Brief description of patient problem/setting: An 82-year-old male at a Long Term Care Center has moderate Alzheimer's dementia with worsening agitation, nighttime wandering, and aggressive behaviors despite environmental modifications and behavioral interventions. The healthcare team is considering initiation of an atypical antipsychotic but is concerned about potential adverse effects.

Search Question: In adults aged ≥ 65 years with dementia-related agitation residing in long-term care facilities, does atypical antipsychotic therapy compared with nonpharmacologic management improve agitation and behavioral symptoms while increasing mortality, stroke, falls, and hospitalization?

Question Type: What kind of question is this?

☐Prevalence ☐Screening ☐Diagnosis ☐Prognosis ☐**Treatment** ☐**Harms**

Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)?

Assuming the highest level of evidence available to answer my question would be a systematic review or meta-analysis, I would next look for randomized controlled trials (RCTs), as they are considered the gold standard for evaluating treatment efficacy and potential harms due to their ability to minimize bias through randomization. If RCTs were limited or did not fully address my clinical question, I would then consider large prospective cohort studies, particularly because important outcomes such as mortality, stroke, falls, and hospitalization may require larger populations and longer follow-up periods than many RCTs provide. Although I anticipate finding systematic reviews and meta-analyses for this topic, I would still consider including a large cohort study if it reported clinically meaningful outcomes or provided real-world data that were not captured in the pooled analyses. I would also consider a more recent study if it was published after the search period of the available systematic reviews, or if it more closely matched my specific patient population, such as older adults residing in long-term care facilities. Case-control and cross-sectional studies would only be considered if higher levels of evidence were unavailable, and their limitations would be acknowledged. Ultimately, the goal is not only to identify the highest level of evidence, but also the evidence that most directly and reliably answers the clinical question.

PICO search terms:

P	I	C	O
Dementia	Atypical Antipsychotics	Nonpharmacologic management	Agitation

Age ≥ 65	Risperidone	Behavioral interventions	Behavioral symptoms
Long-term care	Olanzapine	Music therapy	Cerebrovascular events
Alzheimer's	Quetiapine	Environmental modifications	Adverse events
Neurocognitive disorder	Aripiprazole	Placebo	Stroke
Elderly	Second-generation antipsychotics	Usual care	Falls
Residential care			Hospitalization
Skilled nursing facility			Mortality

Search Terms

	Pubmed	**Cochrane Library**	**Google Scholar**	**JAMA**
Search Terms	(dementia OR Alzheimer's OR "neurocognitive disorder") AND ("long-term care" OR "nursing home" OR "residential care" OR "skilled nursing facility") AND ("atypical antipsychotic" OR "second-generation antipsychotic" OR risperidone OR olanzapine OR quetiapine OR aripiprazole) AND ("nonpharmacologic" OR "behavioral intervention" OR placebo OR "usual care") AND (agitation OR "behavioral symptoms" OR mortality OR "adverse events" OR "cerebrovascular events" OR Stroke OR falls)	antipsychotics dementia agitation	atypical antipsychotic dementia agitation nonpharmacologic nursing home mortality adverse events	antipsychotic dementia agitation mortality

Filters	Publication date: 2006- 2026, English language, Humans, Aged 65+, Meta-analysis, Systematic Review, Randomized Controlled Trial, Midline	Cochrane Reviews, Trials, Publication date: 2015- 2026	Publication date: Since 2015, Review articles, sorted by relevance	JAMA Psychiatry, JAMA Network Open, 2015- 2026
Results	About 11	About 8	About 1,160	About 16
Selected	Choose 0 articles	Chose 1 article	Choose 0 articles	Chose 2 article

- After applying the initial search terms and database-specific filters, a large number of studies were identified, particularly through Google Scholar. One challenge I encountered was finding recent high-level evidence in PubMed and Cochrane, as many of the foundational studies on antipsychotic use in dementia were published in the early 2000s/2010s. Because of this, I expanded the publication window to include studies from 2015 onward to ensure that I captured both landmark articles and more current evidence. To narrow the results, I first reviewed article titles and abstracts to determine relevance to my specific PICO question. Priority was given to studies evaluating atypical antipsychotics for dementia-related agitation and behavioral symptoms while also reporting clinically important safety outcomes such as mortality, stroke, falls, hospitalization, and serious adverse events. I preferentially selected systematic reviews and meta-analyses, followed by randomized controlled trials and large cohort studies when they provided important information not captured in the pooled analyses. The final articles were chosen because they offered a balance between treatment efficacy and potential harms, included older adults with dementia similar to my patient population, and provided data that could be directly applied to clinical decision-making in a long-term care setting.

<u>Article 1:</u> Antipsychotics for Agitation and Psychosis in People With Alzheimer's Disease and VascularDementia

Mühlbauer V, Möhler R, Dichter MN, et al. Antipsychotics for agitation and psychosis in people withAlzheimer's disease and vascular dementia. *Cochrane Database Syst Rev*. 2021;12:CD013304. doi:10.1002/14651858.CD013304.pub2

<u>Abstract</u>

Background: Typical and atypical antipsychotics are widely used to treat agitation and psychosis in dementia. However, whether or not they are beneficial is uncertain. Some trials have yielded negative results and effectiveness may be outweighed by harms.

Objectives: To assess the efficacy and safety of antipsychotics for the treatment of agitation and psychosis in people with Alzheimer's disease and vascular dementia.
Search methods: We searched ALOIS, the Cochrane Dementia and Cognitive Improvement Group's register, MEDLINE (Ovid Sp), Embase (Ovid SP), PsycINFO (Ovid SP), CINAHL (EBSCOhost), Web of Science Core Collection (ISI Web of Science), LILACS (BIREME), ClinicalTrials.gov and the World Health Organization's meta‐register, and the International Clinical Trials Registry Portal on 7 January 2021. Two review authors independently screened the title and abstract of the hits, and two review authors assessed the full text of studies that got through this screening.
Selection criteria: We included randomised, placebo‐controlled, parallel‐arm trials comparing the effects of antipsychotics and placebo for the treatment of agitation or psychosis in people with dementia due to Alzheimer's disease or vascular dementia, or both, irrespective of age, severity of cognitive impairment, and setting. (The majority of) participants had to have clinically significant agitation (including aggression) or psychosis or both at baseline. We excluded studies about antipsychotics that are no longer available in the USA or EU, or that are used for emergency short‐term sedation. We also excluded head‐to‐head trials and antipsychotic withdrawal trials.
Data collection and analysis: The primary outcomes were (1) reduction in agitation or psychosis in participants with agitation or psychosis, respectively at baseline, and (2) the number of participants with adverse events: somnolence, extrapyramidal symptoms, any adverse event, any serious adverse event (SAE), and death.
Two review authors independently extracted the necessary data and assessed risk of bias with the Cochrane risk of bias tool. We calculated the pooled effect on agitation and psychosis for typical and atypical antipsychotics separately, and the pooled risk of adverse effects independent of the target symptom (agitation or psychosis). We used RevMan Web for the analyses.
Main results: The search yielded 8233 separate hits. After assessing the full‐text of 35 studies, we included 24 trials that met the eligibility criteria. Six trials tested a typical antipsychotic, four for agitation and two for psychosis. Twenty trials tested an atypical antipsychotic, eight for agitation and 12 for psychosis. Two trials tested both drug types. Seventeen of 26 comparisons were performed in patients with Alzheimer’s disease specifically. The other nine comparisons also included patients with vascular dementia or mixed dementia. Together, the studies included 6090 participants (12 to 652 per study). The trials were performed in institutionalised, hospitalised and community‐dwelling patients, or a combination of those. For typical antipsychotics (e.g. haloperidol, thiothixene), we are uncertain whether these drugs improve agitation compared with placebo (standardised mean difference (SMD) ‐0.36, 95% confidence interval (CI) ‐0.57 to ‐0.15, 4 studies, n = 361); very low‐certainty evidence, but typical antipsychotics may improve psychosis slightly (SMD ‐0.29, 95% CI ‐0.55 to ‐0.03, 2studies, n= 240; low‐certainty evidence) compared with placebo. These drugs probably increase the risk of somnolence (risk ratio (RR) 2.62, 95% CI 1.51 to 4.56, 3 studies, n = 466; moderate‐certainty evidence) and increase extrapyramidal symptoms (RR 2.26, 95% CI 1.58 to 3.23, 3 studies, n =

467; high‐certainty) evidence. There was no evidence regarding the risk of any adverse event. The risks of SAEs (RR 1.32, 95% CI 0.65 to 2.66, 1 study, n = 193) and death (RR 1.46, 95% CI 0.54 to 4.00, 6 studies, n = 578) may be increased slightly, but these estimates were very imprecise, and the certainty was low. The effect estimates for haloperidol from five trials were in line with those of the drug class. Atypical antipsychotics (e.g. risperidone, olanzapine, aripiprazole, quetiapine) probably reduce agitation slightly (SMD ‐0.21, 95% CI ‐0.30 to ‐0.12, 7 studies, n = 1971; moderate‐certainty evidence), but probably have a negligible effect on psychosis (SMD ‐0.11, 95% CI ‐0.18 to ‐0.03, 12 studies, n = 3364; moderate‐certainty evidence). These drugs increase the risk of somnolence (RR 1.93, 95% CI 1.57 to 2.39, 13 studies, n ‐ 3878; high‐certainty evidence) and are probably also associated with slightly increased risk of extrapyramidal symptoms (RR 1.39, 95% CI 1.14 to 1.68, 15 studies, n = 4180; moderate‐certainty evidence), serious adverse events (RR 1.32, 95% CI 1.09 to 1.61, 15 studies, n= 4316; moderate‐certainty evidence) and death (RR 1.36, 95% CI 0.90 to 2.05, 17 studies, n= 5032; moderate‐certainty evidence), although the latter estimate was imprecise. The drugs probably have a negligible effect on the risk of any adverse event (RR 1.05, 95% CI 1.02 to 1.09, 11 studies, n = 2785; moderate‐certainty evidence). The findings from seven trials for risperidone were in line with those for the drug class.
Authors' conclusions: There is some evidence that typical antipsychotics might decrease agitation and psychosis slightly in patients with dementia. Atypical antipsychotics reduce agitation in dementia slightly, but their effect on psychosis in dementia is negligible. The apparent effectiveness of the drugs seen in daily practice may be explained by a favourable natural course of the symptoms, as observed in the placebo groups. Both drug classes increase the risk of somnolence and other adverse events. If antipsychotics are considered for sedation in patients with severe and dangerous symptoms, this should be discussed openly with the patient and legal representative.

- This Cochrane systematic review and meta-analysis was selected because it represents the highest level of evidence available to answer my clinical question. This Cochrane systematic review included 24 randomized controlled trials with 6,090 participants, making it the most comprehensive evaluation of this topic. What makes this article particularly valuable is that it evaluates both efficacy and safety outcomes. While atypical antipsychotics were associated with a small improvement in agitation (SMD −0.21), they were also associated with increased risks of somnolence (RR 1.93), serious adverse events (RR 1.32), and death (RR 1.36). The use of GRADE methodology also allows for assessment of the certainty of the evidence, which is important when applying findings to clinical practice. One finding that stood out to me was the substantial improvement seen in placebo groups, suggesting that some behavioral symptoms may improve over time without pharmacologic intervention. The review also found little to no clinically meaningful improvement in psychosis symptoms. This is highly relevant to my patient because it highlights the central question of whether a modest reduction in agitation

justifies the increased risk of serious adverse outcomes in an 82-year-old veteran with Alzheimer's dementia.

Key Finding

- This review included 24 randomized placebo-controlled trials with a total of 6,090 participants across institutionalized, hospitalized, and community-dwelling dementia patients, making it one of the most comprehensive reviews on this topic
- Atypical antipsychotics (risperidone, olanzapine, aripiprazole, quetiapine) probably reduce agitation slightly compared to placebo, with a standardized mean difference (SMD) of -0.21 (95% CI -0.30 to -0.12), based on 7 studies with 1,971 patients, this was rated as moderate-certainty evidence
- However, atypical antipsychotics had a negligible effect on psychosis(SMD -0.11, 95% CI -0.18 to -0.03, 12 studies, n = 3,364), meaning they barely improved hallucinations and delusions beyond what placebo did
- Somnolence (excessive drowsiness) was significantly increased with atypical antipsychotics, with a risk ratio (RR) of 1.93 (95% CI 1.57 to 2.39), meaning patients were nearly twice as likely to experience somnolence, this was high-certainty evidence from 13 studies with 3,878 patients
- Extrapyramidal symptoms (stiffness, tremor, movement problems) were also increased with atypical antipsychotics (RR 1.39, 95% CI 1.14 to 1.68, 15 studies, n = 4,180; moderate-certainty evidence)
- Serious adverse events were probably increased slightly (RR 1.32, 95% CI 1.09 to 1.61, 15 studies, n = 4,316; moderate-certainty evidence), and mortality was also probably increased slightly (RR 1.36, 95% CI 0.90 to 2.05, 17 studies, n = 5,032), although this estimate was imprecise because the confidence interval crossed 1.0
- Typical antipsychotics (haloperidol, thiothixene) showed even worse safety profiles, with a 2.6-fold increase in somnolence (RR 2.62) and a 2.3-fold increase in extrapyramidal symptoms (RR 2.26), which was rated as high certainty evidence
- The authors concluded that the apparent effectiveness of antipsychotics seen in daily practice may partly be explained by the favorable natural course of symptoms observed in placebo groups, meaning agitation and psychosis often improve on their own over time without medication

<u>Article 2:</u> Antipsychotics, Other Psychotropics, and the Risk of Death in Patients With Dementia: Number Needed to Harm

Maust DT, Kim HM, Seyfried LS, et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. *JAMA Psychiatry*. 2015;72(5):438-445. doi:10.1001/jamapsychiatry.2014.3018

Abstract:

Importance: Antipsychotic medications are associated with increased mortality in older adults with dementia, yet their absolute effect on risk relative to no treatment or an alternative psychotropic is unclear.

Objective: To determine the absolute mortality risk increase and number needed to harm (NNH) (ie, number of patients who receive treatment that would be associated with 1 death) of antipsychotic, valproic acid and its derivatives, and antidepressant use in patients with dementia relative to either no treatment or antidepressant treatment.

Design, Setting, and Participants: A retrospective case-control study was conducted in the Veterans Health Administration from October 1, 1998, through September 30, 2009. Participants included 90 786 patients 65 years or older with a diagnosis of dementia. Final analyses were conducted in August 2014.

Exposures: A new prescription for an antipsychotic (haloperidol, olanzapine, quetiapine, and risperidone), valproic acid and its derivatives, or an antidepressant (46 008 medication users).

Main Outcomes and Measures: Absolute change in mortality risk and NNH over 180 days of follow-up in medication users compared with nonmedication users matched on several risk factors. Among patients in whom a treatment with medication was initiated, mortality risk associated with each agent was also compared using the antidepressant group as the reference, adjusting for age, sex, years with dementia, presence of delirium, and other clinical and demographic characteristics. Secondary analyses compared dose-adjusted absolute change in mortality risk for olanzapine, quetiapine, and risperidone.

Results: Compared with respective matched nonusers, individuals receiving haloperidol had an increased mortality risk of 3.8% (95% CI, 1.0%-6.6%; $P < .01$) with an NNH of 26 (95% CI, 15-99); followed by risperidone, 3.7% (95% CI, 2.2%-5.3%; $P < .01$) with an NNH of 27 (95% CI, 19-46); olanzapine, 2.5% (95% CI, 0.3%-4.7%; $P = .02$) with an NNH of 40 (95% CI, 21-312); and quetiapine, 2.0% (95% CI, 0.7%-3.3%; $P < .01$) with an NNH of 50 (95% CI, 30-150). Compared with antidepressant users, mortality risk ranged from 12.3% (95% CI, 8.6%-16.0%; $P < .01$) with an NNH of 8 (95% CI, 6-12) for haloperidol users to 3.2% (95% CI, 1.6%-4.9%; $P < .01$) with an NNH of 31 (95% CI, 21-62) for quetiapine users. As a group, the atypical antipsychotics (olanzapine, quetiapine, and risperidone) showed a dose-response increase in mortality risk, with 3.5% greater mortality (95% CI, 0.5%-6.5%; $P = .02$) in the high-dose subgroup relative to the low-dose group. When compared directly with quetiapine, dose-adjusted mortality risk was increased with both risperidone (1.7%; 95% CI, 0.6%-2.8%; $P = .003$) and olanzapine (1.5%; 95% CI, 0.02%-3.0%; $P = .047$).

Conclusions and Relevance : The absolute effect of antipsychotics on mortality in elderly patients with dementia may be higher than previously reported and increases with dose.

- This large retrospective cohort study was selected because it provides real-world safety data that randomized controlled trials and meta-analyses often cannot capture. This retrospective cohort study included 90,786 veterans aged 65 years and older with

dementia, making it highly applicable to my clinical scenario involving a veteran residing in a VA long-term care facility. One of the most useful findings was the calculation of the number needed to harm (NNH), which translates mortality risk into a measure that can be more easily applied during clinical decision-making. The study found an NNH of 26 for haloperidol, 27 for risperidone, 40 for olanzapine, and 50 for quetiapine over 180 days. Additionally, higher doses of atypical antipsychotics were associated with greater mortality risk, demonstrating a dose-response relationship. Although this study is observational and confounding by indication is possible, it remains one of the most influential studies evaluating mortality associated with antipsychotic use in older adults with dementia. It is particularly valuable because it quantifies risk in a real-world population that closely mirrors my patient population.

Key Finding:

- This was a large retrospective cohort study of 90,786 veterans aged 65 and older with dementia in the VA healthcare system, tracked over 180 days of follow-up, making it one of the largest real-world studies on antipsychotic-related mortality in dementia
- The study calculated the number needed to harm (NNH), meaning how many patients need to be treated before one additional death occurs, for each antipsychotic compared to matched non-users
- Haloperidol had the highest mortality risk, with an absolute increase of 3.8% and an NNH of 26, meaning for every 26 patients treated with haloperidol, one additional death could be expected over 180 days
- Risperidone had an absolute mortality increase of 3.7% with an NNH of 27, followed by olanzapine at 2.5% increase (NNH = 40), and quetiapine at 2.0% increase (NNH = 50)
- When compared specifically to antidepressant users (rather than non-users), the mortality risk was even more striking: haloperidol had an NNH of just 8 (meaning 1 in 8 patients treated with haloperidol instead of an antidepressant could be expected to die), and quetiapine had an NNH of 31
- There was a clear dose-response relationship, higher doses of atypical antipsychotics were associated with 3.5% greater mortality compared to low doses (95% CI 0.5%–6.5%), confirming that the risk increases as the dose goes up
- When comparing atypical antipsychotics directly to each other, both risperidone (1.7% increase) and olanzapine (1.5% increase) had significantly higher dose-adjusted mortality compared to quetiapine, suggesting quetiapine may be the least harmful option, though it also has the least evidence of benefit
- The authors noted that their mortality estimates were 2 to 4 times higher than the original estimates from Schneider et al.'s meta-analysis of RCTs (which reported an NNH of 100), likely because the 180-day follow-up period better reflects real-world prescribing patterns compared to the 6-12 week RCT durations

- A key limitation is that this was an observational study using VA claims data, which lacks information on dementia severity and the specific behavioral symptoms that prompted the prescription, so some of the increased mortality could be related to the severity of the condition itself rather than the medication alone

Article 3: Assessment of Reported Comparative Effectiveness and Safety of Atypical Antipsychotics in the Treatment of Behavioral and Psychological Symptoms of Dementia: A Network Meta-Analysis

Yunusa I, Alsumali A, Garba AE, Regestein QR, Eguale T. Assessment of reported comparative effectiveness and safety of atypical antipsychotics in the treatment of behavioral and psychological symptoms of dementia: a network meta-analysis. *JAMA Netw Open*. 2019;2(3):e190828. doi:10.1001/jamanetworkopen.2019.0828

Abstract:

Importance: Atypical antipsychotics offer modest effectiveness compared with placebo but with serious safety risks, including a boxed warning for the risk of death in the treatment of behavioral and psychological symptoms of dementia (BPSD). Their comparative effectiveness and safety are not fully known.

Objective To assess the relative benefits and safety of atypical antipsychotics in the treatment of BPSD shown in randomized clinical trials using network meta-analysis.

Data Sources PubMed/MEDLINE, Embase, PsychINFO, and Cochrane Library were searched from their inception until May 31, 2018. Key terms included dementia and atypical antipsychotics.

Study Selection: Randomized clinical trials comparing any atypical antipsychotic with another atypical antipsychotic or with placebo were included in the analysis.

Data Extraction and Synthesis: Two independent reviewers used a standardized data extraction and quality assessment form. Random-effects network meta-analyses were performed. Effect sizes were reported as standardized mean differences (SMDs) for continuous outcomes and odds ratios (ORs) for dichotomous outcomes with 95% CIs. In addition to ORs, the surface under the cumulative ranking curve (SUCRA) was ascertained, which represents the percentage of the effectiveness or safety for each treatment compared with a hypothetical treatment that would be ranked first without uncertainty.

Main Outcomes and Measures: The primary effectiveness outcome assessed was the Neuropsychiatric Inventory (NPI); secondary effectiveness outcomes were the Brief Psychiatric Rating Scale (BPRS) and Cohen-Mansfield Agitation Inventory (CMAI). The primary safety outcomes were death and cerebrovascular adverse events (CVAEs). Secondary safety outcomes were extrapyramidal signs/symptoms; somnolence/sedation; falls, fracture, or injury; and urinary tract infection/incontinence.

Results: Seventeen studies (5373 patients) were included. The mean (SD) age of all participants was 80.8 (3.1) years, and most were women (3748 [69.8%]). Compared with placebo, aripiprazole was associated with improvement in outcomes on the NPI (SMD, −0.17; 95% CI, -0.31 to −0.02), BPRS (SMD, −0.20; 95% CI, −0.35 to −0.05), and CMAI (SMD, −0.30; 95% CI, −0.55 to −0.05); quetiapine was associated with improvement in outcomes on the BPRS (SMD, −0.24; 95% CI, −0.46 to −0.01), and risperidone was associated with improvement in outcomes on the CMAI (SMD, −0.26; 95% CI, −0.37 to −0.15). Differences between atypical antipsychotics were not significant for effectiveness, death, or CVAE. Compared with placebo, risperidone (OR, 3.85; 95% CI, 1.55-9.55) and olanzapine (OR, 4.28; 95% CI, 1.26-14.56) were associated with increased risk of CVAEs. The SUCRA estimated relative ranking of treatments suggested that aripiprazole might be the most effective and safe atypical antipsychotic and that olanzapine provides the least benefit overall; however, these results should be interpreted with caution where point estimates (OR and SMD) show that there is no statistically significant difference.

Conclusions and Relevance: This network meta-analysis supports the existence of a trade-off between the effectiveness and safety of atypical antipsychotics in the treatment of BPSD and confirms that a single most effective and safe treatment option does not exist. Clinicians should individualize the assessment of safety risks against expected benefits when prescribing these

- This network meta-analysis of randomized controlled trials was selected because it directly compares individual atypical antipsychotics for both efficacy and safety outcomes. This network meta-analysis included 17 randomized controlled trials with 5,373 patients and assessed both efficacy and safety outcomes in patients with behavioral and psychological symptoms of dementia. Unlike the Cochrane review, which evaluated atypical antipsychotics collectively, this study ranked individual medications using SUCRA analysis. The authors found that aripiprazole demonstrated the greatest improvement in behavioral symptoms, while olanzapine, quetiapine, and risperidone did not show statistically significant improvement compared with placebo. Importantly, risperidone and olanzapine were associated with significantly increased risks of cerebrovascular adverse events, with odds ratios of 3.85 and 4.28, respectively. What I found most valuable about this study is that it demonstrates there is no single atypical antipsychotic that is both the most effective and the safest option. Every medication involves a trade-off between potential benefit and potential harm. This directly relates to my clinical question because it reinforces that the decision to initiate antipsychotic therapy should be individualized and based on careful consideration of both efficacy and safety outcomes rather than assuming all atypical antipsychotics perform similarly.

Key Findings:

- This network meta-analysis included 17 randomized clinical trials with 5,373 patients (mean age 80.8 years, 69.8% women), and uniquely compared atypical antipsychotics

head-to-head against each other (not just against placebo), using a method called SUCRA ranking to determine which drug is most likely the best and safest

- For overall behavioral symptoms (measured by the NPI), only aripiprazole showed statistically significant improvement over placebo (SMD -0.17, 95% CI -0.31 to -0.02), while olanzapine, quetiapine, and risperidone did not reach significance, aripiprazole had the highest SUCRA ranking for effectiveness at 85.3%
- For agitation specifically (measured by the CMAI), both aripiprazole (SMD - 0.30) and risperidone (SMD - 0.26) significantly improved agitation compared to placebo, while olanzapine and quetiapine did not
- For general psychiatric symptoms (measured by the BPRS), aripiprazole and quetiapine showed significant improvement over placebo, while olanzapine and risperidone did not
- Regarding mortality, none of the individual atypical antipsychotics reached statistical significance compared to placebo or each other, but the confidence intervals were wide due to small numbers of deaths in the trials, placebo had the highest safety probability (SUCRA 87.3%), and olanzapine had the lowest (SUCRA 32.4%)
- Cerebrovascular adverse events (strokes/TIAs) were significantly increased with risperidone (OR 3.85, 95% CI 1.55-9.55) and olanzapine(OR 4.28, 95% CI 1.26- 14.56) compared to placebo, while aripiprazole and quetiapine were not associated with increased stroke risk
- For extrapyramidal symptoms, quetiapine was ranked as the safest (SUCRA 94.2%) and risperidone as the worst (SUCRA 3.7%), risperidone had a nearly 4-fold higher risk of extrapyramidal symptoms compared to quetiapine (OR 3.75, 95% CI 1.61-8.73)
- For somnolence/sedation, all atypical antipsychotics increased the risk compared to placebo, but quetiapine was actually the worst for causing sedation (SUCRA 15.5%), while risperidone was the least sedating among the antipsychotics (SUCRA 66.2%)
- Interestingly, risperidone was the only antipsychotic associated with a decreased risk of falls compared to placebo (OR 0.79, 95% CI 0.64- 0.98), which may seem counterintuitive but could be related to its effectiveness in reducing agitation-related behaviors that lead to falls
- The overall conclusion was that no single atypical antipsychotic is both the most effective and the safest, there is a clear trade-off, and the SUCRA rankings suggest aripiprazole may offer the best overall balance of effectiveness and safety, while olanzapine provides the least overall benefit

What is the clinical "bottom line" derived from these articles in answer to your question?

The overall weight of the evidence suggests that atypical antipsychotics provide a small improvement in agitation and behavioral symptoms in older adults with dementia, but this benefit must be weighed against meaningful increases in adverse outcomes including somnolence, extrapyramidal symptoms, serious adverse events, cerebrovascular events, and mortality. The highest level of evidence comes from the 2021 Cochrane systematic review, which

demonstrated only a modest reduction in agitation (SMD −0.21) while showing increased risks of serious adverse events and death. An important finding from this review was that patients in placebo groups also experienced substantial improvement in behavioral symptoms, suggesting that some agitation may improve over time without pharmacologic treatment and reinforcing the importance of nonpharmacologic interventions as first-line therapy. The potential harms appear clinically significant. The large VA cohort study by Maust et al. demonstrated increased mortality across all antipsychotics studied, with a number needed to harm ranging from 26 for haloperidol to 50 for quetiapine over 180 days. This finding is particularly important because it provides real-world estimates of risk in a veteran population similar to the patients commonly encountered in VA long-term care settings. The evidence also suggests that atypical antipsychotics should not be viewed as a uniform drug class. The network meta-analysis by Yunusa et al. found important differences in both efficacy and safety among individual agents. Aripiprazole appeared to provide the most favorable balance between effectiveness and safety, while risperidone and olanzapine were associated with significantly increased cerebrovascular adverse event risk. No single medication emerged as both the most effective and the safest option.

Therefore, for an 82-year-old patient with Alzheimer's dementia and worsening agitation, nonpharmacologic interventions should remain first-line management. However, atypical antipsychotics remain appropriate when symptoms are severe, dangerous, or cause significant distress to the patient or caregivers despite behavioral interventions. If initiated, treatment should be individualized, started at the lowest effective dose, reassessed frequently, and continued only when the benefits clearly outweigh the risks. Shared decision-making with family members and caregivers is essential given the known association between antipsychotic use and increased mortality in this population.