Pharmacological treatment of neuropsychiatric symptoms of dementia
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Study Type: Review article from a systematic review

Purpose: Neuropsychiatric symptoms are common in dementia (agitation, aggressive behavior, delusions, hallucinations, wandering, etc). These symptoms increase hospital stay and often leads to nursing home placement. The goal of this study sheet is to provide the practitioner with an evidence assessment of the pharmacologic treatment of these symptoms of dementia.

Trial Design: articles were identified through Medline and Cochrane, 1966-2004

Study Duration: trials generally ranged from 17 days to 16 weeks

Inclusion: double-blinded, placebo-controlled, randomized control trials, meta-analysis, neuropsychiatric symptoms were reported

Exclusion: trials reporting only depression, only used articles that included patients from the USA, tacrine articles, post-hoc analysis trials.

1. Are the results valid?
   - Does the overview address a focused clinical question? Yes, but a broad look at many treatments
   - Were the criteria for article inclusion appropriate? Yes
   - Is it unlikely that important studies were missed? Yes
   - Was the validity of included studies appraised? Yes
   - Were results similar from study to study? No, varying results within class

2. What were the results?
   - 187 articles identified, 78 were reviewed, 25 RCT’s and 4 MA met inclusion criteria

Typical Antipsychotics
   - MA concluded that 18 of 100 patients benefit for neuropsychiatric symptoms of dementia
   - Haloperidol versus placebo – aggressive symptoms, behavioral symptoms improve, but not agitation
   - Extrapyramidal symptoms and somnolence were twice as likely with haloperidol
   - Perphenazine was not found to be effective.

Atypical Antipsychotics
   - 4 of 6 RCT’s report benefit for neuropsychiatric symptoms of dementia
   - olanzapine at doses of 5mg and 10 mg reported improvement in scores (NPI), but NOT 15 mg
   - another olanzapine trial showed no benefit at any dose
   - injectable olanzapine showed improvement at 2 hours for neuropsychiatric symptoms of dementia
   - Risperidone improves neuropsychiatric symptoms of dementia over placebo (NNT=8 for 1 mg dose and NNT=6 for the 2 mg dose). There was no difference between the 1 mg and 2 mg dose.
   - Another risperidone study showed no benefit.
   - No data on other atypical agents
   - No difference between haloperidol and risperidone for primary outcome.

Antidepressants
   - Of 5 RCT’s with sertraline, fluoxetine, citalopram and trazadone, only citalopram showed any benefit. In this trial only agitation and labiality were found to be different versus placebo

Mood Stabilizers
   - Valproate – 2 studies – neither study show effectiveness for neuropsychiatric symptoms of dementia. Sedation is the most common side effect.
   - Carbamazepine – 2 very small studies and no conclusions can be confirmed.
   - Lithium – no data

Cholinesterase inhibitors
   - 5 of 8 studies show benefit, 2 being meta-analysis
   - 2 RCT’s with galantamine – one showing benefit and the other not
   - 4 trials with donepezil – one showing better outcomes in agitation/aggression, NNT = 6
   - one trial of 4 years showed no treatment difference in NPI scores
3. **Will the results help me**
   - **Issues to consider:** There are 24 neuropsychiatric symptom scales. What is the standard? How do we define clinically significant improvement in neuropsychiatric symptoms of dementia. How do you interpret multiple outcomes from multiple scales with varying results. We must consider the risk of strokes and TIA’s when using the atypical agents (risperidone ARI 2.2%, NNH 45, pooled analysis; olanzapine ARI 0.9%, NNH 111, pooled analysis). Studies need to distinguish between dementia like Lewy body dementia, which does not respond to atypical antipsychotics and could actually harm the patient.

**What to do?** This reports recommends proper assessment looking for environmental causes first, then nonpharmacologic treatment (i.e., music therapy, aromatherapy, pet therapy, Caregiver education) and then pharmacologic management. The authors recommend the following pharmacotherapy plan:

- Use antidepressants (SSRI) if there is anxiety, but benzodiazepines should be avoided.
- Try cholinesterase inhibitors if the patient is not on one
- Antipsychotics, especially risperidone or olanzapine if patient has psychotic symptoms.
- Use combination treatment.
- The evidence for any treatment is poor and lacking and the authors recommend non-industry funded trials.

**Conclusion:** Doses of 5 to 10 mg of olanzapine and 1 mg of Risperidone appear modestly effective for the treatment of neuropsychiatric symptoms of dementia. The incidence of EP side effects are highest with haloperidol, but somnolence is a concern with all agents. SSRI’s do not appear to be very effective for neuropsychiatric symptoms of dementia, but does help for depression associated with this problem. The studies thus far do not support the use of valproate or carbamazepine. The trials for cholinesterase inhibitors have shown statistical significance, but the effect is small and of questionable clinical significance.