

Multimorbidity and Polypharmacy

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Speaker Disclosures

Dr. Little has no financial relationship(s) to disclose.

Learning Objectives

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

- Define multimorbidity and describe its impacts
- Identify factors related to patient complexity and treatment burden
- Utilize patient-level interventions to reduce treatment burden in polypharmacy
- Describe the current evidence base and future research directions of multimorbidity
- Apply aspects of successful patient-centered interventions into practice

Defining good health and care from the perspective of persons with multimorbidity: results from a qualitative study of focus groups in eight European countries.

Leijten FRM, Hoedemakers M, Struckmann V, et al. *BMJ Open* 2018;8:e021072. doi:10.1136/bmjopen-2017-021072

“...it’s true, I am sick, but the disease is not me. I don’t want to be reduced to my diseases.”

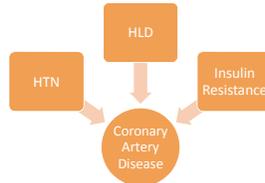
-- Focus Group Participant, Austria

“So I would have wished for a doctor that, to put it this way, had the overview of the whole human being, that he shouldn’t treat a heart disease just in isolation, you have another disease, and a third...”

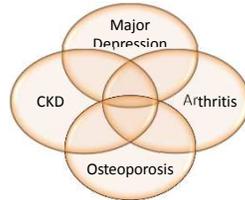
-- Focus Group Participant, Norway

Co-morbidity versus Multimorbidity

INDEX DISEASE WITH ONE OR MORE CONDITIONS



COEXISTENCE OF TWO OR MORE CHRONIC DISEASES



Complex Multimorbidity

‘Co-occurrence of three or more chronic conditions affecting three or more body systems within one person, without defining an index condition’.

Trevena, L. *AIGP* Vol. 47, No. 4, April 2018



Why is multimorbidity so difficult to discuss?

- Still a topic with a small evidence base (only became a MeSH term in 2018)
- Clinical guidelines are single-disease focused and "cookbook" medicine leads to polypharmacy and treatment burden
- What are the "right" outcomes?

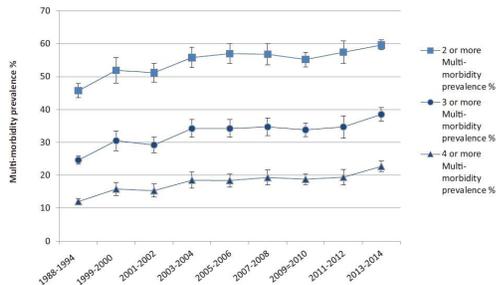
Sinnott, C., et al. 2013. *BMJ Open*, 3.
Leijten FRM, et al. *BMJ Open* 2018;8:e021072.

Prevalence

- Reported ranges 3.5%-100% X. Xu et al. / Ageing Research Reviews 37 (2017) 53–68
- Using NHANES data from 1988-2014
 - 5541 participants in the 2013 to 2014 cycle
 - 59.6% had 2 morbidities
 - 38.5% had 3 morbidities
 - 22.7% had 4 morbidities.
- Prevalence of ≥ 2 morbidities was higher in those aged 65 years or older, female, non-Hispanic white or black, with health insurance, and under poverty

King DR, et al. *J Am Board Fam Med* 2018;31:503–513.

Figure 1. Age-standardized trends in multi-morbidity prevalence for participants 20 years or older from NHANES 1988–2014 by number of comorbidities.



King DR, et al. *J Am Board Fam Med* 2018;31:503–513.

Impact

- Multimorbidity is associated with
 - lower quality of life
 - lower physical function
 - higher acute admission rates
 - increased polypharmacy
 - increased treatment burden
 - increased healthcare costs

Morrison D, et al. *Primary Care Respiratory Medicine* (2016) 26, 16043
 Yarnall AJ, et al. *Age and Ageing* 2017; 46: 882–888

- Multimorbidity increases mortality

B.P. Nunes et al. *Archives of Gerontology and Geriatrics* 67 (2016) 130–138

Risk Factors for Multimorbidity

- Mental Illness (especially depression)
- Lower socioeconomic status
- Tobacco use
- Obesity
- Physical inactivity

X. Xu et al. / *Ageing Research Reviews* 37 (2017) 53–68
 King DR, et al. *J Am Board Fam Med* 2018;31:503–513.
 Holvast F, et al. *Family Practice*, 2017, Vol. 34, No. 5, 539–545
 Volaklis KA, et al. *Scand J Med Sci Sports*. 2018;28:604–612.

The Significant Role of Depression

Table 2. Association between diagnostic group and chronic diseases

Fixed effects	Number of chronic diseases ^a			Multimorbidity ^b		
	PR	95% CI	P value	OR	95% CI	P value
Controls	Reference			Reference		
Depression ^c	1.16	1.10–1.24	<0.001	1.55	1.33–1.81	<0.001
Psychological diagnoses ^c	1.12	1.05–1.18	<0.001	1.34	1.15–1.57	<0.001

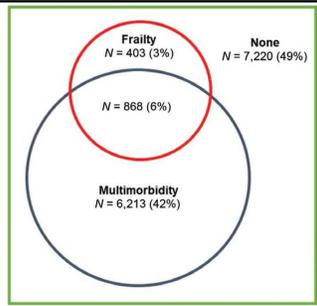
Table 3. Association between diagnostic group and drugs, including antidepressants

Fixed effects	Number of chronic drugs ^a			Polypharmacy ^b			Drug burden index ^c		
	PR	95% CI	P-value	OR	95% CI	P-value	Coefficient	95% CI	P-value
Controls	Reference			Reference			Reference		
Depression ^c	1.46	1.39–1.53	<0.001	2.89	2.41–3.47	<0.001	0.87	0.80 to 0.95	<0.001
Psychological diagnoses ^c	1.16	1.10–1.22	<0.001	1.86	1.58–2.09	<0.001	0.32	0.25 to 0.39	<0.001

Holvast F, et al. *Family Practice*, 2017, Vol. 34, No. 5, 539–545

Frailty

- 70% of frail adults also have multimorbidity
- 1/5 of adults with multimorbidity also have frailty
- Multimorbidity increases risk of frailty nearly twofold



Vetrano DL, et al. *J Gerontol A Biol Sci Med Sci*, 2018, Vol. XX, No. XX, 1-8 doi:10.1093/gerona/gly110

Figure 2. Overlap of frailty and multimorbidity (pooled data from nine studies including community-dwelling people; N = 14,704). Frailty was defined according to the Cardiovascular Health Study (CHS) criteria (by Fried and colleagues) and multimorbidity as 2+ diseases.

Multimorbidity and Patient Complexity

- Multiple Chronic Conditions is only one aspect of medical complexity

Multimorbidity in the Nursing Home Setting

- Highly prevalent, under studied
- ¼ newly admitted nursing home residents have mental-physical multimorbidity (MPM)
 - Care needs differ
 - More likely younger, male, unmarried
 - High number of clinically relevant neuropsychiatric symptoms

A. M. A. van den Brink et al. *International Psychogeriatrics* (2017), 29:6, 1037-1047

Who is more medically complex?

Two 72 year old men recently discharged to SNF from the hospital after suffering heart attacks. They were both given medications to control blood pressure and lipids, and advised to take aspirin, as well as to quit smoking. While in the hospital, they were also diagnosed with diabetes, and given much information about changing diet and exercising.

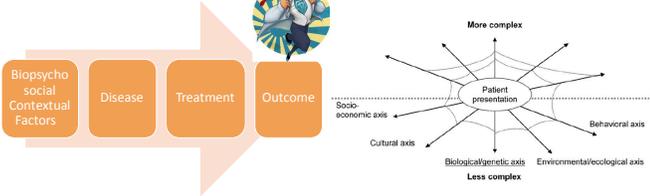
Mr. Jones is European American, lives in an inner city impoverished neighborhood with a sick wife who requires much care, works as a janitor, and has limited health insurance benefits.

Mr. Smith is African American, lives in a suburban neighborhood, has a stable employment situation with good health insurance benefits, and has a supportive family.

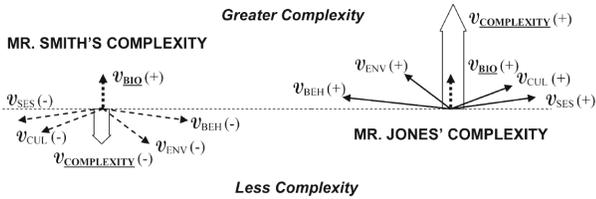
Safford, et al. J Gen Intern Med 22(Suppl 3):382-90

Multimorbidity and Patient Complexity

OUTCOMES ORIENTED MODEL VECTOR MODEL OF COMPLEXITY



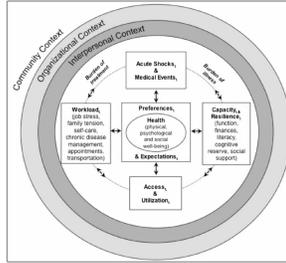
Safford, et al. J Gen Intern Med 22(Suppl 3):382-90



Safford, et al. J Gen Intern Med 22(Suppl 3):382-90

Multimorbidity and Patient Complexity

- Multiple Chronic Conditions is only one aspect of medical complexity
- Five key issues
 - Patient preferences
 - Contextual factors
 - Dynamics
 - Acute shocks
 - Resilience



Zullig LL, et al. J Gen Intern Med 31(3):329-37

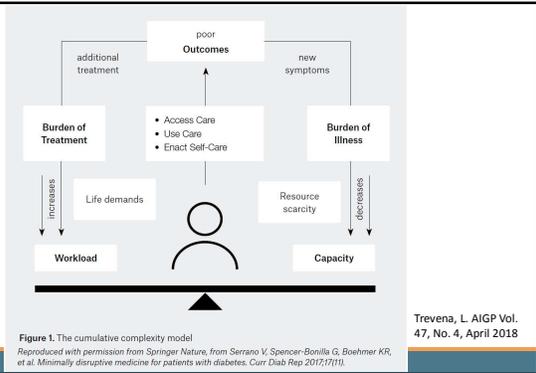
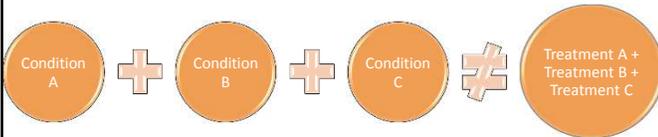


Figure 1. The cumulative complexity model
 Reproduced with permission from Springer Nature, from Serrano V, Spencer-Bonilla G, Boehmer KR, et al. Minimally disruptive medicine for patients with diabetes. Curr Diab Rep 2017;17(1).

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Treatment Burden Adds to Medical Complexity

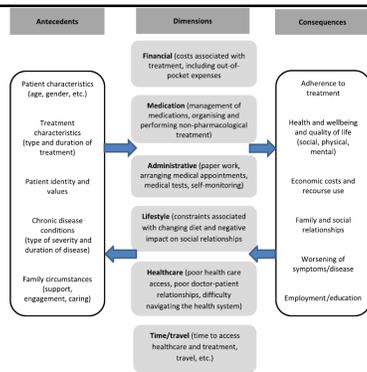


Antecedents and Consequences of Treatment Burden

- More common in women and older adults
- Increased in depression, anxiety, diabetes, functional incapacity, poor symptom control, no caregiver, longer duration of illness, and high number of medications
- High treatment burden leads to non-adherence and poor post-SNF outcomes

Sav et al. Health Expectations, 18, pp.312–324
Schreiner N, et al. J Gerontol Nurs. 2018 Dec 1;44(12):45-52

Treatment Burden Framework



Sav et al. BMC Medical Research
Methodology (2017) 17:140

Treatment Burden Often Not Addressed During Medical Visits

- Patients identify four burden of treatment issues:
 - **Administration** – burdens in correctly delivering or taking treatment
 - **Effects** – unwanted or unintended symptoms or consequences of the prescribed treatment
 - **Access** – patients' efforts or difficulty obtaining treatment in a timely, convenient or affordable manner
 - **Monitoring** – trouble complying with the monitoring required for effective or safe use of medication

Trevena, L. AIGP Vol. 47, No. 4, April 2018
Bohlen K, et al. Diabetes Care 2012;35(1):47–49



Minimizing Risk of Treatment: First Do No Harm

What is the optimal combination of drugs in a multi-morbidity context?

SIROIS, C., RESEARCH IN SOCIAL AND ADMINISTRATIVE PHARMACY, [HTTPS://DOI.ORG/10.1016/J.SAPHARM.2018.09.008](https://doi.org/10.1016/j.sapharm.2018.09.008)

Break-out Exercise

For a person aged 65-75 with type 2 diabetes, heart failure, and chronic obstructive pulmonary disease, which drugs would you recommend as the OPTIMAL BASIC THERAPY?



Multimorbidity and Appropriate Prescribing

- ADR risk prediction tools lack sufficient predictive value to be useful in daily clinical practice
- Multiple NH studies to reduce polypharmacy have been done with many positive but also mixed results
 - No one intervention has consistently proven effective
 - A multi-faceted approach is likely more effective
 - Need more research on clinical decision support systems

Molokhia and Majeed *BMC Family Practice* (2017) 18:70

The delicate choice of optimal basic therapy for multimorbid older adults

- Cross-sectional study
 - Mostly pharmacists responded
 - 10% geriatricians
- Little consensus
 - Median number of recommended drugs: 10 (6-13)
 - 21.6% ≥ 2 medications or classes with a contraindicated interaction (but none of the geriatricians did)
- What is appropriate polypharmacy??

Sirois, C., *Research in Social and Administrative Pharmacy*,
<https://doi.org/10.1016/j.sapharm.2018.09.008>

Polypharmacy in Multimorbidity

- Disease clusters leading to highest polypharmacy rates
 - CHF with osteoporosis
 - CKD with COPD
 - CKD with osteoporosis

Feng X, et al. *Population Health Management*. 2018; 21(2):123-129

- Physical activity inversely associated with polypharmacy in older multimorbid adults

Volaklis KA, et al. *Scand J Med Sci Sports*. 2018;28:604-612.

Pharmacodynamics & Pharmacokinetics

1. How is it going to **ACT** on my patient?

?



2. How is it going to **MOVE THROUGH** my patient?

?

A Word on Protein Binding

- Serum albumin
 - Major drug binding protein
 - Acute phase reactant (↓)
 - Highly protein bound drugs affected
e.g. phenytoin, warfarin, NSAIDs.
- Ordering serum drug levels in older patients?
 - Therapeutic ranges routinely may not be accurate guide to determine toxicity or efficacy, especially in acute or chronic inflammation



Cepeda OA, Morley JE. *Pathy's Principles and Practice of Geriatric Medicine*, 4th ed. London, John Wiley & Sons, Ltd, 2006; pp 215-21.

Volume of Distribution (Vd)

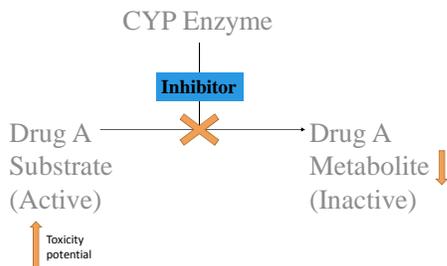
- Fat soluble drugs have *longer half-life* with increased Vd
- side effects mainly after reaching steady state.
- e.g. amiodarone, desipramine, diazepam, haloperidol

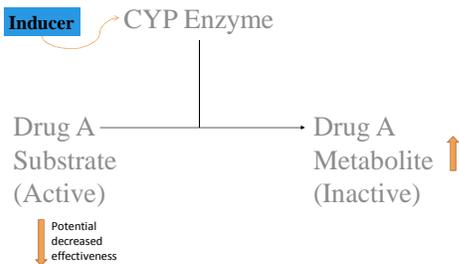
- Water soluble drugs distribute *less effectively* with decreased Vd
- higher plasma concentration, side effects mainly with initial doses.
- e.g. digoxin, aminoglycosides, atenolol, sotalol, theophylline, lithium, sedative-hypnotics

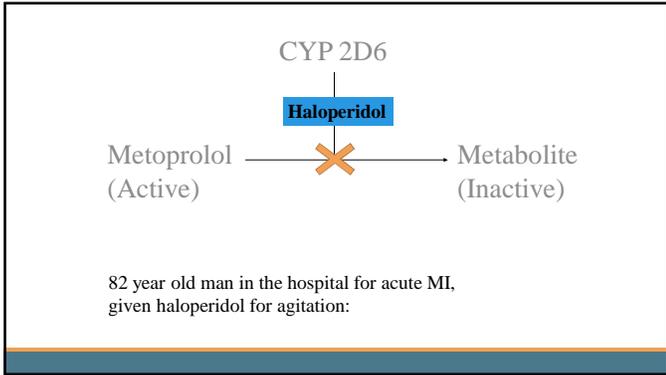


Phase 1 Metabolism: Cytochrome P450 (CYP)

- Substrates: metabolized by particular P450 enzymes
- Inhibitors: impair the ability of specific P450 enzymes to metabolize their target substrates
- Inducers: increase the production of particular P450 enzymes







CYP Enzymes	Substrates	Inhibitors	Substrate side effects	Inducer	Substrate therapeutic effects
1A2					
2C9					
2C19					
2D6					
2D9					
3A4					
Metabolized by liver, enzyme unknown					
Not metabolized by liver					

75 year old woman, lives in assisted living facility

- History of DM, UI, chronic LBP, one previous NSTEMI, and HLD
- Admitted for new onset atrial fibrillation and recurrent MI
- Medications prior to admission
 - glyburide
 - losartan
 - cyclobenzaprine
 - oxybutinin (extended release)
 - simvastatin
 - metoprolol
 - aspirin

75 year old woman, with new onset a fib and MI

- During her hospitalization, started on
amiodarone
clopidogrel
- On discharge to SNF, she is in NSR, has no complaints.
- Within two weeks:
had two episodes of hypoglycemia
became more lethargic
fell twice
lower than her usual blood pressure
constipation and dry mouth
muscle aches

CYP Enzymes	Substrates	Inhibitors	Substrate side effects
1A2	cyclobenzaprine		
2C9	glyburide		
2C19			
2D9	metoprolol simvastatin		
3A4	losartan cyclobenzaprine simvastatin oxybutinin		

CYP Enzymes	Substrates	Inhibitors	Substrate side effects
1A2	cyclobenzaprine	amiodarone	
2C9	glyburide	amiodarone clopidogrel	
2C19			
2D9	metoprolol simvastatin	amiodarone	
3A4	losartan cyclobenzaprine simvastatin oxybutinin amiodarone	amiodarone	

CYP Enzymes	Substrates	Inhibitors	Substrate side effects
1A2	cyclobenzaprine	amiodarone	falls, lethargy
2C9	glyburide	amiodarone clopidogrel	hypoglycemia
2C19			
2D9	metoprolol simvastatin	amiodarone	Myopathy
3A4	losartan cyclobenzaprine simvastatin oxybutinin	amiodarone	low blood pressure falls, lethargy myopathy dry mouth, constipation

CYP Enzymes	Substrates	Inhibitors	Substrate side effects
1A2	cyclobenzaprine	amiodarone	
2C9	glyburide	amiodarone clopidogrel	
2C19			
2D9	metoprolol simvastatin	amiodarone	
3A4	losartan cyclobenzaprine simvastatin oxybutinin	amiodarone	

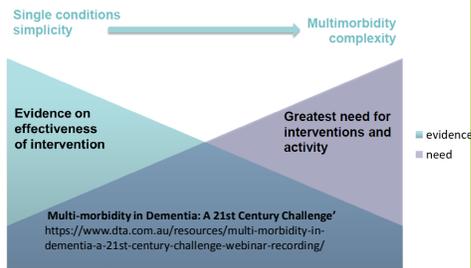
Re-consider new medications from hospital AND/OR
NonRx methods for neck pain, change to Metformin, Pravastatin, Tropicium

Deprescribing in Multimorbidity

- Evidence limited – evidence-based recommendations for stopping medications only possible for bisphosphonates
Swinglehurst D and Fudge N. Br J Gen Pract. 2017 Sep; 67(662): 388–389.
- PRIMUM Trial (pragmatic clustered RTC)
 - Medication regimens unstable over a 3-6 mo time period
 - How does this impact medical complexity, adherence, cost and treatment burden?
von Buedingen et al. BMC Family Practice (2018) 19:131

Evidence Base and Research Priorities

The paradox of evidence and need



Multimorbidity and Key Research Priorities

Given the heterogeneity of multimorbidity, the initial focus of research should be on the determinants of clusters that are most common and/or of greatest impact. (Academy of Medical Sciences, April 2018)



2016 Cochrane Review of 18 RCTs

- Overall the results regarding the effectiveness of interventions were mixed.
- Modest improvements in mental health outcomes
- Modest improvements in functional outcomes
- Are these the right type of studies to do for this topic?

Smith SM, et al. Cochrane Database of Systematic Reviews 2016, Issue 3. Art. No.: CD006560.

Table 2 Utilization and Chronic Condition Measures and Outcomes

Utilization Measures	Study #	Chronic disease-related measures										
		ED visits	Hospital readmission	Outpatient physician visits	Cost	Mortality	HbA1C	Lipids	Blood pressure	BMI	Depression symptoms	Med adherence
≥2 chronic medical conditions	1											
	2		✓ ^{1*}									
≥1 chronic medical condition + depression	3							✓ ^{1*}		✓ ^{1*}	✓ ^{1*}	✓ ^{1*}
	4					✓		✓ ^{1*}	✓ ^{1*}	✓	✓ ^{1*}	✓ ^{1*}
	5				✓ ^{1*}		✓ ^{1*}	✓ ^{1*}	✓ ^{1*}		✓ ^{1*}	✓ ^{1*}
	6										✓ ^{1*}	✓ ^{1*}
	7						✓ ^{1*}				✓ ^{1*}	✓ ^{1*}
	8						✓ ^{1*}	✓	✓	✓	✓ ^{1*}	✓ ^{1*}
	9						✓ ^{1*}				✓ ^{1*}	✓ ^{1*}
Post or predicted high utilization	10	✓	✓ ^{1*}	✓ ^{1*}								
	11	✓	✓	✓								
	12	✓	✓	✓ ^{1*}		✓ ^{1*}	✓					
	13	✓	✓			✓ ^{1*}						
	14	✓	✓			✓ ^{1*}						
	15	✓	✓	✓ ^{1*}		✓						
Total # measuring outcome	4	7	4	4	5	1	4	2	3	2	7	4
Total # with significant change favoring the intervention	0	2	1	2	0	3	1	2	0	7	0	4

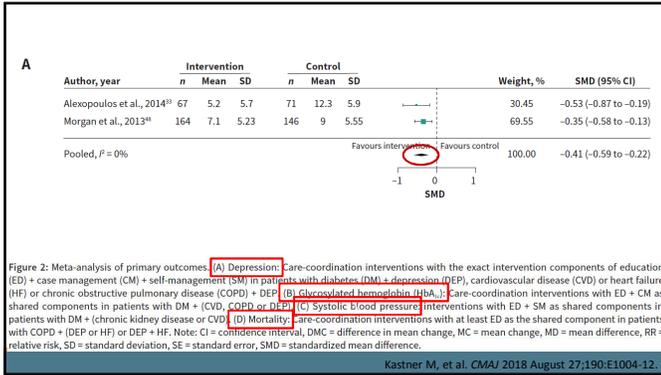
Baker et al. BMC Health Services Research (2018) 18:65

✓ indicates the study measured this outcome
^{1*} indicates an increasing trend among intervention group with statistical significance at p < 0.05
^{1*} indicates a decreasing trend among intervention group with statistical significance at p < 0.05

2018 Systematic Review and Meta-Analysis

- To identify effective multimorbidity interventions
 - To determine which components optimize impact
 - 2/25 studies in PALTC
 - Dementia and Depression cluster
 - Case manager coordination of care and Education of IPT
- Brodsky H, et al. *J Clin Psychiatry* 2003;64:63-72.
 McSweeney K, et al. *Int J Geriatr Psychiatry* 2012;27:1163-71.

Kastner M, et al. *CMAJ* 2018 August 27;190:E1004-12.



Integrated Care Programs

- “Real-work care practices”
- 30 models
 - Chronic Care Model
 - Guided Care Model
 - Ariadne Principles
- **Person-centered Care**

V. Struckmann et al. / *Health Policy* 122 (2018) 23–35
Leijten FRM, et al. *BMJ Open* 2018;8:e021072.
- Evidence of benefit lacking in PALTC continuum

Multimorbidity and Patient-Centered Care: What Patients Want

- Social relationships
- A positive frame of mind or resilience
- Enjoyment of life
- Maintaining independence.

Leijten FRM, et al. *BMJ Open* 2018;8:e021072.

Minimally Disruptive Medicine (MDM)

“A patient-centred approach to care that focuses on achieving patients’ goals for life and health while imposing the smallest possible treatment burden on their lives.”

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Assessing Patient-Centeredness

- Limited evidence of how to do this well and quickly
- Available tools developed for single-disease or specific contexts, not multimorbidity or polypharmacy
- Outcome Prioritization Tool: remaining alive, maintaining independence, reducing pain, and reducing other symptoms.

Mangin D, et al. BMJ Open 2016;6:e010903. doi:10.1136/bmjopen-2015-010903
 Fried TR, et al. Patient Educ Couns. 2011 May; 83(2): 278–282
 UGT van Summeren, et al. Br J Gen Pract 2017; DOI: https://doi.org/10.3399/bjgp17X690485

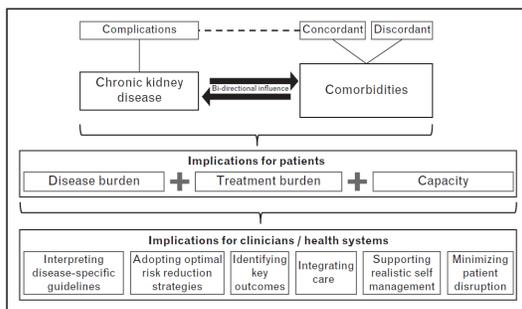


FIGURE 1. CKD and comorbidities and their implications for patients, clinicians and health systems. Fraser SDS and Taal MW. Curr Opin Nephrol Hypertens 2016, 25:465–472

Role of the Leadership Team

Steps to strengthen safety culture:

- Leadership walk rounds, whereby senior managerial and clinical leaders "walk the floor"
- Starting team meetings with a patient story
- Using reflective practice to focus on safety issues
- Mechanisms for reporting safety issues, such as through regular team meetings.



Multimorbidity: Technical Series on Safer Primary Care. Geneva: World Health Organization; 2016. Licence: CC BY-NC-SA 3.0 IGO

Thank you!