# The Great? Placebo

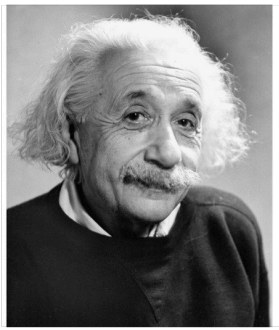

**James McCormack**
**BSc (Pharm), PharmD**
**Professor**
**Faculty of Pharmaceutical Sciences**
**University of British Columbia**
**Vancouver, BC, Canada**


"The history of medical treatment can be characterized largely as the history of the placebo effect"

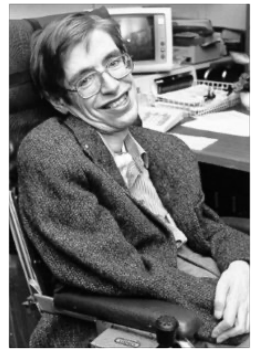
AK Shapiro. The Placebo Response. Modern Perspectives in World Psychiatry. 1971

The placebo is the "most effective medication known to science, subjected to more clinical trials than any other medicament yet nearly always does better than anticipated. The range of susceptible conditions appears to be limitless"

Einstein



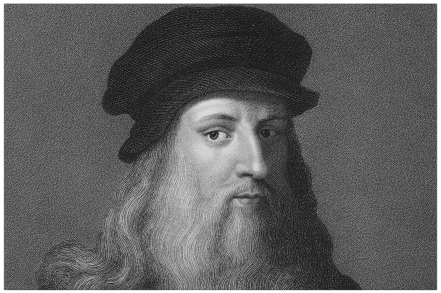

Hawkins



***Understanding*** *and* ***appreciating*** *the* ***placebo EFFECT AND the placebo RESPONSE*** *is one of the most powerful therapeutic concepts in all of medicine*

Curie

da Vinci



Johnson

# Sham/placebo Surgery

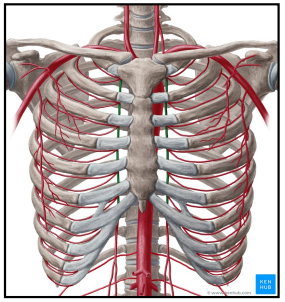
Vol. 260 No. 22 INTERNAL-MAMMARY-ARTERY LIGATION — COBB ET AL.

AN EVALUATION OF INTERNAL-MAMMARY-ARTERY LIGATION BY A DOUBLE-BLIND TECHNIC*

LEONARD A. COBB, M.D.,† GEORGE I. THOMAS, M.D.,‡ DAVID H. DILLARD, M.D.,§
K. ALVIN MERENDINO, M.D.,¶ AND ROBERT A. BRUCE, M.D.‖

SEATTLE, WASHINGTON

**NEJM 1959**



**8 patients had internal mammary/ thoracic artery ligated**

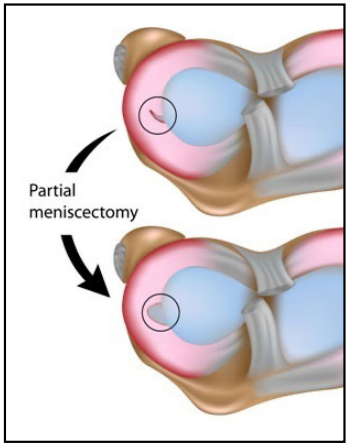
**9 had skin incisions**

**5 in each group reported significant improvement**

Arthroscopic Partial Meniscectomy versus Sham Surgery for a Degenerative Meniscal Tear

Raine Sihvonen, M.D., Mika Paavola, M.D., Ph.D., Antti Malmivaara, M.D., Ph.D., Ari Itälä, M.D., Ph.D., Antti Joukainen, M.D., Ph.D., Heikki Nurmi, M.D., Juha Kalske, M.D., and Teppo L.N. Järvinen, M.D., Ph.D., for the Finnish Degenerative Meniscal Lesion Study (FIDELITY) Group

**NEJM 2013**




**146 patients age 52**
**partial meniscectomy OR SHAM surgery (arthroscopic lavage - asked for all instruments, manipulated the knee etc)**

**No difference in symptoms or knee pain 12 months after**

# Placebo

= an inert substance that provokes perceived benefits

# Nocebo

= an inert substance that causes perceived harm

The most common symptoms - nausea, diarrhea, constipation, dry mouth, drowsiness, anxiety, nervousness, headache, dizziness, asthenia, flushing, flatulence, low blood pressure and a feeling of heaviness

# Inert placebos are used a lot

**77%** of the surveyed physicians prescribed placebo at least once a week, with impure placebos accounting for more than **90%** (Howick et al. 2013)

Colace

Vitamins

Homeopathy

Antibiotics for viral infections



# Understanding


**HELPS YOU FIGURE OUT**

If you should try a medication

When to start with low/very low doses

If a medication is working

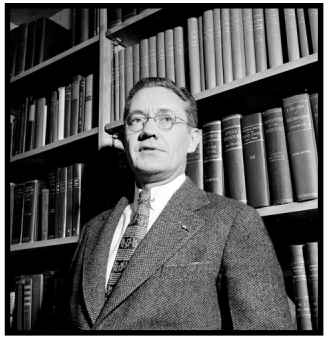
How to empower your patients to help you figure out if the medication is working

The most frequently cited paper on placebo ~2900 citations

J.A.M.A., Dec. 24, 1955

**THE POWERFUL PLACEBO**

*Henry K. Beecher, M.D., Boston*



"It is **evident that placebos have a high degree of therapeutic effectiveness** in treating subjective responses"

He claimed that the symptoms of **35% of 1082 patients in 15 studies were relieved by placebo**

# The Powerful Placebo Effect: Fact or Fiction?

*Gunver S. Kienle* and Helmut Kiene*

Institut für Angewandte Erkenntnistheorie und Medizinische Methodologie, D-79112 Freiburg, Germany

"For 14 out of the 15 trial publications detailed analysis was possible. The overall result was that for **none of these trials was there any reason to assume the existence of the slightest placebo effect."**

"In all these trials the reported outcome in the placebo group can be **fully, plausibly, and easily explained without presuming any therapeutic placebo effect"**

"In some of the original trial publications **even the authors themselves had explicitly written that there were no placebo effects**"

J Clin Epidemiol 1997;50:1311-8

# The Powerful Placebo Effect: Fact or Fiction?

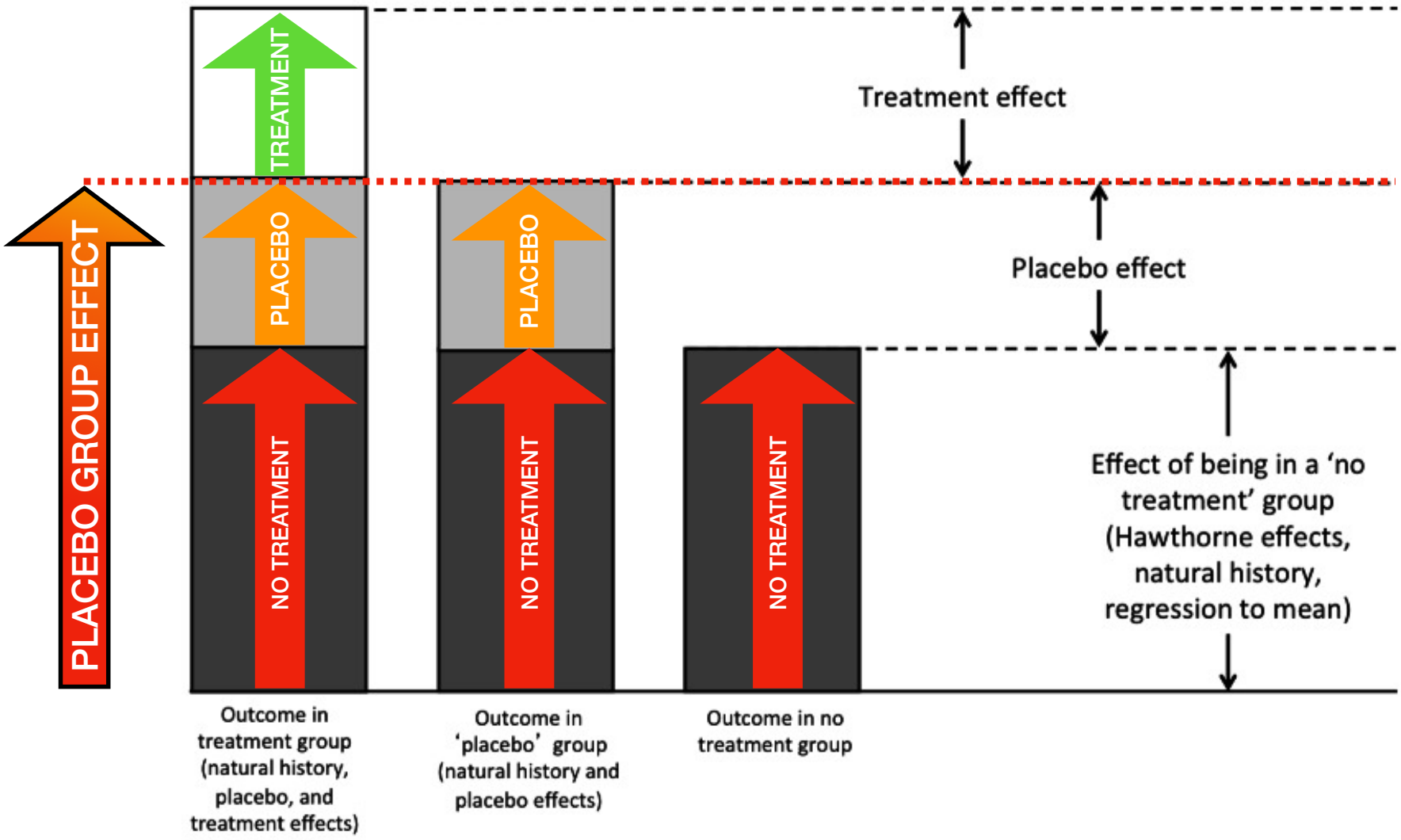
*Gunver S. Kienle* and Helmut Kiene*

Institut für Angewandte Erkenntnistheorie und Medizinische Methodologie, D-79112 Freiburg, Germany

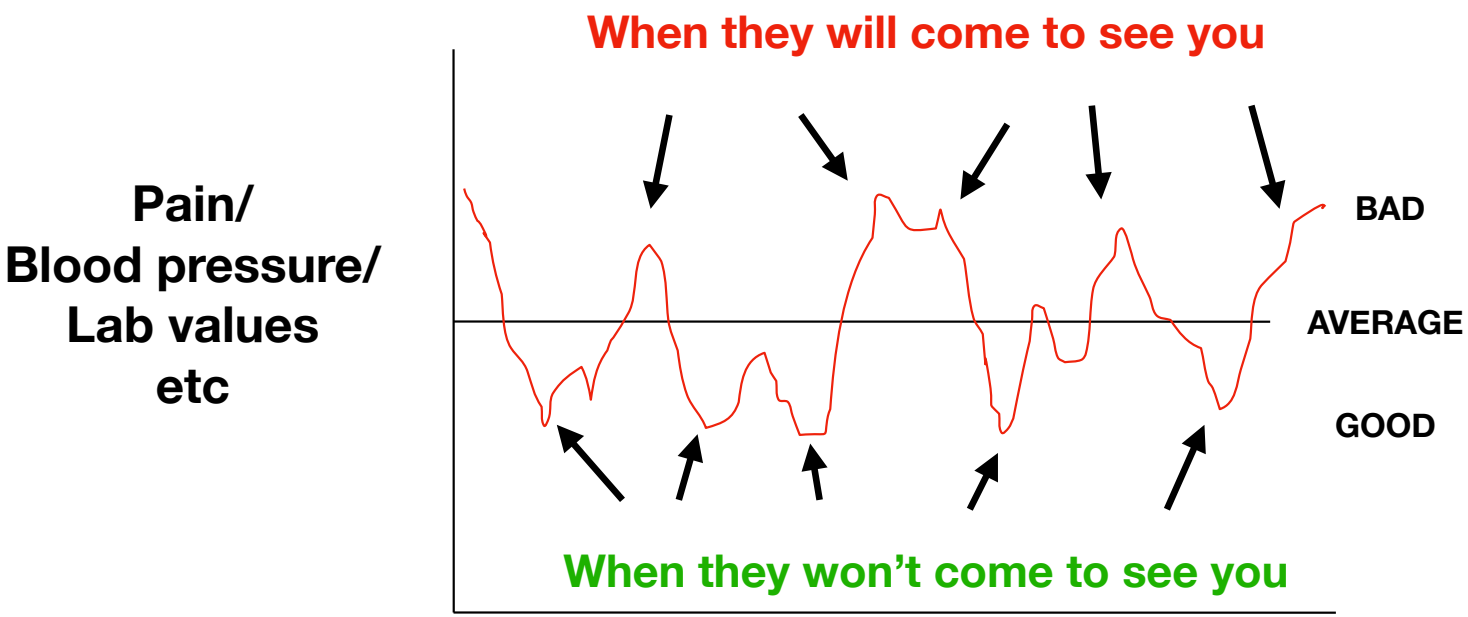
"Beecher misquoted 10 of the 15 trials listed in [his paper]"

"he cited…a percentage of patients" when in fact it was "the number of pills"

J Clin Epidemiol 1997;50:1311-8


PLACEBO GROUP EFFECT
TREATMENT
PLACEBO
PLACEBO
NO TREATMENT
NO TREATMENT
NO TREATMENT
Treatment effect
Placebo effect
Effect of being in a 'no treatment' group (Hawthorne effects, natural history, regression to mean)
Outcome in treatment group (natural history, placebo, and treatment effects)
Outcome in 'placebo' group (natural history and placebo effects)
Outcome in no treatment group

# Regression to the mean



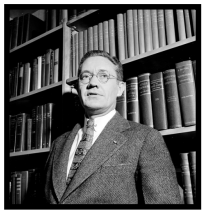

**"If it's bad it will likely get better and if it's good it will likely get worse"**

The most frequently cited paper on placebo

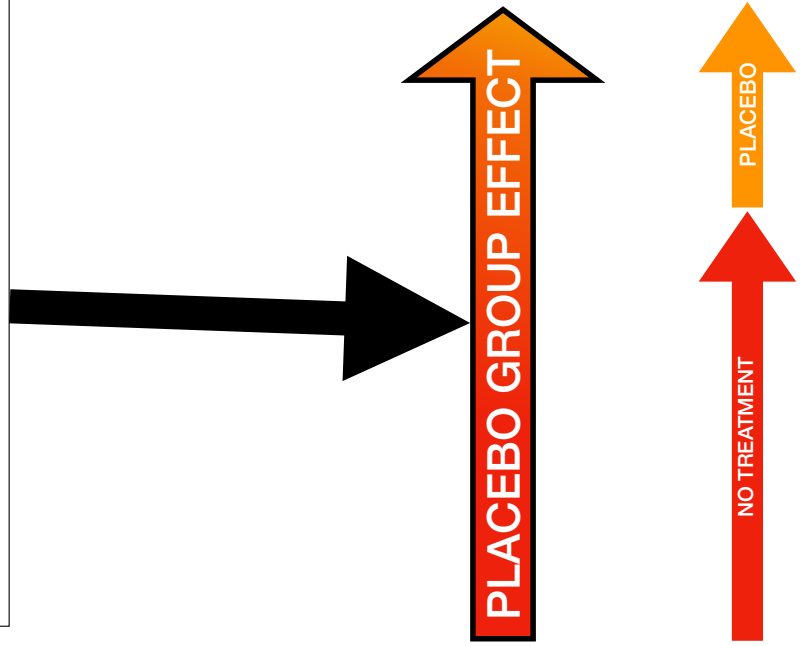
J.A.M.A., Dec. 24, 1955

**THE POWERFUL PLACEBO**

*Henry K. Beecher, M.D., Boston*



"the symptoms of 35% of 1082 patients in 15 studies were relieved by placebo"



**Placebo interventions for all clinical conditions (Review)**

Hróbjartsson A, Gøtzsche PC

CD003974 - 2010

Meta-analysis - 202 trials of placebo versus no treatment

## 60 clinical conditions

**44 studies with BINARY OUTCOMES**

the effect was 0.93 (0.88-0.99) - BUT no statistical effect in conditions (pain, nausea, smoking, depression) investigated by 3 or more trials BUT still had similar relative differences

**158 trials with CONTINUOUS OUTCOMES**

found an effect (Standard Mean Difference) on pain (~0.2), nausea (0.25), asthma (0.35) and phobia (0.63) - effects on phobia and asthma uncertain due to high risk of bias

SMD of 0.2 is considered small - for pain this would be ~0.5 on a 10 point scale

**Placebo effects in low back pain: A systematic review and meta-analysis of the literature** **Eur J Pain 2021;25:1876–97**

a significant moderate effect size of placebo for pain intensity (SMD = 0.57) and disability (SMD = 0.52)

**Effectiveness of placebo interventions for patients with nonspecific low back pain: a systematic review and meta-analysis** **Pain 2021 162;2792–2804**

placebo interventions are more effective than no intervention for pain intensity at short-term follow-up (SMD -0.37) - corresponds to about 8 point on a 0 to 100 scale

ORIGINAL ARTICLE

# Active Albuterol or Placebo, Sham Acupuncture, or No Intervention in Asthma

N Engl J Med 2011;365:119-26.

Michael E. Wechsler, M.D., John M. Kelley, Ph.D., Ingrid O.E. Boyd, M.P.H., Stefanie Dutile, B.S., Gautham Marigowda, M.B., Irving Kirsch, Ph.D., Elliot Israel, M.D., and Ted J. Kaptchuk

## FEV1 - Objective Outcomes
no effect

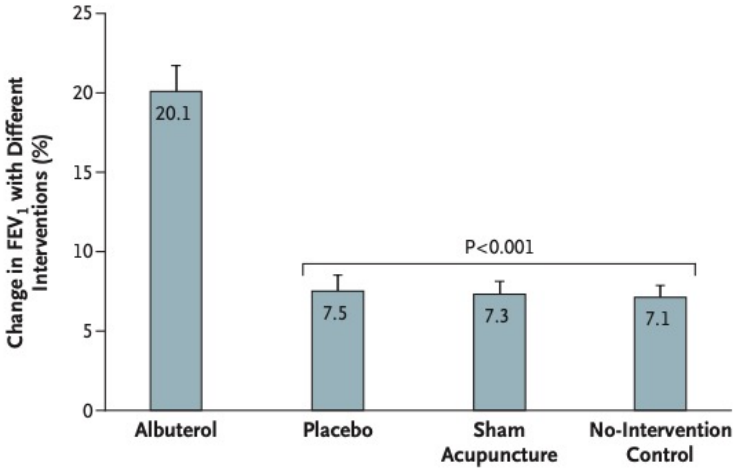



**Figure 3. Percent Change in Maximum Forced Expiratory Volume in 1 Second ($FEV_1$) with Each of the Four Interventions.**

The relative improvement in $FEV_1$ achieved with albuterol was significantly greater than that achieved with each of the other three interventions (P<0.001). No other differences among the four experimental conditions were significant. T bars indicate standard errors.

## Symptoms - Subjective Outcomes
## 20% absolute

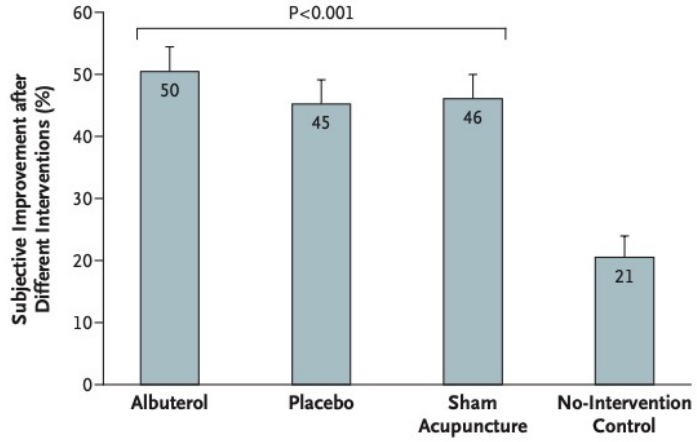



**Figure 4. Percent Change in Subjective Improvement with Each of the Four Interventions.**

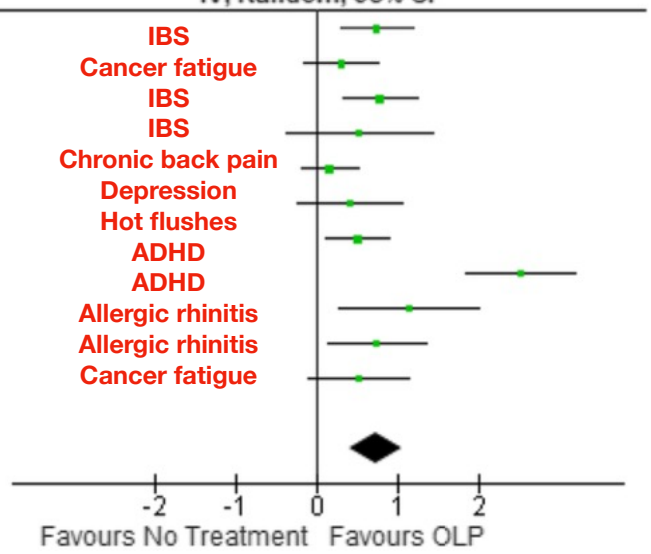
The relative improvement in subjective outcomes, assessed with the use of a visual-analogue scale (with 0 indicating no improvement and 10 indicating complete improvement), was significantly greater with the albuterol inhaler, placebo inhaler, and sham acupuncture interventions than with the no-intervention control (P<0.001). No other differences among the four experimental conditions were significant. T bars indicate standard errors.

# Effects of open-label placebos in clinical trials: a systematic review and meta-analysis

| Study or Subgroup | OLP Mean | OLP SD | OLP Total | No Treatment Mean | No Treatment SD | No Treatment Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Carvalho 2014 | 2.86 | 3.91 | 41 | 0.02 | 3.73 | 42 | 10.3% | 0.74 [0.29, 1.18] |
| Hoenemeyer 2018 | -45.7 | 22.7 | 39 | -52.9 | 24.1 | 35 | 10.2% | 0.30 [-0.15, 0.76] |
| Kaptchuk 2010 | 5 | 1.5 | 37 | 3.9 | 1.3 | 43 | 10.2% | 0.78 [0.32, 1.24] |
| Kelley 2012 | 1.64 | 4.52 | 11 | -0.67 | 4 | 9 | 6.5% | 0.51 [-0.38, 1.41] |
| Kleine-Borgmann 2019 | -4.75 | 2.27 | 63 | -5.1 | 1.99 | 59 | 11.0% | 0.16 [-0.19, 0.52] |
| Nitzan 2020 | -9.33 | 4.97 | 18 | -11.15 | 3.65 | 20 | 8.5% | 0.41 [-0.23, 1.06] |
| Pan 2020 | -10.72 | 9.73 | 50 | -15.15 | 7.78 | 50 | 10.7% | 0.50 [0.10, 0.90] |
| Sandler 2010 | -20.2 | 3.6 | 33 | -29.8 | 4 | 29 | 8.3% | 2.50 [1.82, 3.17] |
| Schaefer 2016 | 0.88 | 0.64 | 12 | 0.23 | 0.464 | 13 | 6.8% | 1.13 [0.28, 1.99] |
| Schaefer 2018 | -2.66 | 0.75 | 26 | -3.32 | 1.02 | 20 | 8.9% | 0.74 [0.14, 1.34] |
| Zhou 2019 | 32.7 | 11.1 | 20 | 27 | 10.81 | 20 | 8.6% | 0.51 [-0.12, 1.14] |
| **Total (95% CI)** | | | **350** | | | **340** | **100.0%** | **0.72 [0.39, 1.05]** |

Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 41.14$, $df = 10$ ($P < 0.0001$); $I^2 = 76\%$

Test for overall effect: $Z = 4.28$ ($P < 0.0001$)




**"gives healthcare-providers the possibility to administer placebos without deception and thus, with fewer ethical concerns"**

Sci Rep 2021;11(1):3855. doi: 10.1038/s41598-021-83148-6

The Atlantic
October 13, 2014

HEALTH

# The Power of Drug Color

A pill's hue can affect how it's judged by patients, how it's marketed, and even how well it works.

By Tessa Fiorini Cohen

# Effect of colour of drugs: systematic review of perceived effect of drugs and of their effectiveness

BMJ1996;313:1624-6

**Author's conclusion "the available evidence suggests that green and blue may have more sedative effects and red and orange may have more stimulant effects"**

**CITED 400+ times**
**TYPICAL COMMENT**
**"The typical finding that has emerged from much of the previous research is that changing the colour of a medicine can indeed influence perceived efficacy"**

## 6 publications - NONE SINCE 1978

Nagao - **1968** - **ARTICLE IN JAPANESE** - "large trial" analgesic after dental surgery - "79% of patients experienced adequate pain relief with **RED** tablets, whereas 73% of patients reported adequate pain relief with WHITE tablets"

Schapira **1970** - 48 patients with anxiety - oxazepam - different colors "though the **difference between RED, YELLOW and GREEN tablets DID NOT REACH STATISTICAL SIGNIFICANCE** certain trends were observed"

Cattaneo **1970** - 120 patients awaiting surgery - placebo - **ORANGE** vs **BLUE** capsules - **NO DIFFERENCE IN SLEEP**

Blackwell **1972** - 100 medical students - placebo - told they would either get a stimulant or sedative "66% of subjects on blue capsules felt less alert compared with 26% on **PINK**; 72% on BLUE capsules felt more drowsy compared to 37% on pink" - no other info given

Huskisson - **1974** - 22 patients - analgesics for arthritis - 3 different meds (narcotic/aspirin) and placebo - all **RED**, **BLUE**, **GREEN** or **YELLOW** - **NO EFFECT OF COLOR IF A DRUG** but if placebo at 2-6 hours (but not 1) **RED** was better

Lucchelli **1978** - 96 hospitalized insomniacs - hepabarbital and placebo - **ORANGE** or **BLUE** - **NO DIFFERENCE IN NUMBERS OF PEOPLE WITH A "GOOD SLEEP" NOR "UNSATISFACTORY" SLEEP** - they were also asked when they woke up the next day - how long it took them to fall asleep and how long they slept - **BLUE** fell asleep 32 minutes faster (took them ~1.5-2 hours to fall asleep) and slept 33 minutes longer

# Examining a Powerful Healing Effect through a Cultural Lens, and finding Meaning

Daniel E. Moerman, PhD*

"In a series of experiments in Italy.., blue sleeping tablets, or blue placebos worked better than did tablets of other colours, for Italian women; blue tablets tended to have a stimulating effect on men!"

"Checking with an Italian-American anthropologist colleague, we came up with this speculation."

"Many Italian women have a special relationship with the Virgin who is, in Roman Catholic tradition, the protector of women; in religious art, the Virgin Mary is almost always shown in blue."

"What about men. "Azzuri" is the name (and the colour) of the Italian national football team. Blue, for many Italian men, is not a colour of solace but of excitement and stimulation, of joy and madness, of exhilaration and, too often, of catastrophe. But it's hardly the colour of sleep."

# Colours of Psychotropics

**Question - does industry use colours designed to enhance their intended medicinal action?**

1. **Stimulants/antidepressants** - primarily bright in colour - **ORANGE**, **YELLOW**, **RED**
2. **Anxiolytics/sedatives/hypnotics/anti-panic/anti-mania/anti-psychotics** - primarily darker in colour - **GREEN**, **BLUE**, **PURPLE**
3. **Neutral** - **WHITE**, **GREY**

| 176 medications/doses | COLOUR corresponded to "desired effect" (%) |
|---|---|
| Antianxiety | 50 |
| Antidepressant | 46 |
| Antimania | 23 |
| Antipanic | 29 |
| Antipsychotic | 16 |
| Sedative | 33 |
| Stimulant | 46 |

**Only ~1/3 of the time did the colour correspond to the "best" colour**

**Psychopharmacology 2010;211:113–22**

# Placebos in clinical care: a suggestion beyond the evidence

The recent enthusiasm for the clinical use of placebos seems driven by myths and misunderstandings

“the notion that placebo pill appearance is important is based on a very small and weak evidence base ”

10.5694/mja2.51230 - 2021

# Placebo effect - the bottom line

their likely is some sort of a placebo effect for some people for a few conditions

it is nowhere close to 30-35%

the placebo group effect is >>> than the placebo effect

understand how to “harness” the placebo group effect (of which a little bit could be the placebo effect - but it doesn’t really matter)

there are no ethical issues around the placebo group effect

# Ethics of using actual placebos

**Clinical Care**

undermine trust

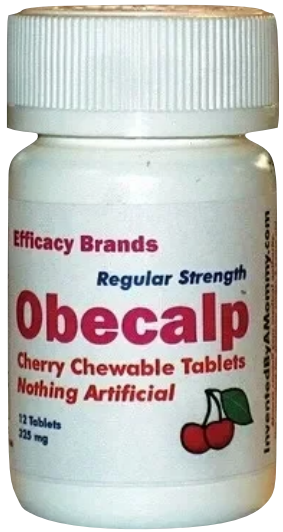
compromise the patient-clinician relationship

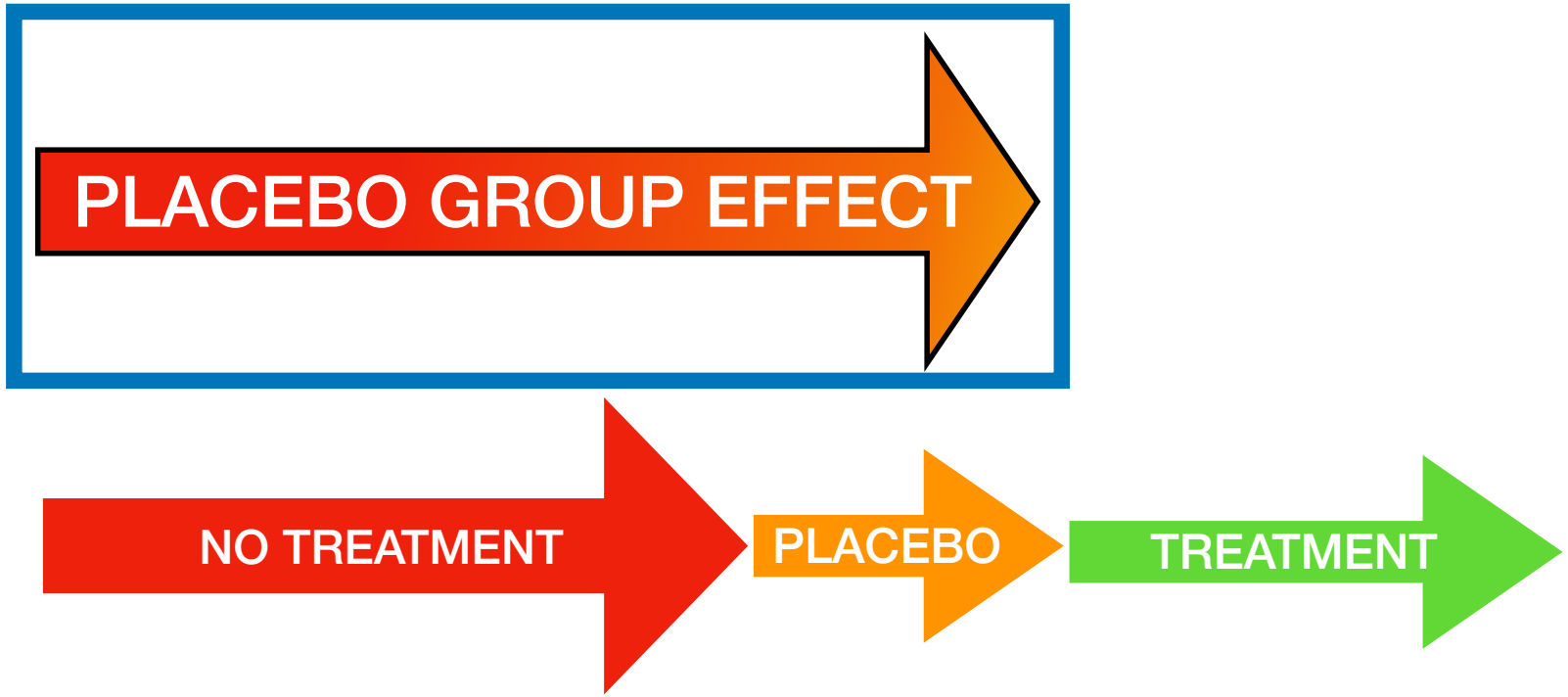
**Clinical Research**

Use of placebos when you have a proven treatment - debate

All hinges on appropriate consent

If we can do “first-in-human” trials then we can certainly do placebo controlled trials in conditions for which we already have effective treatments - subjects just need to be informed




PLACEBO GROUP EFFECT
NO TREATMENT
PLACEBO
TREATMENT

# The Placebo Group Effect

these are ballpark numbers and depend somewhat on the outcome measured

~0% - general anesthesia

~5% - psychosis, ankylosing spondylitis (remission)

~10% - sildenafil, OCD, rheumatoid arthritis (remission), Crohn's (remission)

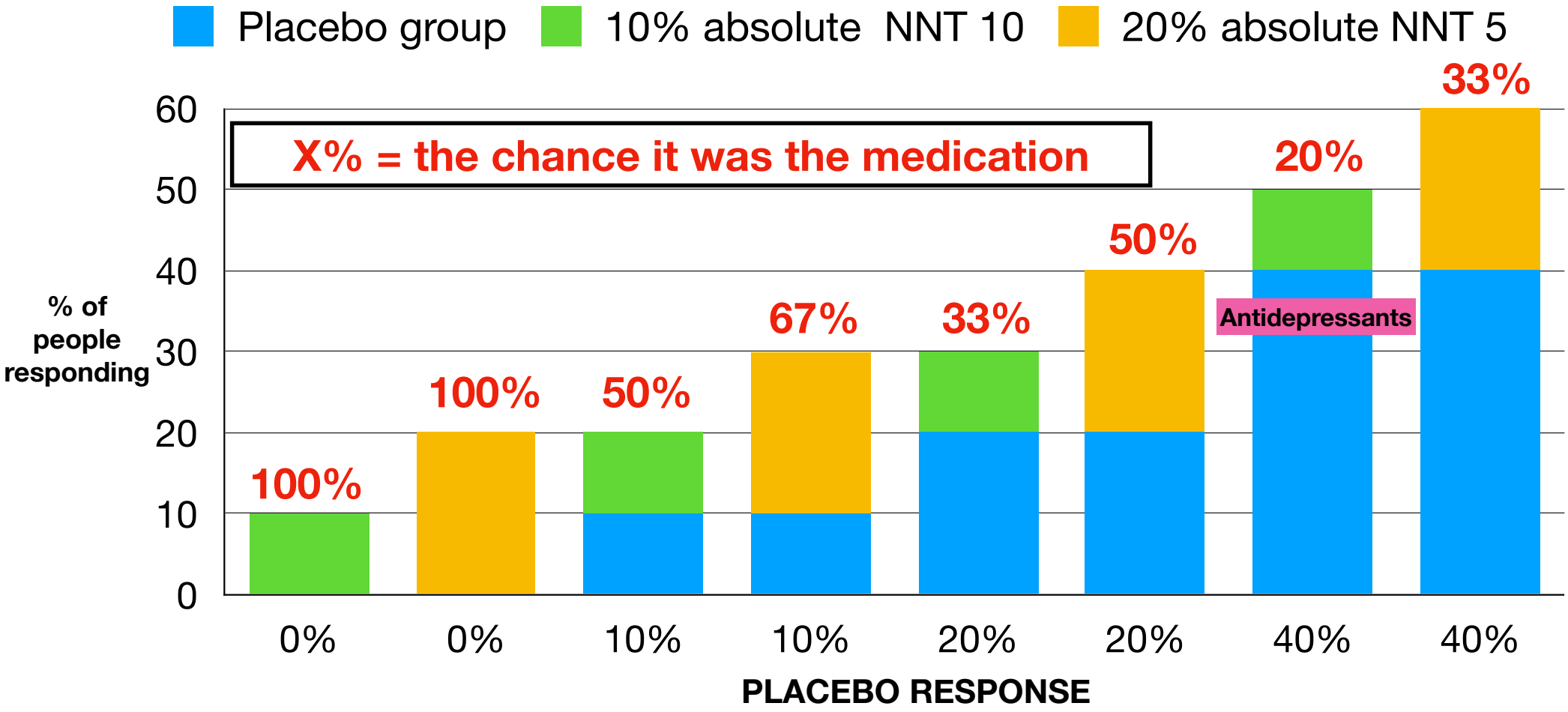
~20% - Alzheimer's meds, acetaminophen for headaches, Crohn's disease, side effects (nocebo)

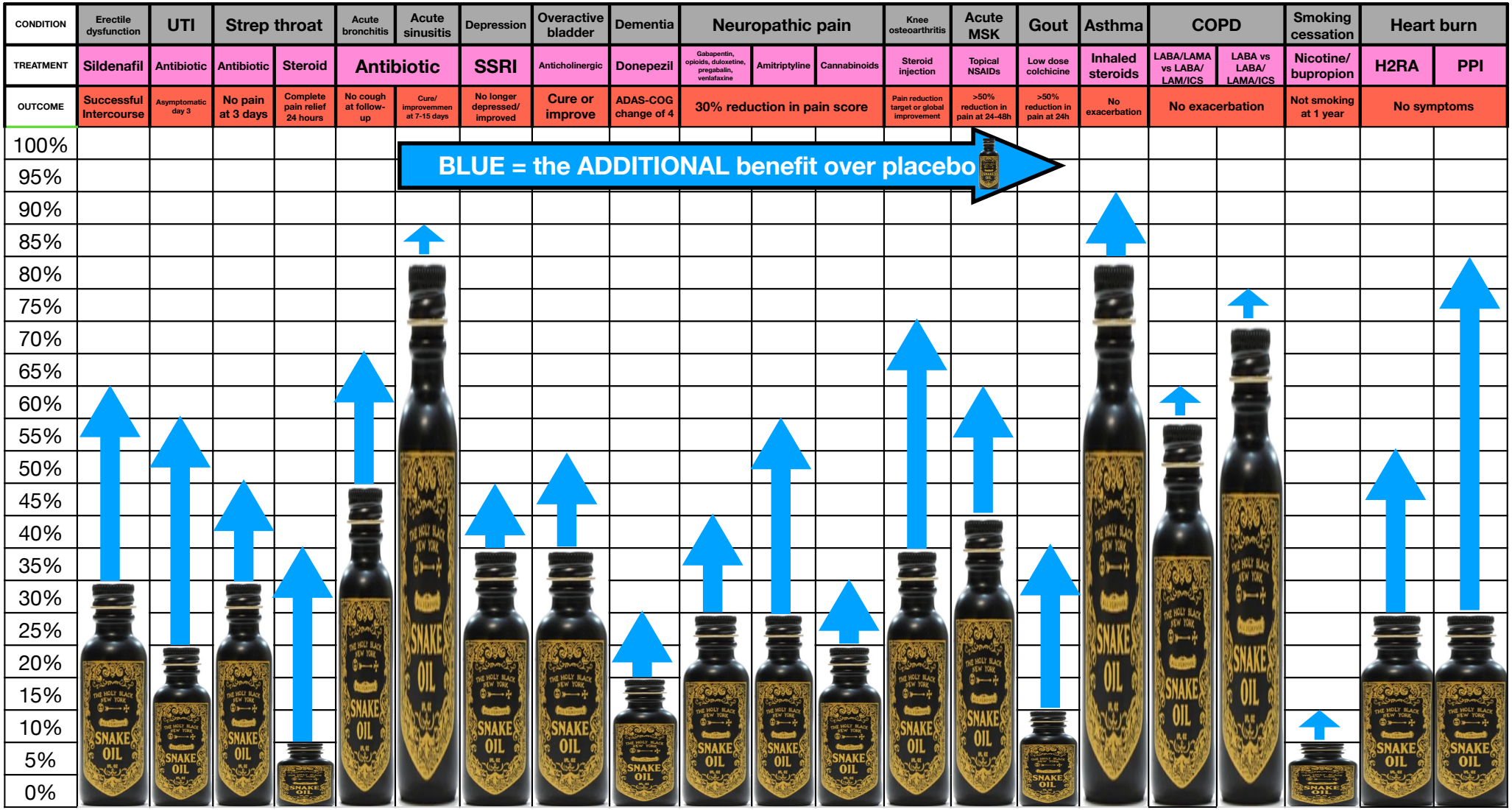
~25% - menopausal symptoms, migraine (frequency/severity), ulcerative colitis

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

~40% - panic disorders

# You need to know what goes on in the placebo group




CONDITION
Erectile dysfunction
UTI
Strep throat
Acute bronchitis
Acute sinusitis
Depression
Overactive bladder
Dementia
Neuropathic pain
Knee osteoarthritis
Acute MSK
Gout
Asthma
COPD
Smoking cessation
Heart burn
TREATMENT
Sildenafil
Antibiotic
Antibiotic
Steroid
Antibiotic
SSRI
Anticholinergic
Donepezil
Gabapentin, opioids, duloxetine, pregabalin, venlafaxine
Amitriptyline
Cannabinoids
Steroid injection
Topical NSAIDs
Low dose colchicine
Inhaled steroids
LABA/LAMA vs LABA/ LAM/ICS
LABA vs LABA/ LAMA/ICS
Nicotine/ bupropion
H2RA
PPI
OUTCOME
Successful Intercourse
Asymptomatic day 3
No pain at 3 days
Complete pain relief 24 hours
No cough at follow-up
Cure/ improvemmen at 7-15 days
No longer depressed/ improved
Cure or improve
ADAS-COG change of 4
30% reduction in pain score
Pain reduction target or global improvement
>50% reduction in pain at 24–48h
>50% reduction in pain at 24h
No exacerbation
No exacerbation
Not smoking at 1 year
No symptoms
100%
95%
90%
85%
80%
75%
70%
65%
60%
55%
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
BLUE = the ADDITIONAL benefit over placebo
SNAKE OIL

**1) Erectile dysfunction**

https://gomainpro.ca/wp-content/uploads/tools-for-practice/1570825833_tfp245pde5ifv.pdf

**2) UTI**

https://www.journalofinfection.com/article/S0163-4453(09)00002-4/fulltext

**3) Strep throat antibiotic**

Cochrane Library CD000023

**4) Strep throat steroids**

https://gomainpro.ca/wp-content/uploads/tools-for-practice/1418054647_tfp127steroidssorethroatfv.pdf

**5) Bronchitis**

https://doi.org/10.1002/14651858.CD000245.pub4

**6) Sinusitis**

Cochrane Library CD000243

**7) Depression**

https://www.bmj.com/content/360/bmj.k1073

**8) Overactive bladder**

https://gomainpro.ca/wp-content/uploads/tools-for-practice/1433184756_updatedtfp54overactivebladderandanticholinergicdrugs.pdf

**9) Dementia**

https://gomainpro.ca/wp-content/uploads/tools-for-practice/1397843505_20140218_085747.pdf

**10) Neuropathic pain**

https://peerevidence.ca/wp-content/uploads/2022/04/PEER-Decision-Aid-Neuropathic-Pain.pdf

https://www.cfpc.ca/CFPC/media/Resources/Addiction-Medicine/Cannabinoid_Guidelines_One-Pager.pdf

**11) Knee osteo**

https://www.cfp.ca/content/cfp/66/3/191.full.pdf

**12) Acute MSK**

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4163964/pdf/emss-57980.pdf

**13) Gout Low dose colchicine**

Arth Rheum 2010;62:1060-8

14) **Asthma exacerbations on inhaled steroids** – depends what numbers/evidence you use – the bottom line is the absolute benefit is ~10-15%

Lancet 2003; 361: 1071–76

Mild persistent asthma budesonide vs placebo (adults and children)

45% of patients on placebo (vs 31% on budesonide) received inhaled, oral, or systemic steroids during

Severe exacerbation 6% vs 3% over 2 years

Cochrane Library CD011032

Intermittent ICS, with treatment initiated at the time of early symptoms,

Exacerbations requiring oral corticosteroids

School age children 48% vs 35% over 44 weeks

Adults – 6 months 3.5% vs 0.3%

Cochrane Library CD003135

Fluticasone versus placebo for chronic asthma in adults and children

Withdrawal due to clinical asthma exacerbation 11% vs 2% in adults

Cochrane Library CD002738

Withdrawal due to asthma exacerbation – children and adults

15% vs 3%

Mild to Moderate asthma

15% vs 6%

Overall exacerbations of asthma

6% vs 6%

15) **COPD exacerbations**

Cochrane Library CD012620

16) **Nicotine/bupropion smoking cessation**

Cochrane Library CD000146, Cochrane Library CD000031

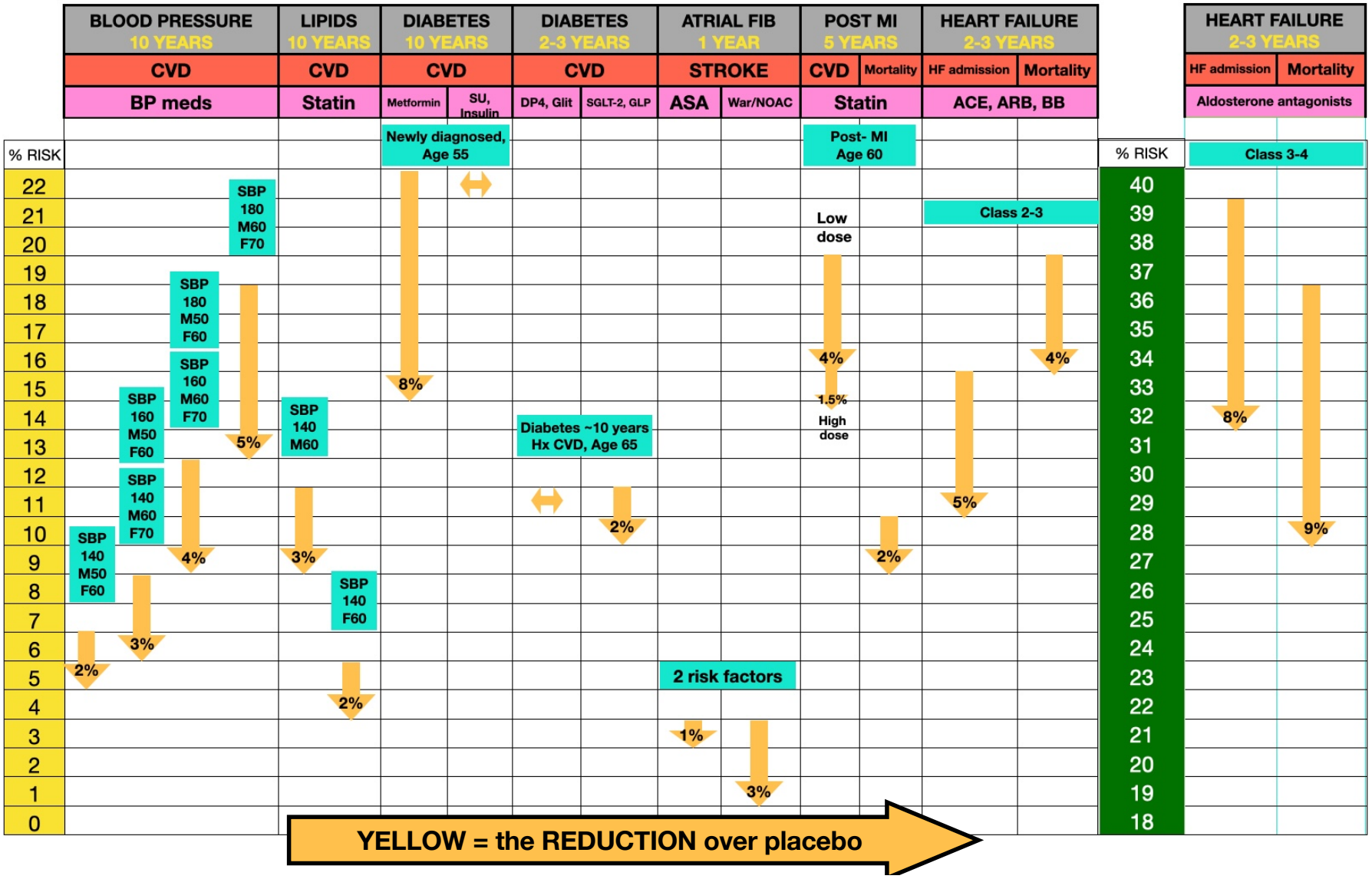
17) **Heartburn**

Cochrane Library CD003244

# All of this only applies if you are treating a symptom

None of this applies to preventative treatments

You can NEVER know if a preventative treatment worked  - other than the surrogate marker and even then the measurement variation is >> than the effect


BLOOD PRESSURE
10 YEARS
CVD
BP meds
LIPIDS
10 YEARS
CVD
Statin
DIABETES
10 YEARS
CVD
Metformin
SU, Insulin
DIABETES
2-3 YEARS
CVD
DP4, Glit
SGLT-2, GLP
ATRIAL FIB
1 YEAR
STROKE
ASA
War/NOAC
POST MI
5 YEARS
CVD
Mortality
Statin
HEART FAILURE
2-3 YEARS
HF admission
Mortality
ACE, ARB, BB
HEART FAILURE
2-3 YEARS
HF admission
Mortality
Aldosterone antagonists
% RISK
22
21
20
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Newly diagnosed, Age 55
Post- MI Age 60
Class 2-3
Class 3-4
SBP 180 M60 F70
SBP 180 M50 F60
SBP 160 M60 F70
SBP 160 M50 F60
SBP 140 M60 F70
SBP 140 M50 F60
SBP 140 M60
SBP 140 F60
Diabetes ~10 years Hx CVD, Age 65
Low dose
High dose
2 risk factors
8%
5%
4%
3%
2%
4%
1.5%
2%
5%
4%
8%
9%
2%
3%
2%
1%
3%
% RISK
40
39
38
37
36
35
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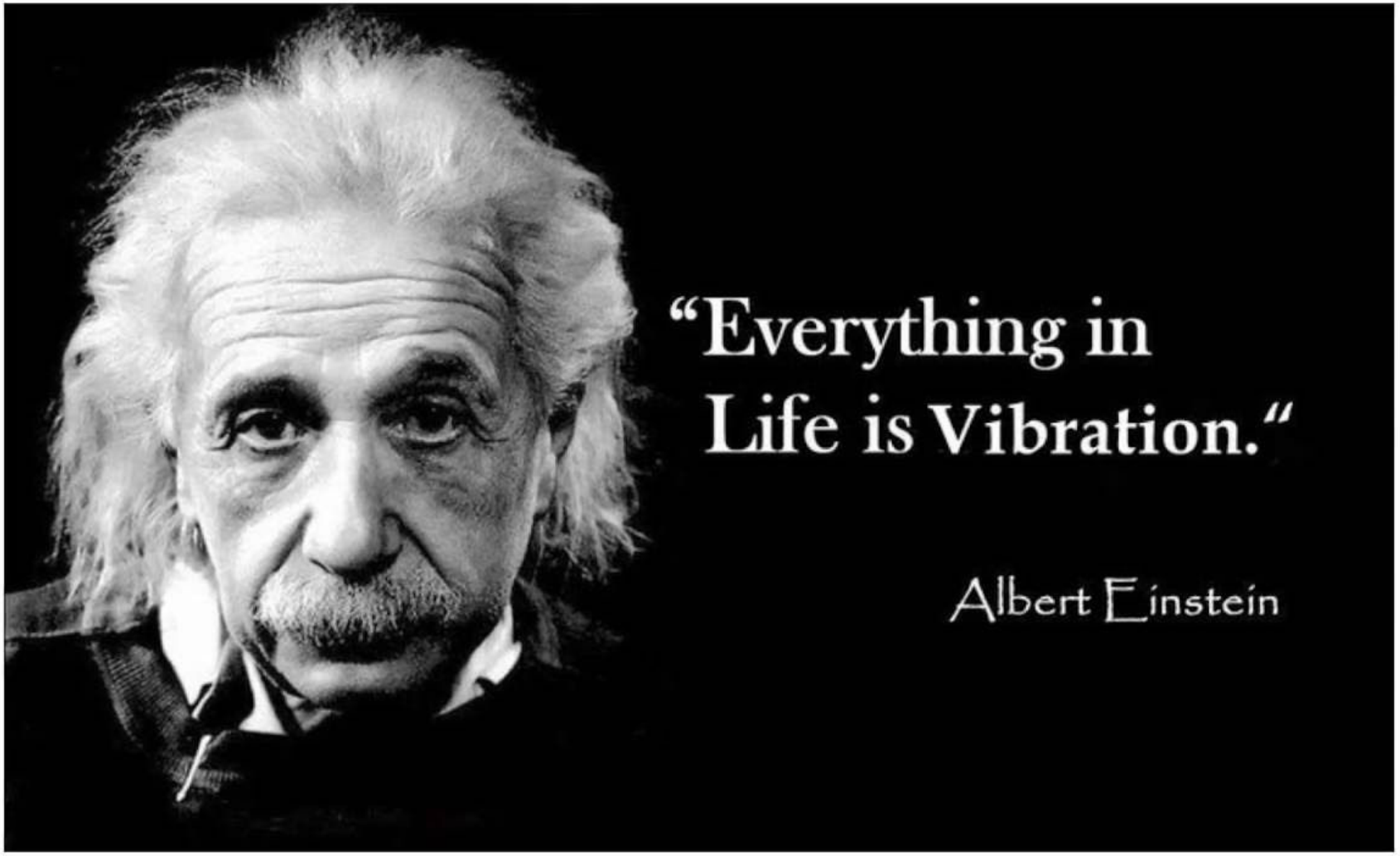
YELLOW = the REDUCTION over placebo


"Everything in
Life is Vibration."
Albert Einstein

# The Natural Fluctuation of Pain Scores

## Morning pain scores for 25 people with osteoarthritis - 3 months

**Average pain is ~5/10**

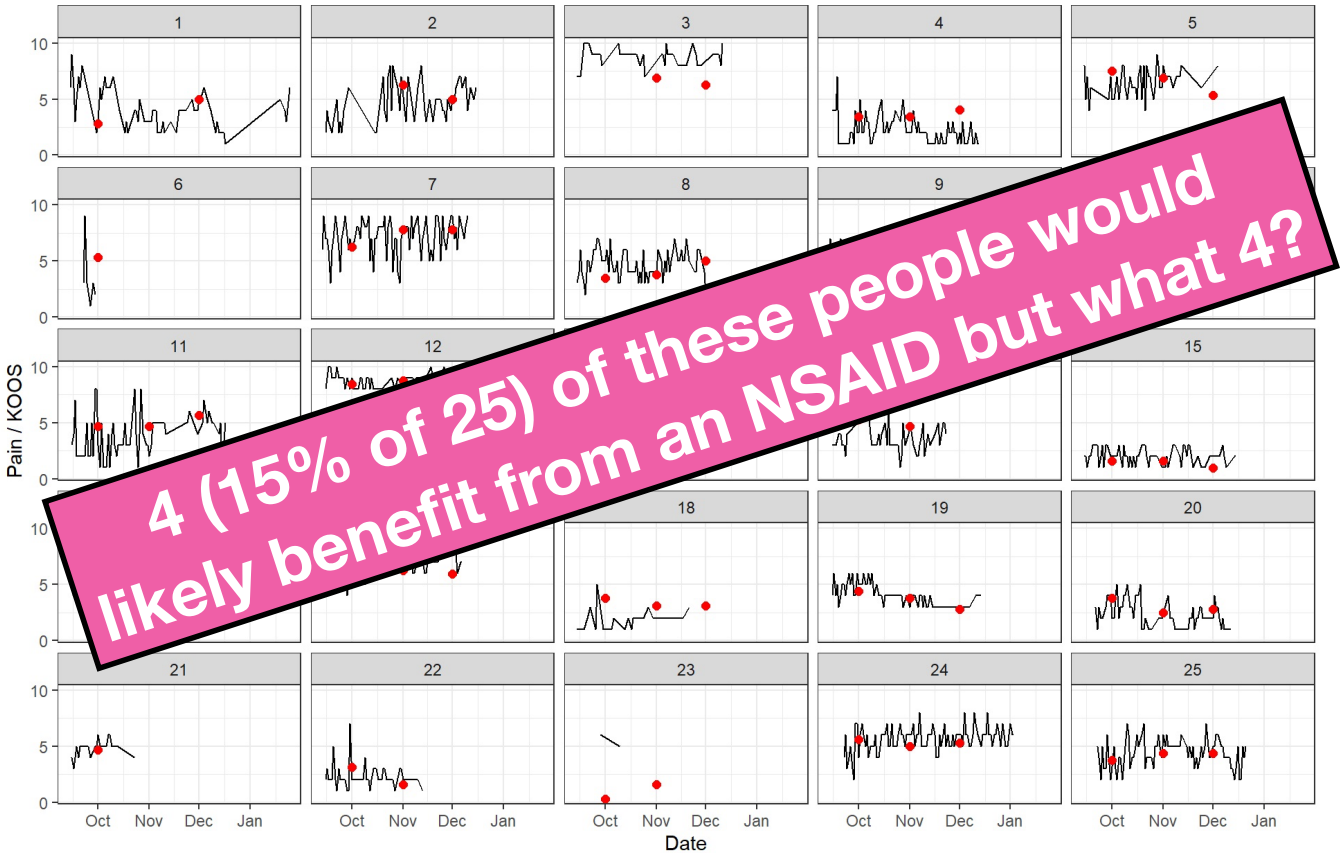
20+ of the 25 people had fluctuations of ≥ 2.5/10 = ~50% of their baseline pain

## NSAIDS

Outcome = 30-50% reduction in pain

~60% on drug

~45% on placebo




**The red dots are the respective Knee Injury and Osteoarthritis Outcome Score (KOOS) for each month.**

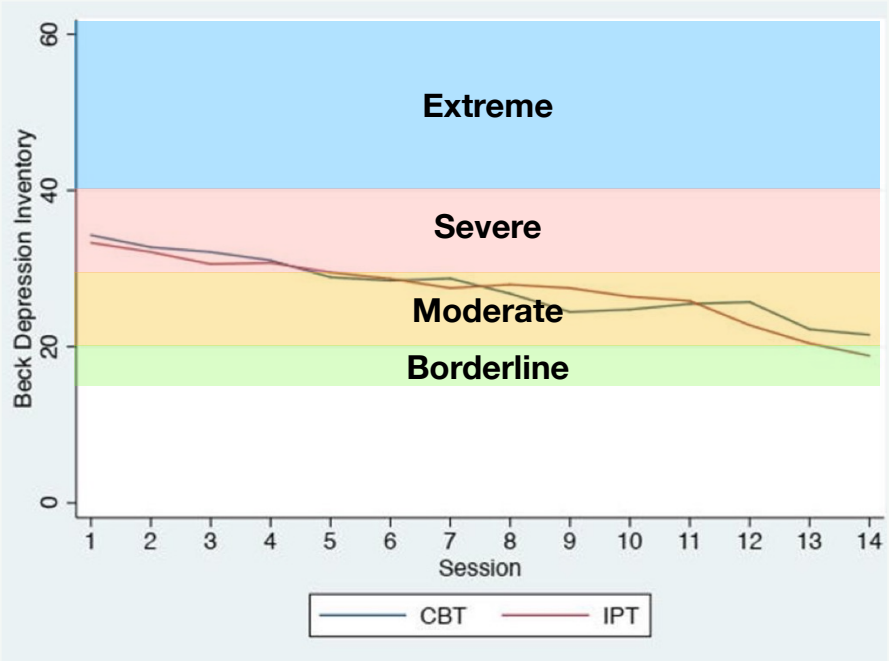
https://acrabstracts.org/abstract/the-day-to-day-variability-of-pain-and-the-relationship-with-physical-activity-in-people-with-knee-osteoarthritis-a-longitudinal-observational-feasibility-study/

# The Fluctuation of Depression Scores

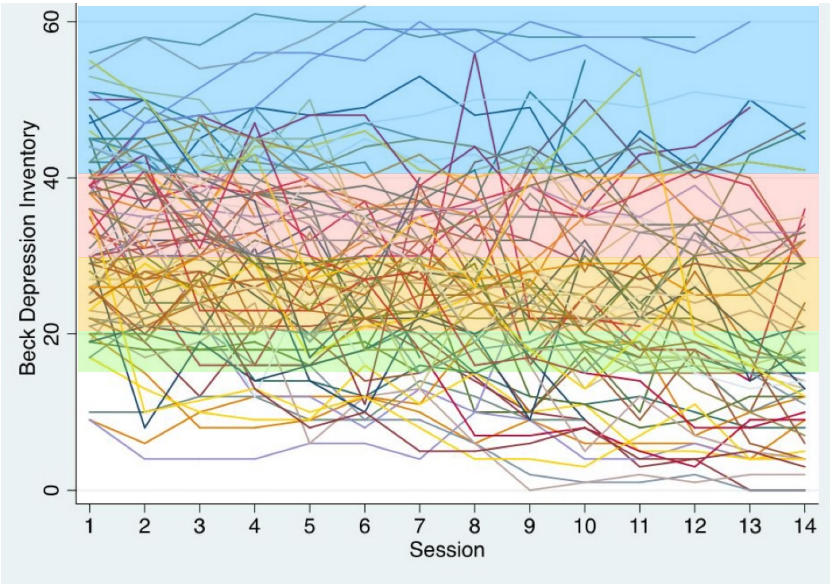
96 patients - interpersonal psychotherapy (IPT) vs cognitive behavioral therapy (CBT)

Results - 21 item MCID ~30% reduction - ~50% in both groups had at least an 8 change

**Average Change**




**Individual Change**




Journal for Person-Oriented Research 2019;5:65-79

# OTHER FLUCTUATIONS

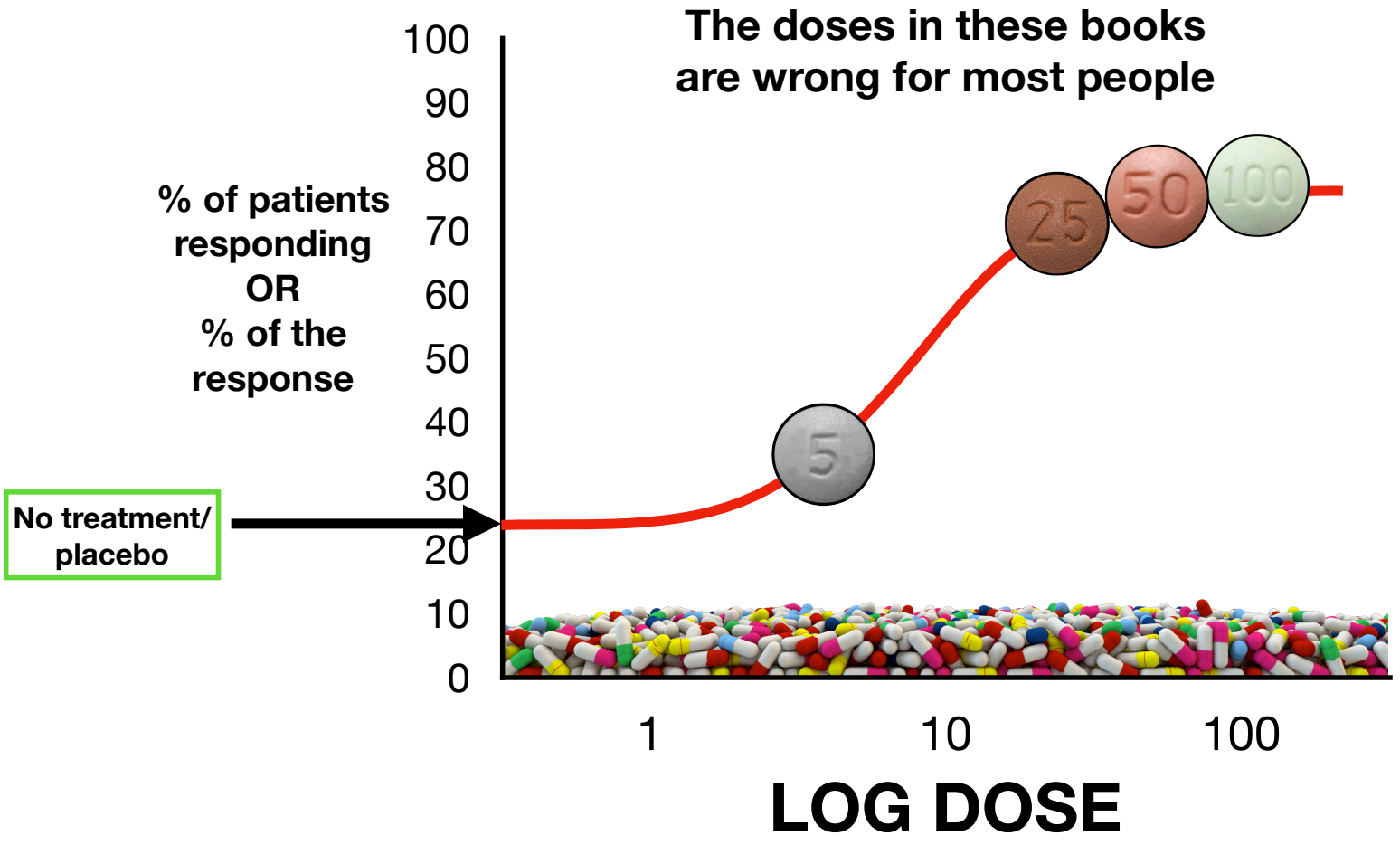
COPD SYMPTOMS
Daily and/or weekly
symptom variability: 63%
**45% during the day**
**54% during the week**
Seasonal symptom variability: **60%**

*Eur Respir J* 2011;37:264–272

SYSTOLIC BLOOD PRESSURE
the within-individual coefficient of variation
between clinic visits is 10% (~13-15
mmHg) for systolic blood pressure

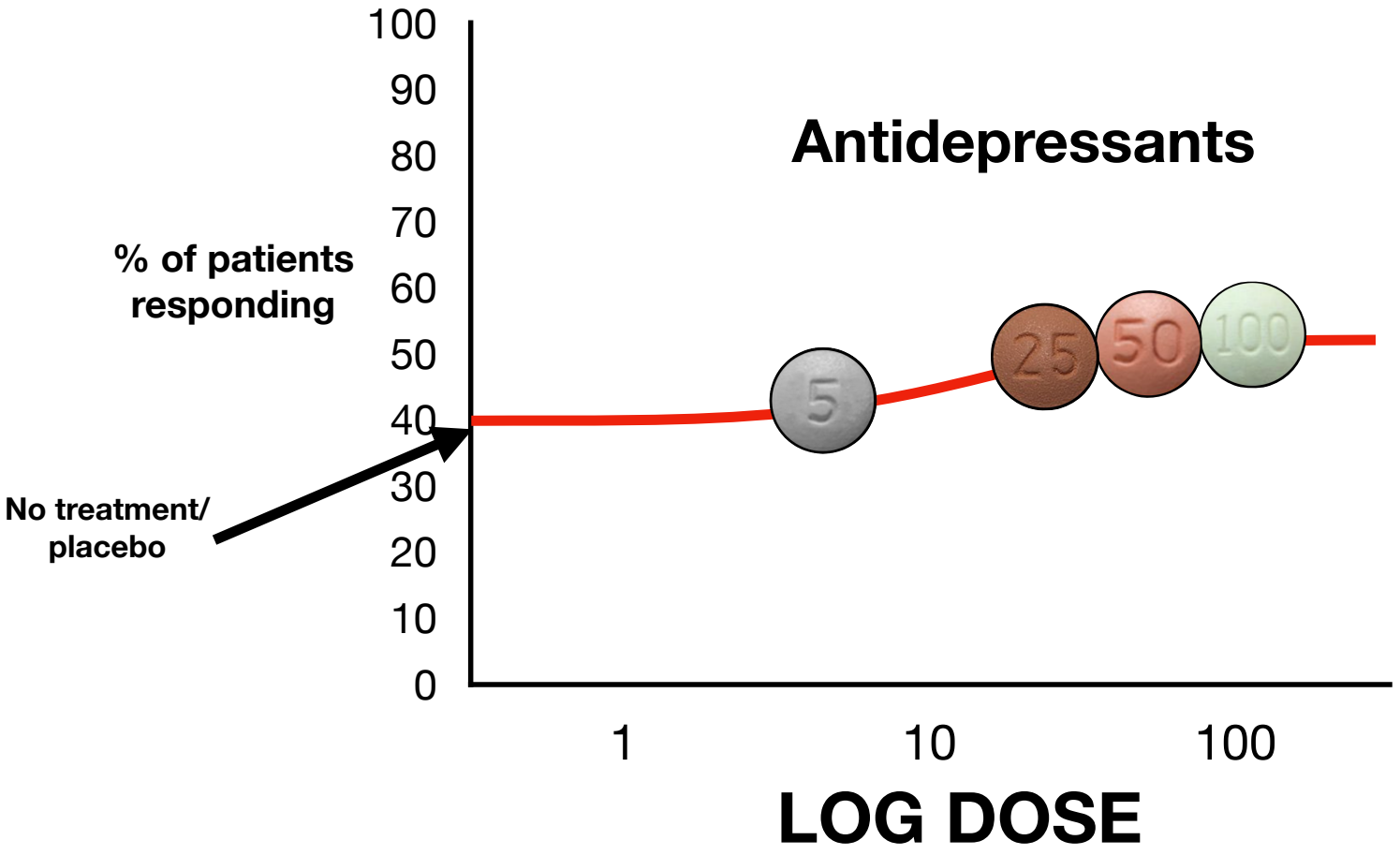
*Am J Hyper 2008;21:3–4*

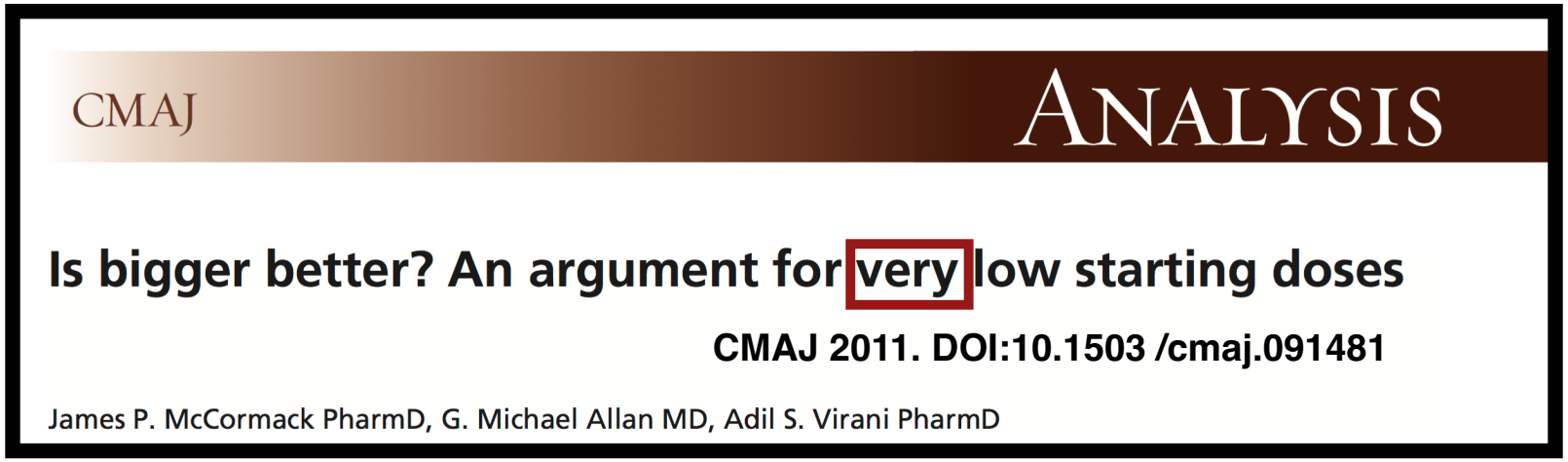
# Dose Response Curve




**May be the MOST important concept to understand when it comes to prescribing**

# But sometimes it is like this






”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)”

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

# Getting all the POWER of a placebo WITHOUT the deception

Use **VERY-LOW** doses - you will get **ALL** the placebo effect - and likely **FEWER** side effects

Patients are engaged in the process of finding the **best dose** for them

**Cost savings** can be considerable and most **adverse events can be minimized**

Most clinically relevant **drug interactions can be avoided**