Behavioral Management of Persons with Alzheimer’s Disease

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Disclosures

Wisconsin Association of Medical Directors
Objectives

1. Develop a plan to assess the behavioral and psychological symptoms of dementia (BPSD), including medical and psychosocial contributions.

2. Describe the psychopharmacological options that may be useful for patients with BPSD.

3. Develop an approach to the management of each of their patients with BPSD that includes psychosocial interventions as primary and psychotropic medications as secondary.
Natural history of BPSD

Cumulative prevalence of specific BPSD

Assessment of BPSD

• patients should be assessed:
  • for the type, frequency, severity, pattern, and timing of symptoms
  • for pain and other potentially modifiable contributors to symptoms as well as for factors, such as the subtype of dementia, that may influence choices of treatment

The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia (2016)
The DICE approach

Describe: caregiver describes problematic behavior: context, environment, patient perspective, degree of distress

Investigate: provider investigates possible causes: meds, pain, medical conditions, psychiatric comorbidity, sleep, sensory changes, loss of control, boredom

Create: caregiver and team collaborate to create and implement treatment plan: respond to physical problems, strategize behavioral interventions

Evaluate: provider evaluates whether interventions have been implemented, and have been safe and effective

Kales et al  JAGS 2014; DOI:10.1111/jgs.12730
Psychosocial interventions

- activities
  - e.g., introduce activities that tap into preserved capabilities and previous interests
- caregiver education and support
- communication
  - e.g., use simple verbal commands, use a calm & reassuring tone
- simplify environment
- simplify tasks
  - e.g., provide structured daily routines

Pharmacological options for agitation & psychosis

• in general, limited benefits with significant potential for side effects
• best evidence base for atypical antipsychotics, esp. risperidone, olanzapine & aripiprazole
• modest evidence for antidepressants
• weakest evidence for anticonvulsants, benzodiazepines, cognitive enhancers, dextromethorphan & prazosin
• all choices are off-label usages
Benefits & risks of antipsychotics

1. Nonemergency antipsychotic medication should only be used for the treatment of agitation or psychosis in patients with dementia when symptoms are severe, are dangerous, and/or cause significant distress to the patient (emphasis added)

2. Review the clinical response to nonpharmacological interventions prior to nonemergency use of an antipsychotic medication

3. Before treatment, the potential risks and benefits from antipsychotic medication should be assessed by the clinician and discussed with the patient, surrogate decision maker, or other family member

*The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia* (2016)
Antipsychotics

atypical antipsychotics
risperidone
olanzapine
aripiprazole
quetiapine
clozapine

typical antipsychotics
haloperidol
Atypical antipsychotics: efficacy

- best evidence for risperidone, olanzapine and aripiprazole (agitation) and risperidone (psychosis)
- overall, small effect on behavioral symptoms:
  - pooled effect size = 0.16
  - NNT = 6 (range 5-14)
  - significant placebo effects (30-50% response rates)
- response usually in first 2-4 weeks
- three head-to-head trials compared atypicals – none was found superior
- no studies of: ziprasidone, lurasidone, asenapine, brexipiprazole

AHRQ Comparative Effective Review 43, 2011;
## Comparative effectiveness review

<table>
<thead>
<tr>
<th>Effect in dementia</th>
<th>aripiprazole</th>
<th>olanzapine</th>
<th>quetiapine</th>
<th>risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>overall</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>psychosis</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>agitation</td>
<td>+</td>
<td>++</td>
<td>+/-</td>
<td>++</td>
</tr>
</tbody>
</table>

++ moderate or high evidence of efficacy  
+ low or very low evidence of efficacy  
+/- mixed results

**Note:** no trials of ziprasidone or newest antipsychotics
## Antipsychotics: the data that led to the FDA Black Box warning

<table>
<thead>
<tr>
<th></th>
<th>trials</th>
<th>deaths Rx</th>
<th>deaths placebo</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>risperidone</td>
<td>5 1954</td>
<td>3.8%</td>
<td>2.8%</td>
<td>1.30 (0.76-2.23)</td>
</tr>
<tr>
<td>olanzapine</td>
<td>5 1662</td>
<td>2.6%</td>
<td>1.3%</td>
<td>1.91 (0.79-4.59)</td>
</tr>
<tr>
<td>quetiapine</td>
<td>3 637</td>
<td>5.4%</td>
<td>2.8%</td>
<td>1.67 (0.70-4.03)</td>
</tr>
<tr>
<td>aripiprazole</td>
<td>3 951</td>
<td>3.5%</td>
<td>1.7%</td>
<td>1.73 (0.70-4.30)</td>
</tr>
<tr>
<td>overall</td>
<td>16 5204</td>
<td>3.5%</td>
<td>2.2%</td>
<td>1.54 (1.06-2.23)</td>
</tr>
</tbody>
</table>

NNH=100 (95% CI = 53-1000)

Schneider et al *JAMA* 2005; 294: 1934-43
The latest on mortality

<table>
<thead>
<tr>
<th>medication</th>
<th>case-control pairs (N)</th>
<th>deaths (vs nonusers)</th>
<th>risk difference</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>haloperidol</td>
<td>1921</td>
<td>20.7% (vs 8.4%)</td>
<td>3.8%</td>
<td>26</td>
</tr>
<tr>
<td>risperidone</td>
<td>6338</td>
<td>13.9% (vs 8.5%)</td>
<td>3.7%</td>
<td>27</td>
</tr>
<tr>
<td>olanzapine</td>
<td>1908</td>
<td>13.9% (vs 9.8%)</td>
<td>2.5%</td>
<td>40</td>
</tr>
<tr>
<td>quetiapine</td>
<td>4621</td>
<td>11.8% (vs 8.2%)</td>
<td>2.0%</td>
<td>50</td>
</tr>
<tr>
<td>antidepressant</td>
<td>29,704</td>
<td>8.3% (vs 8.0%)</td>
<td>0.6%</td>
<td>166</td>
</tr>
</tbody>
</table>

Survival after antipsychotic discontinuation

Cochrane review of antipsychotic withdrawal

• review of 9 RCTs of antipsychotic discontinuation (N=606)
• overall, no difference in outcomes (BPSD, remaining off antipsychotic) in discontinuation versus continuation
• subjects with more severe baseline risk may be at higher risk of recurrence of symptoms

Declercq et al, Cochrane Database Syst Rev 2013
Dosing, duration & monitoring (1)

1. Treatment should be initiated at a low dose and titrated up to the minimum effective dose as tolerated.

2. If the patient experiences a clinically significant side effect, the potential risks and benefits of the antipsychotic should be reviewed by the clinician to determine if tapering and discontinuing is indicated.

3. If there is no clinically significant response after a 4-week trial of an adequate dose of an antipsychotic drug, the medication should be tapered and withdrawn.
Dosing, duration & monitoring (2)

4. In a patient who has shown a positive response to treatment, decision making about possible tapering of antipsychotic medication should be accompanied by a discussion with the patient, surrogate decision maker, or other family member.

5. An attempt to taper and withdraw the drug should be made within 4 months of initiation, unless the patient experienced a recurrence of symptoms with prior attempts at tapering of antipsychotic medication.

6. In patients with dementia whose antipsychotic medication is being tapered, assessment of symptoms should occur at least monthly during the taper and for at least 4 months after medication discontinuation to identify signs of recurrence and trigger a reassessment of the benefits and risks of antipsychotic treatment.

The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia (2016)
## Summary of antipsychotics

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Evidence</th>
<th>Start Dose</th>
<th>Max Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>0.25 bid</td>
<td>0.5-1 bid</td>
<td>Highest risk of EPS</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>++</td>
<td>2.5 qhs</td>
<td>10 qhs</td>
<td>Highest risk of metabolic s/e</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>-</td>
<td>12.5 bid</td>
<td>200 mg/d</td>
<td>1st choice for LBD</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>++</td>
<td>2.5 qhs</td>
<td>10 qhs</td>
<td>Now has largest N</td>
</tr>
<tr>
<td>Clozapine</td>
<td>+</td>
<td>6.25 qhs</td>
<td>50 qhs</td>
<td>Used in LBD only</td>
</tr>
</tbody>
</table>
Antidepressants

- Cochrane review of antidepressants for agitation & psychosis:
  - 9 studies, N=692
  - very modest evidence for sertraline & citalopram
  - antidepressants better tolerated than antipsychotics
- largest RCT of sertraline versus mirtazapine versus placebo (N=326) did not find efficacy for depression
- citalopram 10-30 mg/d effective (CitAD study); response may take 9 weeks
- others: trazodone (+), venlafaxine (-), fluoxetine (-)
- safety concerns: hyponatremia, falls, QT prolongation (citalopram)

Anticonvulsants

- valproate/divalproex
  - Cochrane review: low doses ineffective, higher doses not tolerated
  - multiple negative RCTs
  - evidence of increased atrophy & cognitive decline
- carbamazepine/oxcarbazepine
  - mixed results, with most recent OXC study negative
  - high risk of drug-drug interactions and side effects
- topiramate – as effective as RIS in one small study

Cholinesterase inhibitors

- meta-analysis of 14 studies: only 3 demonstrated benefit, which was modest (effect size ~ 0.1)
  - most studies included BPSD as secondary outcome measures
  - baseline BPSD were not high in most studies
- bottom line: cognitive enhancers may be use to address cognition (and perhaps caregiver burden), but probably not useful for BPSD

Rodda et al, Intl Psychogeriatrics 2009
Memantine

- multiple prospective studies have failed to find evidence of benefit from memantine on BPSD:
  - Fox et al (2012): memantine vs placebo in moderate-to-severe AD (N=149)
  - Hermann et al (2013): memantine vs placebo in moderate-to-severe AD (N=369)
  - MAIN-AD (2015): continue antipsychotic vs switch to memantine – no difference in outcomes (N=199)

Other options

• analgesics
  • N=352 nursing home subjects with AD
  • stepped pain control: APAP (up to 3 gm/d), morphine CR (up to 20 mg/d), bup patch (pts with swallowing difficulties), pregabalin (up to 300 mg/d) x 8 weeks
  • improved in CMAI, esp. verbal agitation, pacing, restlessness

• dextromethorphan-quinidine
  • N=220 subjects with AD and clinically significant agitation
  • dosing: 20/10 qd -> 20/10 bid -> 30/10 bid
  • improvement in NPI, higher rates of falls, diarrhea and UTIs with DXM

• prazosin
  • N=22 subjects with AD and aggression or agitation
  • starting at 1 mg/d, up to 6 mg/d
  • improvement in NPI, no difference in adverse effects or BP

Other types of dementia

- Lewy body disease:
  - clozapine, quetiapine, olanzapine
  - pimavanserin
- frontotemporal dementia:
  - trazodone
Conclusion: a multifaceted approach

- identify & address contributing factors:
  - pain, nutrition, hearing & vision loss, constipation, falls, medications, UTI, electrolyte disturbance
- address caregiver burden & safety issues
- start with behavioral interventions
- judiciously use medications:
  - if safety issues or if other interventions ineffective
  - SSRI or antipsychotic
  - consider cognitive enhancer (but not necessarily for BPSD)
- monitor, regularly reassess & consider discontinuation
Thank you

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