LESS IS MORE

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MORE OR LESS

therapeuticseducation.org
medicationmythbusters.com

TO GET A HANDOUT GO HERE
http://therapeuticseducation.org/handouts

Rationale Drug Therapy Encompassing the Evidence

applying evidence to our complex, elderly and frail patients to assist with decision making regarding medication use, particularly with regard to deprescribing

The agenda

statins

A fib/new oral anticoagulants

glucose

blood pressure

PPIs

bone density/fractures

antipsychotics in dementia

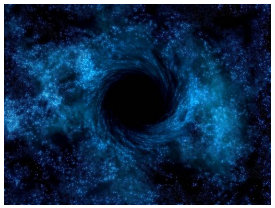
No approach is really wrong, but few are likely really right

AGE **40** **50** **60** **70** **80** **90**

RISKS (Heart attacks/strokes/fractures) go up

THEORETICAL BENEFIT GOES UP

THE EVIDENCE BECOMES A BLACK HOLE



SYMPTOMS (pain, cognition, disability etc) INCREASE

BENEFITS FROM TREATMENTS STAY THE SAME?

ABILITY TO EXCRETE MEDICATIONS GOES DOWN

SIDE EFFECTS FROM MULTIPLE MEDICATIONS GOES UP

PATIENT AND FAMILY VALUES

THE INEVITABLE

Risk …

Risk markers - associated with a bad outcome

Risk factors - modifiable?

Risky behaviors - smoking, nutrition, activity

Risk of disease - CVD, MI, strokes, fractures

Risk of treatment - harms, costs

Risk of over diagnosis - inconvenience, labelling, worry

Risk Factors versus Clinical Endpoints

"a risk factor/marker is a variable associated with an increased risk of disease"

Not As Important	Very Important
blood pressure	symptoms/exacerbations
cholesterol	heart attacks
glucose/diabetes	strokes
bone density	heart failure
heart rate	death
CRP	dialysis
proteinuria	amputation
family history	fractures
age	blindness
gender	revascularization
race	angina
FEV1	TIAs

Evidence-based risk communication

"There is likely no single best method of communicating probabilities to patients but rather several good options with some better suited to certain risk scenarios."

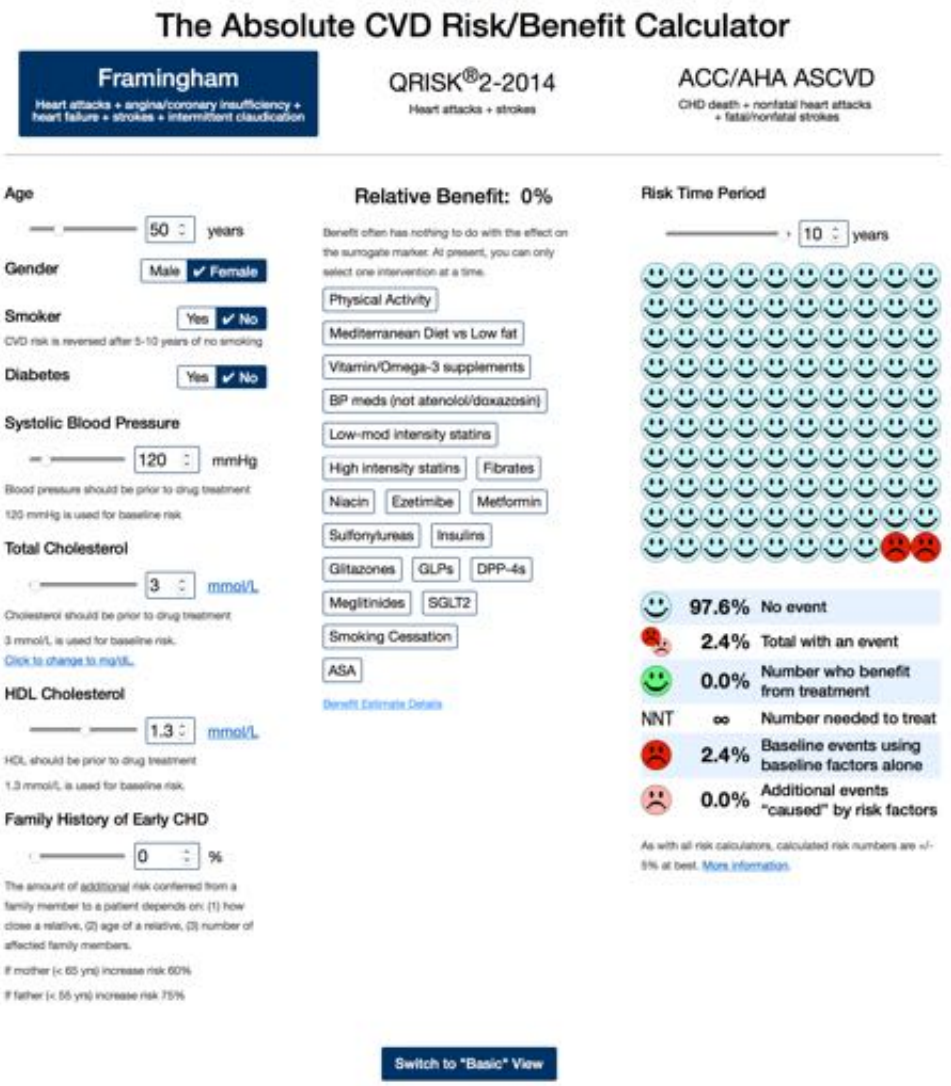
Ann Intern Med 2014;161:270-80

Recommended approaches

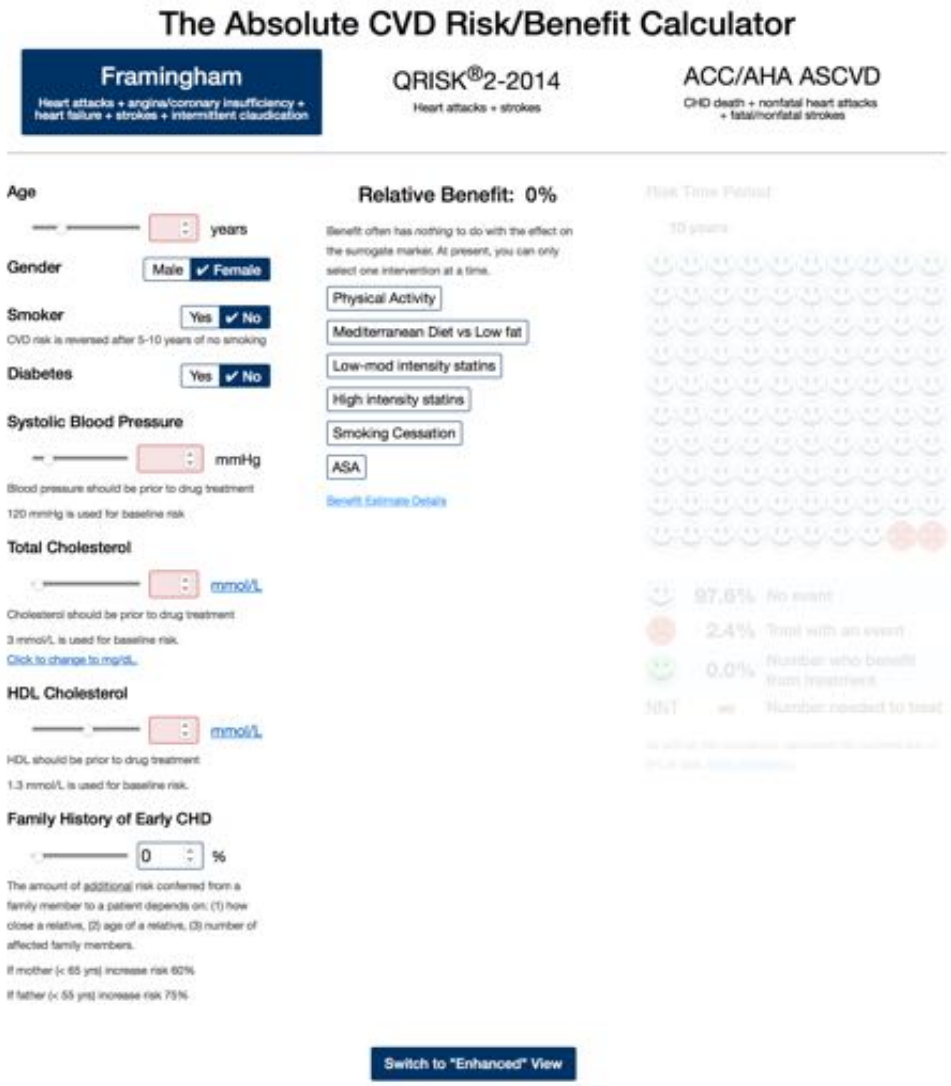
GENERAL SUGGESTIONS - these are “relative”
use percentages or natural frequencies(numerator/denominator)
use absolute terms
add bar graphs or icon arrays
use incremental risk format with icon arrays in the same array
avoid use of NNTs
if use relative risks add baseline risks

Ann Intern Med 2014;161:270-80

Enhanced



Basic



cvdcalculator.org

SPARC - Stroke Prevention in Atrial Fibrillation Risk Tool
for estimating risk of stroke and benefits & risks of antithrombotic therapy in patients with chronic atrial fibrillation

references/notes
version 7, January 2015
Developed by Peter Loewen, ACPR, Pharm.D., FCSHP
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PERCENT PER YEAR

THERAPY	Stroke / Embolism		Major Bleeding	
	CHADS2	CHA2DS2-VASc	Pop.Avg.	HAS-BLED
NO THERAPY	3.6%	4.3%	0.6%	
ASPIRIN	2.8%	3.4%	1.1%	
ASPIRIN+CLOP	2.0%	2.4%	3.8%	
WARFARIN	1.2%	1.4%	3.8%	2.2%
DABIGATRAN 110	1.2%	1.4%	3.0%	1.8%
DABIGATRAN 150	0.8%	0.9%	3.8%	2.2%
RIVAROXABAN	1.2%	1.4%	3.8%	2.2%
APIXABAN	0.9%	1.1%	2.6%	1.5%
EDOXABAN 30	1.2%	1.4%	1.8%	1.0%
EDOXABAN 60	1.2%	1.4%	3.0%	1.8%

RIVAROXABAN	0.4%	0.2%	3.8%	1.2%
APIXABAN	0.3%	0.2%	2.6%	0.8%
EDOXABAN 30	0.4%	0.2%	1.8%	0.6%
EDOXABAN 60	0.4%	0.2%	3.0%	1.0%

percent per year

http://www.sparctool.com

An even easier A fib table

	Patient's ~ ANNUAL risk (%) of ischemic stroke			Difference in benefit between ASA and OAC
$CHADS_2$ Score	No therapy	ASA	OAC	
0	2	1.5	0.5	~1
1	3	2.5	1	~1.5
2	4	3	1	~2
3	6	5	2	~3
4	9	7	3	~4
5	18	14	6	~8

PPIs	Absolute Number Differences
THE GOOD	
Healing/symptoms at 8 weeks	~ 55% over placebo ~ 30% over H_2RA
Reduce relapse at 1 year	~ 55% over placebo ~ 35% over H_2RA
Prevent NSAID-induced ulcers	~20% over placebo - endoscopic ?? clinical ulcers - 1-2%??
Reduce stress ulcers - ICU	~ 8% over placebo ~ 0% over H_2RA
Withdrawal - rebound	~ 15% rebound symptoms ~ 50% can lower dose ~ 33% go on H_2RA ~ 10-20% off drugs
THE BAD	
Interactions	Clopidogrel - likely 0% Other drugs?
Fractures/year	If real 0.3% vertebral and 0.025% hip
Pneumonia	If real 0.25%?
C difficile	~ 1.5% in hospital ~ 0.1% in community
Iron/B12	??
Cancer	??

Testing for Osteoporosis

True. Study of risk factors to predict osteoporosis

An index on age and weight ≥ other published indices

4 systematic reviews from 2007-2010, with 36 studies & 72,315 women supported the findings[1-4]

Age - Weight (kg), If > -10, increased risk of osteoporosis and BMD is warranted

60 yrs – 60kg = 0 High Risk

60 yrs – 100kg = -40 Low Risk

#44. "Screening for Osteoporosis": http://www.acfp.ca/whatwedo/toolsforpractice.aspx

Does your patient have osteoporosis?

(Osteoporosis Self-assessment Tool)

Age – weight (kg) = ????

CHANCE OF OSTEOPOROSIS

> 20 – approx 50-60%

0-20 – approx 15-20%

<0 – less than 5%

An example
60 years old
130 lbs = 60 kg
Score = 0

Valid in men as well

Mayo Clin Proc 2003;78:723-7

Mayo Clin Proc. 2002;77:629-637
The Singapore Family Physician Jul-Sep 2003;29:12
MOH Osteoporosis clinical practice guidelines - Singapore Mar 2002

Simple is better

"Simple models based on age and BMD alone or age and fracture history alone predicted 10-year risk of hip, major osteoporotic, and clinical fracture as well as more complex FRAX models"

Arch Intern Med 2009;169:2087-94

10 year fracture risk %

Major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture)/Hip

RISK FACTORS	Zero				One				Two			
BMI	35	30	25	20	35	30	25	20	35	30	25	20
Female												
50	2	3	3	3	4	4	5	5	6	6	7	8/1
60	5	6	6	7/2	7	9	10/1	10/4	11/1	13/2	14/2	16/6
70	8/1	9/2	10/2	11/4	11/2	13/3	15/4	17/7	16/4	18/6	21/7	25/12
80	14/4	16/5	19/7	21/11	20/8	23/10	27/13	31/20	28/14	33/18	38/22	43/32
Male												
50	2	2	2	2	3	3	4	4	4	5	6	6
60	3	4	4	4	5	6	6	7/1	7	8	10/1	10/2
70	4	5/1	6/1	6/2	6	7	8/2	9/4	8	10	12/4	13/6
80	6/2	7/3	9/4	9/5	9/4	11/5	13/7	14/10	13/7	16/9	19/12	21/16

Risk factors - Previous fracture “atraumatic”, Parent hip fracture, Smoker, Rheumatoid arthritis, Glucocorticoids - now or more than 3 months, >3 drinks a day

FRAX® WHO Fracture Risk Assessment Tool

10 year fracture risk %

Major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture)/Hip

RISK FACTORS	Zero			One			Two		
t-score	-1.5	-2.5	-3.5	-1.5	-2.5	-3.5	-1.5	-2.5	-3.5
Female									
50	4	5/1	9/4	6	8/2	14/7	8	12/3	21/11
60	7	10/2	16/6	10/1	14/3	23/9	14/1	20/5	32/14
70	9/1	13/3	21/7	12/1	18/4	30/11	16/2	25/6	41/16
80	13/3	18/6	29/14	17/6	26/12	40/24	24/10	35/20	52/37
Male									
50	4	5/2	11/6	5	8/3	16/10	8/1	12/5	24/16
60	6/1	9/3	15/8	8/1	12/4	21/11	12/2	18/6	29/17
70	6/2	10/4	16/8	9/3	14/6	22/13	12/4	19/10	31/20
80	7/3	11/5	16/9	11/5	16/9	23/16	15/9	22/15	32/25

Risk factors - Previous fracture “atraumatic”, Parent hip fracture, Smoker, Rheumatoid arthritis, Glucocorticoids - now or more than 3 months, >3 drinks a day

FRAX® WHO Fracture Risk Assessment Tool

Absolute (and relative) benefits of Bisphosphonate therapy over 5 years

~30% reduction in risk

	Vertebral Fractures		Non-Vertebral		Hip Fracture	
	1º	2º	1º	2º	1º	2º
Alendronate[1]	2% (45%)	6% (45%)	ns	2% (23%)	ns	1% (53%)
Risedronate[2]	ns	5% (39%)	ns	2% (20%)	ns	1% (26%)
Etidronate[3]	ns	5% (47%)	ns	ns	ns	ns

1) Cochrane 2008; 1: CD001155. 2) Cochrane 2008; 1: CD004523. 3) *Cochrane Database Syst Rev. 2008(1):003376.*

• Osteoporosis Drugs Benefit - 2-3 years •

RELATIVE BENEFITS	FRACTURE RISK REDUCTION*		
	Vertebral	Non-vertebral	Hip
Bisphosphonates**	~ 50%	~ 20%	~40%
Raloxifene	~ 40%	NS	NS
Teriparatide	~ 70%	~ 40%	NS
Vitamin D usually with calcium	~15-25%	~15-25%	~15-30%
Denosumab	~ 70%	~ 20%	~40%
Strontium	~40%	~ 15%	NS
ALL DRUGS	~50%	~20%	~25%

ABSOLUTE BENEFITS	FRACTURE RISK REDUCTION*		
	Vertebral	Non-vertebral	Hip
Bisphosphonates**	~4-8%	~2%	~0.5-1%
Raloxifene	~4%	NS	NS
Teriparatide	~10%	~4%	NS
Vitamin D usually with calcium	1-2%	1-2%	~1%
Denosumab	~5%	~2%	~0.5%
Strontium	~8%	~2%	NS
ALL DRUGS	~5%	~2%	~0.5%

*~ 90% of the studies enrolled patients with a history of fractures with the exception of the VitaminD/calcium studies where this was ~ 50%
** etidronate has only been shown to reduce vertebral fractures in secondary prevention

Retesting BMD

When do you retest her BMD

We say: Not for at least 3 years

True,

- Alendronate yearly increase = variation in BMD
- Variation in BMD= 2.4% to 5% (over 2 weeks)
- Alendronate “sufficient” BMD for 97.5% after 3 yrs
- However, if no change[2] or even decreased BMD[3] still reduced fracture risk.

Can Fam Physician. 2010 Dec;56(12):1299.

Stopping therapy

A 65 year old woman on Alendronate 5 years is asking if any meds can be stopped?

We say: You can stop Alendronate

True: (FIT & Horizon Trials) Continue or Stop Alendronate (after 5 yrs) or Zoledronic (3yrs)

- No effect fractures1,2
- 2 Weaker studies show the same thing3

FDA requires label that duration unknown

1) JAMA 2006;296:2927-2938. 2) J Bone Min Res 2011; Oct 25. DOI 10.1002/jbmr.1494
3) NEJM 2004;350:1189-99 Osteoporos Int 2008;19:365-72. 4) NEJM 2012; 366:2048-51

Agitation in Dementia

Dementia can > agitation and violent behavior

- Also can delirium and associate problems

Hard to manage

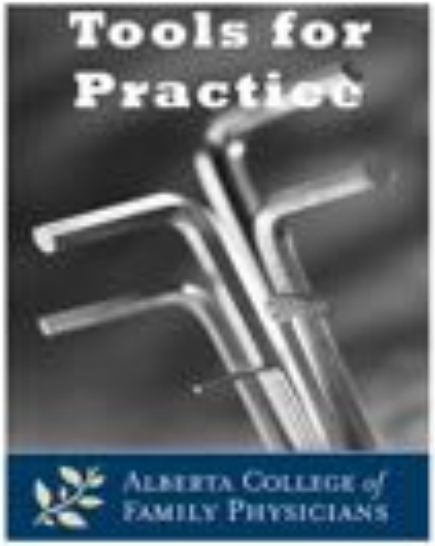
Consider undiagnosed pain

Some other key points from the literature,…

Interventions (Not anti-psychotics)

- Meta-analysis: Non-Pharmaceutical Interventions for Agitation
  - Sensory interventions reduces (SMD -1.07; -1.76 to -0.38)
- Meta-analysis: Cholinesterase inhibitors[2]
  - No effect
- RCT: Pain control reduced agitation mean 17%
  - 2/3 got acetaminophen (rest opioid or pregabalin)[2]

1) Aging Ment Health. 2009 Jul;13(4):512-20. 2) Clin Interv Aging. 2008;3(4):719-28. 3) BMJ. 2011 Jul 15;343:d4065.



Agitation in Dementia: Are benzos a back-up?

<u>Clinical Question</u>: Are benzodiazepines a reasonable pharmaceutical alternative for management of agitation in demented elders?

<u>Bottom-Line</u>: 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 the Anti-Psychotics?

Meta-analyses of Anti-psychotics[1-3]

- Few studies published (5 of 16).
- Small effect on aggression & psychosis
  - Benefit antipsychotic (0.45) over placebo (0.32) small

Meta-analysis of Harms from RCTs (most 10-12 wks)[4]

- Death RR = 1.65 (1.29-2.29), NNH = 77
- Conventional (versus atypical) not better.[5]

Anti-psychotics also worsen cognition:[6]

- Equivalent to 1 year deterioration

1) Cochrane Database Syst Rev. 2006 Jan 25;(1):CD003476. 2) Psychother Psychosom. 2007;76(4): 213-8. 3) Int J Geriatr Psychiatry. 2007;22(5):475-84. 4) JAMA 2005; 294: 1934-43. 5) NEJM 2005;353: 353:2335-41. 6) Am J Psychiatry 2011; 168:831–9

What about Stopping Anti-psychotics

DART-AD: RCT, 165 patients, mean age 85, 76% female, long-term care

Withdraw antipsychotic (placebo) or continue

Outcomes

- Behavior: None stat sign.
- Mortality: at 2 years, 71% continued anti-psychotic vs 46% placebo, (Diff = 25%, NNT 4)

Lancet Neurol 2009; 8:151–57. *PLoS Med 5(4): e76.doi:10.1371/journal.pmed.0050076*

Treating dementia

What is the scientific evidence for Cholinesterase Inhibitors in the treatment of Alzheimer's disease.

22 Trials: 12 donepezil, 5 rivastigmine, 5 galantamine: 27 to 978 pt/trial, 6 wks-3yrs long

Findings: 1.5-3.9 (ADAS-cog & Min clinical sign ≥ 4)

Limitations: Numerous

ITT flaws (pt exclusion after randomization)= 15/22 (68%),

Last Observation Carried Forward (declining illness)

Use of Means (in scales),

No correction for multiple comparison

Funding (often authored by employees)

BMJ 2005; 331: 321-27

Cholinesterase Inhibitors: Summary

Cholinesterase trials vs Placebo

Poor reporting (e.g. 12% of donepezil report mortality)

ADAS-cog=4 is clinical significant, MMSE = 3.

Quality of Life scores unchanged

	Donepezil[1]	Galantamine[2]	Rivastigmine[3]	All[4]
MMSE	1.44	?	0.82	1.37
ADAS - Cog	2.81	3.38	1.99	2.73
ADAS – Cog of 4	?	NNT 6	NNT 18	?
Glob Clin State	NNT 10	NNT 7	NNT 14	NNT 14
Adverse Events	NNH 18	?	NNH 6	NNH 8

* Not given

1) Cochrane. 2006;(1):CD001190 (10mg x 6 months). 2) Cochrane 2006; 1: CD001747.
3) Cochrane 2009; 2: CD001191. 4) Cochrane 2006; Issue 1: CD005593.

Other Outcomes: Example Donepezil

ADL & IADL: Most statistically significant

- Lots of different ones used, so summing up hard
- Basically, move about 4% on different scales.

Quality of Life: Patient rated.

- No difference.

Behavior: Primarily NPI used

- No difference 12 wks, 10mg
- Difference (24 wks, 10 mg): 2.94 (out of 144)

Cochrane Database Sys Rev 2006; 1: CD001190. Ann Intern Med. 2008;148:379-397.

Adverse Events: Example Donepezil

Statistically significant

- Anorexia: 7.3% vs 2.1%, NNH 20
- Diarrhea: 14.5% vs 5.3%, NNH 11
- Nausea: 14.5% vs 5.4%, NNH 11
- Vomiting: 11.3% vs 4.7%, NNH 16
- Weight Loss: 8.2% vs 4.5%, NNH 28
- Fatigue: 9.4% vs 4%, NNH 19
- Asthenia (weakness): 7.9% vs 4.7%, NNH 32
- Dizziness: 8.1% vs 5.4%, NNH 38
- Insomnia: 9.9% vs 4.4%, NNH 19

Others Borderline (accidental injury, rhinitis)

Ann Intern Med. 2008;148:379-397. Adverse Event Appendix Table 4

Is one better than another?

3 Trials compare Head to Head[1]

Multiple Flaws & potentially biased

Industry funded, Employee written, results favoring sponsor. (Therefore, no difference)

In Meta-analysis : “There is no evidence of any difference between them”[2]

1) Lancet Neurol 2004; 3: 622:26. Therapeutics Letter 2005; 56:1-4. 2) Cochrane Database Syst Rev. 2006 Jan 25;(1):CD005593

Prevention of Dementia

Vitamin E : No help

Meta-analysis Donepezil:

In 1 of 2 trials, 1 of 5 scores had a 3% less decline

Stopping due to adverse events: NNH 7.

Meta-analysis Galantamine:

Marginal to no clinical Benefit

++ Harms: NNH (for death) = 94.

1) NEJM 2005; 352:2379-88. 2) Cochrane Database Syst Rev. 2006;3:CD006104. 3) Cochrane Database Syst Rev. 2006;(1):CD001747. Therapeutics Letter 2005; 56:1-4.

What about withdrawing?

295 Community dwelling Patients on Donepezil (most >2 yrs)

- mean age 77, mean MSE 9, followed 1 yr.
- Stopping of med worsened MSE by 1.9 pts
  - Less effect if severe dementia (<9 MSE)
  - Don't give number attaining MCID (1.4)
- Withdrawal from study more if stopped!
- Death: no difference

N Engl J Med 2012;366:893-903

Summary: Summary Cholinesterases

Biased & flawed Research

Benefit

Small but present

Cost and Side-effects

If patients and care-givers are considering, frank discussion about expectations.