Dementia…after the diagnosis

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Yale SCHOOL OF MEDICINE

Eastern Caribbean Health Outcomes Research Network

www.echorn.org

NIMHD

GOAL:

Establish a unique regional research infrastructure to generate action-oriented chronic disease research and to facilitate policy translation, local capacity strengthening, and community engagement to reduce the burden of NCDs in the Eastern Caribbean

ECHORN: Principal Investigators

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Disclosures

I have no financial or personal conflicts of interest.

Objectives

At the end of this presentation, attendees should…

1. Know the names and doses of medications used to slow the progression of dementia
2. Understand the challenges of treating neuropsychiatric symptoms
3. Appreciate the importance of considering life expectancy before pursuing screening for persons with dementia

Overview

- Dementia Symptoms & Signs
- Dementia Medications
- Symptom Management
- Screening & Prognostication

Types of Dementia

- Alzheimer's disease
- Vascular (multi-infarct) dementia
- Dementia associated with Lewy bodies
- Parkinson's disease
- Fronto-temporal dementia (Pick's disease)
- Neurosyphilis
- Alcohol induced
- AIDS

Diagnostic Features of Dementia Syndromes

Feature	Alzheimer's Disease	Vascular Dementia	Lewy Body Dementia	Fronto-temporal
Onset	Gradual	Sudden or stepwise	Gradual	Gradual, age< 60
Symptoms	Memory	Varies	Behavioral	Exec fct
Motor symptoms	Apraxia (late)	Varies	Parkinsonism	None
Progression	8-10 yrs	Stepwise	<AD	<AD
Lab tests	Normal	Normal	Normal	Normal
Imaging	Global atrophy	Cortical or subcortical	Global atrophy	Frontal, temporal atrophy

Symptoms and Signs of AD

- Memory impairment
- Gradual onset, progressive cognitive decline
- Impaired social, occupational function
- Difficulty learning, retaining new information
- Aphasia, apraxia, disorientation, visuospatial dysfunction
- Impaired initiation, decision making, judgment
- Behavior and mood changes
- Delusions, hallucinations, aggression, wandering

Treatment & Management

- Primary goals:
  - Enhance quality of life (patient & caregiver)
  - Maximize functional performance by improving cognition, mood, and behavior
- Specific symptom management
  - Pharmacologic
  - Nonpharmacologic

Pharmacologic

- Cholinesterase inhibitors
- N-methyl-D-aspartate (NMDA) receptor antagonist
- Antidepressants
- Antipsychotics

Dementia medications

Drug	FDA approved	Starting Dose	Maximum Dose
Donepezil (Aricept)	1996	5 mg daily	10 mg daily 23 mg daily
Rivastigmine (Exelon)	2000	1.5 mg bid	6 mg bid
Patch		4.6 mg/24 hrs	9.5 mg/24 hrs 13.3 mg/24 hrs
Galantamine (Razadyne)	2001	4 mg bid	12 mg bid
ER		8 mg daily	24 mg daily
Memantine (Namenda)	2003	5 mg daily	10 mg bid
XR**		7 mg daily	28 mg daily

Dementia Medications (cont.)

Drug	FDA approved	Renal Dose	Standard Dose
MemantineXR /Donepezil (Namzaric)**	2014	14/10 mg	28/10 mg

Medication Effectiveness

- Review article analyzed 96 publications

Findings

- Consistent effects improving cognition but small effect sizes
- Effects on behavior and quality of life less consistent

Caveats

- Most studies focus only on Alzheimer's disease patients
- Most studies short in duration (6 months)
- No difference in effectiveness of various cholinesterase inhibitors

Raina P et al. *Ann Intern Med* 2008;148:379-397

Cholinesterase Inhibitor Side Effects

- GI (Nausea, diarrhea)
- Urinary incontinence
- Vivid dreams
- Additional associations
  - Hospital visits for syncope: HR, 1.76
  - Hospital visit for bradycardia: HR, 1.69
  - Pacemaker insertion: HR, 1.49
  - Hip Fracture: HR, 1.18

Gill SS et al. *Arch Intern Med* 2009; 169(9):867-873

Medical Foods

Axona

- Metabolized by the liver to form ketone bodies; ketone bodies serve as an alternative fuel source for the brain
- Phase 2 trials (safety & best dose) only
- Prescription: one packet daily with water

Vivimind

- Tramiprosate, modified taurine (amino acid), blocks deposits of beta amyloid in the brain
- Phase 3 trials (effectiveness) inconclusive
- Prescription: 1-2 tablets BID w/meals

Memory Supplements

Prevagen

- Brain health supplement made from apoaequorin (substance found in jellyfish)
- Goal to improve verbal learning
- FDA issued a warning letter to the manufacturer, Quincy Bioscience
- Failed to report serious side effects e.g. seizure, strokes, chest pain, tremors and fainting
- Apoqequorin used in Prevagen is synthetically made

Ginkgo Evaluation & Memory (GEM) Study

- 3,069 participants 75 years or older with normal cognition or mild cognitive impairment at 4 sites
- Dose: 120 mg *gingkgo biloba* extract BID for 6 months
- Average follow-up: 6 years
- No difference in rates of development of dementia between placebo & treatment group
- No significant side effects of Ginkgo

DeKosky ST et al. *JAMA* 2008;300(19):2253-2262

Curcumin (Source of Tumeric)

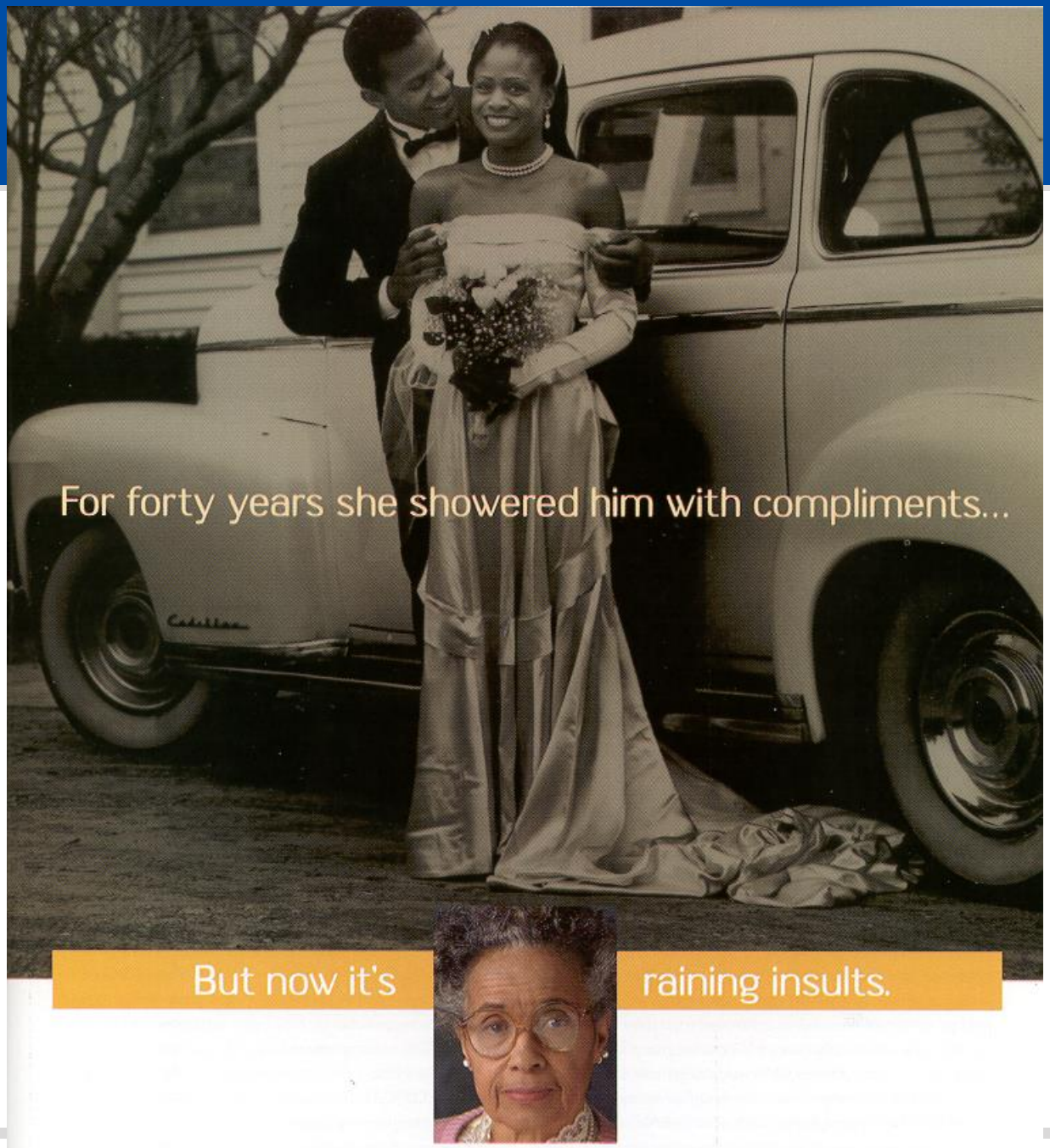
- Anti-inflammatory effects thought to prevent AD
- Potential effective dose unknown
- Stimulates bile secretion, 20-40 mg caused gallbladder contractions in healthy people
- Chronic use can cause liver toxicity
- Interacts with blood thinning agents, NSAIDs, black pepper extract (pepperine)

Mishra S, Palanivelu K. *Ann Indian Acad Neurol* 2008 Jan-Mar 11(1):13-19

Symptom Management

- Neuropsychiatric symptoms observed in 60-98% of dementia patients
- Depression
- Sleep disturbances
- Psychoses (delusions, hallucinations)
- Aggression, agitation

Sink KM, Holden KF, Yaffe K. *JAMA* 2005;293:596-608


For forty years she showered him with compliments...
But now it's
raining insults.

Treating Depression

- Selective Serotonin Reuptake Inhibitors (SSRIs)
  - Citalopram (Celexa) *
  - Sertraline (Zoloft)
  - Escitalopram (Lexapro)
  - Fluoxetine (Prozac)
  - Paroxetine (Paxil)
- Selective Serotonin and Norepinephrine Reuptake Inhibitor (SSNRI)
  - Duloxetine (Cymbalta)
- Bupropion (Wellbutrin)
- Mirtazapine (Remeron)
- Venlafaxine (Effexor)

Antipsychotics & Doses used in Older Adults with Dementia

Drug	Starting Dose	Peak Effective Dose
Quetiapine (Seroquel)	12.5-25 mg daily	150 mg daily
Haloperidol (Haldol)	0.25 at bedtime	3-5 mg daily
Olanzapine* (Zyprexa)	1.25-2.5 mg at bedtime	5 mg daily
Risperidone* (Risperdal)	0.25-0.5 mg at bedtime	1-1.5 mg daily

Antipsychotics & Risk of Death

- 17 Placebo controlled trials
- 5106 elderly demented participants with behavioral disorders
- Olanzapine (Zyprexa), Apripiprazole (Abilify)**, Risperidone (Risperdal) & Quetiapine (Seroquel)
- 1.6-1.7 increase in mortality with treatment
- Cause of death: heart related events or infections
- FDA Black Box warning issued April 11, 2005: Use of atypical and typical antipsychotic drugs is associated with an increased risk of death
- *www.fda.gov/cder/drug/advisory/antipsychotics.htm*

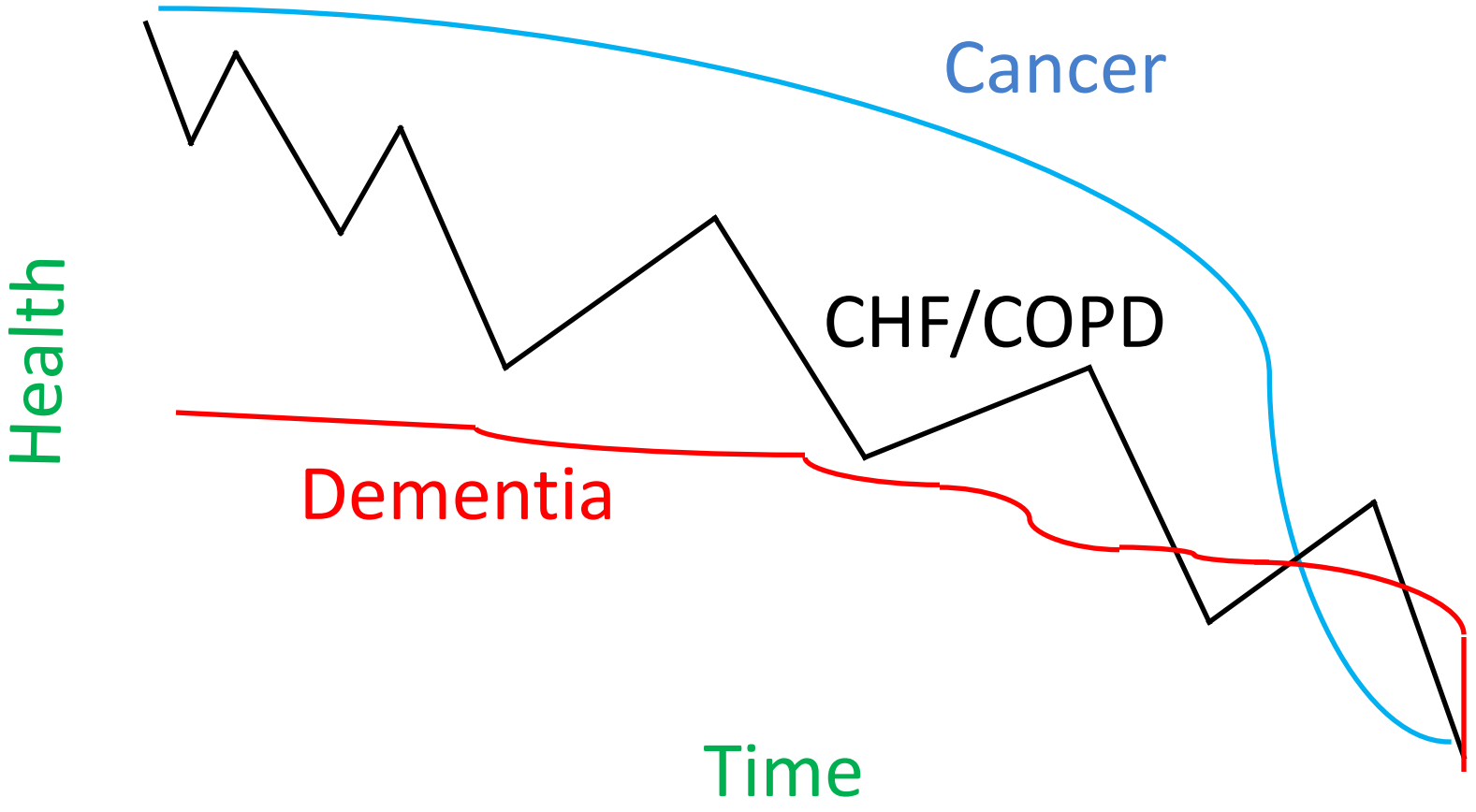
Managing Sleep Disturbances

- Improve sleep hygiene (e.g, consistent bedtime, comfortable setting)
- Provide daytime activity, prevent daytime sleeping
- Treat associated depression, delusions
- If the above do not succeed, consider:
    - Trazodone (Desyrel) 25-150 mg
    - Nefazodone (Serzone)** 100-500 mg
    - Ramelteon (Rozerem)** 4-16 mg
    - Melatonin 0.3 mg (12 mg max. in studies)
- Avoid benzodiazepines or antihistamines if possible

Managing Aggression and Agitation

- Behavioral interventions: distraction, supervision, routine, structure
- Behavior modification using rewards
- Pharmacologic interventions: antipsychotics, antidepressants, mood stabilizers, buspirone, β-blockers

Chronic Illness Trajectories



Lag time to benefit

- The time between a preventive intervention to the time when improved health outcomes are seen
- When will it help?
- If life expectancy << lag time to benefit for a screening test, the patient is exposed to the risks of the tests with little likelihood of receiving any benefits

Screening & life expectancy

- Estimate the patient's life expectancy
- Estimate the screening test's lag time to benefit
- If life expectancy >> lag time to benefit → screen
- If life expectancy << lag time to benefit→ do not screen
- If life expectancy = lag time →patient preference

Lee SJ, Leipzig RM, Walter LC. *JAMA* 2013;310(24):2609-2610

End stage Dementia symptoms

- Prospective cohort study of older nursing home residents with dementia
- 177/323 (54.8%) died over 18 months
- In the last 3 months of life
  - Febrile episodes: 32.2%
  - Pneumonia: 37.3%
  - Eating problems: 90.4%

Mitchell SL et al. *NEJM* 2009;361:1529-1538

Dementia Prognostic indicators

- Reviewed 7 dementia studies, pt. mortality w/in 6 mo
- Nutrition/Nourishment/Eating habits (7/7)
- Increased risk on dementia rating scale (6/7)
- Comorbid conditions (6/7)
- Functional/Cognitive Impairment (5/7)
- Ambulation/Mobility problems (4/7)
- Unstable medical condition (4/7)
- Demographics (4/7)
- Speech/Language problems (2/7)
- Hematological abnormalities (2/7)
- Signs of suffering: screams and pain (2/7)

Brown MA et al. *Palliat Med* 2012;27(5):389-400

ePrognosis

- Estimating prognosis for Elders
- Developed by UCSF Geriatrics Division
- www.eprognosis.org

ePrognosis

ePrognosis — Estimating Prognosis for Elders

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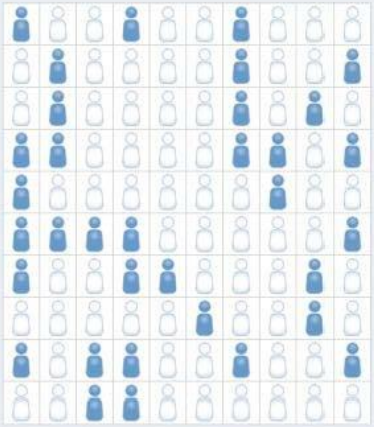
Walter Index

- Population: Hospitalized adults age 70 and older
- Outcome: All cause 1 year mortality
- Scroll to the bottom for more detailed information

As illustrated by the graphic below, out of 100 hospitalized adults age 70 and older with similar answers, 34 will die (shaded) and 66 will survive (un-shaded) over the next year.

Risk calculators cannot predict the future for any one individual. Risk calculators give an estimate of **how many** people with similar risk factors will live and die, but they cannot identify **who** will live and who will die.



Graphic adapted from Han 2011

Results Based on Score:

Your total score is **6**

One Year Mortality	
Points	**Risk of 1 year mortality (95% CI)**
0 - 1 points	4% (2-4)
2 - 3 points	19% (15-23)
4 - 6	34% (29-39)
> 6	64% (58-70)

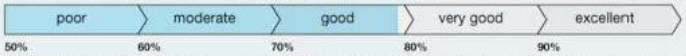
Now that you have seen this information, what is your best guess of one year mortality risk?
-- select --

Did you find this information useful?
-- select --

Did this information affect a clinical decision?
-- select --

Finish | Print Report | Email Report

- This index was developed in 1495 elderly hospitalized individuals between 1993 and 1997 at the University of Hospitals Cleveland (mean age 81, 67% female, 60% white, 33% 1-year mortality)
- The index was internally validated in 1427 elderly hospitalized individuals between 1993 and 1997 at the Akron City Hospital (mean age 79, 61% female, 88% white, 28% 1-year mortality)
- This index was externally validated for 6 month risk mortality in 840 consecutively admitted participants to a hospital in Italy
- Discrimination: This risk calculator sorts patients who died from patients who lived correctly 79% of the time (c-statistic)



- Calibration: The model was well calibrated across all risk levels, with less than 10% difference between estimated and actual mortality rates
- Citation: Walter LC, Brand RJ, Counsell SR, Palmer RM, Landefeld CS, Fortinsky RH, Covinsky KE. Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. JAMA 2001;285:2987-2994.
- Independent Validation Citation: Rozzini R, Sabatini T, Trabucchi M. Prediction of 6 month mortality among older hospitalized adults. JAMA. 2001;286(11):1315-1316.

Summary

- Cholinesterase inhibitors and Memantine demonstrate modest improvement in cognition; effect on behavioral disturbances varies
- Lower maximal dose of cholinesterase inhibitors in persons with bradycardia; Memantine dose should be lowered in persons with renal insufficiency
- SSRI (citalopram) improves depression; effects on neuropsychiatric symptoms equivocal
- Antipsychotic medications should be used with caution given association with mortality
- Especially in persons with dementia lag time to benefit should be considered before pursuing screening

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Questions