Universität Basel

Open-label placebo
Wirkt nichts gut genug?

Freitagskolloquium, 21. April 2023

Psychiatrischen Kolloquium der Klinik für Psychiatrie, Psychotherapie und Psychosomatik (KPPP) der Psychiatrischen Universitätsklinik Zürich (PUK)

Prof. Dr. Jens Gaab
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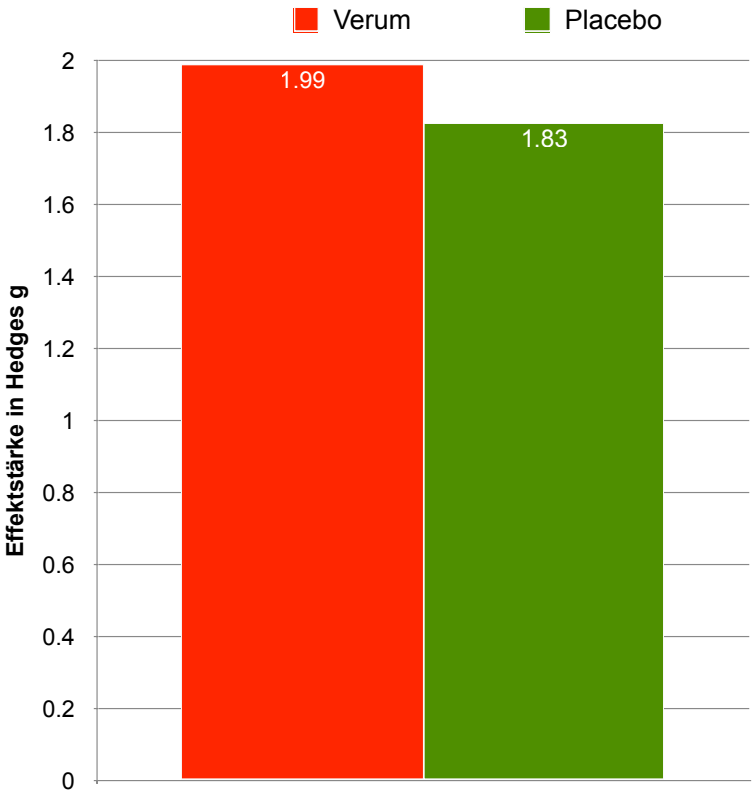
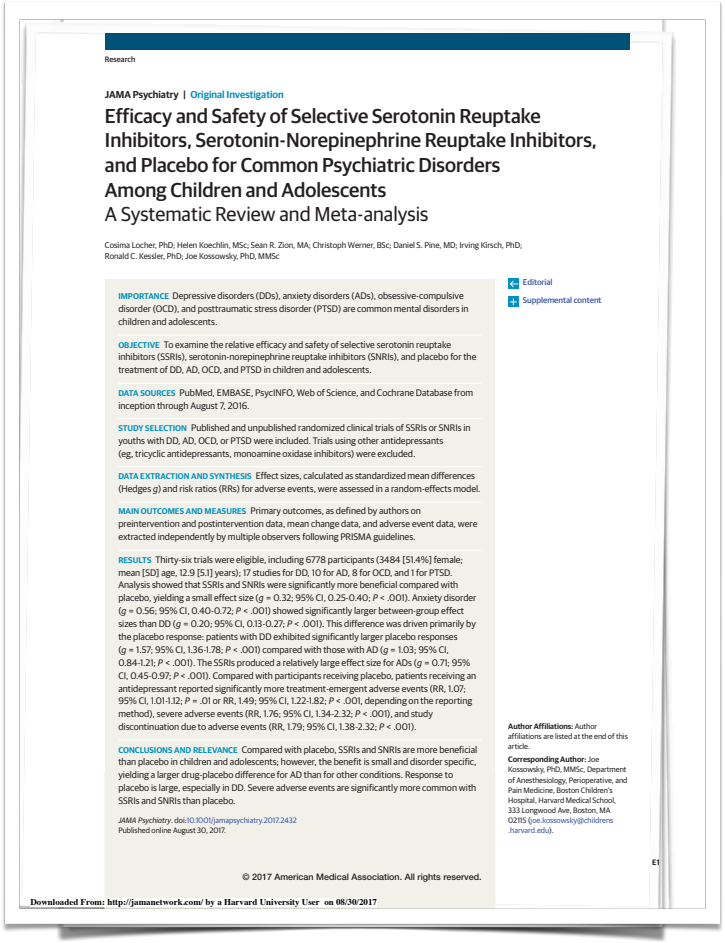
Klinisches/Ethisches Dilemma



diff d=0.16
Placebo 92% der Wirkung vom Verum

Verum vs Placebo

- Severe adverse events (SAE), RR 1.99
- Behandlungsabbruch wegen AE's: RR 1.66



Research

JAMA Psychiatry | Original Investigation

Efficacy and Safety of Selective Serotonin Reuptake Inhibitors, Serotonin-Norepinephrine Reuptake Inhibitors, and Placebo for Common Psychiatric Disorders Among Children and Adolescents
A Systematic Review and Meta-analysis

Cosima Locher, PhD; Helen Koechlin, MSc; Sean R. Zion, MA; Christoph Werner, BSc; Daniel S. Pine, MD; Irving Kirsch, PhD; Ronald C. Kessler, PhD; Joe Kossowsky, PhD, MMSc

IMPORTANCE Depressive disorders (DDs), anxiety disorders (ADs), obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD) are common mental disorders in children and adolescents.

OBJECTIVE To examine the relative efficacy and safety of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and placebo for the treatment of DD, AD, OCD, and PTSD in children and adolescents.

DATA SOURCES PubMed, EMBASE, PsycINFO, Web of Science, and Cochrane Database from inception through August 7, 2016.

STUDY SELECTION Published and unpublished randomized clinical trials of SSRIs or SNRIs in youths with DD, AD, OCD, or PTSD were included. Trials using other antidepressants (eg, tricyclic antidepressants, monoamine oxidase inhibitors) were excluded.

DATA EXTRACTION AND SYNTHESIS Effect sizes, calculated as standardized mean differences (Hedges *g*) and risk ratios (RRs) for adverse events, were assessed in a random-effects model.

MAIN OUTCOMES AND MEASURES Primary outcomes, as defined by authors on preintervention and postintervention data, mean change data, and adverse event data, were extracted independently by multiple observers following PRISMA guidelines.

RESULTS Thirty-six trials were eligible, including 6778 participants (3484 [51.4%] female; mean [SD] age, 12.9 [5.1] years); 17 studies for DD, 10 for AD, 8 for OCD, and 1 for PTSD. Analysis showed that SSRIs and SNRIs were significantly more beneficial compared with placebo, yielding a small effect size (*g* = 0.32; 95% CI, 0.25-0.40; *P* < .001). Anxiety disorder (*g* = 0.56; 95% CI, 0.40-0.72; *P* < .001) showed significantly larger between-group effect sizes than DD (*g* = 0.20; 95% CI, 0.13-0.27; *P* < .001). This difference was driven primarily by the placebo response: patients with DD exhibited significantly larger placebo responses (*g* = 1.57; 95% CI, 1.36-1.78; *P* < .001) compared with those with AD (*g* = 1.03; 95% CI, 0.84-1.21; *P* < .001). The SSRIs produced a relatively large effect size for ADs (*g* = 0.71; 95% CI, 0.45-0.97; *P* < .001). Compared with participants receiving placebo, patients receiving an antidepressant reported significantly more treatment-emergent adverse events (RR, 1.07; 95% CI, 1.01-1.12; *P* = .01 or RR, 1.49; 95% CI, 1.22-1.82; *P* < .001, depending on the reporting method), severe adverse events (RR, 1.76; 95% CI, 1.34-2.32; *P* < .001), and study discontinuation due to adverse events (RR, 1.79; 95% CI, 1.38-2.32; *P* < .001).

CONCLUSIONS AND RELEVANCE Compared with placebo, SSRIs and SNRIs are more beneficial than placebo in children and adolescents; however, the benefit is small and disorder specific, yielding a larger drug-placebo difference for AD than for other conditions. Response to placebo is large, especially in DD. Severe adverse events are significantly more common with SSRIs and SNRIs than placebo.

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Editorial
Supplemental content

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The powerful placebo: Regelmässige Einnahme rettet Leben…

Cite this article as: BMJ, doi:10.1136/bmj.38875.675486.55 (published 21 June 2006)

Research

BMJ

A meta-analysis of the association between adherence to drug therapy and mortality

Scot H Simpson, Dean T Eurich, Sumit R Majumdar, Rajdeep S Padwal, Ross T Tsuyuki, Janice Varney, Jeffrey A Johnson

Abstract

Objective To evaluate the relation between adherence to drug therapy, including placebo, and mortality.
Design Meta-analysis of observational studies.
Data sources Electronic databases, contact with investigators, and textbooks and reviews on adherence.
Review methods Predefined criteria were used to select studies reporting mortality among participants with good and poor adherence to drug therapy. Data were extracted for disease, drug therapy groups, methods for measurement of adherence rate, definition for good adherence, and mortality.
Results Data were available from 21 studies (46 847 participants), including eight studies with placebo arms (19 633 participants). Compared with poor adherence, good adherence was associated with lower mortality (odds ratio 0.56, 95% confidence interval 0.50 to 0.63). Good adherence to placebo was associated with lower mortality (0.56, 0.43 to 0.74), as was good adherence to beneficial drug therapy (0.55, 0.49 to 0.62). Good adherence to harmful drug therapy was associated with increased mortality (2.90, 1.04 to 8.11).
Conclusion Good adherence to drug therapy is associated with positive health outcomes. Moreover, the observed association between good adherence to placebo and mortality supports the existence of the "healthy adherer" effect, whereby adherence to drug therapy may be a surrogate marker for overall healthy behaviour.

Introduction

About one in four people do not adhere well to prescribed drug therapy.[1] Following principles of evidence based medicine, clinicians use the most relevant and available evidence to guide decisions on drug therapy. Once the prescription is written, however, the fate of drug therapy is with the patient. Poor adherence is considered a critical barrier to treatment success and remains one of the leading challenges to healthcare professionals.[2]

Much of the literature on adherence focuses on methods for measuring adherence and identification of risk factors for poor adherence,[3–6] with the premise that good adherence must be associated with good health outcomes.[2] Although the most detailed systematic review on adherence in the literature included a wide array of disease states, drug therapy was only one element within a range of therapeutic interventions.[2] Combining adherence to drug therapy with adherence to other behavioural and therapeutic interventions limits the ability to examine specifically the relation between adherence to drug therapy and health outcomes.

Ideally the effect of adherence should be measured on an objective health outcome, such as mortality. Individual studies have reported that good adherence to prescribed drug therapy—even to placebo—was associated with a lower risk of mortality.[w1–w3] This is contrary to the proposition that a placebo has little effect on health outcomes[4] and has led to speculation that adherence to drug therapy may act as an identifiable marker for overall healthy behaviour, the so called healthy adherer effect.[w1 w4 8–10] We tested this hypothesis by summarising published observations of the relation between adherence to drug therapy and mortality, with a particular interest in placebo arms of controlled studies.

Methods

We used standard systematic review methods.[11] Eligible for inclusion in our study were randomised controlled trials, retrospective analyses of data from randomised controlled trials, and observational studies evaluating the association between adherence to drug therapy and mortality. We applied no language restrictions.

A professional librarian (JV) carried out the literature search. She searched several electronic databases from inception date to 20 June 2005: Allied and Complementary Medicine (AMED), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, Educational Research Information Center (ERIC), HealthSTAR, Medline, PsycINFO, and the Web of Science. Articles were identified using synonyms for adherence and mortality as database specific subject headings and keywords. We also checked references from textbooks[12–14] and review articles[1 2 9 10 15–17] on adherence for additional articles.

After excluding editorials, conference proceedings, letters, news articles, government reports, and practice guidelines, two investigators (SHS, DTE) independently screened titles and abstracts to identify potentially relevant citations. A citation was retained for further evaluation if either investigator selected it. Citations were excluded that did not report original data, have human participants, evaluate drug adherence, or report patient adherence.

Each potentially relevant article was reviewed to determine if it met the following inclusion criteria: described original research, explained the method used to measure adherence (for example, self report, electronic drug event monitoring system, pharmacy refill data, clinician estimation, tablet count), provided a clear definition for good adherence, stratified patients into good and poor adherence groups, and reported mortality

Web references w1-w22 and author details are on bmj.com

…..Bei Studienteilnehmer mit einer **regelmässigen Einnahme von Placebos** war das **Mortalitätsrisiko um die Hälfte geringer** als bei Studienteilnehmern, die ihre Placebos nicht regelmässig einnahmen……

Wer hat's erfunden? placebo Domino in regione vivorum

Perspectives

The art of medicine

Placebo controls, exorcisms, and the devil

In 1784, Benjamin Franklin and Antoine Lavoisier undertook medicine's first publicly performed placebo-controlled experiments; they were seeking to debunk the healing practices of mesmerism. Franz Anton Mesmer had developed his curative methods after investigating a notorious exorcist-priest and showing that he could obtain similar results without appeals to Jesus. Mesmer claimed to have uncovered "animal magnetism", a new "fluid", analogous to gravitation. Invisible forces directed towards the mesmerist patients (usually women) would initiate a "crisis" that led to unusual bodily sensations, crying, fainting, uncontrolled gestures, fits, or violent convulsions. After treatment and "crisis", many of Mesmer's patients claimed to have experienced profound salubrious effects.

Controversy ensued and Louis XVI appointed a royal commission. The dispute was not whether mesmeric magnetism could heal, but whether there was a genuine new physical force. What we would now call placebo-controlled experiments were undertaken; the scientific team administered bogus "mesmerised" objects or treatments or, in a crossover manner, secretly dispensed the genuine articles. If the patients reacted from a dummy exposure or did not react to the bona fide article, the claims could be discounted. For example, a patient who was sensitive to the presence of "mesmerised" trees, passed out and needed to be carried out of the garden when he touched a tree deceptively labelled as "treated". Earlier, he was not affected when he touched a tree secretly "mesmerised" beforehand. Other patients went into a crisis with plain water after being told it was mesmerised, but had no sensations from surreptitiously administered authentic "magnetic" water. The commission concluded that "this agent, this fluid has no existence" and any effects were due to "imagination".

What is peculiar about the Franklin commission's report is that the placebo controls are introduced without any explanation, as if they were routine. The report does not mention that the direct inspiration for its methods came from Christian exorcism rites enacted at least 200 years earlier. It was not necessary to state the obvious: readers of the report were familiar with what were called "trick trials" from the celebrated devil controversies of the 16th century.

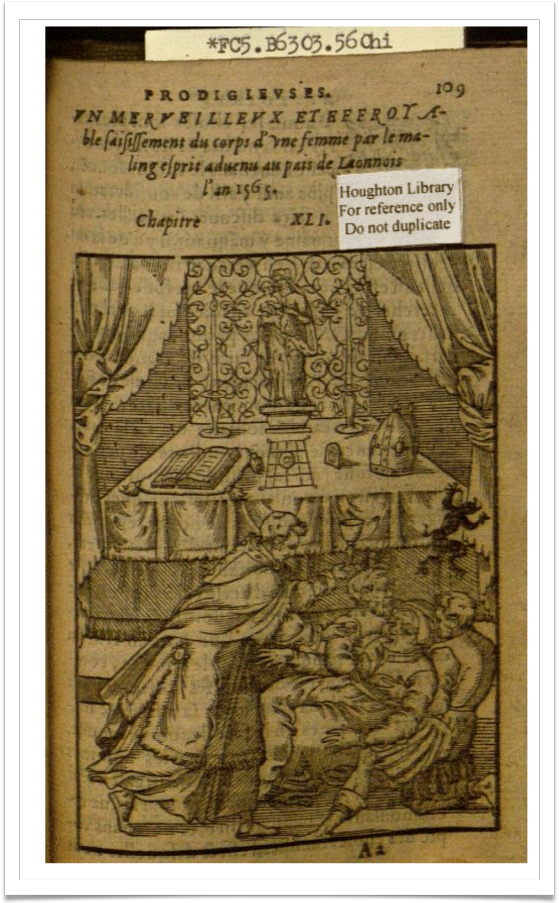
The basis for Reformation and Counter-Reformation exorcisms harkened back to the Gospels. Jesus of Nazareth stated: "in my name, shall they cast out devils" (Mark 16:17). Despite being the "father of lies" (John 8:45), "the devils also believe and tremble" (James 2:19) and could be commanded to acquiesce and speak truth and be a reliable witness. Typically, the devil recognised the authority of Jesus as the "Son of God most high." (Matt 8:29, Mark 5:7, Luke 8:28).

During the violent collision of the early modern religious wars, most notable in France, this power to cast out the devil and his confederates became a persuasive tool for demonstrating apostolic authority. This was especially the case for Catholics who were more comfortable with miraculous displays. These Counter-Reformation exorcisms depended on the "common knowledge" that demons could not tolerate direct divine contact (eg, holy water, consecrated wafer, or readings from the Latin scriptures). Such exposures caused the demons to writhe in pain and flee with a consequent "cure" for the victim who had been possessed. Not surprisingly, Catholic priests would abjure devils to testify to their fondness of Protestants and fear of Rome.

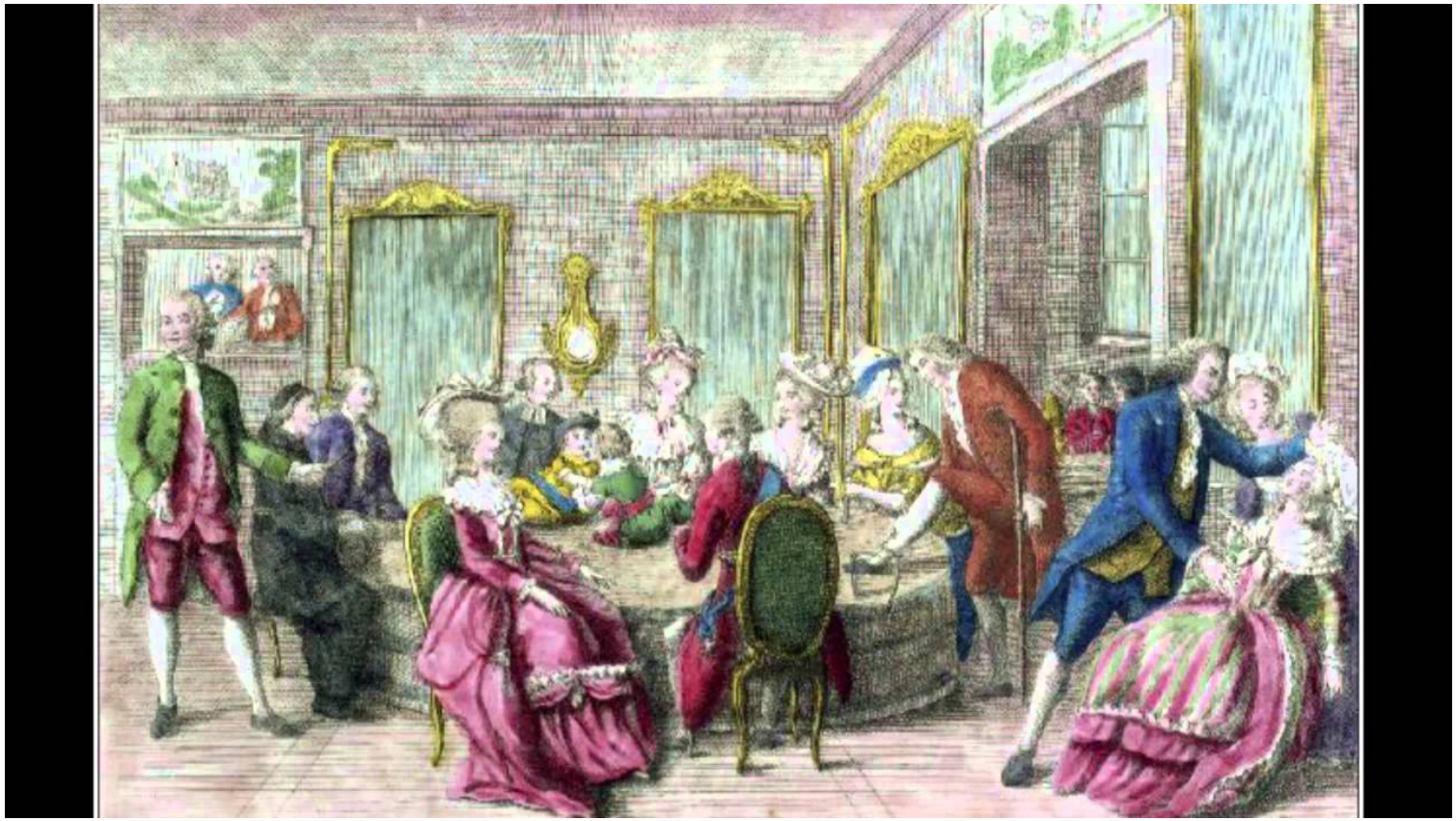
Exorcisms could become colossal revival meetings performed on elevated platforms built inside or outside churches with religious processions, mass proselytising, and collective confessing, singing, and praying. In bawdy relief, the possessed demoniacs provided entertainment with erotic ditties, lewd gesticulations, wild gyrations, grotesque grimaces, and shrieking animal roars. Breathtaking feats of physical prowess were exhibited in the wrestling between teams of strongmen and demoniacs. Audiences could reach 20 000 and pamphlets publicising the exhibitions throughout Europe indicated the intense interest in these spectacles.

Exorcisms were not without controversy. Much of the Catholic hierarchy worried that charismatic exorcisms opened the church to chaotic folk practices. The mostly Catholic supporters of the rites countered that these campaigns of dispossession showed the Church to be the legitimate inheritor of Jesus' authority. Protestants, who generally had an antimagical critique of Catholicism, were suspicious and easily discounted these superstitious events. Some argued that possessed victims—who were overwhelmingly women—probably had severe illnesses, were coerced by zealot preachers, or simply gave false testimony.

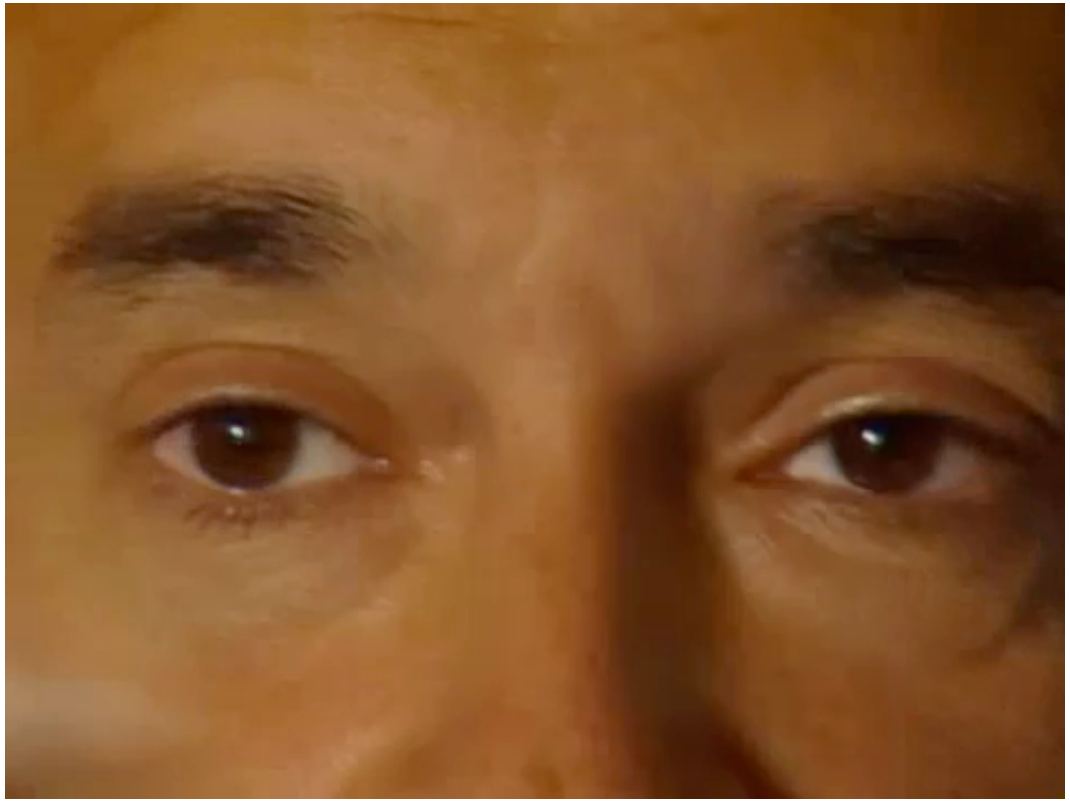
The "trick trial" was developed in response to this criticism, suspicion, and scepticism. The most prominent and emblematic such trial occurred in 1599, in a small town in the Loire Valley of France. A high stake political struggle set the stage and the trial is documented in multiple contemporary sources. In 1598, Henri IV formalised peace with the Huguenots (French Calvinists) with the Edict of Nantes. Although some Catholics exhausted from the Wars of Religion supported this rapprochement, others did not. It was against this background that a family from Romorantin claimed that Beelzebub and other demons had possessed their daughter, Marthe Brossier. During a process of almost daily repeated exorcisms by priests, who also happened to oppose the religious détente, the demons possessing the young woman testified that "all the Huguenots belonged



Wer hat’s benutzt? Animalischer Magnetismus



Mesmer revisited. Eye movement desensitization and reprocessing (EMDR)



Pergamon

Journal of Anxiety Disorders, Vol. 13, No. 1–2, pp. 225–236, 1999

0887-6185/99 $-see front matter

PII S0887-6185(98)00049-8

EMDR and Mesmerism: A Comparative Historical Analysis

Richard J. McNally, ph.d.

Harvard University, Cambridge, Massachusetts, USA

Abstract—Eye movement desensitization and reprocessing (EMDR) is among the fastest growing interventions in the annals of psychotherapy. Although many psychologists have commented on its presumably unusual origins and dissemination, history reveals its many parallels with Mesmerism, a previous therapy that spread rapidly throughout 18th century Europe and America. The purpose of this article is to document the many striking similarities between the history of Mesmerism and the history of EMDR.

Few recent psychotherapies have received as much praise or as much criticism as has Eye Movement Desensitization and Reprocessing (EMDR). Originally presented as a variant of Wolpe's (1958) systematic desensitization (Shapiro, 1989a), EMDR is now described as a complex, multifaceted intervention heralded as a major breakthrough in the field of mental health (Shapiro & Forrest, 1997). Many people praise its power for overcoming traumatic memories, whereas others view it as little more than a deftly packaged placebo, a variant of traditional exposure therapy, or both (e.g., Lilienfeld, 1996). Few would disagree, though, that the EMDR movement has grown faster than either the psychoanalytic or the behavior therapy movements.

I am very grateful to those who have reviewed previous drafts of this article including Harvard University attorney Frank J. Connors, J. D., attorney Kathleen Moore, J. D., Margaret Dale, J. D., Associate Dean for Faculty Affairs, Harvard Medical School, and psychologists Gerald C. Davison, Ph.D., Richard Gist, Ph.D., Jerome Kagan, Ph.D., Scott O. Lilienfeld, Ph.D., Elizabeth F. Loftus, Ph.D., Steven Reiss, Ph.D., and Gerald M. Rosen, Ph.D. I also thank four EMDR experts who provided excellent critiques, but who requested anonymity.

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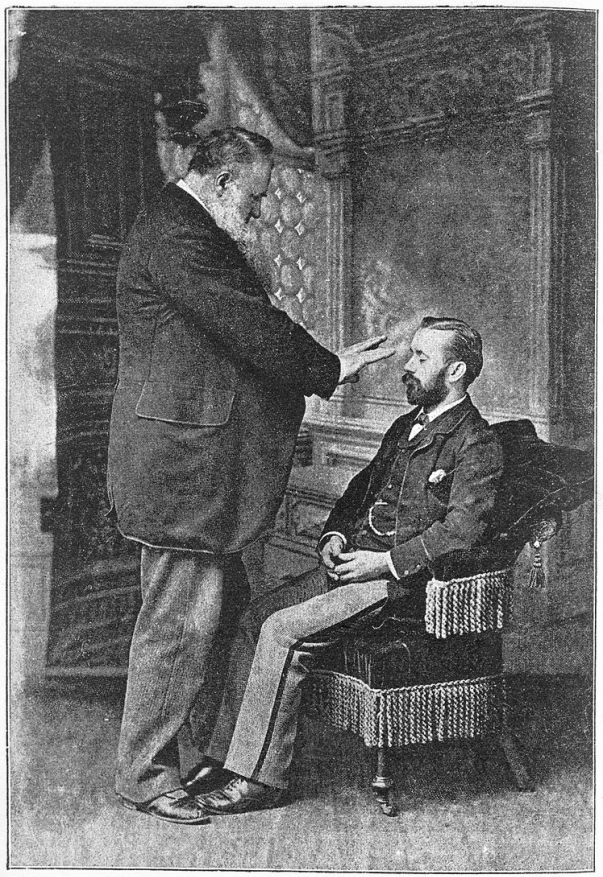
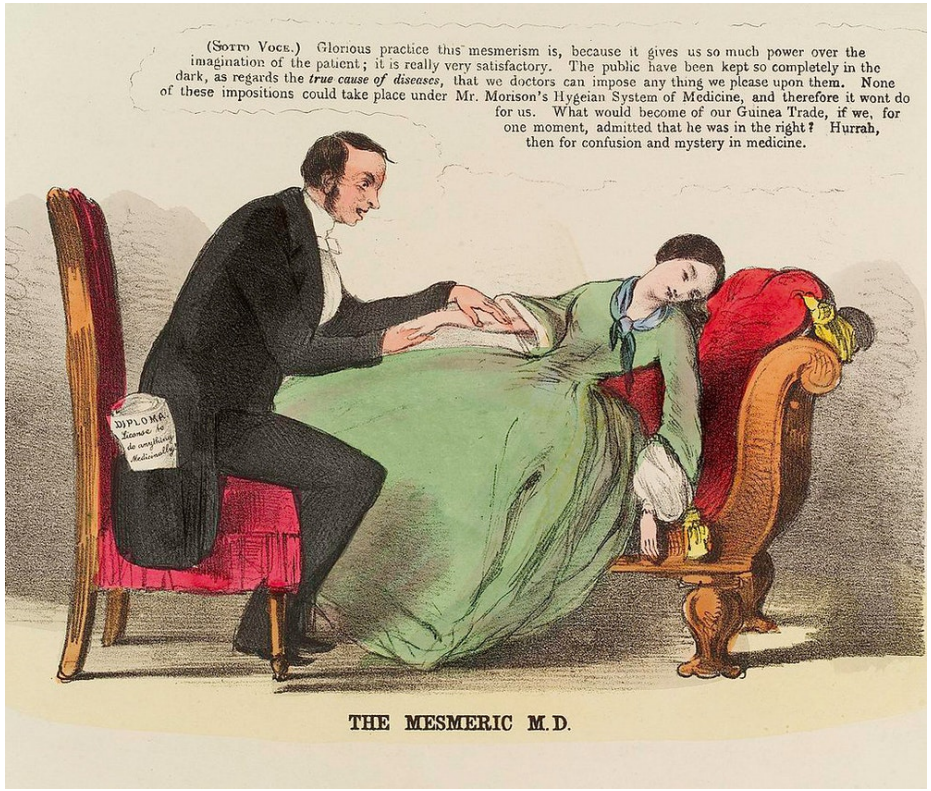
Requests for reprints should be sent to Richard J. McNally, Department of Psychology, Harvard University, 33 Kirkland Street, Cambridge, MA 02138; E-mail: rjm@wjh.harvard.edu

Magnetischer Schlaf



MAKING THE MAGNETIC PASS, FOR PRODUCING OR DEEPENING THE MESMERIC SLEEP.



Jean-Martin Charcot (1825-1893)

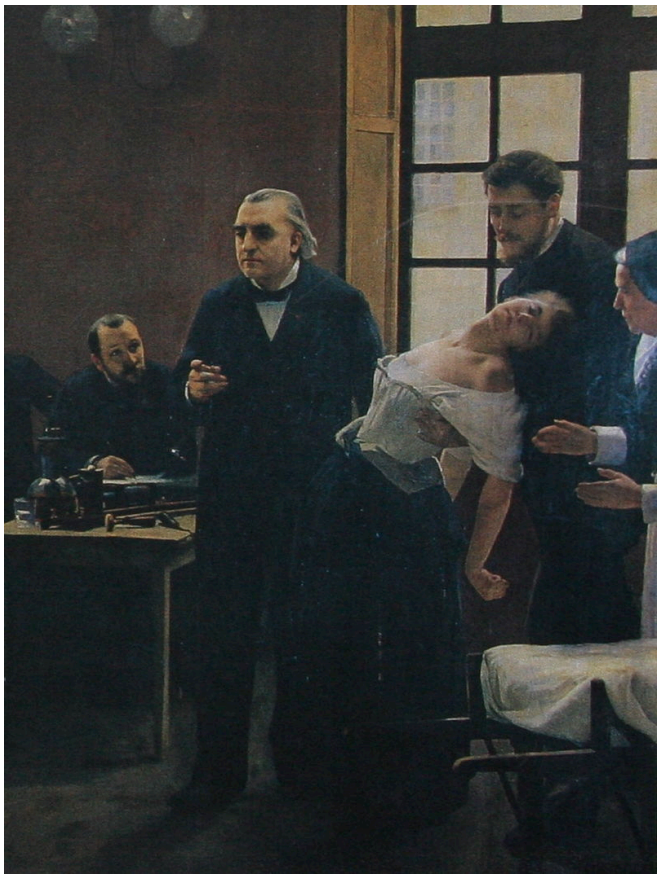
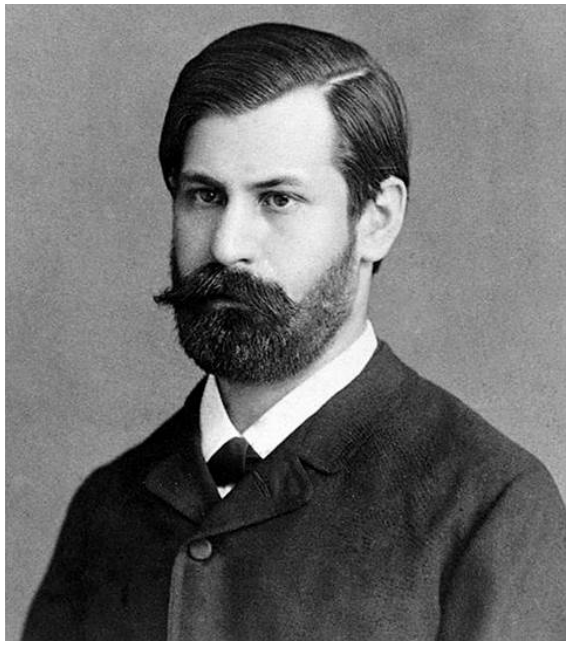


Planche XIV.

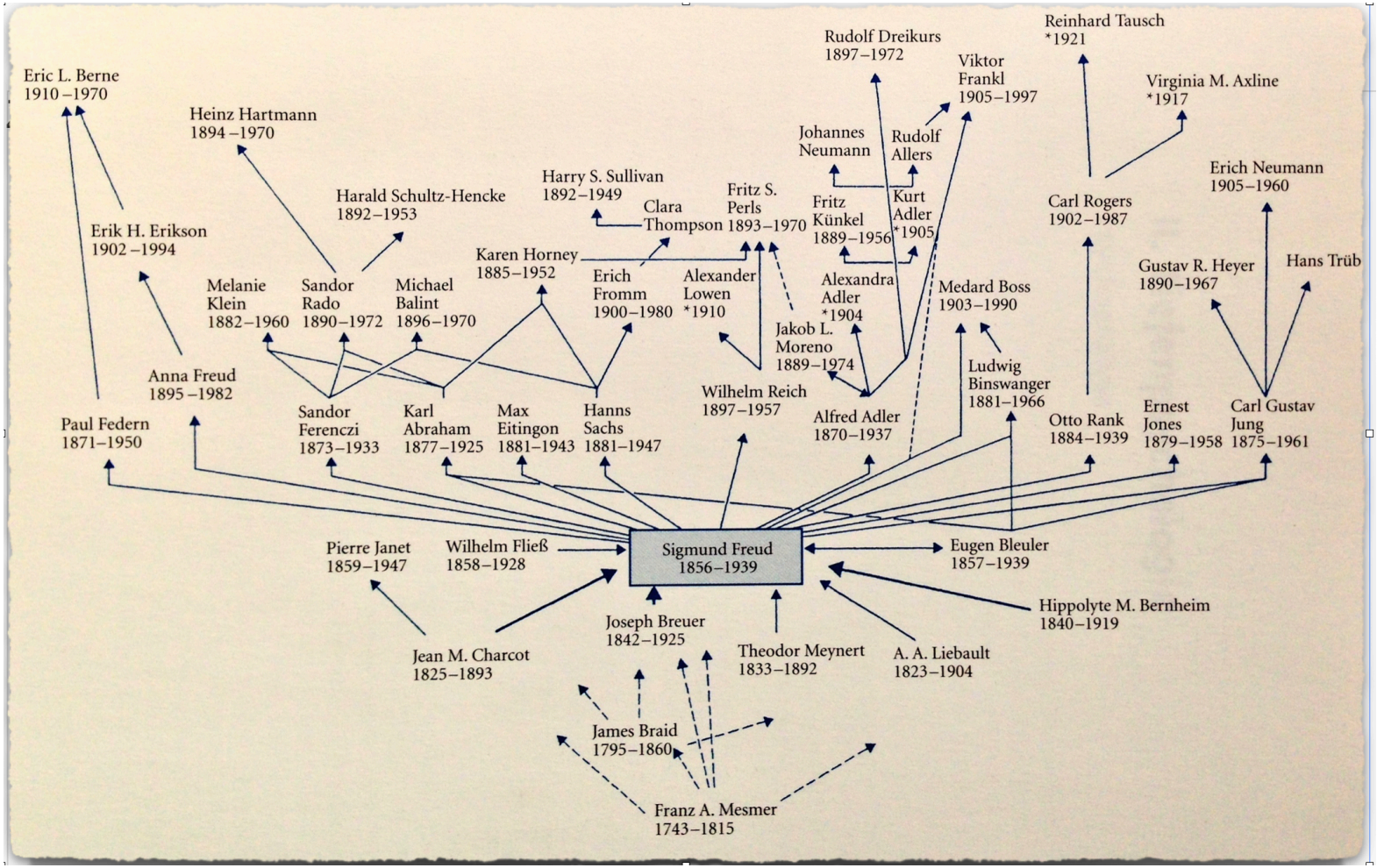
HYSTÉRO-ÉPILEPSIE

ÉTAT NORMAL

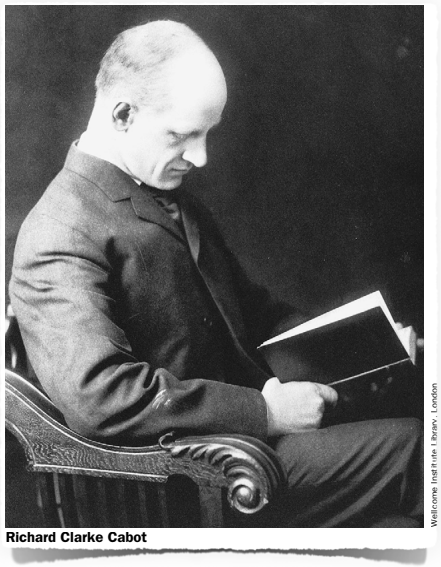
Sigmund Freud



Psychotherapie. Wer hat's erfunden…?



Einsatz von Placebo in der Medizin



Richard Clarke Cabot

„I was brought up, as I suppose every physician is, to use placebo, bread pills, salt water injections . . . I doubt if there is a physician in this room who has not used them and used them pretty often . . . I used to give them by the bushels.“

Richard Cabot (1868–1939), Harvard Medical School

Closer to reality? Placebos in clinical practice.

Clinical Psychology Review, Vol. 13, pp. 375–391, 1993
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0272-7358/93 $6.00 + .00

THE POWER OF NONSPECIFIC EFFECTS IN HEALING: IMPLICATIONS FOR PSYCHOSOCIAL AND BIOLOGICAL TREATMENTS

Alan H. Roberts
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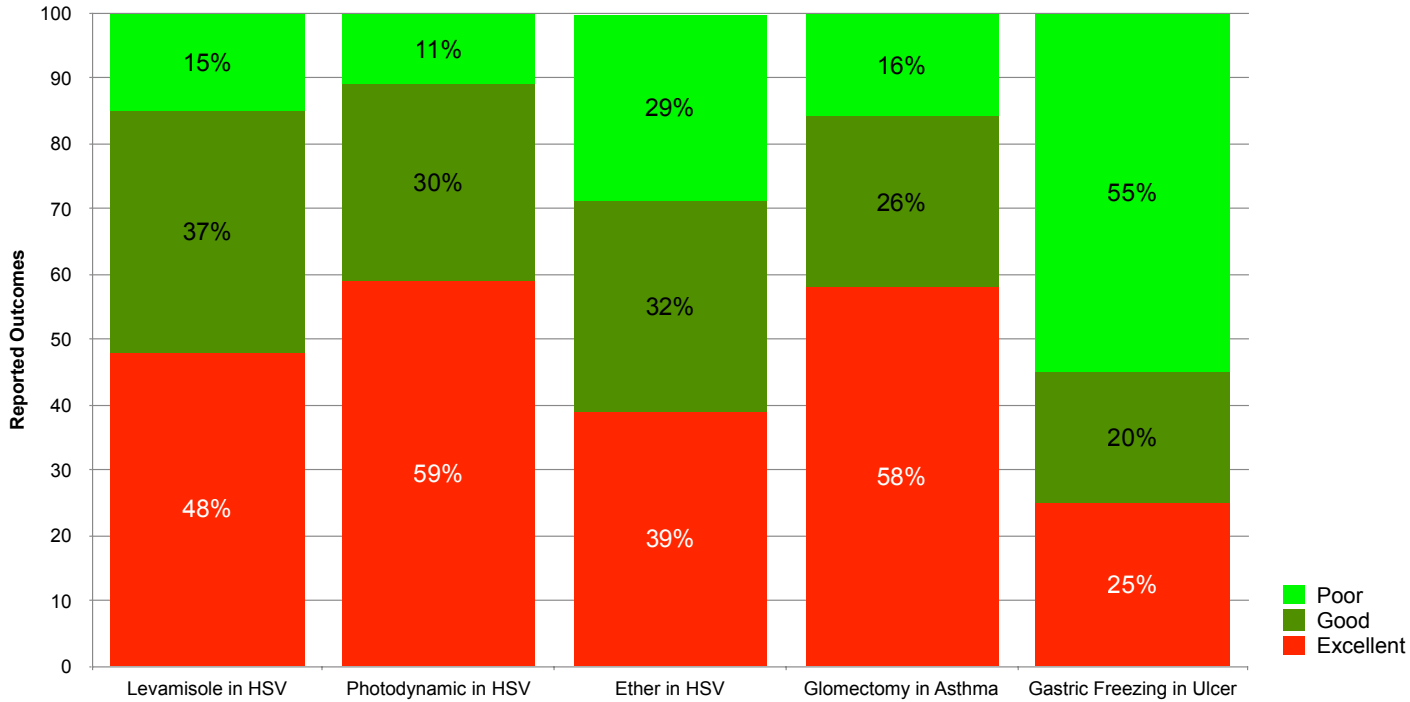
Donald G. Kewman
University of Michigan
Lisa Mercier
Mel Hovell
Graduate School of Public Health, San Diego State University

ABSTRACT. *We evaluate the hypothesis that the power of nonspecific effects may account for as much as two thirds of successful treatment outcomes when both the healer and the patient believe in the efficacy of a treatment. Five medical and surgical treatments, once considered to be efficacious by their proponents but no longer considered effective based upon later controlled trials, were selected according to strict inclusion criteria. A search of the English literature was conducted for all studies published for each treatment area. The results of these studies were categorized, where possible, into excellent, good, and poor outcomes. For these five treatments combined, 40% excellent, 30% good, and 30% poor results were reported by proponents. We conclude that, under conditions of heightened expectations, the power of nonspecific effects far exceeds that commonly reported in the literature. The implications of these results in evaluating the relative efficacy of biological and psychosocial treatments is discussed.*

The issue of specific and nonspecific effects in psychiatric and psychological interventions continues to be a matter of intense interest and debate. Controversies involve both biological (Fisher & Greenberg, 1989a; Margraf et al., 1991) and psychosocial (Beutler,

Correspondence should be addressed to Alan H. Roberts, Scripps Clinic and Research Foundation, Division of Medical Psychology, 10666 N. Torrey Pines Road, La Jolla, CA 92037.



Roberts et al., 1993
Clin Psych Rev

Antidepressiva vs. Placebo.

Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

Andrea Cipriani, Toshi A Furukawa, Georgia Salanti*, Anna Chaimani, Lauren Z Atkinson, Yusuke Ogawa, Stefan Leucht, Henricus G Ruhe, Erick H Turner, Julian P T Higgins, Matthias Egger, Nozomi Takeshima, Yu Hayasaka, Hissei Imai, Kiyomi Shinohara, Aran Tajika, John P A Ioannidis, John R Geddes*

Summary

Background Major depressive disorder is one of the most common, burdensome, and costly psychiatric disorders worldwide in adults. Pharmacological and non-pharmacological treatments are available; however, because of inadequate resources, antidepressants are used more frequently than psychological interventions. Prescription of these agents should be informed by the best available evidence. Therefore, we aimed to update and expand our previous work to compare and rank antidepressants for the acute treatment of adults with unipolar major depressive disorder.

Methods We did a systematic review and network meta-analysis. We searched Cochrane Central Register of Controlled Trials, CINAHL, Embase, LILACS database, MEDLINE, MEDLINE In-Process, PsycINFO, the websites of regulatory agencies, and international registers for published and unpublished, double-blind, randomised controlled trials from their inception to Jan 8, 2016. We included placebo-controlled and head-to-head trials of 21 antidepressants used for the acute treatment of adults (≥18 years old and of both sexes) with major depressive disorder diagnosed according to standard operationalised criteria. We excluded quasi-randomised trials and trials that were incomplete or included 20% or more of participants with bipolar disorder, psychotic depression, or treatment-resistant depression; or patients with a serious concomitant medical illness. We extracted data following a predefined hierarchy. In network meta-analysis, we used group-level data. We assessed the studies' risk of bias in accordance to the Cochrane Handbook for Systematic Reviews of Interventions, and certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation framework. Primary outcomes were efficacy (response rate) and acceptability (treatment discontinuations due to any cause). We estimated summary odds ratios (ORs) using pairwise and network meta-analysis with random effects. This study is registered with PROSPERO, number CRD42012002291.

Findings We identified 28 552 citations and of these included 522 trials comprising 116 477 participants. In terms of efficacy, all antidepressants were more effective than placebo, with ORs ranging between 2·13 (95% credible interval [CrI] 1·89–2·41) for amitriptyline and 1·37 (1·16–1·63) for reboxetine. For acceptability, only agomelatine (OR 0·84, 95% CrI 0·72–0·97) and fluoxetine (0·88, 0·80–0·96) were associated with fewer dropouts than placebo, whereas clomipramine was worse than placebo (1·30, 1·01–1·68). When all trials were considered, differences in ORs between antidepressants ranged from 1·15 to 1·55 for efficacy and from 0·64 to 0·83 for acceptability, with wide CrIs on most of the comparative analyses. In head-to-head studies, agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were more effective than other antidepressants (range of ORs 1·19–1·96), whereas fluoxetine, fluvoxamine, reboxetine, and trazodone were the least efficacious drugs (0·51–0·84). For acceptability, agomelatine, citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine were more tolerable than other antidepressants (range of ORs 0·43–0·77), whereas amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine, trazodone, and venlafaxine had the highest dropout rates (1·30–2·32). 46 (9%) of 522 trials were rated as high risk of bias, 380 (73%) trials as moderate, and 96 (18%) as low; and the certainty of evidence was moderate to very low.

Interpretation All antidepressants were more efficacious than placebo in adults with major depressive disorder. Smaller differences between active drugs were found when placebo-controlled trials were included in the analysis, whereas there was more variability in efficacy and acceptability in head-to-head trials. These results should serve evidence-based practice and inform patients, physicians, guideline developers, and policy makers on the relative merits of the different antidepressants.

Funding National Institute for Health Research Oxford Health Biomedical Research Centre and the Japan Society for the Promotion of Science.

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See Comment page 1333

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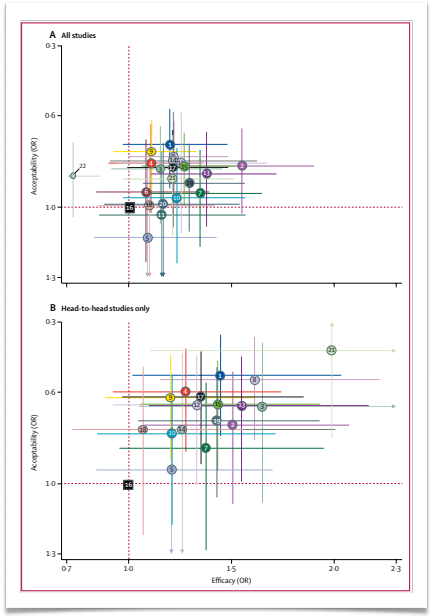

The relative efficacy of antidepressants compared with placebo is also shown for remission (appendix pp 152, 153). The random-effects summary SMD for all antidepressants was 0·30 (95% CrI 0·26–0·34; p<0·0001; appendix pp 150, 151). In terms of dropouts due to

Antidepressiva vs. Placebo.

RESEARCH

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Response to acute monotherapy for major depressive disorder in randomized, placebo controlled trials submitted to the US Food and Drug Administration: individual participant data analysis

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ABSTRACT

OBJECTIVES
To characterize individual participant level response distributions to acute monotherapy for major depressive disorder in randomized, placebo controlled trials submitted to the US Food and Drug Administration from 1979 to 2016.

DESIGN
Individual participant data analysis.

POPULATION
232 randomized, double blind, placebo controlled trials of drug monotherapy for major depressive disorder submitted by drug developers to the FDA between 1979 and 2016, comprising 73 388 adult and child participants meeting the inclusion criteria for efficacy studies on antidepressants.

MAIN OUTCOME MEASURES
Responses were converted to Hamilton Rating Scale for Depression (HAMD17) equivalent scores where other measures were used to assess efficacy. Multivariable analyses examined the effects of age, sex, baseline severity, and year of the study on improvements in depressive symptoms in the antidepressant and placebo groups. Response distributions were analyzed with finite mixture models.

RESULTS
The random effects mean difference between drug and placebo favored drug (1.75 points, 95% confidence interval 1.63 to 1.86). Differences between drug and placebo increased significantly (P<0.001) with greater baseline severity. After controlling for participant characteristics at baseline, no trends in treatment effect or placebo response over time were found. The best fitting model of response distributions was three normal distributions, with mean improvements from baseline to end of treatment of 16.0, 8.9, and 1.7 points. These distributions were designated Large, Non-specific, and Minimal responses, respectively. Participants who were treated with a drug were more likely to have a Large response (24.5% *v* 9.6%) and less likely to have a Minimal response (12.2% *v* 21.5%).

CONCLUSIONS
The trimodal response distributions suggests that about 15% of participants have a substantial antidepressant effect beyond a placebo effect in clinical trials, highlighting the need for predictors of meaningful responses specific to drug treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Clinical trials of antidepressants in major depressive disorder show substantial mean improvement with both drug and placebo
Meta-analyses have confirmed that antidepressants have greater efficacy than placebo, but the mean difference is small

WHAT THIS STUDY ADDS

After accounting for participant baseline severity, age, and sex, placebo responses and drug effects were stable over time
Antidepressants and placebo showed the same three modal responses
The small mean advantage of antidepressants is because of differences between drug and placebo in a minority of participants in the likelihood of achieving a Large response or avoiding a Minimal response

Introduction

Depression is a leading cause of disability worldwide, affecting 300 million people globally, causing a major reduction in quality of life, with domestic costs (including costs related to work) estimated at more than $210.5 (£175.3; €207.1) billion annually.[1 2] About 13% of Americans use antidepressants, and use of antidepressants in economically developed countries more than doubled between 2000 and 2015.[3 4] Although many factors affect depression and suicide rates, the hope was that wider use of antidepressants would improve these rates. Nonetheless,[5] these rates have generally increased,[6] particularly in younger age groups, highlighting the importance of understanding the magnitude and determinants of the efficacy of antidepressant drugs.

Previous reviews have assessed the effects of antidepressants by analyzing aggregate trial data[7-14] or participant level data from limited datasets. Meta-analyses have shown small mean differences between drug and placebo arms, and the clinical significance of these differences continues to be debated.[7-18] Patients do not feel the difference in response between drug and placebo (drug effect); rather, patients have an overall drug response in the context of pharmacotherapy. How much was attributable to placebo effects is unobservable. In this paper, we use the term drug or placebo response to indicate change from baseline with the drug or placebo, and the term drug or placebo effect to indicate the component specifically attributable to the drug or placebo.[19]

Lack of knowledge about the distributions of individual responses has hampered discussions of the clinical significance of mean effects. Whether treatment responses in clinical drug trials are best described by one or multiple underlying distributions

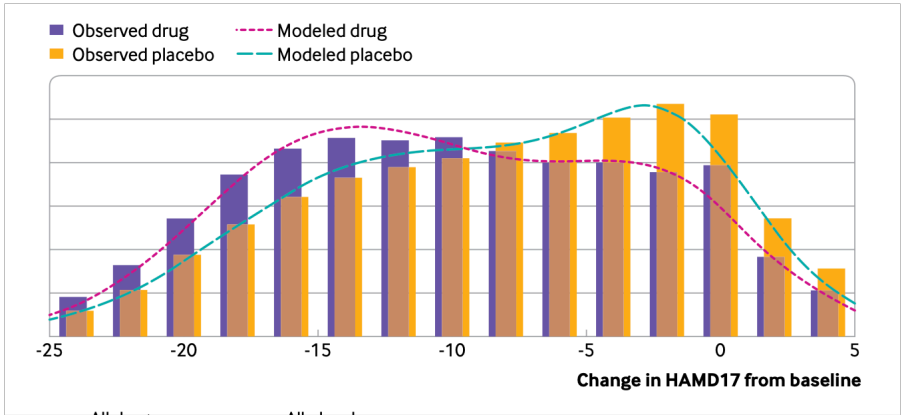
Treatment effects

The random effects mean changes (supplement eTable 2) were improvements of 9.8 points (95% confidence interval 9.5 to 10.0) with active drug and 8.0 points (7.8 to 8.3) with placebo. The difference between drug and placebo was 1.75 points (1.63 to 1.86). The magnitude of the difference was unchanged when the analysis was done separately in subgroups with native HAMD17 scores (1.75, 95% confidence interval 1.57 to 1.93; standardized mean difference 0.232, 95% confidence interval 0.210 to 0.255) and converted scores (1.75, 1.59 to 1.91; 0.245, 0.223 to 0.267).

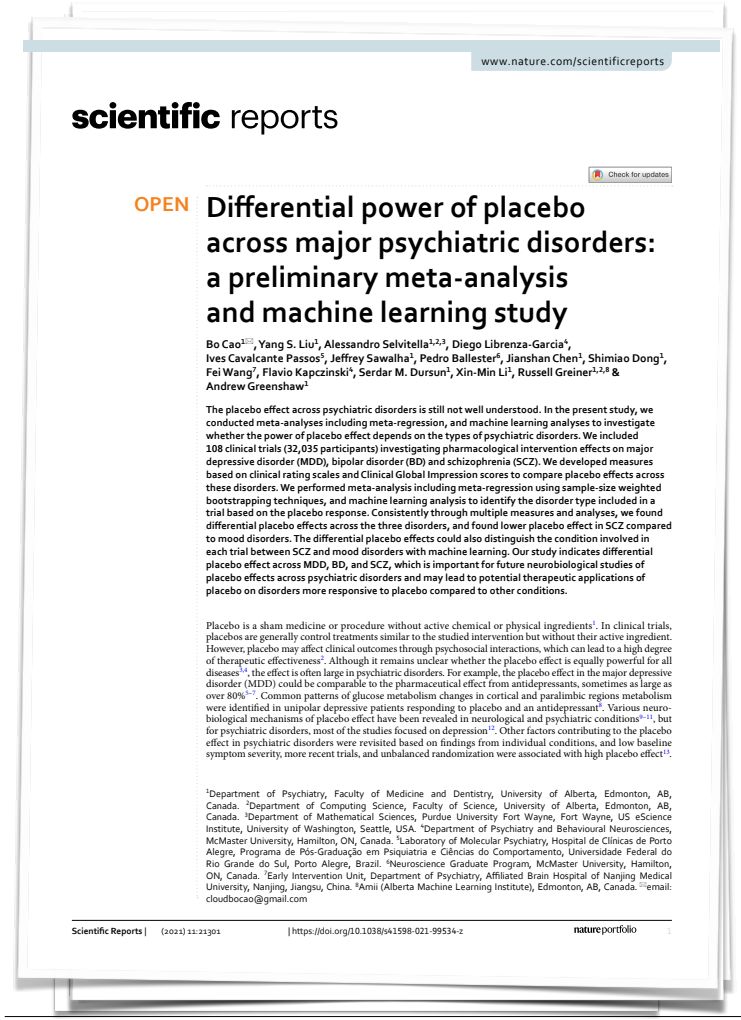
CONCLUSIONS

The trimodal response distributions suggests that about 15% of participants have a substantial antidepressant effect beyond a placebo effect in clinical trials, highlighting the need for predictors of meaningful responses specific to drug treatment.

Introduction



Placebo effect across disorders. MDD, BD, SCZ.



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Differential power of placebo across major psychiatric disorders: a preliminary meta-analysis and machine learning study

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The placebo effect across psychiatric disorders is still not well understood. In the present study, we conducted meta-analyses including meta-regression, and machine learning analyses to investigate whether the power of placebo effect depends on the types of psychiatric disorders. We included 108 clinical trials (32,035 participants) investigating pharmacological intervention effects on major depressive disorder (MDD), bipolar disorder (BD) and schizophrenia (SCZ). We developed measures based on clinical rating scales and Clinical Global Impression scores to compare placebo effects across these disorders. We performed meta-analysis including meta-regression using sample-size weighted bootstrapping techniques, and machine learning analysis to identify the disorder type included in a trial based on the placebo response. Consistently through multiple measures and analyses, we found differential placebo effects across the three disorders, and found lower placebo effect in SCZ compared to mood disorders. The differential placebo effects could also distinguish the condition involved in each trial between SCZ and mood disorders with machine learning. Our study indicates differential placebo effect across MDD, BD, and SCZ, which is important for future neurobiological studies of placebo effects across psychiatric disorders and may lead to potential therapeutic applications of placebo on disorders more responsive to placebo compared to other conditions.

Placebo is a sham medicine or procedure without active chemical or physical ingredients[1]. In clinical trials, placebos are generally control treatments similar to the studied intervention but without their active ingredient. However, placebo may affect clinical outcomes through psychosocial interactions, which can lead to a high degree of therapeutic effectiveness[2]. Although it remains unclear whether the placebo effect is equally powerful for all diseases[3,4], the effect is often large in psychiatric disorders. For example, the placebo effect in the major depressive disorder (MDD) could be comparable to the pharmaceutical effect from antidepressants, sometimes as large as over 80%[5–7]. Common patterns of glucose metabolism changes in cortical and paralimbic regions metabolism were identified in unipolar depressive patients responding to placebo and an antidepressant[8]. Various neurobiological mechanisms of placebo effect have been revealed in neurological and psychiatric conditions[9–11], but for psychiatric disorders, most of the studies focused on depression[12]. Other factors contributing to the placebo effect in psychiatric disorders were revisited based on findings from individual conditions, and low baseline symptom severity, more recent trials, and unbalanced randomization were associated with high placebo effect[13].

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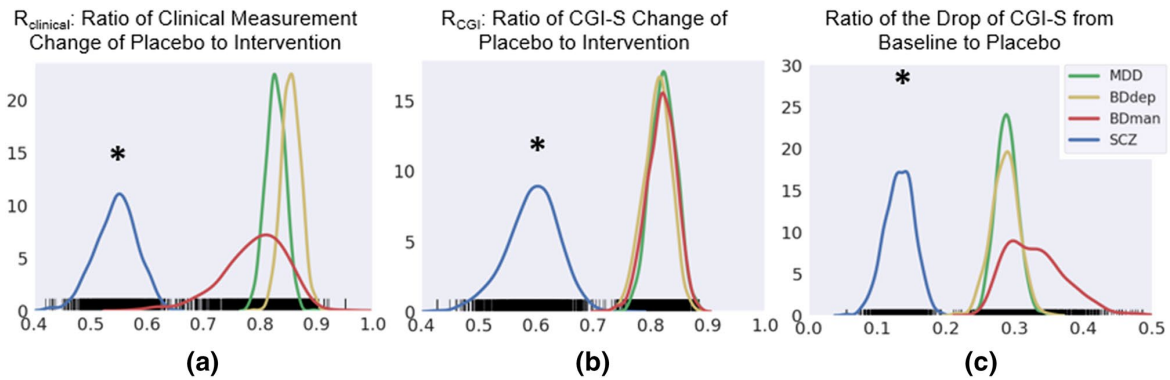
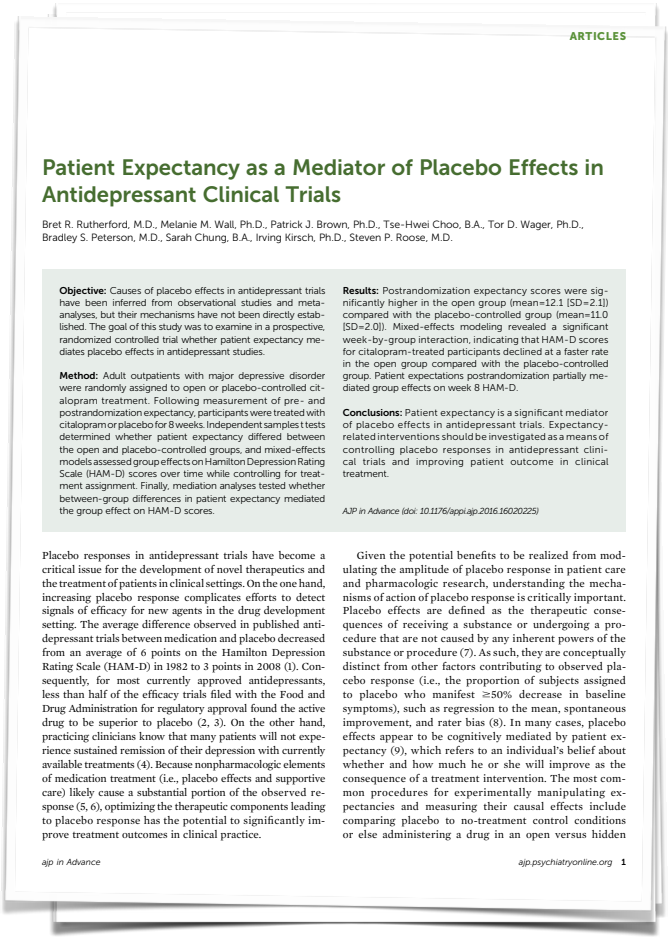
(a) $R_{clinical} = \frac{\Delta Clinical\ Scales_{Placebo}}{\Delta Clinical\ Scales_{Active\ Drug}}$, the ratio of the average clinical measurement change from baseline for placebo to the active drug; the $\Delta Clinical\ Scales$ was calculated as the baseline measurement minus the endpoint measurement to indicate a decrease of the symptoms.

(b) $R_{CGI} = \frac{\Delta CGI_{Placebo}}{\Delta CGI_{Active\ Drug}}$, the ratio of the average CGI-S change from baseline for placebo to the active drug; the ΔCGI was calculated as the baseline CGI-S minus the endpoint CGI-S to indicate a decrease of the clinical severity.

(c) $R_{CGI\ Basline} = \frac{\Delta CGI_{Placebo}}{CGI\ Basline_{Placebo}}$, the ratio of the average CGI-S decrease at the end of the study to the average CGI-S baseline for placebo.



The powerful placebo: Erwartung



ARTICLES

Patient Expectancy as a Mediator of Placebo Effects in Antidepressant Clinical Trials

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Objective: Causes of placebo effects in antidepressant trials have been inferred from observational studies and meta-analyses, but their mechanisms have not been directly established. The goal of this study was to examine in a prospective, randomized controlled trial whether patient expectancy mediates placebo effects in antidepressant studies.

Method: Adult outpatients with major depressive disorder were randomly assigned to open or placebo-controlled citalopram treatment. Following measurement of pre- and postrandomization expectancy, participants were treated with citalopram or placebo for 8 weeks. Independent samples t tests determined whether patient expectancy differed between the open and placebo-controlled groups, and mixed-effects models assessed group effects on Hamilton Depression Rating Scale (HAM-D) scores over time while controlling for treatment assignment. Finally, mediation analyses tested whether between-group differences in patient expectancy mediated the group effect on HAM-D scores.

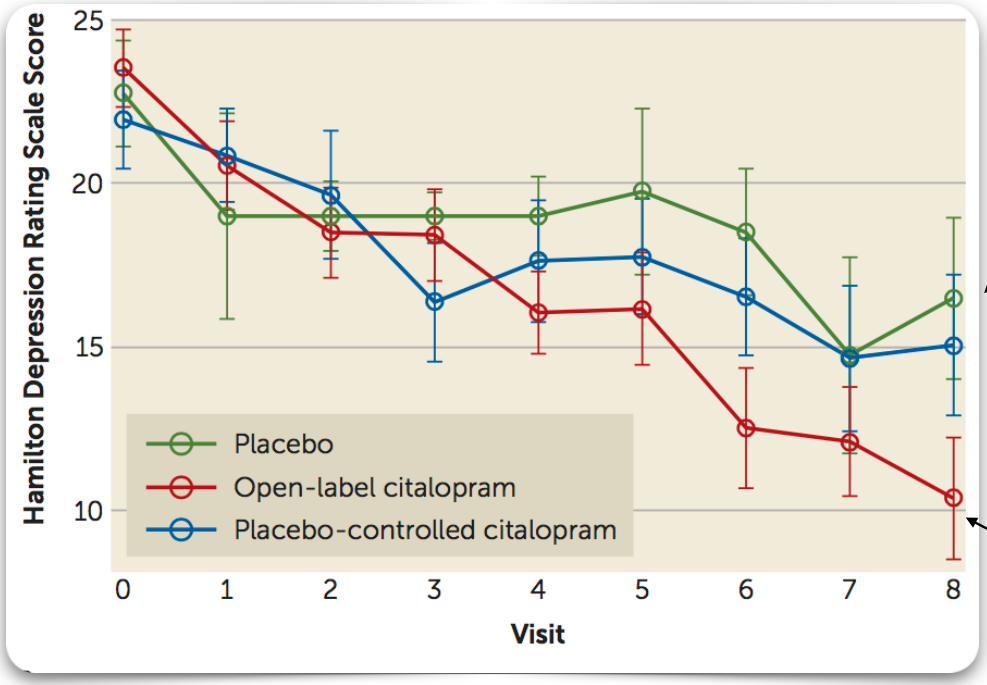
Results: Postrandomization expectancy scores were significantly higher in the open group (mean=12.1 [SD=2.1]) compared with the placebo-controlled group (mean=11.0 [SD=2.0]). Mixed-effects modeling revealed a significant week-by-group interaction, indicating that HAM-D scores for citalopram-treated participants declined at a faster rate in the open group compared with the placebo-controlled group. Patient expectations postrandomization partially mediated group effects on week 8 HAM-D.

Conclusions: Patient expectancy is a significant mediator of placebo effects in antidepressant trials. Expectancy-related interventions should be investigated as a means of controlling placebo responses in antidepressant clinical trials and improving patient outcome in clinical treatment.

AJP in Advance (doi: 10.1176/appi.ajp.2016.16020225)

Placebo responses in antidepressant trials have become a critical issue for the development of novel therapeutics and the treatment of patients in clinical settings. On the one hand, increasing placebo response complicates efforts to detect signals of efficacy for new agents in the drug development setting. The average difference observed in published antidepressant trials between medication and placebo decreased from an average of 6 points on the Hamilton Depression Rating Scale (HAM-D) in 1982 to 3 points in 2008 (1). Consequently, for most currently approved antidepressants, less than half of the efficacy trials filed with the Food and Drug Administration for regulatory approval found the active drug to be superior to placebo (2, 3). On the other hand, practicing clinicians know that many patients will not experience sustained remission of their depression with currently available treatments (4). Because nonpharmacologic elements of medication treatment (i.e., placebo effects and supportive care) likely cause a substantial portion of the observed response (5, 6), optimizing the therapeutic components leading to placebo response has the potential to significantly improve treatment outcomes in clinical practice.

Given the potential benefits to be realized from modulating the amplitude of placebo response in patient care and pharmacologic research, understanding the mechanisms of action of placebo response is critically important. Placebo effects are defined as the therapeutic consequences of receiving a substance or undergoing a procedure that are not caused by any inherent powers of the substance or procedure (7). As such, they are conceptually distinct from other factors contributing to observed placebo response (i.e., the proportion of subjects assigned to placebo who manifest ≥50% decrease in baseline symptoms), such as regression to the mean, spontaneous improvement, and rater bias (8). In many cases, placebo effects appear to be cognitively mediated by patient expectancy (9), which refers to an individual's belief about whether and how much he or she will improve as the consequence of a treatment intervention. The most common procedures for experimentally manipulating expectancies and measuring their causal effects include comparing placebo to no-treatment control conditions or else administering a drug in an open versus hidden



„Entweder Placebo oder Medikament"

50% Erwartung

„Medikament!"

100% Erwartung

Rutherford et al., 2016
Am J Psychiatry

Play the man, not the ball…

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JOURNAL OF AFFECTIVE DISORDERS

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Brief report

Psychiatrist effects in the psychopharmacological treatment of depression

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Available online 28 February 2006

Abstract

Background: The National Institutes of Mental Health's (NIMH) 1985 Treatment of Depression Collaborative Research Program (TDCRP) reported that imipramine hydrochloride with clinical management (IMI-CM) was significantly more beneficial than placebo with clinical management (PLA-CM) for individuals undergoing treatment for depression. Unfortunately, in analyzing the NIMH TDCRP data, researchers ignored the potential effect that psychiatrists have on patient outcomes, thereby assuming that psychiatrists are equally effective. However, this assumption has yet to be supported empirically. Therefore, the purpose of the current study is to examine psychiatrist effects in the NIMH TDCRP study and to compare the variation among psychiatrists to the variation between treatments.
Method: Data from 112 patients [IMI-CM (n=57, 9 psychiatrists); PLA-CM (n=55, 9 psychiatrists)] from the NIMH TDCRP study were reanalyzed using a multi-level model.
Results: The proportion of variance in the BDI scores due to medication was 3.4% ($p<.05$), while the proportion of variance in BDI scores due to psychiatrists was 9.1% ($p<.05$). The proportion of variance in the HAM-D scores due to medication was 5.9% ($p<.05$), while the proportion of variance in HAM-D scores due to psychiatrist was 6.7% ($p=.053$). Therefore, the psychiatrist effects were greater than the treatment effects.
Conclusions: In this study, both psychiatrists and treatments contributed to outcomes in the treatment of depression. However, given that psychiatrists were responsible for more of the variance in outcomes it can be concluded that effective treatment psychiatrists can, in fact, augment the effects of the active ingredients of anti-depressant medication as well as placebo.

Keywords: Psychopharmacology; Anti-depressants; Therapist effects; Depression

In 1985 the National Institute of Mental Health (NIMH) (Rockville, MD) commissioned the Treatment of Depression Collaborative Research Program (TDCRP). The dual aim of the TDCRP was to test the feasibility and value of the collaborative clinical trial model in psychotherapy research and to examine the effectiveness of two forms of psychotherapy — cognitive behavioral therapy (CBT) and interpersonal psychotherapy (IPT). These psychotherapies were further compared to both a "reference treatment condition" for which efficacy had already been established, in this case, imipramine hydrochloride with clinical management (IMI-CM) and placebo with clinical management condition (PLA-CM). In this study, IMI-CM was found to be superior to PLA-CM (Elkin et al., 1985, 1989, 1995; Elkin, 1999).

With some exceptions (i.e. Kim et al., in press), the analyses employed in the NIMH TDCRP studies have traditionally not considered the role that treatment providers play in patients' improvement (Elkin et al., 1985,

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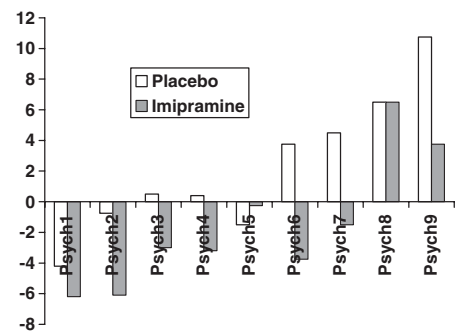

Fig. 1. BDI residual gain score as a function of type of treatment (PLA-CM v. IMI-CM) for each psychiatrist (1–9). Note that lower scores indicate better outcomes; negative residualized gain scores indicate better than average outcomes.

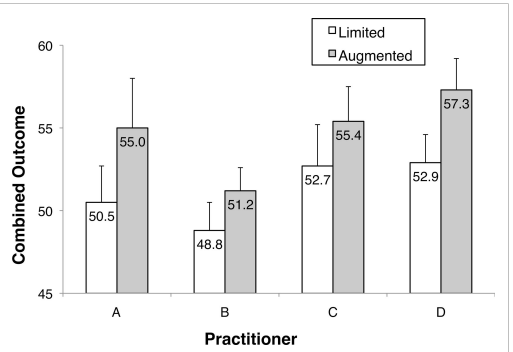

Figure 2. Practitioner effects by treatment group. Error bars represent standard error of the mean.

Patient and Practitioner Influences on the Placebo Effect in Irritable Bowel Syndrome

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Objective: To determine whether placebo responses can be explained by characteristics of the patient, the practitioner, or their interpersonal interaction. **Methods:** We performed an analysis of videotape and psychometric data from a clinical trial of patients with irritable bowel syndrome who were treated with placebo acupuncture in either a warm empathic interaction (Augmented, n = 96), a neutral interaction (Limited, n = 97), or a waitlist control (Waitlist, n = 96). We examined the relationships between the placebo response and a) patient personality and demographics; b) treating practitioner; and c) the patient-practitioner interaction as captured on videotape and rated by the Psychotherapy Process Q-Set. **Results:** Patient extraversion, agreeableness, openness to experience, and female gender were associated with placebo response, but these effects held only in the augmented group. Regression analyses controlling for all other independent variables suggest that only extraversion is an independent predictor of placebo response. There were significant differences between practitioners in outcomes; this effect was twice as large as the effect attributable to treatment group assignment. Videotape analysis indicated that the augmented group fostered a treatment relationship similar to a prototype of an ideal healthcare interaction. **Conclusions:** Personality and gender influenced the placebo response, but only in the warm, empathic, augmented group. This suggests that, to the degree a placebo effect is evoked by the patient-practitioner relationship, personality characteristics of the patient will be associated with the placebo response. In addition, practitioners differed markedly in effectiveness, despite standardized interactions. We propose that the quality of the patient-practitioner interaction accounts for the significant difference between the groups in placebo response. **Key words:** placebo effect, irritable bowel syndrome, acupuncture, personality, patient-practitioner relationship.

IBS = irritable bowel syndrome; **FFI** = Five Factor Inventory; **PQS** = Psychotherapy Process Q-Set; **M-PQS** = Modified Psychotherapy Process Q-Set.

INTRODUCTION

Patients in the placebo arms of randomized controlled trials in a variety of disorders often experience considerable clinical improvement. However, a well-publicized meta-analysis suggested that this improvement is attributable to natural history and regression to the mean rather than a placebo effect (1). Contrary to this meta-analysis, our team recently completed a trial consisting of patients with irritable bowel syndrome (IBS) that demonstrated a response to placebo beyond regression and natural history (2). The current study uses data from the parent study to determine whether particular characteristics of the patient, the practitioner, or their interpersonal interaction are associated with the placebo effect.

To date, no specific patient characteristics have been shown consistently to affect the placebo response in clinical trials (3–6). There is evidence that practitioners can have differential effects on patient outcomes in clinical trials (7–10); however, to our knowledge, no one has yet investigated practitioner influences on the placebo effect. Likewise, a great deal has been written on the importance of the patient-practitioner relationship for good clinical outcomes (11–13); however, the effect of the patient-practitioner relationship on the placebo response has not been rigorously analyzed.

In the current study, we sought to determine whether specific patient or practitioner characteristics, or the quality of their interpersonal interactions are associated with the placebo effect. To answer these questions, we used data gathered in a large (n = 289), single-center clinical trial of placebo acupuncture for the treatment of patients with IBS. Specifically, in this report, we analyzed the following three sets of variables: 1) patient personality and demographics; 2) practitioner effects; and 3) the nature of the patient-practitioner interaction as captured on videotapes of treatment sessions.

METHODS

Study Design

The parent study was a single-blind clinical trial in which 289 patients were randomized for 3 weeks to: a) Waitlist (n = 96): patient symptoms were monitored periodically but no treatment was delivered; b) Limited (n = 97): placebo acupuncture was delivered twice a week by a neutral practitioner; and c) Augmented (n = 96): placebo acupuncture was delivered twice a week by a warm, empathic practitioner. In the parent study, after the 3-week primary end point, patients were seamlessly re-randomized to either continue on placebo acupuncture or to receive genuine acupuncture. As the current report focuses on placebo effects, we report the results for the 3-week primary end point only. The three treatment groups were designed to add progressively more placebogenic elements at each level. The waitlist group was designed to control for regression to the mean and natural history, but it also provided patients with two potentially placebogenic factors: 1) attention from the study staff who conducted assessments; and 2) the expectation that they would receive genuine treatment at the conclusion of the trial. The limited group included two sessions of placebo acupuncture per week for 3 weeks with only minimal interaction with the practitioner. Finally, the augmented group also included two sessions of placebo acupuncture per week for 3 weeks; however, in contrast to the limited group, the interaction with the practitioner was warm and empathic. We hypothesized that patient improvement in response to our placebo treatments would be ordered as follows: Augmented > Limited > Waitlist. Details of this design and the clinical results have been published

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Psychotherapie und Placebo sind beides psychologische Interventionen

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REVIEW ARTICLE

Comparison of psychotherapies for adult depression to pill placebo control groups: a meta-analysis

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Background. The effects of antidepressants for treating depressive disorders have been overestimated because of selective publication of positive trials. Reanalyses that include unpublished trials have yielded reduced effect sizes. This in turn has led to claims that antidepressants have clinically insignificant advantages over placebo and that psychotherapy is therefore a better alternative. To test this, we conducted a meta-analysis of studies comparing psychotherapy with pill placebo.

Method. Ten 10 studies comparing psychotherapies with pill placebo were identified. In total, 1240 patients were included in these studies. For each study, Hedges' *g* was calculated. Characteristics of the studies were extracted for subgroup and meta-regression analyses.

Results. The effect of psychotherapy compared to pill placebo at post-test was *g* = 0.25 [95% confidence interval (CI) 0.14–0.36, I^2 = 0%, 95% CI 0–58]. This effect size corresponds to a number needed to treat (NNT) of 7.14 (95% CI 5.00–12.82). The psychotherapy conditions scored 2.66 points lower on the Hamilton Depression Rating Scale (HAMD) than the placebo conditions, and 3.20 points lower on the Beck Depression Inventory (BDI). Some indications for publication bias were found (two missing studies). We found no significant differences between subgroups of the studies and in meta-regression analyses we found no significant association between baseline severity and effect size.

Conclusions. Although there are differences between the role of placebo in psychotherapy and pharmacotherapy research, psychotherapy has an effect size that is comparable to that of antidepressant medications. Whether these effects should be deemed clinically relevant remains open to debate.

Received 11 July 2012; Revised 1 February 2013; Accepted 5 February 2013

Key words: Depression, meta-analysis, placebo, psychotherapy.

Introduction

Comparisons of psychotherapy for depression *versus* antidepressants have direct relevance to practice guidelines and to policy issues concerning deployment of clinical resources. Provision of medication and psychotherapy require different clinician training and skills and certification and licensure. However, previous estimates of the efficacy of antidepressants relative to pill placebo conditions based on published trials have been shown to be exaggerated because of selective publication. Meta-analyses incorporating data from both published and unpublished trials obtained from the US Food and Drug Administration (FDA) have yielded markedly lower estimates than those based on published data alone (Melander *et al.* 2003; Turner *et al.* 2008). Although these meta-analyses did not evaluate psychotherapy for depression, some have drawn inferences about the relative efficacy of antidepressants *versus* psychotherapy. The claim is that antidepressants have clinically insignificant advantages over pill placebo, and therefore alternative treatments such as psychotherapy should be exhausted before turning to medication for depression (Kirsch *et al.* 2008).

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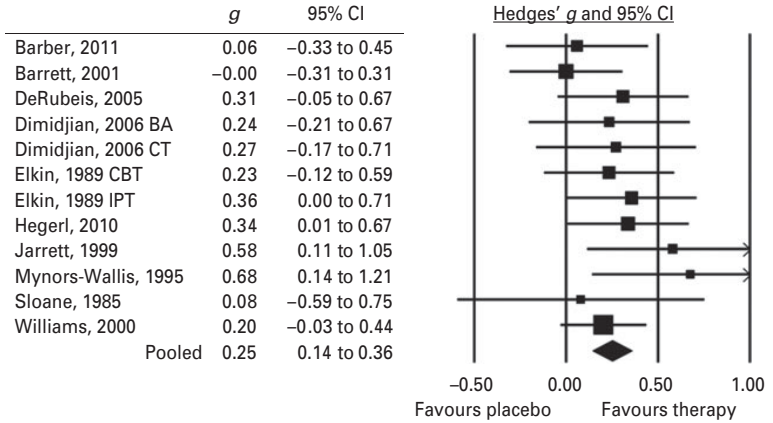

	g	95% CI
Barber, 2011	0.06	−0.33 to 0.45
Barrett, 2001	−0.00	−0.31 to 0.31
DeRubeis, 2005	0.31	−0.05 to 0.67
Dimidjian, 2006 BA	0.24	−0.21 to 0.67
Dimidjian, 2006 CT	0.27	−0.17 to 0.71
Elkin, 1989 CBT	0.23	−0.12 to 0.59
Elkin, 1989 IPT	0.36	0.00 to 0.71
Hegerl, 2010	0.34	0.01 to 0.67
Jarrett, 1999	0.58	0.11 to 1.05
Mynors-Wallis, 1995	0.68	0.14 to 1.21
Sloane, 1985	0.08	−0.59 to 0.75
Williams, 2000	0.20	−0.03 to 0.44
Pooled	0.25	0.14 to 0.36

Fig. 2. Standardized effect sizes of psychotherapy for adult depression compared with control conditions: Hedges' *g*.

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Clinical Psychology Review 32 (2012) 280–291

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Clinical Psychology Review

The efficacy of non-directive supportive therapy for adult depression: A meta-analysis

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ABSTRACT

The effects of non-directive supportive therapy (NDST) for adult depression have been examined in a considerable number of studies, but no meta-analysis of these studies has been conducted. We selected 31 studies on NDST from a comprehensive database of trials, examining psychotherapies for adult depression, and conducted meta-analyses in which NDST was compared with control groups, other psychotherapies and pharmacotherapy. We found that NDST is effective in the treatment of depression in adults (g = 0.58; 95% CI: 0.45–0.72). NDST was less effective than other psychological treatments (differential effect size g = −0.20; 95% CI: −0.32 to −0.08, p < 0.01), but these differences were no longer present after controlling for researcher allegiance. We estimated that extra-therapeutic factors (those processes operating in waiting-list and care-as-usual controls) were responsible for 33.3% of the overall improvement, non-specific factors (the effects of NDST compared with control groups) for 49.6%, and specific factors (the effects of NDST compared with other therapies) for 17.1%. NDST has a considerable effect on symptoms of depression. Most of the effect of therapy for adult depression is realized by non-specific factors, and our results suggest that the contribution of specific effects is limited at best.

Contents

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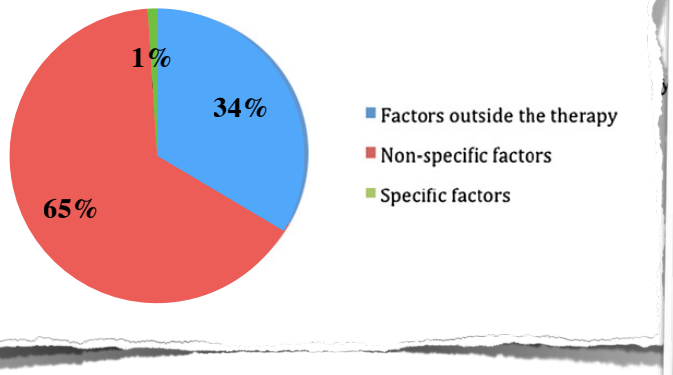

Results: We identified 146 eligible meta-analyses that synthesised data from a total of 1198 unique RCTs. Only 25 of the meta-analyses (17.2%) reported allegiance and only 6 (4.1%) used a proper method to control its effect. Of the 1198 eligible primary RCTs, 793 (66.3%) were allegiant. Authors in 25 of these 793 RCTs (3.2%) reported their allegiance while only one study (0.2%) controlled for its effect.

Open Access Research

BMJ Open

Disclosure of researcher allegiance in meta-analyses and randomised controlled trials of psychotherapy: a systematic appraisal

Elena Dragioti,[1] Ioannis Dimoliatis,[1] Evangelos Evangelou[1,2]

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► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2014-007206).

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ABSTRACT

Objective: Psychotherapy research may suffer from factors such as a researcher's own therapy allegiance. The aim of this study was to evaluate if researcher allegiance (RA) was reported in meta-analyses and randomised controlled trials (RCTs) of psychotherapeutic treatments.

Design: Systematic approach using meta-analyses of different types of psychotherapies.

Data sources: Medline, PsycINFO and Cochrane Database of Systematic Reviews.

Methods: We evaluated meta-analyses of RCTs regarding various types of psychotherapies. Meta-analyses were eligible if they included at least one RCT with RA and they were published in journals in Medline, PsycINFO and Cochrane Database of Systematic Reviews with an impact factor larger than 5.

Results: We identified 146 eligible meta-analyses that synthesised data from a total of 1198 unique RCTs. Only 25 of the meta-analyses (17.2%) reported allegiance and only 6 (4.1%) used a proper method to control its effect. Of the 1198 eligible primary RCTs, 793 (66.3%) were allegiant. Authors in 25 of these 793 RCTs (3.2%) reported their allegiance while only one study (0.2%) controlled for its effect.

Conclusions: The vast majority among a group of published meta-analyses and RCTs of psychotherapeutic treatments seldom reported and evaluated the allegiance effect. The results of the present study highlight a major lack of this information in meta-analyses and their included studies, though meta-analyses perform slightly better than RCTs. Stringent guidelines should be adopted by journals in order to improve reporting and attenuate possible effects of RA in future research.

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Strengths and limitations of this study

- Researcher allegiance is widely discussed as a potential factor that influences a researcher's actions and the reporting of results in the conducted studies. However, information on the reporting of allegiance in published meta-analyses has not yet been systematically estimated.
- This is the first research article that systematically evaluates the reporting of researcher allegiance in a large scale dataset of 146 meta-analyses and 1198 unique randomised controlled studies of psychotherapy for a broad range of outcomes.
- The criterion of selecting eligible meta-analyses based on a journal's impact factor must be considered with caution.

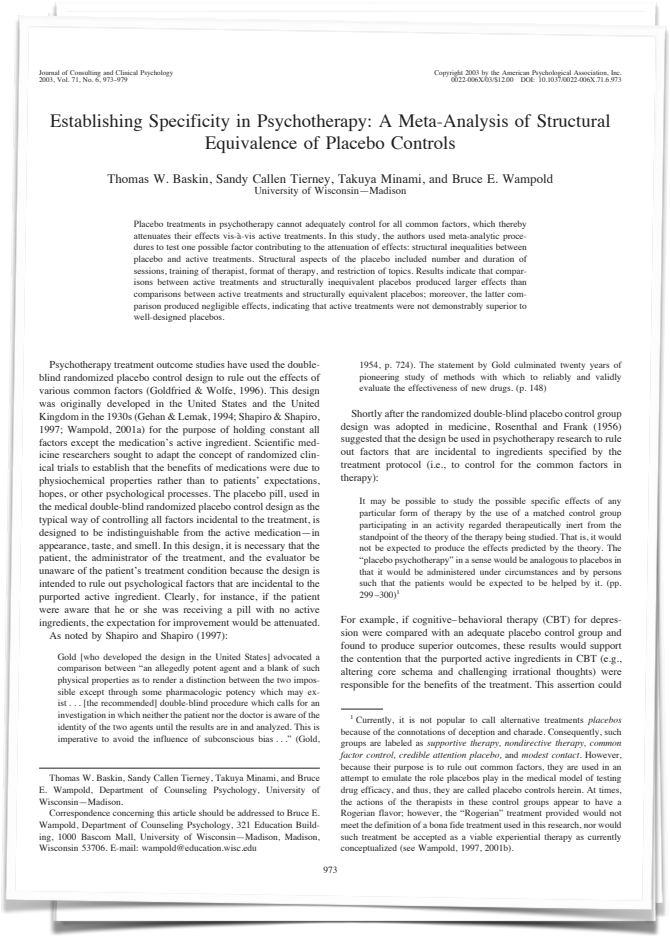
INTRODUCTION

The researcher allegiance (RA) effect is of special concern in studies that are designed to evaluate the treatment effectiveness of different forms of psychotherapy,[1–8] as the investigator may portray allegiances in particular therapies which are correlated with the pattern of the results.[9 10] RA has been defined as a researcher's 'belief in the superiority of a treatment and in the superior validity of the theory of change that is associated with the treatment' (p55).[3] Psychotherapy research was probably one of the very first fields that conceptualised potential allegiance effects for clinical interventions.[11] Luborsky *et al*[12 13] have shown that RA accounted for two-thirds of the variance in treatment effect in favour of the preferred treatment. Similar potential personal expectations and financial relationships favouring positive results have also been found to affect biomedical research.[14 15]

The contamination of RA in the psychotherapy era is a long-standing debate. Meta-analyses have found larger effect estimates in psychotherapy studies when RA is observed.[16–18] These effects are attenuated when appropriate statistical methods for controlling for RA are performed.[1 4 6 12 13 16–22] The aforementioned findings led some researchers to support the existence of allegiance bias,[1 12 13 19 21 23] which overestimates the effect and threatens the validity of the clinical trials.[1 21 23] On the other hand, other

Cuijpers et al., 2012 Clin Psych Rev

3. Psychotherapie und Placebo sind beides psychologische Interventionen



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Establishing Specificity in Psychotherapy: A Meta-Analysis of Structural Equivalence of Placebo Controls

Thomas W. Baskin, Sandy Callen Tierney, Takuya Minami, and Bruce E. Wampold
University of Wisconsin—Madison

Placebo treatments in psychotherapy cannot adequately control for all common factors, which thereby attenuates their effects vis-à-vis active treatments. In this study, the authors used meta-analytic procedures to test one possible factor contributing to the attenuation of effects: structural inequalities between placebo and active treatments. Structural aspects of the placebo included number and duration of sessions, training of therapist, format of therapy, and restriction of topics. Results indicate that comparisons between active treatments and structurally inequivalent placebos produced larger effects than comparisons between active treatments and structurally equivalent placebos; moreover, the latter comparison produced negligible effects, indicating that active treatments were not demonstrably superior to well-designed placebos.

Psychotherapy treatment outcome studies have used the double-blind randomized placebo control design to rule out the effects of various common factors (Goldfried & Wolfe, 1996). This design was originally developed in the United States and the United Kingdom in the 1930s (Gehan & Lemak, 1994; Shapiro & Shapiro, 1997; Wampold, 2001a) for the purpose of holding constant all factors except the medication's active ingredient. Scientific medicine researchers sought to adapt the concept of randomized clinical trials to establish that the benefits of medications were due to physiochemical properties rather than to patients' expectations, hopes, or other psychological processes. The placebo pill, used in the medical double-blind randomized placebo control design as the typical way of controlling all factors incidental to the treatment, is designed to be indistinguishable from the active medication—in appearance, taste, and smell. In this design, it is necessary that the patient, the administrator of the treatment, and the evaluator be unaware of the patient's treatment condition because the design is intended to rule out psychological factors that are incidental to the purported active ingredient. Clearly, for instance, if the patient were aware that he or she was receiving a pill with no active ingredients, the expectation for improvement would be attenuated. As noted by Shapiro and Shapiro (1997):

> Gold [who developed the design in the United States] advocated a comparison between "an allegedly potent agent and a blank of such physical properties as to render a distinction between the two impossible except through some pharmacologic potency which may exist . . . [the recommended] double-blind procedure which calls for an investigation in which neither the patient nor the doctor is aware of the identity of the two agents until the results are in and analyzed. This is imperative to avoid the influence of subconscious bias . . ." (Gold, 1954, p. 724). The statement by Gold culminated twenty years of pioneering study of methods with which to reliably and validly evaluate the effectiveness of new drugs. (p. 148)

Shortly after the randomized double-blind placebo control group design was adopted in medicine, Rosenthal and Frank (1956) suggested that the design be used in psychotherapy research to rule out factors that are incidental to ingredients specified by the treatment protocol (i.e., to control for the common factors in therapy):

> It may be possible to study the possible specific effects of any particular form of therapy by the use of a matched control group participating in an activity regarded therapeutically inert from the standpoint of the theory of the therapy being studied. That is, it would not be expected to produce the effects predicted by the theory. The "placebo psychotherapy" in a sense would be analogous to placebos in that it would be administered under circumstances and by persons such that the patients would be expected to be helped by it. (pp. 299–300)[1]

For example, if cognitive–behavioral therapy (CBT) for depression were compared with an adequate placebo control group and found to produce superior outcomes, these results would support the contention that the purported active ingredients in CBT (e.g., altering core schema and challenging irrational thoughts) were responsible for the benefits of the treatment. This assertion could

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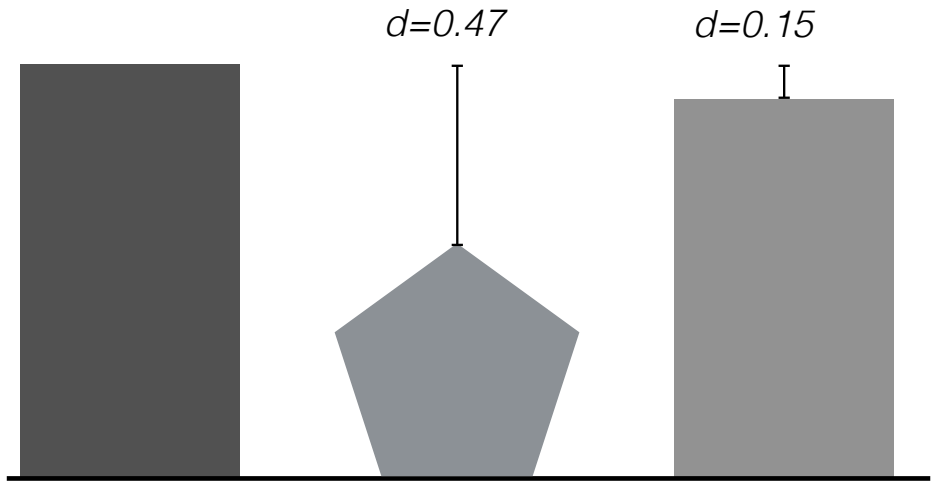
[1] Currently, it is not popular to call alternative treatments *placebos* because of the connotations of deception and charade. Consequently, such groups are labeled as *supportive therapy*, *nondirective therapy*, *common factor control*, *credible attention placebo*, and *modest contact*. However, because their purpose is to rule out common factors, they are used in an attempt to emulate the role placebos play in the medical model of testing drug efficacy, and thus, they are called placebo controls herein. At times, the actions of the therapists in these control groups appear to have a Rogerian flavor; however, the "Rogerian" treatment provided would not meet the definition of a bona fide treatment used in this research, nor would such treatment be accepted as a viable experiential therapy as currently conceptualized (see Wampold, 1997, 2001b).

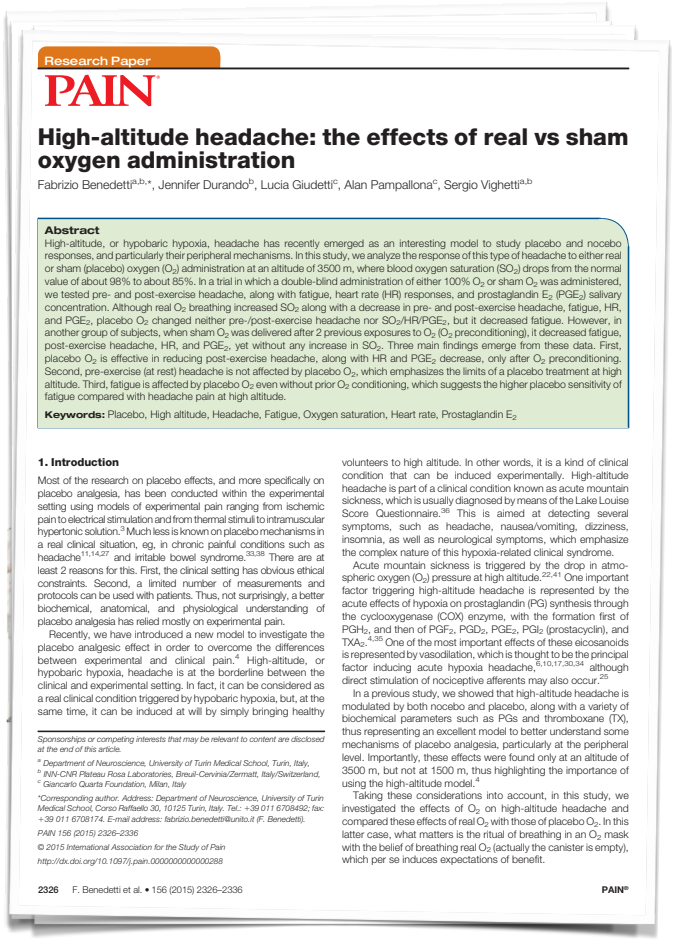


Criteria for structural equivalence

- Number, format and duration of sessions
- Training of therapists
- Topic restriction

Baskin et al. (2003). **Establishing Specificity in Psychotherapy: A Meta-Analysis of Structural Equivalence of Placebo Controls** Journal of Consulting and Clinical Psychology, 71/6, 973–979

Tief einatmen: Fake air!



Research Paper

PAIN

High-altitude headache: the effects of real vs sham oxygen administration

Fabrizio Benedetti[a,b,*], Jennifer Durando[b], Lucia Giudetti[c], Alan Pampallona[c], Sergio Vighetti[a,b]

Abstract

High-altitude, or hypobaric hypoxia, headache has recently emerged as an interesting model to study placebo and nocebo responses, and particularly their peripheral mechanisms. In this study, we analyze the response of this type of headache to either real or sham (placebo) oxygen (O_2) administration at an altitude of 3500 m, where blood oxygen saturation (SO_2) drops from the normal value of about 98% to about 85%. In a trial in which a double-blind administration of either 100% O_2 or sham O_2 was administered, we tested pre- and post-exercise headache, along with fatigue, heart rate (HR) responses, and prostaglandin E_2 (PGE_2) salivary concentration. Although real O_2 breathing increased SO_2 along with a decrease in pre- and post-exercise headache, fatigue, HR, and PGE_2, placebo O_2 changed neither pre-/post-exercise headache nor SO_2/HR/PGE_2, but it decreased fatigue. However, in another group of subjects, when sham O_2 was delivered after 2 previous exposures to O_2 (O_2 preconditioning), it decreased fatigue, post-exercise headache, HR, and PGE_2, yet without any increase in SO_2. Three main findings emerge from these data. First, placebo O_2 is effective in reducing post-exercise headache, along with HR and PGE_2 decrease, only after O_2 preconditioning. Second, pre-exercise (at rest) headache is not affected by placebo O_2, which emphasizes the limits of a placebo treatment at high altitude. Third, fatigue is affected by placebo O_2 even without prior O_2 conditioning, which suggests the higher placebo sensitivity of fatigue compared with headache pain at high altitude.

Keywords: Placebo, High altitude, Headache, Fatigue, Oxygen saturation, Heart rate, Prostaglandin E_2

1. Introduction

Most of the research on placebo effects, and more specifically on placebo analgesia, has been conducted within the experimental setting using models of experimental pain ranging from ischemic pain to electrical stimulation and from thermal stimuli to intramuscular hypertonic solution.[4] Much less is known on placebo mechanisms in a real clinical situation, eg, in chronic painful conditions such as headache[11,14,27] and irritable bowel syndrome.[33,38] There are at least 2 reasons for this. First, the clinical setting has obvious ethical constraints. Second, a limited number of measurements and protocols can be used with patients. Thus, not surprisingly, a better biochemical, anatomical, and physiological understanding of placebo analgesia has relied mostly on experimental pain.

Recently, we have introduced a new model to investigate the placebo analgesic effect in order to overcome the differences between experimental and clinical pain.[4] High-altitude, or hypobaric hypoxia, headache is at the borderline between the clinical and experimental setting. In fact, it can be considered as a real clinical condition triggered by hypobaric hypoxia, but, at the same time, it can be induced at will by simply bringing healthy volunteers to high altitude. In other words, it is a kind of clinical condition that can be induced experimentally. High-altitude headache is part of a clinical condition known as acute mountain sickness, which is usually diagnosed by means of the Lake Louise Score Questionnaire.[36] This is aimed at detecting several symptoms, such as headache, nausea/vomiting, dizziness, insomnia, as well as neurological symptoms, which emphasize the complex nature of this hypoxia-related clinical syndrome.

Acute mountain sickness is triggered by the drop in atmospheric oxygen (O_2) pressure at high altitude.[22,41] One important factor triggering high-altitude headache is represented by the acute effects of hypoxia on prostaglandin (PG) synthesis through the cyclooxygenase (COX) enzyme, with the formation first of PGH_2, and then of $PGF_{2\alpha}$, PGD_2, PGE_2, PGI_2 (prostacyclin), and TXA_2.[4,35] One of the most important effects of these eicosanoids is represented by vasodilation, which is thought to be the principal factor inducing acute hypoxia headache,[6,10,17,30,34] although direct stimulation of nociceptive afferents may also occur.[25]

In a previous study, we showed that high-altitude headache is modulated by both nocebo and placebo, along with a variety of biochemical parameters such as PGs and thromboxane (TX), thus representing an excellent model to better understand some mechanisms of placebo analgesia, particularly at the peripheral level. Importantly, these effects were found only at an altitude of 3500 m, but not at 1500 m, thus highlighting the importance of using the high-altitude model.[4]

Taking these considerations into account, in this study, we investigated the effects of O_2 on high-altitude headache and compared these effects of real O_2 with those of placebo O_2. In this latter case, what matters is the ritual of breathing in an O_2 mask with the belief of breathing real O_2 (actually the canister is empty), which per se induces expectations of benefit.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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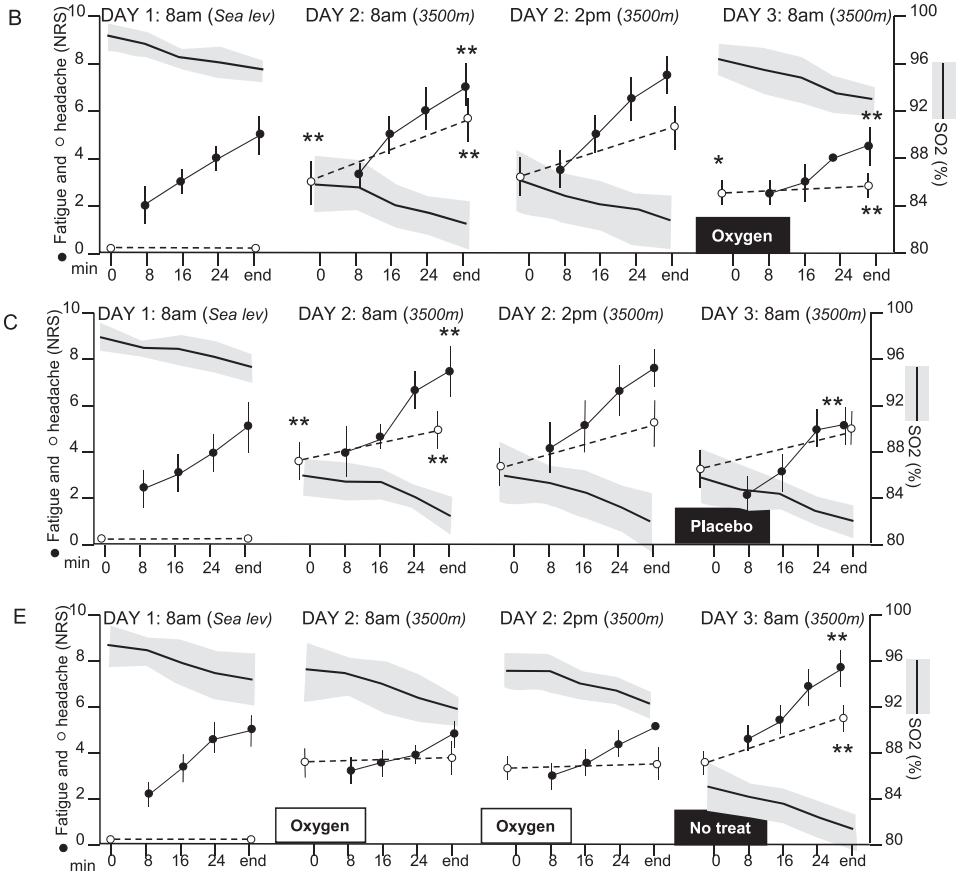
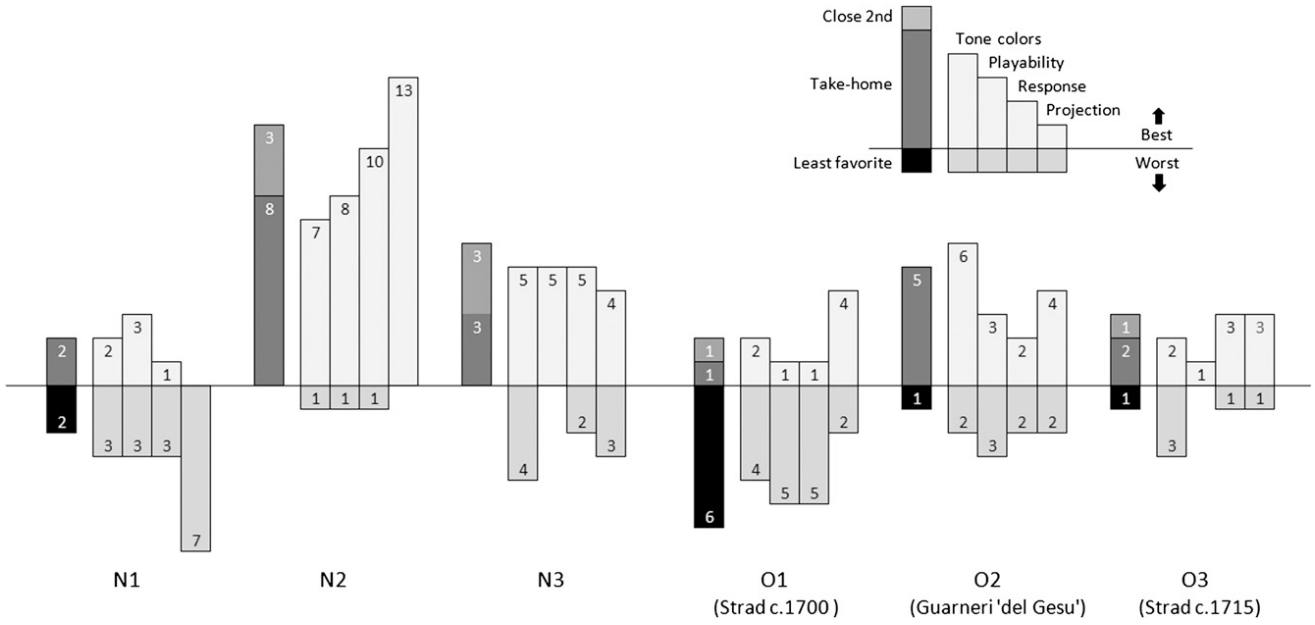


The powerful placebo: Stradivari…

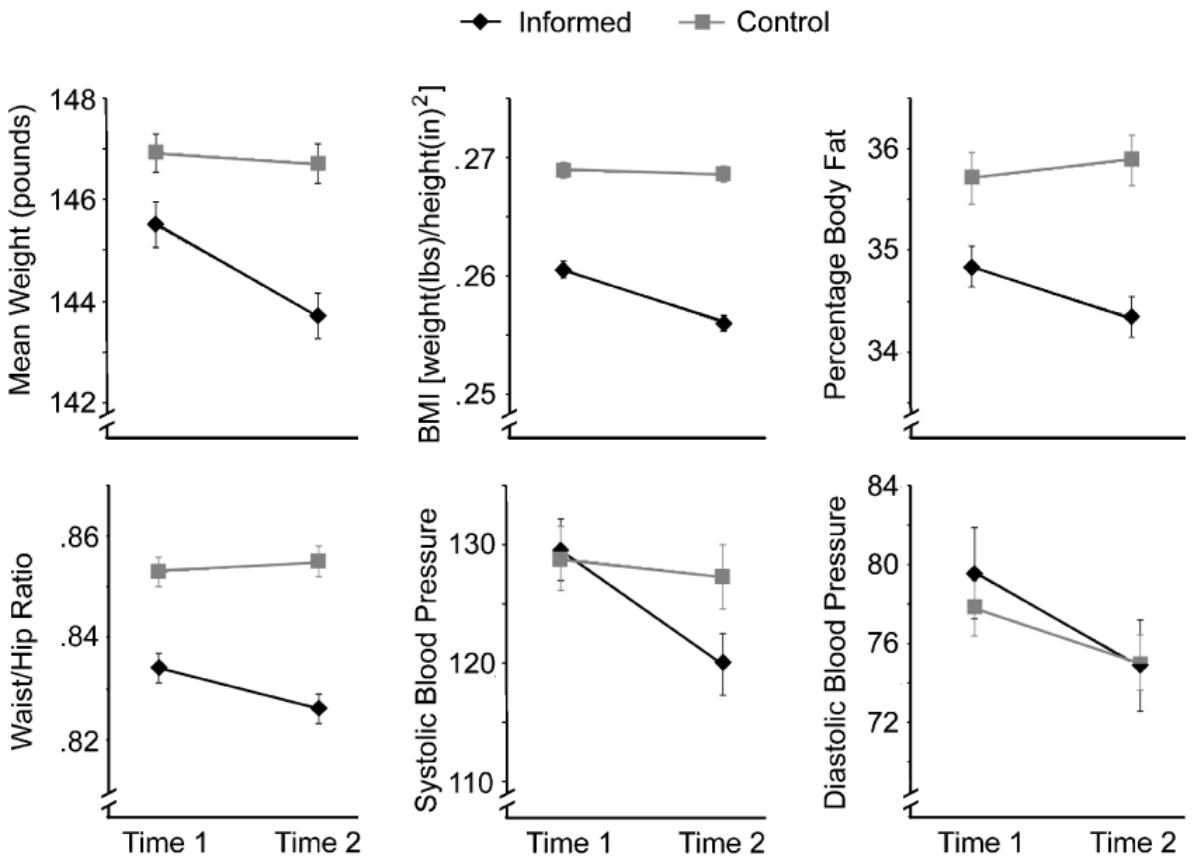


circa 100’000 Dollar

circa 10 Millionen Dollar

Fritz et al., 2012. Proceedings of the National Academy of Sciences

The powerful placebo: Putzen ist gesund…



Crum & Langer, 2007 Psych Science

In vino veritas...

Contents lists available at ScienceDirect

Food Quality and Preference

journal homepage: www.elsevier.com/locate/foodqual

Price information influences the subjective experience of wine: A framed field experiment

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ARTICLE INFO

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ABSTRACT

Past experimental laboratory and correlational data from observational research has shown that knowledge of the price of wine influences the consumer's subjective experience. However, there is limited prior research that has explicitly manipulated price information in a realistic wine tasting setting. A total of 140 participants tasted three different low-, mid- and high-priced wines with open, deceptive, or no price information and rated them for taste intensity and pleasantness. In our community sample, intensity of taste ratings for open, deceptive and blind price information reflected retail prices, thus more expensive wines were rated as more intense in taste. However, while pleasantness ratings did not differ for open and no price information, deceptive up-pricing of low-price wine significantly influenced ratings for pleasantness, whereas deceptive down-pricing of high-price wine had no effect on pleasantness ratings. Thus, pricing information differentially influences the consumer's subjective experience of wine, with no effects on intensity of taste ratings and no effects on pleasantness ratings with correct or no price information, but increased pleasantness of low-price wine when provided with a deceptive higher price. Thus, in wine may lay the truth, but its subjective experience may also lie in the price.

1. Introduction

When evaluating goods, more expensive products are assumed to have a higher intrinsic quality and should therefore lead to a superior consumer experience compared with cheaper products (Boyle & Lathrop, 2009). The assumption of a positive association between the price and intrinsic qualities of a product is central to consumer behavior and should also be true for wine.

To investigate the impact of different information on consumers evaluation of goods it is often useful, if not necessary to present deceptive information. The use of deception in research is a controversial topic in economics, with pleas to proscribed deception in experiments completely (Friedman & Sunder, 1994) to the acknowledgment of its potential benefits for the validity of data and experimental control (Bonetti, 1998). Contrary to economists, psychological researchers have embraced deception for years and developed ethical guidelines when it is acceptable to use deception. The American Psychological Association's ethical principles of psychologists and code of conduct states that deception of experimental participants is acceptable when the study's deceptive techniques are justified by the significant prospective scientific, educational, or applied value and that nondeceptive alternative procedures are not feasible (American Psychological Association, 2016).

Besides the price there are many other sources of information that can influence a consumer's expectations about the quality of a wine, like expert ratings, geographic information about the country of origin, and certification of organic production (Lockshin & Corsi, 2012). Experimental studies have demonstrated that consumers generally follow the advice of experts. When exposing wine consumers to expert opinions, Chocarro and Cortiñas (2013) have demonstrated that consumers' ratings of wine improved if exposed to positive reviews and decreased if exposed to negative reviews. Similarly using an experimental approach, Hilger, Rafert, and Villas-Boas (2010) found that demand decreases for wines scoring low according to experts and increases for average or higher scoring wines. Further, multiple studies showed the important association between consumers' wine evaluation and the wine's country or region of origin (Balestrini & Gamble, 2006; Corduas, Cinquanta, &

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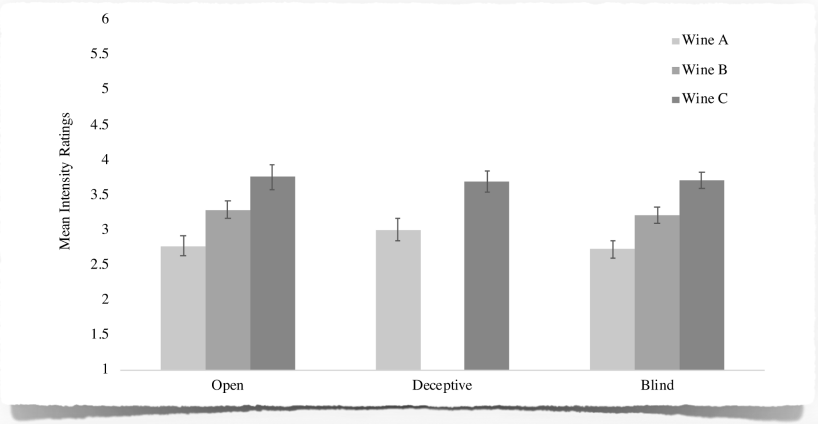

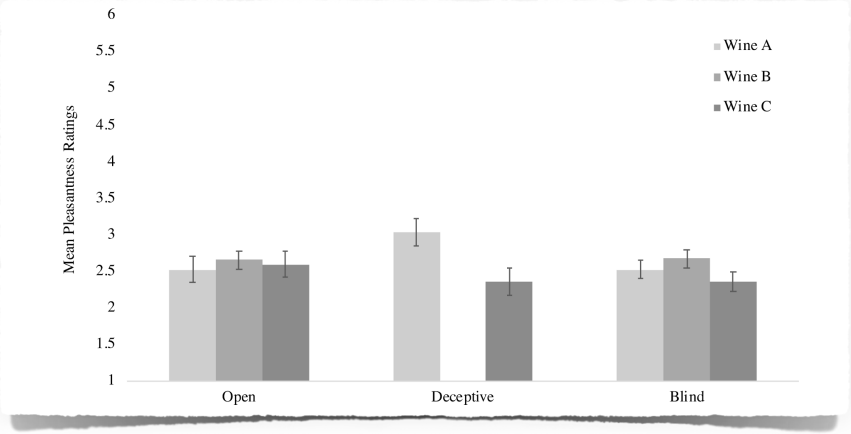

Wein 1= CHF10

Wein 2= CHF 32

Wein 3= CHF65

Werner et al., 2021, Food Quality and Preference

Anima sana in corpore sano?

Aerobic Exercise and the Placebo Effect: A Controlled Study

RAYMOND DESHARNAIS, PhD, JEAN JOBIN, PhD, CHARLES CÔTÉ, MSc,
LUCIE LÉVESQUE, MSc, AND GASTON GODIN, PhD

An experiment was conducted with 48 healthy young adults engaged in a supervised 10-week exercise program to determine whether a placebo effect is involved within the exercise-psychological enhancement connection. Based on an expectancy modification procedure, one-half of the subjects were led to believe that their program was specifically designed to improve psychological well-being (experimental condition) whereas no such intervention was made with the second half (control condition). Expectations for psychological benefits and aerobic capacity (VO_{2max}) were measured before and after completion of the program. Self-esteem, as the indicator of psychological well-being, was measured on four specific occasions: at the beginning, after the fourth and seventh weeks, and upon completion of the training program. The results showed similar significant increases in fitness levels in both conditions. Moreover, self-esteem was significantly improved over time in the experimental but not in the control condition. These findings provide evidence to support the notion that exercise may enhance psychological well-being via a strong placebo effect. Implications of the results with regard to exercise prescription are discussed.

Key words: exercise, placebo effect, self-esteem, psychological enhancement, aerobic capacity.

INTRODUCTION

Despite a growing body of popular and scientific literature supporting the notion that exercise enhances psychological well-being, the question of how this effect operates remains unanswered (1). Different physiological, biochemical, and psychological hypotheses have been proposed but at the present time, because of conceptual as well as methodological inadequacies, no single theory has received substantial empirical support (2–5). Difficulties in reaching a clear consensus around those proposed mechanisms have given additional impetus to the provocative hypothesis that exercise enhances psychological well-being via a strong placebo effect (6).

Shapiro and Shapiro (7) define a placebo as "any therapy or component of therapy that is deliberately used for its nonspecific, psychological, or psychophysiological effect, or that is used for its presumed specific effect but is without specific activity for the condition being treated" (p. 372). A placebo effect is defined as "the psychological or psychophysiological effect produced by placebos" (7) (p. 372). The placebo effect has been the subject of steadily growing interest during the last four decades (8). Since the mid-1940s, it has been common practice in medical research to test new drugs by comparing them with pharmacologically inert placebos under double-blind conditions. Similar practices have also emerged in psychotherapy research, and there has been growing recognition of the fact that the placebo effect itself is therapeutic (9). Along these lines, Shapiro and Morris (10) went as far as to claim that the "placebo effect is an important component and perhaps the entire basis for the existence, popularity, and effectiveness of numerous methods of psychotherapy" (p. 369). Initially viewed as an artefact to be controlled for, the placebo effect is now considered a powerful psychological mechanism in itself (11). Some authors have even suggested that the placebo effect should be maximized in all therapeutic treatment so as to favor patient well-being (12, 13), although no consensus has been reached regarding this position (14).

The hypothesis that a placebo effect is involved within the exercise-psychological influence cannot be ruled out at the present time, especially as current results from exercise psychology research provide some support for the presence of such a mechanism. The most widely accepted cognitively based explanation for the placebo effect is that it is based on patients' expectations of therapeutic benefit. According to Lundh (9), it is a well-established fact that medical and psychological treatments may lead to beliefs taking the form of: "this treatment is going to cure me" and such placebo beliefs, similar to Bandura's definition of outcome expectancies (15), may add to the therapeutic results. In North America, people's expectations of psychological benefit from

From the Laboratoire des sciences de l'activité physique (R.D., C.C., L.L.); Ecole des sciences infirmières (J.J., G.G.); and Institut de Cardiologie de Québec, Hôpital Laval (J.J.), Québec, Canada.
Address reprint requests to: Raymond Desharnais, PhD, Laboratoire des Sciences de l'activité physique, Universite Laval, Ste-Foy, Quebec G1K 7P4, Canada.
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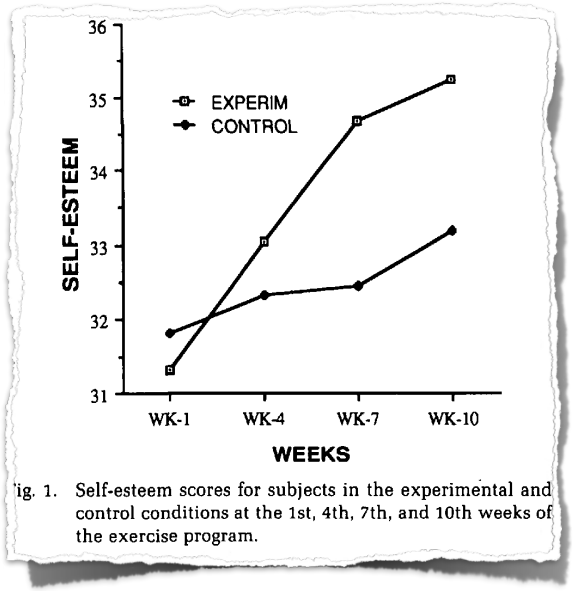


ig. 1. Self-esteem scores for subjects in the experimental and control conditions at the 1st, 4th, 7th, and 10th weeks of the exercise program.

Desharnais et al., 1993 Psysom Med

Placebo ist Psychotherapie ist Placebo

Opposing Breathing Therapies for Panic Disorder: A Randomized Controlled Trial of Lowering vs Raising End-Tidal Pco_2

Sunyoung Kim, PhD; Eileen Wollburg, PhD; and Walton T. Roth, MD

ABSTRACT

Background: Teaching anxious clients to stop hyperventilating is a popular therapeutic intervention for panic. However, evidence for the theory behind this approach is tenuous, and this theory is contradicted by an opposing theory of panic, the false-suffocation alarm theory, which can be interpreted to imply that the opposite would be helpful.

Objective: To test these opposing approaches by investigating whether either, both, or neither of the 2 breathing therapies is effective in treating patients with panic disorder.

Method: We randomly assigned 74 consecutive patients with *DSM-IV*–diagnosed panic disorder (mean age at onset = 33.0 years) to 1 of 3 groups in the setting of an academic research clinic. One group was trained to raise its end-tidal Pco_2 (partial pressure of carbon dioxide, mm Hg) to counteract hyperventilation by using feedback from a hand-held capnometer, a second group was trained to lower its end-tidal Pco_2 in the same way, and a third group received 1 of these treatments after a delay (wait-list). We assessed patients physiologically and psychologically before treatment began and at 1 and 6 months after treatment. The study was conducted from September 2005 through November 2009.

Results: Using the Panic Disorder Severity Scale as a primary outcome measure, we found that both breathing training methods effectively reduced the severity of panic disorder 1 month after treatment and that treatment effects were maintained at 6-month follow-up (effect sizes at 1-month follow-up were 1.34 for the raise-CO_2 group and 1.53 for the lower-CO_2 group; $P < .01$). Physiologic measurements of respiration at follow-up showed that patients had learned to alter their Pco_2 levels and respiration rates as they had been taught in therapy.

Conclusions: Clinical improvement must have depended on elements common to both breathing therapies rather than on the effect of the therapies themselves on CO_2 levels. These elements may have been changed beliefs and expectancies, exposure to ominous bodily sensations, and attention to regular and slow breathing.

Trial Registration: ClinicalTrials.gov identifier: NCT00183521

J Clin Psychiatry 2012;73(7):931–939

Submitted: *April 13, 2011; accepted January 27, 2012 (doi:10.4088/JCP.11m07068).*
Corresponding author: *Sunyoung Kim, PhD, Department of Psychology, University of Hawaii, Hilo, HI 96720 (skk7@hawaii.edu).*

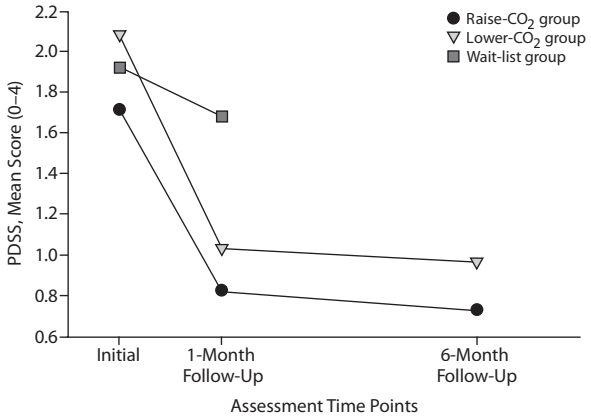
Breathing therapy has been widely used as a component of cognitive-behavioral therapy packages for panic disorder[1,2] and sometimes has been the sole component.[3–8] Generally, the rationale for breathing therapy is a hyperventilation theory of anxiety,[9–11] which assumes that hypocapnea caused by hyperventilation is associated with anxiety[12–15] (for a review, see Hardonk and Beumer[16]). To counteract hyperventilation, patients in breathing therapy are instructed to breathe slowly and abdominally, which is expected to increase Pco_2 (the partial pressure of carbon dioxide, mm Hg) to normal levels. In a recent study, we showed that a therapy teaching panic disorder patients to raise their Pco_2 using capnometer feedback was much more effective than a delayed treatment control.[6] Here we report a study comparing our original treatment to an almost identical therapy that is the theoretical opposite, in that patients are taught to lower rather than to raise their Pco_2. Raising Pco_2 has a possible rationale in the false-suffocation alarm theory,[16,17] which postulates that an overly sensitive hypothalamic mechanism produces a feeling of suffocation and panic attacks. This mechanism is triggered by rising Pco_2, to which panic disorder patients are particularly sensitive.

Evidence for and against the 2 respiratory theories has been inconclusive. The following findings support the hyperventilation theory: Voluntary hyperventilation increases anxiety in anxious patients, even triggering panic attacks.[18] Hypocapnea accompanies the panic attacks elicited by CO_2, lactate, bicarbonate, and epinephrine.[19–21] Respiratory stimulants such as doxapram and cholecystokinin can produce panic.[22,23] Hypocapnea has repeatedly emerged as a difference between panic disorder patients and comparison groups during baseline assessment.[13,24–27] However, other studies did not find baseline hypocapnea in panic disorder.[28,29] Even more problematic for hyperventilation theory is the absence of hypocapnea during many naturally occurring panic attacks. In 1 study,[30] 2 of 5 panic attacks were not accompanied by hypocapnea; in another study,[31] 8 of 15; and, in another,[32] 23 of 24. Ley[33] has suggested that perhaps only severe or initial attacks are accompanied by hyperventilation, conceding that the hyperventilation theory of anxiety is limited as an explanation of panic attacks.

Evidence for the false-suffocation alarm theory comes from diverse observations on the fear of suffocation in normal subjects and in panic patients.[16] Perhaps most convincing is the effect of CO_2 inhalation, which precipitates panic attacks in panic disorder patients. Evidence against the false-suffocation alarm theory is the existence of panic disorder patients who do not complain of dyspnea during attacks or who show no respiratory responses. This is compatible with a heterogeneity among panic patients, in that some may fit a respiratory subtype, while others do not.[24,33,34]

Both theories justify respiratory training as a treatment for panic attacks but imply opposite respiratory goals for the training to be effective. If hyperventilation theory is valid, successful prevention of hyperventilation should be necessary and sufficient for eliminating

Figure 2. Mean Scores for Panic Disorder Severity Scale (PDSS) at Pretreatment, 1-Month Follow-Up, and 6-Month Follow-Up



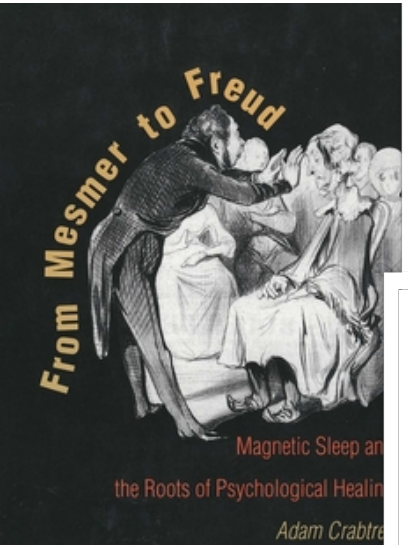
Effektstärken (Cohens d)

- Therapy A vs Waitlist: 1.53
- Therapy B vs. Waitlist: 1.34

Prädiktoren

- 1 month follow-up: Beziehung
- 6-month follow-up: Plausibilität

Kim et al., 2012 J Clin Psychiat
Kim et al., 2015 Bull Menn Clinic



Ann. N.Y. Acad. Sci. ISSN 0077-8923

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *Perspectives on the Self*

"Much ado to know myself. . .": Insight in the talking cures

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CHAPTER THIRTEEN

Placebo and Psychotherapy: Differences, Similarities, and Implications

Jens Gaab*,[1], Cosima Locher*, Charlotte Blease[†,‡]
*Clinical Psychology and Psychotherapy, University of Basel, Basel, Switzerland
[†]School of Psychology, University College Dublin, Dublin, Ireland
[‡]Program in Placebo Studies and the Therapeutic Encounter, Harvard Medical School, Boston, MA, United States
[1]Corresponding author: e-mail address: jens.gaab@unibas.ch

Contents

Placebo Insight: The Rationality of Insight-Oriented Psychotherapy

David A. Jopling
York University

It is widely believed that the insight-oriented psychotherapies provide t
clients with valid methods of self-exploration that lead to bona fide
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APA CENTENNIAL FEATURE

The Effects of Psychotherapy: An Evaluation

H. J. Eysenck
Institute of Psychiatry, Maud
University of Lond

The recommendation of the Committee on Training in Clin-
ical Psychology of the American Psychological Association re-
linical psychologists in the field of
riticized by the writer in a series of
arguments presented in favor of the
Committee, the most cogent one is
to the social need for the skills pos-
ssist. In view of the importance of the
worth while to examine the evidence
ts of psychotherapy, in an attempt to
nt of fact.

History of the Human Sciences
24(1) 95–107

Pergamon

0005-7967(94)E0008-7

Behav. Res. Ther. Vol. 32, No. 5, pp. 477–493, 1994

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INVITED ESSAY

THE OUTCOME PROBLEM IN PSYCHOTHERAPY: WHAT HAVE WE LEARNED?

H. J. EYSENCK
Department of Psychology, Institute of Psycl

Summary—The outcome problem in psychot
theories underlying the methods used. It is su
that without them we cannot even specify cr
have in essence failed to disconfirm the view
effectiveness than spontaneous remission or
spontaneous remission and placebo treatme
findings and meta-analyses published over t
remission, placebo treatment, psychotherapy
considerations and cost-effectiveness issues.

THE ROLE

In 1952, I wrote my first paper on "Th
reprinted in the *Journal of Consulting an*
Events of the intervening 40 years have beer
not caused me to change my verdict ol
psychotherapists have provided unambiguc
to no treatment, to placebo treatment or to
regarded as old-fashioned. Thus, Garfield
stated that in his opinion "Eysenck has ac
remission, the placebo response and the cc
forms of therapy" (p. 129). Similarly, Gras
Smith, Glass and Miller (1980) and Lamb
these results we can regard Eysenck's genc
done with" (p. 135)—a conclusion the truth
Even the media, with typical arrogant ig
that: "Today, researchers have enough da
1993). As the only people consulted were pr
been predicted. After all, the very existence
not expect them to imitate the lemmings! .
the concept of phlogiston to the death, long
no scientific value, so the varied theories u
and the media.
I believe that the differences between my
and others are much greater and more ser

When a Placebo Is Not a Placebo: Problems and Solutions to the Gold Standard in Psychotherapy Research

Cosima Locher[1], Jens Gaab[1] and Charlotte Blease[2,3]*
*[1] Division of Clinical Psycholc
[2] Program in Placebo Studies
School, Harvard, MA, United*

From medicine to psychotherapy: the placebo effect

Stewart Justman
University of Montana

Abstract
If placebos have been squeezed out of medicine to t
clinical trials designed to identify their own cor
nevertheless thrives in psychotherapy. Not only do
effects that are less available to medicine as it bec
preoccupied with body parts, but factors of the s
medicine have no equivalent in psychology. Medicir
effect in a way psychotherapy is not. Psychotherapy
a disconcerting paradox as successful sham surge
once pretended to treat the patient's body while a
the psychotherapist can treat the mind in all
psychotherapy is less burdened by doubts about t
come to its aid when it was orphaned by medicine
so long a history as the placebo effect to disappear

Keywords
ethics, evidence, medicine, placebo, psychotherapy

If medical history until recently is a chronicle of the
1997: 2), that does not mean the use of placebos die

VOL. 83, NO. 5 SEPT

Psychological Bulletin

Systematic Desensitization and Nonspecific Treatment Eff
A Methodological Evaluation

Alan E. Kazdin and Linda A. Wilcoxon
Pennsylvania State University

This paper evaluates the extent to which the therapeutic effects of systemat
desensitization may be attributed to a specific therapy ingredient beyond no
specific treatment effects. The vast majority of studies have not determine
empirically whether desensitization and nonspecific treatment control condition
are equal in credibility and expectancy for improvement generated in th
clients. Recent research suggests that control conditions commonly employe
in desensitization research are less credible than desensitization and general
less expectancy for improvement on the part of the clients, and that desens
tization is not superior to control groups that unambiguously rule out as
rival hypothesis differential expectancies across treatment and control cond
tions. A review of the research that has controlled for expectancies for im
provement does not support the proposition that desensitization has a specif
therapeutic ingredient. This review does not impugn the efficacy of desensitiza
tion. However, on purely methodological grounds, it appears that nonspecif
treatment effects, at least at present, cannot be ruled out in accounting for th
effects of desensitization. Strategies to control for differential credibility an
expectancies for therapeutic change generated by treatment and comparis
groups are presented.

Numerous articles on systematic desensi-
tization have appeared, including extremely
valuable reviews of the empirical literature as
well as theoretical and conceptual treatises
(Bandura, 1969; Davison & Wilson, 1973;
Jacobs & Wolpin, 1971; Murray & Jacobson,
1971; Paul, 1969a, 1969b; Rachman, 1967;

cific therapeutic ingredients be
cific treatment factors account
change. We examine from a pu
logical standpoint whether this
supported. The specific questior
whether the effects of desensiti
accounted for by some aspect

Placebo Psychotherapy: Synonym or Oxymoron?

Irving Kirsch
University of Plymouth

Contrary to some recent claims, the placebo effect is real and in some cases very substantial. Placebo effects can be produced or enhanced by classical conditioning, but consistent with virtually all contemporary conditioning theories, these effects are generally mediated by expectancy. Expectancy can also produce placebo effects that are inconsistent with conditioning history. Although expectancy also plays an important role in psychotherapy outcome, the logic of placebo-controlled trials does not map well onto psychotherapy research. The idea of evaluating the efficacy of psychotherapy by controlling for nonspecific or placebo factors is based on a flawed analogy and should be abandoned. © 2005 Wiley Periodicals, Inc. J Clin Psychol 61: 791–803, 2005.

Keywords: placebo; placebo effect; psychotherapy; expectancy; conditioning

A placebo is a sham treatment that may be used clinically to placate a patient or experimentally to establish the efficacy of a drug or other medical procedure. The placebo

Clinical ethics

Deception as treatment: the case of depression

Charlotte Blease

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Revised 7 September 2010
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20 October 2010

ABSTRACT
Is it ever right to prescribe placebos to patients in clinical practice? The General Medical Council is ambivalent about the issue; the American Medical Association asserts that placebos can be administered only if the patient is (somehow) 'informed'. The potential problem with placebos is that they may involve deception: indeed, if this is the case, an ethical tension arises over the patient's autonomy and the physician's requirement to be open and honest, and the notion that medical care should be the primary concern. This paper examines the case of depression as an entry point for understanding the complexities of the prescription of placebos. Recent important meta-analyses of antidepressants claim that they are not significantly more effective in a clinical setting than placebos. Given that antidepressants have numerous adverse side effects and are hugely expensive, this provocative research has serious potential ethical and practical implications for patients and medical providers. Should placebos be prescribed in place of antidepressants? The case of depression highlights another important issue which medical ethical codes have hitherto overlooked: well-being is not synonymous with being realistic about oneself, one's circumstances and the future. While severely depressed individuals are unduly pessimistic about themselves and the world around them, treatment of depressed individuals can be deemed successful when patients have successfully attained those positive illusions that are indicative of psychological health. This is exactly what successful psychological treatments of depression seem to achieve. It is therefore possible that there may be a limited unavoidable role for deception in medicine.

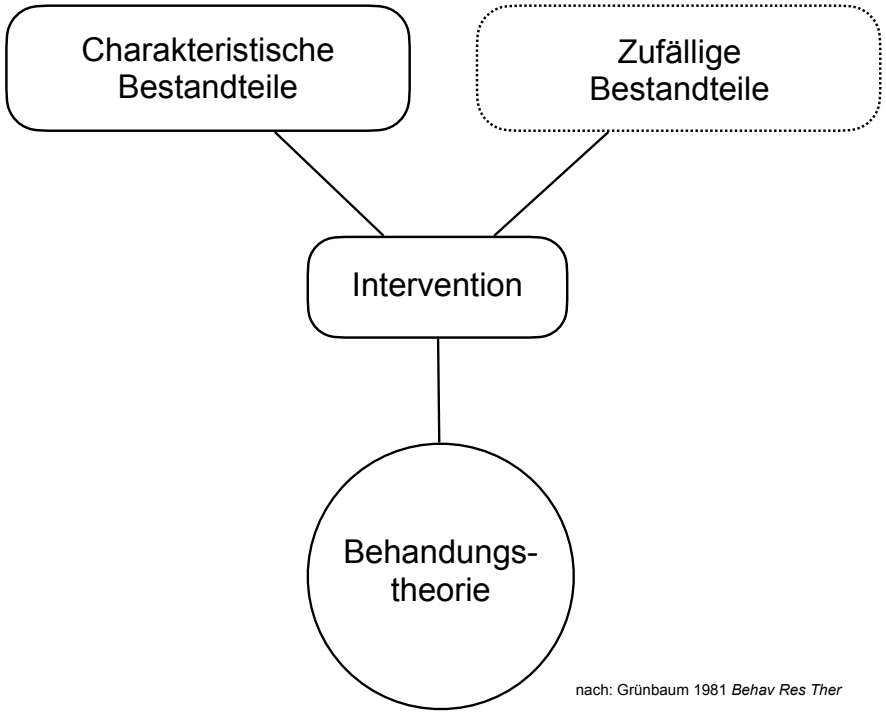
Gone are the days of 'therapeutic privilege' whereupon the physician was at liberty to withhold information from a patient. Today, patients' autonomy and openness in patient–doctor relationships are regarded as imperatives in clinical practice. The idea that a physician is permitted to deceive a patient about his or her prognosis is now deemed out of the question. The General Medical Council's (GMC's) code of ethics asserts that physicians must be satisfied that they have 'consent or other valid authority' before under-

beneficial in cases of analgesia—how should physicians proceed?[2] Does the administration of placebos breach existing ethical codes in medicine? The GMC instructs physicians to 'make the care of your patient your first concern', so does placebo usage compromise other directives on honesty?[3]

I argue that current ethical guidelines about placebo use are equivocal: medical codes explicitly rule out deception yet (doubtless because of their efficacy), placebos are not proscribed; in addition, the nature of placebo deception needs to be established. The importance of understanding the role of deception in medicine is highlighted by examining the case of depression, drawing on recent provocative research which indicates that antidepressants are not significantly more effective in a clinical setting than placebos. These findings have important repercussions for physicians; they indicate that physicians ought to weigh up the relative effectiveness of placebos with important palliative concerns about the use of antidepressants given their common side effects.

Indeed, is there any way to circumvent the problems with antidepressants by employing alternative treatments that might avoid the issue of side effects and deception? Before addressing the issue of successful alternatives, I contend that medical bodies such as the GMC and AMA need to pay much closer attention to the very nature of mental health. Well replicated evidence from social psychology indicates that positive illusions are indicative of well-being; more than this, it seems that individuals who are very mildly depressed exhibit a higher degree of realism about their lives. While it certainly appears that severely depressed individuals display highly negative illusions (ie, they are pessimistic about themselves and the world around them), it seems that *any* successful form of therapy necessarily involves some degree of deception in order to restore full health. In short, if medical bodies accept that placebos involve some form of deception and, as a result, decide to prohibit their usage, this will also rule out the successful treatment of depression, *tout court*. In fact, the current most successful forms of treatment for depression appear to involve methods which instil those optimistic illusions that are

Definition. What ist eigentlich ein Placebo?



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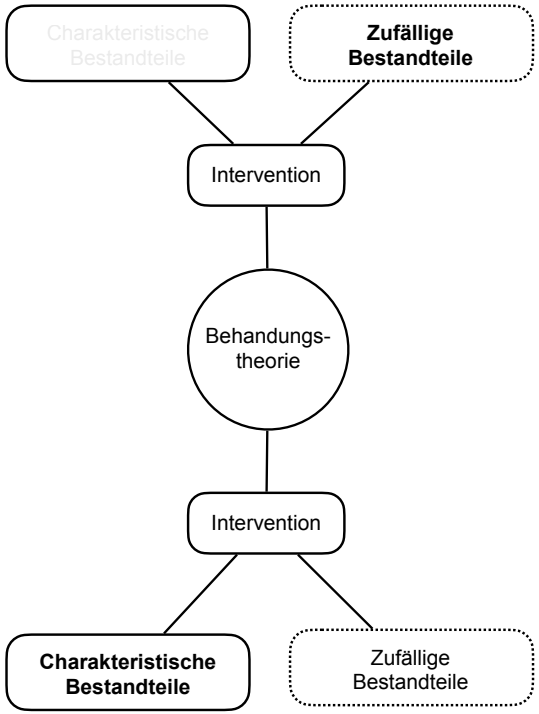
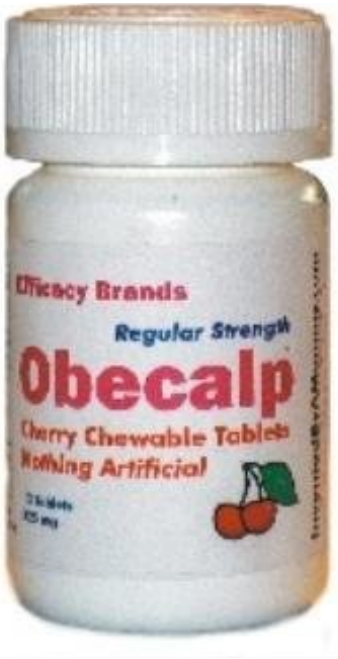


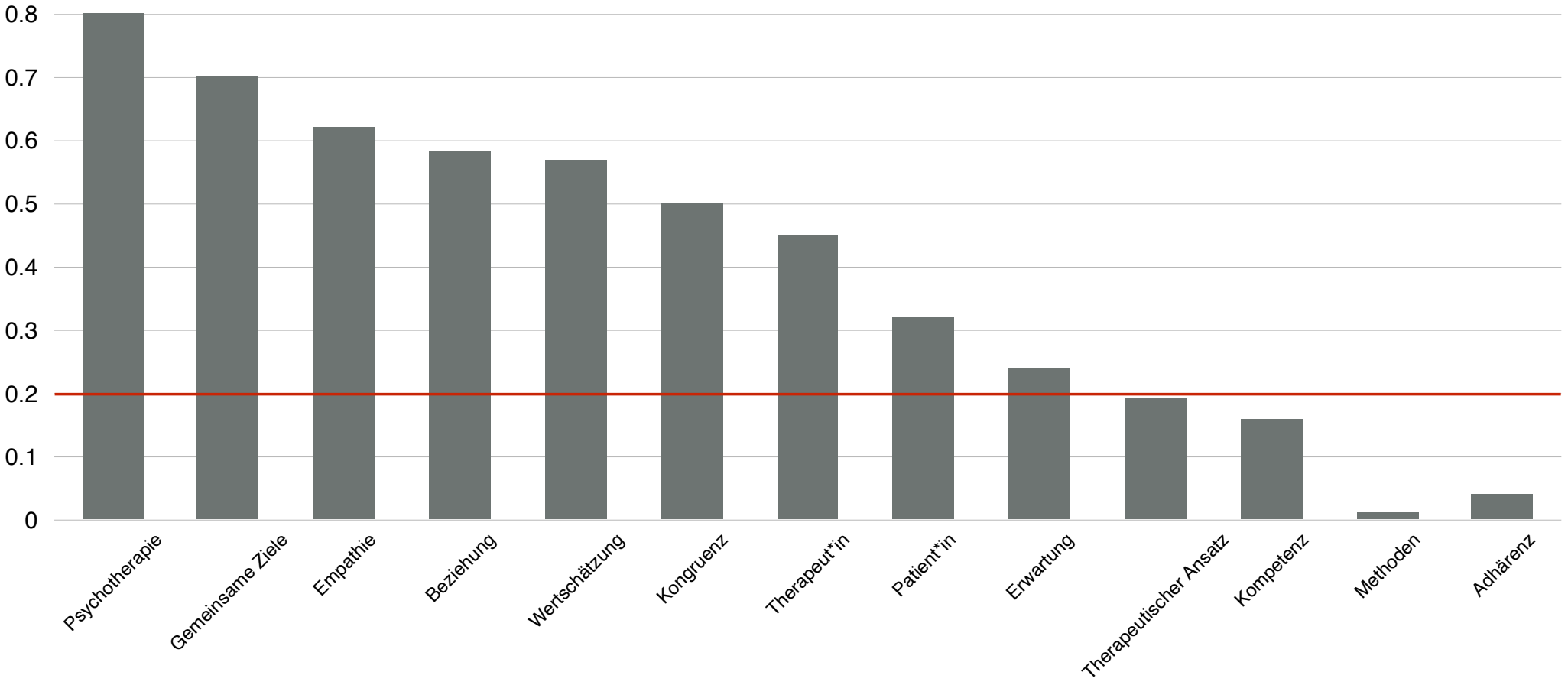
Placebo

Verum

Placebo is not a placebo



Therapeutische Faktoren in der Psychotherapie



Wampold & Imel, 2015

Psychotherapie und Placebo sind beides psychologische Interventionen

The old debate about whether or not psychotherapy and placebos have similar mechanisms consists of ascertaining whether psychotherapy is nothing but a placebo effect, and thus whether **a placebo procedure is a very simple form of psychotherapy.**

Benedetti (2009). **Placebo Effects: Understanding the Mechanisms in Health and Disease.**
Oxford University Press, p.141-143

There is a problem with identifying psychotherapy with the placebo effect. A placebo is something that is sham, fake, false, inert, and empty. **Psychotherapy is none of these.**

Kirsch (2005). **Placebo Psychotherapy: Synonym or Oxymoron?**
J Clin Psychology Vol. 61(7), 791–803

Was wirkt, ist nicht immer gut

Placebo. *Nichts* wirkt besser, aber *nichts* ist verboten.

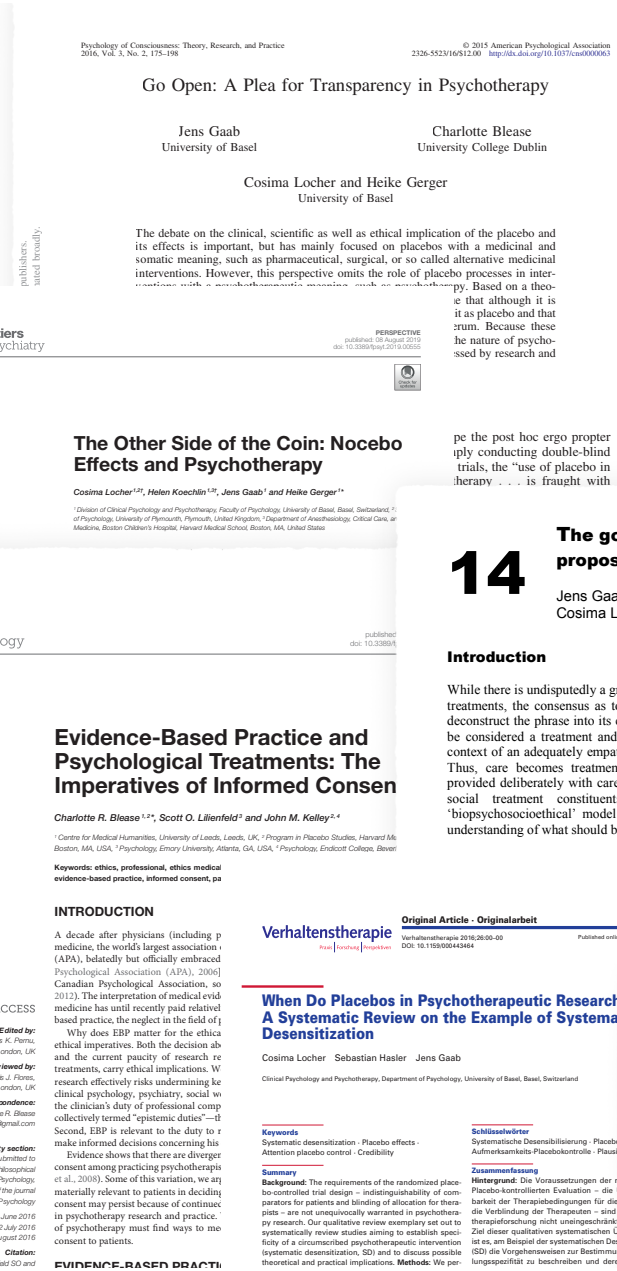
Autonomie
- freie Entscheidung
- informierte Einwilligung
- Werte, Präferenzen und Wünsche von Patient:innen

Non-Maleffizienz
- primum non nocere

Benefizienz
- Sorgepflicht
- Abwägung von Risiken und Benefits

Gerechtigkeit
- Alle müssen behandelt werden

sensu Beauchamp & Childress, 2012



Psychology of Consciousness: Theory, Research, and Practice
2016, Vol. 3, No. 2, 175–198

2326-5523/16/$12.00 http://dx.doi.org/10.1037/cns0000063

Go Open: A Plea for Transparency in Psychotherapy

Jens Gaab
University of Basel

Charlotte Blease
University College Dublin

Cosima Locher and Heike Gerger
University of Basel

The debate on the clinical, scientific as well as ethical implication of the placebo and its effects is important, but has mainly focused on placebos with a medicinal and somatic meaning, such as pharmaceutical, surgical, or so called alternative medicinal interventions. However, this perspective omits the role of placebo processes in inter-

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PERSPECTIVE
published: 08 August 2019
doi: 10.3389/fpsyt.2019.00555

Check for updates

The Other Side of the Coin: Nocebo Effects and Psychotherapy

Cosima Locher[1,2†], Helen Koechlin[1,3†], Jens Gaab[1] and Heike Gerger[1]*

[1] Division of Clinical Psychology and Psychotherapy, Faculty of Psychology, University of Basel, Basel, Switzerland, [2] ... of Psychology, University of Plymouth, Plymouth, United Kingdom, [3] Department of Anesthesiology, Critical Care, ... Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA, United States

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trials, the "use of placebo in
herapy . . . is fraught with

ogy

published:
doi: 10.3389/f

Evidence-Based Practice and Psychological Treatments: The Imperatives of Informed Consen

Charlotte R. Blease[1,2], Scott O. Lilienfeld[3] and John M. Kelley[2,4]*

[1] Centre for Medical Humanities, University of Leeds, Leeds, UK, [2] Program in Placebo Studies, Harvard Me... Boston, MA, USA, [3] Psychology, Emory University, Atlanta, GA, USA, [4] Psychology, Endicott College, Bever...

Keywords: ethics, professional, ethics medical evidence-based practice, informed consent, pa...

INTRODUCTION

A decade after physicians (including p... medicine, the world's largest association ... (APA), belatedly but officially embraced ... Psychological Association (APA), 2006]; ... Canadian Psychological Association, so... 2012). The interpretation of medical evid... medicine has until recently paid relative... based practice, the neglect in the field of ...

Why does EBP matter for the ethica... ethical imperatives. Both the decision ab... and the current paucity of research re... treatments, carry ethical implications. W... research effectively risks undermining ke... clinical psychology, psychiatry, social w... the clinician's duty of professional comp... collectively termed "epistemic duties"—th...

Second, EBP is relevant to the duty to r... make informed decisions concerning his...

Evidence shows that there are diverger... consent among practicing psychotherapis... et al., 2008). Some of this variation, we ar... materially relevant to patients in decidin... consent may persist because of continuec... in psychotherapy research and practice. ... of psychotherapy must find ways to me... consent to patients.

EVIDENCE-BASED PRACTI...

Verhaltenstherapie
Praxis | Forschung | Perspektiven

Original Article · Originalarbeit

Verhaltenstherapie 2016;26:00–00
DOI: 10.1159/000443464

Published online: January 28, 2016

When Do Placebos in Psychotherapeutic Research ... A Systematic Review on the Example of Systema... Desensitization

Cosima Locher Sebastian Hasler Jens Gaab

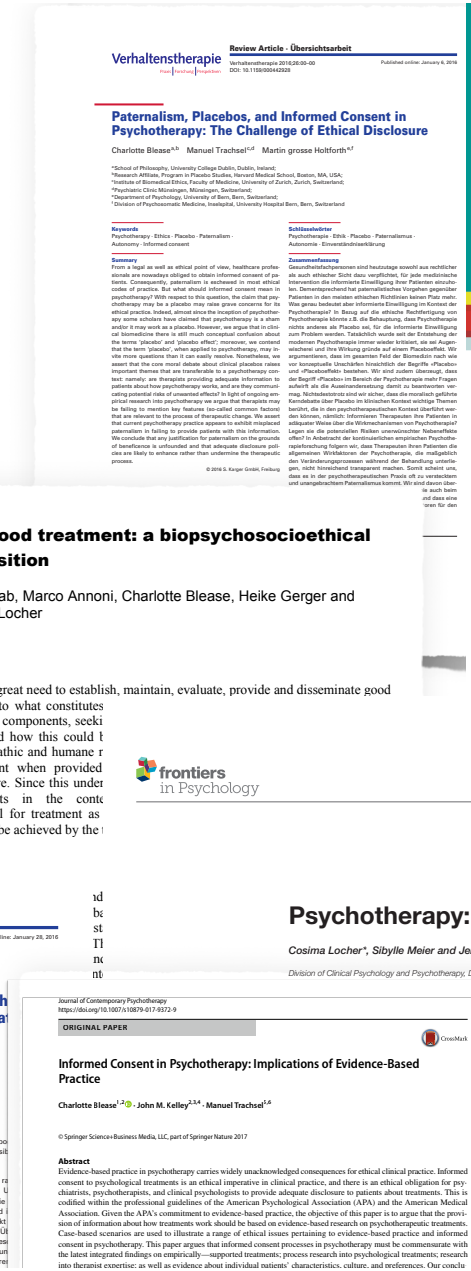
Clinical Psychology and Psychotherapy, Department of Psychology, University of Basel, Basel, Switzerland

Keywords
Systematic desensitization · Placebo effects · Attention placebo control · Credibility

Schlüsselwörter
Systematische Desensibilisierung · Placebo... Aufmerksamkeits-Placebokontrolle · Plausib...

Summary
Background: The requirements of the randomized place-bo-controlled trial design – indistinguishability of com-parators for patients and blinding of allocation for thera-pists – are not unequivocally warranted in psychothera-py research. Our qualitative review exemplary set out to systematically review studies aiming to establish speci-ficity of a circumscribed psychotherapeutic intervention (systematic desensitization, SD) and to discuss possible theoretical and practical implications. **Methods:** We per-

Zusammenfassung
Hintergrund: Die Voraussetzungen der r... Placebo-kontrollierten Evaluation – die U... barkeit der Therapiebedingungen für die ... die Verblindung der Therapeuten – sind ... therapieforschung nicht uneingeschränkt ... Ziel dieser qualitativen systematischen Ü... ist es, am Beispiel der systematischen Des... (SD) die Vorgehensweisen zur Bestimmun... lungsspezifität zu beschreiben und dere...



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Paternalism, Placebos, and Informed Consent in Psychotherapy: The Challenge of Ethical Disclosure

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Keywords
Psychotherapy · Ethics · Placebo · Paternalism · Autonomy · Informed consent

Schlüsselwörter
Psychotherapie · Ethik · Placebo · Paternalismus · Autonomie · Einwilligungsaufklärung

Summary
From a legal as well as ethical point of view, healthcare profes-sionals are nowadays obliged to obtain informed consent of pa-tients. Consequently, paternalism is eschewed in most ethical codes of practice. But what should informed consent mean in psychotherapy? With respect to this question, the claim that psy-chotherapy may be a placebo may raise grave concerns for its ethical practice. Indeed, almost since the inception of psychother-apy some scholars have claimed that psychotherapy is a sham and/or it may work as a placebo. However, we argue that in clini-cal biomedicine there is still much conceptual confusion about the terms 'placebo' and 'placebo effect'; moreover, we contend that the term 'placebo', when applied to psychotherapy, may in-vite more questions than it can easily resolve. Nonetheless, we assert that the core moral debate about clinical placebos raises important themes that are transferable to a psychotherapy con-text: namely: are therapists providing adequate information to patients about how psychotherapy works, and are they communi-cating potential risks of unwanted effects? In light of ongoing em-pirical research into psychotherapy we argue that therapists may be failing to mention key features (so-called common factors) that are relevant to the process of therapeutic change. We assert that current psychotherapy practice appears to exhibit misplaced paternalism in failing to provide patients with this information. We conclude that any justification for paternalism on the grounds of beneficence is unfounded and that adequate disclosure poli-cies are likely to enhance rather than undermine the therapeutic process.

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Zusammenfassung
Gesundheitsfachpersonen sind heutzutage sowohl aus rechtlicher als auch ethischer Sicht dazu verpflichtet, für jede medizinische Intervention die informierte Einwilligung ihrer Patienten einzuho-len. Dementsprechend hat paternalistisches Vorgehen gegenüber Patienten in den meisten ethischen Richtlinien keinen Platz mehr. Was genau bedeutet aber informierte Einwilligung im Kontext der Psychotherapie? In Bezug auf die ethische Rechtfertigung von Psychotherapie könnte z.B. die Behauptung, dass Psychotherapie nichts anderes als Placebo sei, für die informierte Einwilligung zum Problem werden. Tatsächlich wurde seit der Entstehung der modernen Psychotherapie immer wieder kritisiert, sie sei Augen-wischerei und ihre Wirkung gründe auf einem Placeboeffekt. Wir argumentieren, dass im gesamten Feld der Biomedizin nach wie vor konzeptuelle Unschärfen hinsichtlich der Begriffe «Placebo» und «Placeboeffekt» bestehen. Wir sind zudem überzeugt, dass der Begriff «Placebo» im Bereich der Psychotherapie mehr Fragen aufwirft als die Auseinandersetzung damit zu beantworten ver-mag. Nichtsdestotrotz sind wir sicher, dass die moralisch gefühlte Kernddatte über Placebo im klinischen Kontext wichtige Themen berührt, die in den psychotherapeutischen Kontext übertitrt wer-den können, nämlich: Informieren Therapeuten ihre Patienten in adäquater Weise über die Wirkmechanismen von Psychotherapie? Legen sie die potenziellen Risiken unerwünschter Nebeneffekte offen? In Anbetracht der kontinuierlichen empirischen Psychothe-rapieforschung folgern wir, dass Therapeuten ihren Patienten die allgemeinen Wirkfaktoren der Psychotherapie, die maßgeblich den Veränderungsprozessen während der Behandlung unterlie-gen, nicht hinreichend transparent machen. Somit scheint uns, dass es in der psychotherapeutischen Praxis oft zu versteckten und unangebrachten Paternalismus kommt. Wir sind davon über-

Psychotherapie-Ethik

Manuel Trachsel
Jens Gaab
Nikola Biller-Andorno

Standards der Psychotherapie

Controlling for the Placebo Effect in Psychotherapy: Noble Quest or Tilting at Windmills?

Irving Kirsch
Harvard Medical School

Bruce Wampold
University of Wisconsin–Madison and Modum Bad Psychiatric Center, Vikersund, Norway

John M. Kelley
Endicott College and Harvard Medical School

This study explores the conceptual relationship between the placebo effect and psy-chotherapy. There is considerable evidence that the placebo effect can be exceptionally powerful under some circumstances. This begs the question: How much of the effec-tiveness of psychotherapy is attributable to the placebo effect? In an effort to answer this question, researchers have attempted to design sham psychotherapies for use in randomized, controlled trials. However, these efforts to develop placebo psychothera-pies have been plagued by definitional and conceptual problems. In the context of medical treatment, placebo effects are relatively easy to define. The placebo effect in medicine is produced by factors other than the physical properties of the treatment. However, the effect of psychotherapy is—by definition of the term psychotherapy—produced by something other than the physical properties of the treatment. Therefore, using the medical definition of placebo, the effects of psychotherapy are ipso facto placebo effects, and psychotherapy is ipso facto a placebo. The problem is that the definition of placebo in medicine does not map well onto the domain of psychother-

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The Oxford Handbook of PSYCHOTHERAPY ETHICS

frontiers in Psychology

CONCEPTUAL ANALYSIS
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14 The good treatment: a biopsychosocioethical proposition

Jens Gaab, Marco Annoni, Charlotte Blease, Heike Gerger and Cosima Locher

Introduction

While there is undisputedly a great need to establish, maintain, evaluate, provide and disseminate good treatments, the consensus as to what constitutes ... deconstruct the phrase into its components, seeki... be considered a treatment and how this could b... context of an adequately empathic and humane r... Thus, care becomes treatment when provided ... provided deliberately with care. Since this under... social treatment constituents in the conte... 'biopsychosocioethical' model for treatment as ... understanding of what should be achieved by the ...

Psychotherapy: A World of Meanings

Cosima Locher, Sibylle Meier and Jens Gaab*

Division of Clinical Psychology and Psychotherapy, Department of Psychology, University of Basel, Basel, Switzerland

...y is an effective psychological intervention, ... change are still in debate. It has been ...ovide a context which enables clients to ... symptoms in such a way as to help clients ...ever, psychotherapy is not the only health ...h "meaning": the reason why placebo has ...ning response." Thus, it has been argued ... impact on beneficial (and by extension, ...e strong empirical support of a contextual ...s, the aim of this conceptual analysis is to ...ation in psychotherapy—in general—and ...herapy modalities.

...lacebo

Journal of Contemporary Psychotherapy
https://doi.org/10.1007/s10879-017-9372-9

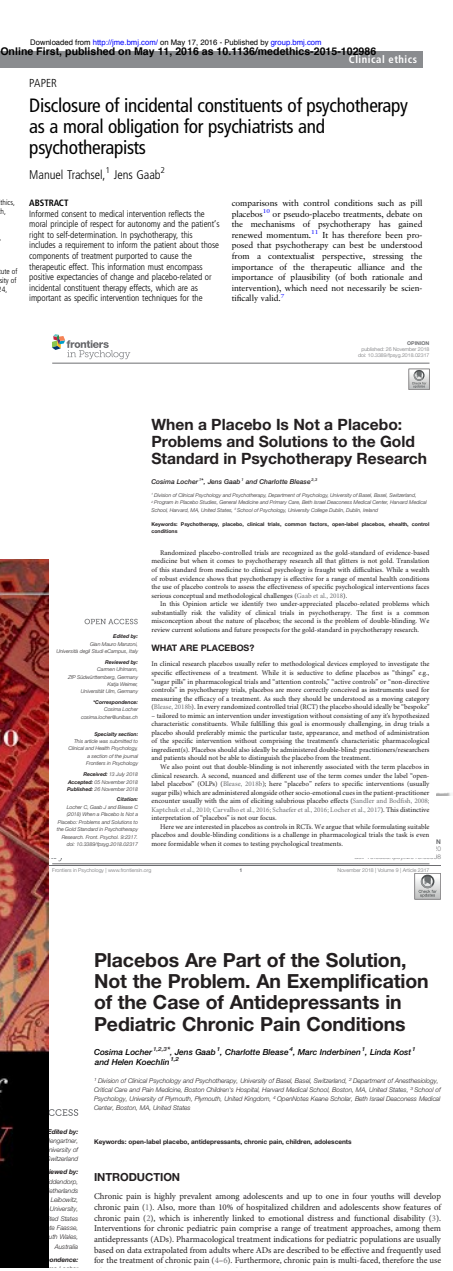
ORIGINAL PAPER

CrossMark

Informed Consent in Psychotherapy: Implications of Evidence-Based Practice

Charlotte Blease[1,2] · John M. Kelley[2,3,4] · Manuel Trachsel[5,6]

Abstract
Evidence-based practice in psychotherapy carries widely unacknowledged consequences for ethical clinical practice. Informed consent to psychological treatments is an ethical imperative in clinical practice, and there is an ethical obligation for psy-chiatrists, psychotherapists, and clinical psychologists to provide adequate disclosure to patients about treatments. This is codified within the professional guidelines of the American Psychological Association (APA) and the American Medical Association. Given the APA's commitment to evidence-based practice, the objective of this paper is to argue that the provi-sion of information about how treatments work should be based on evidence-based research on psychotherapeutic treatments. Case-based scenarios are used to illustrate a range of ethical issues pertaining to evidence-based practice and informed consent in psychotherapy. This paper argues that informed consent processes in psychotherapy must be commensurate with the latest integrated findings on empirically—supported treatments; process research into psychological treatments; research into therapist expertise: as well as evidence about individual patients' characteristics, culture, and preferences. Our conclu-



JME Online First, published on May 11, 2016 as 10.1136/medethics-2015-102986

Clinical ethics

PAPER

Disclosure of incidental constituents of psychotherapy as a moral obligation for psychiatrists and psychotherapists

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ABSTRACT
Informed consent to medical intervention reflects the moral principle of respect for autonomy and the patient's right to self-determination. In psychotherapy, this includes a requirement to inform the patient about those components of treatment purported to cause the therapeutic effect. This information must encompass positive expectancies of change and placebo-related or incidental constituent therapy effects, which are as important as specific intervention techniques for the comparisons with control conditions such as pill placebos[10] or pseudo-placebo treatments, debate on the mechanisms of psychotherapy has gained renewed momentum.[11] It has therefore been pro-posed that psychotherapy can best be understood from a contextualist perspective, stressing the importance of the therapeutic alliance and the importance of plausibility (of both rationale and intervention), which need not necessarily be scien-tifically valid.[7]

frontiers in Psychology

OPINION
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When a Placebo Is Not a Placebo: Problems and Solutions to the Gold Standard in Psychotherapy Research

Cosima Locher[1], Jens Gaab[1] and Charlotte Blease[2,3]*

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Keywords: Psychotherapy, placebo, clinical trials, common factors, open-label placebos, ehealth, control conditions

Randomized placebo-controlled trials are recognized as the gold-standard of evidence-based medicine but when it comes to psychotherapy research all that glitters is not gold. Translation of this standard from medicine to clinical psychology is fraught with difficulties. While a wealth of robust evidence shows that psychotherapy is effective for a range of mental health conditions the use of placebo controls to assess the effectiveness of specific psychological interventions faces serious conceptual and methodological challenges (Gaab et al., 2018).

In this Opinion article we identify two under-appreciated placebo-related problems which substantially risk the validity of clinical trials in psychotherapy. The first is a common misconception about the nature of placebos; the second is the problem of double-blinding. We review current solutions and future prospects for the gold-standard in psychotherapy research.

WHAT ARE PLACEBOS?

In clinical research placebos usually refer to methodological devices employed to investigate the specific effectiveness of a treatment. While it is seductive to define placebos as "things" e.g., "sugar pills" in pharmacological trials and "attention controls," "active controls" or "non-directive controls" in psychotherapy trials, placebos are more correctly conceived as instruments used for measuring the efficacy of a treatment. As such they should be understood as a moving category (Blease, 2018b). In every randomized controlled trial (RCT) the placebo should ideally be "bespoke" – tailored to mimic an intervention under investigation without consisting of any it's hypothesized characteristic constituents. While fulfilling this goal is enormously challenging, in drug trials a placebo should preferably mimic the particular taste, appearance, and method of administration of the specific intervention without comprising the treatment's characteristic pharmacological ingredient(s). Placebos should also ideally be administered double-blind: practitioners/researchers and patients should not be able to distinguish the placebo from the treatment.

We also point out that double-blinding is not inherently associated with the term placebo in clinical research. A second, nuanced and different use of the term comes under the label "open-label placebos" (OLPs) (Blease, 2018b); here "placebo" refers to specific interventions (usually sugar pills) which are administered alongside other socio-emotional cues in the patient-practitioner encounter usually with the aim of eliciting salutrious placebo effects (Sandler and Bodfish, 2008; Kaptchuk et al., 2010; Carvalho et al., 2016; Schaefer et al., 2016; Locher et al., 2017). This distinctive interpretation of "placebos" is not our focus.

Here we are interested in placebos as controls in RCTs. We argue that while formulating suitable placebos and double-blinding conditions is a challenge in pharmacological trials the task is even more formidable when it comes to testing psychological treatments.

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Check for updates

Placebos Are Part of the Solution, Not the Problem. An Exemplification of the Case of Antidepressants in Pediatric Chronic Pain Conditions

Cosima Locher[1,2,3], Jens Gaab[1], Charlotte Blease[4], Marc Inderbinen[1], Linda Kost[1] and Helen Koechlin[1,2]*

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Keywords: open-label placebo, antidepressants, chronic pain, children, adolescents

INTRODUCTION

Chronic pain is highly prevalent among adolescents and up to one in four youths will develop chronic pain (1). Also, more than 10% of hospitalized children and adolescents show features of chronic pain (2), which is inherently linked to emotional distress and functional disability (3). Interventions for chronic pediatric pain comprise a range of treatment approaches, among them antidepressants (ADs). Pharmacological treatment indications for pediatric populations are usually based on data extrapolated from adults where ADs are described to be effective and frequently used for the treatment of chronic pain (4–6). Furthermore, chronic pain is multi-faced, therefore the use

Go open! Placebo zeigt uns den Weg…

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ARTICLE

WILEY

Effects of placebos without deception compared with no treatment: A systematic review and meta-analysis

James E.G. Charlesworth[1] | Grace Petkovic[1] | John M. Kelley[2,3] | Monika Hunter[4] | Igho Onakpoya[1] | Nia Roberts[5] | Franklin G. Miller[6] | Jeremy Howick[1]

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1 | INTRODUCTIO

Surveys from around the wor
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These authors contributed equally to th

J Evid Based Med. 2017;10:97–10

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

Melina von Wernsdorff[1,2], Martin Loef[3], Brunna Tuschen-Caffier[2] & Stefan Schmidt[1,4]

Open-label placebos (OLPs) are placebos without deception in the sense that patients know that they are receiving a placebo. The objective of our study is to systematically review and analyze the effect of OLPs in comparison to no treatment in clinical trials. A systematic literature search was carried out in February 2020. Randomized controlled trials of any medical condition or mental disorder comparing OLPs to no treatment were included. Data extraction and risk of bias rating were independently assessed. 1246 records were screened and thirteen studies were included into the systematic review. Eleven trials were eligible for meta-analysis. These trials assessed effects of OLPs on back pain, cancer-related fatigue, attention deficit hyperactivity disorder, allergic rhinitis, major depression, irritable bowel syndrome and menopausal hot flushes. Risk of bias was moderate among all studies. We found a significant overall effect (standardized mean difference = 0.72, 95% CI 0.39–1.05, $p < 0.0001$, $I^2 = 76\%$) of OLP. Thus, OLPs appear to be a promising treatment in different conditions but the respective research is in its infancy. More research is needed, especially with respect to different medical and mental disorders and instructions accompanying the OLP administration as well as the role of expectations and mindsets.

Placebos have been the subject of many studies in the last two decades[1] and the number of clinical trials to examine a placebo treatment as the primary intervention is rapidly growing[2]. Research has shown that symptoms can be reduced in a significant way by receiving an inert medication[3–5]. Placebos are also increasingly used in medical practice outside of clinical trials[6,7]. A survey in the UK revealed that 77% of general practitioners use placebos regularly[8]. Considering not only the benefits for patients (i.e. no pharmacological side effects) but also economic effects like low priced pills[9], deceptive placebos appear to be a promising alternative to active substances in medicine.

However, the use of placebos in primary treatment raises ethical concerns because the physicians' prescriptions may be considered to be deceptive[10]. Patients need to be informed completely, accurately and comprehensively about their treatment[11], otherwise the essential base for a healthy relationship between physician and patient is jeopardized[12,13]. Despite some these ethical concerns, a few researchers contend that deceptive placebos are acceptable in a limited number of circumstances (e.g.[14–16]) since the therapeutic encounter can still be beneficial to the patient. Others say that physicians are still lying to patients "in order to bring about positive expectations surrounding treatment outcomes"[17 p. 2] which might harm the fiduciary patient-doctor relationship. This dilemma raises the question of whether the deception in placebo treatments is coercively necessary for achieving a placebo effect.

In 1965, Park and Covi[18] were the first researchers who examined if full transparency regarding the placebo treatment would still result in an observable placebo effect. Surprisingly, they found a reduction in symptoms even if patients knew that they received a placebo treatment with inert sugar pills. This line of research was not pursued further until the first randomized controlled trial (RCT) was published in 2008, which examined the placebo-effect without deception (open-label placebo, OLP) as a "dose-extender" in children with attention deficit hyperactivity disorder (ADHD)[19,20]. In 2010, a ground-breaking study was published by Kaptchuk et al.[21], in which they found significant effects of OLPs in patients with irritable bowel syndrome.

Several recent reviews[22–25] provide an overview of current advances in clinical OLP research and formulate first hypotheses as to why placebos without deception may still have beneficial effects. The general problem in the research of placebo treatments is to differentiate adequately between a *placebo effect* (effect due to the

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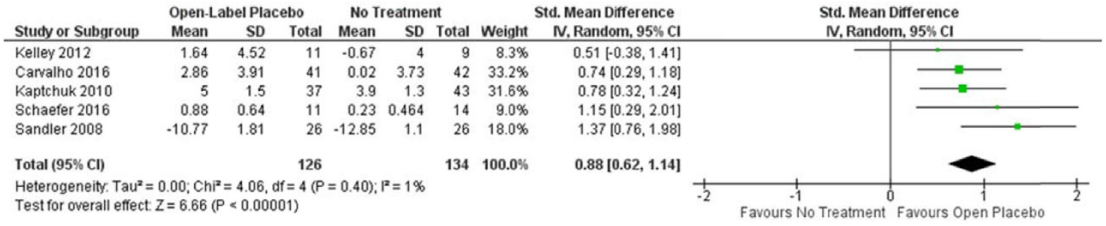

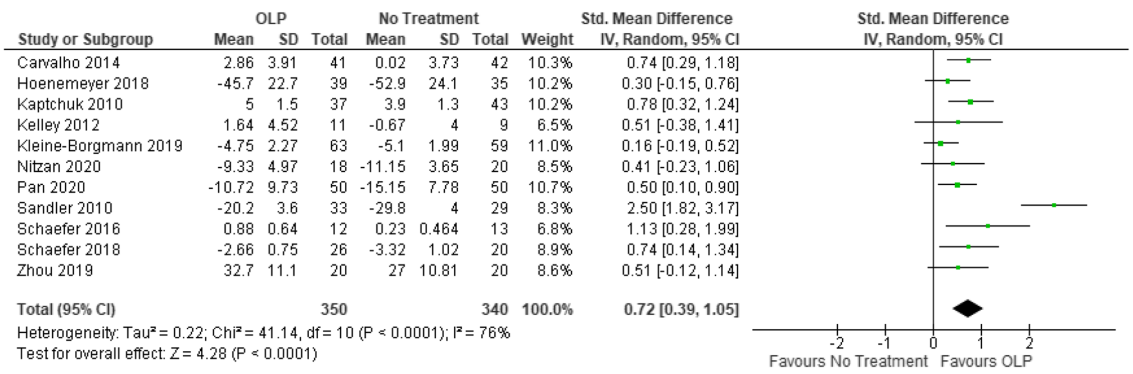

Figure 4. Forest plot for main outcome. Studies with open-label placebo (OLP) group and no treatment group were weighted using sample size (Total), means and standard deviations (SD). The means are shown by the green squares and the whiskers are representing the 95% confidence interval (CI). Overall standardized mean difference was calculated using the random effects model.

Dose-expander. Open-label placebo als Medikamentenersatz

Original Article

Conditioned Placebo Dose Reduction: A New Treatment in Attention-Deficit Hyperactivity Disorder?

Adrian D. Sandler, MD,* Corrine E. Glesne, PhD,* James W. Bodfish, PhD†‡

ABSTRACT: ***Objective:*** **This study examined if pairing a placebo with stimulant medication produces a placebo response that allows children with attention-deficit hyperactivity disorder (ADHD) to be maintained on a lower dose of stimulant medication. The primary aim was to determine the efficacy, side effects, and acceptability of a novel conditioned placebo dose reduction procedure.** ***Method:*** **Participants included 99 children ages 6 to 12 years with ADHD. After an initial double-blind dose finding to identify optimal dose of mixed amphetamine salts, subjects were randomly assigned to 1 of 3 treatments of 8-week duration: (a) conditioned placebo dose reduction condition (50% reduced dose/placebo [RD/P]) or (b) a dose reduction only condition (RD) or (c) a no reduction condition (full dose). The innovative conditioned placebo dose reduction procedure involved daily pairing of mixed amphetamine salts dose with a visually distinctive placebo capsule administered in open label, with full disclosure of placebo use to subjects and parents.** ***Results:*** **Seventy children completed the study. There were no differences in subject retention among the 3 groups. Most subjects in the RD/P group remained stable during the treatment phase, whereas most in the RD group deteriorated. There was no difference in control of ADHD symptoms between the RD/P group and the full dose group, and both RD/P and full dose groups showed better ADHD control than the RD group. Treatment emergent side effects were lowest in the RD/P group.** ***Conclusion:*** **Pairing placebos with stimulant medication elicits a placebo response that allows children with ADHD to be effectively treated on 50% of their optimal stimulant dose.**

(J Dev Behav Pediatr 31:369–375, 2010) **Index terms:** ADHD, treatment, placebo, stimulant.

Attention deficit hyperactivity disorder (ADHD) is the most prevalent neurobehavioral disorder in children, with prevalence estimates of 3% to 12%. Despite clear evidence of the beneficial effects of stimulant therapy in the treatment of ADHD,[1,2] there continue to be widespread concerns about over-use of stimulant therapy.[3,4] Treatment-emergent side effects are common,[5,6] and their long-term significance is not fully known.[4] Many parents worry about short- and long-term side effects associated with stimulant therapy, and these attitudinal factors contribute to nonadherence, premature stimulant discontinuation, and consequently increasing morbidity. For these reasons, parents and professionals are united in the desire to treat children with the lowest effective doses.[1,7]

Strong placebo effects have been shown in clinical trials of treatments for several psychiatric disorders, including depression, anxiety disorders, and autism.[8,9] Placebo response rates in depression seem to be even higher in pediatric samples than in adult samples.[10] Similarly, high placebo response rates have been found in children with ADHD.[4,11] Previous clinical trials of stimulants show 30% of children with ADHD are clinical responders to placebo in double-blind trials.[2,11,12]

There are no previous studies of open-label placebo in children. Brown[13] proposed the ethical use of open-label placebo as treatment for mild depression in adults. That article included some discussion about the extent to which placebo treatment may be ineffective if both clinician and patient know the placebo is pharmacologically inactive. Only 1 published study has examined the impact of patient's knowledge of the placebo's true nature, suggesting that such knowledge did not preclude the possibility of beneficial response.[14]

Several studies have suggested that placebo effects may in part represent conditioning phenomena and that learning processes may influence the response to placebo.[15–17] In classical (Pavlovian) conditioning, biologically neutral events associated with the administration of pharmacologic agents can become conditioned stimuli capable of producing responses similar to those produced by the active drugs. In behavioral terms, the pharmacological effect of a drug is the unconditioned

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Adrian Sandler and Corrine Glesne participated in the design and implementation of the study. Adrian Sandler had full access to all the data in the study and had the final responsibility for the decision to submit for publication. James Bodfish participated in the design of the study and data analysis.

The NIMH had no involvement in any aspects of the study or this paper.

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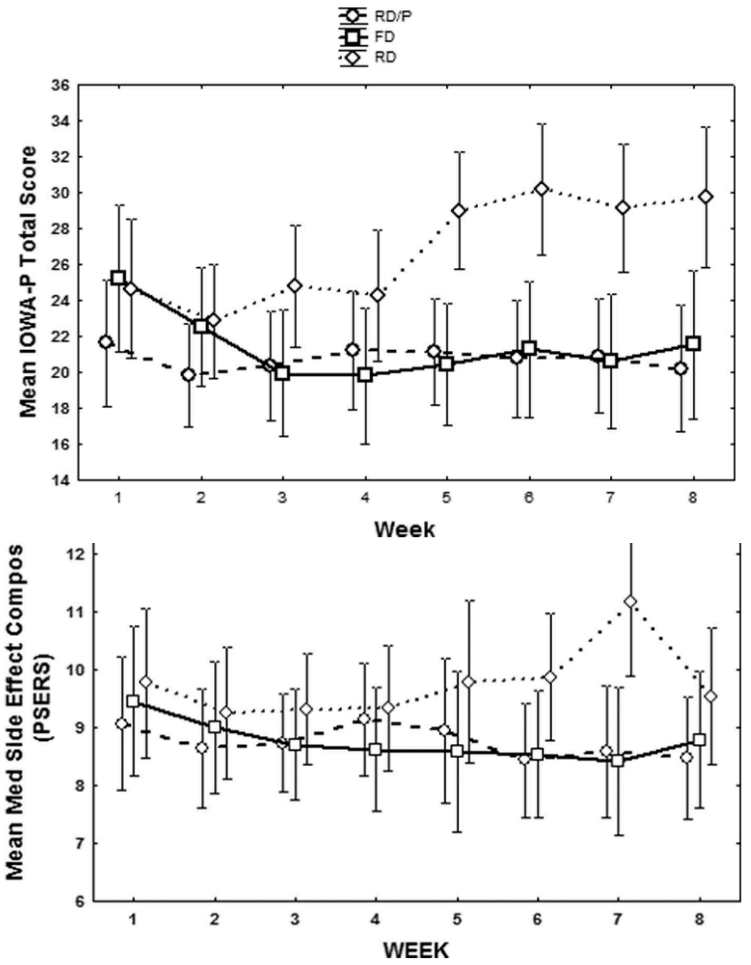
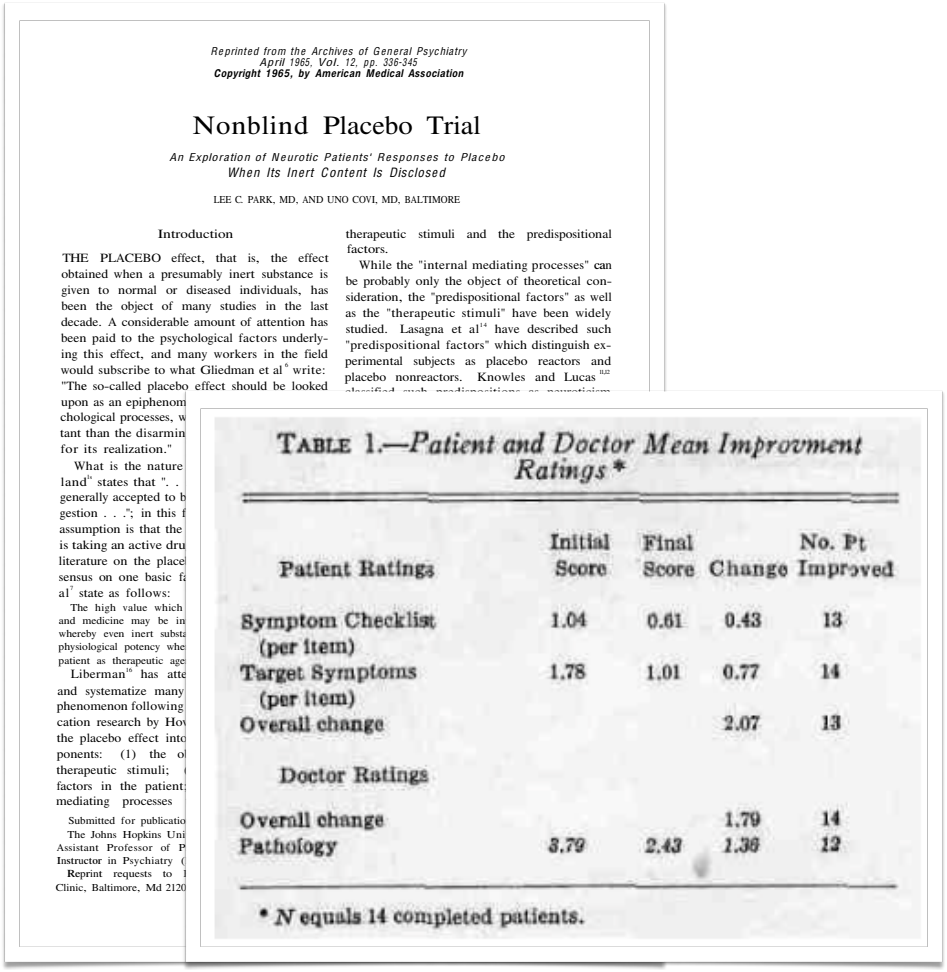


Nothing new under the sun



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April 1965, Vol. 12, pp. 336-345

Nonblind Placebo Trial

An Exploration of Neurotic Patients' Responses to Placebo When Its Inert Content Is Disclosed

LEE C. PARK, MD, AND UNO COVI, MD, BALTIMORE

Introduction

THE PLACEBO effect, that is, the effect obtained when a presumably inert substance is given to normal or diseased individuals, has been the object of many studies in the last decade. A considerable amount of attention has been paid to the psychological factors underlying this effect, and many workers in the field would subscribe to what Gliedman et al[6] write: "The so-called placebo effect should be looked upon as an epiphenom... chological processes, w... tant than the disarmin... for its realization."

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therapeutic stimuli and the predispositional factors.

While the "internal mediating processes" can be probably only the object of theoretical consideration, the "predispositional factors" as well as the "therapeutic stimuli" have been widely studied. Lasagna et al[14] have described such "predispositional factors" which distinguish experimental subjects as placebo reactors and placebo nonreactors. Knowles and Lucas[11,12] ...

TABLE 1.—*Patient and Doctor Mean Improvment Ratings* *

Patient Ratings	Initial Score	Final Score	Change	No. Pt Improved
Symptom Checklist (per item)	1.04	0.61	0.43	13
Target Symptoms (per item)	1.78	1.01	0.77	14
Overall change			2.07	13
Doctor Ratings				
Overall change			1.79	14
Pathology	3.79	2.43	1.36	12

* *N* equals 14 completed patients.

Patient C was a 28-year-old married female, mother of five children, who complained of extreme tension, shortness of breath, trembling, crying spells, insomnia, suicidal thoughts, and poor appetite with weight loss. She indicated her symptoms centered around inter- personal relations with her husband, who somewhat sadistically provoked her with acting-out behavior. She had previously received medication for her symptoms (mostly anticonvulsants and a sedatives) with no improvement.

(…) the patient said that she needed something really strong; on the other hand, she was quite hesitant about taking medicine because of her (…) mother (…) had (attempted) suicide (…) with drugs.

As soon as it was clear to her that these pills were inactive, she dropped her objections and eagerly agreed to take the pills. She reported at that point, "I do feel better today, I'll be honest with you. Before I came in here I was very upset and when I was talking with you before I was very upset." At the subsequent visit the patient re- ported she had been doing "fine." "I've had more control and I've felt better." Her somatic symptoms had almost completely disappeared.

She made it clear that she never considered the pills to be anything but placebo and reported no side-reactions.

Commenting on the factors accounting for her marked improvement, the patient remarked that if a person takes a pill "in the right frame of mind," she may feel improved because the pill gives her "moral support." She also felt that the doctor was quite reassuring. Finally, the patient stated, "I think that I had a lot to do with it myself, to be honest. By knowing myself that I had to control myself to keep myself in the right frame of mind."

She then indicated that the most important factor in her improvement was that she helped herself. Our feeling was that the patient did help herself but that she was able to do this only after the placebo gave her an alternative solution to that chosen by her mother in such situations. The patient wanted to continue seeing the doctor, but unfortunately, was not asked whether she wanted to continue with the pills.

Open-label placebo. Irritable bowel syndrome.

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PLoS one

Placebos without Deception: A Randomized Controlled Trial in Irritable Bowel Syndrome

Ted J. Kaptchuk[1,2]*, Elizabeth Friedlander[1], John M. Kelley[3,4], M. Norma Sanchez[1], Efi Kokkotou[1], Joyce P. Singer[2], Magda Kowalczykowski[1], Franklin G. Miller[5], Irving Kirsch[6], Anthony J. Lembo[1]

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Abstract

Background: Placebo treatment can significantly influence subjective symptoms. However, it is widely believed that response to placebo requires concealment or deception. We tested whether open-label placebo (non-deceptive and non-concealed administration) is superior to a no-treatment control with matched patient-provider interactions in the treatment of irritable bowel syndrome (IBS).

Methods: Two-group, randomized, controlled three week trial (August 2009-April 2010) conducted at a single academic center, involving 80 primarily female (70%) patients, mean age 47±18 with IBS diagnosed by Rome III criteria and with a score ≥150 on the IBS Symptom Severity Scale (IBS-SSS). Patients were randomized to either open-label placebo pills presented as "placebo pills made of an inert substance, like sugar pills, that have been shown in clinical studies to produce significant improvement in IBS symptoms through mind-body self-healing processes" or no-treatment controls with the same quality of interaction with providers. The primary outcome was IBS Global Improvement Scale (IBS-GIS). Secondary measures were IBS Symptom Severity Scale (IBS-SSS), IBS Adequate Relief (IBS-AR) and IBS Quality of Life (IBS-QoL).

Findings: Open-label placebo produced significantly higher mean (±SD) global improvement scores (IBS-GIS) at both 11-day midpoint (5.2±1.0 vs. 4.0±1.1, $p<.001$) and at 21-day endpoint (5.0±1.5 vs. 3.9±1.3, $p=.002$). Significant results were also observed at both time points for reduced symptom severity (IBS-SSS, $p=.008$ and $p=.03$) and adequate relief (IBS-AR, $p=.02$ and $p=.03$); and a trend favoring open-label placebo was observed for quality of life (IBS-QoL) at the 21-day endpoint ($p=.08$).

Conclusion: Placebos administered without deception may be an effective treatment for IBS. Further research is warranted in IBS, and perhaps other conditions, to elucidate whether physicians can benefit patients using placebos consistent with informed consent.

Trial Registration: ClinicalTrials.gov NCT01010191

Citation: Kaptchuk TJ, Friedlander E, Kelley JM, Sanchez MN, Kokkotou E, et al. (2010) Placebos without Deception: A Randomized Controlled Trial in Irritable Bowel Syndrome. PLoS ONE 5(12): e15591. doi:10.1371/journal.pone.0015591

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Competing Interests: AJL has worked as a consultant for Ironwood, GSK, Salix, Alkermes, and Ardelyx. These companies have had no relationship to this study. All other authors report no competing interest or appearance of competing interest.

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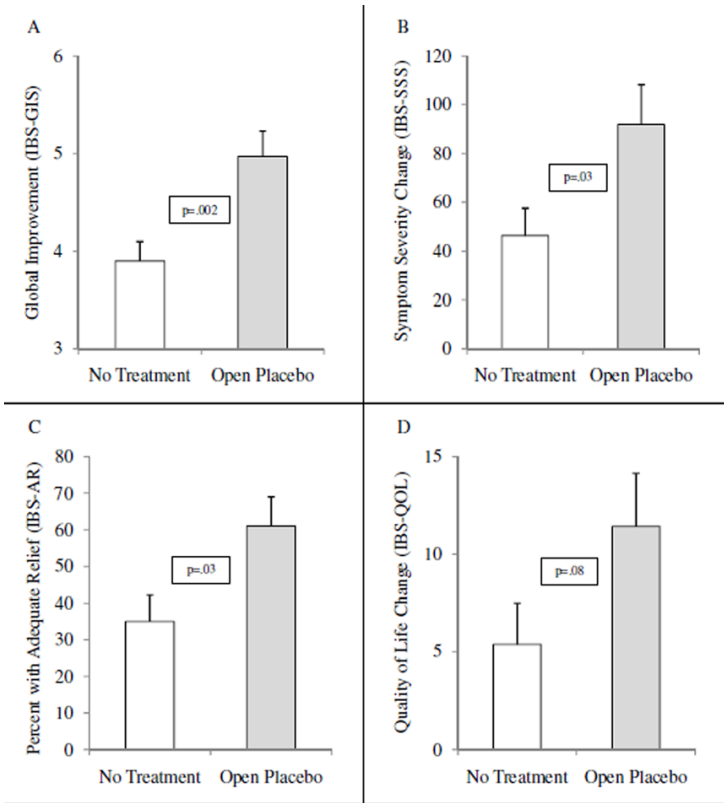
Introduction

Placebo treatment can have a significant impact on subjective complaints. [1] Furthermore, recent studies have shown measurable physiological changes in response to placebo treatment that could explain how placebos alter symptoms. [2] A critical question is establishing how physicians and other providers can take optimal advantage of placebo effects consistent with their responsibility to foster patient trust and obtain informed consent. Directly harnessing placebo effects in a clinical setting has been problematic because of a widespread belief that beneficial responses to placebo treatment require concealment or deception. [3] This belief creates an ethical conundrum: to be beneficial in clinical practice placebos require deception but this violates the ethical principles of respect for patient autonomy and informed consent. In the clinical setting, prevalent ethical norms emphasize that "the use of a placebo without the patient's knowledge may undermine trust, compromise the patient-physician relationship, and result in medical harm to the patient." [4] Nevertheless, a recent national survey of internists and rheumatologists in the US found that while only small numbers of



Kaptchuk et al., 2010, PLOS ONE

Go open! Placebo zeigt uns den Weg…

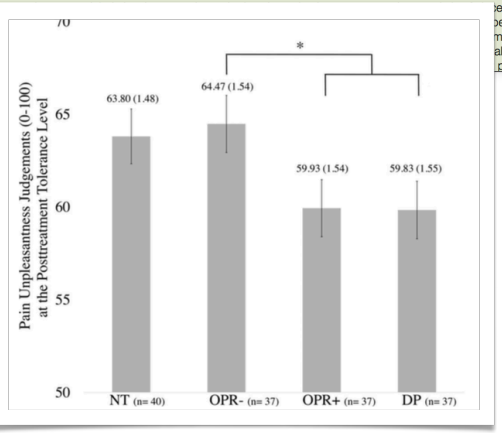
PAIN

Is the rationale more important than deception? A randomized controlled trial of open-label placebo analgesia

Cosima Locher[a,*], Antje Frey Nascimento[a], Irving Kirsch[b], Joe Kossowsky[a,c], Andrea Meyer[d], Jens Gaab[a]

Abstract

…ebo effects. Yet, comparisons …pen-label placebos and DPs in …mized controlled trial in healthy …ale (OPR-), open-label placebo … pain threshold and tolerance.



Research Paper

PAIN

OPEN

Open-label placebo treatment in chronic low back pain: a randomized controlled trial

Cláudia Carvalho[a,*], Joaquim Machado Caetano[b], Lidia Cunha[c], Paula Rebouta[c], Ted J. Kaptchuk[d], Irving Kirsch[d]

Abstr…

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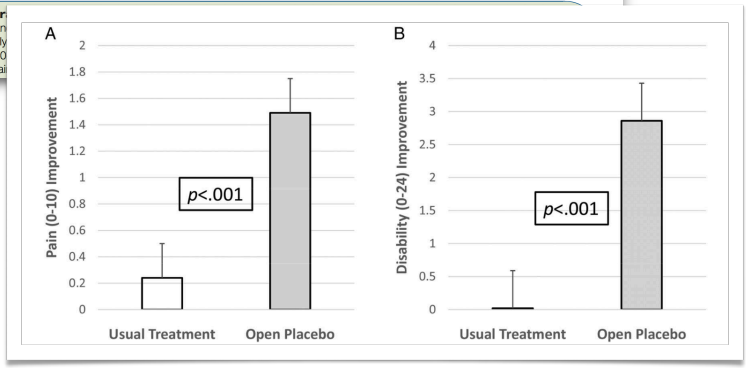


Research Paper

PAIN

Open-label placebo for chronic low back pain: a 5-year follow-up

Claudia Carvalho[a,*], Maria Pais[b], Lidia Cunha[c], Paula Rebouta[c], Ted J. Kaptchuk[d], Irving Kirsch[d]

Abstract

Long-term follow-up of patients treated with open-label placebo (OLP) are nonexistent. In this article, we report a 5-year follow-up of a 3-week OLP randomized controlled trial (RCT) in patients with chronic low back pain. We recontacted the participants of original RCT and reassessed their pain, disability, and use of pain medication. We obtained follow-up data from 55 participants (82% of those who took OLP during the parent RCT), with a mean elapsed time between the end of the 3 weeks placebo trial and the follow-up interview of 55 months (SD = 7.85). We found significant reductions in both pain and disability between the baseline assessment immediately before the 3 weeks trial with placebo pills and the original trial endpoint ($P < 0.00001$ for the 2 primary outcomes of pain and disability). At the 5-year follow-up, we found no significant differences in either outcome between original trial endpoint and follow-up. Improvements persisted after 5 years and were accompanied by substantial reductions compared with baseline in the use of pain medication (from 87% to 38%), comprising analgesics (from 80% to 31%), antidepressants (from 24% to 11%), and benzodiazepines (from 15% to 5%). By contrast, the use of alternative approaches to pain management increased (from 18% to 29%). Although the reduction in pain and medication is comparable with the improvements that occurred in the original study, a major limita… Nonetheles…

Keyword…

1. Introduc…

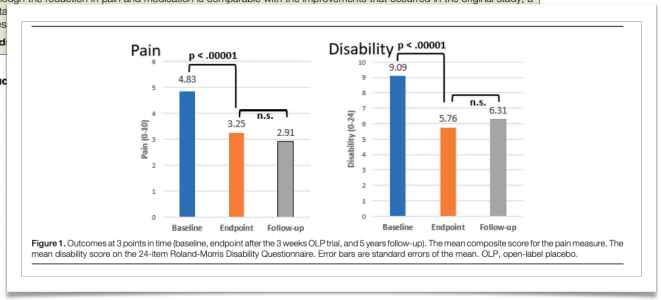
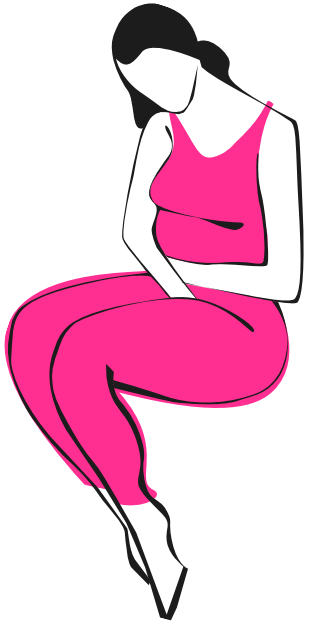
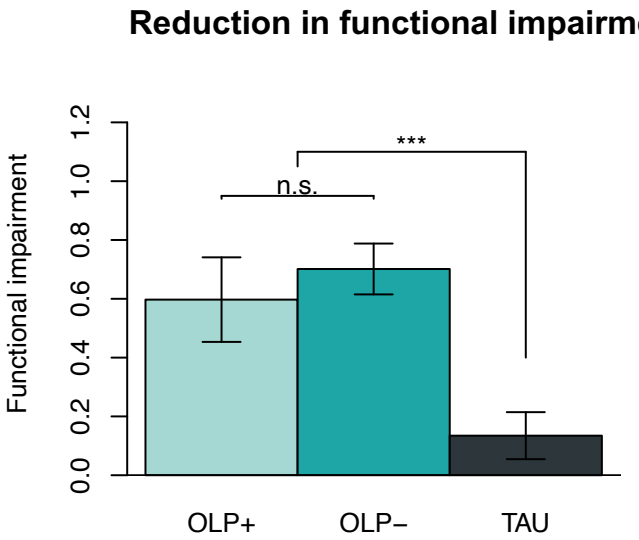
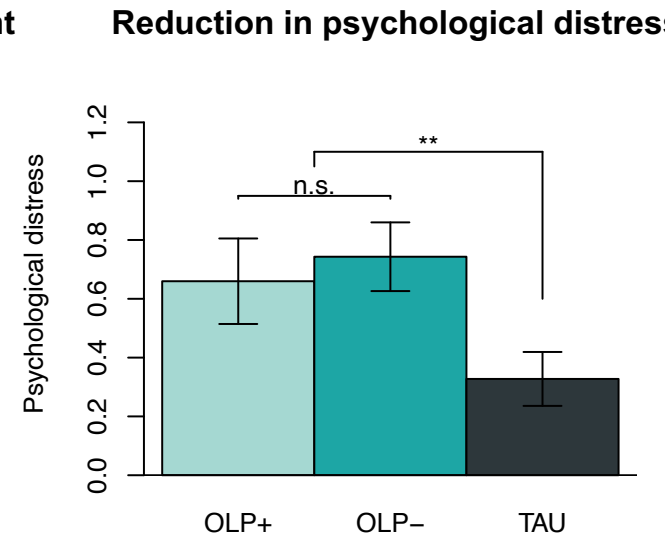


Figure 1. Outcomes at 3 points in time (baseline, endpoint after the 3 weeks OLP trial, and 5 years follow-up). The mean composite score for the pain measure. The mean disability score on the 24-item Roland-Morris Disability Questionnaire. Error bars are standard errors of the mean. OLP, open-label placebo.

Open-label placebo. Premenstrual Syndrom.







Bürgler, Degen, Frey Nascimento, Gaab & Locher, poster presented SIPS2019

Anstelle von Beichte und Busse. OLP bei Schuldgefühlen.

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Deceptive and open-label placebo effects in experimentally induced guilt: a randomized controlled trial in healthy subjects

Dilan Sezer[1✉], Cosima Locher[2,3] & Jens Gaab[1]

Placebos are known to yield significant effects in many conditions. We examined deceptive and open-label placebo effects on guilt, which is important for self-regulation and a symptom of mental disorders. Following an experimental induction of guilt, healthy subjects were randomized to deceptive placebo (DP; *n* = 35), open-label placebo (OLP; *n* = 35), or no treatment (NT; *n* = 39). The primary outcome was guilt responses assessed in area under the curve (AUC). Secondary outcomes were shame, guilt, and affect. We hypothesized that DP and OLP would reduce guilt compared to NT. Guilt responses were higher in the NT group than in the placebo groups (estimate = 2.03, 95% CI = 0.24–3.82, *d* = 0.53), whereas AUC guilt did not differ significantly between the placebo groups (estimate = −0.38, 95% CI = −2.52–1.76, *d* = −0.09). Placebos are efficacious in reducing acute guilt responses, regardless of the placebo administration (i.e., open vs. deceptive). Furthermore, we observed narrative-specific effects with significant changes of guilt but not shame, pride, or affect. These results indicate not only that guilt is amenable to placebos but also that placebos can be administered in an ethical and potentially emotion-specific manner.

Placebos have been found to have clinically significant effects on subjective and objective outcomes in a variety of conditions[1,2]. This especially holds true for acute and chronic pain, where the administration of a placebo has led to analgesia in healthy and clinical populations[3–5], as well as for depressive disorders, for which placebo responses have been found to be so substantial that differences between a placebo and antidepressant medication are a subject of constant debate[6,7].

Placebo effects have also been demonstrated in a number of nonclinical psychological domains, such as in reducing social pain[8]; facilitating social trust and approach behavior[9]; increasing happiness and reducing stress and depression[10,11]; increasing short- and midterm subjective well-being[12]; reducing unpleasantness, sadness and rumination[13–16]; diminishing disgust[17]; and increasing the subjective pleasantness of wine[18]. However, in contrast to the plethora of established experimental pain paradigms, such as the Cold Pressure Test e.g.[19–21], experimentally induced heat pain[22,23], or intracutaneous electrical stimulation[24,25], comparable experimental paradigms are scarce in placebo research on psychological and behavioral outcomes. For example, experimentally inducing sadness by watching a sad movie[15,26], reading self-deprecating statements[27], listening to sad music[28,29], or inducing anxiety by looking at fearful pictures[30,31] are rare examples of experimental paradigms in nonpain placebo research. Given that comparable experimental paradigms would enable important insights into the inner workings of clinically relevant phenomena it is of vital importance for placebo research to extend the range of experimental nonpain paradigms.

One area in current placebo research where experimental paradigms would be of great importance is research into the ethical application of placebo interventions. This field of research has recently gained continuous attention and has provided initial evidence that placebos can also work when they are fully disclosed and administered transparently[32]. Such open-label placebos (OLPs) have been found to have significant effects, for example, in pain conditions (e.g.,[33–35]) and for test anxiety[36], with mixed results for depression[37,38]. In a pilot study with a diagnosed sample of major depression[37], the OLP group did not significantly differ compared to the no treatment control group, which can possibly be explained by the lack of power due to a small sample size of only 20 participants. The

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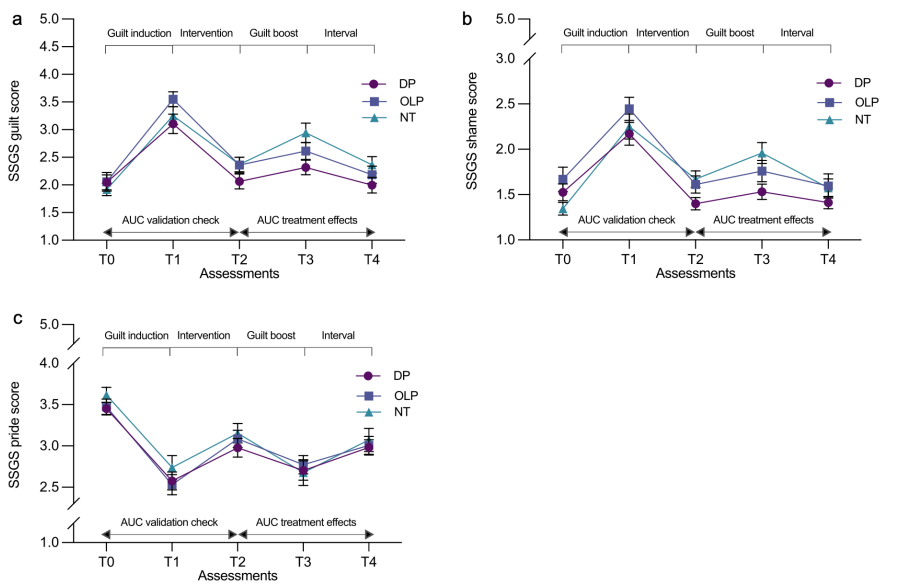

Open-label placebo ist Psychotherapy. Imagine, it works...

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Imaginary pills and open-label placebos can reduce test anxiety by means of placebo mechanisms

Sarah Buergler[1✉], Dilan Sezer[1], Niels Bagge[2], Irving Kirsch[3], Cosima Locher[4,5], Claudia Carvalho[6] & Jens Gaab[1]

Placebos have been shown to be beneficial for various conditions even if administered with full transparency. Hence, so-called open-label placebos (OLPs) offer a new way to harness placebo e ethically. To take this concept one step further, this study aimed at evaluating placebo effects w the use of a physical placebo, i.e., by imagining taking a pill. Healthy students (*N* = 173) with self reported test anxiety were either randomized to an imaginary pill (IP; n = 55), an OLP (n = 59) or control group (CG; n = 59). Both intervention groups were instructed to take two pills daily for th weeks. Primary outcome was test anxiety, secondary outcomes were sleep quality, general well and test performance. Groups test anxiety differed at study-endpoint, $F(2,169) = 11.50$, $p < .001$, anxiety was lower in the intervention groups compared to the CG, $t(169) = -4.44$, $p < .001$, $d = -0$. The interventions did not differ significantly, i.e., both were similarly efficacious, $t(169) = 0.61$, $p = .540$, $d = 0.11$. The interaction between group and time in explaining test anxiety was signific $F(5,407.93) = 6.13$, $p < .001$. OLPs and IPs reduced test anxiety in healthy participants compared CG. This finding opens the door for a novel and ethical method to harness placebo effects.

Placebo effects are clinically highly relevant and the need to harness these effects has been voiced[1]. In this open-label placebos (OLPs) administered with full disclosure and transparency can be deemed both and feasible as they avoid the use of deception[2]. Interestingly, meta-analyses show medium sized to lar cally relevant effects of OLPs in patients with various clinical conditions compared to control groups[3,4]. placebos also work without deception, it implies that it is not necessarily the pill serving as a symbol fo medication that triggers these effects. The investigation of underlying mechanisms by eliminating the p treatment constituent (i.e., the pill itself) can reveal the power of the purely psychological component of a p For this reason, we aimed to evaluate placebo effects without the use of a placebo by having participants taking a pill rather than actually taking one.

The concept of an imaginary pill (IP) was first introduced by De Shazer in 1984 in the context of hypnosis[5]. More recently, Niels Bagge, a Danish clinician, independently introduced the same idea hypnosis[6]. Although seemingly farfetched, recent data supports its plausibility: For instance, pharmac placebos can be effective even when only possessed, but not applied[7]. Also, psychotherapeutic, non-p cological placebos have been shown to be effective[8] and the idea of triggering placebo effects without a pill is discussed in sports performance[9], healthcare[10] and in research on the moderating role of mind Additionally, a study by Peerdeman et al.[11] indicated that mental imagery of reduced pain can induce placi expectancy effects on pain. Thus, placebos can also be purely psychological in nature and still produce be effects. With regard to the underlying mechanisms of such psychological placebos, it yet needs to be inves whether their efficacy is purely mediated by the meaning that is attributed to these rituals or the expe of improvement that are being formed as a consequence[12,13]. Despite the elimination of the physical a it is plausible that an IP relies in principle on the same underlying mechanisms as an OLP. Besides expe conditioning could for instance play a role, as even imagining something can activate correspondin areas and associated learning mechanisms (e.g.[14]). In addition, placebo mechanisms have also been disc relation to the theory of embodied cognition, which states that our experiences are not only conscious

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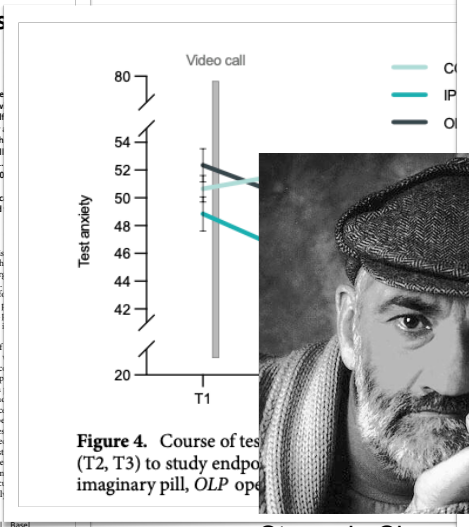

Figure 4. Course of tes
(T2, T3) to study endpo
imaginary pill, *OLP* ope

Steve de Shazer

30

THE IMAGINARY PILL TECHNIQUE

Steve de Shazer, Director, Brief Family Therapy Center,
6815 West Capitol Drive, Suite 105, Milwaukee, Wisconsin 53216

Abstract

The purpose of this essay is to describe a hypnotherapy and self-hypnosis technique that has been useful for a variety of complaints for which the client has taken or is taking pills or medication. Asthma attacks, chronic headaches, insomnia have all been treated successfully using this technique.

The understanding of this technique (and perhaps others as well) has been hindered by asking the wrong question: How does the imaginary work to stop head attacks, etc.? A new a different frame me of the mystery: ls" any more or any han imaginary pills?

ffective therapeutic developed which are ratic to a particular erapist can fit the is conceptual scheme, , it does not seem mportant or unique. gh these techniques f the therapist's retrieved when useful. rever, an effective developed to fit with ase, but the explana- nique is difficult to conceptual scheme. demands a revision of the conceptual scheme and other times it means that the therapist's explana- tion includes a not very useful perspective which prevents his fitting it with his framework.

Most therapists spend a lot of time and energy helping clients eliminate hallucinations and other types of magical thinking. However, under the influence of Milton H. Erickson, these same patterns of magical thinking can be utilized to promote changing; i.e., the therapist can promote the hallucinations and the magical thinking. This follows Erickson's ideas about taking what the client brings as the starting point of therapy. That is, in some situations some types of thinking are magical (leading to changing) even though these thoughts are hallucinations.

I have been using the "Imaginery Pill Technique" since 1972. For the past six years, I have repeatedly thought about writing this paper, and for the past three years other therapists have been urging me to write it up for publication. But I continued to hesitate. I continued to want more cases, more data, more follow-up instead of focusing down on what it is that is most important about the technique. This sort of thinking can be a handicap, because sometimes more data is more confusing than less. But most of all, I have never felt that I really understood what it is that is going on here; I just knew that the tech- nique worked. None of my explanations explained enough.

In part, this lack of understanding has something to do with the nature of patterns, and in part, it has something to do with the nature of labels. Labels can blind us, prevent us from seeing patterns because labels tell us what to look for; how to interpret what we see. For example, the label "depression" suggests what the therapist should look for. If we are seeing a "depressed man" and his wife, we can establish a goal of ending the depression, but if instead we see an interaction pattern, then we might establish a different goal involving the

OLP bei Opioid Use Disorder

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Original Investigation | Substance Use and Addiction

Effectiveness of Conditioned Open-label Placebo With Methadone in Treatment of Opioid Use Disorder

A Randomized Clinical Trial

Annabelle M. Belcher, PhD; Thomas O. Cole, MA; Ebonie Massey, MA; Amy S. Billing, MSSA; Michael Wagner, PhD; William Wooten, MS; David H. Epstein, PhD; Stephen W. Hoag, PhD; Emerson M. Wickwire, PhD; Aaron D. Greenblatt, MD; Luana Colloca, MD, PhD; John Rotrosen, MD; Lawrence Magder, PhD; Eric Weintraub, MD; Eric D. Wish, PhD; Ted J. Kaptchuk

Abstract

IMPORTANCE Methadone treatment is the most effective evidence-based treatment for opioid use disorder (OUD), but challenges related to dosing and premature treatment dropout argue for adjunct interventions to improve outcomes. One potential behavioral intervention with low risk involves harnessing placebo effects.

OBJECTIVE To determine the effect of a pharmacologically conditioned open-label placebo (C-OLP) on 90-day methadone dose, retention, drug use, withdrawal, craving, quality of life, and sleep.

DESIGN, SETTING, AND PARTICIPANTS This 2-arm, open-label, single-blind randomized clinical trial was conducted between December 5, 2017, and August 2, 2019, in an academically affiliated community opioid treatment program. Analyses were conducted between October 1, 2019, and April 30, 2020. A total of 320 newly enrolled adults seeking treatment for moderate to severe OUD were assessed for study eligibility; 131 met eligibility criteria, provided informed consent, and were randomized to either C-OLP or treatment as usual (TAU) in an unequal-block (3:2) manner. Exclusion criteria were pregnancy, hospital/program transfers, and court-ordered treatment.

INTERVENTIONS Participants randomized to C-OLP received pharmacologic conditioning and a placebo pill and methadone, and participants randomized to TAU were given methadone only. Participants met with the study team 5 times: at baseline (treatment intake) and 2, 4, 8, and 12 weeks postbaseline. Interactions were balanced between the 2 groups.

MAIN OUTCOMES AND MEASURES Outcomes included 90-day methadone dose (primary) and treatment retention, drug use, withdrawal, craving, quality of life, and sleep quality (secondary). Analyses were conducted as intention-to-treat.

RESULTS Of the 131 people enrolled in the study, 54 were randomized to TAU and 77 to C-OLP. Mean (SD) age was 45.9 (11.2) years; most of the participants were Black or African American (83 [63.4%]) and male (84 [64.1%]). No significant group differences were observed in the mean (SD) 90-day methadone dose (83.1 [25.1] mg for group TAU, 79.4 [19.6] mg for group C-OLP; $t = 0.621_{95}$; $P = .43$), but the groups differed significantly in their retention rates: 33 (61.1%) for TAU and 60 (77.9%) for C-OLP ($\chi^2_1 = 4.356$; $P = .04$; number needed to treat for the beneficial outcome of 3-month treatment retention, 6; 95% CI, 4-119). C-OLP participants also reported significantly better sleep quality.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, C-OLP had no effect on the primary outcome of 90-day methadone dose. However, C-OLP participants were significantly more

(continued)

Key Points

Question Can conditioned open-label placebo (C-OLP) help increase the efficacy of treatment with methadone for opioid use disorder?

Findings In this 2-group, single-blind randomized clinical trial including 131 individuals, 90-day retention in treatment and quality of sleep were significantly improved with C-OLP vs treatment as usual. Methadone dose, the prespecified primary outcome, did not differ significantly between groups.

Meaning The findings of this trial suggest that C-OLP may improve opioid use disorder treatment outcomes; further exploration of C-OLP as an inexpensive, low-risk adjunct to methadone treatment may be beneficial.

+ Visual Abstract
+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Figure 2. Mean Methadone Doses at Various Intervals Up to 90 Days

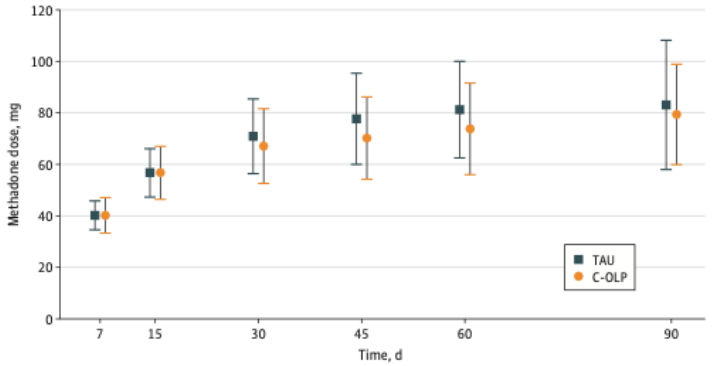
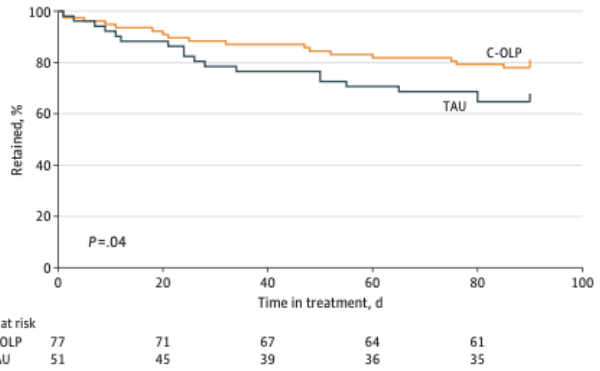


Figure 3. Probability of Treatment Retention by Group



No. at risk

C-OLP	77	71	67	64	61
TAU	51	45	39	36	35

61% vs. 79%


PLACEBO

Fin