Medications - not too little, not too much

How to use evidence, values and common sense when reviewing medications

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therapeuticseducation.org
mystudies.org
@medmyths

Presenter Disclosure

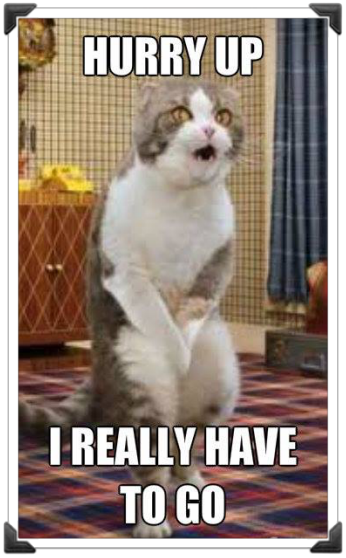
- Presenter's Name: James McCormack
- I have no current or past relationships with commercial entities
- Speaking Fees for current learning activity:
  - I have received a speaker's fee from the UBC Pharmacy Office of Experiential Education for this learning activity.

Commercial Support Disclosure

- This Learning Activity has received no financial or in-kind support from any commercial or other organization

Objectives/Agenda

	Agenda	Learning Objectives
8:30am	Registration and Light Breakfast	1.To be able to do a thorough patient-centred medication review 2.To be able to prioritize medications with regard to medication re-evaluation 3.To be able to individualize doses of medications based on the evidence and individual patient response 4.To be able to use healthy skepticism around the best available evidence when it comes to getting people on just the right amount of medication
8:45am	• Philosophy of Medication Reviews • Dose Issues	
10:15am	Break	
10:30am	• Group work - review of specific medication classes • Report back to group	
12:00pm	Lunch	
1:00pm	• Discussion of Specific Medication Classes • Your cases - work in pairs	
2:30pm	Break	
3:00pm	• Your cases - report to group	
4:00pm	Workshop Concludes	



The Goldilocks Dilemma

POLYPHARMACY

does NOT= >5 meds

It means taking medications/supplements which

For symptoms

are not providing a complete or clinically important effect or are given at doses larger than is required to achieve that effect

For prevention

if one was fully informed by the best available evidence about benefits and harms one would not take them

BOTH COULD BE POLYPHARMACY

Terminology

Polypharmacy

Medication overload

Medication review

Medication checkup

Dr RL (a Family MD)

Late Feb - 2015

Her Grandmother (LC) - 90 year old very frail female

MEDICAL HISTORY

Atrial fibrillation, hypertension, angina, congestive heart failure, familial tremor, macular degeneration and recently diagnosed with diabetes

Hb A1C - 8.3

Never smoked

Suffered a compression fraction of a thoracic vertebrae after a fall

Echocardiogram from the fall - not much of anything

Clinically she gets tachycardia and short of breath walking 15 feet

HR 81

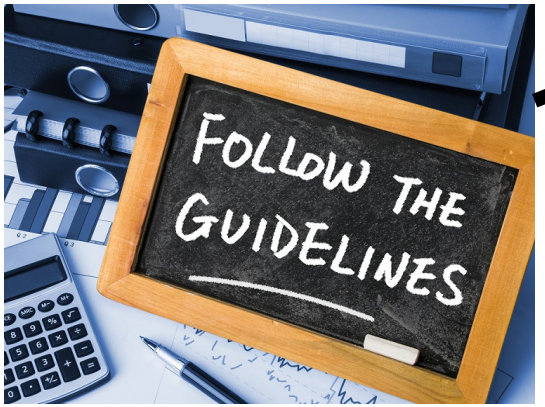
BP sitting 139/65

BP standing after 1 minute 154/73 and heart rate 73

20 regular meds
Gliclazide 30mg daily
Potassium chloride 600mg daily
Ramipril 10mg daily
Metoprolol 100mg twice daily
Furosemide 40mg daily
Valsartan 160mg daily
Digoxin 0.0625mg daily
Hydromorphone 3mg twice daily
Vitamin D 1000 IU daily
Calcium 1250mg daily
B12 250mg daily
Vitamin C 500mg daily
Vitalux daily
Omega 3s daily
Warfarin 2mg daily/3mg every other day
Atorvastatin 20mg daily
Zopiclone 3.75mg daily
Sennoside 12mg daily
Nitro patch 0.4mg qhs
Atrovent
Flovent
AS NEEDED Ativan 0.5 mg sl for anxiety/SOB
AS NEEDED Nitro spray
AS NEEDED Hydromorphone 1mg
AS NEEDED Gravol

MEDICAL HISTORY

Atrial fibrillation, hypertension, angina, congestive heart failure, familial tremor, macular degeneration and recently diagnosed with diabetes



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Calcium 1250mg daily
B12 250mg daily
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Vitalux daily
Omega 3s daily
Warfarin 2mg daily/3mg every other day
Atorvastatin 20mg daily
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Nitro patch 0.4mg qhs
Atrovent
Flovent
AS NEEDED Ativan 0.5 mg sl for anxiety/SOB
AS NEEDED Nitro spray
AS NEEDED Hydromorphone 1mg
AS NEEDED Gravol

= “undertreated”
“unmeet needs”

Guiding principles for a medication check-up

All medication decisions (be it starting or stopping) will be informed by the best available evidence.

All medications decisions will be guided by the principles of shared-decision making.

The approach to a medication check-up needs to be one that is systematic and that covers the vast majority of medications and indications.

It will require strong communication efforts between all decision-makers.

There is no need to tackle the ENTIRE list of medications in one visit or consultation. A medication check-up will be a longitudinal process which may require several visits for instituting a safer prescribing plan and for monitoring for development of symptoms over time.

THE INITIAL FRAMING OF THE PROCESS

What does the patient want
to get out of this process?

What are their goals?

What ones don’t they like taking?
Which ones do they feel are helping them?
Are there cost/inconvenience issues?

The 6 Steps

STEP 1 - Do a comprehensive medication review

STEP 2 - Prioritize the medications

- Will it Reduce Symptoms?
- Will it Reduce the Risk of Future Illness?
- Will it Cause Harm?

STEP 3 - Identify if the lowest dose has been determined

STEP 4 - Let the patient help you figure out the “right” meds

STEP 5 - Use ‘tricks’ to get patient interest

STEP 6 - Use common sense when stopping medications

Approaches differ depending on outcome

Every patient is an experiment - dose and effect

SYMPTOMS - we can usually figure out if it is working - but it is tricky

PREVENTION - one will never know if it worked

Expectations

Symptoms

You primarily need to know IF it works and DID it work

Safety, cost and convenience

Older medications first - safety

Head-to-head studies are uncommon

Doses in the CPS are “wrong”

N-of-1 studies

Let the patient tell you

Symptom NNTs

PPIs, sildenafil - NNT ~2

NSAIDs, opioids - pain NNT ~3-5

Antidepressants - severe depression - NNT ~10

Ipratropium - asthma attack - NNT ~11

Cholinesterase inhibitors - ADAS-Cog >4 - NNT ~10

Sleeping pills - improvement in sleep quality - NNT ~13

Steroids - sore throat - NNT ~3, Bell's palsy - NNT ~10

Antibiotics - acute COPD exacerbation - NNT ~5

Topical antibiotics - bacterial conjunctivitis - NNT ~7

But you need to know what goes on in the placebo group

	If a person has responded, what is the % chance it was the medication	
Response in the placebo group	RCT Benefit 10% - NNT 10	RCT Benefit 20% - NNT 5
0%	~100%	~100%
10%	~50%	~66%
20%	~33%	~50%
30%	~25%	~40%
40%	~20%	~33%

The Placebo Group Effect

NOT the placebo effect and these are ballpark numbers

~0% - general anesthesia

~5% - psychosis

~10% - sildenafil, OCD

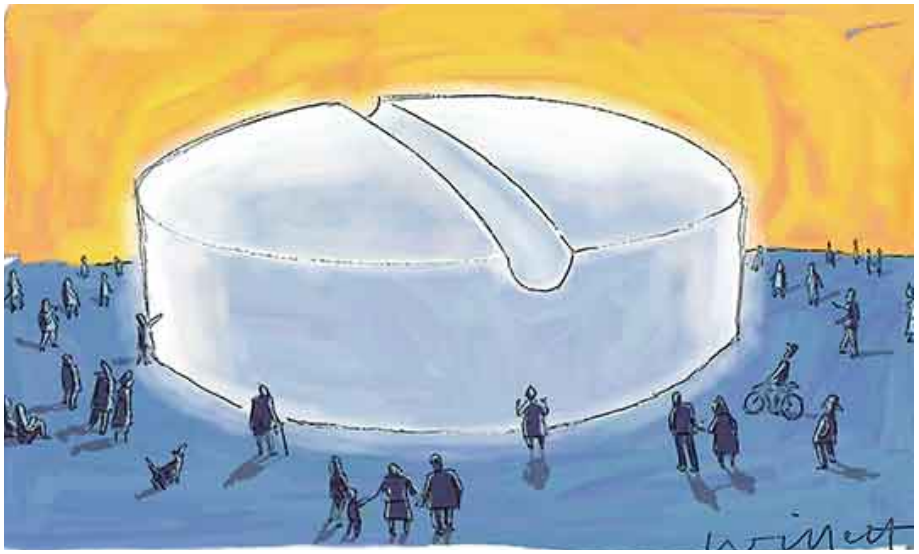
~20% - Alzheimer's meds, acetaminophen for headaches, side effects

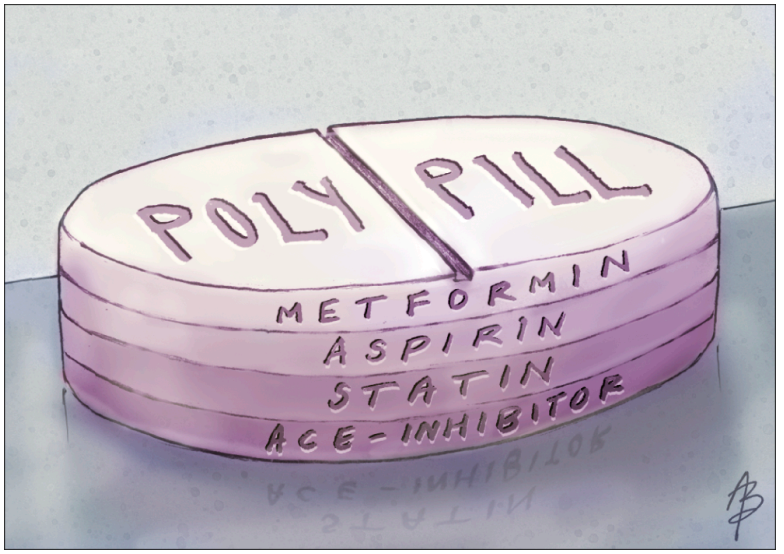
~25% - menopausal symptoms, migraine (frequency/severity)

~30% - blood pressure goal, depression, anxiety, PTSD, PPIs/H2RA, sore throat, NSAIDs of OA, inhalers for COPD

~40% - panic disorders

Prevention





Risk of future illness
CVD risk/benefit

(most people don't benefit despite a lifetime of treatment)

Prescriber
September 2015

— Assume a person's lifetime risk of CVD is that of a male with two CVD risk factors - roughly 50% (NEJM 2012;366:321-9)

\- Assume with multiple risk factor modification we can ⇩ that risk relatively by 60% (VERY optimistic)

—— Risk goes from 50% ➡ 20%

\- 30% of individuals BENEFIT

\- 70% DO NOT despite a LIFETIME of treatment

Ballpark absolute benefits (%) for CVD medications

	Primary Prevention 5 years		T2DM (glucose) 3-5 years		Secondary prevention 2-3 years
	BP	Statins	Most meds	SGLT2, GLP, metformin?	ACEI, BB, ARB, Statins
Cardiovascular events	2-5	1-2	0	2-5	5-10
Mortality	<1	<1	0	1-2	2-5
RELATIVE BENEFITS	30-50%	25-35%	15%		

mystudies.org, cvdcalculator.com

All the large RCTs evaluating the impact of glucose lowering medications on CVD Outcomes

RCTs evaluating the impact of medications on CVD outcomes in T2DM

YEAR	NAME		MEDICATION	RESULT	OUTCOME CHANGED	ABSOLUTE DIFFERENCE/ TIME
1970	UGDP	SU	tolbutamide (Orinase)	NEGATIVE	CVD mortality	↑8%/5 years
1971		BG	phenformin (DBI)	NEGATIVE	Mortality	↑ 6%/5-8 years
1976		SU	tolbutamide (Orinase)	NEGATIVE	Fatal MI	↑ 5%/5 years
1982		IN	insulin	NEUTRAL		
1998	UKPDS 33/34	IN,SU	insulin, chlorpropamide, glyburide/glibenclamide, glipizide	NEUTRAL		
1998		IN,SU,BG	metformin, insulin, chlorpropamide, glyburide/glibenclamide, glipizide	NEUTRAL except POSITIVE for metformin	Mortality MI	↓7%/11 years ↓ 6%/11 years
2003	STOP-NIDDM	OTH	acarbose (Precose)	POSITIVE	MI	↓ 1.5%/3 years
2005	PROACTIVE	GLIT	pioglitazone (Actos)	POSITIVE	MI	↓ 1.5%/3 years
2007	RECORD	GLIT	rosiglitazone (Avandia)	NEGATIVE	Heart failure	↑ 1%/4 years
2012	ORIGIN	IN	insulin	NEUTRAL		
2013	EXAMINE	DPP4	alogliptin (Nesina)	NEUTRAL		
2014	SAVOR-TIMI 53	DPP4	saxagliptin (Onglyza)	NEGATIVE	Heart failure	↑ 1%/2 years
2014	ALECARDIO	OTH	aleglitizar	NEUTRAL		
2015	ELIXA	GLP	lixisenatide (Adlyxin)	NEUTRAL		
2015	TECOS	DPP4	sitagliptin (Januvia)	NEUTRAL		
2015	EMPA-REG	GLIF	empagliflozin (Jardiance)	POSITIVE	Mortality Heart failure	↓ 2.5%/3 years ↓ 1.5%/3 years
2016	SUSTAIN 6	GLP	semaglutide (Ozempic)	POSITIVE	Combined outcome	↓ 2%/2 years
2016	LEADER	GLP	liraglutide (Victoza)	POSITIVE	Mortality Combined outcome	↓ 1%/4 years ↓ 2.5%/4 years
2017	CANVAS	GLIF	canagliflozin (Invokana)	POSITIVE	Combined outcome Heart failure Amputations	↓ 2%/3.5years ↓ 1%/3.5 years ↑ 1%/3.5 years
2017	EXSCEL	GLP	exenatide (Byetta)	NEUTRAL		
2017	ACE	OTH	acarbose (Procose)	NEUTRAL		
2017	Omarigliptin	DPP4	omarigliptin	NEUTRAL		
2018	HARMONY	GLP	albiglutide (Tanzeum)	POSITIVE	Combined outcome	↓ 2%/2 years
2018	CARMELINA	DPP4	linagliptin (Tradjenta)	NEUTRAL		
2018	DECLARE-TIMI 58	GLIF	dapagliflozin (Farxiga)	POSITIVE	Combined outcome (primarily heart failure)	↓ 1%/4 years

mystudies.org

Atrial Fibrillation - benefits/harms

Score	Risk of Stroke/Yr	On ASA ~22% relative benefit	On OAC ~66% relative benefit
Age <65 - 0 RF	0.7%	0.5%	0.2%
<65 - 1 RF 65-74 - 0 RF	1.5%	1.2%	0.5%
<65 - 2 RF 65-74 - 1 RF >75 - 0 RF	2.9%	2.3%	1.0%
<65 - 3RF 65-74 - 2RF >75 - 1RF	4.3%	3.4%	1.4%
<65 - 4RF 65-74 - 3RF >75 - 2RF	6.5%	5.1%	2.1%
<65 - 5RF 65-74 - 4RF >75 - 3RF	10%	7.8%	3.3%
Annual risk of major bleeding	0.5%	1%	2-10%

CVD, Female, CHF, HTN, or T2DM = 1 RF

Previous stroke/ TIA = 2 RF

http://www.sparctool.com

Heart failure - if you can get to higher doses (Absolute changes)

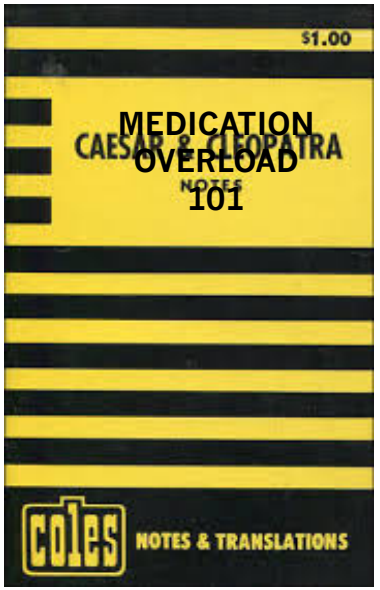
OUTCOME	ACEI ~ 2 years	ARB ~ 4 years	BB ~ 1.5 years
Hospitalization for heart failure	No difference	3% less	No difference
Heart failure worsening	5% less	3% less	No difference
Hypotension	3% more	2.5% more	No difference
Dizziness	5% more	Not reported	14% more
Hyperkalemia	2.5% more	3% more	Not reported
Increase SCr	2.5% more	6% more	Not reported
Cough	2.5% less	Not reported	Not reported

Mortality no difference

PLOS ONE Meta-analysis Feb 28th, 2019

Do a Comprehensive Medication History

UNTIL PROVEN OTHERWISE



The drug and the dose are WRONG!!!!!!

Questions to Ask

rephrase as open-ended questions when possible

Do you know the names of all of your medications and how to take them?

Do you know that most medications have 2 names - a generic and a brand name?

Do you know what each of your medications does?

What medications do you think you need and why?

What medications seem to be working for you and how can you tell?

What medications don’t seem to be working for you and how can you tell?

Have you ever stopped any of these medications on your own or with supervision?

Have you ever been afraid to tell your health care provider how you take (or don’t take) you medications?

Do you have any symptoms that you think might be related to your medications and if so what are they?

Do you ever have to skip medications or not take some medications some months because the cost is too

Which ones do you skip or do you not take in that case

cmaj
BEST EVIDENCE • BEST PRACTICE • BEST HEALTH

Jan 28, 2019

Why do patients often lie to their doctors?

JAMA Network Open

Original Investigation | Medical Education

Prevalence of and Factors Associated With Patient Nondisclosure of Medically Relevant Information to Clinicians

TYPE OF INFORMATION	Ever avoided informing the clinician
Disagreed with a recommendation	~30-45%
Did not understand clinicians instructions	~25-30%
Had an unhealthy diet	~20-25%
Did not take prescription as instructed	~20%
Took a certain medication and deliberately didn't say	~10-15%

REASONS	
Didn't want to be judged	~65-80%
Embarrassed	~50-60%
Didn't want to look difficult	~40-50%
Didn't want to look stupid	~30-40%
Didn't want info in medical record	~30-35%

"Future research should test interventions aiming to increase the trust and communication between patients and their clinicians as well as patients' comfort with disclosing information to their clinicians"

JAMA Network Open. 2018;1(7):e185293. doi:10.1001/jamanetworkopen.2018.5293

Use tricks to get buy-in

THEIR ARGUMENTS

I've been on these for years and now you are telling me I don't need them

But these are for my heart!!

It's OK, I don't pay for my medications

But my "insert any specialist" says I need these

If it ain't broke don't fix it

YOUR ARGUMENTS

Well your renal function/hepatic function are decreased

Look what you've been able to do for yourself

You take control and figure out the dose - you teach me what works

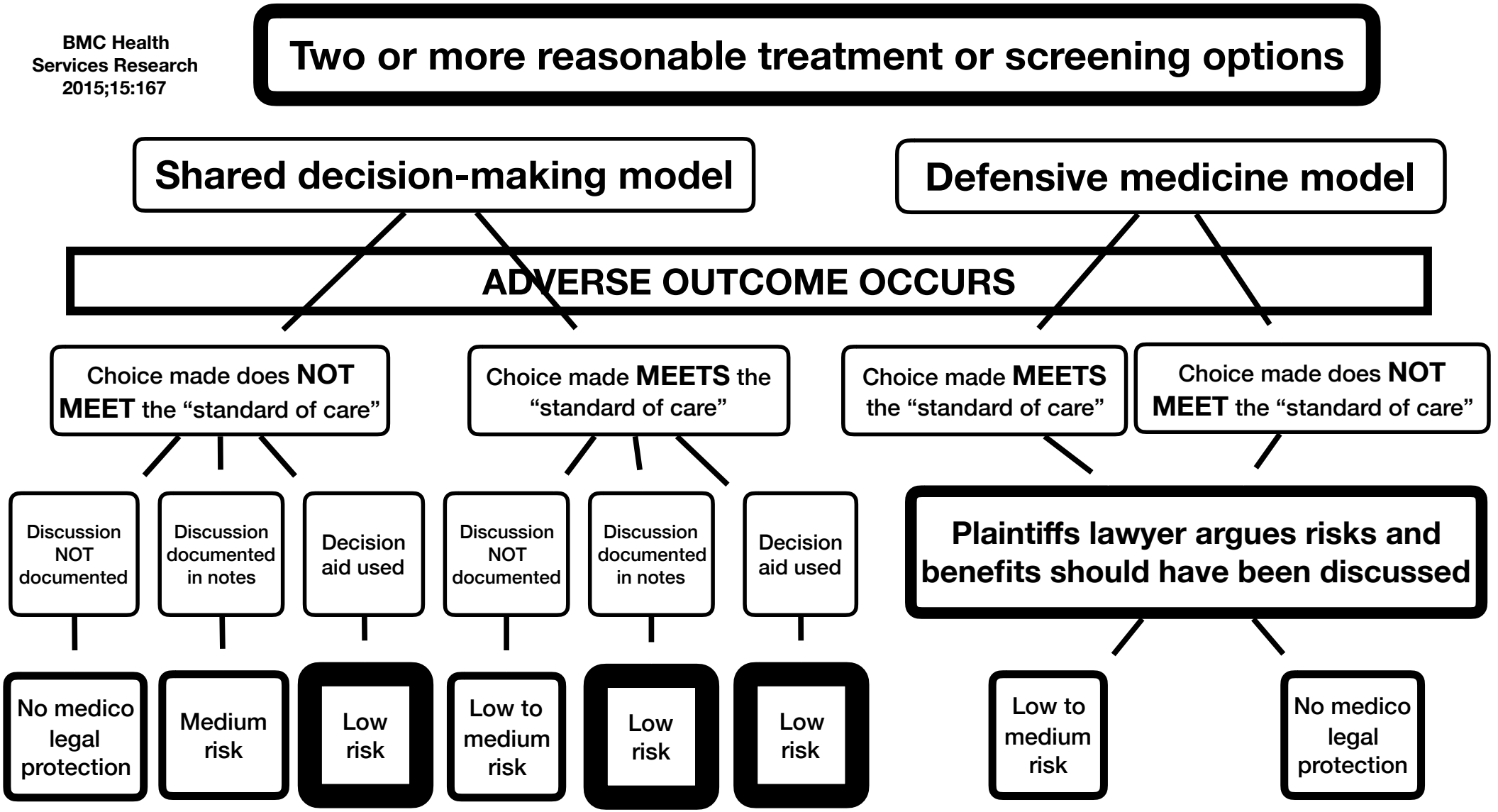
Your specialist doesn't know you like I do

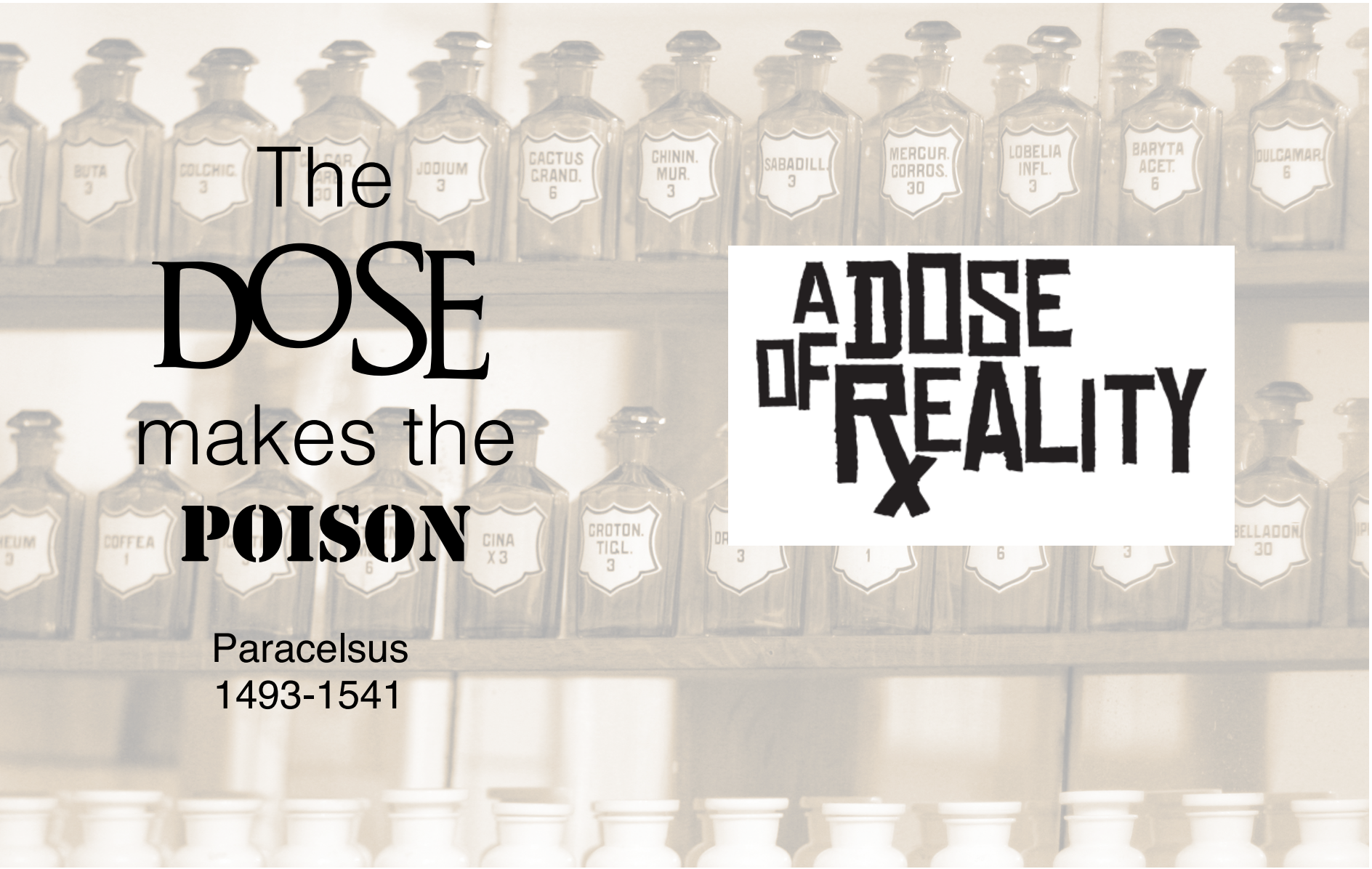
If needed, we can always restart

Intelligent non-adherence

Institutionalised patients!!! - “forced” adherence

BMC Health Services Research 2015;15:167





The
DOSE
makes the
POISON

Paracelsus
1493-1541

A DOSE OF REALITY

This simple concept can eliminate most medication problems

USE VERY LOW DOSES

CMAJ ANALYSIS

Is bigger better? An argument for very low starting doses

James P. McCormack PharmD, G. Michael Allan MD, Adil S. Virani PharmD

”Unless the condition is severe or life-threatening, drug treatment can be started at a very low dose (half or one-quarter the recommended starting dose)”

CMAJ 2011. DOI:10.1503 /cmaj.091481

Most of the effect of a medication comes from the “low” starting doses AND doubling a dose never doubles the effect - in fact it sometimes has no additional effect

Dose Response

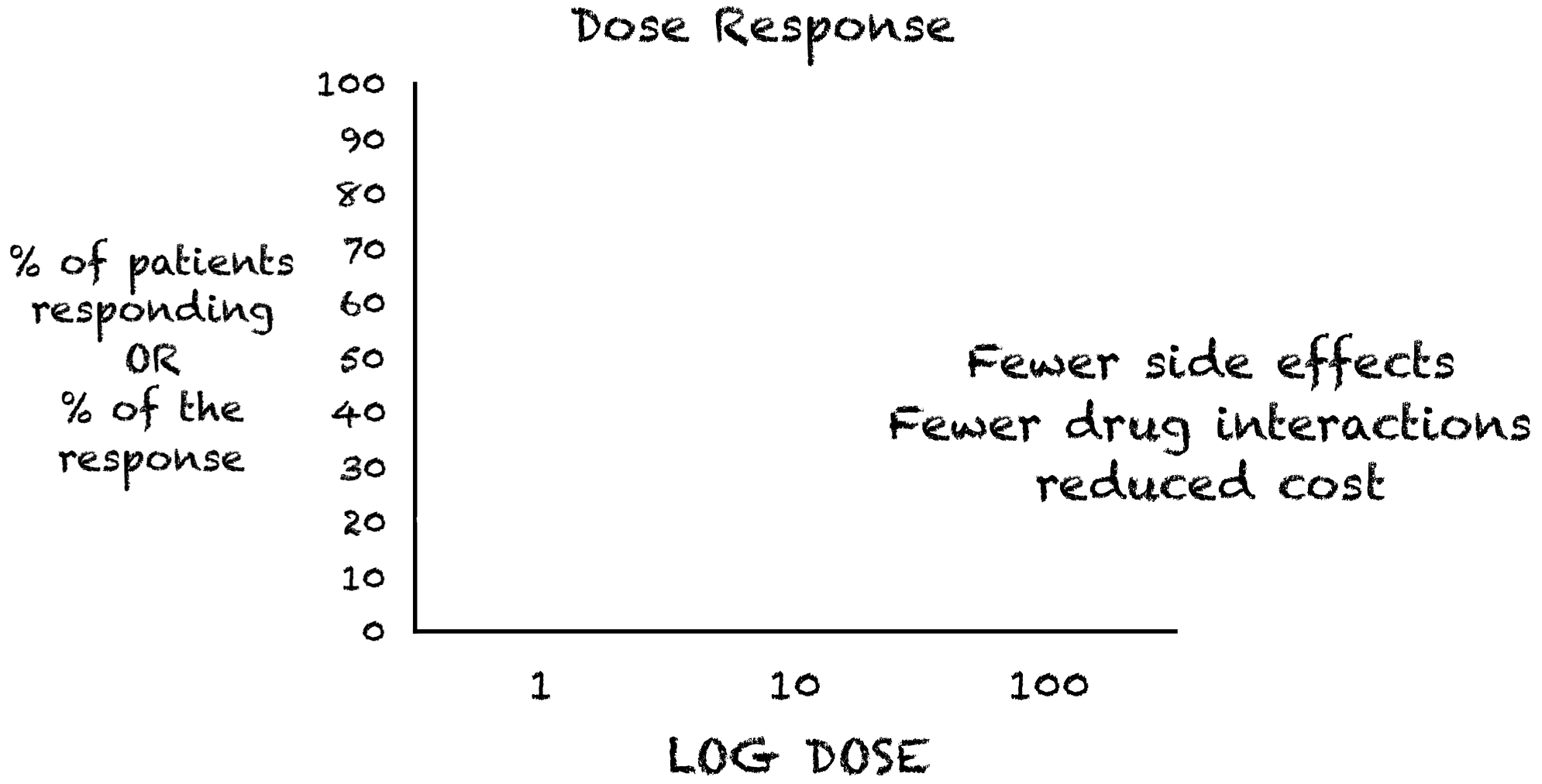
The doses in these books
are wrong for most people

% of patients
responding
OR
% of the
response

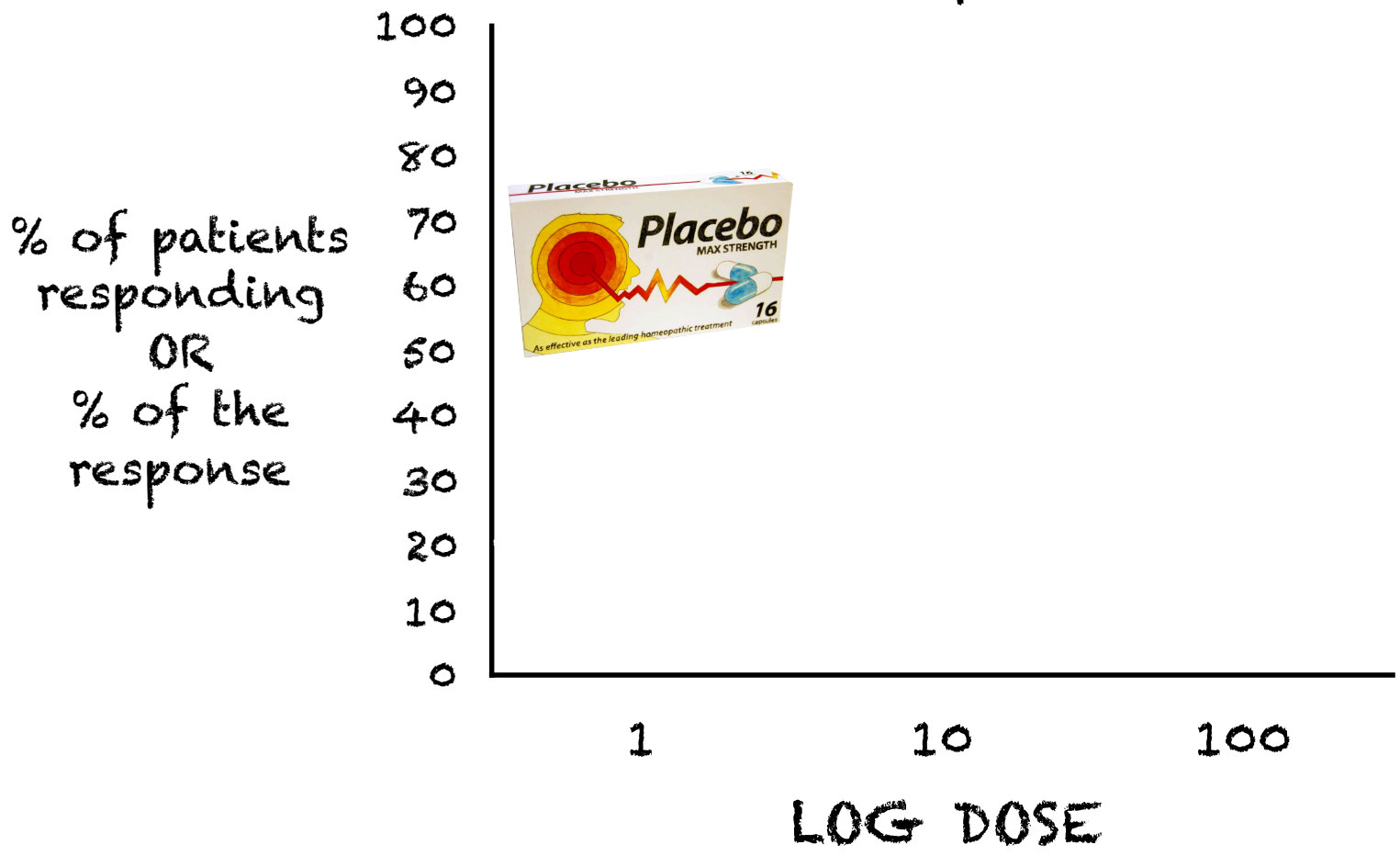
100
90
80
70
60
50
40
30
20
10
0

1 10 100

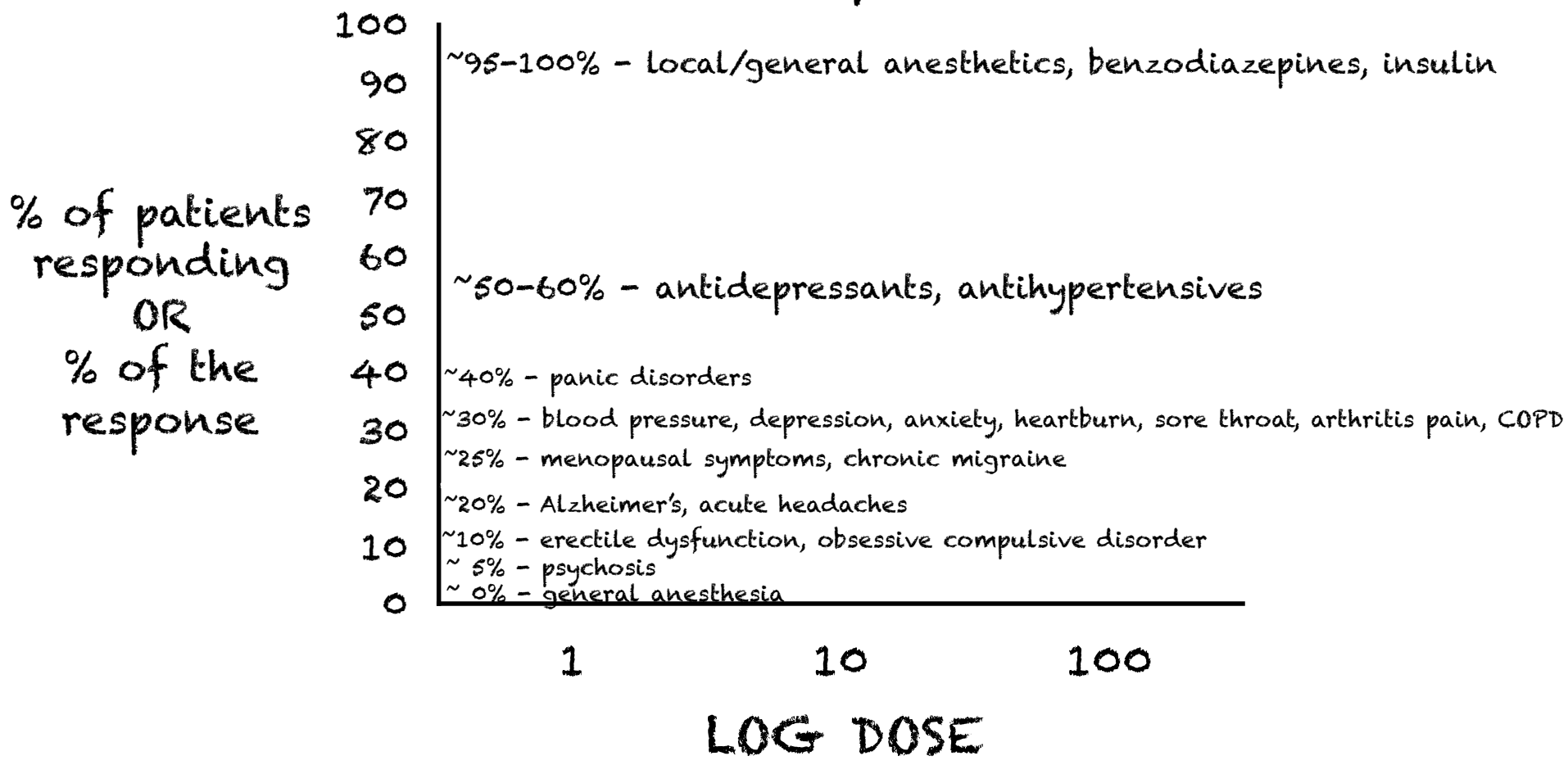
LOG DOSE

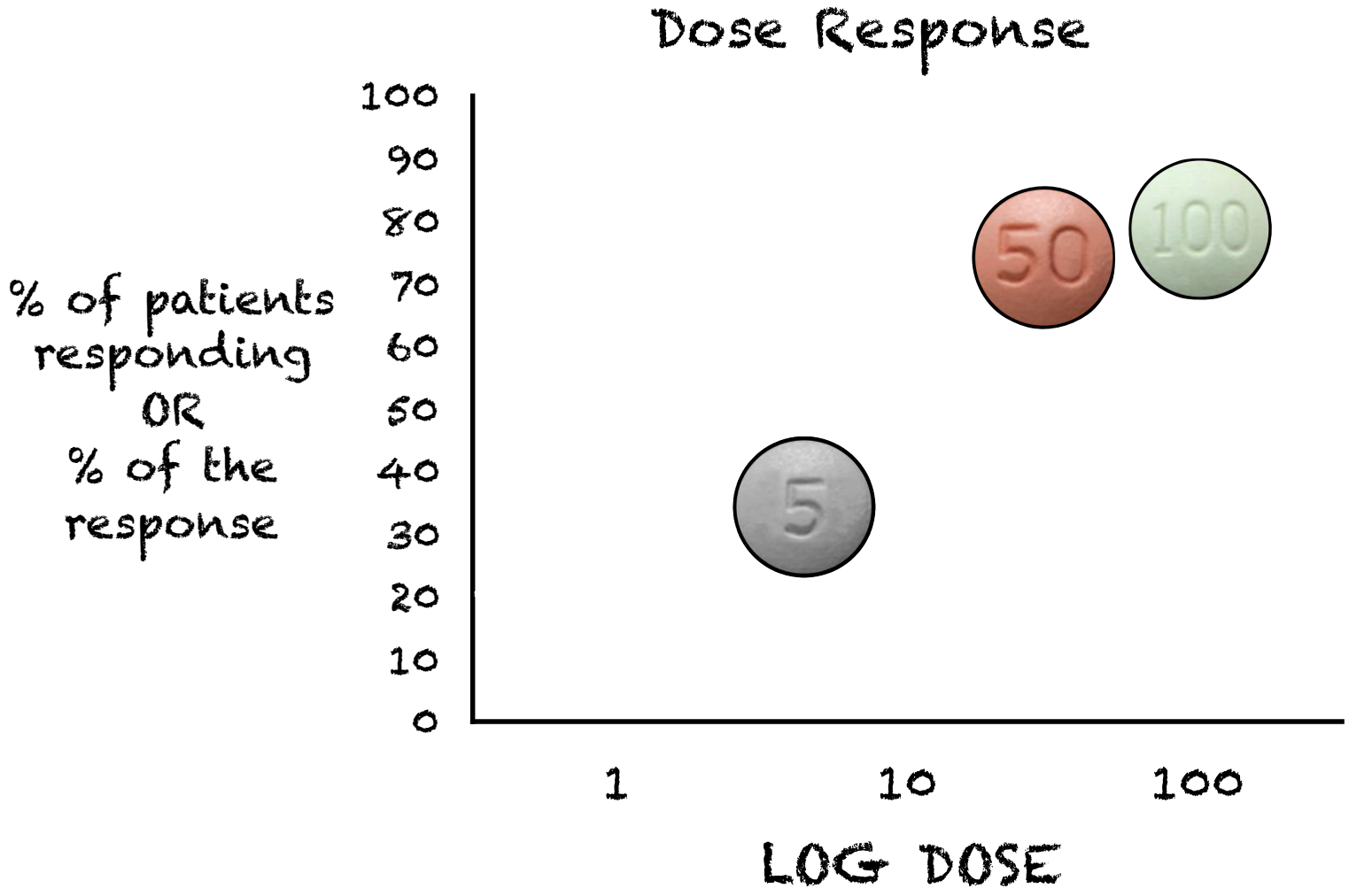

Dose Response
100
90
80
70
60
50
40
30
20
10
0
% of patients responding OR % of the response
Fewer side effects
Fewer drug interactions
reduced cost
1
10
100
LOG DOSE

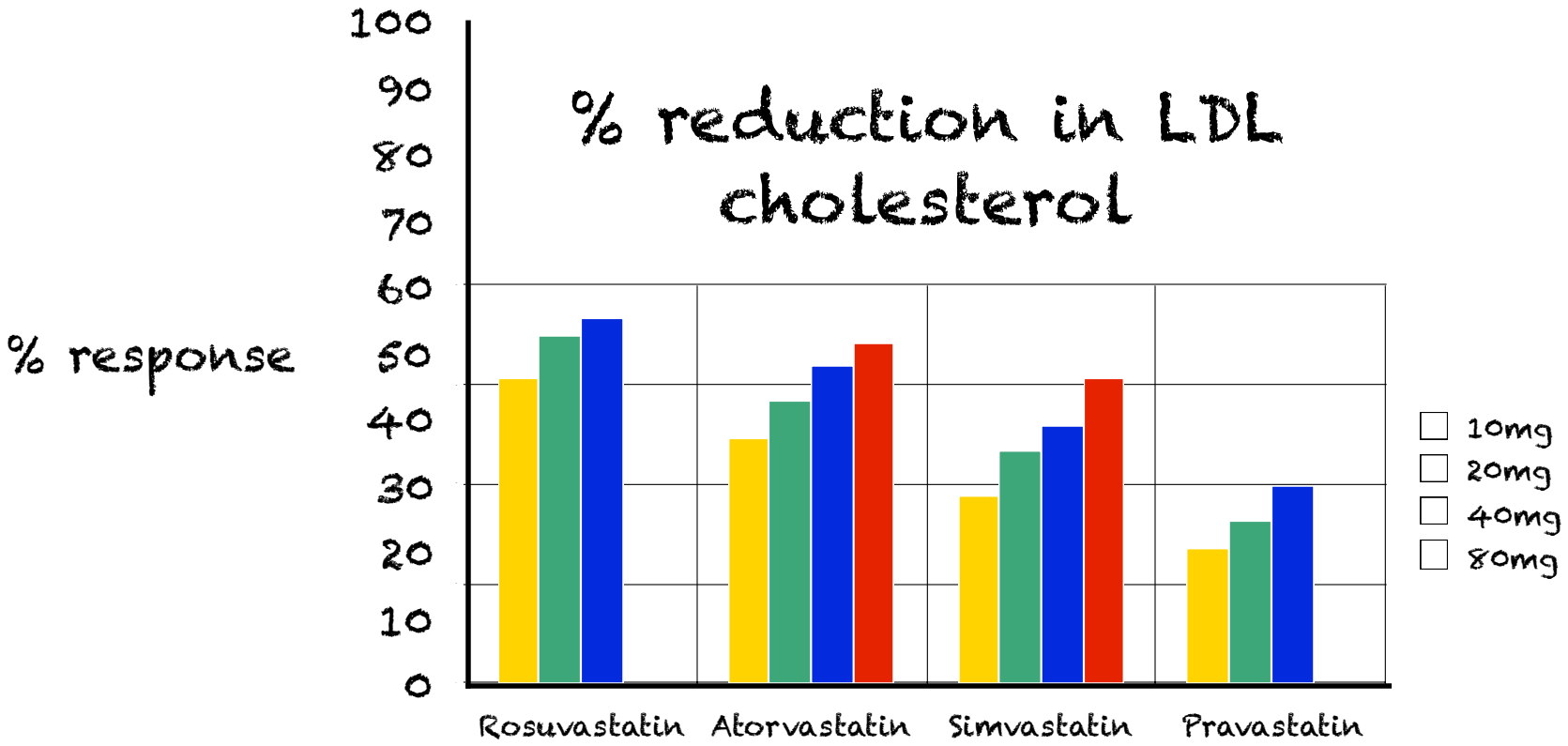
Dose Response

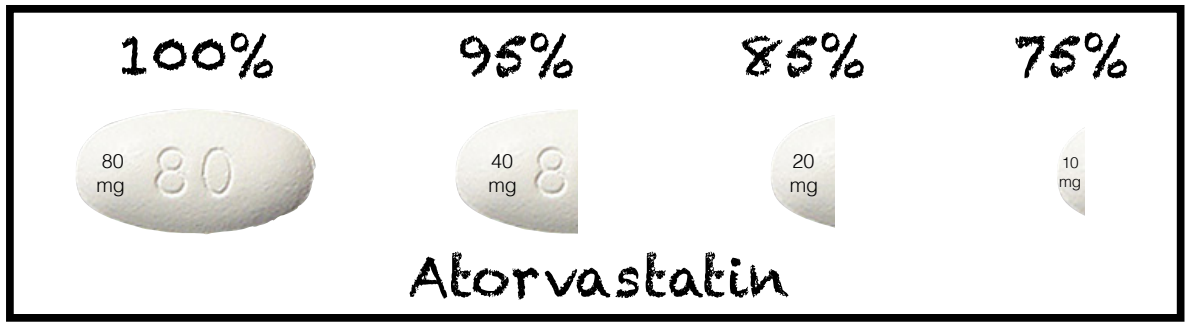


Dose Response

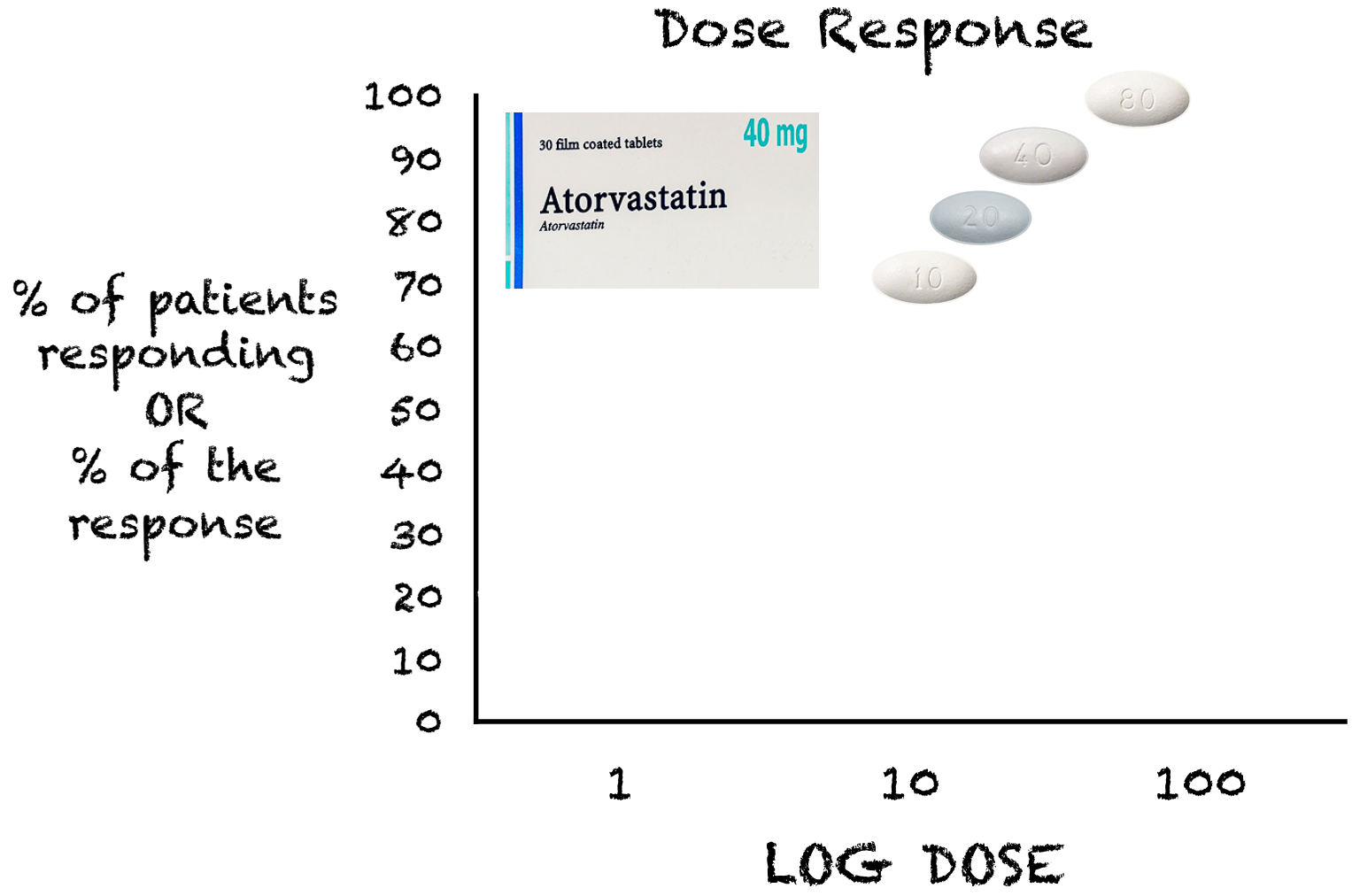


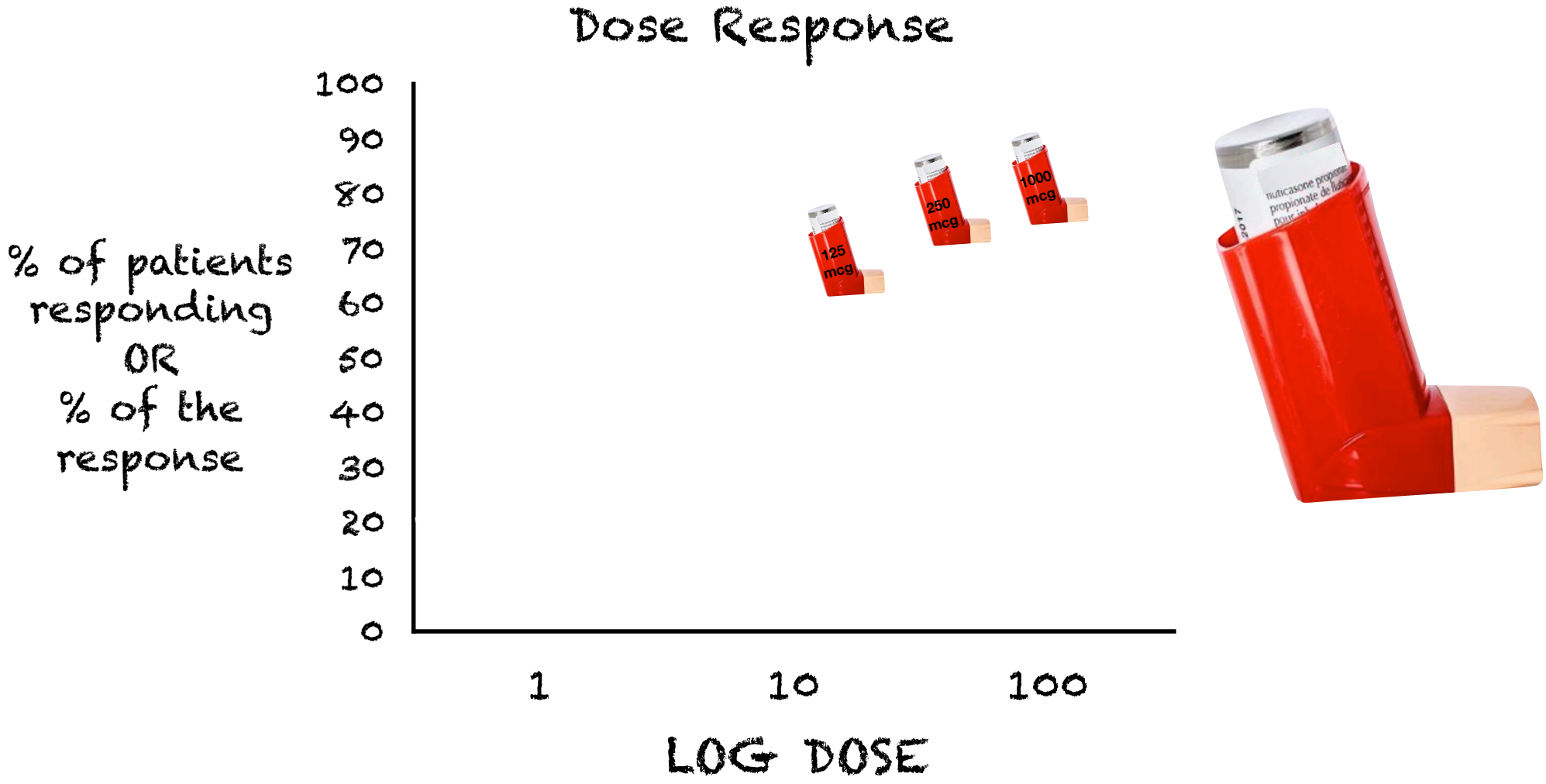

Dose Response
100
90
80
70
60
50
40
30
20
10
0
% of patients responding OR % of the response
50
100
5
1
10
100
LOG DOSE

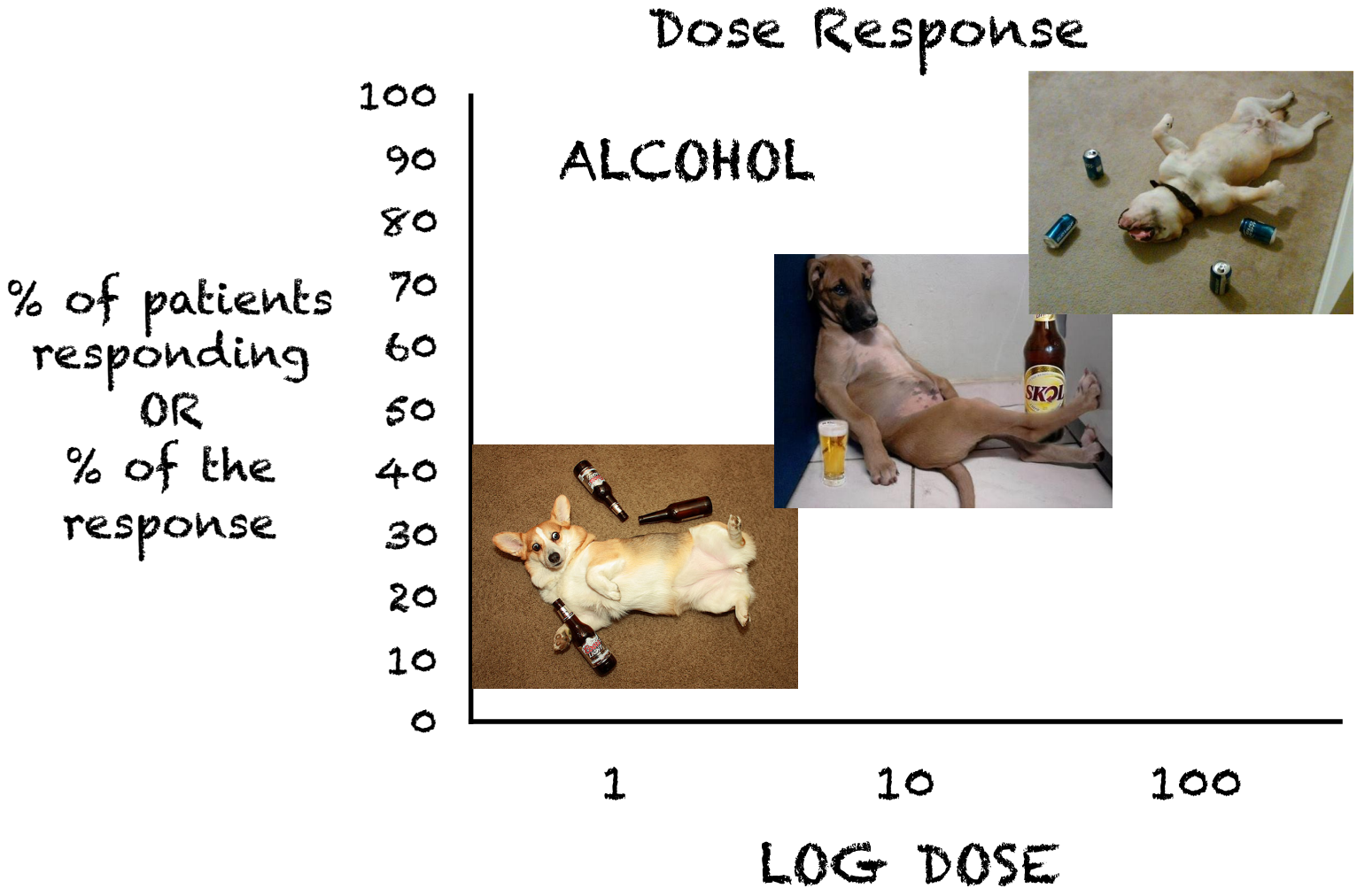

% reduction in LDL cholesterol
% response
100
90
80
70
60
50
40
30
20
10
0
Rosuvastatin
Atorvastatin
Simvastatin
Pravastatin
10mg
20mg
40mg
80mg


100%
95%
85%
75%
80 mg
40 mg
20 mg
10 mg
Atorvastatin

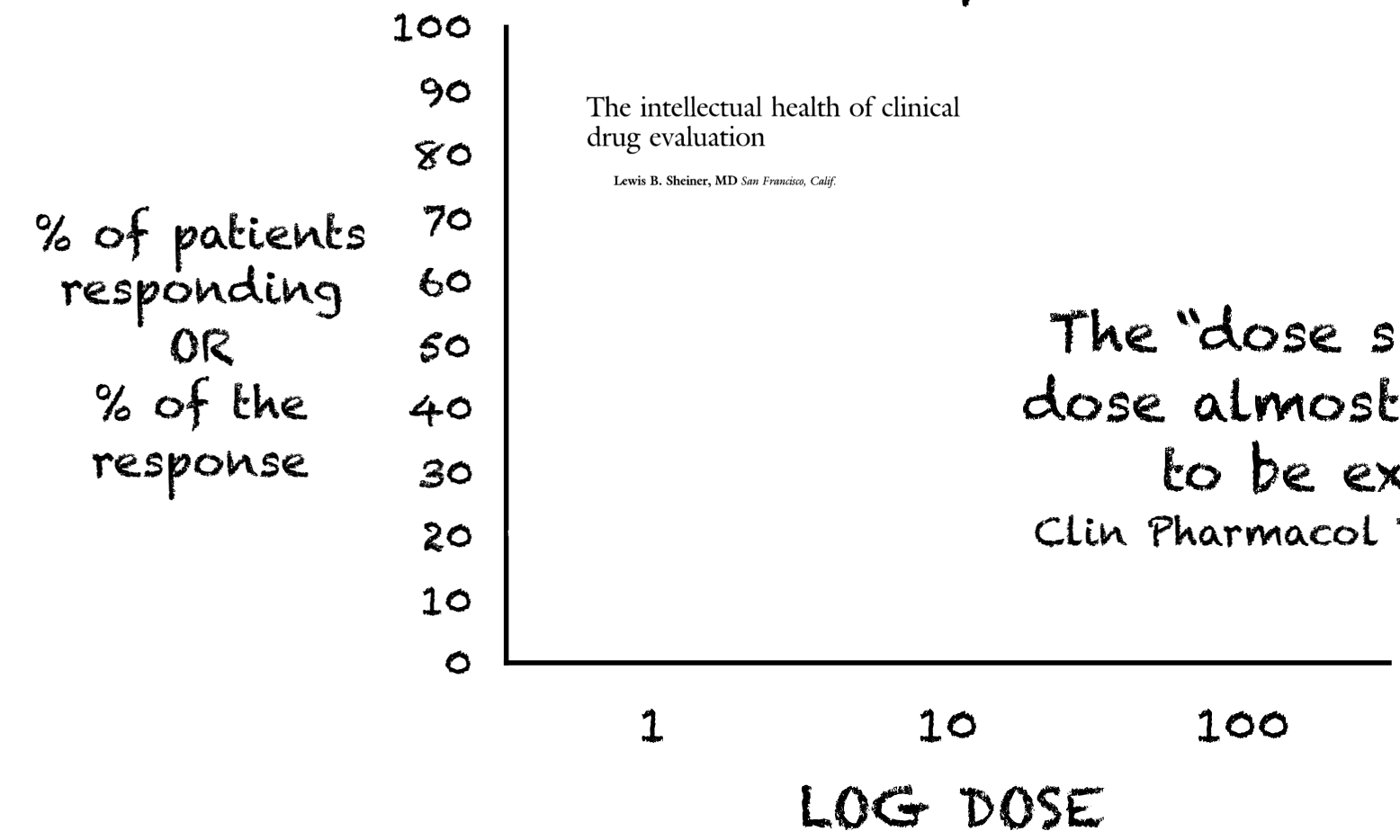
Dose Response




Dose Response
100
90
80
70
60
50
40
30
20
10
0
% of patients responding OR % of the response
125 mcg
250 mcg
1000 mcg
1
10
100
LOG DOSE


Dose Response
ALCOHOL
% of patients responding OR % of the response
100
90
80
70
60
50
40
30
20
10
0
1
10
100
LOG DOSE

Dose Response



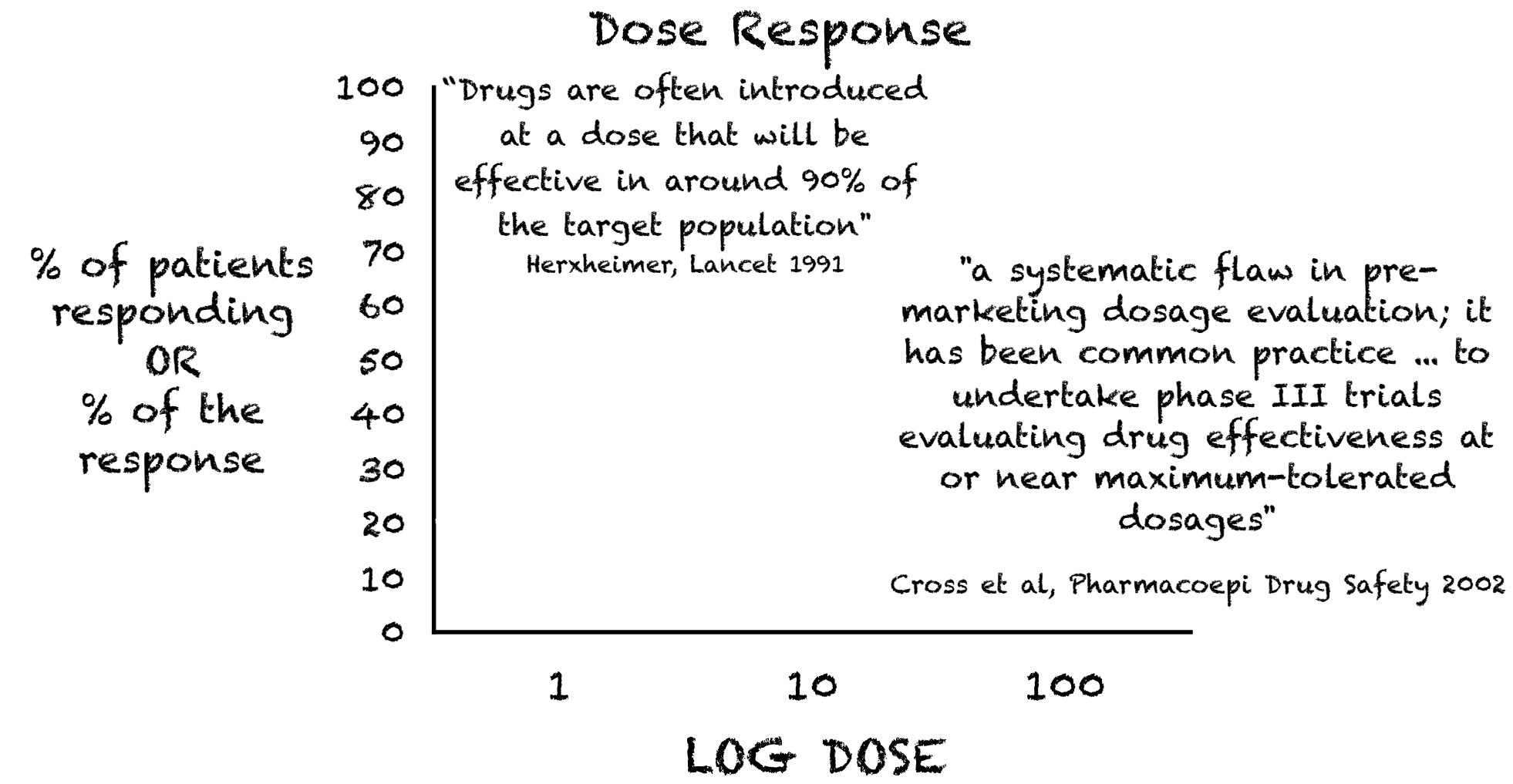
The intellectual health of clinical drug evaluation

Lewis B. Sheiner, MD *San Francisco, Calif.*

The "dose studied is a dose almost guaranteed to be excessive"

Clin Pharmacol Ther 1991;50:4-9

Dose Response



A sample of Low-Dose RCT Evidence

12.5 mg hydrochlorothiazide	first marketed at 50 to 200 mg daily
5 mg daily fluoxetine (Prozac)	similar effects to those seen at 20 mg and 40 mg daily
150 mg daily bupropion (Zyban)	produces the same rate of smoking cessation at one year as 300 mg daily
0.5 mg BID varenicline (Champix)	produces the same rate of smoking cessation at one year as 1.0 mg BID
25 mg ranitidine (Zantac)	as effective as 75 mg and 125 mg for heartburn relief
25 mg sumatriptan (Imitrex)	works as well as100 mg
0.25 mg ezetimibe (Ezetrol)	1/40th of the recommended initial starting dose provides 50% of the LDL lowering effect
1, 3 and 6 mg doxepin (Sinequan)	all doses equally effective for sleep - originally used 25-50 mg
25 mg sildenafil (Viagra)	effective as 50, 100 mg for erectile dysfunction
200 mg ibuprofen (Motrin)	as effective as 400 mg for migraine headache
1.8 mg colchicine	as effective as 4.8mg for acute gout with less adverse events
15 mg elemental iron daily	as effective for anemia in elderly as 50 mg and 150 mg with a lower incidence of side effects
6.25 mg captopril (Capoten)	25 mg PO TID is still a commonly recommended initial starting dose for hypertension

CMAJ 2011. DOI:10.1503 /cmaj.091481

The JAMA Forum

Deprescribing Policies: Time for a Fresh Approach

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"One of the most difficult clinical tasks is deprescribing a medicine that was previously prescribed"

JAMA 2019;321:1341-2

Swimming Against the Tide: Primary Care Physicians' Views on Deprescribing in Everyday Practice

"Physicians described deprescribing as "swimming against the tide" of patient expectations, the medical culture of prescribing, and organizational constraints. They said deprescribing came with inherent risks for both themselves and patients and conveyed a sense of vulnerability in practice. The only incentive to deprescribing they identified was the duty to do what was right for the patient."

Ann Fam Med 2017;15:341-346

Tapering is just a subset of the dose issue

Use common sense when tapering medications

if the medication is causing an important problem just stop it

most medications could probably just be stopped BUT…

typically recommend one at a time BUT be realistic

cutting the dose in half can reduce apprehension

rebound - psychiatric/CVD medications for symptoms - IHD/blood pressure

Tapering specifics

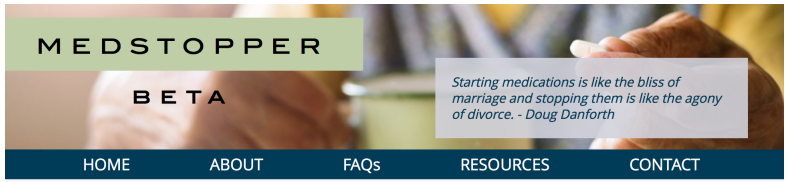
most medications could probably just be stopped BUT some medications (especially those that affect the CNS central or are for serious conditions) in general should be tapered off

the approach very much depends on the specific medication, duration of use, dose, and the underlying condition

there is no definitive way to do this (and almost no evidence) but it will involve reducing the dose by somewhere between 10% and 50% every few days/weeks/months and monitoring to minimize any withdrawal symptoms and if the condition re-appears (this is NOT a failure!!) make a reassessment

tapering can take a while but the result is rewarding for both the patient and prescriber when the medication is ultimately either successfully stopped or the dose is lowered

MEDSTOPPER



MedStopper is a deprescribing resource for healthcare professionals and their patients.

1 Frail elderly?

2 Generic or Brand Name:

hydro

3 Select Condition Treated:

Generic Name	Brand Name	Condition Treated	Add to MedStopper
dihydroergotamine	DHE 45	Select Condition	ADD
hydrochlorothiazide	Microzide	blood pressure	ADD
hydrocodone	Vicodin	Select Condition	ADD
hydrocortisone		Select Condition	ADD

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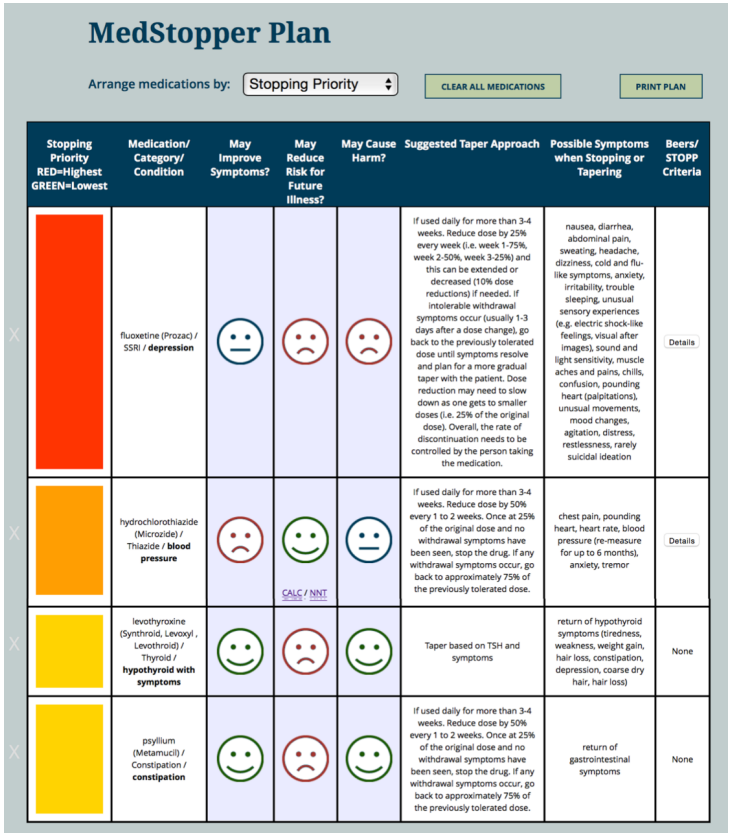


medstopper.com

GROUP WORK

SAYS HE'S
GOING TO
HELP BUT
HE'S NOT
FOR THE
WHOLE TIME
HAS NO IDEA
WHAT IS
GOING ON

Classes to discuss

Meds for Prevention

Glucose

Blood pressure

Cholesterol

Bone density

Vitamins/supplements

OTHERS?

Meds for Symptoms

Inhalers

Heart failure

Pain

GI - heartburn, diarrhea constipation

Antipsychotics

Depression

Dementia

FOR YOUR MEDICATION CLASS, WHAT FURTHER INFORMATION DO YOU REQUIRE TO FACILITATE RE-EVALUATION

WHAT ARE YOUR "KNOWLEDGE" GAPS?

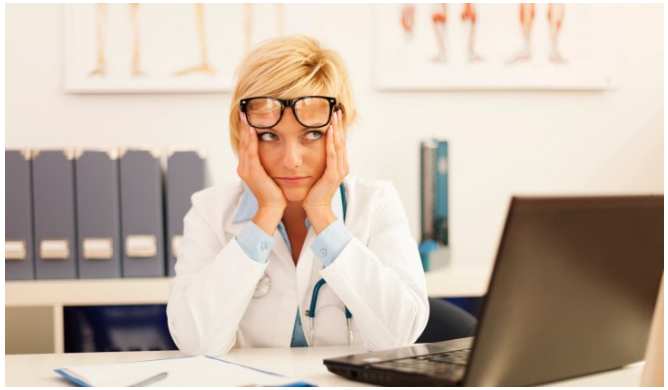
What evidence would you like?

What do you need to help you re-evaluate?

What approaches to use to reduce/taper the dose?

What are the road blocks?

Now your cases



If you can't find any problems, did you look for any of the following?

Any drug that was not started at the very lowest dose

Any drug that has been added without the patient having been given an informed choice

Any drug that hasn't been re-evaluated "annually"

Any drug that doesn't make the patient feel better

Work in pairs - 45 minutes

FOR YOUR CASE

Until proven otherwise the medication and dose are wrong

Place the medications in a useful order

State what specifically you would like to do

Impediments to you doing this

Your solutions