
  - Wilson’s Disease
  - Creutzfeld-Jacob Disease, HIV encephalopathy
- Non-antipsychotic Medications
  - SSRI’s, Lithium
  - Metoclopramide (Maxeran)
Atypical AP’s and side effects

- **Risperidone, Olanzapine**
  - EPS, Gait disturbance
  - Infection risk (UTI, URTI)
  - Peripheral edema, orthostasis (Risp)
  - Metabolic syndrome, wt gain uncommon

- **Quetiapine**
  - Orthostasis, sedation
  - Prolong QTc
  - Agitation, insomnia (norquetiapine)

- **Aripiprazole**
  - Insomnia, akathisia-like
Weighing Risk vs. Benefits of Atypicals

- NNT for benefit: 5 - 14 patients
- NNH for mortality: 100 patients
- 1 patient death for every 9 – 25 who benefit
Pharmacotherapy for BPSD

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Anticonvulsants

- Anticonvulsants also have evidence for use in BPSD. However, studies of valproic acid, carbamazepine, oxcarbazepine and gabapentin have been shown conflicting results.

- Valproic acid is not usually recommended at this time due to negative trials and toxicity in elderly.

- Gabapentin dosing reduced in those with renal impairment. Pregabalin?
Benzodiazepines

- not typically recommended in the elderly as they increase risk of falls, fractures and confusion

- For individuals who are bed-bound and resistive to nursing care, fast acting benzodiazepines, such as lorazepam

- Short-term use may sometimes be warranted, but long-half life benzodiazepines should be avoided (eg: diazepam)
Best Practice Guideline for Accommodating and Managing Behavioural and Psychological Symptoms of Dementia in Residential Care

A Person-Centered Interdisciplinary Approach

October 25, 2012
BPSD tools

- BC BPSD Project (www.bcbpsd.ca)
  - Interdisciplinary group including Drs. Elisabeth Drance and Carol Ward
  - Part 1: Interdisciplinary Decisional Support for BPSD
  - Part 2: Reassessment with Family Physician or Nurse Practitioner for BPSD
BPSD: Apathy

Need to treat?

Bupropion, Modafinil

ChEI’s, (Memantine)

Other: Psychostimulants, DA agonists, Pain meds

Apathy
Affective Anticonvulsants, esp. Gabapentin
SSRI Antidepressant or Trazodone or Quetiapine
Anticonvulsants, esp. Gabapentin
ChEI’s?? Memantine?
Other: Benzo’s?? pramipexole? Methotrimeprazine? Cannabinoid?
BPSD: Affective (Dysphoria, Irritability, Anxiety)
BPSD: Psychosis

Psychosis

Antidepressant

Need to treat?

Antipsychotic

Other: Cognitive enhancer?
BPSD: Physical Aggression

- Antipsychotic
- SSRI Antidepressant
- Memantine
- Other: Prazosin, Anticonvulsant, Trazodone, Pain Meds, Sufentanyl (care), nabilone?
Take Home Points

- Consider stepwise approach to pain, if at all suspected, especially in advanced dementia
- SSRI’s are possible alternatives to antipsychotics but have risks also
- Antipsychotics used for aggression and psychosis, but consent should be obtained by a substitute decision-maker
- Cognitive enhancers can be safely combined with other psychotropics
Web Resources

 BLL BPSD tools: www.bpsdbc.ca
 BLL BC Psychogeriatric Association. VCHA Algorithm for withdrawing antipsychotics
 BLL http://www.bcpga.bc.ca/2013/Atypical_Antipsychotics_Agents.pdf

www.bcmj.org