CLINICAL EVIDENCE REVIEW

Mirtazapine as Appetite Stimulant in Long-Term Care: Safety and Efficacy in the Elderly, Dementia, and Weight Loss

Prepared for: Long-Term Care Clinical Practice | April 2026

Section 1: American Geriatrics Society Position Summary

The American Geriatrics Society (AGS) has addressed mirtazapine use in older adults through two distinct but complementary mechanisms: the **2023 AGS Beers Criteria®** and the **AGS Choosing Wisely® Campaign**. Together, these represent the Society's most authoritative guidance on this topic. Clinicians prescribing mirtazapine — particularly for appetite stimulation — should understand both layers of guidance before initiating therapy.

1.1 The 2023 AGS Beers Criteria® — "Use with Caution"

Mirtazapine is listed in **Table 4 of the 2023 Beers Criteria®** under the designation **"Use with Caution"** — not on the primary "Avoid" list. This distinction carries clinical meaning: the designation reflects a concern that harms may not clearly outweigh benefits in all patients, but that meaningful risks warrant explicit awareness and monitoring.

2023 Beers Criteria® — Mirtazapine: Use with Caution

Primary Concern: May exacerbate or cause SIADH or hyponatremia. Monitor sodium levels closely when initiating or dose-adjusting.

Quality of Evidence: Moderate **Strength of Recommendation:** Strong

Reference: J Am Geriatr Soc. 2023;71:2052–2081. DOI: 10.1111/jgs.18372

The specific safety concerns flagged in the 2023 Beers Criteria® for mirtazapine include:

- **SIADH / Hyponatremia:** Elderly patients — especially those on diuretics or with baseline sodium instability — are at heightened risk. A baseline sodium level before starting and rechecks within 2–4 weeks of initiation are clinically prudent.
- **Falls and Fractures:** Mirtazapine falls under the antidepressant drug class, which is listed in the Beers Criteria® as potentially inappropriate in patients with a history of falls or fractures. The 2023 update downgraded the level of evidence for this class-level risk from "high" to "moderate," but the concern remains.
- **Sedation and CNS Effects:** Mirtazapine may cause confusion and over-sedation in elderly patients. Its half-life is prolonged after age 55 (men: ~32 hours; women: ~41 hours), increasing cumulative CNS exposure with daily dosing.

- **Renal and Hepatic Impairment:** Clearance is reduced with moderate-to-severe renal impairment and with even mild hepatic impairment, both common in LTC residents. Drug levels may accumulate without dose adjustment.

1.2 AGS Choosing Wisely® Campaign — Explicit "Avoid" for Appetite Stimulants

This is the more directly relevant and more strongly worded of the two AGS positions for the context of using mirtazapine specifically **to treat weight loss or anorexia** in older adults.

> **AGS Choosing Wisely® Recommendation (affirmed 2014, updated 2015, referenced in 2019 and 2023 Beers updates):**
>
> *"Avoid using prescription appetite stimulants or high-calorie supplements for treatment of anorexia or cachexia in older adults; instead, optimize social supports, discontinue medications that may interfere with eating, provide appealing food and feeding assistance, and clarify patient goals and expectations."*
>
> Reference: AGS Choosing Wisely Workgroup. J Am Geriatr Soc. 2014;62(5):950–960. DOI: 10.1111/jgs.12770

The Choosing Wisely recommendation encompasses all prescription appetite stimulants used in older adults, explicitly including mirtazapine. The AGS bases this recommendation on several foundational findings:

- **No RCTs specifically in older adults for weight gain:** No randomized controlled trials have evaluated mirtazapine solely as an appetite stimulant in a geriatric population. Existing weight data is derived from depression trials in which weight change was a secondary or incidental outcome.
- **Lack of evidence on patient-centered outcomes:** There is no evidence that mirtazapine (or any prescription appetite stimulant) improves quality of life, functional status, or survival when prescribed for weight loss. Weight gain in short-duration trials has not translated into meaningful clinical benefit in controlled studies.
- **Evidence base is mixed even in favorable populations:** In two retrospective studies of older nursing home residents with depression and weight loss, mirtazapine showed no differential advantage over sertraline or other non-TCA antidepressants on weight gain outcomes.
- **Off-label use without FDA approval:** Mirtazapine is not FDA-approved for appetite stimulation or weight gain in any population. All appetite-stimulant use is off-label, without the regulatory evidence threshold that approved indications require.

1.3 The Critical Exception: Co-existing Depression

The AGS guidance draws a meaningful clinical distinction. Mirtazapine used **to treat confirmed depression** in an older adult — where weight gain is a welcome secondary effect

— is a different clinical scenario than prescribing it **solely for appetite stimulation.** The Choosing Wisely recommendation targets the latter use case specifically.

AGS Clinical Logic:

"Mirtazapine is likely to cause weight gain or increased appetite when used to treat depression, but there is little evidence to support its use to promote appetite and weight gain in the absence of depression."

Source: AGS Choosing Wisely / AAFP AFP 2014

This framing has direct implications for LTC practice:

- If a resident has documented major depression AND anorexia/weight loss, mirtazapine is a clinically defensible choice — treating depression is the primary indication, and weight gain is an acceptable or desirable side effect.
- If a resident has weight loss WITHOUT depression, the AGS recommends against mirtazapine as primary pharmacotherapy and instead directs clinicians toward identifying and treating the root cause of weight loss, optimizing the eating environment, and addressing polypharmacy.
- Residents with dementia require particular scrutiny — emerging safety data (see Section 5) suggests possible mortality signal in this population that may further shift the risk-benefit calculus.

1.4 AGS Beers Criteria® — Summary Table

Drug	Concern	Recommendation	Evidence Quality	Strength
Mirtazapine	SIADH / hyponatremia; monitor sodium closely when starting or adjusting dose	**Use with Caution**	Moderate	Strong
Antidepressants (class, includes mirtazapine)	Falls and fractures risk in patients with prior fall history	**Avoid in fall-risk patients**	Moderate (downgraded 2023)	Strong
Prescription appetite stimulants (class, includes mirtazapine)	No evidence of improved QoL, function, or survival; risk of ADEs; off-label use	**Avoid for anorexia/cachexia (Choosing Wisely)**	Moderate to Low	Strong

Source: 2023 American Geriatrics Society Beers Criteria® (J Am Geriatr Soc. 2023;71:2052–2081) and AGS Choosing Wisely Workgroup (J Am Geriatr Soc. 2014;62:950–960)

Section 2: Clinical Bottom Line

Summary for LTC Practice

The evidence base for mirtazapine as a standalone appetite stimulant in long-term care residents is weak, mixed, and not supported by the AGS. The most applicable LTC-specific data shows no differential weight gain advantage over comparator antidepressants. The only study with directly favorable data in an LTC/dementia population (Vandel 2012) lacks a control group. A 2025 Australian LTCF cohort of 5,409 residents found a 16% higher all-cause mortality with mirtazapine versus sertraline — a signal that demands caution particularly in dementia patients.

The AGS, through Choosing Wisely, recommends against prescription appetite stimulants for weight loss in older adults. Mirtazapine is most defensible when depression is the co-primary indication. When prescribed solely for weight loss without a co-existing indication, the risk-benefit calculus is unfavorable by current evidence standards.

Prescribing Decision Framework

Clinical Scenario	AGS Guidance	Evidence Support
Weight loss with confirmed major depression	Acceptable — treat depression; weight gain is a welcome side effect	Moderate (depression trials; weight change secondary outcome)
Weight loss without depression, no other indication	**Not recommended (Choosing Wisely Avoid)**	Weak — no RCTs; retrospective data mixed
Weight loss with dementia (no depression diagnosis)	**Use with caution — emerging mortality signal (Healy 2025, SYMBAD)**	Conflicting; possible harm signal in dementia
Anorexia of aging / cachexia without treatable underlying cause	**Not recommended (Choosing Wisely Avoid)**	No controlled trials show QoL or survival benefit
Patient with history of falls and weight loss	**Avoid — falls risk (Beers Table 3) + no appetite stimulant evidence**	Class-level falls risk; Beers moderate

		evidence, strong recommendation
Hyponatremia history or diuretic use + weight loss	Use with caution — SIADH risk; check sodium baseline + within 2–4 weeks	Beers Criteria: moderate evidence, strong recommendation

Section 3: Evidence Review — Efficacy for Appetite and Weight Gain

3.1 Mechanism of Action

Mirtazapine's orexigenic properties arise from antagonism of two receptor types:

- **H1 (histamine-1) blockade:** Stimulates appetite and increases caloric intake, also responsible for significant sedation.
- **5-HT2C (serotonin-2C) blockade:** Disinhibits appetite regulation, promoting increased food-seeking behavior and caloric consumption.

Critically, lower doses (7.5–15 mg) produce more prominent H1 blockade relative to noradrenergic effects, making them more strongly associated with appetite stimulation and sedation than higher doses. This counterintuitive dose-response (more sedation and appetite stimulation at lower doses) is pharmacologically well-established but clinically underappreciated.

3.2 The Mechanistic Ceiling: Caloric Access Dependency

A critical and often overlooked constraint: **mirtazapine increases hunger signals, but weight gain only occurs if the patient can act on that hunger.** Controlled metabolic ward studies in healthy volunteers demonstrate that when caloric intake is fixed at maintenance levels, mirtazapine produces no weight gain despite measurable increases in hunger — it shifts energy substrate metabolism toward carbohydrate preference but cannot create weight gain from caloric restriction alone.

This has direct implications for LTC settings where meal portions are standardized, dietary restrictions are common (cardiac, diabetic, renal diets), and residents may have limited ability to seek additional food between scheduled meal times. The orexigenic benefit may be substantially blunted in institutionally constrained eating environments.

3.3 LTC-Specific Evidence

3.3a Goldberg 2002 — Nursing Home Residents with Depression

Study: Retrospective chart review, depressed nursing home residents, mirtazapine vs. comparison antidepressants.

Finding: No statistically significant differential weight gain with mirtazapine compared to comparator antidepressants. Weight changes observed in both groups likely reflected depression treatment response rather than a specific orexigenic pharmacological effect.

Limitation: Retrospective, no placebo control, single site, small sample.

Citation: Goldberg RJ. Weight change in depressed nursing home patients on mirtazapine. J Am Geriatr Soc. 2002;50(8):1461. DOI: 10.1046/j.1532-5415.2002.50374.x

3.3b Mihara et al. 2005 — Nursing Facility Residents, Weight Change vs. Non-TCA Antidepressants

Study: Retrospective database analysis of nursing facility residents prescribed mirtazapine vs. non-TCA antidepressants.

Finding: No significant difference in weight change between mirtazapine and comparator antidepressants. Mirtazapine was associated with less anxiolytic co-prescribing, suggesting some benefit on anxiety/agitation, but the weight data did not support a preferential advantage.

Citation: Mihara IQT, McCombs JS, Williams BR. The impact of mirtazapine compared with non-TCA antidepressants on weight change in nursing facility residents. Consult Pharm. 2005;20(3):217–223. DOI: 10.4140/tcp.n.2005.217

3.3c Nelson et al. 2006/2007 — Depressed Nursing Home Residents ≥85 Years

Study: Prospective open-label study of mirtazapine ODT in nursing home residents aged ≥85 years with depression.

Finding: Mirtazapine ODT was well-tolerated and produced meaningful antidepressant response. Weight gain was noted as a secondary outcome in responders. No placebo comparator; weight findings cannot be attributed to appetite stimulation independent of depression treatment.

Citation: Nelson JC, Hollander SB, Betzel J, et al. Mirtazapine orally disintegrating tablets in depressed nursing home residents 85 years of age and older. Int J Geriatr Psychiatry. 2006;21:898–901. DOI: 10.1002/gps.1589

3.4 Dementia-Specific Evidence

3.4a Vandel et al. 2012 — Alzheimer's Patients Prescribed Mirtazapine for Weight Loss

Study: Retrospective chart review, Alzheimer's patients in memory units prescribed mirtazapine specifically for appetite loss and weight loss.

Finding: 77–82% of patients gained weight over 3–6 months. This is the most directly favorable data point for the specific indication of appetite stimulation in dementia patients.

Critical Limitation: No control group; weight gain may reflect regression to the mean, disease fluctuation, improved care attention, or concurrent interventions. Cannot establish causal relationship between mirtazapine and weight gain.

Citation: Vandel P, et al. Mirtazapine use in Alzheimer's disease with weight loss. J Nutr Health Aging. 2012.

3.4b HTA-SADD Trial 2011 — Depression in Dementia

Study: Banerjee S, et al. Randomized, double-blind, placebo-controlled trial. Sertraline vs. mirtazapine vs. placebo for depression in Alzheimer's dementia.

Finding: Neither sertraline nor mirtazapine was significantly more effective than placebo for depression in dementia at 13 or 39 weeks. Adverse events were more common in both active treatment groups. No weight-specific outcomes reported as primary data.

Citation: Banerjee S, et al. Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised, multicentre, double-blind, placebo-controlled trial. Lancet. 2011;378:403–411. DOI: 10.1016/S0140-6736(11)60830-1

Section 4: Cross-Population Evidence Synthesis

Mirtazapine's appetite and weight effects are best understood as context-dependent rather than reliably generalizable. The table below synthesizes the evidence across populations relevant to LTC practice:

Population	Study Type	Weight/Appetite Finding	Quality	AGS Guidance
Depressed adults (all ages)	RCTs, meta-analyses	~2 kg gain at 6 weeks; most consistent evidence	High	Acceptable — depression is primary indication
Older depressed adults	Retrospective, open-label	No differential weight advantage vs. comparators in LTC	Low-Moderate	Acceptable if depression confirmed
Alzheimer's / dementia (weight loss)	Retrospective only (Vandel 2012)	77–82% gained weight; no control group	Very Low	Use with caution; emerging mortality signal
Cancer cachexia	RCTs	Mixed; most RCTs negative on primary weight endpoints	Moderate	Not recommended (Choosing Wisely)

Anorexia of aging / LTC weight loss (no depression)	No RCTs; retrospective only	Insufficient data; ~50% appetite response in uncontrolled hospitalized cohort	Very Low	**Avoid (Choosing Wisely)**

The key insight from this synthesis: mirtazapine's weight gain effect is well-established when treating depression in the context where it was studied (general adult population, food-unrestricted, depression as primary diagnosis). The further a patient deviates from that context — elderly, food-access-restricted, dementia, severe catabolism — the weaker and less reliable the weight gain effect becomes, while safety risks remain or increase.

Section 5: Safety Profile in Long-Term Care

5.1 The 2025 Mortality Signal — Healy et al., Age & Ageing

ALERT: Emerging Mortality Signal in LTCF Residents

Study: Healy et al. (2025). Risk of adverse outcomes associated with mirtazapine compared to sertraline use among older people living in long-term care facilities. Age & Ageing. DOI: 10.1093/ageing/afae287

Design: Active comparator, new-user cohort study. 5,409 LTCF residents. Australia. Propensity score-weighted.

Key Finding: Mirtazapine was associated with 16% higher all-cause mortality vs. sertraline (HR ~1.16). Also associated with increased risk of falls and fractures.

Significance: This is the largest, most methodologically rigorous real-world safety study of mirtazapine specifically in LTCF populations. The mortality signal is directionally consistent with the SYMBAD dementia trial (Banerjee 2023). It is not definitive, but it constitutes a meaningful safety flag that should inform prescribing decisions — particularly for off-label appetite stimulation.

5.2 SYMBAD Trial — Mirtazapine in Alzheimer's Agitation

Study: Banerjee S, et al. SYMBAD trial. Pragmatic RCT, mirtazapine and carbamazepine vs. placebo for agitation in Alzheimer's dementia. Health Technol Assess. 2023.

Finding: No benefit over placebo for agitation. Mirtazapine was associated with a directionally higher (though non-statistically significant) mortality trend. The trial was stopped early, partly due to futility.

Relevance: Provides biological plausibility for the mortality signal seen in Healy 2025. Two independent studies pointing in the same direction in dementia populations warrants clinical caution.

5.3 Additional Safety Considerations in LTC

- **Hyponatremia / SIADH:** Class risk for antidepressants; mirtazapine specifically flagged. Elderly LTC residents on diuretics face compounded risk. Baseline BMP and repeat sodium at 2–4 weeks after initiation is a reasonable monitoring standard.
- **Sedation and fall risk:** Mirtazapine is among the most sedating antidepressants; somnolence occurs in approximately 50% of patients in clinical trials. In LTC residents with baseline gait instability, this represents a meaningful incremental fall risk.
- **Anticholinergic burden:** Mirtazapine has weak muscarinic blockade. While not as strongly anticholinergic as TCAs or first-generation antihistamines, it adds to total anticholinergic burden in residents already on multiple medications.
- **Drug interactions:** CYP1A2 and CYP3A4 involvement; potential interactions with azole antifungals, macrolide antibiotics, and anticonvulsants — all common in LTC.
- **Prolonged half-life:** The extended half-life in the elderly (32–41 hours) means drug accumulation with daily dosing. Clinical effects, including sedation and fall risk, may be more pronounced than the acute dose response suggests.

Section 6: AGS-Preferred Alternatives for Weight Loss in LTC

The AGS Choosing Wisely recommendation is not merely a prohibition — it directs clinicians toward a structured non-pharmacological approach that has a more favorable evidence base than any prescription appetite stimulant:

Intervention	Implementation in LTC	Evidence Basis
Identify and treat root cause	Depression screening (PHQ-9/Cornell Scale for Depression in Dementia), dental evaluation, dysphagia assessment, pain management, constipation treatment	Strong — most modifiable weight loss in LTC is cause-attributable
Deprescribing appetite-suppressant medications	Review for TCAs, digoxin, metformin, SSRIs (some), amphetamines, certain antibiotics — all can impair appetite	Moderate — up to 250 common medications can affect appetite
Liberalize dietary restrictions	Remove sodium, carbohydrate, or texture restrictions where clinically safe; evidence shows minimal mortality benefit from restricted diets in advanced age/frailty	Moderate

Optimize eating environment	Assisted feeding, preferred foods, social mealtimes, adequate time allowed, positioning optimization	Moderate — systematic reviews support improved intake
Oral nutritional supplements	Protein/calorie supplementation between meals (not replacing meals); Cochrane review shows modest but consistent weight gain; mortality benefit in undernourished subgroup	Moderate; preferred over appetite stimulants by AGS
Goals of care discussion	For residents with advanced illness, goals alignment may shift focus from weight gain to comfort and dignity; appetite loss is often part of natural disease trajectory	Expert consensus; AGS Choosing Wisely specifically references clarifying patient goals

Appendix: Reference Summaries

1. 2023 AGS Beers Criteria® — AGS Update Expert Panel. J Am Geriatr Soc. 2023;71:2052–2081. DOI: 10.1111/jgs.18372

The most current edition of the AGS Beers Criteria® lists mirtazapine under "Use with Caution" due to risk of SIADH/hyponatremia (moderate evidence, strong recommendation). Antidepressants as a class remain flagged for fall/fracture risk. The 2023 update downgraded the falls evidence from high to moderate. Mirtazapine is not on the primary "Avoid" list unless the patient has a history of falls or fractures.

2. AGS Choosing Wisely® — Appetite Stimulants — AGS Choosing Wisely Workgroup. J Am Geriatr Soc. 2014;62(5):950–960. DOI: 10.1111/jgs.12770

Explicitly recommends against prescription appetite stimulants (including mirtazapine) for anorexia or cachexia in older adults. Notes that mirtazapine may cause weight gain when used to treat depression, but there is little evidence for its use as a primary appetite stimulant. Directs clinicians toward non-pharmacological approaches and identification of root causes.

3. Healy et al. 2025 — Age & Ageing. DOI: 10.1093/ageing/afae287

Active comparator new-user cohort study of 5,409 LTCF residents in Australia comparing mirtazapine to sertraline. Propensity score-weighted. Mirtazapine was associated with 16% higher all-cause mortality and increased falls/fractures risk vs. sertraline. The most methodologically rigorous LTC-specific safety study available. Results require replication but represent the strongest available safety signal in this population.

4. Banerjee et al. 2011 (HTA-SADD) — Lancet. 2011;378:403–411. DOI: 10.1016/S0140-6736(11)60830-1

Randomized, double-blind, placebo-controlled trial of sertraline and mirtazapine for depression in Alzheimer's dementia. Neither agent was more effective than placebo at 13 or 39 weeks. Adverse events were more common in active treatment arms. Landmark study demonstrating that antidepressant efficacy in dementia does not mirror efficacy in non-demented populations.

5. Banerjee et al. 2023 (SYMBAD) — Health Technol Assess. 2023;27:1–108. DOI: 10.3310/VPDT7105

Pragmatic RCT of mirtazapine and carbamazepine for agitation in Alzheimer's dementia. Mirtazapine showed no benefit over placebo for agitation and had a directionally (though not statistically) higher mortality trend. Provides biological plausibility for the mortality finding in Healy 2025.

6. Goldberg 2002 — J Am Geriatr Soc. 2002;50(8):1461. DOI: 10.1046/j.1532-5415.2002.50374.x

Retrospective chart review of depressed nursing home residents on mirtazapine vs. comparison antidepressants. No statistically significant differential weight gain. Weight

changes observed likely reflected depression treatment response. Foundational LTC-specific weight study with key null finding.

7. Mihara et al. 2005 — Consult Pharm. 2005;20(3):217–223. DOI: 10.4140/tcp.n.2005.217

Retrospective database analysis of nursing facility residents. No significant weight advantage for mirtazapine vs. non-TCA antidepressants. Notable finding: mirtazapine was associated with less anxiolytic co-prescribing, suggesting some benefit in anxiety/agitation management independent of weight outcomes.

8. Nelson et al. 2006 — Int J Geriatr Psychiatry. 2006;21:898–901. DOI: 10.1002/gps.1589

Prospective open-label study of mirtazapine ODT in depressed nursing home residents ≥85 years. Demonstrated tolerability and antidepressant response in the oldest LTC cohort studied. Weight gain noted in responders but as secondary outcome in context of depression treatment, not primary appetite stimulation.

9. Vandel et al. 2012

Retrospective chart review of Alzheimer's patients in memory units prescribed mirtazapine specifically for appetite loss and weight loss. Found 77–82% gained weight over 3–6 months — the most favorable data for direct appetite stimulation use in dementia. Major limitation: no control group; cannot rule out confounding from disease fluctuation, regression to mean, or concurrent care improvements.

10. Fox CB, Treadway AK, Blaszczyk AT, Sleeper RB. 2009 — Pharmacotherapy. 2009;29(4):383–397. DOI: 10.1592/phco.29.4.383

Systematic review of megestrol acetate and mirtazapine for unplanned weight loss in the elderly. Concluded that both agents appear effective for appetite stimulation in some settings, but applicability to elderly populations is unclear and adverse events were not benign. Emphasized individual-patient evaluation before initiating pharmacotherapy and assessment of all underlying causes first.

11. Howard ML et al. 2019 — Ann Pharmacother. 2019;53:261–267.

Retrospective study of 38 hospitalized patients using appetite stimulants (42% mirtazapine). Approximately half experienced increased appetite with no serious adverse effects. No control group. Frequently cited as real-world evidence; the ~50% response rate is arguably the most representative efficacy estimate for appetite stimulation in a mixed inpatient population.

12. Gay L, Sheth S, Horstman MJ. 2021 — J Hosp Med. Published online October 2021. DOI: 10.12788/jhm.3652

"Things We Do for No Reason" series article on prescribing appetite stimulants to hospitalized older adults with unintentional weight loss. Reviews evidence for and against mirtazapine, megestrol, cyproheptadine, and dronabinol. Directly applies AGS Choosing Wisely framework. Provides structured guidance for hospitalists and generalists on when appetite stimulants are and are not indicated.

Disclosure & Methodology: This report was prepared as a clinical evidence synthesis for internal LTC practice use. Literature search was conducted via PubMed/MEDLINE and clinical databases through April 2026. This document is not a substitute for individualized clinical judgment, institutional formulary review, or formal systematic review methodology. The author has no conflicts of interest to disclose related to mirtazapine or any named pharmaceutical product.