2016 Geriatric Year in Review

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Disclosures

Off-label use of dextromethorphan to be discussed in context of research study
Display of proprietary app software for educational purposes only
AGS Multiple Chronic Conditions “champion”

Learning Objectives

By the end of the session, participants will be able to:

• Consider practice changes based on recent publications
• Identify controversial that may affect the direction of research or practice
• Incorporate techniques of critiquing publications that emphasize geriatric outcomes

Selection Criteria

• Goal: improving care frail elders
• Focus: Continuum of care
  • Focus: reducing morbidity and/or improving function
• Themes

Outline

• Multiple Chronic Conditions
• (Deprescribing)
• Advance care planning
• Calcium & Vitamin D
• Hypertension treatment target
• Dementia

Prevalence of multiple chronic conditions in the aging population

Source: Medical Expenditure Panel Survey, 2006
Comorbidities: CMS data

2008

Source: CMS. Chronic Conditions among Medicare Beneficiaries, 2011.

Medical condition = pill

Management of each multiple chronic condition (MCC)?

- Generalization to old-old is questionable
  - Most subjects middle aged or young-old
  - Most trials excluded cognitive conditions
  - NF residents generally excluded
- Following concomitant clinical guidelines:
  - Polypharmacy!
  - Confusing, expensive, and potentially dangerous
- Alternative: ascertain patient care goals!

MCC: there's an app for that!

Better management of complex medication regimens

- Deprescription
  - Needs a talk by itself
- Better prescription of currently used drugs
  - Addressed by BEERS 2015
  - Renal dosing
- Recognition: management takes more time!
  - Newer codes: CCM, TCM, ACP

You are invited to the prescribing/ deprescribing breakout session today!
Justice Anthony Scalia

- Sudden cardiac death
  - at 79 years and 11 mo.
- Right until death he was:
  - Hearing cases in highest court
  - Participating in a hunting trip
  - Dining in a luxury resort with friends on his last night
- Many (most?) older adults live their remaining days with infirmity, loss of dignity, and may be in an ICU or nursing home.

Serious Illness & Advance Care Planning

NOT, in general, = hospice discussion

- One serious illness, OR
- Multiple chronic conditions
- Rising appreciation of the need to have better ACP “upstream” from hospice

Centers for Medicare & Medicaid Services

- 99497 and if applicable 99498
- Can be used with
  - Annual Wellness Visit (AWV) or with
  - Any other type of visit
- AWV: no co-insurance or deductible
- Time-based code
  - Bill when half-way through

Definition per CMS

- face-to-face service between a physician (or other qualified health care professional) and the patient discussing advance directives, with or without completing relevant legal forms. An advance directive is a document appointing an agent and/or recording the wishes of a patient pertaining to his/her medical treatment at a future time should he/she lack decisional capacity at that time

More details

- Who? Physician, Non-physician practitioners
  - “Incident to” is allowed
- Primary v. specialty? Not limited
- Outpatient v. inpatient? Not restricted but
  - Not certain critical care services including “neonatal and pediatric critical care”
- Can be in a nursing home
- Frequency per year? Per provider? Other qns?
  - Contractors deciding for now

Does ACP pay?

<table>
<thead>
<tr>
<th>CPT / HCPCS</th>
<th>Description</th>
<th>Work RVUs</th>
<th>Non-Facility</th>
<th>Facility</th>
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<tbody>
<tr>
<td>99212</td>
<td>Est visit level 2</td>
<td>0.48</td>
<td>$43.68</td>
<td>$25.42</td>
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<tr>
<td>99213</td>
<td>Est visit level 3</td>
<td>0.97</td>
<td>$108.13</td>
<td>$79.13</td>
</tr>
<tr>
<td>99214</td>
<td>Est visit level 4</td>
<td>1.5</td>
<td>$108.13</td>
<td>$79.13</td>
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<tr>
<td>99495</td>
<td>Trans care mgmt 14 day d/c</td>
<td>2.11</td>
<td>$165.42</td>
<td>$111.35</td>
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<td>99496</td>
<td>Trans care mgmt 7 day d/c</td>
<td>3.05</td>
<td>$233.09</td>
<td>$161.12</td>
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<tr>
<td>99497</td>
<td>Advanced care plan 30 min</td>
<td>1.50</td>
<td>$85.93</td>
<td>$79.49</td>
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<tr>
<td>99498</td>
<td>Advanced care plan 30 min</td>
<td>1.4</td>
<td>$74.83</td>
<td>$74.47</td>
</tr>
<tr>
<td>99490</td>
<td>Chf care mgmt svc 20 min</td>
<td>0.61</td>
<td>$40.82</td>
<td>$31.51</td>
</tr>
</tbody>
</table>

How important in 2016 is:

- **Vitamin D**
  - Uusi-Rasi in Finland. JAMA int med 2015
  - Hansen in Wisconsin. JAMA int med 2015

### Finnish group: 74 yo F fallers
- 2 year study, high-er risk pts
  - Would you have referred a high risk pt to this study?
- Adding Vit D to nearly normal Vit D levels did not alter risk injurious falls
- **Message:**
  - Multi-dimensional exercise is a stronger intervention than 800 U Vit D with normal or nearly normal levels of vitamin D

### Wisconsin: 61 yo F Vit D insuff
- Only 1 year duration
- Vitamin D was not deficient
- This group is too young to have many falls, fractures
  - FRAX low risk
- No message
  - Would hip density have improved with longer duration treatment? In those with Vit D deficiency?

### Summary

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### Monthly v. Daily

### Vitamin D supplementation

- 1 year, DB, RCT in Zurich
- 200 M, W 70+ yo in community, prior fall
- 3 treatment arms of Vitamin D3
  - one tsp of monthly 24K IU + 3 PL caps, OR
  - one tsp of monthly 60K IU + 3 PL caps, OR
  - One tsp placebo, 2 caps 12K IU each + 1 cap 300 μg calcifediol (liver metabolite of Vit D)

#### Results
- Mean age 78 (5); 67% F
- Vitamin D levels at baseline:
  - 42% ≥ 20 ng/mL
  - 58% < 20 ng/mL
  - 13% severely deficient (< 10 ng/mL)
- 9 dropped out over 1 year (4.5%)
  - 2 died, 2 strokes, 2 NH, hip surg, frail, w/drew c/s
- All groups had similar reduction in iPTH
- No difference in SPPB between groups
- 60.5% fell during the 1-year study

### Outcome

- Exclude
  - M,W taking > 800 IU/d Vit D at baseline
  - M, W unwilling to d/c additional calcium, Vit D supplementation
  - MMSE < 27 (of 30)
- **Outcome:**
  - Short Physical Performance Battery
  - 25-OH-Vit D level > 30 ng/mL at 6 & 12 months
  - Falls (secondary outcome)
Results

Figure 2. Unadjusted 25(OH)D Levels by Treatment at Baseline, 6 Months, and 12 Months

![Bar chart showing 25(OH)D levels by treatment at baseline, 6 months, and 12 months.](Bischoff-Ferrari. JAMA Int Med 2016)

Comments

- No one received placebo, or
  - Daily vitamin D 800 U/d
- Dietary Calcium?
- High risk community but not necessarily “frail”
- Higher pulsed doses
  - 60,000 IU/mo or 24,000 IU/mo w/ 300 IU calcifediol
  - Associated with higher # falls and fallers than 24,000 IU/month total Vitamin D

Too much of a good thing?

- 500,000 Units/year cholecalciferol
  - “average” 1370 U/d
- Versus placebo
- Initial serum Vit D 49 nmol/L
- Level reached 120 nmol/L at 30d
- ↑ 15% risk falls, ↑25% fractures

Sanders. JAMA. 2010

How important in 2016 is:

- Calcium
  - Calcium and bone density. BMJ 2015
  - Calcium and fracture risk. BMJ 2015
Calcium may not be benign

- Prevents or impairs absorption of
  - Fluoroquinolones, Tetracyclines
  - Betapace (sotalol)
  - Diltiazem, verapamil, Levothyroxine,
- May increase absorption of
  - Lanoxin (digoxin)
  - Dietary Aluminum

Calcium intake and fracture risk
Systematic review

- Fractures not primary outcome in any
- Studies 37 dietary calcium; 14 milk; 8 dairy
- Most found: no association btw intake & fx risk
- 26 RCT of calcium supplements (69K subjects)
  - 20 studies, n=59K. RR total fracture
    • 0.89 (95% 0.81-0.96)
  - 12 studies, n=49K. RR vertebral fracture
    • 0.86 (95% 0.74-1.0)
  - 13 studies, n=57K. RR hip fracture
    • 0.95 (0.76-1.18)
- Eggers & visual inspection suggest most: publication bias
- No association at all if only lower biased studies used

What else do we need to know?

- Calcium: very small BMD improvement
  - COULD ↓ fracture risk in frail elders?
- Role fruits/vegetables under-appreciated
  - Alkalizing effect to reduce resorption of bone
- Diets rich in fruits vegetables in youth
  - Associated with ↑ peak bone mass
  - Particular in girls Tylavsky, Am J Clin Nutr. 2004
- DASH diet x 3 months Lin, J Nutr 2003
  - Resulted in decrease markers bone turnover

Adding calcium supplement in treating osteoporosis

- Hard to find an osteoporosis study w/o calcium
  - Subjects generally rec’d “adequate” calcium, vit D
- 2-yr study 700 post-menopausal women
  - Mean 20 year post-menopause
  - Subgroup with alendronate AND calcium-rich diet AND vitamin D 400 IU/d
  - RCT additional Ca++ 1000 mg/d OR placebo
  - Outcome: No difference in 2-year bone density
  - Ca++ suppl group had lower Ur NTx
    • Longer treatment- will it reduce future fracture risk?

Only 4 lower biased studies!

- Jackson 2006 (WHI)
  - 50-79 48
  - 7 yrs. 1000 mg Ca++, 400 IU Vit D
  - Hip density. NS. Fx. ↓ Risk renal stone
- Grant 2005
  - 70+ 38 2 yrs. 1000 mg Ca++, 800 IU vit D
  - NS Fx
- Prince 2006
  - 70+ 67.87 5 yrs. 1200 mg Ca++
  - NS ITT. ↓34% risk total fx in compliant patients
- Reid 2006
  - 74 52 5 yr. 1000 mg/d
  - Less bone loss. NS Fx

Bolland. BMJ. 2015

Favors calcium. Favors placebo

Calcium & % change in Hip BMD

Tai & Bolland. BMJ. 2015

Bolland. BMJ. 2015

Bonnick. Curr Med Res Opin. 2007
Calcium message:

- Calcium may reduce fracture risk slightly
  - Amount calcium needed unknown - likely have to be compliant
  - Benefit (if any) in high-risk patients (ours!!)
  - Modest amounts may be fine
    - If compliant, if adequate Vitamin D
    - AND if not interacting with other medications

SPRINT trial

- 9,361 adults > 50y, sBP > 130 mmHg +
  - Framingham Risk 15% or higher, or
  - 75+ years, BUT EXCLUDE those with
    - DM, stroke, dementia, proteinuria, GFR < 20
    - Standing sBP < 110
- 5 year RCT to sBP target < 120 v. < 140
- Intensive: start 2-3 drugs. If > 75, start 1 drug
- Outcomes:
  - 1st: Composite of Stroke, heart failure, mortality
  - 2nd: Individual components; eGFR by 30% or 50%; incident U. albuminuria; cognitive

OMRON 907 Automated cuff

Mean of 3 measurements, seated, after 5 minutes of rest. Monthly visits until target

Target blood pressure by age (no compelling indications)

<table>
<thead>
<tr>
<th>Guide/ Age (yrs)</th>
<th>JNC 7 2003</th>
<th>JNC 8 2015</th>
<th>AHA/ ACC 2011</th>
<th>Europe 2013</th>
<th>CHEP 2013</th>
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<tbody>
<tr>
<td>&lt; 60</td>
<td>140/90</td>
<td>140/90</td>
<td>-</td>
<td>140/90</td>
<td>140/90</td>
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<tr>
<td>60 – 79</td>
<td>140/90</td>
<td>140/90</td>
<td>140/90</td>
<td>150/90 or &lt; 140/90 if “fit”</td>
<td>140/90</td>
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<tr>
<td>80+</td>
<td>140/90</td>
<td>140/90</td>
<td>140-145 and NOT &lt; 130/65*; 150/90 or ? if frail</td>
<td>150/90</td>
<td></td>
</tr>
<tr>
<td>80+ or frail</td>
<td>--</td>
<td>Discretionary</td>
<td>Discretionary</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>

*Based on Denardo, AJM, 2010

Study Methods

- 102 clinical sites in US + Puerto Rico
- Sponsor: NHLBI, Neuro, NIA
- Free formulary drugs - all major classes
  - Chlorthalidone (diuretics); Amlodipine (CCB’s)
  - Takeda & Arbor pharma contributed:
    - Azilsartan & azilsartan/chlorthalidone
- Assumed 1st event rate of 2.2%/year
- Independent data/safety monitoring
  - Stopped the study after median of 3.3 years
  - Lower rate 1st composite outcome achieved

Results

- Mean age 68 years; 36% F; 29.5% 31.1%
- 28.2% were 75+; 28.4% with CKD (eGFR < 60)
- Baseline Mean BP 140/78
  - 31.8% between 132 and 145 mm Hg
  - Mean BMI 30; Mean # antihypertensives: 1.8
  - 9.4% were not taking any anti-hypertensives
  - 13% current tobacco; < half took statins
  - Half took aspirin
- Dropouts (d/c, lost, w/drew consent)
  - Intensive: 10.5%; standard: 10.6%
sBP in the SPRINT trial

Mean 1.8 anti-hypertensives

Mean 2.8 anti-hypertensives - target not reached

Primary Composite Outcome
2.2%/yr std, 1.65%/yr intensive

Sprint. NEJM. 2015

Serious adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Intensive # (%)</th>
<th>Standard # (%)</th>
<th>HR (p value)</th>
</tr>
</thead>
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<tr>
<td>Hypotension</td>
<td>83 (1.8)</td>
<td>37 (0.8)</td>
<td>2.52 (&lt;.001)</td>
</tr>
<tr>
<td>Syncope</td>
<td>64 (1.4)</td>
<td>28 (0.6)</td>
<td>2.15 (.06)</td>
</tr>
<tr>
<td>Electrolyte abn</td>
<td>69 (1.5)</td>
<td>48 (1.0)</td>
<td>1.58 (.05)</td>
</tr>
<tr>
<td>AKI or ARF</td>
<td>88 (1.9)</td>
<td>34 (0.7)</td>
<td>3.14 (&lt;.001)</td>
</tr>
</tbody>
</table>

* No difference in injurious falls!

Greater CKD is associated with greater abnormal White matter volume in brain

SPRINT. NEJM. 2015

SPRINT. NEJM. 2015

SPRINT. NEJM. 2015

SPRINT. NEJM. 2015
Comments on SPRINT
- Benefit above and below 75 yr old
- Target sBP between 120 and 125 mmHg resulted in
  - 1st outcome, mortality
  - Including adults 75+ o/w healthy

SPRINT. NEJM. 2015

Caution re: SPRINT
- What if the subjects were better optimized (i.e. taking aspirin, statins)?
- Cannot extend to
  - frail elders (older subjects more “fit” than elders in the community)
  - dementia; severe CKD
  - diabetics, NF residents
- Intensive control MAY ➔ higher risk of
  - Progression to CKD (mind-kidney connection?)
  - Hypotension, syncope, AKI/ARF, dehydration

SPRINT. NEJM. 2015

Cognitive outcome?
- SPRINT-MIND subgroup (2,800 subjects over 48 months) 2 outcomes: cognitive; volume of brain white matter
- Baseline group is published (neurology 2016)
- Awaiting peer review publication relative to the target blood pressures

FDA approved drugs for dementia

<table>
<thead>
<tr>
<th>Medication</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholinesterase inhibitors:</td>
<td></td>
</tr>
<tr>
<td>Donepezil (Aricept)</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Rivastigmine (Exelon)</td>
<td>Nausea</td>
</tr>
<tr>
<td>Galantamine (Razadyne)</td>
<td>Syncope</td>
</tr>
<tr>
<td></td>
<td>Bradycardia</td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
</tr>
<tr>
<td>Memantine (Namenda)</td>
<td>Dizziness</td>
</tr>
<tr>
<td></td>
<td>Insomnia or fatigue</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td>Donepezil &amp; Memantine (Namzaric)</td>
<td>All of the above</td>
</tr>
</tbody>
</table>

Sheffrin. JAGS. 2015

Time to lost 10 # NNH 21 over 1 year (95% CI 12.5 – 71.4)

Drugs on the Horizon for Alzheimer's Disease?
- Three categories of drugs 2002 - 2014
  - Symptomatic (36.6%)
  - Disease modifying- small molecule (35.1%)
  - Disease modifying- immunotherapy (18%)
- Since 2002
  - 413 AD trials with 244 drugs
  - 1 approved by FDA (memantine in 2004)
  - 99.6% approval failure rate
- As of 2/2014, only 22 drugs in Phase I
- Desperate need to have more drugs in pipeline

Cummings. Alz Res & Therapy. 2014

Symptom Control Agitation in AD
- Common, distressing to caregiver
  - Aggressive physical (destroy, grab, fight), and/or
  - Aggressive verbal (scream, curse), and/or
  - Non-aggressive physical (pacing, fighting)
- No FDA approved treatment
Agitation in Alzheimer Disease Dementia

- Dextromethorphan-quinidine 30/10 bid
- Phase 2 RCT, DB, placebo controlled. All settings
  - Clinical Global Impression-Severity agitation score 4+
    - Serial, parallel, comparative design
    - Two 5-week stages to manage placebo effect
      - Stage 1: 93 to drug, 127 to placebo
      - Stage 2: placebo non-responders re-randomized drug v. PL
  - Outcome:
    - change in NPI agitation/aggression domain
    - ADCS CGIC, PGIC, ADL, Cornell scale, MMSE, QTc

Results

- Mean age 77.8 yr, 56.5% W, 88% outpatient
- More than 88% retention rate
- Baseline
  - MMSE 17.3 (of 30), Caregiver Strain Index 6.8 (of 26)
- Concomitant drugs:
  - 73% AChI; 49% memantine;
  - 56% anti-depressants; 20% antipsychotics
- Common adverse effects:
  - Falls (8.6 v. 3.9%); diarrhea (5.9% v. 3.1%);
  - UTI (5.3% v. 3.9%); dizziness (4.6% v. 2.4%)
- ↑ Mean QTc during study: 5.3 ms
  - 10% on drug & 6.7% on placebo had ↑30 ms in QTc

Cautious Comments

- Improvements in agitation & caregiver strain
  - May facilitate staying longer in community
  - May not apply to NH residents
- Need longer follow-up
- Will likely see this novel study design in future
- ↑ QTc small but may be important for some
- More falls in treated group
  - Baseline h/o falls unevenly distributed (17.2% v. 12.6%)
- Awaiting phase 3 trial

Did you need some coffee to get through my presentation?

- Observational study
  - Nurses’ Health Study- 74,908 W
  - Health Professionals FU Study – 40,557 M
- Consumption total, caffeinated, decaf intake
- Results:
  - Interaction with smoking
  - Non-linear relationship
  - Overall slightly less mortality with 1-5 C/d !!

Mortality inversely related to coffee (even decaf) consumption

- Ding. Circulation AHA. 2015
Summary

- Multiple Chronic Conditions:
  - Patient centered care goals
  - Deprescription- including hi-dose Ca++ & vit D
- Hypertension
  - Consider lower goals for healthy but at-risk elders
  - Monitor eGFR and orthostasis
- Progression of cognitive impairment
  - No successful drugs in the immediate future
  - Anticipate research focused on symptom management

Subgroups in SPRINT

<table>
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<tr>
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<th>Standard # (%)</th>
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<td>125 (2.7)</td>
<td>58 (1.2)</td>
<td>2.24 (&lt;.001)</td>
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<td>Syncope</td>
<td>94 (2.0)</td>
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<td>Bradycardia</td>
<td>51 (1.1)</td>
<td>29 (0.6)</td>
<td>1.68 (0.05)</td>
</tr>
<tr>
<td>Electrolyte</td>
<td>93 (2.0)</td>
<td>62 (1.3)</td>
<td>1.61 (.02)</td>
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<tr>
<td>Injurious fall</td>
<td>36 (0.8)</td>
<td>23 (0.5)</td>
<td>2.22 (0.05)</td>
</tr>
<tr>
<td>AKI or ARF</td>
<td>96 (2.1)</td>
<td>36 (0.8)</td>
<td>3.13 (&lt;.001)</td>
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SAE or ED visit

- 365 deaths
  - 155 in intensive treatment
  - 210 in the standard treatment
  - HR 0.73 (95% CI 0.60 to 0.90)
- NNT
  - 61 to prevent primary outcome event
  - 90 to prevent death from any cause
  - 172 death from cardiovascular cause

SPRINT v. ACCORD

Both with intensive BP arm

Questions?

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THE END!
Drugs and Behavioral and Psychological Symptoms of Dementia

- CATIE-AD 2006: anti-psychotics ineffective for dementia with psychosis, aggression, or agitation
  - Known adverse effects: stroke, TIA, diabetes, death in demented elders
- Donepezil &/or Memantine
  - Efficacy with behavior in secondary analyses
  - Benefit not seen with larger, better-designed studies
- Antiepileptic drugs: carbamazepine, gabapentin, valproate
  - Gabapentin: CS reports, series, retrospective chart reviews
  - Benefit, wide range of doses (100 – 2400 mg/24 h) mainly young/middle-aged
  - Kim, Williams, Tampi. Drugs Aging 2008
- Benzodiazepines: Systematic review 2014 by Tampi
  - Total 5 RCT. 4/5 did not support benzo use
  - High dropout rate, confusion, falls in older adults
- Cit-AD 2014: 30 mg/d citalopram reduced agitation
  - Prolonged QTc. MMSE 1 point lower in treated group

Aging and blood pressure

- Poorly controlled BP in midlife
  - Dementia, other adverse outcomes late life
  - What is optimal control in late life?
- 1,861 geriatric unit patients 75+
  - Years 2000-2004
- Data: VS, Exam, MMSE, BADL & IADL, GFR
  - Comorbidities, medication classes
  - Most took antihypertensives
- Analysis: age strata, gender, education, comorbidities, renal function

DANTE Study Leiden

- Community based, RCT, blinded outcome, 2014
- 385 adults, 75+ y, MMSE 21-27, 16 weeks
- sBP ≤ 160 mm Hg on antihypertensives
  - If PAD, CAD, DM sBP ≤ 140 mm Hg
- Intervention: DC antihypertensives
  - By algorithm until sBP by 20 mm Hg
  - Control: continue
- 1st Outcome: change in compound cognition
  - 2nd outcome: GDS 15, functional impairment, quality life
- Result:
  - sBP in discontinued group about 10 mm Hg higher than control

Perspective on treating BPSD

- Non-pharmacological FIRST and THROUGHOUT
  - Reducing somatic, psychological symptoms caused by environment
  - Training the caregiver(s) re:
    - Non-escalation; de-escalation
- Pharmacological approach
  - #1 Cognitive enhancer (indicated!!)
  - Antipsychotic if physically aggressive, dangerous
  - Gabapentin (few ADE but least evidence) or other AED’s
  - Consider melatonin at night; low dose benzo’s
  - Dextromethorphan & quinidine (high cost)

DC Antihypertensive discontinuation

- Groningen Activity Restriction Scale (18 ADL qns, 1-4pts each qn)
  - Higher score ----> more impairment

Results: sBP, function, cognition related for lower functioning elders

- Ogliari. JAGS. 2015

Groningen Activity Restriction Scale (18 ADL qns, 1-4pts each qn)
  - Higher score ----> more impairment
Comparing BP studies

**Milano**
- Cross-section
- Geriatrics “Unit”
- Mean age: 82, DM 12%
- Antihypertensives: 2/3
- Alzheimer’s disease: 25%
- Mean MMSE = 26
- Outcome: MMSE
- Result: In low functioning elders, cognition in mid & high tertiale sBP (144, 169 mm Hg) differ from lower tertiale (124) but not from each other

**Dante**
- Deprescription study
- Community, MMSE 21-27
- Mean age: 81, DM 21%
- Alzheimer’s disease: unk
- Median MMSE = 26
- Outcome: compound of psychomotor speed, recall, executive function
- Result: sBP about 10 pts higher than control at 16 wks
- No cognitive differences
- Majority subjects would fall into the middle tertial of Milano before/after the intervention

Milan Geriatrics. Ogliari. JAGS. 2015