

Placebo Effects in Medicine

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THREE CLINICAL EXPERIMENTS

Can placebo effects be administered in a way analogous to dose dependence?

What is the relationship between effective pharmaceuticals and placebo effects? Can a single word change the effect of pharmaceuticals?

Can placebo pills be administered honestly without deception or concealment and induce placebo effects?



“I want you to take this placebo two times a day for ten days. If your condition doesn't improve, I'll give you a stronger one.”

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HYPOTHESIS:

{INTAKE} < {INTAKE + PLACEBO} < {INTAKE + PLACEBO + ENGAGEMENT}



**Intake +
No
Treatment**

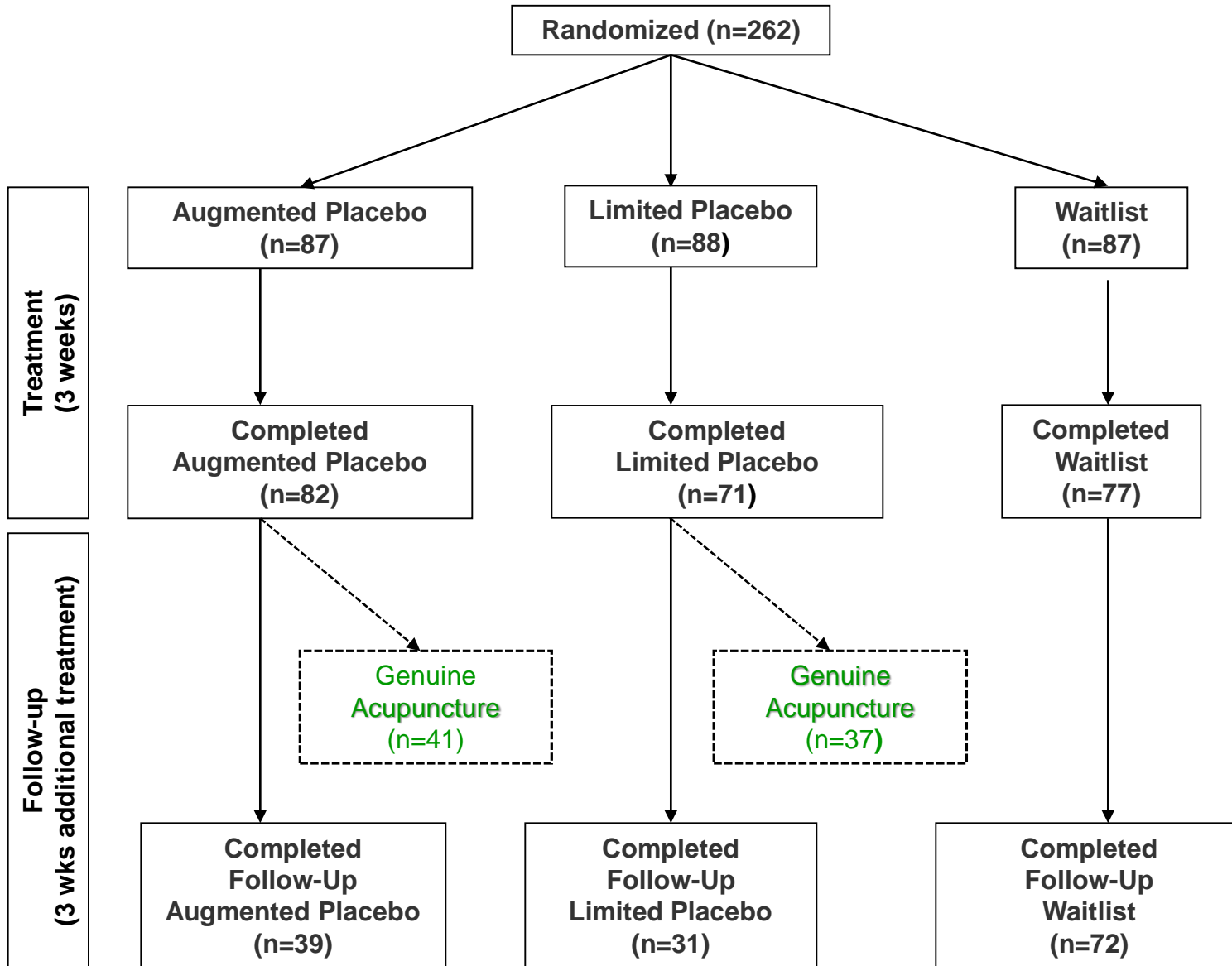


**Intake +
Placebo but
No engaged care**

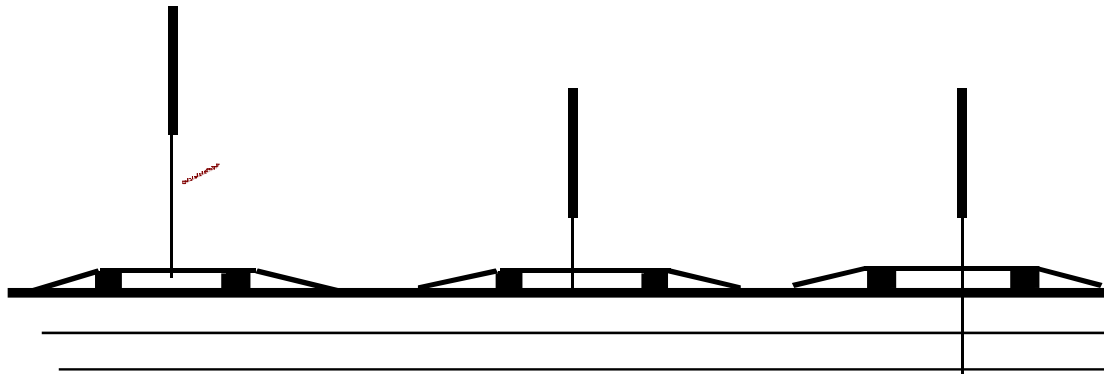


**Intake +
Placebo +
Engaged
care**

Flow of Participants in Placebo-IBS Study



PLACEBO ACUPUNCTURE NEEDLE



a) acupuncture needle

b) placebo needle

c) verum needle

Streitberger. Lancet 1998

OUTCOME MEASURES

IBS Adequate Relief

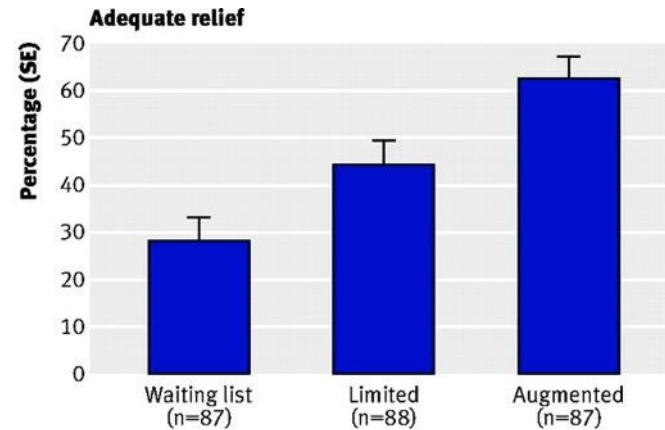
IBS Global Improvement

IBS Symptom Severity Scale

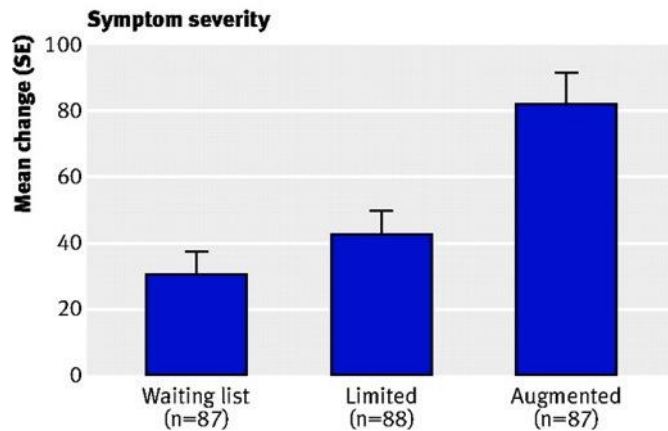
IBS QoL



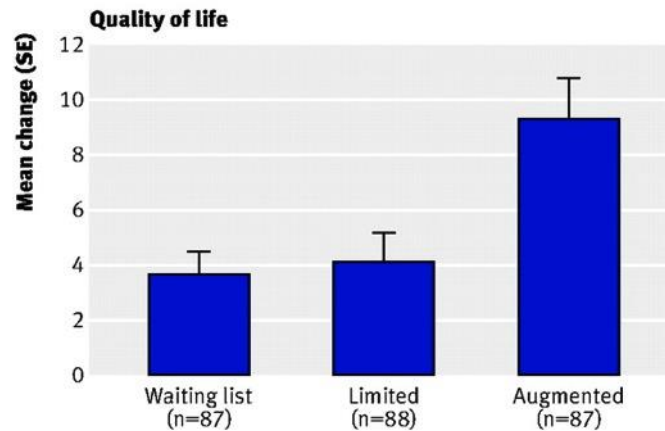
Test of trend: $P < 0.001$; 95% CI 0.18 to 0.90 for limited v waiting list; 0.32 to 1.11 for augmented v limited



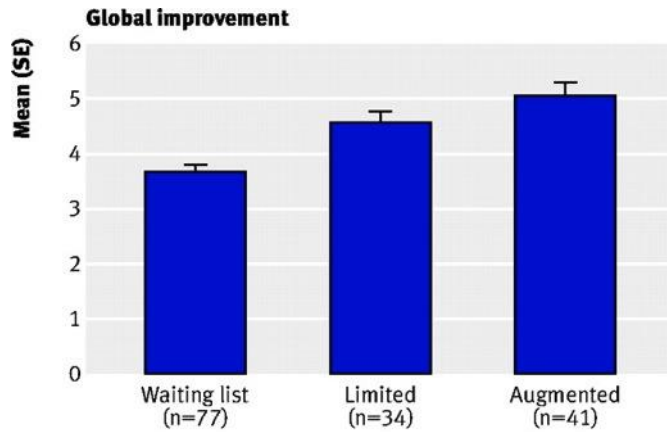
Test of trend: $P < 0.001$; 95% CI 2.7 to 30.7 for limited v waiting list; 3.2 to 32.3 for augmented v limited



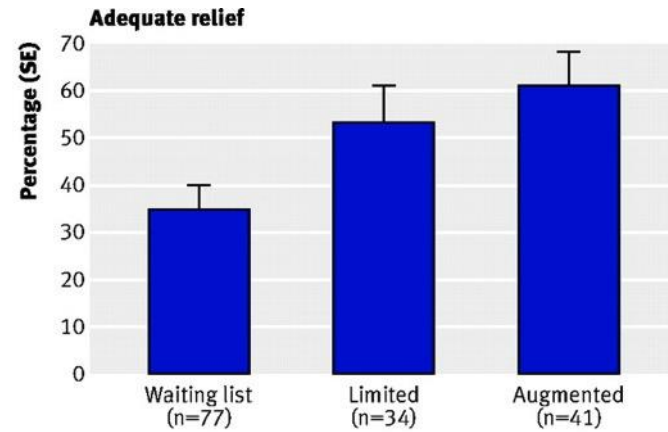
Test of trend: $P < 0.001$; 95% CI -7.9 to 31.2 for limited v waiting list; 16.2 to 63.2 for augmented v limited



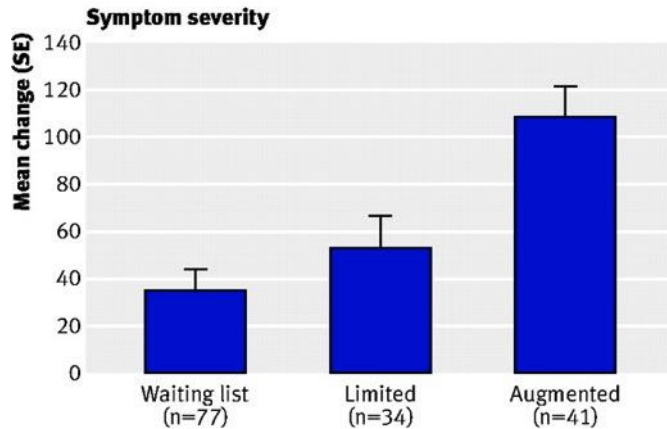
Test of trend: $P < 0.001$; 95% CI -2.1 to 3.2 for limited v waiting list; 1.7 to 8.8 for augmented v limited



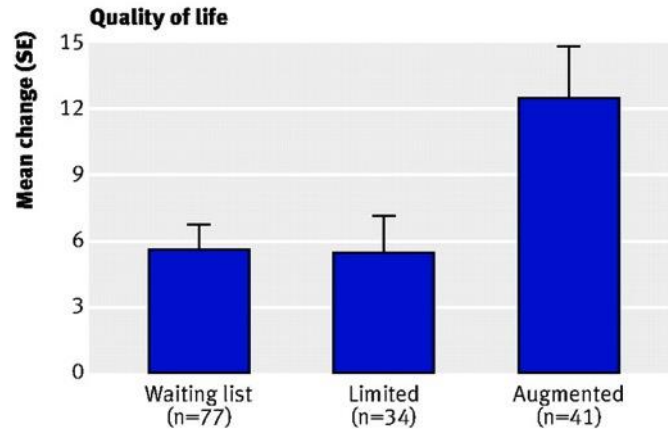
Test of trend: $P < 0.001$; 95% CI 0.5 to 1.4 for limited v waiting list; -0.1 to 1.1 for augmented v limited



Test of trend: $P = 0.005$; 95% CI -2 to 38 for limited v waiting list; -14 to 30 for augmented v limited



Test of trend: $P < 0.001$; 95% CI -14.6 to 50.5 for limited v waiting list; 15.7 to 95.2 for augmented v limited



Test of trend: $P = 0.002$; 95% CI 4.2 to -4.4 for limited v waiting list; 0.9 to 13.0 for augmented v limited

MIGRAINE

Altered Placebo and Drug Labeling Changes the Outcome of Episodic Migraine Attacks

Slavenka Kam-Hansen,¹ Moshe Jakubowski,² John M. Kelley,^{3,4,5} Irving Kirsch,^{5,6}
David C. Hoaglin,⁷ Ted J. Kaptchuk,^{5*} Rami Burstein^{2*†}

Migraine Study Design: Label Change

	Placebo	Maxalt
Label		
Placebo	Correct	Incorrect
Maxalt or Placebo	Correct	Correct
Maxalt	Incorrect	Correct

MIGRAINE STUDY

DESIGN 2 X 3 + 1

N=66 X 7 ATTACKS = 459 DOCUMENTED BASELINES

OUTCOME: PAIN REDUCTION AT 2.5 HOURS. RESCUE RX

RESULTS

General Outcomes:

N=66 x 7 attacks = 459 documented baselines

Yielded: 435 2.5 hr. outcomes and 18 imputed

453 analyzable attacks using Generalized Linear Mixed Models with a random component and a logarithmic link function

Specific Results:

Treatment (Maxalt vs. placebo): $p < 0.001$

Labeling of Pill: $p = 0.010$

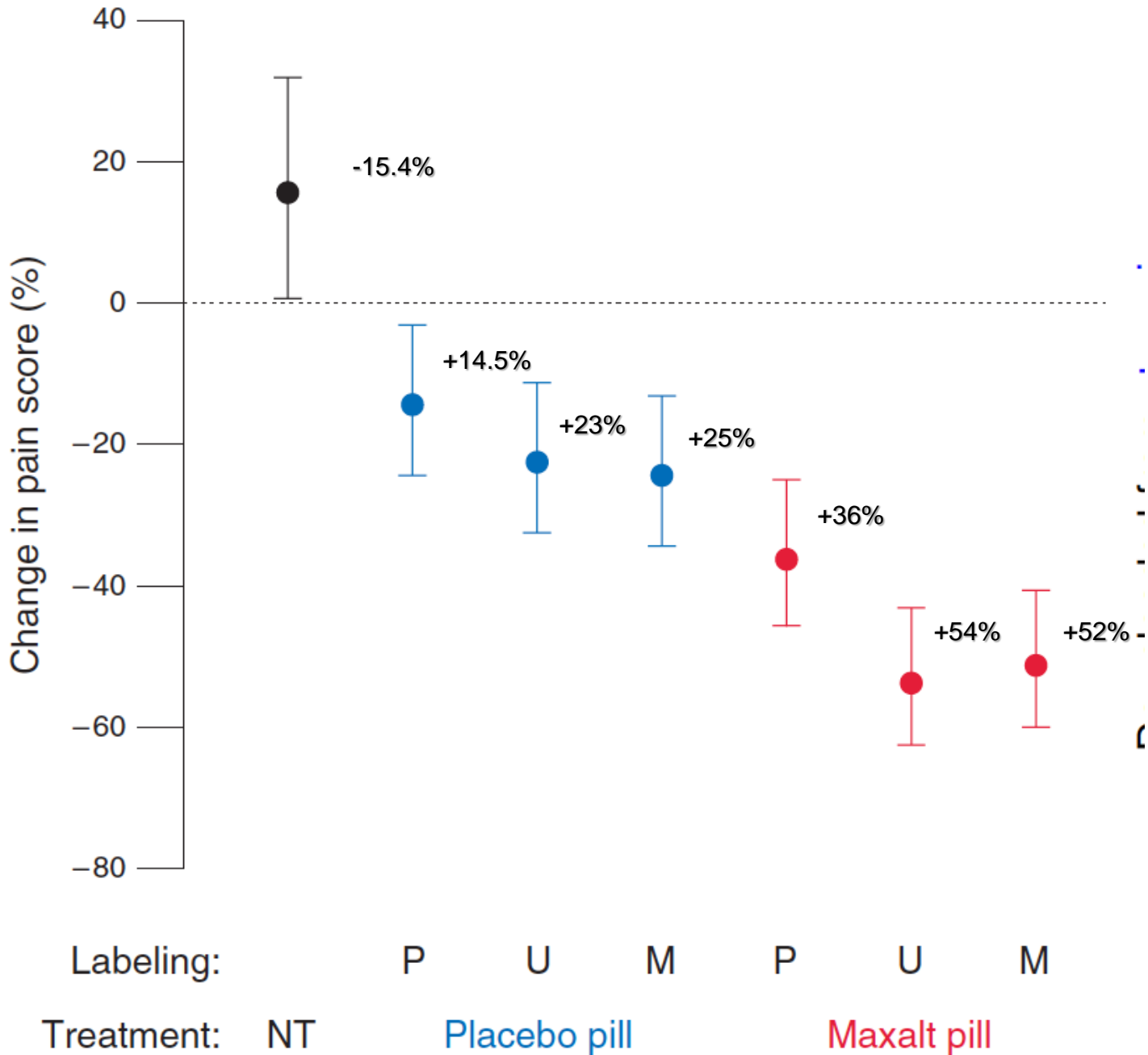
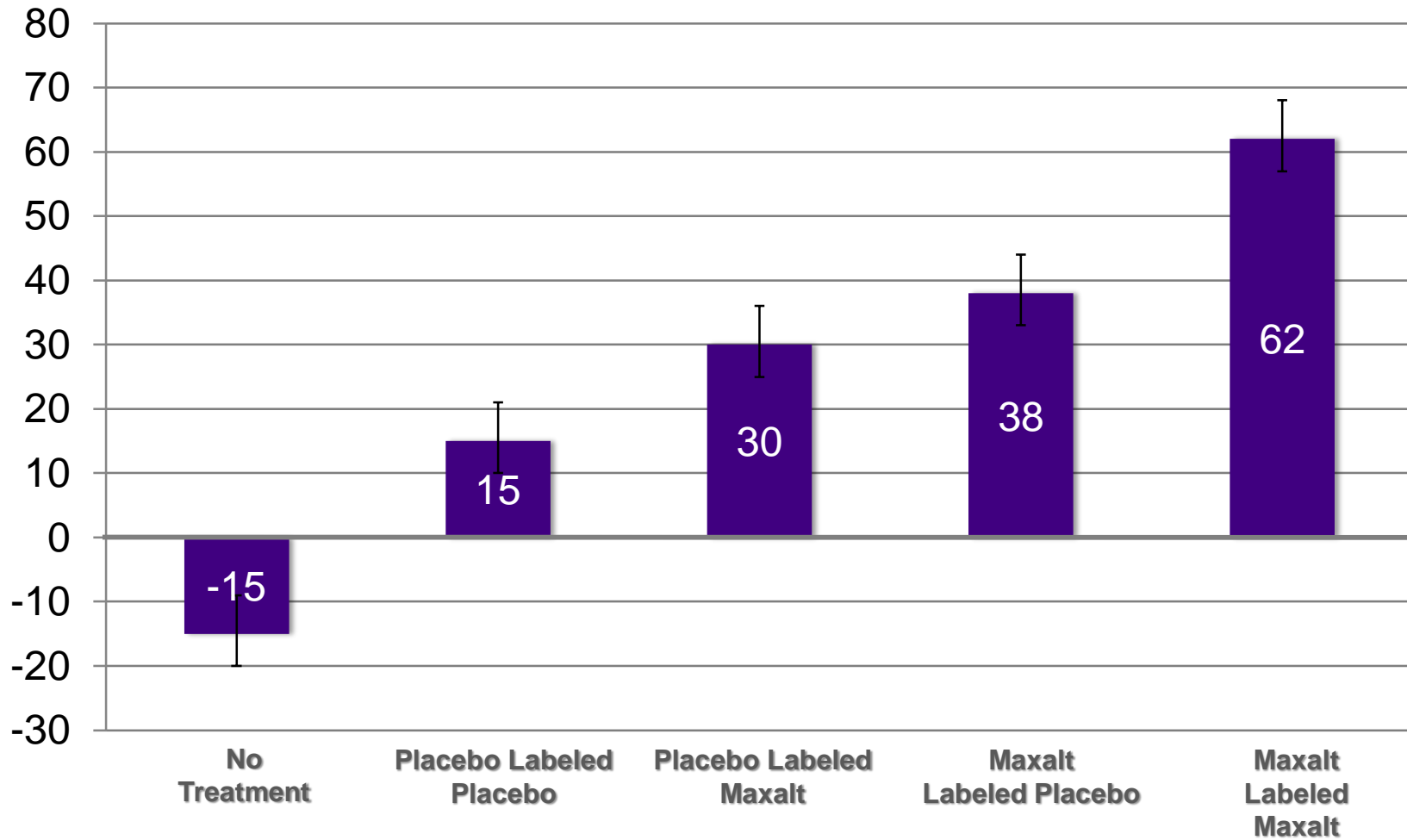


Fig. 3. Changes in headache intensity as a percentage of the 30-min pain score. The data are estimates for the seven experimental conditions,

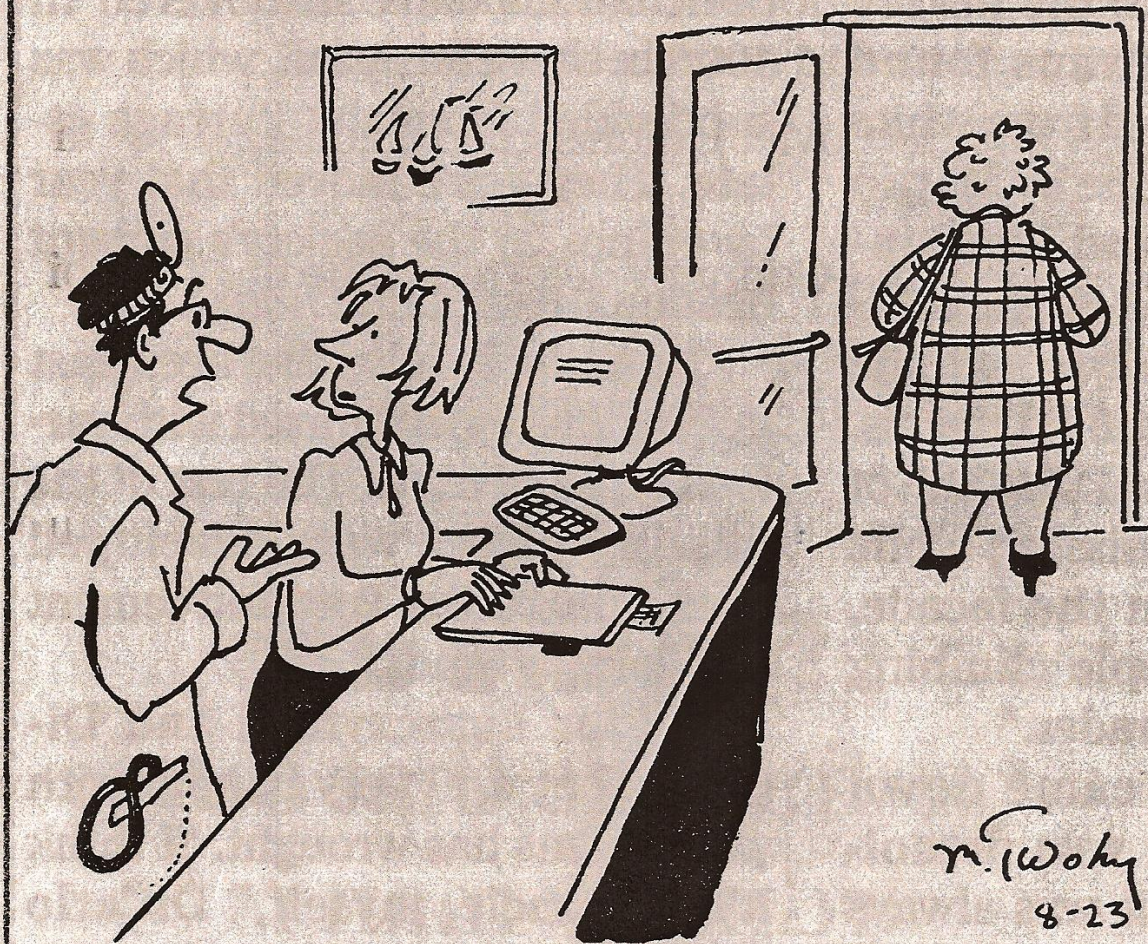
Percent Reduction in Pain



THAT'S LIFE by Mike Twohy

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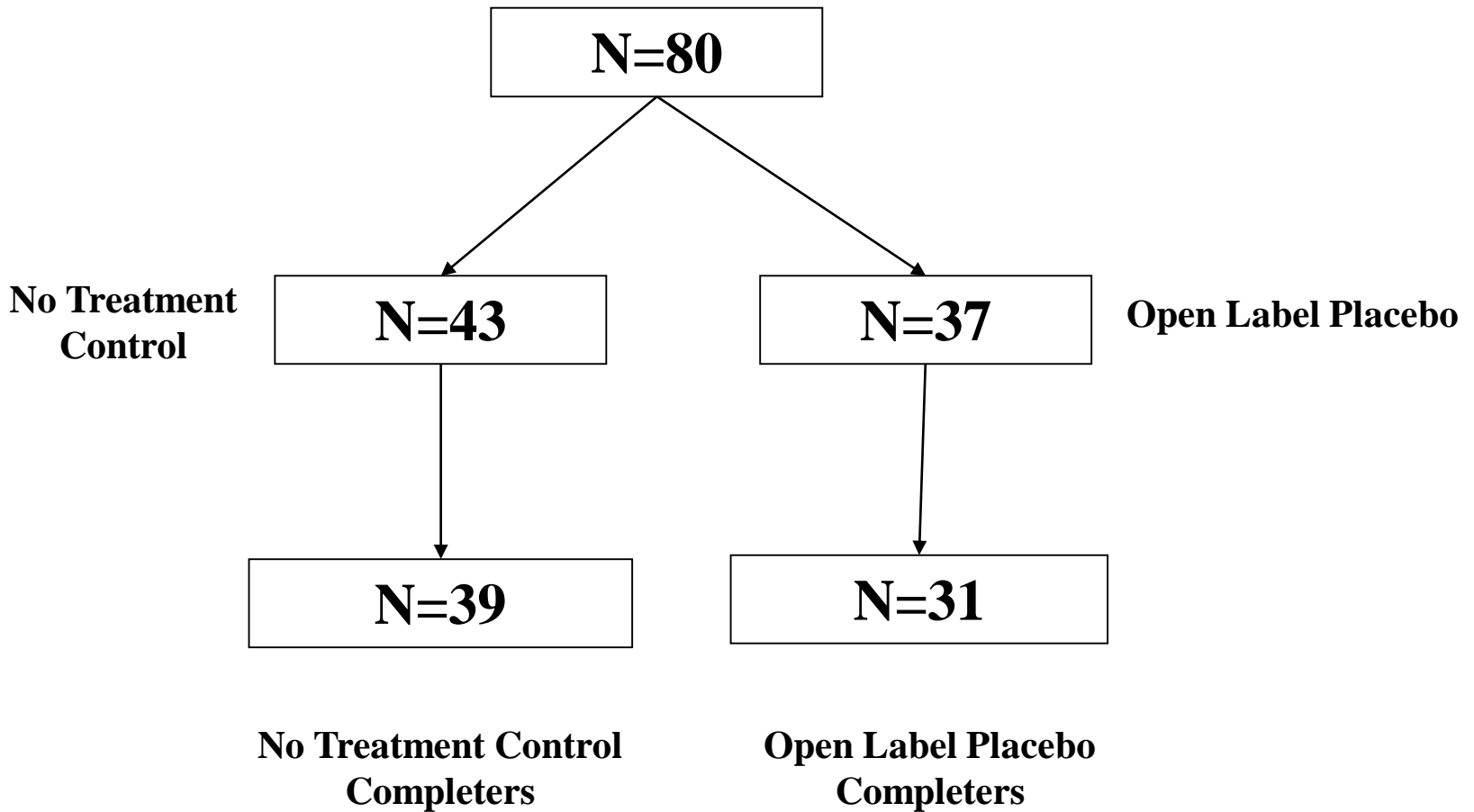


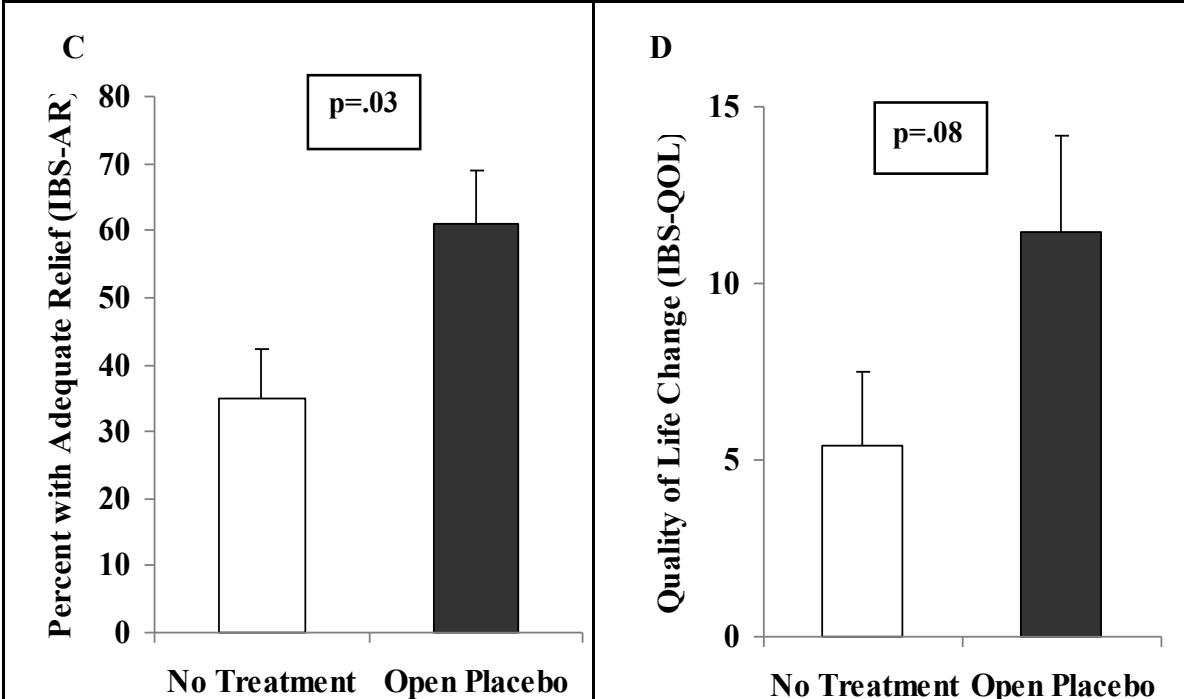
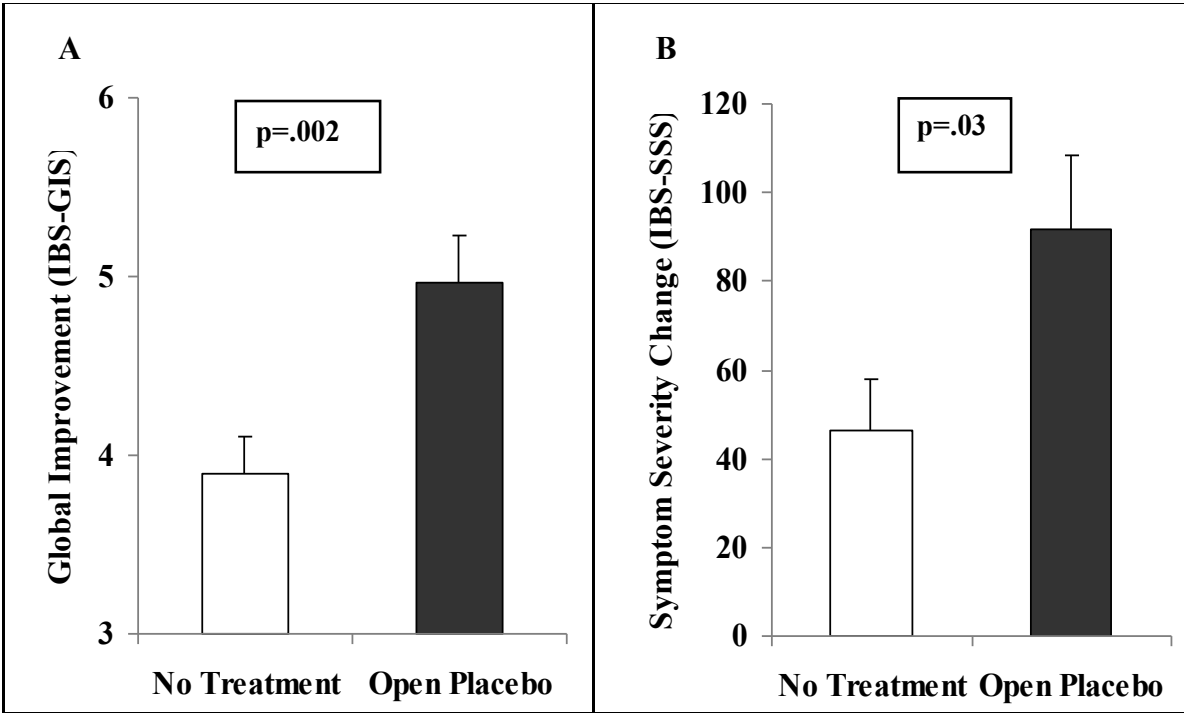
M. Twohy
8-23

"If you tell them they're in the placebo group, it ruins it!"



OPEN-LABEL PLACEBO IN IBS: PILOT STUDY FLOW





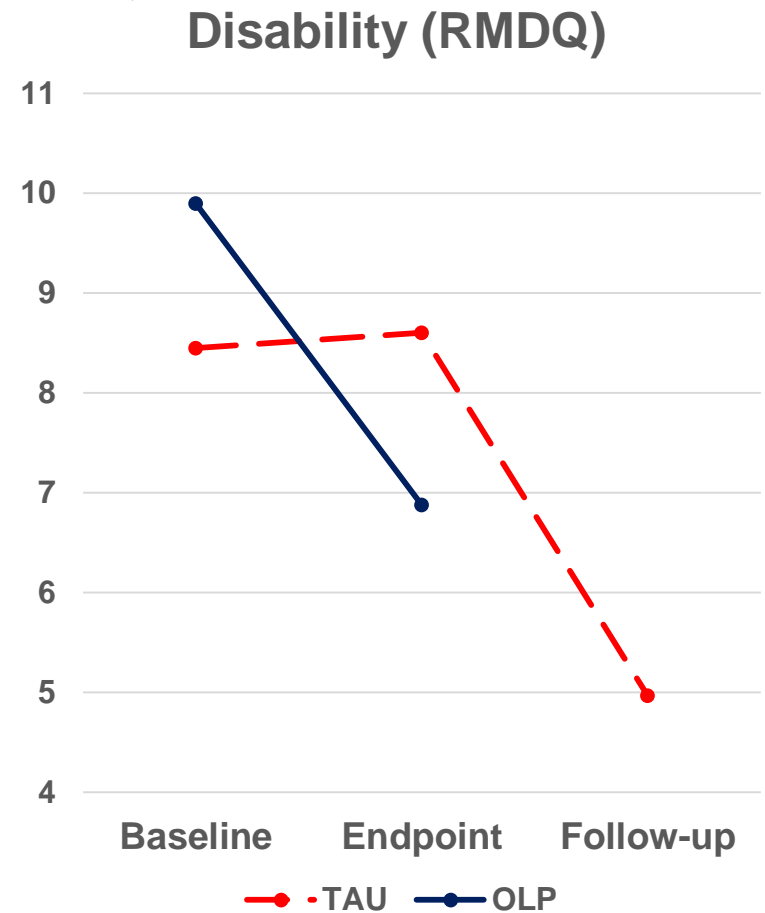
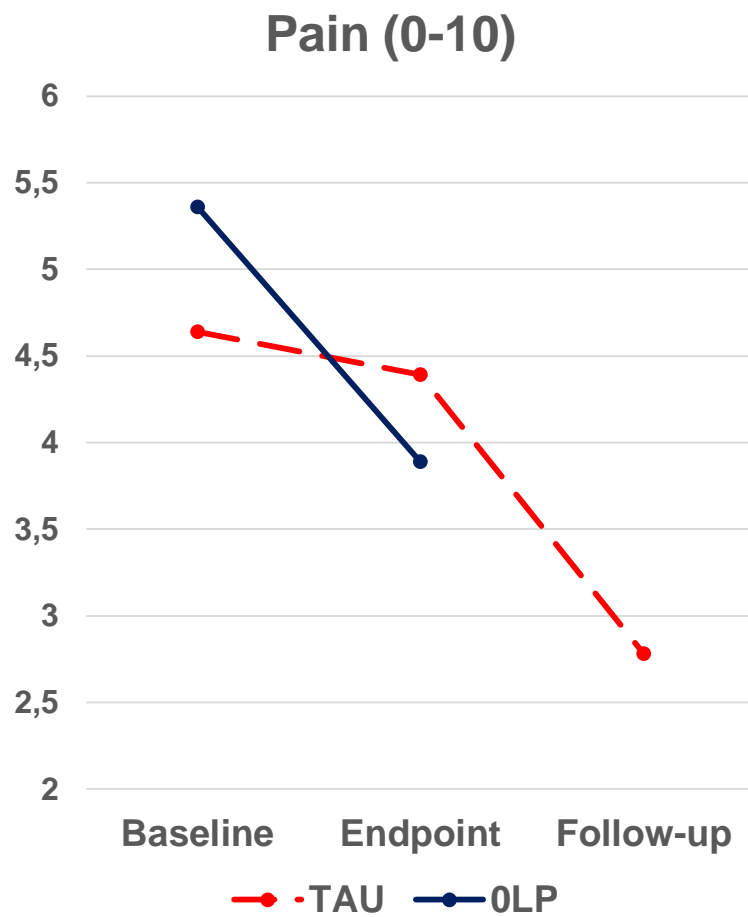


PLACEBO
EFFECT


msnbc.com

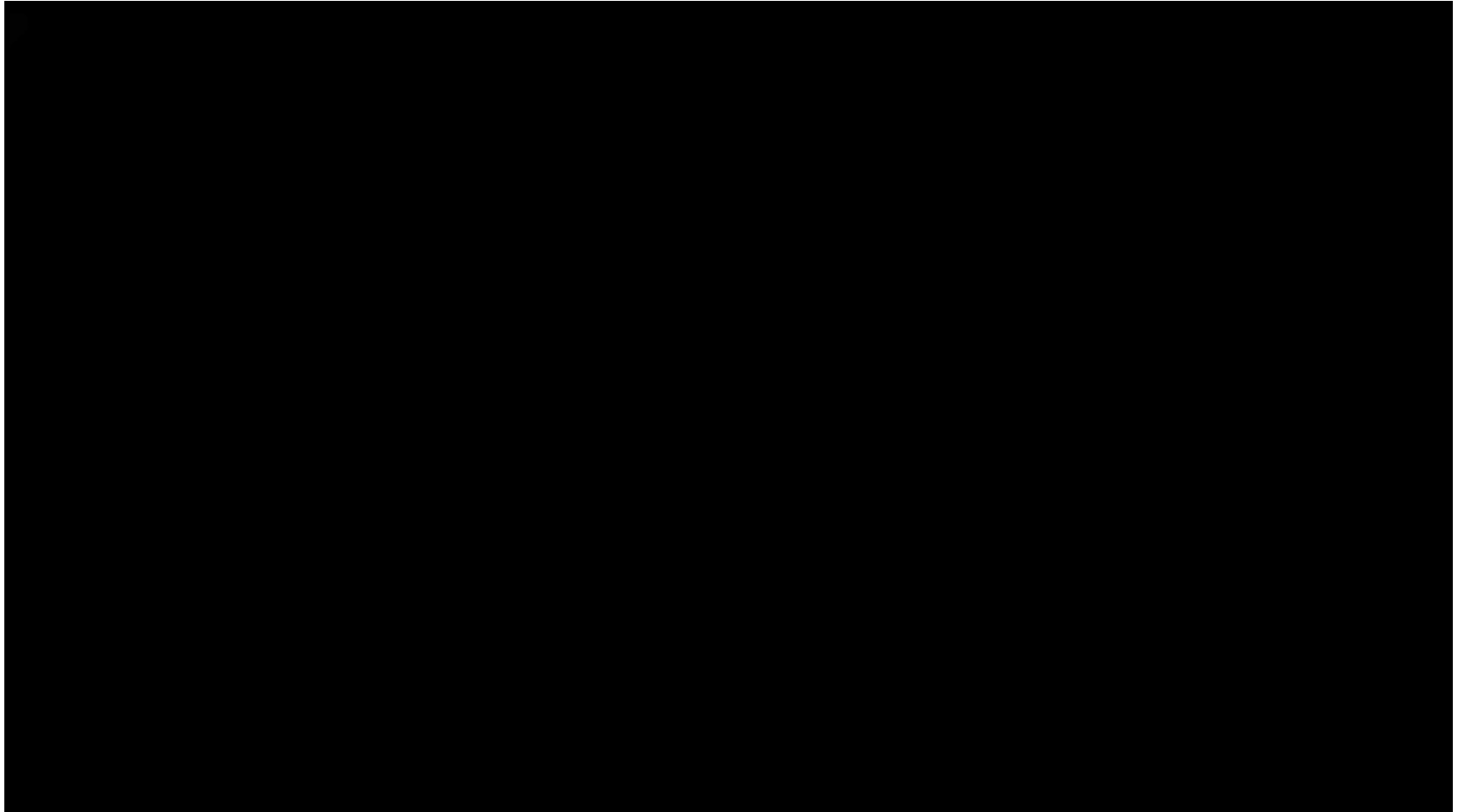
OPEN LABEL PLACEBO FOR CHRONIC LOW BACK PAIN

CARVALHO ET AL., 2016



OPEN LABEL PLACEBO FOR CHRONIC LOW BACK PAIN

CARVALHO ET AL., 2016



THANK YOU!



Genetics and the placebo effect: the placeboome

Kathryn T. Hall^{1,2}, Joseph Loscalzo³, and Ted J. Kaptchuk^{1,2}

Table 1. Polymorphisms in candidate genes that may be part of the placeboome

Placebo pathway	Gene name	Gene symbol	Chromosomal location	Placebo SNPs
Dopamine	Catechol-O-methyltransferase	<i>COMT</i>	22q11.2	rs4680
	Monoamine oxidase	<i>MAO-A</i>	Xp11.3	rs6323, rs6609257
	Dopamine B hydroxylase	<i>DBH</i>	9q34	rs2873804
	Dopamine receptor 3	<i>DRD3</i>	3q13.31	rs6280
	Brain-derived neurotropic factor	<i>BDNF</i>	11p14.1	rs6265
Serotonin	Tryptophan hydroxylase-2	<i>TPH2</i>	12q21.1	rs4570625
	5-Hydroxytryptamine transporter	<i>SLC6A4</i>	17q11.2	rs4251417
	5-Hydroxytryptamine receptor 2A	<i>HTR2A</i>	13q14.2	rs2296972, rs622337
	Serotonin transporter gene-linked polymorphic region	<i>5-HTTLPR</i>	17q11.2	Variable tandem nucleotide repeat
Opioid	Opioid receptor	<i>OPRM1</i>	6q25.2	rs510769
Endocannabinoid	Fatty acid amide hydrolase	<i>FAAH</i>	1p33	rs324420

Catechol-O-Methyltransferase val158met Polymorphism Predicts Placebo Effect in Irritable Bowel Syndrome

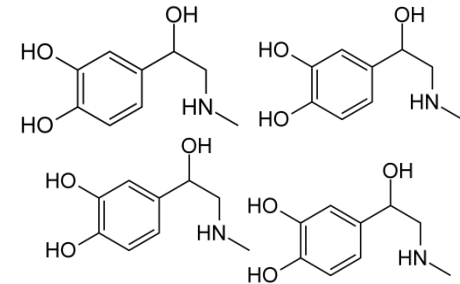
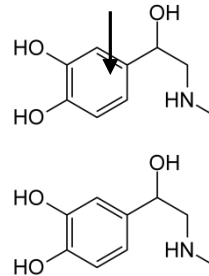
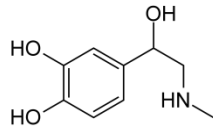
Kathryn T. Hall^{1,2*}, Anthony J. Lembo^{2,3}, Irving Kirsch^{2,4}, Dimitrios C. Ziogas⁵, Jeffrey Douaiher⁶, Karin B. Jensen^{2,7}, Lisa A. Conboy², John M. Kelley^{2,7,8}, Efi Kokkotou^{2,3}, Ted J. Kaptchuk^{1,2}

PLoS 2012

COMT val158met rs4680

valine
high-activity

methionine
low-activity



val/val
high-activity
less dopamine

val/met

met/met
low-activity
more dopamine

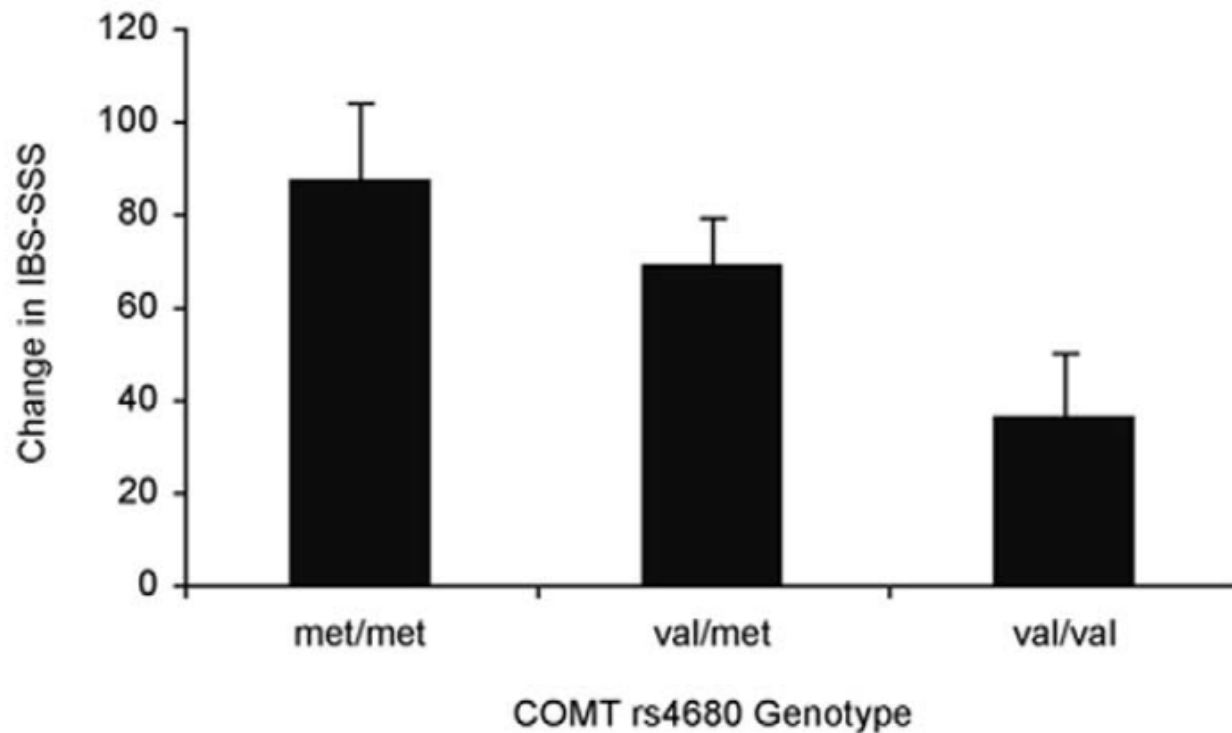
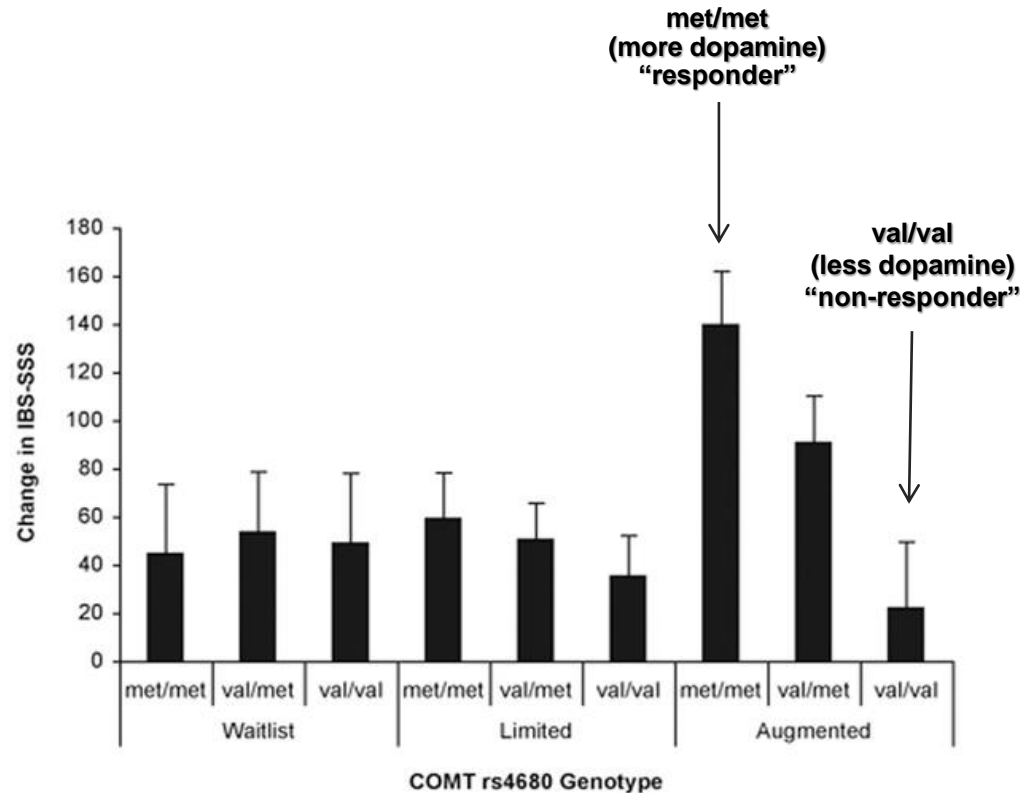


Figure 1. Effect of COMT genotype on change in IBS-SSS.

Number of val158met met alleles showed a significant linear effect on IBS-SSS (beta = 0.17; p = .032). IBS-SSS includes abdominal pain severity, abdominal pain frequency, abdominal distention severity, dissatisfaction with bowel habits, and disruption of quality of life. Change in IBS-SSS = (IBS-SSS at baseline – IBS-SSS at 3-weeks). Regression model included COMT genotype (number of met alleles) and baseline IBS-SSS. Error bars indicate the standard error of the mean. N = 104.

doi:10.1371/journal.pone.0048135.g001

Catechol-O-Methyltransferase (COMT) genotype is associated with IBS placebo response



COMT genotype ($\beta = 0.19$; $p = .02$)
COMT genotype x treatment arm ($\beta = 0.17$; $p = .035$)
(N=104)

Incidence of drug side-effect and nocebo effects in 34 participants during 83 attacks

Symptom	Number of subjects	Number of attacks	Percent of attacks (%)	
			Maxalt treatments	Placebo treatments
Chest tightness	11	23	57	43
Heart palpitation	10	22	45	55
Throat tightness	11	20	60	40
Skin sensitivity	9	21	71	29
Gastrointestinal	11	17	71	29
Drowsiness	10	14	93	7
Other*	7	8	38	62

* Including: lip tingling, cheek tingling, scalp and toe tingling, dry mouth, throbbing, moodiness, tiredness.