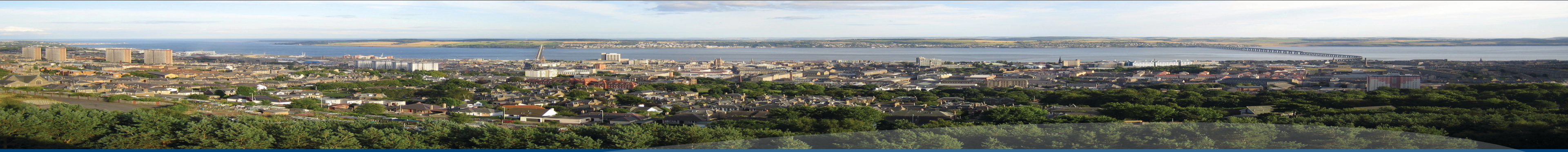

New approaches for clinical trials and guidelines

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NHS
National Institute for Health Research

Outline

- Background
- Multimorbidity
- Polypharmacy
- Guidelines and multimorbidity
- Possible changes to guideline development
- Better evidence?

Background

- Medical education, research and delivery is largely designed for single diseases
- Evidence and guidelines reflect that assumption
- Guidelines have improved practice, but their use is complicated in people with multimorbidity

Multimorbidity

Condition	This condition only	This condition + 1 other	+ 2 others	+ 3 or more others
Heart failure	3	9	14	74
Stroke/TIA	6	14	18	62
Atrial fibrillation	7	13	16	65
Coronary heart disease	9	16	19	56
Painful condition	13	21	21	46
Diabetes	14	20	19	47
COPD	18	19	17	47
Hypertension	22	24	19	35
Cancer	23	21	17	39
Epilepsy	31	23	16	29
Asthma	48	20	12	21
Dementia	5	13	18	64
Anxiety	7	17	20	56
Schizophrenia/bipolar	13	21	21	46
Depression	23	22	18	36

0% 20% 40% 60% 80% 100%

Percentage of patients with each condition who have other conditions

Barnett K et al. The Lancet 2012; 380: 37-43.

Barnett K et al *Lancet* 2012

Multimorbidity

- Education, research, service delivery is primarily disease focused
  - Generalist primary care and care of the elderly
  - Specialist everything else
- But people very often have multiple conditions
  - Co-morbidity (a more specialist and guideline view)
  - Multimorbidity (a more generalist view)
  - Interaction with socioeconomics
  - Interaction with frailty and capacity/resources
  - Survivorship with multimorbidity is the price of success

Guidelines and multimorbidity

Percentage of patients with this condition who also have this condition

	CHD	Hypertension	Heart failure	Stroke/TIA	Atrial fibrillation	Diabetes	COPD	Painful condition	Depression	Dementia	No other condition
Coronary heart disease		52	14	13	11	22	13	24	17	3	9
Hypertension	18		5	10	6	18	8	19	14	2	22
Heart failure	59	57		16	26	23	18	23	17	4	3
Stroke/transient ischaemic attack	29	61	8		13	19	12	22	21	5	6
Atrial fibrillation	37	55	21	20		19	13	18	14	5	7
Diabetes	23	54	6	9	6		8	21	18	2	18
Chronic obstructive pulmonary disease	19	33	6	8	6	11		23	18	2	14
Painful condition	16	36	3	6	3	13	10		31	3	13
Depression	10	23	2	5	2	9	7	27		3	25
Dementia	21	41	6	18	10	13	9	17	32		5

Barnett K et al *Lancet* 2012; Guthrie B et al *BMJ* 2012

Guidelines and multimorbidity

- 78 year old woman with 5 conditions and who smokes
  - MI, T2DM, OA knees, COPD and depression
- NICE guidelines recommend
  - A minimum of 11 drugs (+/- another 10)
  - A minimum of nine self-care/lifestyle activities
  - Attend 8-10 routine primary care appointments, 4-6 other medical appointments, 8-30 psychosocial intervention appointments +/- smoking cessation, pulmonary rehabilitation
- ~25% of over-75 year olds have ≥5 conditions

Hughes L et al *Age and Ageing* 2013 (US version Boyd C et al *JAMA* 2005)

Principles for management

- American Geriatrics Society
- Five domains
  1. Patient preferences
  2. Interpreting the evidence
  3. Prognosis
  4. Clinical feasibility
  5. Optimising therapies and care plan

JAGS 2012;60:1957

Domain 2: Interpreting the evidence

- Guiding Principle: Recognizing the limitations of the evidence base, interpret and apply the medical literature specifically to the multimorbid
  - Applicability and quality of the evidence
  - Outcomes
  - Harms and burdens
  - Absolute vs relative benefits
  - Time horizon to benefit

Number of people with diabetes (Living Well dataset)

12000
10000
8000
6000
4000
2000
0

0-4 years
5-9 years
10-14 years
15-19 years
20-24 years
25-29 years
30-34 years
35-39 years
40-44 years
45-49 years
50-54 years
55-59 years
60-64 years
65-69 years
70-74 years
75-79 years
80-84 years
85 years and over

ACCORD
ADVANCE
PROactive
RECORD
VADT

Number of people with diabetes (Living Well dataset)

0
2000
4000
6000
8000
10000
12000

CKD and HF
HF only
CKD only
No CKD or HF

0-4 years
5-9 years
10-14 years
15-19 years
20-24 years
25-29 years
30-34 years
35-39 years
40-44 years
45-49 years
50-54 years
55-59 years
60-64 years
65-69 years
70-74 years
75-79 years
80-84 years
85 years and over

ACCORD
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Absolute vs relative benefits

Treatment of hypertension with up to 3 drugs for 4.5 years (≥60) or 2 years (≥80)

	≥60 years	≥80 years
Cardiovascular morbidity/ mortality		
Relative risk	0.72	0.75
NNT all	23	34
NNT low risk	24	40
NNT high risk	9	16
Total mortality		
Relative risk	0.90	0.98
NNT all	84	Infinite
NNT low risk	100	
NNT high risk	33	

Musini et al. Cochrane Library 2009

Estimating harms

- Harm is poorly quantified and on a different scale from most trial-estimated benefits
- Quantifying 'potentially significant interactions'
  - Guidelines for **heart failure, depression, type 2 diabetes,** CHD, HT, AF, osteoarthritis, rheumatoid arthritis, COPD, dementia, CKD, neuropathic pain
  - Heart failure: 115 potential interactions, 6 first line
  - Depression: 135 potential interactions: 6 first line
  - T2DM: 89 potential interactions: 5 first line
- Focus on common *and* serious

Domain 3: Prognosis

- Guiding Principle: Frame clinical management decisions within the context of risks, burdens, benefits, and prognosis (e.g., remaining life expectancy, functional status, quality of life)
  - Frame a focused clinical question
  - Determine the relevant outcome(s)
  - Choose an instrument and estimate prognosis
  - Integrate information into the decision process

Relative benefits of different treaments

- 85 year old with hypertension, atrial fibrillation, moderate left ventricular systolic dysfunction, and osteoarthritis
- NNT for total mortality
  - Using 1-3 antihypertensives over 2 years = infinite
  - Use warfarin over 1 year to prevent stroke = 59
  - Use an ACEI over 90 days = 36
- NNT for analgesia?

Life expectancy for men with upper/lower quartiles (England 2004-2006 data)

Life expectancy

12
10
8
6
4
2
0

80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100

Age in years

LifeExpectancy
Lower quartile
Upper quartile

Domain 1: Patient preferences

Listen to the patient
He is telling you the diagnosis

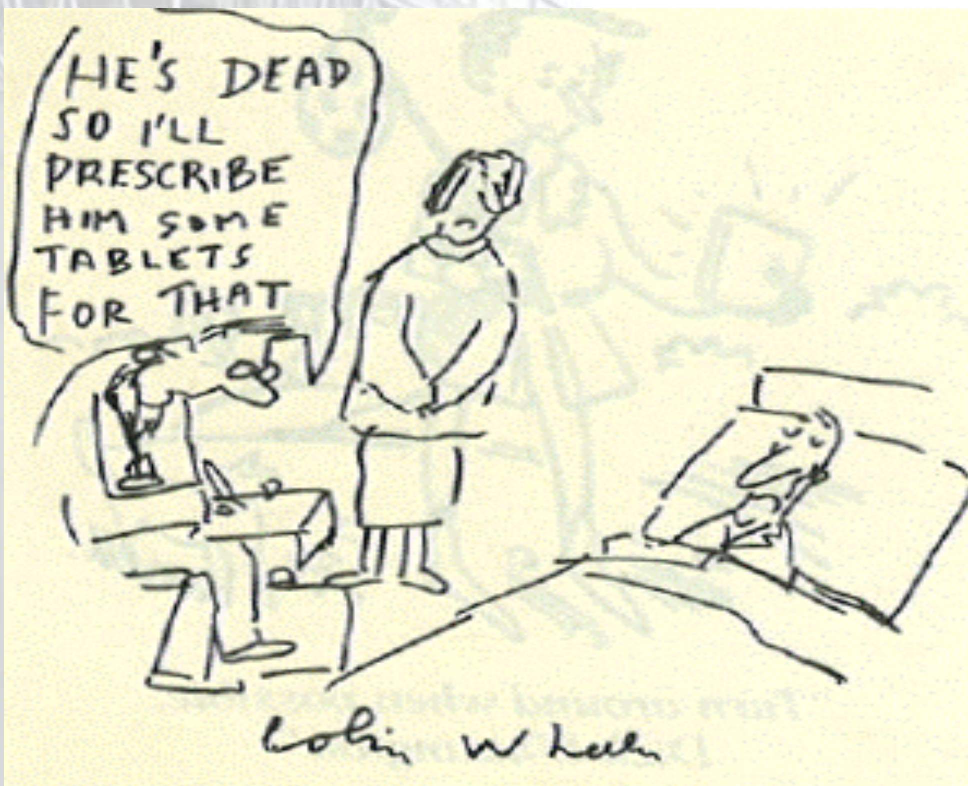
SIR WILLIAM OSLER

Listen to the patient
She is telling you her treatment goals

PROFESSOR JAN DE MAESENEER

Discussion

- Can we improve guidelines?
  - Clearer accounting for applicability
  - Better define absolute benefit of treatment
  - Better define relative benefit of different treatments
  - Explicitly consider likely drug-drug interactions
- Evidence in populations excluded from trials
  - Older people, people with MM or polypharmacy
  - Never be trials in every population, but trials could report findings in consistently defined sub-groups
  - Meantime, modelling is as good as it gets…



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Thank you!