



Making a difference in indifference? Medications for apathy in dementia

CLINICAL QUESTION

In patients with dementia, how safe and effective are stimulants, antidepressants, and antipsychotics for treating apathy?

BOTTOM LINE

Methylphenidate may improve apathy scores by a small but potentially clinically meaningful amount compared to placebo (example: 5 points more on a 72-point scale) at ~12 weeks. Methylphenidate does not impact cognition in randomized, controlled trials (RCTs). Antipsychotics and antidepressants do not improve apathy compared to placebo.

EVIDENCE

- Results statistically different unless indicated. Comparisons versus placebo.
- Two systematic reviews (4-7 RCTs, 346-1341 patients) from the last 5 years of treating apathy in mild-moderate Alzheimer's dementia over 2-24 weeks.^{1,2}
- Methylphenidate (immediate-release 10mg BID). Reporting most inclusive systematic review (4 RCTs, 346 patients):²
 - Apathy (mix of informant- and clinician-rated)
 - 72-point apathy scale (Baseline ~50; 3.3-point change clinically significant).³⁻⁶

- 6 point improvement versus 1 point (placebo) at ≤ 12 weeks.²
 - 12-point apathy scale (Baseline ~ 7 ; 1-2 point change clinically significant).^{2,3,5,7}
 - No difference versus placebo at < 12 weeks.²
 - 4.5 point improvement versus 3.1 (placebo) at 24 weeks.²
 - Clinicians' global impression:
 - Any improvement: 46% versus 34% (placebo).²
 - Mini-mental state exam:
 - No difference.²
 - Any adverse events or dropouts due to adverse events:
 - No difference.²
- Antipsychotics (2 RCTs, 421-649 patients):¹
 - Apathy: No difference.
- Antidepressants:
 - SSRIs (2 RCTs, 43-83 patients, neither required apathy diagnosis):¹
 - Apathy: Inconsistent results.^{8,9}
 - Bupropion (One RCT not in systematic reviews, 108 patients) versus placebo:¹⁰
 - Apathy: No difference.
 - Quality of Life (52-point scale): 1.2 points worse versus 0.4 better (placebo).
- Limitations: Small studies; one cross-over RCT (26 patients) negatively skewed meta-analyzed results;⁵ apathy a secondary outcome in antidepressant and antipsychotic RCTs; trial exclusion criteria (examples: cardiac abnormalities, uncontrolled hypertension, agitation) limit generalizability and safety data.

CONTEXT

- No improvement in apathy with cholinesterase inhibitors alone versus placebo,² but 60-100% of RCT methylphenidate patients used cholinesterase inhibitors.^{1,2}
- Methylphenidate associated with weight loss, behavioural changes, insomnia, and cardiovascular harms.¹¹
- Depression and apathy often overlap and can be difficult to distinguish in practice.¹²
- Non-pharmacologic options include sensory stimulation (example music therapy) and pet therapy based on low-quality evidence of benefit.¹³

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