

Agitation/Aggression in Elderly: What works

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Background: Agitation in Dementia

- Dementia can > agitation and violent behavior
 - Also can delirium and associate problems.
- Hard to manage.
- Consider undiagnosed pain
- Some other key points from the literature,...

Scores

- **Cohen-Mansfield Agitation Inventory (CMAI):** Assesses the frequency of manifestations of agitated behaviors in elderly people.
 - 29 measures agitation behaviour, score 1 (never) to 7 (several / hour)
 - Score is 29-203. Higher worse.
 - No MCID. Score of ≥ 39 = agitation. *
- **Brief Psychiatric Rating Scale (BPRS):** Not specifically agitation.
 - 18 measures behaviour, score 1 (not present) to 7 (extremely severe)
 - Score is 18-126. Higher worse.
 - Mildly ill ≥ 31 , moderate ≥ 41 , markedly ≥ 53
 - MCID = 25% improvement

Scores

- **Neuropsychiatric Inventory (NPI):** measures physical & verbal aggression, hallucinatory behaviour, & abnormal thought content
 - 12 measures behaviour, Frequency/severity/disruption score 0-12
 - Scores: 0-144, higher worse.
 - Mild <20, moderate 20-50, severe ≥ 50
 - MCID 4 - 9 points,
- **Behave-AD:** Behavioural symptoms of dementia,
 - 25 behaviours, rated 0-3
 - Score 0-75, higher worse.
- **Clinical Global Impression Scale:** 7-point scale with scores ranging from 1 (no aggressive behaviour) to 7 (severely aggressive behaviour).
 - Can be used a Clinical Global Impression of Change. MCID=1

What happens when you give placebo?

	Baseline	3 weeks	9 weeks
Neurobehavioral Rating Scale agitation subscale (NBRS-A)	7.8 (3.0)	5.7 (3.1)	5.4 (3.2)
Cohen-Mansfield Agitation Inventory (CMAI)	28.7 (6.7)	26.9 (6.7)	26.7 (7.4)
Neuropsychiatric Inventory Agitation/Aggression domain (NPI A/A)	8.0 (2.4)	4.9 (3.1)	4.9 (3.8)
Neuropsychiatric Inventory (NPI)-Total	37.3 (17.7)	26.1 (16.1)	28.4 (22.1)
Clinical Global Impression of Change (CGI-C)	n/a	29% “improved”	26% “improved”
Mental Status Exam (MSE)	14.4	14.9	15.7

- Biggest effect in first weeks.
- Also, more severe scores got greater benefit.

10 years ago, What did we know?

- Atypical Anti-psychotic for Behavioral problems in Dementia¹
 - Mean effect size for 7 placebo-controlled studies:
 - 0.45 (95% CI = 0.16-0.74) for atypical antipsychotics,
 - 0.32 (95% CI = 0.10-0.53) for placebo. (No difference)
- Cochrane Meta-analysis² (16 placebo controlled trials, 9 sufficient data for meta-analysis, 5 full published in peer reviewed journals)
 1. There was a significant improvement in aggression with risperidone and olanzapine treatment compared to placebo.
 2. There was a significant improvement in psychosis amongst risperidone treated patients.
 3. Risperidone and olanzapine treated patients had a significantly higher incidence of serious adverse cerebrovascular events (including stroke), extra-pyramidal side effects and other important adverse outcomes.
 4. There was a significant increase in drop-outs in risperidone (2 mg) and olanzapine (5-10 mg) treated patients.
 5. The data were insufficient to examine impact upon cognitive function.

1) Psychother Psychosom. 2007;76(4):213-8. 2) Cochrane Database Syst Rev. 2006 Jan 25;(1):CD003476.

Anti-Psychotics: Benefits

- Systematic review: 16 RCTs (5050 pt)
 - median 10 weeks (range 6-26)
- Score changes (over placebo):
 - CMAI, mean diff= -1.84, (-0.67 to -3.01)
 - NPI, mean diff= -2.81 (-1.28 to -4.35)
 - BPRS, mean diff= -1.58 (-0.65 to -2.52)
 - CGI-C, mean diff= -0.32, (-0.20 to -0.44)
- All these changes are small.

Anti-Psychotics: Benefits, Other Reviews

- Cochrane:¹ Over 10-13 weeks,
 - Risperidone CMAI, Mean Diff = -1.17 [-0.32, -2.02]
 - Olanzapine NPI-NH, Mean Diff -2.46 [-5.53, 0.61]
- Quetiapine:² 5 RCTs (1118 pts), 6-10 weeks
 - NPI, Mean Diff = 3.05 (-0.01 to -6.10)
 - CGI-C, Mean Diff = -0.31 (-0.08 to -0.54)
- Haloperidol:³ 5 RCTs, 3-16 weeks.
 - Any agitation SMD = -0.12 [-0.33 to 0.08], not sign.
 - Any aggression SMD = -0.31 (-0.13 to -0.49), sign
 - Clinical meaning unknown (likely small)

But how many actually get better?

- Systematic Review: 16 RCTs (5110 pts), 8-12 weeks.

Drug	50% improvement in this outcome	Odds Ratio	Treatment rate	Placebo Rate	NNT
Aripipazole	NPI	1.50 (1.14 – 1.99)	48.5%	38.2%	10
Risperidone	BEHAVE-AD	1.79 (1.37 – 2.33)	46.3%	32.6%	8
Risperidone	CGI – C (much /very much improved)	2.01 (1.49-2.72)	64.7%	47.8%	6
Haloperidol*	CGI-C (improved)	1.50 (0.88 – 2.55)	67.4%	59%	ns

- While scales do not seem to change meaningfully, around 50% of patients will get a meaningful improvement.
- Furthermore, 1 in 6 to 1 in 10 will do meaningfully better than placebo.

What are the Adverse Events?

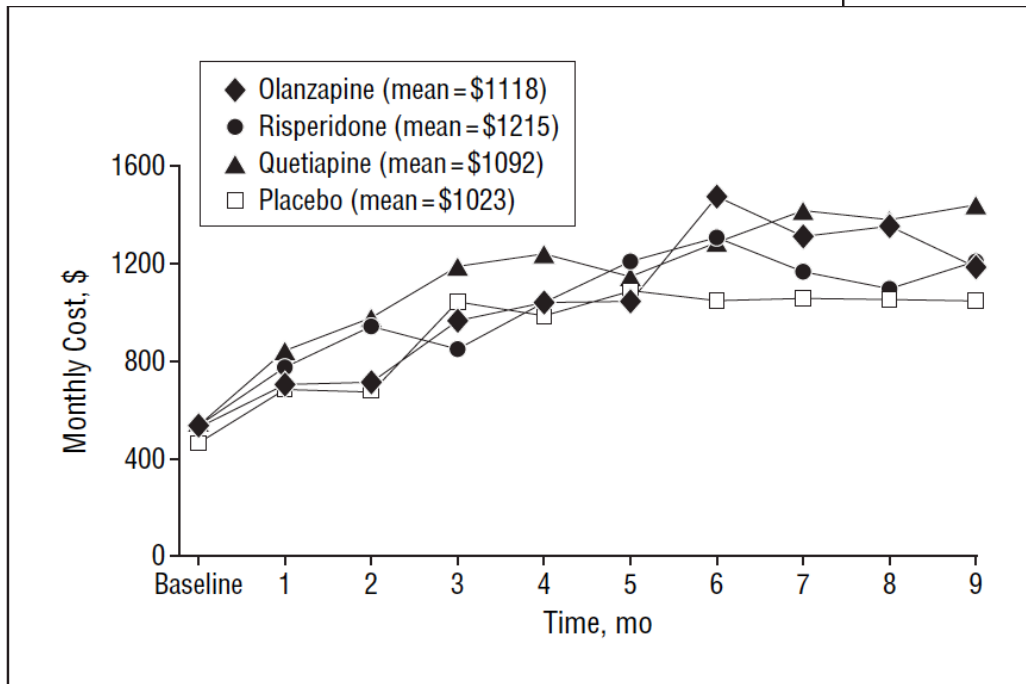
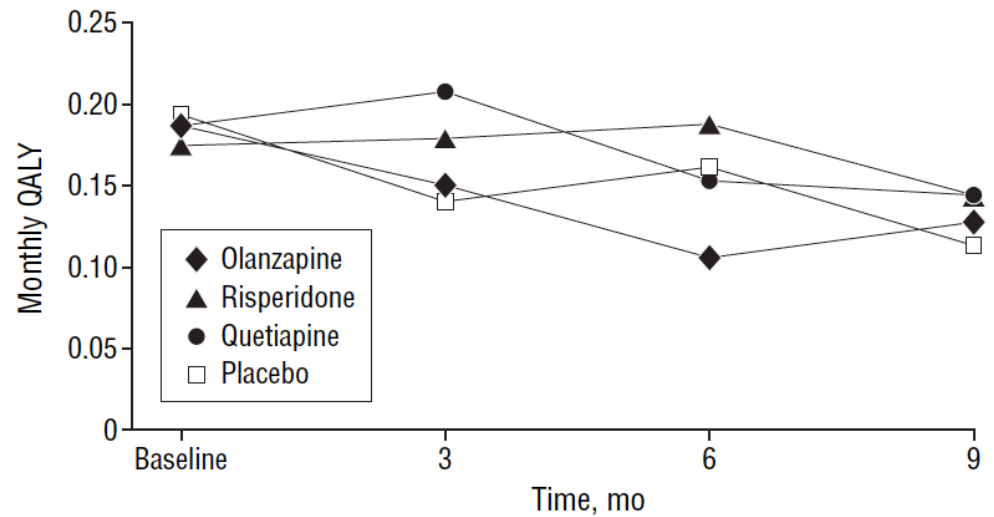
Outcome	RCTs	Odds Ratio	Treatment Rate	Placebo Rate	NNH
Mortality	14	1.52 (1.06-2.18)	3.6%	2.3%	77
Cerebrovascular	9	2.50 (1.36-4.60)	2.1%	0.9%	84
Extrapyramidal	12	1.74 (1.41-2.41)	15.2%	8.6%	16
Somnolence	11	2.95 (2.33-3.75)	17.0%	7.2%	11
Gait Abnormality	7	3.35 (2.06-5.46)	6.9%	1.7%	20
Agitation	9	0.80 (0.65-0.98)	10.6%	13.3%	38 NNT
Peripheral Edema ²	8	1.99 (1.20 –3.30)	9%	4%	20
UTI ²	11	1.51 (1.07 - 2.12)	13%	9.4%	28
MSE ²	7	Mean Difference	Worse by 0.73 (0.38 to 1.09)		

Adverse Events, Continued

- Withdrawal due to Adverse Events
 - Risperidone 1mg:¹ OR 1.43 [1.01, 2.03]. 11.8% vs 9.2%, NNH 39
 - Olanzapine 5-10mg:¹ OR 3.34 [1.69, 6.59]. 11.5% vs 3.7%, NNH 13
 - Haloperidol:² OR 2.52 [1.22, 5.21], 17% vs 7.2%, NNH 11
- Bottom-Line: Lots of harms, and some very concerning ones.

1) Cochrane 2006; 1: CD003476. 2) Cochrane 2002; 2: CD002852.

Are anti-psychotics cost effective?



- Bottom-line: Anti-psychotics are not cost effective because they had little effect (over placebo) but were more costly.

Stopping Anti-psychotics

- DART-AD:¹ RCT, 165 patients, mean age 85, 76% female, long-term care
 - Withdraw antipsychotic (placebo) or continue
- Outcomes: Behavior,² None stat sign.
 - Mortality: at 2 years, 71% continued anti-psychotic vs 46% placebo, (Diff = 25%, NNT 4)
- Sys Review: 9 trials. No diff behaviour³ except 1 RCT⁴
 - 110 pts with verified good response on Risperidone 1mg, withdrawn after 4-8 months:
 - 30% worsening of NPI: 60% placebo vs 33% risperidone, NNH 4
- **Bottom-Line:** Better to withdrawal soon unless you are sure they have had a good response and likely need it.

1) Lancet Neurol 2009; 8:151–57. 2) PLoS Med 5(4): e76.doi:10.1371/journal.pmed.0050076 3) Cochrane 2013;3: CD007726. 4) N Engl J Med 2012;367:1497-507.

Summing Up

BENEFITS

1. There was a statistically significant improvement in agitation/aggression behaviour scales with placebo.
2. There was a statistically significant but small improvement in agitation/aggression behaviour scales from anti-psychotics, compared to placebo.
3. When looking at numbers with meaningful change, that will occur in ~50% of patients on anti-psychotic, that is ~10-15% more than placebo.

HARMS

1. Antipsychotics have lots of harms, and some are very serious (stroke and Mortality), with NNH of ~80 (in 3 months).
2. Even though agitated and dementia, Adverse events will still cause 1 in 10 to 1 in 40 to withdrawal (over placebo)
3. Anti-psychotics reduce MSE by 0.73 (in 3 months)

Withdrawal

1. Withdrawal of anti-psychotics will delay one death for every 4 withdrawn, without worsening behaviour in most cases
2. Behaviour may worsen (for one in 4 over placebo) in cases in which benefit from anti-psychotic is verified.

Benzodiazepines

- 8 RCTs, benzodiazepine vs anti-psychotics, placebos or other drugs:
 - Diazepam vs Thioridazine (40 pts x 4wks): Thioridazine statistically better¹
 - Nurses rating of improvement: 70% Thioridazine vs 15% Diazepam. NNT=2.
 - Oxazepam vs Haloperidol vs Diphenhydramine (59 pts x 8 wks):² No statistical difference but Oxazepam worse behavioral scores.
 - Alprazolam vs Haloperidol (48 pts x 12 wks):³ Both treatments worse than baseline but no statistical difference.
 - Lorazepam vs Olanzapine vs placebo (272 pts x1d):⁴ Lorazepam 1mg similar to Olanzapine (5mg and 2.5mg), and all better than placebo.
 - 40% improved PANSS-EC (measures agitation) at 2 hours: Lorazepam 72%, Olanzapine 62-67%, placebo 37%. Lorazepam NNT=3.

1) South Med J. 1975;68: 719-724. 2) Am J Psychiatry. 1990;147:1640-5. 3) J Am Geriatr Soc. 1998;46:620-5. 4) Neuropsychopharmacology. 2002;26:494-504. 5) Clin Ther. 1984;6:546-59. 6) Dis Nerv Syst 1965; 26: 591-5. 7) Geriatrics. 1965 ;20:739-46. 8) Int Clin Psychopharmacol 1991; 6:141-6.

Benzodiazepines

- 8 RCTs, continued:
 - Diazepam vs Thioridazine vs placebo (610 pts x4wks):⁵ Diazepam worse than Thioridazine but better than placebo on some scales.
 - 1 point improvement on one anxiety scale: 65% Diazepam, 77% Thioridazine, 42% placebo.
 - Oxazepam vs placebo (100 pts):⁶ Oxazepam better.
 - “Moderate improvement” clinical response: Oxazepam NNT=2.
 - Oxazepam vs placebo (94 pts x8wks):⁷ Oxazepam better.
 - “Slight improvement” or better clinical response: Oxazepam NNT=5.
 - Temazepam vs Lorazepam (11pts x 1d):⁸ No statistical difference
- Harms: Poor reporting of harms.
 - Mild-moderate sedation: Lorazepam (10.3%) vs. Olanzapine 5mg (4.2%) vs Olanzapine 2.5mg (3%), placebo (3%).⁴

1) South Med J. 1975;68: 719-724. 2) Am J Psychiatry. 1990;147:1640-5. 3) J Am Geriatr Soc. 1998;46:620-5.
4) Neuropsychopharmacology. 2002;26:494-504. 5) Clin Ther. 1984;6:546-59. 6) Dis Nerv Syst 1965; 26:
591-5. 7) Geriatrics. 1965 ;20:739-46. 8) Int Clin Psychopharmacol 1991; 6:141-6.

Benzodiazepines

- Guidelines for agitation in dementia vary:⁹
 - Some (example British Columbia) discourage benzodiazepines because adverse events
 - Others (example American Psychiatric Association and NICE-UK) suggest considering short-acting benzodiazepines as needed for infrequent agitation.
- **Bottom-Line:** Many trials are old, most are short and/or small, and the results are inconsistent. Benzodiazepines appear, at best, equivalent to antipsychotics in reducing agitation in the short-term, but superior to placebo. If used, they should be stopped as soon as possible due to potential harms.

What about Anti-Cholinesterases?

- Meta-analysis of behavioral and psychological symptoms of Dementia: 12 studies (9 with enough data for analysis)
- ChEIs as a class had a beneficial effects on reducing BPSD:
 - BPSD = Behavioral and Psychiatric Symptoms of Dementia
 - SMD of -0.10 (CI; -0.18, -0.01) and
 - WMD of -1.38 neuropsychiatry inventory point (CI; -2.30, -0.46).
 - In mild AD patients, the WMD was -1.92 (CI; -3.18, -0.66);
 - In severe AD patients, the WMD was -0.06 (CI; -2.12, +0.57).
- Bottom-Line: “Clinical Relevance of this effect remains unclear”

The “other” med: Memantine

- Mostly Moderate - Severe Dementia
 - ADCS -ADL score, Severe impairment battery, Functional assessment Staging, Clinician Impression of Change (CIBIC): All 0-4% change
 - Possibly <agitation (NNT= 63) - if already on
 - Well Tolerated (no diff in drop-out due to AE)
 - Other studies use SMD statistic & can't interpret.³
- **Bottom-Line: Effects are small & inconsistent.**

Other Medications: Antidepressants

- SSRI:¹ 9 RCTs (692 patients)
 - Vs Placebo: CMAI, Mean Diff -0.89 [-0.57, -1.22]
 - No increased Withdrawal for AE.
 - Vs Haldol: CMAI, Mean Diff, 4.66 [-3.58, 12.90], favors Haldol
- Trazodone:² 2 RCTs (180 pts but not pooled):
 - Vs Placebo: No effect
 - Vs Haldol:¹ CMAI, Mean Diff, 3.28 [-3.28, 9.85], favors Trazodone

1) Cochrane 2011; 2: CD008191. 2) Cochrane: 2004; 3: CD004990.

Other Medications: Valproate

- Valproate: 5 RCTs (412 pts) x 6 wks
 - Outcomes
 - CMAI Mean Diff: -2.20 [-6.38, 1.99], No diff
 - BPRS Mean Diff: 0.23 [-2.14, 2.60], No diff
 - Any adverse event OR 1.99 (1.29-3.08), 75% vs 60% (NNH 7)
- **Bottom-Line:** SSRI Trazodone and Valproate likely have little to no reliable effect.

Remember pain

- RCT of assessing for pain
 - 920 Nursing home residents
 - 420 had moderate-severe dementia with behavioural disturbance (352 included)
 - 201 (57%) assessed as having pain (on the mobilisation-observation-behaviour-intensity-dementia-2 pain scale)
- Outcomes
 - 68% needed only acetaminophen, 32% got buprenorphine patch, pregabalin, & rarely morphine).
 - CMAI: -7.0 (-3.7 to -10.3). Others improved as well.
- Bottom-Line: Remember agitation may be from pain and as little as acetaminophen may help meaningfully.

Summing Up

- None of the other medicines (benzodiazepines, SSRI, trazodone, cholinesterase inhibitors, valproate) work well.
- Maybe benzo's as a back-up, but they may well work less than anti-psychotics and there is no evidence they are safer.
- Remember Pain as a possible cause of agitation.

Non-Pharmaceutical Interventions

- 1 Shiatsu & Acupressure
- 2 Aromatherapy
- 3 Massage therapy
- 4 Light (Bright) Therapy
- 5 Sensory Garden & Horticultural Activities
- 6 Music & Dance Therapy
- 7 Dance Therapy
- 8 Snoezelen Multisensory stimulation therapy
- 9 Transcutaneous electrical nerve stimulation.
- 10 Exercise therapy
- 11 Animal-Assisted Therapy
- 12 Combination of Therapies
- 13 Cognitive Stimulation
- 14 Reminiscence therapy
- 15 Validation Therapy
- 16 Simulated Presence therapy
- 17 Behavioral Management
- 18 Family care Support
- 19 Assisted Living Support
- 20 Residential Support
- 21 Animal-Assisted Therapy
- 22 Special Care Units
- 23 Dementia Care Map
- 24 Patient-Centred Care
- 25 Simulated Presence
- 26 *Many variations on themes above*

Non-Pharmaceuticals: Some that May Work

1. Activities (group or individual): e.g. cooking
2. Music Therapy (protocol)
3. Sensory Interventions
4. Working thru paid caregivers for person-centred care & Communication Skills
5. Dementia Care Map
6. Behavioral Management

Most are unclear as inadequate evidence:

- Example: Pet Therapy

Some are Don't Work

- Example Aromatherapy.

Ineffective Non-Pharmaceutical: Aroma therapy Example

- Early research:¹ pooled in “sensory” gave large change (Standard mean diff=1.07)
 - Pooled too many things and stats poorly reported
- Cochrane:² 7 RCTs (428 pts), mostly lavender
 - 5 RCTs used 3 agitation scales, results equivocal.
 - Adverse Events: equal between groups.
- HTA:³ 6 RCTs (276 pts)
 - good evidence from high-quality studies: no effect.
- **Bottom-Line**: Aroma therapy does not work!

Inadequate Nonpharmaceutical: Example Pet-Therapy

Pet Therapy

- HTA: 3 studies (non-randomized) with 26 participants total!
 - No statistical changes in agitation etc.
- 10 studies: 3 case-control or 7 time-series analysis
 - May be helpful but unclear
- Bottom-Line: Inadequate research.

Simulated Presence

- Simulated Presence
- 3 RCTs (144 pts)
 - Research soup (Two were 4 arms & one was three; two used cross-over, numbers small, varying measures some positive at some points versus some comparators).
- Bottom-Line: We don't know?

Non-Pharmaceutical: Things that likely work

	Effect Size	Studies (patients)
Activities (group or individual): e.g. cooking	-0.8 to -0.6	8 RCT (587) + 2 lower
Music Therapy (protocol)	-0.8 to -0.5	6 RCT (335) + 4 lower
Sensory Interventions	-1.3 to -0.6	7 RCT (508) +6 lower
Working thru paid caregivers for Person-Centred Care & Communication Skills	-1.8 to -0.3	7 RCT (952) + 1 lower
Dementia Care Map	-1.4 to -0.6	2 RCTs (226)
Behavioral Management	Not calculated	1 RCT (31)

- Lots of overlaps.
 - Example activities or sensory might have music as part them.
 - Example DCM and PCC often overlap in same

Non-Pharmaceutical: Activities

- HTA: 8 RCT (587)
 - Estimated Effect: SMD: -0.6 to -0.8
- Their Summary
 - Overall, activities in care homes reduce emergent agitation and decrease symptomatic agitation in care homes during the time they are in place.
 - Individualising activities does not appear to make significant additional reductions in agitation.
 - There is no evidence for those who are severely agitated or who are not in care homes.
- Bottom-Line: Does not persist after interventions regular use (1-4 weeks later), behaviour returns. Real uncertainty if there is an effect.

Non-Pharmaceutical: Music

5 or more sessions with a warm-up (familiar song), then listening, then joining in. Often 2 times per week for 6 weeks or more

- **HTA:** 6 RCTs (335 pts)
 - In care homes, music therapy by protocol is effective for emergent agitation and decreasing symptomatic agitation, but has no long-term usefulness in agitation.
 - There is no evidence for people with severe agitation. There is minimal evidence outside care homes.
- **Cochrane:** 16 RCTs (620 patients)
- **Findings:**
 - emotional well-being & quality of life (6 RCTs, 181 pts): SMD 0.32 (-0.08 to 0.71)
 - overall behaviour problems (6 RCTs, 209 pts): SMD -0.20 (-0.56 to 0.17)
 - agitation or aggression (12 RCTs, 515 pts): SMD -0.08 (-0.29 to 0.14).

Two others more positive.

Bottom-Line: The most unbiased work raises doubt whether music therapy can improve agitation in dementia.

Livingston. Health Technol Assess 2014;18(39). Cochrane 2017; 5: CD003477.
Front Psychol. 2017 May 16;8:742. Ageing Res Rev. 2017 May;35:1-11.

Non-Pharmaceutical: Sensory

- HTA: 7 RCT (508 pts): Therapeutic touch, massage, acupuncture, snoezelen, bathing with music, etc.
 - Estimated effect: SMD -0.6 to -1.3
- Their Summary
 - Sensory interventions significantly improved emergent agitation, symptomatic agitation, and severe agitation during the time the intervention took place.
 - Therapeutic touch has no added advantages.
 - There is insufficient evidence about long-term effects or in settings outside care homes.
- Cochrane: 7 possible RCTs, but only 2 used (but done 2006):
 - Too little evidence to say.
- **Bottom-Line:** Maybe but if an effect, not clear for how long.

Patient-Centred Care

- HTA: 7 RCT (952)
 - Estimated Effect: SMD -0.3 to -1.8
- One of the few with consistent evidence of benefit, often from higher quality studies, and persistence of effect (even up to 20 weeks)
- Their Summary
 - There is convincing evidence that training paid caregivers in communication or person-centred care skills is effective for symptomatic and severe agitation, both immediately and up to 6 months, in the care home setting.
 - There is preliminary evidence that it helps to prevent emergent agitation.
 - Evidence for settings other than care homes is limited.
- **Bottom-Line:** This likely work. It is tangled with Dementia Care Maps and Communication/Behavioural but the combination likely very helpful.

Dementia Care Mapping & Communication/Behavioural Management

- HTA: 2 RCTs (226)
 - Estimated Effect: SMD -0.6 to -1.4
- Their Summary
 - There is some evidence that DCM is effective immediately and over 4 months for severe agitation in care homes.
 - There is little evidence for emergent agitation or symptomatic agitation, or in other settings.
- Bottom-line: Likely works
- HTA: 1 RCT (31)
- Their Summary:
 - There is preliminary evidence that training paid caregivers in behavioural management and communication skills is effective in reducing agitation symptoms in assisted living settings in the short term.
 - There is no evidence in this setting for the longer-term effects.
- Bottom-line: Likely works

Complex Tools with education: Do they reduce anti-psychotic use?

- Cochrane: 4 RCTs (69 clusters of 4337 residents)
 - Complex educational/training & meetings for psychosocial interventions to reduce anti-psychotic use

Study	Follow-up Months	Treatment		Control		Final Difference
		Baseline > Finish	Diff	Baseline > Finish	Diff	
Avorn	6	29% > 24%	5%	26% > 25%	1%	4%
Fossey	12	47% > 23%	24%	50% > 42%	8%	16%
Schmidt	13	40% > 33%	7.0%	38% > 35%	3%	4%
Meador*	6	25 > 19	5.6 d	26 > 26	0.2 d	5.4 d

* Reported as antipsychotic use per 100 Patient Days

- **Bottom-Line: They work!**

Complex: Specialized Care Units

- Specialized Care Units: features of trained staffing, special programming, a modified physical environment, and family involvement
- Cochrane: No RCTs but 8 observational, at 6 months
 - NPI: 4.3 better vs placebo but others (e.g. CMAI) not statistical better.
 - Likely reduce used of restraints: Odds Ratio 0.46 [0.27, 0.80], 46% vs 61%, NNT 7
- Bottom-Line: As SCU include a lot of the features of complex interventions, they provide some benefit.

Summing Up

- Despite lots of great ideas, little good evidence to support non-drug measures
- Simple Interventions with possible benefit include activities, music and sensory stimulus. Sadly, there is still real uncertainty if these work reliably.
- Complex Interventions like Dementia Care Maps and trained Patient-Centred Care work but are complex and require broader system level commitment.