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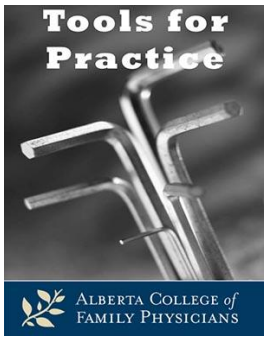

Agitation in Dementia: Quantifying the effects of antipsychotics

Clinical Question: What are the benefits and harms of antipsychotics for agitation in dementia?

Bottom Line: A strong placebo effect explains most of the perceived efficacy, with antipsychotics providing little additional improvement over placebo on agitation scales (~3 additional points out of 144). However, 50% improvement in behaviour occurs in ~46% on antipsychotic versus ~33% on placebo. Harms are serious (increased death or cerebrovascular events for 1 in ~80, for each over placebo) and common (somnolence or gait troubles 1 in ~10 or 20, for each). Antipsychotics should be reserved for cases of severe aggression and withdrawal attempted as soon as possible.

Evidence:
Six systematic reviews [5-16 Randomized Controlled Trials (RCTs), 856-5,110 patients], most followed ~10-12 weeks.[1-6] Statistically significant unless indicated:

- Placebo has large effects.[7] Example:
  - Improves 11-points on 144-point neuropsychiatric scale, a clinically meaningful difference.
- Atypical antipsychotics:
  - Mean improvement over placebo on multiple scales trivial at best:[1-3]
    - Example 3-points on 144-point neuropsychiatric scale, unlikely clinically meaningful.
  - Individual antipsychotics (risperidone,[2] olanzapine,[2] quetiapine[5]) found similar.
    - Exception was improvement on the global change scale of 0.32 points on 7-point scale, likely clinically detectable.
  - Proportion of patients attaining 50% improvement in scales.[4]
    - Example: Risperidone 46% versus 33%, Number Needed to Treat (NNT)=8.
- Atypical antipsychotic harms:
  - Stopping due to adverse events:[2] Number Needed to Harm (NNH)=13-39.
  - Serious harms: Death (NNH=77-84),[1,4] cerebrovascular events (NNH=48-104).[1,2,4]
  - Mini-Mental Status Exam 0.73 worse (not significant).[4]

- Other:[1,2,4] Somnolence (NNH=7-11), gait abnormalities (NNH=11-20), extrapyramidal symptoms (NNH=16-44), and peripheral edema (NNH=20-25).
- First generation antipsychotics (example haloperidol) appear to have similar rates of harms but inconsistent benefits.[6]

Context:

- Cholinesterase inhibitors, SSRIs, trazodone, and valproate provide no meaningful improvement in agitation.[8-11]
  - Benzodiazepines may approach antipsychotics for efficacy in agitation but also have harms.[12]
- Stopping antipsychotics may reduce death (NNT=4 at two years) with little impact on neuropsychiatric symptoms.[13]
- While highlighting harms, guidelines support atypical antipsychotic use:
  - In severe aggression if risk to patient/others. Balance benefit versus risk of death and cerebrovascular events.[14]
  - Target agitation without sedation.[15]

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References:

1. Ma H, Huang Y, Cong Z, *et al*. J Alzheimers Dis. 2014; 42(3):915-37.
2. Ballard C, Waite J. Cochrane Database Syst Rev. 2006; 1:CD003476.
3. Yury CA, Fisher JE. Psychother Psychosom. 2007; 76(4):213-8.
4. Schneider LS, Dagerman K, Insel PS. Am J Geriatr Psychiatry. 2006; 14:191-210.
5. Cheung G, Stapelberg J. N Z Med J. 2011; 124:39-50.
6. Lonergan E, Luxenberg J, Colford J. Cochrane Database Syst Rev. 2002; 2:CD002852.
7. Rosenberg PB, Drye LT, Porsteinsson AP, *et al*. Int Psychogeriatr. 2015; 27:2059-67.
8. Campbell N, Ayub A, Boustani MA, *et al*. Clin Interv Aging. 2008; 3(4):719-28.
9. Seitz DP, Adunuri N, Gill SS, *et al*. Cochrane Database Syst Rev. 2011; 2:CD008191.
10. Martinon-Torres G, Fioravanti M, Grimley EJ. Cochrane Database Syst Rev. 2004; 4:CD004990.
11. Lonergan E, Luxenberg J. Cochrane Database Syst Rev. 2009; 3:CD003945.
12. McCracken R, Allan GM. Tools for Practice. Available at: https://www.acfp.ca/wp-content/uploads/tools-for-practice/1425325257_tfp133benzosagitationdementiafv.pdf. Last Accessed: October 3, 2017.
13. Allan GM, Behn Smith D. Tools for Practice. Available at: https://www.acfp.ca/wp-content/uploads/tools-for-practice/1397830928_20140408_114248.pdf. Last Accessed: October 3, 2017.
14. Toward Optimized Practice. Cognitive Impairment Clinical Practice Guideline; 2017. Available at: http://www.topalbertadoctors.org/download/2111/Cogn%20Imp%202-Diagnosis%20to%20Management.pdf. Last Accessed: September 28, 2017.
15. National Institute for Health and Care Excellence. Dementia: supporting people with dementia and their carers in health and social care; 2016. Available at: https://www.nice.org.uk/guidance/cg42/chapter/1-Guidance. Last Accessed: September 28, 2017.

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