Teaching Course 14

Neuropsychiatric and behavioural symptoms in neurodegenerative diseases - Level 1

Management of neuropsychiatric symptoms in Alzheimer’s disease and vascular dementia

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Neuropsychiatric symptoms in AD and VaD

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Disclosure

Pasquale Calabrese has received honoraria for speaking at scientific meetings, serving at scientific advisory boards and consulting activities from Actelion, Bayer-Schering, Biogen Idec, EISAI, Lundbeck, Merck Serono, Novartis, Teva, and Sanofi-Aventis, the Swiss Multiple Sclerosis Society, and the Swiss National Research Foundation.
Beheavoural and Psychological Symptoms of Dementia (BPSD)

- Heterogeneous range of psychiatric symptoms, psychological reactions and behaviours occurring in people with dementia of any etiology.
- Any verbal, vocal, or motor activity not being related to the needs of the individual or the requirements of the situation.
- Almost 95% of people with dementia develop BPS during the course of the disease; the prevalence increases with disease severity.

Frequency of BPSD before and after diagnosis

(Jost & Grossberg, 1996)
Epidemiology of BPSD

Dementia prevalence:
† 60% of community-dwelling elders
† >80% of nursing home residents

BPSD prevalence:
† 90% of people with dementia develop a neuropsychiatric or behavioral symptom during the course of the disease
† Prevalence increases with disease severity

Peak Frequency of Behaviors in AD as Disease Progresses
(Jost & Grossberg, 1996)

Frequency of BPSD before and after diagnosis
mood
cognition
ADL
behaviour
mobility
worsening
mild moderate severe

Gauthier, 1998

The Spectrum of neuropsychiatric disturbances in dementia “positive” and “negative Symptoms”

Depression/Dysphoria
psychosis, delusions, hallucinations
euphoria, disinhibition, mania, screaming, crying

motor disturbances and night-time behaviors and stereotyped behaviors
sleep disturbances

Irritability/lability
social withdrawal
reduction of drive/apathy

irritability, aggression
Factors affecting BPSD

**Clinical Condition**
- Acute infection (e.g. UTI, pneumonia)
- Dehydration
- Pain
- Hypoxia
- Constipation

**Drug Induced**
- Anticholinergics
- Benzodiazepines

**Psychological**
- Loneliness
- Frustration
- Inability to communicate
- Unfamiliarity with setting/people

**Environmental**
- Positional discomfort
- Disrupted routines
- Inappropriate light
- Sensory deficits
- Noise

When is a Behavior Not a Problem?

If the behavior doesn’t harm the person with the disease or others.

If the behavior is manageable and occurs only once or over a short period of time.

If the behavior can be easily redirected or stops with appropriate intervention.

If the behavior does not contribute to distress/suffering for the individual with the disease.
Factors affecting BPSD

Assessment of BPSD
- Assess whether symptoms arise from a) unmet needs, b) medical conditions or c) environmental problems:
  - a) acute onset may indicate a medical condition (pain, infection, medication, dehydration...)
  - b) unmet needs (hunger, thirst, mobility, relief of pain...)
  - c) environmental problems (light levels, roommate, over-/understimulation...)

The most consistent finding from the studies comparing vascular dementia (VaD) with AD is:
- a higher prevalence and severity of depression
- anxiety,
- similar rates of psychotic symptoms,
- and less severe aberrant motor behavior among subjects with VaD,
- Although a substantial overlap can exist between the two dementia syndromes.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrahm-Pizzuti et al. (2000)</td>
<td>30 AD + 30 VaD</td>
<td>Aggression, depression, anxiety and apathy significantly more severe in VaD than in AD.</td>
</tr>
<tr>
<td>Ballard et al. (2000)</td>
<td>92 AD + 92 VaD</td>
<td>Depression and anxiety more common in VaD than in AD. Psychotic symptoms similarly common in VaD and in AD.</td>
</tr>
<tr>
<td>Chiu et al. (2008)</td>
<td>85 AD + 32 VaD</td>
<td>VaD with higher incidence of paranoid and delusional ideation and affective disturbance.</td>
</tr>
<tr>
<td>Fernandez Martinez et al. (2008a)</td>
<td>37 AD + 28 VaD</td>
<td>Sleep disturbances and appetite changes more prevalent in AD than in VaD. Aberrant motor activity more common in subcortical VaD.</td>
</tr>
<tr>
<td>Fernandez Martinez et al. (2008b)</td>
<td>81 AD + 14 VaD</td>
<td>Similar prevalence of BPSD in AD and VaD.</td>
</tr>
<tr>
<td>Fu et al. (2008)</td>
<td>329 AD + 212 VaD</td>
<td>Similar prevalence in AD, cortical VaD, subcortical VaD, and mixed VaD. More severe sleep disturbance in cortical VaD than in AD.</td>
</tr>
<tr>
<td>Hoss et al. (2009)</td>
<td>77 AD + 77 VaD</td>
<td>Higher prevalence of nighttime behavior (sleep disturbance) in AD, higher prevalence of depression in VaD. Similar prevalence of delusions, hallucinations, and agitation in AD and VaD.</td>
</tr>
<tr>
<td>Ikeda et al. (2004)</td>
<td>21 AD + 28 VaD</td>
<td>Delusions and aberrant motor behavior more likely in AD.</td>
</tr>
<tr>
<td>Kim et al. (2003)</td>
<td>99 AD + 26 VaD</td>
<td>Depression and anxiety significantly more severe in VaD than in AD.</td>
</tr>
<tr>
<td>Lyketsos et al. (2000)</td>
<td>214 AD + 62 VaD</td>
<td>Delusions more likely in AD and depression more frequent in VaD.</td>
</tr>
<tr>
<td>Lyketsos et al. (2002)</td>
<td>258 AD + 104 non-AD</td>
<td>Similar prevalence in AD and non-AD dementia, except for more frequent aberrant motor behavior in AD.</td>
</tr>
<tr>
<td>Singh et al. (2005)</td>
<td>44 AD + 31 VaD</td>
<td>Similar symptom profile in AD and in VaD.</td>
</tr>
<tr>
<td>Thompson et al. (2010)</td>
<td>371 AD + 14 VaD</td>
<td>No significant difference in AD and VaD patients on the BPCL or on the RMBPCL.</td>
</tr>
</tbody>
</table>
Assessment of BPSD

- Assess whether symptoms arise from a) unmet needs, b) medical conditions or c) environmental problems:
  
  - a) acute onset may indicate a medical condition (pain, infection, medication, dehydration...)
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**Anxiety**

Psychosis
Anxiety can emerge when paranoia or other hallucinatory/delusional thoughts are present.

Realistic fears
Anxiety can emerge if caregivers are abusive or if they are living in an area that prevents the individual from living in a safe environment.

Depression
Is one of the most common reasons for anxiety in individuals with Alzheimer's disease.

The person's ability does not match others' expectations of them
When individuals are required to process/perform/manage tasks beyond what they are able to do, anxiety often emerges. This may happen when individuals are required to do things they are not able to do.

Boredom

Medication side effects

Incorporate simple relaxation exercises, such as deep breathing, hand massage, or perhaps soothing aroma/music activities.

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**Depression**

Most common symptom in this population is ANXIETY, including excessive worry, rumination. Other symptoms might include sleep disturbance, changes in appetite, irritability, physical or verbal aggression, withdrawal, loss of interest in previously enjoyed activities, self-deprecating comments, expressing wishes of wanting to die, suicidal threats or gestures. A significant percentage of those individuals presenting with combative behavior are primarily depressed.

Consider antidepressant or attention in dosage of existing antidepressant. Watch for trends in symptom relief and adjust dosage accordingly.

Structured activity that is pleasant and meaningful
Often historical ways they spent their time are less available. New activities should be added. That may include having visitors for tea, addition of new hobbies such as watercolor painting, or may include participation in an adult day program.

Reduction of environmental stressors such as exposure to family conflict, high arousal, negative interactions and communication.

Engage in therapeutic conversation:

- Listen to feelings embedded in their words and conversations
- Affirm that their current challenges are not the fault of themselves, that they have made

Ensure there is no access to weapons, not only to prevent self-injury, but also to prevent risk to others if agitation, hostility and/or if paranoia is part of the manifested depressive symptoms.

May require geriatric psychiatric hospitalization, if combative and possibly self-damaging, or to others if symptoms interfere in care and provide refusal of medications.
non-pharmacological approaches

- sensory
  - light therapy
  - massage
  - Snoezelen
  - evening Spa
- environmental
  - environmental adjustment
- cognitive
  - music-therapy
  - R-O-T validation
  - caregiver education
  - caregiver training

Medication Side Effects
Recent falls, sudden increase in confusion, increased anxiety, increased agitation, excessive sleep/seems sedated, increased unsteadiness on their feet, a change in their level of function, decreased sleep.

- Dosage consistent through changes in body weight?
- Recent increased dose or change in timing of dose administration?
- Use of PRN medication?
- Multiple doctors?
- Large number of medications?
- Possibility of self medication or inappropriate dosing?
- New medication?
- Alcohol or street drug use or withdrawal?

Over-the-counter meds including vitamins, herbs, natural, sleep aids.
Medication

Antidementia drugs

- cholinesterase inhibitors:
  - donepezil (Aricept)
  - rivastigmine (Exelon)
  - galantamine (Reminyl)

- Memantine (Ebixa, Axura [in some countries])
Risperidone is the only licensed drug for the treatment of BPSD (aggression).

Antidementia drugs are licensed for treatment of cognition not behaviour in restricted severity groups:
- Cholinesterase inhibitors for mild to moderate AD
- Rivastigmine for mild to moderate Parkinson’s Disease Dementia
- Memantine for moderate to severe AD

BPSD: other Medication

- Antidepressants
- Anxiolytics
- Hypnotics
- Antipsychotics
- Anticonvulsants
BPSD: Cholinesterase-Inhibitors (ChEI)

- Systematic review & meta-analysis
- Statistically significant vs placebo
- Modest clinical benefit
- Biggest response on apathy, hallucinations,

BPSD: Memantine

- Several RCTs vs placebo
  (eg Reisberg, et al; Tariot et al; Van Dyck et al; Gauthier et al)
- Small effect on aggression and agitation
Depression in dementia: Cochrane review

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Dose</th>
<th>Study</th>
<th>N</th>
<th>Duration</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertraline</td>
<td>25-150mg</td>
<td>Lyketos et al 2003</td>
<td>44</td>
<td>12 wks</td>
<td>positive</td>
</tr>
<tr>
<td></td>
<td>25-100mg</td>
<td>Petracca et al 1996</td>
<td>21</td>
<td>6 wks</td>
<td>positive</td>
</tr>
<tr>
<td>Imipramine</td>
<td>50 -150mg</td>
<td>Reifler et al 1989</td>
<td>61</td>
<td>8 wks</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

- Study of Antidepressants in Dementia
  (Banerjee et al Lancet 2011)

- Mirtazapine & sertraline vs placebo
- No significant benefits against placebo

Depression in dementia: SADD-study

- Trend reduced irritability & apathy
- Reduced hallucinations
CATIE-AD study Citalopram effects on BPSD  
(Siddique et al 2009)

- Trend reduced irritability & apathy
- Reduced hallucinations

Antidepressants in dementia: Conclusion

- Modest evidence efficacy
- May benefit agitation
Antipsychotics in dementia: RCT evidence

- Haloperidol
- Risperidone
- Quetiapine
- Olanzapine
- Aripiprazole

CATIE-AD Trial

- First cost-benefit analysis of second generation antipsychotics in treating non-cognitive symptoms in AD patients
- N = 421 AD patients with psychosis and aggression where randomly assigned to olanzapine, quetiapine, risperidone, or placebo of “watchful waiting” over 9 months in 42 sites
- No statistical differences between groups, although placebo most often superior in net health benefit analysis
- Olanzapine group – more impaired on ADL testing (sedation, gait disturbance)
- Placebo group – best ADL score, lower dependence score, lower total health care costs
- Several methodological drawbacks:
  - Subjects were outpatients, less impaired then in other BPSD trials
  - High dropout rate compared to other RCTs (likely a design feature)
  - No washout period
  - Dosage likely too low for quetiapine (mean 56.5mg/day)
- Authors concluded adverse events offset advantages in efficacy

Antipsychotics in dementia: meta-analysis evidence

- Medium effect size
- Benefit for severe aggression, delusions

Antipsychotics in dementia

- 2-3 x increased risk cerebrovascular adverse events
- 1-2% increased risk death

Defensible prescribing of antipsychotics in Dementia

- Consider non-pharmacological alternatives first
- Address vascular risk factors
- Assess consent / capacity / best interests
- Discuss risks & benefits with patients or caregivers
- Identify target symptoms (psychosis, hostility, aggression)
- Choose effective drug & dosage
- Choose time-frame during which to assess benefits (discontinue if no evidence of benefit or if harm)
- Review need & aim to withdraw periodically
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Antipsychotics in dementia

<table>
<thead>
<tr>
<th></th>
<th>start</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>0.25mg</td>
<td>0.5 to 2mg/day</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.50mg</td>
<td>2.5-10mg /day</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>25.0mg</td>
<td>25-100mg</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>2.0mg</td>
<td>5-10mg</td>
</tr>
</tbody>
</table>
### Anticonvulsants in dementia

- Review of RCTs
- Weak to modest evidence for carbamazepine; further trials needed
- Poor evidence / negative for valproate
- Mostly no significant difference
- Adverse events more frequent in treatment groups

### Benzodiazepines in dementia

- RCTs: BZD reduce agitation
- Adverse effects: falls, sedation, worsen cognition
Using medication in BPSD

- Pharmacotherapy can be effective for BPSD
- First step: identify target symptoms
- Correct reversible factors
- Try environmental & psychological approaches first unless high risk of harm to self / others
- Use medication carefully, “start low go slow”
- Review treatment