PainWeek

ADVANCED EDUCATION

CERTIFICATION SERIES

Deprescribing in Palliative Care

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Titles and Affiliations

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Disclosures

Learning Objectives

- Describe the nature of polypharmacy, and how deprescribing can be used as an antidote.
- Given a simulated patient with an advanced illness, evaluate the benefits and burdens of their medication regimen.
- Given a simulated patient with an advanced illness, describe a communication strategy to use with family members regarding deprescribing.

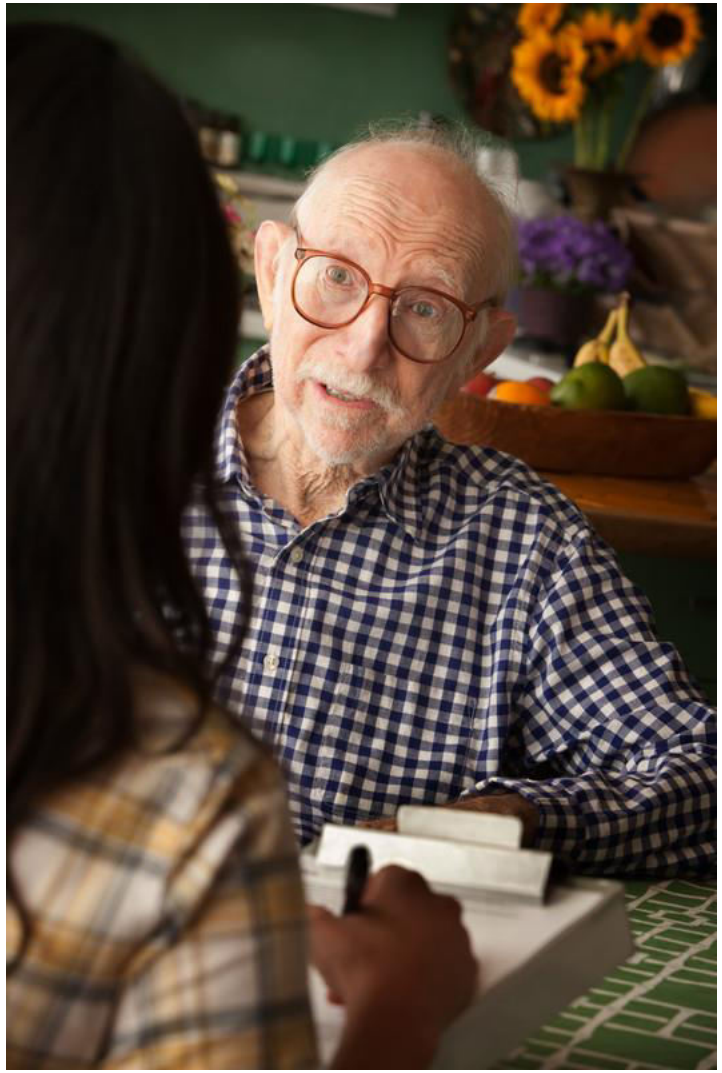
What's the Sitch?

- Thanks to advances in medical science…
  - People are living longer, albeit with multiple comorbid conditions
  - Multimorbidity often required more complex medication regimens
  - Polypharmacy (the concurrent use of 5 or more medications) is steadily increasing
    - 8.2% from 1999-2000
    - 15% in 2011-2012
  - Polypharmacy in long term care facilities:
    - 91% of residents receive more than 5 medications
    - 74% receive more than 9 medications
    - 65% receive more than 10 medications
  - Polypharmacy increases the risk of medication-associated adverse effects

Kantor et al. *JAMA*. 2015;314(17):1818-1831.
Jokanovic et al. *J Am Med Dir Assoc*. 2015;16(6).

Consequences of Polypharmacy in Older Adults

- Increased risk of adverse effects
- Frailty, delirium, cognitive decline
- Disability, hospitalization
- Mortality



What's the scoop with hospice/palliative care patients?
We add MORE medications for pain
and symptom management!
High anticholinergic, sedation burden
Often elderly, reduced functional status

Medication Use at the End of Life

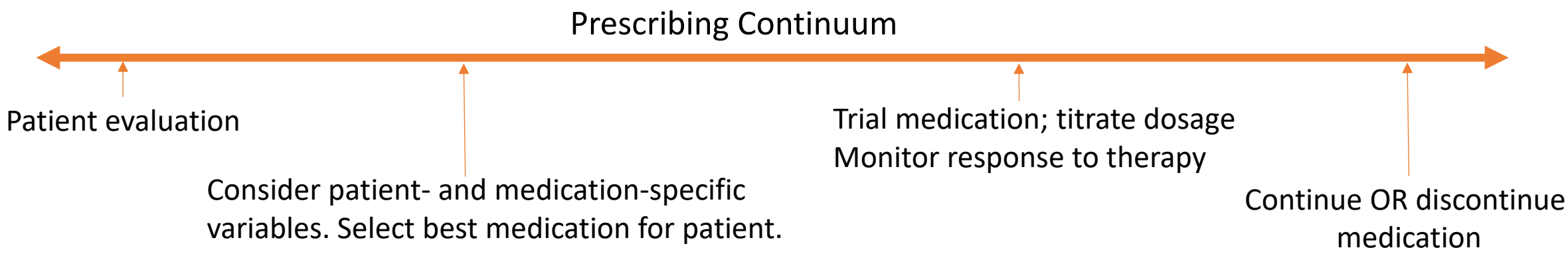
- Do patients take MORE medications as they approach the end of life?
- Are practitioners stopping medically futile medications in advanced illness?
  - Medications that slow disease progression, preventative medications
- Patients at EOL are likely frailer than the general population
  - Greater risk for medication-induced adverse effects
  - Declining organ function
  - Age-related changes in pharmacodynamics and pharmacokinetics
- Study in Sweden – in year before death, % of patients taking ≥ 10 medications increased from 30.3% to 47.2%

Morin, Vetrano, Rizzuto, Calderón-Larrañaga, Fastbom, Johnell. *Am J Med*. 2017;130(8):927-936.e9.

If polypharmacy is the problem….

- What's the solution?
- WITHDRAWING medications
  - De-intensification
  - The "geriatrician's salute"
  - **Deprescribing**

Deprescribing:
"The process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes."



Hilmer. *Age Ageing*. 2018;47:638-640; Reeve. *Br J Clin Pharmacol*. 2015;80:1254-1268.

Views, Attitudes, Barriers, Enablers – What do patients say?

Patients

- 80% agreed they are comfortable with the number of medications they take
- 75% said they would like to reduce the number of medications they take

Medicare Patients

- 92% agreed they would be okay stopping one or more meds if their MD okayed
- 67% agreed they would like to reduce the number of meds they take

Long TC Patients

- 40% said they wished to stop taking one or more medications
- 80% said they were okay stopping one or more meds if their MD okayed

Sirois. *Res Soc Admin Pharm*. 2017;13:864-870; Kalogianis. *Res Soc Admin Pharm*. 2016;12:784-788; *JAMA Intern Med*. 2017.

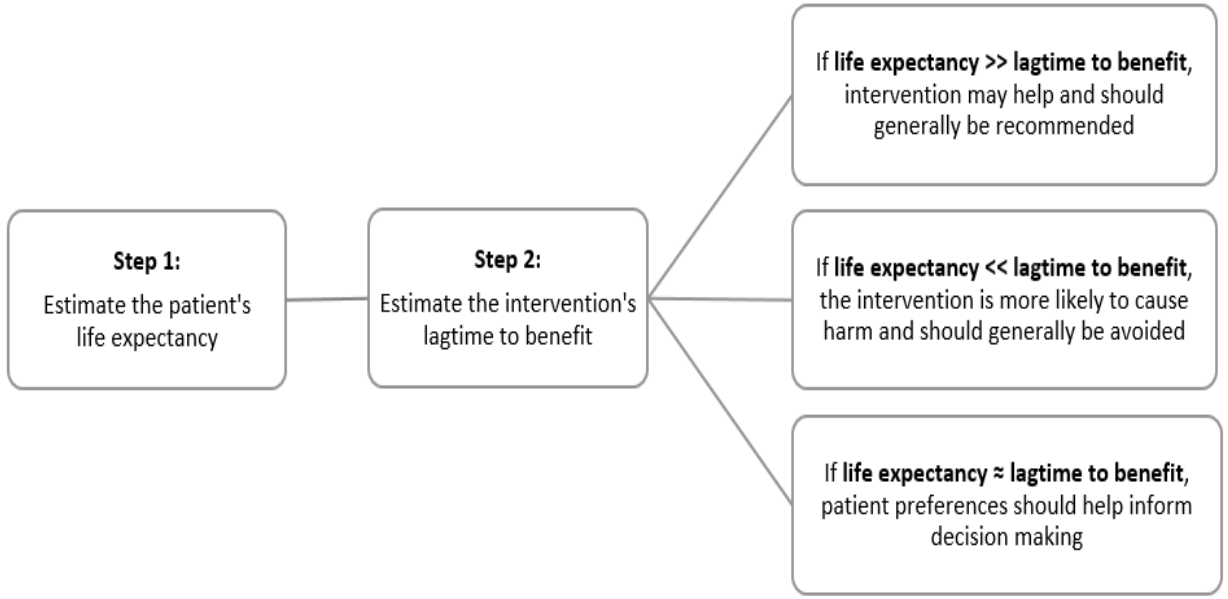
What do physicians say about this?

- 75% of physicians said they were confident in deprescribing
- Fewer are comfortable stopping guideline-recommended meds
- 40% of physicians are reluctant to stop a medication started by another physician
- 45% of physicians are reluctant to stop a medication that the patient or caregiver thought was important to continue
- Some MD's felt deprescribing is like "swimming against the tide"
- Barriers include medical culture of deprescribing, patient expectations, and organizational constraints

Djatche. *J Clin Pharm Ther*. 2018;43:550-555; Wallis. *Ann Fam Med*. 2017;15:341:346.

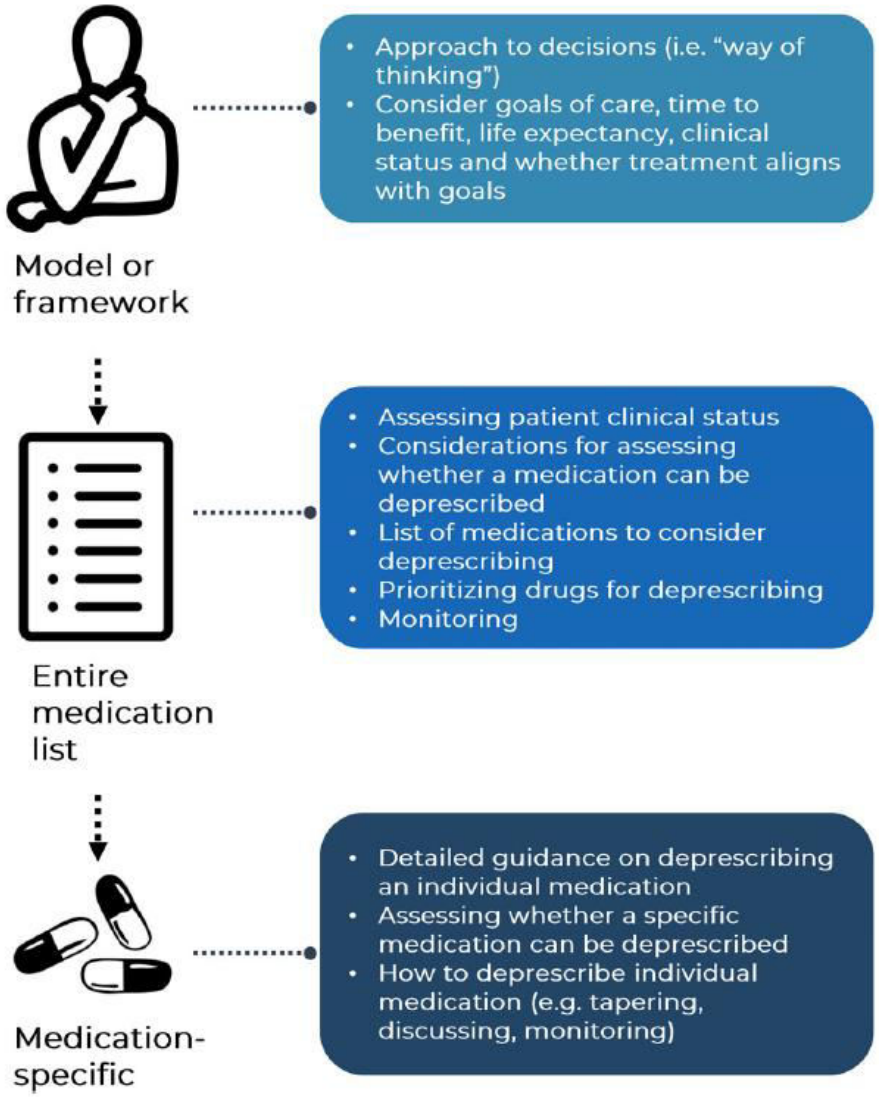
What do prescribers think about this?

- 321 physicians surveyed about prescribing practices at the EOL
- ~75% agreed that patients at EOL receive too many medications
- Given a hypothetical case, tremendous variability in deprescribing
- What data informs deprescribing at EOL?
  - Remaining life expectancy
  - Time until benefit
  - Goals of care
  - Treatment targets
  - NNT (# needed to treat)
  - NNH (# needed to harm)
  - Persistence of benefit

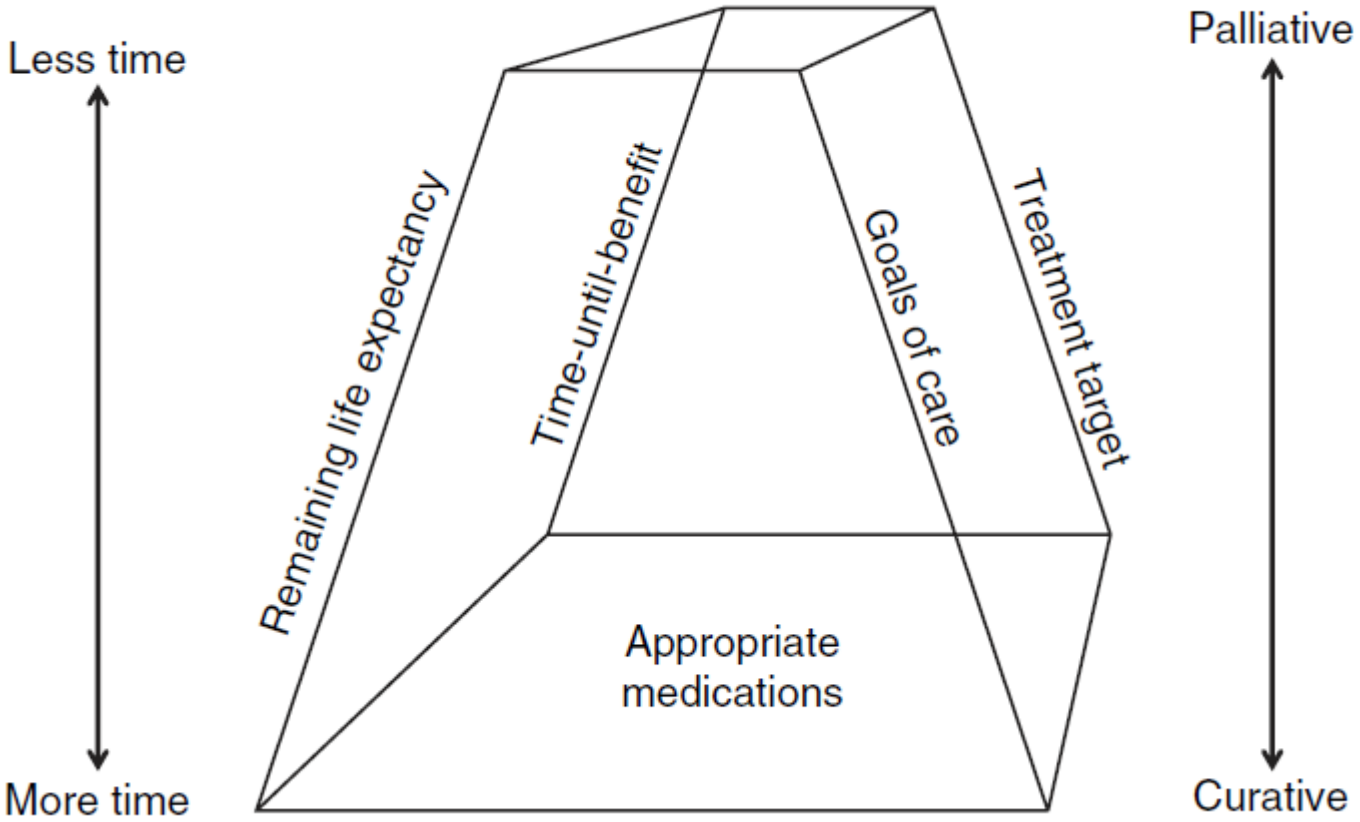


Geijteman, Huisman, Dees, et al. *J Palliat Med*. 2018;21(8):1166-1170.

- Tools for Deprescribing in Frail Older Persons and Those with Limited Life Expectancy: A Systematic Review



Thompson, Lundby, Graabaek, et al. *J Am Geriatr Soc*. 2019;67(1):172-180.



Holmes. *Clin Pharmacol Ther*. 2009;85(1):103-107.

Drugs are rarely indicated if they do not confer a…

Patient

Important

Outcome

Preventive Drugs

- ***Those that prevent future morbid events***
  - ***Statins, warfarin, bisphosphonates***
- Supplements (MVI, calcium, folic acid, ferrous sulfate…)
- Bisphosphonates
  - DC'ing alendronate after 5 years of treatment results in no increase in osteoporotic fractures over the ensuing 5 years
  - Ceasing use of statins for primary prevention after taking for years results in no increase in cardiovascular events 8 years after discontinuation

Statins: Let It Go, Let It Go (no, seriously, let it go!)

- Overview
  - Multicenter, unblinded trial to evaluate the safety and clinical impact of discontinuing statins in the palliative care setting.
- Study Participants
  - English-speaking patients ≥ 18 years of age
  - ≥ 3 months on a statin for primary/secondary prevention with recent functional decline, no active cardiovascular disease
  - Advanced life-limiting disease, defined as:
    - Treating MD “would not be surprised if the patient died within a year”
    - Life expectancy of > 1 month
    - Recent deterioration of AKPS to < 80% in last 3 months

Kutner, Blatchford, Taylor, et al. [published correction appears in *JAMA Intern Med*. 2015 May;175(5):869] [published correction appears in *JAMA Intern Med*. 2019 Jan 1;179(1):126-127]. *JAMA Intern Med*. 2015;175(5):691-700.

Methods

- 381 patients (49% cancer)
- Patients randomized 1:1 to discontinue or continue statin medication
- Pearson chi-square to compare responses between study groups and between those with and without cancer.

Kutner, Blatchford, Taylor, et al. [published correction appears in *JAMA Intern Med*. 2015 May;175(5):869] [published correction appears in *JAMA Intern Med*. 2019 Jan 1;179(1):126-127]. *JAMA Intern Med*. 2015;175(5):691-700.

Overall Results of Study

- Primary endpoint – rate of death within 60 days
  - Not significantly different among:
  - Those who discontinued statins (20.3%)
  - Those who continued (23.8%)
  - Those who DC'ed statins had a longer median time to death (229 days) vs 190 days for those who continued statin therapy (not ss)
- Cost estimates on money saved if patients with prognosis < 1 year discontinued statins
  - $603 million in the USA
  - In 2040, could reach $1 billion/year

Kutner, Blatchford, Taylor, et al. [published correction appears in *JAMA Intern Med*. 2015 May;175(5):869] [published correction appears in *JAMA Intern Med*. 2019 Jan 1;179(1):126-127]. *JAMA Intern Med*. 2015;175(5):691-700.

Medication Perception Questions

- Patients surveyed to determine if they were worried about having statin discontinued
  - < 5% of patients felt that indicated their physician was giving up on them
  - < 15% thought stopping statin meant taking the statin previously was a waste of time
  - Only 11% worried about unintended consequences of discontinuing their statin

Kutner, Blatchford, Taylor, et al. [published correction appears in *JAMA Intern Med*. 2015 May;175(5):869] [published correction appears in *JAMA Intern Med*. 2019 Jan 1;179(1):126-127]. *JAMA Intern Med*. 2015;175(5):691-700.

Slowing Disease Progression/Complications

- ***Metabolic syndrome***
  - ***Dyslipidemia, hypertension, diabetes***
- Neurodegeneration diseases
  - ALS
  - Alzheimer's disease
- Cancer
- Pulmonary hypertension

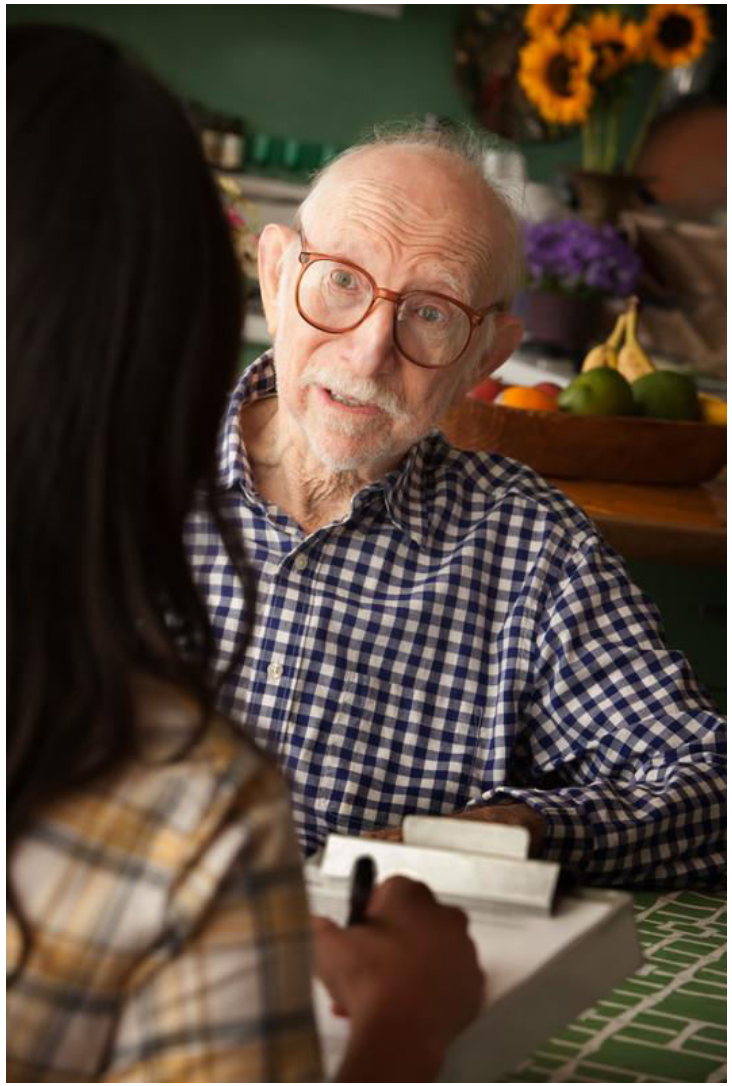
Metabolic Syndrome?

- A group of risk factors that raise the risk of heart disease, diabetes, stroke, and other health problems
- According to the American Heart Association, about 1/3 of all adults have metabolic syndrome

Diagnosed with 3 of 5 Risk Factors

- National Cholesterol Education Program Adult Treatment Panel
  (NCEP ATP) III
- Metabolic syndrome is defined as:
  - Central obesity (defined by waist circumference)
  - Plus 2 of the following 4 factors:
    - Increased triglycerides, or treatment thereof
    - Reduced HDL cholesterol, or treatment thereof
    - Increased blood pressure or treatment thereof
    - Raised fasting plasma glucose or previously diagnosed diabetes

Mr. Herndon



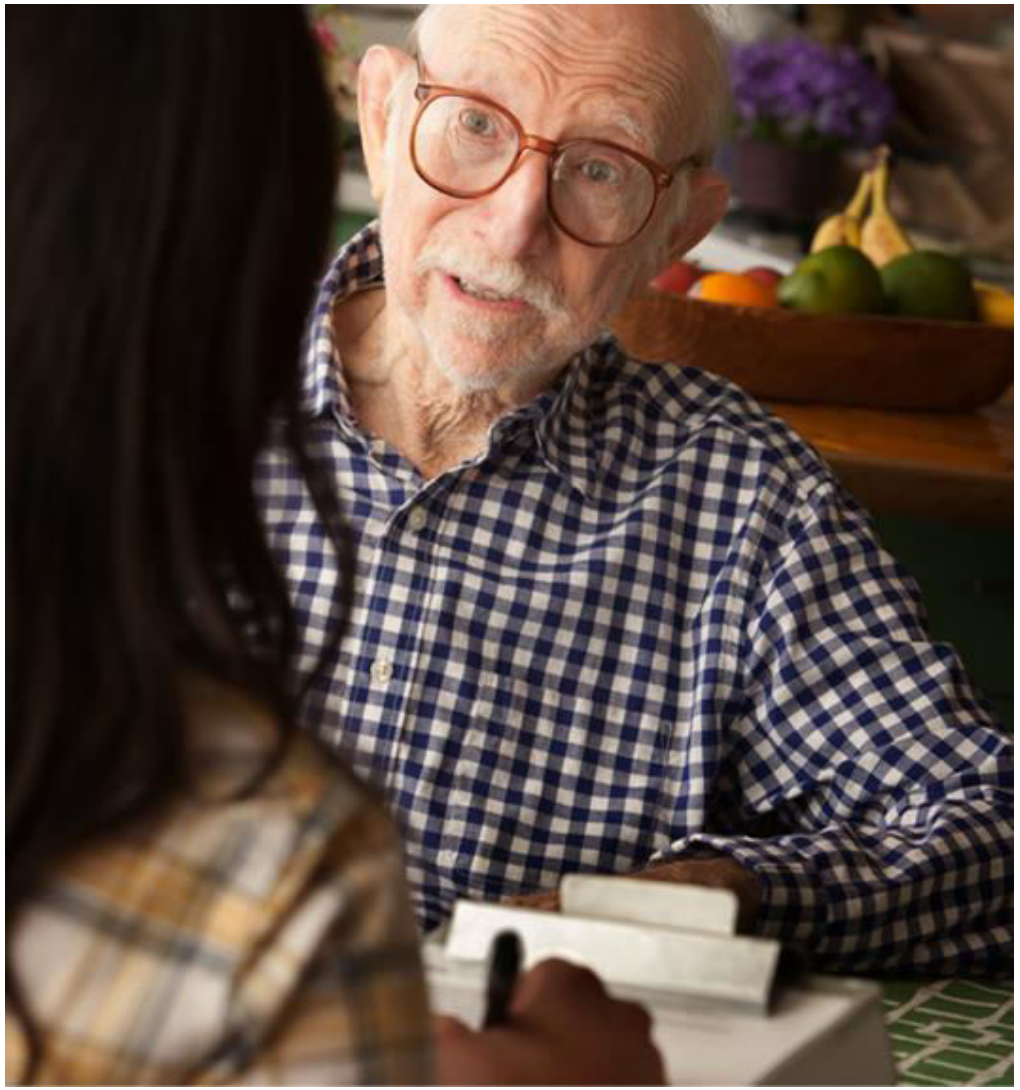
- 76-year-old man admitted to hospice with stage 4 nonsmall cell lung cancer.
- Prognosis is 4-6 weeks according to his oncologist
- He has comorbid conditions of:
  - Type 2 diabetes mellitus
  - Hypertension
  - Chronic kidney disease stage 4
  - Dyslipidemia
  - 80 pack-year history of smoking; stopped 1 year ago when diagnosed with lung CA

Medication History

Medication	Directions for Use/Indication	Date Started
Atorvastatin 40 mg (Lipitor)	Once a day for dyslipidemia	2010
Metformin ER 1,000 mg	2 tablets diabetes for T2DM	2009
Lantus insulin	20 units at bedtime daily for T2DM	2014
NovoLog insulin	Sliding scale 4 times daily for T2DM	2019
Lisinopril 10 mg	Once daily for hypertension	2015
Amlodipine 5 mg	Once daily for hypertension	2016
Multivitamin with iron	Once daily for general health	2000
Acetaminophen XR 650 mg	2 capsules every 8 hours for pain	2020
MS Contin 30 mg	Every 12 hours for pain	2021
Roxanol 10 mg	Every 2 hours as needed for pain	2021
Senna	2 tablets daily	2021

Mr. Herndon

- 5’10”
- Weighs 165 pounds at present (lost 100 pounds since diagnosis)
- Waist circumference 34
- Rarely, if ever, uses sliding scale NovoLog insulin
- Complaints of hypoglycemia symptoms occasionally
- Last A1c 6.9% six months ago
- BP about 120/70 seated, gets “woozy” when he stands

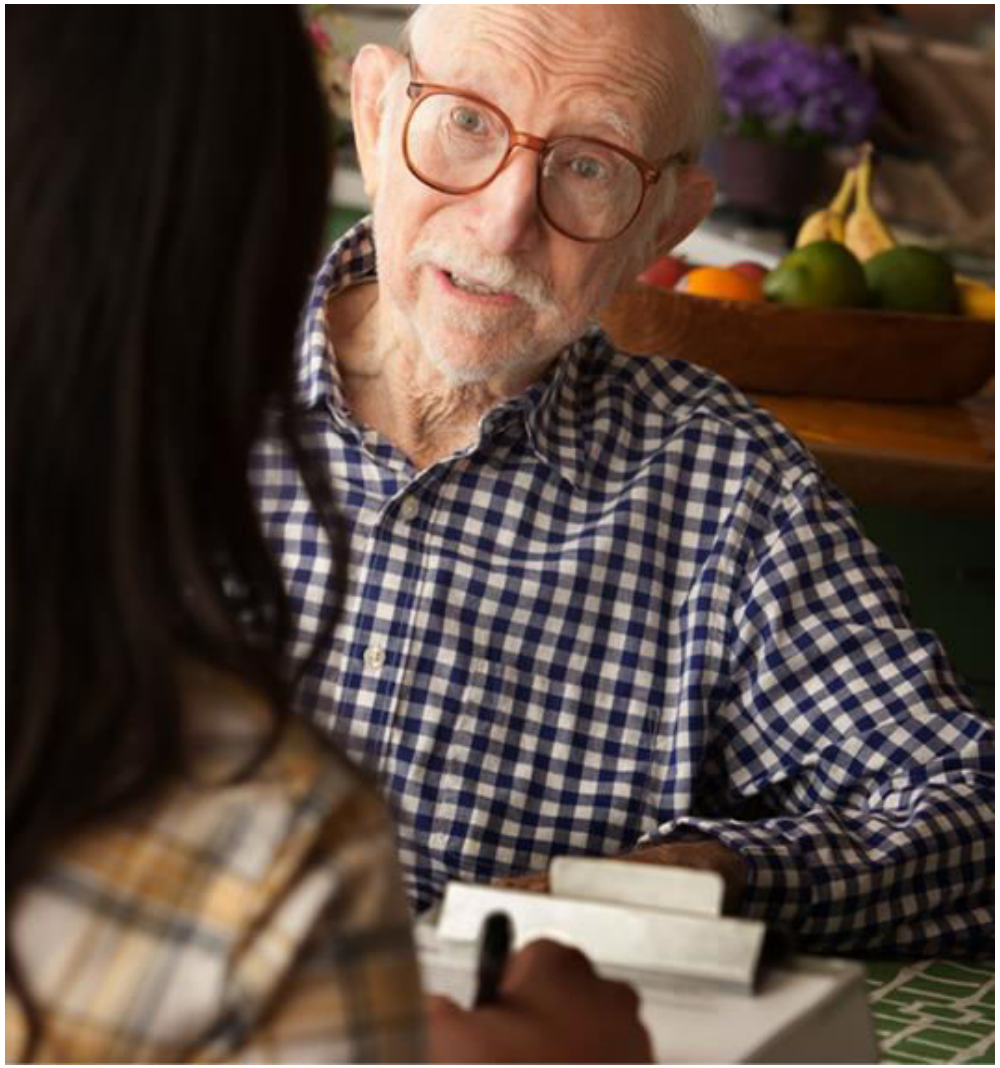


Mr. Herndon

- When you suggest slimming down his medication regimen, he gets VERY upset and cries:

- “WHAT? My heart doctor and regular doctor said I had to stay on these medications til the day I die! Are you saying I’m going to die tomorrow? You young whipper-snappers always want to upset the apple cart!”

- So, young whipper-snapper, how do you respond?



Multivitamin with Iron

- If Mr. Herndon feels strongly about keeping this medication, that's fine
- The iron and vitamins/minerals are probably increasing his risk of constipation and may cause a little nausea
- The iron may also turn his stools dark, making it hard for us to determine if he's bleeding internally, but that's unlikely
- Let's throw him a bone with the MVI!

Analgesics and Laxative

- Once someone is taking 60-70 mg a day of oral morphine, they can't tell the difference with or without acetaminophen
  - Patient's wishes? Liver disease? Alcoholism?
- Is morphine controlling the pain?
- Is Senna maintaining normal bowel function?

Atorvastatin

- Patient has been taking for DECADES! No wonder he's attached to it!
- Never had an MI or CVI (but no guarantee he won't)
- Kutner, et al. evaluated 381 patients within 1 year of death, taking a statin
  - Randomized to continue or stop statin therapy
  - Primary outcome – rate of death at 60 days
  - No statistically significant difference

Discontinued Statin	20.3% died by 60 days	Median time to death 229 days
Continued Statin	23.8% died by 60 days	Median time to death 190 days

- Anglo-Scandinavian Cardiac Outcomes Trial:
  8 years AFTER study completed evaluating atorvastatin impact, patients who HAD been taking atorvastatin had fewer deaths from CV and non-CV disease!

Sever, Dahlöf, Poulter, et al. *Lancet*. 2003;361(9364):1149-1158. doi:10.1016/S0140-6736(03)12948-0.

Statin Chat…

- “Mr. Herndon, kudos to you for taking atorvastatin all these years.
- Obviously, it’s been providing you benefit because you’ve not had a heart attack or stroke.
- But the good news is that research has shown that the benefit you accrued from taking atorvastatin all those years was like putting money in the bank, and even if we discontinue the atorvastatin now, you will continue to reap the benefits.
- Research has further shown there is not an increased risk of a heart attack or stroke for people clinically similar to you.
- While statins do not cause major side effects, it would be one less tablet you have to take, and you’d have less risk of side effects such as muscle weakness.”

Antihypertensives

- HELLO – Mr. Herndon is experiencing side effects from his antihypertensive regimen right NOW!
- His BP is low-normal and he is complaining of orthostasis
- Minimally we should stop one (lisinopril or amlodipine) now
- He’s lost 100 pounds, so his BP has naturally declined
- Let’s stop the amlodipine and re-evaluate
- Chances are good we can reduce the lisinopril to 5 mg for a few days, then stop that as well

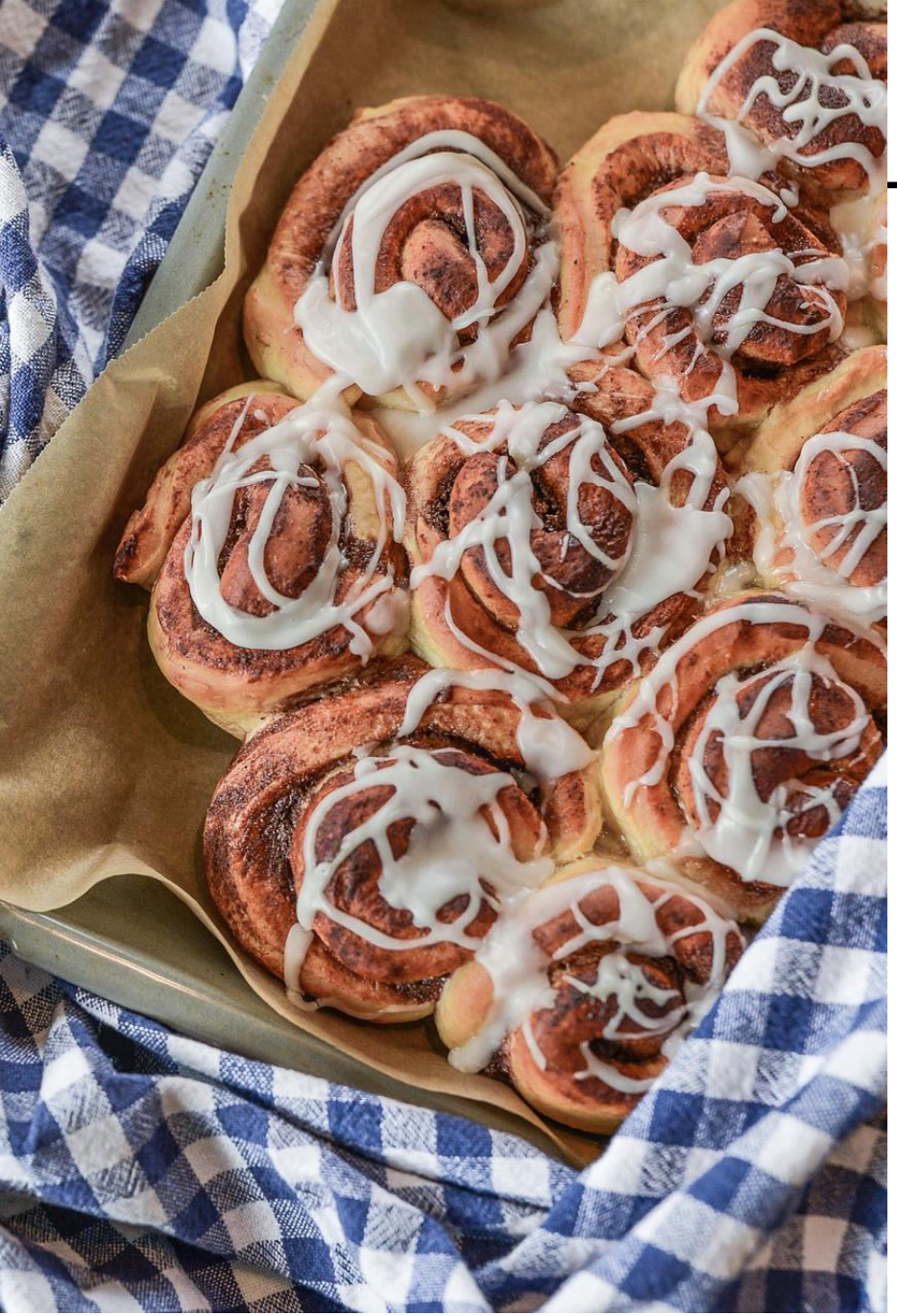
Antihyperglycemics

Mr. Herndon has had diabetes for many years and is on:	Metformin	NovoLog sliding scale insulin	Lantus? First…
• Metformin XR 1000 mg, 2 tablets per day • Lantus insulin 20 units at bedtime • NovoLog insulin sliding scale 4 times daily	• Patient has chronic kidney disease, stage 4, CLcr 15-30 ml/min; contraindicated	• Not requiring; increases risk of hypoglycemia	• Let's consider what we know about diabetes and glucose control first before we address the Lantus

DCCT Trial – Early 1990s

- Patients with T1DM divided into 2 groups – tight BG control and usual BG control
  - Half had no complications of DM; half had early complications
- Those who achieved tight BG control had a 40%-60% reduction in development of complications; and those with complications had much slower progression.
- Fast forward to 17 years after STARTING the DCCT trial
  - Those who had been in the tight glycemic arm had:
    - 42% risk reduction in any cardiovascular event
    - 57% risk reduction in risk of nonfatal MI, stroke, or death from CV disease

Mazze, Bergenstal, Ginsberg. *Int J Clin Pharmacol Ther*. 1995;33(1):43-51.



What does this mean for Mr. Herndon?

- All those years he watched his diet, took his medications, monitored his BG – it was like putting money in the bank!
- Now we can loosen the reins a bit and he can "draw his dividends," secure in the knowledge that his risk of diabetes-related complications is extremely low
- We will monitor him for symptoms suggestive of hyperglycemia

So what about the Lantus?

- Let's stop the metformin and NovoLog insulin now
- Let's check the fasting BG 3 times in the next week
- Even if his BG is up to 200 mg/dl, it's probably ok
- We may be able to reduce the Lantus, or even stop it at some point
- STOP checking his BG 4 times a day – that's NOT very palliative!

Diabetes Convo…

- “Mr. Herndon, you deserve an ENORMOUS amount of credit for following your diet and your diabetes medication regimen for all these years.
- And like the statins, research has shown that tighter blood glucose control starting at the time of diabetes diagnosis leads to an accrued benefit in reduction of complications later in life.
- You’re not even using the NovoLog insulin because your blood glucose isn’t getting high enough to warrant it.
- You’ve lost a lot of weight and you’re not eating like you used to.

Diabetes Convo…

- Given your kidney disease, we really should stop the metformin so you won't have any side effects.
- Let's stop the metformin and the NovoLog insulin.
- Let's follow your blood glucose over the next week or so and make a decision about whether or not to continue the Lantus at your current dose, or to reduce it.
- In the meantime, we can liberalize your meal plan, and stop checking your blood glucose so frequently."

Mr. Herndon

A. Sir, you are a few weeks away from death; does it really matter what your cholesterol, blood pressure, and blood glucose are?

B. You aren't dying TODAY but within a month or so, and it's really unlikely you'll have a heart attack or stroke, so I feel lucky!

C. No, obviously you aren't dying today, but all medications have risks and benefits, and no medication is meant to be continued FOREVER (and you start humming "Let It Go" under your breath)

D. We'll take a look at each of your medications, and you and I and your family will discuss this with your doctor and our doctor, and make decisions that give you the most benefit from your medications, and cause the least harm. Sound good?

Slowing Disease Progression/ Complications

- Metabolic syndrome
  - Dyslipidemia, hypertension, diabetes
- Neurodegeneration diseases
  - ALS
  - ***Alzheimer's disease***
- Cancer
- Pulmonary hypertension

The Case of Miss Judy

Judy is a 78-year-old female

- **CC:** Repeated falls in the past 3 months
- **PMH:** Breast cancer, hypertension, dyslipidemia, nonvalvular atrial fibrillation (no h/o CVA), Alzheimer's disease (FAST 7C - > 10% weight loss, recent UTI)
- Lives with daughter, Laura, in Maryland
- Son, Frederick, is a lawyer who lives in California

The Case of Miss Judy

Judy is a 78-year-old female

Current Medication Regimen

- Donepezil (Aricept®)
- Memantine (Namenda®)
- Lisinopril
- Atorvastatin (Lipitor®)
- Warfarin
- MVI
- Ferrex
- Calcium and vitamin D3

- When you suggest slimming down on the medications, Laura is agreeable.
- Frederick, on the other hand, goes ballistic and angrily says, **"What's WRONG with you people – are you TRYING to kill her off?"**
- So…..any issues here?

“Cognitive Enhancers”

Drug Category	Drug Name(s)	Indication(s)
Cholinesterase Inhibitors ($6-8/day)	Donepezil	Treatment of dementia of the Alzheimer’s type. Efficacy has been demonstrated in patients with mild, moderate and severe Alzheimer’s dementia.
	Galantamine	Treatment of mild to moderate dementia of the Alzheimer’s type.
	Rivastigmine	Treatment of mild, moderate and severe dementia of the Alzheimer’s type. Treatment of mild to moderate dementia associated with Parkinson’s disease.
NMDA Antagonist ($6-8/day)	Memantine	Treatment of moderate to severe dementia of the Alzheimer’s type.

FAST Criteria

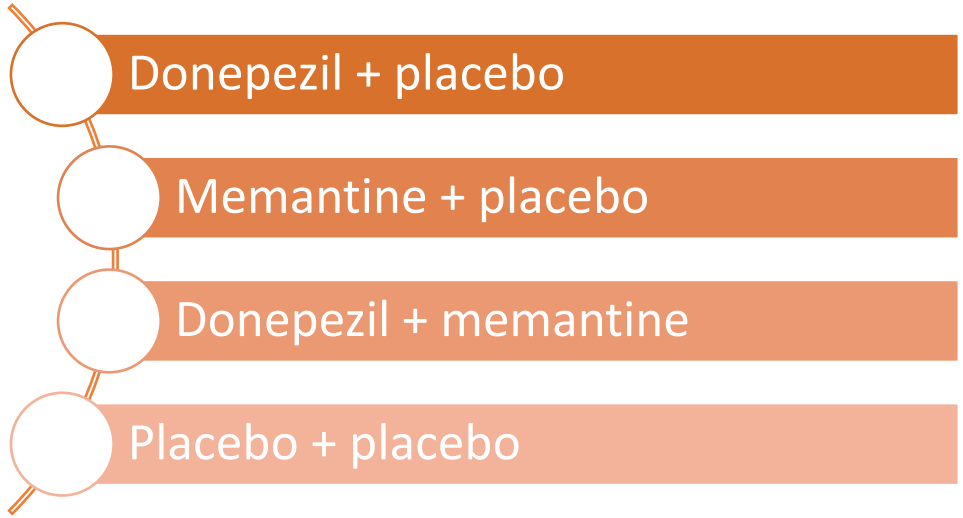
1. Normal adult
2. Normal older adult
3. Early dementia
4. Mild dementia
5. Moderate dementia
6. Moderately severe dementia
7. Severe dementia

- 7a. Ability to speak limited to approximately a half dozen different words or fewer, in the course of an average day or in the course of an intensive interview.
- 7b. Speech ability limited to the use of a single intelligent word in an average day or in the course of an interview (the person may repeat the word over and over).
- 7c. Ambulatory ability lost (cannot walk without personal assistance)
- 7d. Ability to sit up without assistance lost (eg, the individual will fall over if there are no lateral rests [arms] on the chair)
- 7e. Loss of the ability to smile

avalonmemorycare.com/the-seven-stages-of-dementia-understanding-the-fast-scale/.

Donepezil and Memantine for Moderate-to-Severe AD

- 295 community-dwelling moderate-to-severe AD patients treated with donepezil for at least 3 months (MMSE 5-13); 52 weeks
- Stratified by
  - Study center
  - Duration of donepezil treatment before entry (3-6 mo vs ≥ 6 mo)
  - Baseline MMSE (5-9 vs 10-13)
  - Age (< 60; 60-74; ≥75)



Howard, McShane, Lindesay, et al. *N Engl J Med*. 2012;366(10):893-903.

Donepezil and Memantine for Moderate-to-Severe AD

- Outcomes:
  - Score on MMSE - Clinically important difference:
    - **Scoring 1.4 points or greater higher than comparator**
  - Caregiver-rated Bristol activities of Daily Living Scale (BADLS): Clinically important difference:
    - **Scoring 3.5 points or greater lower than comparator**
- Baseline MMSE 9.1-9.2 in all groups
- Baseline BADLS 26.9-28.6

Howard, McShane, Lindesay, et al. *N Engl J Med*. 2012;366(10):893-903.

Donepezil and Memantine for Moderate-to-Severe AD

- Clinically important difference:
  - MMSE ≥ 1.4 point increase or greater
  - BADLS ≥ 3.5 point decrease or greater

Treatment group	MMSE	BADLS
All donepezil vs no donepezil	**+1.9**	-3.0
All memantine vs no memantine	+1.2	-1.5

- Effect of donepezil and memantine did not differ significantly in the presence or absence of either
- Donepezil plus memantine showed no difference vs donepezil alone

Howard, McShane, Lindesay, et al. *N Engl J Med*. 2012;366(10):893-903.

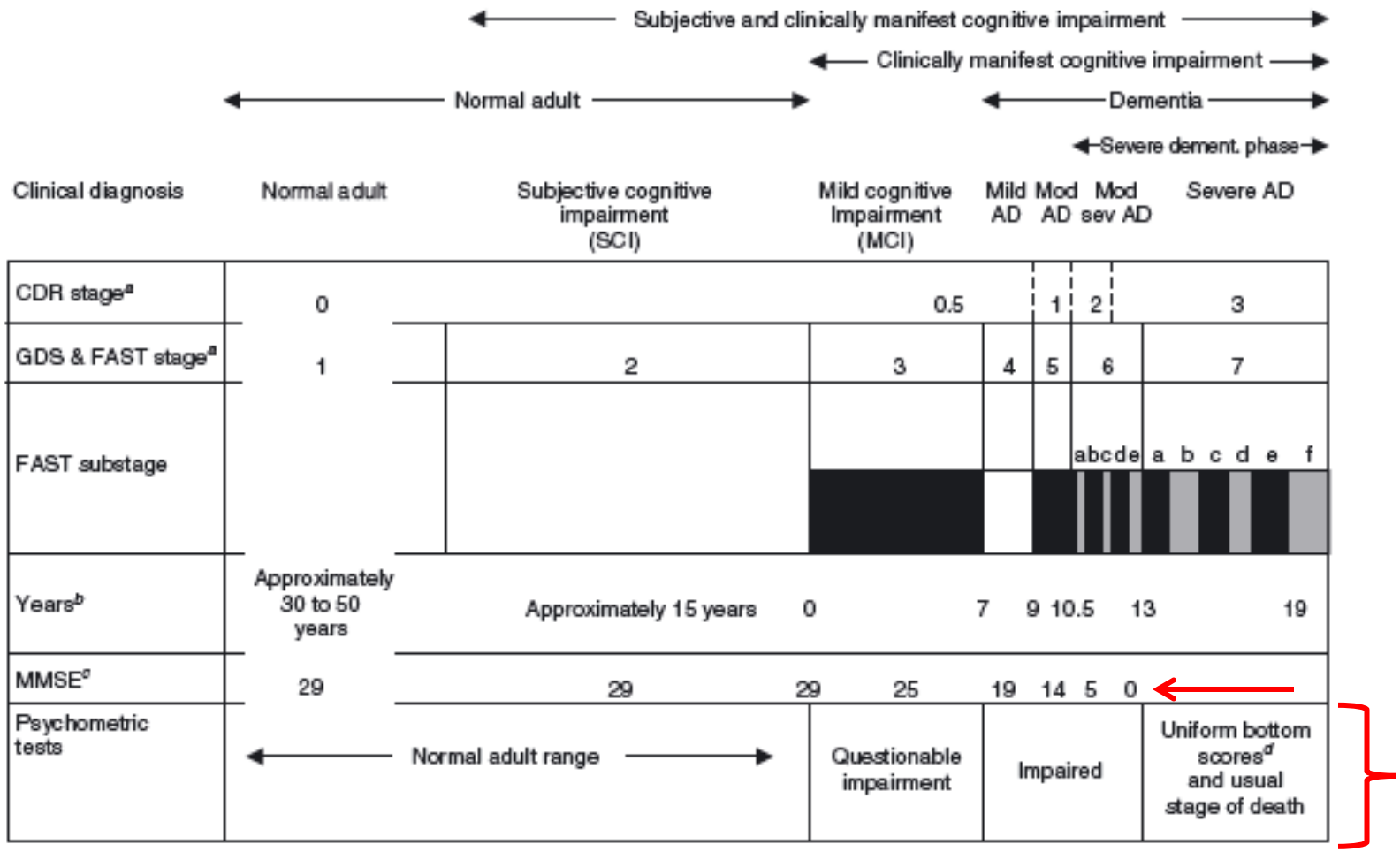
Donepezil and Memantine for Moderate-to-Severe AD

Baseline MMSE	Impact of donepezil therapy on MMSE
MMSE 10-13	**+2.6**
MMSE 5-9	+1.3

Donepezil only showed clinical significance in patients with baseline MMSE ≥ 10

Howard, McShane, Lindesay, et al. *N Engl J Med*. 2012;366(10):893-903.

FAST and MMSE



Reisberg. *Prin Prac Ger* Psy, 3rd ed. Used with permission, John Wiley and Sons.

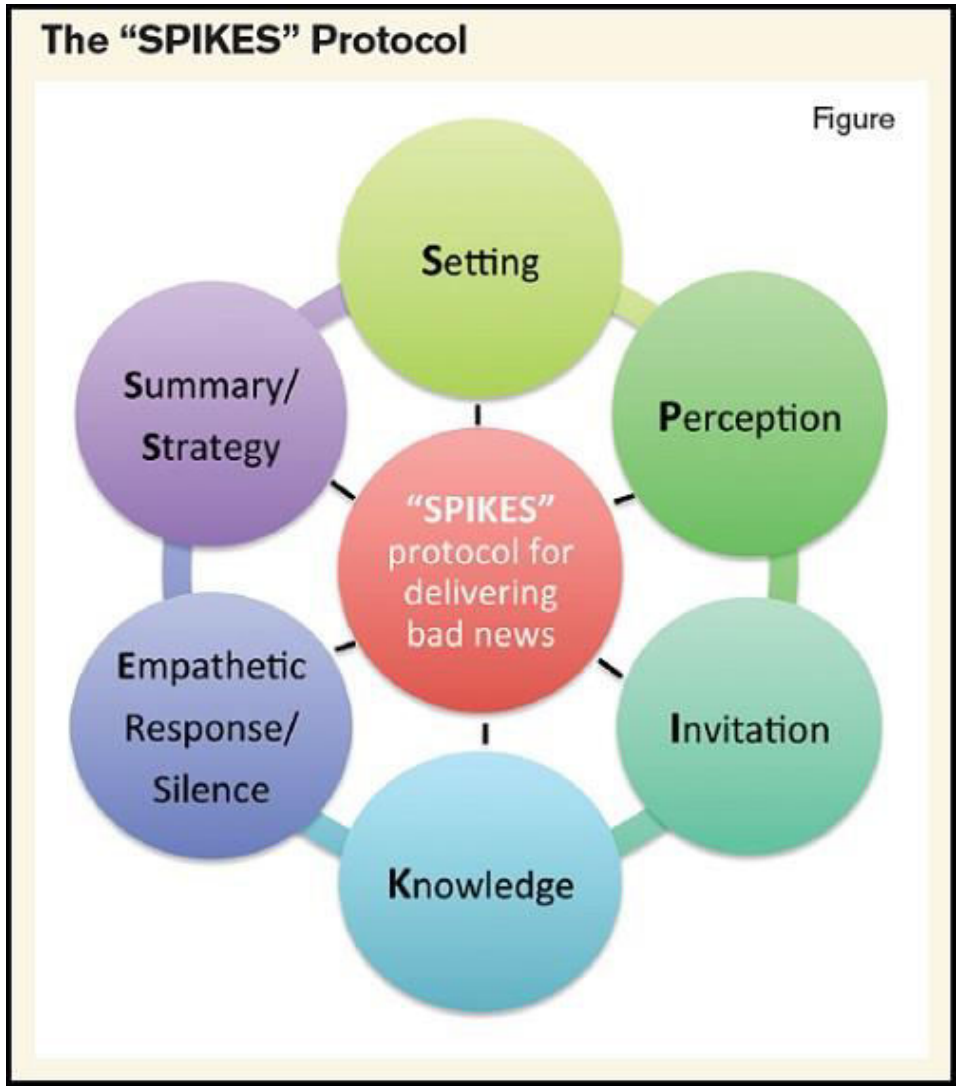
Bottom Line: Dementia Drugs

- Dementia medications are LESS HELPFUL and MORE HARMFUL in advanced disease (see adverse effects)
- NOT indicated or provided with FAST 7 without clear and ongoing benefit in managing identifiable and distressing behaviors
- MAY be covered with FAST 6; discuss goals/outcomes with hospice physician or pharmacist
- 2 week tapering supply should be provided if medication discontinued

But is Frederick buying what you're selling?

SPIKES – Having those Conversations

- S – setting
- P – perception
- I – invitation
- K – knowledge
- E – emotion
- S – summarize recommendation



Slide from McPherson, Walker, Pruskowski, Talebreza. "Right Sizing Medication Regimens in Serious Illness: Doing the Prescribing and Deprescribing Dance"

Having the Conversation: Breaking "Bad" News: SPIKES

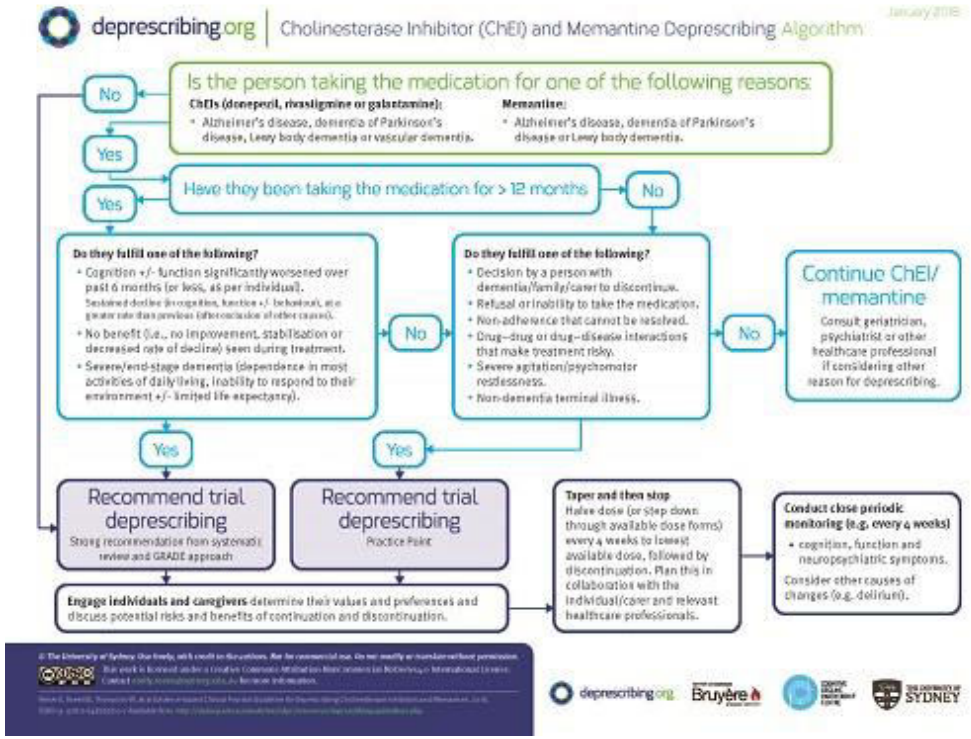
- Setting up the interview – privacy, confidentiality, support
- Perception – how much does the patient (caregiver) know?
- Invitation – find out how much the patient (caregiver) WANTS to know
- Knowledge – giving knowledge and information to patient (caregiver)
- Emotions – addressing patient/s (caregiver's) emotions with empathy
- Strategy and Summary – planning and follow-through

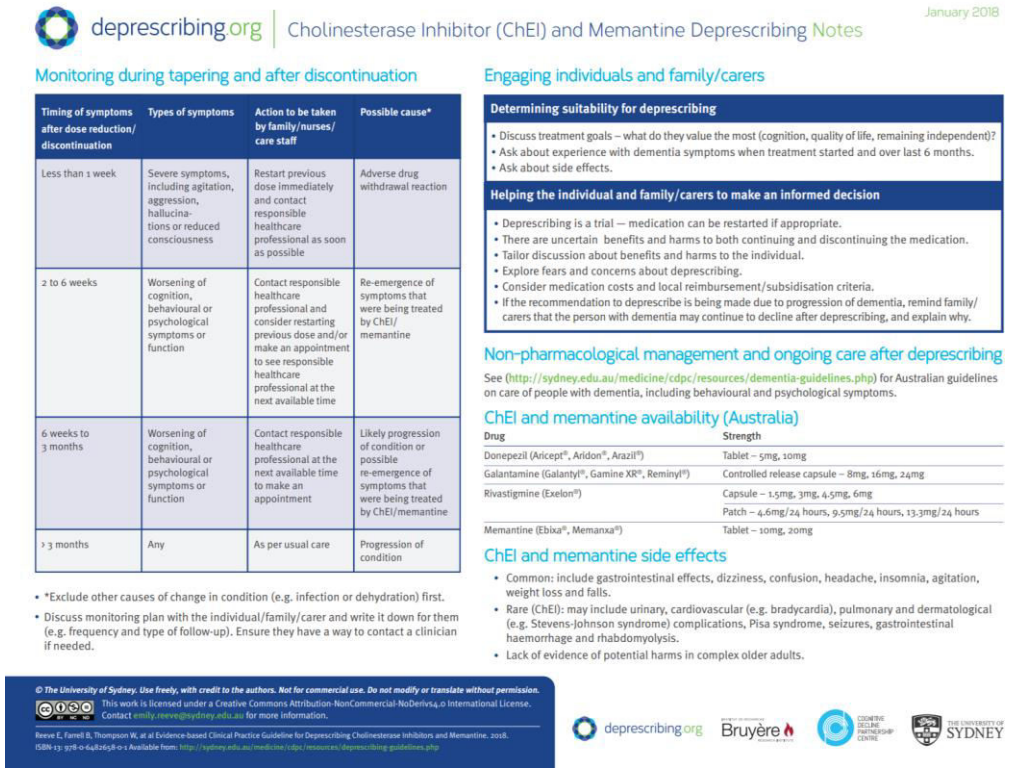
www.cetl.org.uk/learning/feedback_opportunities/data/downloads/breaking_bad_news.pdf.

Deprescribing Cholinesterase Inhibitors/Memantine

- Developing organizations:
  - The University of Sydney
  - NHMPRC Partnership Centre: Dealing with Cognitive and Related Functional Decline in Older People (Cognitive Decline Partnership Centre)
  - Bruyere Research Institute, Deprescribing Guidelines in the Elderly Project

- sydney.edu.au/medicine/cdpc/resources/deprescribing-guidelines.php
- EBR – evidence-based recommendations
- CBR – consensus-based recommendations
- PP – practice points



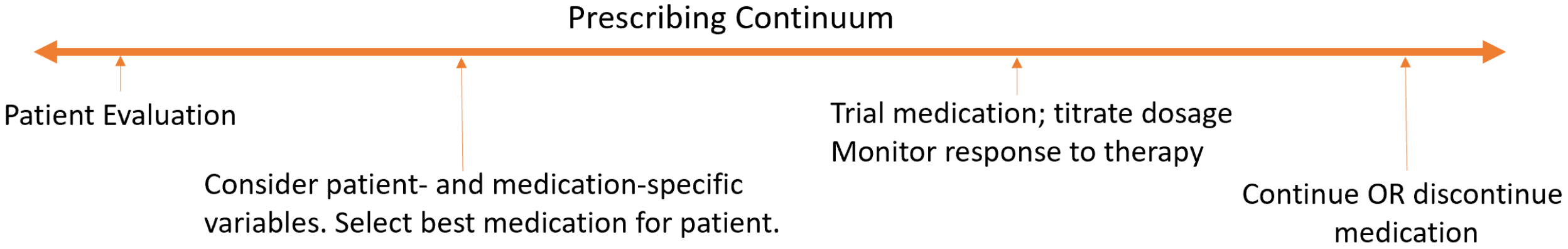


Proton pump inhibitors; antihyperglycemics; antipsychotics; benzodiazepine receptor antagonists

Deprescribing.org; specifically: cdpc.sydney.edu.au/wp-content/uploads/2019/06/algorithm-for-deprescribing.pdf.

Conclusion

- Deprescribing is part of the prescribing continuum



- Practitioners must weigh the benefits and burdens of drug therapy in all patients, but especially in advanced or serious illness
- Conversations with patients, families and other healthcare providers are VERY important

Additional References

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Deprescribing in Palliative Care

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