Chapter 7
The Placebo and Nocebo Effect

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If a placebo were submitted to the FDA for approval, they would no doubt be impressed with its efficacy, but would probably not approve it due to its frequent side effects.

Abstract There are four general reasons for clinical improvement in a patient's condition: (1) natural history of the disease; (2) specific effects of the treatment; (3) regression to the mean; and (4) nonspecific effects of the treatment that are attributable to factors other than the specific active components. The latter effect is included under the heading 'placebo effect'. In this chapter the placebo effect will be discussed, with some emphasis on regression to the mean. Placebos ('I will please') and their lesser known counterpart's nocebo's (I will harm') are sham treatments. The difference is in the response to the inert therapy. A beneficial response to an inert substance is a placebo response; a side effect to an inert substance is a nocebo response.

Keywords Placebo • Nocebo • Regression to the mean • Placebo mechanisms • Placebo in clinical trials • Placebo ethics • Placebo characteristics

Placebo has been cited in PubMed over 170,000 times indicating that placebo has set the standard for how clinical research and particularly clinical trials are conducted. On the other hand, some have argued that placebo effects are overstated and can be explained by other variables (e.g. changes in the natural history of the disease, regression to the mean, methodological issues, conditioned answers, etc.). The importance,

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Table 7.1 Four general reasons for clinical improvement in a patient's condition

Natural history of the disease
Specific effects of the treatment
Regression to the mean
Placebo effect

controversy, and to date inadequate study of the placebo effect, warrants an in depth review of this topic. In addition, the discussion of placebos requires an understanding of the ethics of clinical trials, intention to treat analysis, surrogate endpoints and many of the other areas that have already been discussed in prior chapters.

Placebos ('I will please') and their lesser-known counterpart's nocebos ('I will harm') are sham treatments. The difference between placebo and nocebo is in the response to the inert therapy. A beneficial response to an inert substance is a placebo response; a side effect to an inert substance is a nocebo response.

There are four general reasons for clinical improvement in a patient's condition: (1) natural history of the disease; (2) specific effects of the treatment; (3) regression to the mean; and (4) nonspecific effects of the treatment that are attributable to factors other than the specific active components (Table 7.1). The latter effect is included under the heading 'placebo effect' [1]. Each time a physician recommends a diagnostic or therapeutic intervention for a patient, built into this clinical decision is the possibility of a placebo effect, that is, a clinical effect unrelated to the intervention itself [2]. Simple diagnostic procedures such as phlebotomy or more invasive procedures such as cardiac catheterization have been shown to have important associated placebo effects [3, 4]. Chalmers [5] has stated that a simple review of the many abandoned therapies reveals that many patients would have benefited by being assigned to a placebo control group. In fact, what might represent the first known clinical trial, and one in which the absence of a placebo control group led to erroneous conclusions, is a summary attributed to Galen in 250 BC, who stated that 'some patients that have taken this herbivore have recovered, while some have died; thus, it is obvious that this medicament fails only in incurable diseases' [6].

Placebo effects are commonly observed in patients with cardiac disease who also receive drug and surgical therapies as treatments. Rana et al. noted the 'tremendous power of the placebo effect' in patients with end-stage coronary disease in clinical trials of angiogenesis and laser myocardial revascularization [7]. They also commented on the fact that the observed improvements were not limited to 'soft' symptomatic endpoints but were also observed with 'hard' endpoints such as exercise walking time on a treadmill, and in magnetic resonance imaging. Rana et al. also studied the longevity of the placebo effect from published clinical trials. They found that the beneficial effects of placebo (on angina class, angina frequency, and exercise time) persisted for up to 2 years.

Definition

Stedman's Medical Dictionary [7] defines the word 'placebo,' which originates from Latin verb meaning 'I shall please,' to have two meanings. First, a placebo may be an inert substance prescribed for its suggestive value. Second, it may be an inert

substance identical in appearance with the compound being tested in experimental research, and the use of which may or may not be known by the physician or the patient; it is given to distinguish between the action of the compound and the suggestive effect of the compound under study [8].

Currently, there is some disagreement as to the exact definition of a placebo. Many articles on the subject include a broader definition, as given by Shapiro in 1961 [9].

> "*Any therapeutic procedure (or that component of any therapeutic procedure) which is given deliberately to have an effect or unknowingly has an effect on a patient, symptom, syndrome, or disease, but which is objectively without specific activity for the condition being treated. The therapeutic procedure may be given with or without conscious knowledge that the procedure is a placebo, may be an active (noninert) or nonactive (inert) procedure, and includes, therefore, all medical procedures no matter how specific—oral and parenteral medication, topical preparations, inhalants, and mechanical, surgical and psychotherapeutic procedures. The placebo must be differentiated from the placebo effect, which may or may not occur and which may be favorable or unfavorable. The placebo effect is defined as the changes produced by placebos. The placebo is also used to describe an adequate control in research.*"

A further refinement of the definition was proposed by Byerly [10] in 1976 as '*any change in a patient's symptoms that are the result of the therapeutic intent and not the specific physiochemical nature of a medical procedure*.'

Placebo Effect in Clinical Trials

The use of placebo controls in medical research was advocated in 1753 by Lind [11] in an evaluation of the effects of lime juice on scurvy. After World War II, research protocols designed to assess the efficacy and safety of new pharmacologic therapies began to include the recognition of the placebo effect.

The roots of the placebo problem can be traced to a lie told by an Army nurse during World War II as Allied forces stormed the beaches of southern Italy. The nurse was assisting an anesthetist named Henry Beecher, who was tending to US troops under heavy German bombardment. When the morphine supply ran low, the nurse assured a wounded soldier that he was getting a shot of potent painkiller, though her syringe contained only salt water. Amazingly, the bogus injection relieved the soldier's agony and prevented the onset of shock.

Returning to his post at Harvard after the war, Beecher became one of the nation's leading medical reformers. Inspired by the nurse's healing act of deception, he launched a crusade to promote a method of testing new medicines to find out whether they were truly effective. At the time, the process for vetting drugs was sloppy at best, and Pharmaceutical companies would simply dose volunteers with an experimental agent until the side effects swamped the presumed benefits. Beecher proposed that if test subjects could be compared to a group that received a placebo, health officials would finally have an impartial way to determine whether a medicine was actually responsible for making a patient better.

Placebos and their role in controlled clinical trials were recognized in 1946, when the Cornell Conference on Therapy devoted a session to placebos and double-blind methodology. At that time, placebos were associated with increased heart rate, altered respiration patterns, dilated pupils, and increased blood pressure. In 1951, Hill [12] concluded that a change in a patient to be attributable to a specific treatment (for better or worse) the result must be repeatable a significant number of times in other similar patients. Otherwise, the result could be due simply to the natural history of the disease or the passage of time. He also proposed the inclusion of a control group that received identical treatment except for the exclusion of an 'active ingredient.' Thus, the 'active ingredient' was separated from the situation within which it was used. This control group, also known as a placebo group, would help in the investigations of new and promising pharmacologic therapies.

Beecher [13] was among the first investigators to promote the inclusion of placebo controls in clinical trials. He emphasized that neither the subject nor the physician should know what treatment the subject was receiving and referred to this strategy as the 'double unknown technique.' Today, this technique is called the 'double-blind technique' and ensures that the expectations and beliefs of the patient and physician are excluded from evaluation of new therapies. In 1955, Beecher reviewed 15 studies that included 1,082 patients and found that an average of 35 % of these patients significantly benefited from placebo therapy (another third had a lesser benefit). He also concluded that placebos can relieve pain from conditions with physiologic or psychological etiologies. He described diverse objective changes with placebo therapy. Some medical conditions improved; they included severe postoperative wound pain, cough, drug-induced mood changes, pain from angina pectoris, headache, seasickness, anxiety, tension, and the common cold.

The Use of Placebos in Clinical Trials

There has been renewed interest in the use of placebos in clinical trials, and, not just because of the ethical issues involved. For example, from 2001 to 2006, the percentage of new products dropped from development after Phase II clinical trials, when drugs are generally first tested against placebo, rose by 20 %. During that same time period the failure rate in more extensive Phase III trials increased by 11 %, mainly as the result of surprisingly poor showings against placebo. Also, half of all drugs that fail in late-stage trials drop out of the pipeline due to their inability to beat placebo. Some examples are: a new type of gene therapy for Parkinson's disease was abruptly withdrawn from Phase II trials after unexpectedly tanking against placebo, stem-cell trials for Crohn's disease were suspended citing an "unusually high" response to placebo, and clinical trials for a much-touted new drug for schizophrenia was stopped when volunteers showed double the expected level of placebo response. And, it's not only trials of new drugs that are crossing the futility boundary. Some products that have been on the market for decades are faltering in more recent follow-up tests, and in many cases, these are the compounds that, in the

late 1990s, made Big Pharma more profitable than Big Oil, yet if these same drugs were studied now, the FDA might not approve some of them. Further confounding things is the observation that while some drugs are more likely to be superior in American studies than in those done in Europe and South Africa, others are still beating placebo in France and Belgium, but not in the USA.

Finally, since the 1980s, two comprehensive analyses of antidepressant trials have uncovered a dramatic increase in placebo response. One estimated that the effect size in placebo groups had nearly doubled over that time; and, it's not that the old treatments are getting weaker, it's as if the placebo effect is somehow getting stronger.

Characteristics of the Placebo Effect

There appears to be an inverse relation between the number of placebo doses that needs to be administered and treatment outcomes. In a study of patients with postoperative wound pain, 53 % of the subjects responded to one placebo dose, 40 % to two or three doses, and 15 % to four doses [12]. In analyzing the demographics of those who responded to placebo and those who did not, Lasagna et al. [14] found no differences in gender ratios or intelligence quotients between the two groups. They did find significant differences in attitudes, habits, educational backgrounds, and personality structure between consistent responders and nonresponders. In attempting to understand the reproducibility of the placebo effect, some have observed that there was no relation between an initial placebo response and subsequent responses with repeated placebo doses of saline [12]. Beecher concluded that placebos are most effective when stress, such as anxiety and pain, is greatest. But, placebo responses can be associated with dose response characteristics, frequency of dosing, pill color (e.g. blue vs. pink pills are more sedating, yellow vs. green more stimulating) and, "branded placebo" in some studies were more effective than generic placebo (Fig. 7.1). The magnitude of effect is difficult to quantitate due to its diverse nature but it is estimated that a placebo effect accounts for 30–40 % of an interventions benefit.

Placebos can produce both desirable and adverse reactions. Some now use the term placebo for the beneficial effects and nocebo for the adverse effects. Beecher et al. described >35 adverse reactions from placebos; the most common are listed in Table 7.2. The aforementioned reactions were recorded without the patient's or physician's knowledge that a placebo had been administered. In one study in which lactose tablets were given as a placebo, major adverse reactions occurred in three patients [15]. The first patient had overwhelming weakness, palpitation, and nausea after taking both the placebo and then the test drug. In the second patient, a diffuse rash developed with placebo administration, and the rash disappeared after placebo was discontinued. The third patient had epigastric pain followed by watery diarrhea, urticaria, and angioneurotic edema of the lips after receiving the placebo.

Fig. 7.1 Pill color and its placebo effects

Table 7.2 Common adverse reactions to Placebo (Nocebo effect)

Reaction	Incidence (%)
Drowsiness	50
Headache	25
Sensation of heaviness	18
Fatigue	18
Difficulty concentrating	15
Sleep disturbance	10
Nausea	10
Overly relaxed	9

Indeed, because of the substantial evidence of placebo 'efficacy' and placebo 'side effects,' some investigators have wittingly suggested that if placebo were submitted to the United States Food and Drug Administration (FDA) for approval, that the agency, though impressed with the efficacy data, would probably recommend disapproval on the basis of the high incidence of side effects. Some authors have questioned whether placebos are truly inert. Davis pointed out that part of the problem with the placebo paradox is our failure to separate the use of an inert medication (if there is such as substance) from the phenomenon referred to as the placebo effect. It might help us if we could rename the placebo effect the "obscure therapeutic effect" [16].

For instance, in trials of lactase deficiency therapy, could the amount of lactose in placebo tablets actually cause true side effects? Although the small amount of

lactose makes this possibility seem unlikely. Perhaps it is more likely that allergies to some of the so-called inert ingredients in placebos cause reactions in predisposed persons, although this explanation probably could not explain more than a small percentage of placebo side effects.

A validation of the placebo effect occurred in 1962 when the United States enacted the Harris-Kefauver amendments to the Food, Drug, and Cosmetic Act. These amendments required proof of efficacy and documentation of relative safety, in terms of the risk-benefit ratio for the disease to be treated, before an experimental agent could be approved for general use [17]. In 1970, the FDA published rules for 'adequate and well-controlled clinical evaluations.' The federal regulations identified five types of controls (placebo, dose-comparison, active, historical, and no treatment) and identified use of the placebo control as an indispensable tool to achieve the standard [18]. However, the FDA does not mandate placebo controls, and in fact has stated that placebo groups are 'desirable, but need not be interpreted as a strict requirement. The speed with which blind comparisons with placebo and/or positive controls can be fruitfully undertaken varies with the nature of the compound. In the publication regarding 'Draft Guidelines for the Clinical Evaluation of Anti-anginal Drugs,' the FDA further states that '*it should be recognized that there are other methods of adequately controlling studies. In some studies, and in some diseases, the use of an active control drug rather than a placebo is desirable, primarily for ethical reasons.*"

Regression Towards the Mean (or Towards Mediocrity)

An important statistical concept and one that may mimic a placebo response or a clinical response is regression towards the mean or regression towards mediocrity (RTM). RTM identifies a phenomenon that a biologic variable that is extreme on its first measurement will tend to be closer to the center of the distribution on a later measurement. The term originated with Sir Francis Galton who studied the relationship between the height of parents and their adult offspring. He observed that children of tall parents were (on average) shorter than their parents; while, children of short parents were taller than their parents. Galton called this regression towards mediocrity [20]. Another example of RTM is from Ederer, who observed that during the first week of the 1968 baseball season the top ten and bottom ten batters averaged 0.414 and 0.83 respectively. The following week they hit 0.246 and 0.206 respectively, while the average for the league remained stable [19].

At least three types of studies are potentially affected by RTM: a survey in which subjects are selected for subsequent follow-up based upon an initial extreme value, studies with no control groups, and even controlled trials. An example is taken from the Lipid Research Clinics Prevalence Study, a sample population who had elevated total cholesterol was asked to return for reevaluation. According to RTM, it would be expected that the 2nd measurement would on average be lower, and this would not be so had a randomly selected sample been chosen for reevaluation [22].

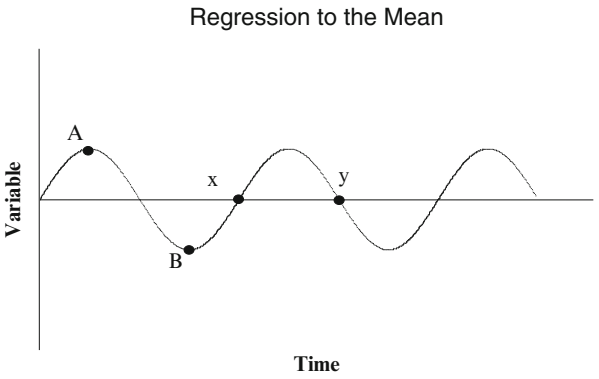

Fig. 7.2 If one measures a variable at its peak value (A in the example) the next measurement is likely to be lower (B, x, or y in this example). Conversely, if one were to measure a variable at its lowest point (B), the next measurement is likely to be higher

The reason that a randomly selected sample would be less likely to demonstrate RTM is because the random sample would have representative values across the spectrum of cholesterol measurements at the start, whereas the selected sample all initially had elevated values.

Another example of the RTM principal comes from the National Diet-Heart Study [23]. It had been repeatedly observed that a low cholesterol diet given to subjects with high cholesterol values resulted in greater cholesterol lowering that when the same diet was given to someone with lower cholesterol values. In the National Diet-Heart Study subjects with a baseline cholesterol >242 mg/dL had a 15 % reduction while those whose baseline cholesterol was 210–241 mg/dL had a 12 % reduction [23]. There are two possible explanations for this observation: one, that the diet hypothesis holds i.e. that subjects with high cholesterol are more responsive to cholesterol lowering treatment than those with lower cholesterol values; and two, that independent of dietary intervention subjects with high cholesterol will (on average) decrease more than those with lower values due to RTM. In fact, it is likely that both could occur simultaneously.

RTM then, is a phenomenon that can make a natural variation in repeated data look like a real change. In biologic systems, most variables increase and decrease around a mean (as, for instance, might be visualized as a sine wave). Thus, it is likely that any value measured at a specific point in time will, by chance, either be above or below the mean, and that a second measurement will be at a different point around the mean and, therefore, different from the first measurement (Fig. 7.2). The presumption is that this variability about the mean will be the same in the placebo group as in the active treatment group (assuming adequate sample size and randomization), so that differences between the two groups relative to regression to the mean will cancel out. In an intervention study, RTM cannot be observed because it is mixed into the genuine intervention effect. This is particularly true of intervention studies where the population selected for study generally is in the high risk groups—that is with values that are high at baseline. Yudkin and Stratton evaluated this by analyzing a group with high baseline cholesterol, and observing a 9 % fall without any intervention [21]. These authors go on to point out

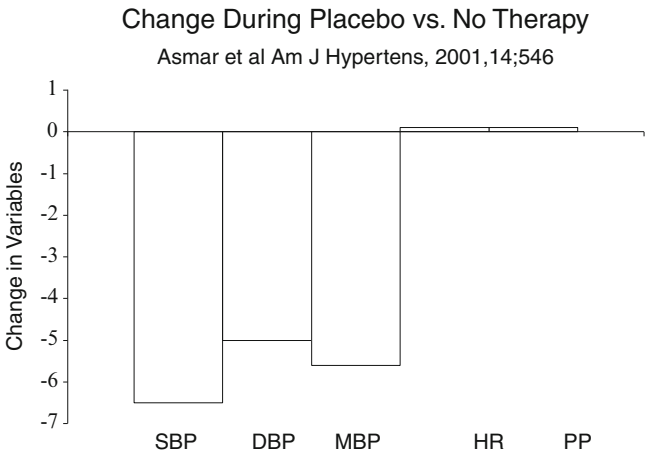

Fig. 7.3 Change in measured variables during placebo vs. no therapy. From Asmar et al. [22]

several ways of estimating the impact of RTM, and three suggested approaches to minimizing the RTM problem. These approaches include the use of an RCT design, since the RTM effect will be part of the total effect of the response in both the intervention and control groups. However, the response in both groups will be inflated by the RTM so the true impact of the intervention is not known and is likely somewhat less that that observed. A second approach to minimizing RTM is to obtain several measurements and average them to determine baseline. The third approach is to use the first measurement as the basis for selection of the subject into the study, and a second measurement that will be used as the baseline from which to assess the effect of the intervention.

The ideal comparator for a study would actually be no therapy vs. the investigational agent, however, the loss of blinding makes this approach problematic as well. There has been little study of the no therapy control, however, Asmar et al. did attempt to evaluate this as part of a larger interventional trial [22]. They used a randomized cross-over approach with a 1 month run-in followed by a 1 month placebo vs. no treatment period. BP and ABPM were measured. The results could be then analyzed in terms of the no treatment effect (no parameters changed in the two periods) and the RTM effect shown in Fig. 7.3.

Mechanism of the Placebo Effect

There has been much discussion regarding the mechanism of the placebo response. However, the mechanism at the cellular level and the role of biochemical mediators continues to escape detection. In an attempt to elucidate some mechanisms of the placebo effect, Beecher [13] described two phases of suffering: first, the initial pain

sensation or other symptom, and second the person's reaction to this sensation or experience by the central nervous system. The first, or somatic, phase is associated with the source of the pain or symptom; the second, or cortical, phase is superimposed on the pain or symptom. An example of the influence of the effect of the mind on the body is the 'Anzio Effect.' During World War II, injured soldiers at Anzio, Italy, complained less of pain after surgery, than typical patients after surgery. This difference was recognized because less than one third of the injured soldiers required morphine, compared with four fifths of patients undergoing similar recovery from the same surgery in non-combatants. For the soldiers, the knowledge that they had survived, combined with the anticipation of returning home, probably reduced their pain. In contrast, typical surgical patients are required to comply with hospital procedures, probably producing anxiety or fear that acts to increase pain [23]. The physiologic mechanism involved with pain begins when fear or anxiety activates the hypothalamus-hypophysis-adrenal axis, resulting in release of catecholamines. These catecholamines act on the body, which then sends feedback to the cerebral cortex via neural connections. The thalamus in the diencephalons, which processes sensory input before relaying it to the cerebral cortex, then sends recurrent axons to the thalamus, presumably to allow modulation of the input received from the thalamus [23, 24].

One theory to explain the placebo effect is classical conditioning, the pairing of an unconditioned stimulus with a conditioned stimulus until eventually the conditioned stimulus alone elicits the same response as the unconditioned stimulus. This effect of the environment on behavior was tested in a study by Voudouris et al. [25]. They studied responses to pain stimulation with and without a placebo cream. A visual analogue scale determined pain perception. To evaluate the effect of verbal expectancy, the patients were informed that the placebo cream had powerful analgesic properties (expectancy) or that the cream was neutral (no expectancy). To determine the role of conditioning, the level of pain stimulus was reduced after application of the cream (conditioning) or was maintained at the same level of pain (no conditioning). The patients were divided into four groups: a group receiving expectancy and conditioning, a group receiving only expectancy, a group receiving only conditioning, and a group receiving neither. Both conditioning and verbal expectancy were important mediators on the placebo response, but conditioning was more powerful [25].

A second explanation for the placebo effect is response by neurohormones, including motor or autonomic nervous systems, hormone systems, and immune systems. Endogenous neuroendocrine polypeptides, including β-endorphins, enkephalins, and antiopioids, are activated by many factors. These factors include placebos, vigorous exercise, and other stressors. Modulation of the opioid system may occur by an antiopiod system of neurotransmitters. γ-Aminobutyric acid, and peptide neurotransmitter, is associated with the secretion of β-endorphin and β-lipotropin [23]. The endorphin group of neurotransmitters is created from the proopiomelanocortitrophin peptide and is linked through β-lipotropin with the regulation of the hypothalamus-hypophysis-adrenal axis. There is no understanding of the exact link between the opioid-antiopioid and β-lipotropin systems of neuroendocrine

peptides. The brain peptides and their actions on presynaptic and postsynaptic receptors on neurons also are not understood. Experiments in animals provide most of the information about control of the genetic expression of the peptides [23].

In a double-blind study by Levine et al. [26], patients received placebo and then intravenous naloxone after tooth extraction. Naloxone, a partial opioid antagonist that competes with β-endorphins for the same receptor in the brain, blocked the placebo effect previously experienced by the patients. Levine et al. concluded that placebo activates β-endorphins in the brain and that naloxone increases the pain by inhibiting the placebo effect [26]. A double-blind study by Hersh et al. found ibuprofen to be more efficacious than placebo or codeine [27]. Naltrexone, a long-acting oral form of naloxone, given before oral surgery reduced the analgesic response to placebo and to codeine received after surgery. In an additional noteworthy finding, pretreatment with naltrexone prolonged the duration of ibuprofen's action rather than diminishing the peak analgesic response. This prolongation of ibuprofen's action was hypothesized to result from increased central stimulation of endogenous opiates by ibuprofen or from competition by naltrexone for liver enzymes involved in the inactivation and elimination of ibuprofen.

A third model of the placebo response is the ability of mental imagery to produce specific and measurable physiologic effects. This model explains the relation between psychological and physiologic components of the placebo effect. There is a conversion in the brain of psychological placebo-related imagery into a physiologic placebo response. A patient may modify his or her imagery content in response to bodily reactions during treatment, in response to the behaviors and attitudes of doctors or nurses, or in response to information about the treatment from other sources (such as other patients, books, and journals) [28]. An example of this model is described in another study [29]. Two matched groups of patients preparing to undergo abdominal surgery received different types of care. In one group, the anesthesiologist told the patients about the operation but not about the postoperative pain. The other group was told about the postoperative pain and assured that medication was available. It was found that the patients informed about postoperative pain needed only half the analgesic and left the hospital 2 days earlier. The authors concluded that this result showed 'a placebo effect without the placebo' [29].

Additional studies have been attempted to both characterize and explore the mechanisms of the placebo effect. One such approach has been based upon the color and shape of pills and how that affects how patients feel about their medication. For example, *ScienceDaily (Jan. 19, 2011)* reported that according to recent research the color, shape, taste and even name of a tablet or pill may have an effect on how patients feel about their medication. Choose an appropriate combination and the placebo effect gives the pill a boost, improves outcomes and might even reduce side effects. In fact, it has been observed that pill color may influence both the placebo and the nocebo effects (Fig. 7.1). Some general observations from this line of research suggests that capsules tend to be more effective than other pill forms, and that red and pink tables are generally more effective than other colors. A study was performed in order to assess the impact of the color of a drug's formulation on its

perceived effect and its effectiveness, and to examine whether antidepressant drugs available in the Netherlands are different in color from hypnotic, sedative, and anxiolytic drugs [33]. The systematic review was of 12 published studies of which six examined the perceived action of different colored drugs and six the influence of the color of a drug on its effectiveness. The studies on perceived action of drugs showed that red, yellow, and orange were associated with a stimulant effect, while blue and green were related to a tranquillizing effect. The analysis of the studies that assessed the impact of the color of drugs on their effectiveness showed inconsistent differences between colors. However, hypnotic, sedative, and anxiolytic drugs were more likely than antidepressants to be green, blue, or purple. Their overall conclusions were that colors affect the perceived action of a drug and may influence the effectiveness of some drugs, that a relation exists between the coloring of drugs that affect the central nervous system and the indications for which they are used, and that further research contributing to a better understanding of the effect of the color of drugs is warranted [33].

Placebo Effect in Various Diseases

Placebo Effect in Ischemic Heart Disease and Chronic, Stable, Exertional Angina Pectoris

The rate of improvement in the frequency of symptoms in patients with chronic, stable, exertional angina pectoris with placebo therapy has been assessed to be 30–80 % [30]. A summary of subjective and objective placebo effects in cardiovascular disease is provided in Table 7.3. Because of the magnitude of the placebo effect, most studies of new antianginal therapies were performed with placebo control. However, the safety of this practice came under scrutiny in the late 1980s because of concern that patients with coronary artery disease would have periods of no drug treatment. As a result, Glasser et al. explored the safety of exposing patients with chronic, stable, exertional angina to placebos during short-term drug trials with an average double-blind period of 10 weeks [31]. The study included all new drug applications (NDAs) submitted to the FDA between 1973 and 2001. The results of these drug trials were submitted, whether favorable or not, and all adverse events were reported. Qualifying studies used symptom-limited exercise tolerance testing as an end point. No antianginal medication, except sublingual nitroglycerin, was taken after a placebo-free or drug-free washout period. A total of 2,921 patients with angina pectoris and an abnormal exercise tolerance test who entered any randomized, double-blind, placebo-controlled trial. Since then, an additional 9 NDAs (representing 63 trials) for angina claims have been submitted to the FDA, resulting in an updated total of 10,865 patients, among whom 607 (5.6 %) were withdrawn from the trials due to an adverse drug event. The relative risk (RR) for withdrawal (placebo compared to drug-treated patients) was not increased (RR = 0.92, 0.78, 1.08; p = 0.28).

Table 7.3 Objective placebo effects in cardiovascular disease

	Placebo effect
Heart failure [37]	
Exercise tolerance testing	
1 or 2 baseline measurements	90–120 s
3–10 baseline measurements	10–30 s
Increase in ejection fraction of 5 %	20–30 % of patients
Hypertension [53]	
Measured by noninvasive automatic ambulatory 24-h monitoring	0 %
Arrhythmia	
Study 1 [63][a]	
A reduction in mean hourly frequency of ventricular tachycardia	<65 %
A reduction in mean hourly frequency of couplets	<75 %
A reduction in mean hourly frequency of all ventricular ectopic beats without regard for complexity	<83 %
Study2 [64][b]	
Baseline VPCs > 100/h	<3 times baseline
Baseline VPCs < 100/h	<10 times baseline
Silent ischemic disease [24]	
Reduction in frequency of ischemic events	44 %
Reduction in ST-segment integral	50 %
Reduction in duration of ST-segment depression	50 %
Reduction of total peak ST-segment depression	7 %
Other [67, 69, 72]	
Compliance with treatment at rate of ≥75 %	<3 times baseline

VPC Ventricular premature complexes

[a]Based on comparison of one control 24 h monitoring period to one 24-h treatment period. Variability is so great that it may be inadvisable to pool individual patient data to detect trends in ectopic frequency in evaluating new potential antiarrhythmic agents in groups of patients

[b]When differentiating proarrhythmia in patients with mixed cardiac disease and chronic ventricular arrhythmias from spontaneous variability, with false-positive rate of only 1 %

Combined events, irreversible harm (CVA, MI, Death), and serious cardiovascular events (MI, CHF, CVA) also had point estimates favoring randomization to placebo (RR = 0.54, 0.26, 1.04; $p < 0.068$ and RR = 0.89; .61, 1.30; $p = 0.56$ respectively). The conclusion was that with a greater number of trials and larger numbers of randomized patients, the results are similar to those reported prior; and, within the limitations of the study, there was no evidence that the use of a placebo control is unsafe in short-term studies of chronic stable angina (Fig. 7.4). This analysis found evidence that supported the safety of a placebo group in short-term drug trials for chronic, stable, exertional angina [37]. An analysis of the safety of a placebo control in trials of anti-hypertensive drugs has also been published [38]. Although a slightly increased risk of reversible symptoms was identified, there was no evidence of irreversible harm as a result of participation in any of these trials. The same caveats apply as discussed in the angina trials-that is, these were short term trials of carefully monitored and selected patients.

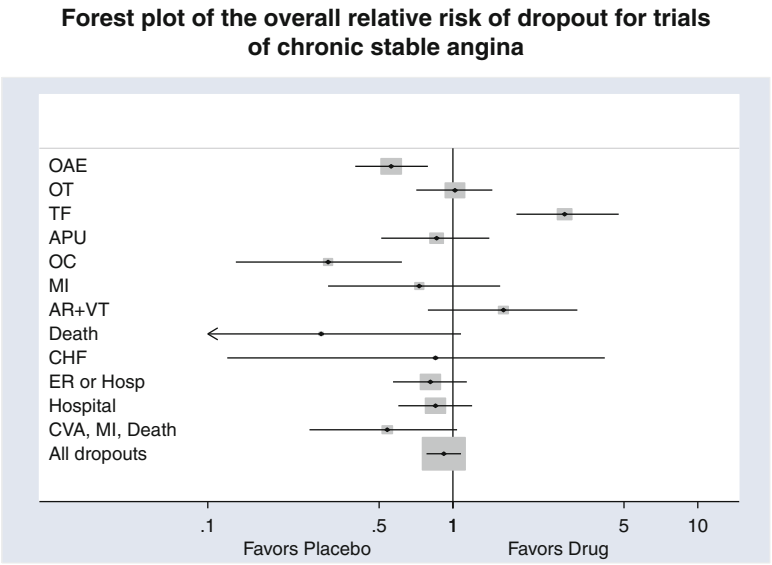

Fig. 7.4 Forest plot of the overall relative risk of dropout for trials of chronic stable angina. From: Glasser et al. [81]

The safety of using placebo in longer-term drug trials for chronic, stable, exertional angina has not been established. A placebo-controlled trial by a European group in 1986 enrolled 35 patients and made observations during a 6-month period of placebo or short-acting nitroglycerin administration [32]. This study of the long-term effects of placebo treatment in patients with moderately severe, stable angina pectoris found a shift toward the highest dosage during the titration period. Seven patients continued to receive the lowest dosage, but the average ending dosage was 65 % more than the initial dosage. Compliance, when determined by pill count, for 27 patients was >80 %. During the first 2.5 months of the trial, noncompliance with the regimen or physical inability to continue to study was ascertained. No patients died or had myocardial infarction [32].

There is a paucity of information regarding any gender differences in placebo response. Women represented 43 % of the population in the aforementioned European study [32] and were more likely to have angina despite normal coronary arteries. Because the placebo effect may be more pronounced in patients with normal coronary arteries, data from men were analyzed separately to compare them with the overall results. However, the data from men were very similar to the overall results. In fact, the functional status of men showed more improvement attributable to placebo (61 %) than overall (48 %) at 8 weeks. The results of this study showed no adverse effects of long-term placebo therapy: 65 % of patients reported subjective, clinical improvement and 27 % of patients reported objective, clinical improvement in exercise performance [32]. Of note, improvement in exercise performance can occur when patients undergo repeated testing [33].

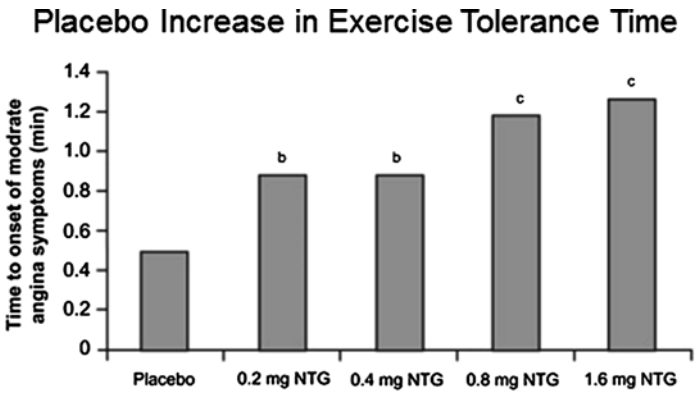

Fig. 7.5 The placebo and nocebo effect. From: Thadani and Wittig [34]

There is a problem inherent in all modern trials of antianginal therapy: because anginal patterns vary and, with modern treatments, are infrequent, a surrogate measure of antianginal effect has been adopted by the FDA and consists of treadmill walking time to the point of moderate angina. Also, just as there is a placebo effect on angina frequency, a patient's treadmill walking time frequently (50–75 %) improves with placebo therapy (Fig. 7.5). Other potential mechanisms also partially explain the improvement in exercise walking time in antianginal studies and are unrelated to a treatment effect: they are the 'learning phenomenon,' and the 'training effect.' Because of the learning phenomenon, patients frequently show an improvement in walking time between the first and second treadmill test in the absence of any treatment. The presumption is that the first test is associated with anxiety and unfamiliarity, which is reduced during the second test. Of greater importance is the training effect, with which the frequency of treadmill testing may result in a true improvement in exercise performance irrespective of treatment.

The effect of placebo on exercise tolerance in patients with angina was demonstrated in the Transdermal Nitroglycerin Cooperative Study [35], which analyzed various doses of transcutaneous-patch nitroglycerin administered for 24-h periods, in comparison with placebo patch treatment. This study was particularly important because it was the first large study to address the issue of nitrate tolerance with transcutaneous patch drug delivery in outpatient ambulatory patients. The result of the study was the demonstration of tolerance in all treated groups; the treated groups performed no better than the placebo group at the study's end. However, there was an equally striking improvement of 80 to 90s in the placebo and active treatment groups in the primary efficacy end point, walking time on a treadmill. This improvement in the placebo group could have masked any active treatment effect,

but it also demonstrated the importance of a placebo control, because without this type of control, significant improvement could have been attributed by deduction to active therapy.

It was once thought that internal mammary artery ligation improved angina pectoris until studies showed a similar benefit in patients in whom a sham operation, consisting of skin incision with no ligation, was performed. Beecher [36] tried to analyze the effect of doctors' personalities on clinical outcomes of internal artery ligation, by comparing the results of the same placebo procedure performed by one of two groups, the 'enthusiasts' or the 'skeptics.' His analysis indicated that the enthusiasts achieved nearly four times more 'complete relief' for patients than did the skeptics, even though the procedure has no known specific effects [36]. Five patients undergoing the sham operation emphatically described marked improvement [37, 38]. In objective terms, a patient undergoing the sham operation had an increase in work tolerance from 4 to 10 min with no inversion of T waves on the electrocardiogram and no pain. The internal mammary artery ligation procedure was used in the United States for 2 years before it was discontinued, when the procedure was disproved by three small, well-planned, double-blind studies [39].

Carver and Samuels also addressed the issue of sham therapy in the treatment of coronary artery disease [40]. They pointed out that although the pathophysiologic features of coronary artery disease are well known, the awareness of many of the expressions of myocardial ischemia are subjective, rendering the placebo effect more important. This factor has resulted in several treatments that are based on testimonials rather than scientific evidence and that have been touted as 'breakthroughs.' Among therapies cited by these authors are chelation therapy, various vitamin therapies, and mineral supplements. It has been estimated that 500,000 patients per year in the United States are treated by these techniques. Before 1995, the data to support claims regarding the effectiveness of chelation therapy were obtained from uncontrolled open-label studies. In 1994, van Rij et al. performed a double-blind, randomized, placebo-controlled study in patients with intermittent claudication and demonstrated no difference in outcomes between chelation and placebo treatments [41] The evaluated variables included objective and subjective measures, and improvement in many of the measures was shown with both therapies. Again, without the use of a placebo control, the results could have been interpreted as improvement as a result of chelation treatment. Adding to the controversy, however, are the results from the chelation arm of the Trial to Assess Chelation Therapy, which showed that infusions of a form of chelation therapy using disodium ethylene diamine tetraacetic acid (EDTA) reduced cardiovascular events by 18 % compared to a placebo treatment [48]. Investigators stated that more research is needed before considering routine use of chelation therapy for all heart attack patients and it remains unapproved by the FDA. The EDTA-based chelation solution also contained high doses of vitamin C, B-vitamins, and other components [42]. In addition, the trial used a composite endpoint (see Chap. 3) and benefits were only seen in the soft endpoints of the composite. TACT also showed some other important deviations from adherence to the scientific principles of a well-controlled trial. The study randomized 1,708 patients, but 311 (18 %) were lost to follow-up, nearly all because of withdrawal of consent (289 patients), and importantly, these withdrawals were not equally distributed

between the treatment groups. Significantly more patients (n = 174) withdrew from the placebo group compared with the chelation group (n = 115; hazard ratio, 0.66; $P = .001$). A similar imbalance in discontinuation from randomized treatment was observed—281 in the placebo group and 233 in the chelation group [43]. The substantial nonretention of study participants alone is sufficient to compromise the validity of the study results.

Placebo Effect in Heart Failure

In the past, the importance of the placebo effect in patients with congestive heart failure had not been recognized [49]. In the 1970s and early 1980s, administration of vasodilator therapy was given to patients in clinical trials without placebo control. Investigators believed that the cause of heart failure was predictable, so placebo-controlled trials were unnecessary. Another view of the unfavorable course of heart failure concluded that withholding a promising new agent was unethical. The ethical issues involved when placebo therapy is considered are addressed later in this chapter.

With the inclusion of placebo controls in clinical trials, a 25–35 % improvement of patients' symptoms was documented in the placebo arms of studies. This placebo response occurred in patients with mild to severe symptoms and did not depend on the size of the study. The assessment of left ventricular (LV) function can be determined by several methods, including noninvasive echocardiography, radionuclide ventriculography, or invasive pulmonary artery balloon-floatation catheterization. These methods measure the patient's response to therapy or the natural progression of the patient's heart failure [44]. Noninvasive measurements of LV ejection fraction vary, especially when the ventricular function is poor and the interval between tests is 3–6 months. Packer found that when a 5 % increase in ejection fraction was used to determine a beneficial response to a new drug, 20–30 % of patients showed improvement while receiving placebo therapy [50]. Overall, changes in noninvasive measures of LV function have not been shown to correlate closely with observed changes in the clinical status of patients with CHF. Most vasodilator and inotropic drugs can produce clinical benefit without a change in LV ejection fraction. Conversely, LV ejection fraction may increase significantly in patients who have heart failure and worsening clinical status [44].

When invasive catheterization is used to evaluate the efficacy of a new drug, interpretation must be done carefully because spontaneous fluctuations in hemodynamic variables occur in the absence of drug therapy. To avoid the attribution of spontaneous variability to drug therapy, postdrug effects should be assessed at fixed times and threshold values should eliminate changes produced by spontaneous variability. Another factor that can mimic a beneficial drug response, by favorably affecting hemodynamic measurements, is measurement performed immediately after catheterization of the right side of the heart or after ingestion of a meal. After intravascular instrumentation, systemic vasoconstriction occurs and resolves after 12–24 h. When pre-drug measurements are done during the post-catheterization

period, any subsequent measurements will show beneficial effects because the original measurements were taken in the vasoconstricted state. Comparative data must be acquired after the post-catheterization vasoconstricted state has resolved [50].

In the past, one of the most common tests to evaluate drug efficacy for heart failure was the exercise tolerance test. An increased duration of exercise tolerance represents a benefit of therapy. However, this increased duration is also recorded during placebo therapy and possibly results from the familiarity of the patient with the test, as in the learning phenomenon described earlier in this chapter for antianginal therapy; and, the increased willingness of the physician to encourage the patient to exercise to exhaustion. Placebo response to repeated exercise tolerance testing can result in an increase in duration of 90–120 s, when only one or two baseline measurements are done. This response can be reduced to 10–30 s, when 3–10 baseline measurements are performed. Another interesting finding was that the magnitude of the placebo response was directly proportional to the number of investigators in the study! Attempts to eliminate the placebo response, including the use of gas exchange measurements during exercise tolerance testing, have failed [44].

Because all methods used to measure the efficacy of a treatment for heart failure include placebo effects, studies must include placebo controls to prove the efficacy of a new drug therapy. Statistical analysis of placebo-controlled studies must compare results between groups for statistical significance. 'Between groups' refers to comparison of the change in one group, such as one receiving a new drug therapy, with the change in another group, such one receiving as a placebo [44]. For example, Archer and Leier reported that placebo therapy for 8 weeks in 15 patients with CHF resulted in a mean improvement in exercise duration of 81 s, to 30 % above baseline [51]. This result was statistically significant compared with the 12-s improvement in the nine patients in the nonplacebo control group. There were no statistically significant differences between the placebo and non-placebo groups at baseline or at week 8 of treatment by between-group statistical analysis. Echocardiography showed no significant improvement in left ventricular function in either group, and no significant differences between the two groups at baseline or during the treatment period. To prove the existence of, and to quantitate the therapeutic power of placebo treatment in CHF, all studies were performed by the same principal investigator with identical study methods and conditions, and all patients were familiarized similarly with the treadmill testing procedure before baseline measurements. Also, the study used a well-matched, nonplacebo control group and this illustrated the spontaneous variability of CHF [45].

Placebo Effect in Hypertension

Some studies of the placebo response in patients with hypertension have shown a lowering of blood pressure [46–51], but others have not [52–56]. In a Medical Research Council study, when active treatment was compared with placebo therapy (given to patients with mild hypertension for several months) similar results were

produced in the two groups—an initial decrease in blood pressure followed by stabilization [46]. Of historical note is a study by Goldring et al. published in 1956. These authors fabricated a sham therapeutic 'electron gun' designed to be as 'dramatic as possible, but without any known physiologic action other than a psychogenic one.' Initial exposure to 'the gun' lasted 1–3 min and was increased to 5 min three times daily. The investigators noticed substantially decreased blood pressure during therapy compared with pre-therapy. In six of nine hospitalized patients there was a systolic/diastolic blood pressure reduction of 39/28 mmHg.

An important factor to consider is the method used to measure blood pressure. With the use of standard sphygmomanometry, in hypertensive patients, blood pressure initially decreases upon multiple measurements. In other studies of BP, 24-h intraarterial pressure measurements and circadian curves did not show a decrease in blood pressure or heart rate during placebo therapy; however, Intraarterial blood pressure measurements at home were lower than measurements at the hospital. The circadian curves from intraarterial ambulatory blood pressure monitoring were reproducible on separate days, several weeks apart [57]. Similar to 24-h invasive intra-arterial monitoring, 24-h noninvasive automatic ambulatory blood pressure also is apparently devoid of a placebo effect. In one study, on initial application of the blood pressure device, a small reduction in ambulatory blood pressure values in the first 8 h occurred with placebo therapy. This effect, however, did not change the mean 24-h value. The home monitoring values were lower than the office measurements. Heart rate also was measured, with no variance in either setting. The office measurement of blood pressure was lower after 4 weeks of placebo therapy, but the 24-h blood pressure measurement was not [58]. This study confirmed the absence of a placebo effect in 24-h noninvasive ambulatory blood pressure monitoring, as suggested by several specific studies on large numbers of patients [59, 60]. The 24-h monitoring was measured by the noninvasive automatic Spacelabs 5300 device (Spacelabs, Redmond, Wash.) [61]. Another important factor in 24-h noninvasive monitoring is that the intervals of measurement were <60 min [62].

In a study on the influence of observer's expectation on the placebo effect in blood pressure measurements, 100 patients were observed for a 2-week single-blind period and for a 2-week double-blind period [63]. During this time, the patients' blood pressures were measured by two methods: a 30-min recording with an automatic oscillometric device and a standard sphygomomanometric measurement performed by a physician. All patients were seen in the same examining room and seen by the same physician and their blood pressure monitored by the same automatic oscillometric device. The results during the single-blind period showed a slight but statistically significant decrease in diastolic blood pressure detected by the automatic oscillometric device and no decrease measured by the physician. During the double-blind period, there was no additional decline in diastolic blood pressure measured by the oscillometric device, but the physician measured significant decreases in systolic and diastolic blood pressures. Overall, the blood pressures measured by the automatic oscillometric device, in the absence of the physician, were lower than those measured by the physician. However, there was significant correlation between the two methods. It should be mentioned that although there

was a placebo effect in the measurement of blood pressure in the landmark Systolic Hypertension in the Elderly Program, it was not as significant as the reduction in blood pressure produced by active therapy in patients ≥60 years of age who had isolated systolic hypertension.

As was true with angina studies, questions have been raised about the safety of placebo control studies in hypertension. As a result, two recent publications have addressed this issue [38, 71]. Al-Khatib et al. performed a systematic review of the safety of placebo controls in short-term trials [70]. In their meta-analysis, they combined the data for death, stroke, MI, and CHF from 25 randomized trials. Each study was relatively small (n = 20–734) but the combined sample size was 6409. They found a difference between the two treatment groups and at the worst there were no more than 6/10000 difference between placebo and active therapy. Lipicky et al. reviewed all original case report forms for deaths and dropouts were reviewed from al anti-hypertensive drug trials submitted to the FDA (as an NDA) between 1973 and 2001 [64]. The population at risk was 86,137 randomized patients; 64,438 randomized to experimental drug, and 21,699 to placebo. Of the 9636 dropouts more were from the placebo group (RR 1.33 for placebo), the majority of the dropouts were, as expected, due to treatment failures, and the patients were simply returned to their original therapies with no sequelae. When serious adverse events were compared (death, irreversible harm, etc.) there were no differences between placebo and experimental drug.

Placebo Effect in Arrhythmia

Spontaneous variability in the natural history of disease or in its signs or symptoms is another reason that placebo controls are necessary. In a study of ventricular arrhythmias, Michelson and Morganroth found marked spontaneous variability of complex ventricular arrhythmias such as ventricular tachycardia and couplets [65]. These investigators observed 20 patients for 4-day periods of continuous electrographic monitoring. They recommended that when evaluating therapeutic agents, a comparison of one 24-h control period to four 24-h test periods must show a 41 % reduction in the mean hourly frequency of ventricular tachycardia and a 50 % reduction in the mean hourly frequency of couplets to demonstrate statistically significant therapeutic efficacy. They also suggested that individual patient data not be pooled to detect trends because individual variability was so great. In another study by Morganroth et al. an algorithm to differentiate spontaneous variability from proarrhythmia in patients with benign or potentially lethal ventricular arrhythmias was provided. Two or more Holter tracings were examined from each of 495 patients during placebo therapy. The algorithm defined proarrhythmia as a >3-fold increase in the frequency of ventricular premature complexes (VPCs) when the baseline frequency of ventricular premature complexes VPCs/h and a >10-fold increase when the frequency was <100 VPCs/h. The false-positive rate was 1 % when this algorithm was used.

The Cardiac Arrhythmia Suppression Trial (CAST) evaluated the effect of antiarrhythmic therapy in patients with asymptomatic or mildly symptomatic ventricular arrhythmia [66]. Response to drug therapy was determined by a ≥80 % reduction in ventricular premature depolarizations or a ≥90 % reduction in runs of unsustained ventricular tachycardia as measured by 24-h Holter monitoring 4–10 days after initiation of pharmacologic treatment, a response previously considered to be an important surrogate measure of antiarrhythmic drug efficacy. One thousand four hundred fifty-five patients were assigned to drug regimens, and ambulatory electrocardiographic (Holter) recording screened for arrhythmias. The CAST Data and Safety Monitoring Board recommended that encainide and flecainide therapy be discontinued because of the increased number of deaths from arrhythmia, cardiac arrest, or any cause compared with placebo treatment. The CAST investigators conclusion emphasized the need for more placebo-controlled clinical trials of antiarrhythmic drugs with a mortality end point.

Relation of Treatment Adherence to Survival in Patients with or Without History of Myocardial Infarction

An important consideration in determining study results is adherence to therapy and the presumption that any differences in adherence rates would be equal in the active versus the placebo treatment groups. The Coronary Drug Project Research Group [67] planned to evaluate the efficacy and safety of several lipid-influencing drugs in the long-term treatment of coronary heart disease. This randomized, double-blind, placebo-controlled, multicenter clinical trial found no significant difference in the 5-year mortality of 1,103 men treated with the fibric acid derivative clofibrate compared with 2,789 men given placebo. However, subjects showing good adherence (patients taking ≥80 % of the protocol drug) had lower mortality than did subjects with low adherence in both the clofibrate group and the placebo group [67].

A similar association between adherence and mortality was found in patients after myocardial infarction in the Beta-Blocker Heart Attack Trial data [72]. This phenomenon was extended to women after myocardial infarction. On analysis of the trial data for 505 women randomly assigned to β-blocker therapy or placebo therapy, there was a 2–2.5-fold increase in mortality within the first 2 years in patients taking <75 % of their prescribed medication. Adherence among men and women was similar, at about 90 %. However, the cause of the increased survival resulting from good adherence is not known. There is speculation that good adherence reflects a favorable psychological profile—a personal ability to make lifestyle adjustments that limit disease progression. Alternatively, adherence may be associated with other advantageous health practices or social circumstances not measured. Another possible explanation is that improved health status may facilitate good adherence [68].

The Lipid Research Clinics Coronary Primary Prevention Trial [69] did not find a correlation between compliance and mortality. These investigators randomly assigned 3806 asymptomatic hypercholesterolemic men to receive cholestyramine

or placebo. The main effects of the drug compared with placebo on cholesterol level and death or nonfatal myocardial infarction were analyzed over a 7-year period. In the group receiving active drug, a relation between compliance and outcome existed, mediated by a lowering of cholesterol level. However, no effect of compliance on cholesterol level or outcome was observed in the placebo group [69, 70].

The Physicians' Health Study included a randomized fashion 22,000 United States male physicians 40–84 years old who were free of myocardial infarction and cerebral vascular disease [71]. This study analyzed the benefit of differing frequencies of aspirin consumption on the prevention of myocardial infarction. In addition, the study identified factors associated with adherence and analyzed the relation of adherence with cardiovascular outcomes in the placebo group. Analysis showed an average compliance of 80 % in the aspirin and placebo groups during the 60 months of follow-up [71]. Adherence during that trial was associated with several baseline characteristics in both the aspirin and placebo groups as follows. Trial participants with poor adherence (<50 % compliance with pill consumption), relative to those with good adherence, were more likely to be younger than 50 years at randomization, to smoke cigarettes, to be overweight, not to exercise regularly, to have a parental history of myocardial infarction, and to have angina. These associations were statistically significant. In a multivariate logistic regression model, cigarette smoking, excess weight, and angina remained significant predictors of poor compliance. The strongest predictor of adherence during the trial was adherence during the run-in period. Baseline characteristics with little relation to adherence included regular alcohol consumption and a history of diabetes and hypertension [71]. Using intention-to-treat analysis, the aspirin group had a 41 % lower risk of myocardial infarction compared with the placebo group. On subgroup analysis, participants reporting excellent (≥95 %) adherence in the aspirin group had a significant, 51 % reduction in the risk of first myocardial infarction relative to those with similar adherence in the placebo group. Lower adherence in the aspirin group was not associated with a statistically significant reduction in first myocardial infarction compared with excellent adherence in the placebo group. Excellent adherence in the aspirin group was associated with a 41 % lower relative risk of myocardial infarction compared with low adherence in the aspirin group. Excellent adherence in the placebo group was not associated with a reduction in relative risk. The rate of stroke was different from that of myocardial infarction. On intention-to-treat analysis, the aspirin group had a nonsignificant, 22 % increased rate of stroke compared with the placebo group. Participants with excellent adherence in the placebo group had a lower rate of strokes than participants in the aspirin or placebo groups with low (<50 %) adherence. Excellent adherence in the placebo group was associated with a 29 % lower risk of stroke compared with excellent adherence in the aspirin group.

Also analyzed in the above study, was the overall relation of adherence to aspirin therapy with cardiovascular risk when considered as a combined end point of all important cardiovascular events, including first fatal or nonfatal myocardial infarction or stroke or death resulting from cardiovascular disease with no previous myocardial infarction or stroke. On intention-to-treat analysis, there was an 18 % decrease in the risk of all important cardiovascular events in the aspirin group compared with the

Table 7.4 Placebo adherence and mortality

Outcome	HR for adherence
Total mortality	.52
CVD mortality	.66
Non CVD mortality	.40
CHD mortality	.54
Incident cancer	.42

Padula et al. [72]

placebo group. Participants with excellent adherence in the aspirin group had a 26 % reduction in risk of a first major cardiovascular event compared with those with excellent adherence in the placebo group. However, participants in the aspirin group with low compliance had a 31 % increased risk of a first cardiovascular event compared with those in the placebo group with excellent adherence. Within the placebo group, there was no association between level of adherence and risk of a first cardiovascular event. In the analysis of death resulting from any cause in persons with a previous myocardial infarction or stroke, low adherence in both the aspirin group and the placebo group was associated with a fourfold increase in the risk of death. When the 91 deaths due to cardiovascular causes were studied, similar elevations in risk were found in both the placebo and aspirin groups with poor adherence compared with those in the placebo group with excellent adherence.

The Physicians' Health Study [71] found results similar to those of the Coronary Drug Project when all cause mortality and cardiovascular mortality were considered [67]. These relations remained strong when adjusted for potential confounding variables at baseline. The strong trend for higher death rates among participants with low adherence in both the aspirin and the placebo groups may be due to the tendency for subjects to decrease or discontinue study participation as their health declines to serious illness. Low adherence in the placebo group was not associated with an increased risk of acute events such as myocardial infarction. Thus placebo effects seem to vary depending on the outcome considered.

Most recently has been an analysis of the Hormone Estrogen Replacement Study, a secondary prevention study of CHD in postmenopausal women (Table 7.4) [30]. Investigators also evaluated the association of placebo adherence and total mortality and found that the more adherent participants had significantly lower mortality than non-adherers HR 0.52 (0.29; 0.93) [72]. They speculated about the possibilities for that observation and suggested that adherence could be a marker for healthier lifestyles and/or that as a fatal illness prodrome, adherence may decrease (an effect-cause artifact).

Miscellaneous

Flaten conducted an experiment in which he told participants that they were receiving either a relaxant, stimulant, or an inactive agent, but in fact gave all of them the inactive agent. Patients who were told they were getting the relaxant showed reduced

stress levels, while those who thought they were receiving the stimulant showed increased arousal levels. In another study, asthmatics that were told they were getting either a bronchodilator or bronchconstrictor and who actually received that particular therapy, had more effective responses when the information received actually matched the drug effect.

Linde et al. evaluated the placebo effect of pacemaker implantation in 81 patients with obstructive hypertrophic cardiomyopathy [78]. The study design was a 3-month multicenter, double-blind, cross-over study. In the first study period 40 patients were assigned to inactive pacing, and were compared to 41 patients with active pacing. During inactive pacing, there was an improvement in chest pain, dyspnea, palpitations, and in the left ventricular outflow gradient. The change in the active pacing group for most parameters was greater.

Clinical Trials and the Ethics of Using Placebo Controls

Since the 1962 amendments to the Food, Drug, and Cosmetic Act, the FDA has had to rely on the results of 'adequate and well-controlled' clinical trials to determine the efficacy of new pharmacologic therapies. Regulations govern pharmacologic testing and recognize several types of controls that may be used in clinical trials to assess the efficacy of new pharmacologic therapies. The controls include (1) placebo concurrent control, (1) dose-comparison concurrent control, (2) no-treatment concurrent control, (4) active-treatment concurrent control, and (5) historical control (Table 7.5). Regulations, however, do not specify the circumstances for the use of these controls because there are various study designs that may be adequate in a given set of circumstances [18].

There is ongoing debate concerning the ethics of using placebo controls in clinical trials of cardiac medications. The issue revolves around the administration of placebo in lieu of a proven therapy. Two articles, by Rothman and Michels [73] and Clark and Leaverton [74], illustrate the debate. Rothman and Michels [73] state that patients in clinical trials often receive placebo therapy instead of proven therapy for the patient's medical condition and assert that this practice is in direct violation of the Nuremberg Code and the World Medical Association's adaptation of this Code in the Declaration of Helsinki. The Nuremberg Code, a 10-point ethical code for experimentation in human beings, was formulated in response to the human experimentation atrocities that were recorded during the post-World War II trial of Nazi physicians in Nuremberg, Germany. According to Rothman and Michels [73],

Table 7.5 Types of treatment controls

Placebo concurrent control
Dose-comparison concurrent control
No-treatment concurrent control
Active-treatment concurrent control
Historical control

violation occurs because the use of placebos as controls denies the patient and best proven therapeutic treatment. It occurs despite the establishment of regulatory agencies and institutional review boards, although these authors seem to ignore that informed consent is part of current practice, as certainly was not the case with the Nazi atrocities. However, a survey of federally funded grants found that despite the process of informed consent almost 25 % of medical research subjects were unaware that they were even part of a research project or that they were receiving investigational therapies. It should be noted, however, that this survey spanned 20 years, and did not include analysis for the more recent time period, when, most would agree, there has been more emphasis on informed consent.

One reason why placebo-controlled trials are approved by institutional review boards is that this type of trial is part of the FDA's general recommendation for demonstrating therapeutic efficacy before an investigational drug can be approved. That is, according to the FDA, when an investigational drug is found to be more beneficial by achieving statistical significance over placebo therapy, then therapeutic efficacy is proven [75]. As more drugs are found to be more effective than placebos in treating diseases, the inclusion of a placebo group is often questioned. However, this question ignores that in many cases drug efficacy in the past had been established by surrogate measures; and, as new and better measures of efficacy become available, additional study becomes warranted. Regarding surrogate measures and their potential to mislead, the study of the suppression of ventricular arrhythmia by antiarrhythmic therapy was later proven to be unrelated to survival; in fact, results with active therapy were worse than with placebo. Likewise, in studies of inotropic therapy for heart failure, exercise performance rather than survival was used as the measure of efficacy, when in fact a presumed efficacious therapy performed worse than placebo when survival was assessed. In the use of immediate short-acting dihydropyridine calcium antagonist therapy for the relief of symptoms of chronic stable angina pectoris, again a subject might have fared better had he or she been randomly assigned to placebo therapy.

Also important to the concept that established beneficial therapy should not necessarily prohibit the use of placebo in the evaluation of new therapies is that the natural history of a disease may change, and the effectiveness of so-called established therapies (e.g., antibiotic agents for treatment of infections) may diminish. When deciding on the use of an investigational drug in a clinical trial, the prevailing standard is that there should be enough confidence to risk exposure to a new drug, but enough doubt about the drug to risk exposure to placebo. Thus, in this situation, the use of a placebo control becomes warranted, particularly as long as other live-saving therapy is not discontinued.

The use of placebo-controlled trials may be advocated on the basis of a scientific argument. When pharmacologic therapy was shown to be effective in previous placebo-controlled trials, conclusions made from current trials without placebo controls may be misleading because the previous placebo-controlled trial then becomes a historical control. Historical controls are the least reliable for demonstration of efficacy [18]. In active-controlled clinical trials without a placebo arm, there is an assumption that the active control treatment is as effective under the new

experimental conditions as it was in the previous placebo-controlled clinical trial. This assumption can result in misleading conclusions when results with an experimental therapy are found to be equivalent to those with the active, proven therapy. This conclusion of equivalence can be magnified by conservative statistical methods, such as the use of the 'intent-to-treat' approach, an analysis of all randomized patients regardless of protocol deviations, and an attempt to minimize the potential for introduction of bias into the study. Concurrent placebo controls account for factors other than drug-effect differences between study groups. When instead of a placebo-control group an untreated control group is used, then blinding is lost and treatment-related bias may occur [18, 74].

Clark and Leaverton [74] and Rothman and Michels [73] agree that the use of placebo controls is ethical when there is no existing treatment to favorably affect morbidity and mortality. Furthermore, there are chronic diseases for which treatment exists that not favorably alter morbidity and mortality. For example, no clinical trial has found the treatment of angina to increase a patient's survival. In contrast, treatment after a myocardial infarction with β-blocking agents has been convincingly proven to increase a patient's survival [74]. However, Clark and Leaverton [74] disagree with Rothman and Michels [73] in that they assert that for chronic disease, a placebo-controlled clinical trial of short duration is ethical because there is usually no alteration in long-term outcome for the patient. The short duration of the trial represents a small segment of the lifetime management of a chronic disease. For instance, the treatment of chronic symptomatic CHF and a low ejection fraction (<40 %) with enalapril was shown to decrease mortality by 16 %. This decrease in mortality was most marked in the first 24 months of follow-up, with an average follow-up period of 40 months. Therefore, only long-term compliance with pharmacologic therapy resulted in some decreased mortality. Another example of a chronic medical condition that requires long-term treatment and in which short-term placebo is probably not harmful is hypertension [76]. In some studies men and women with a history of myocardial infarction and with a ≥80 % compliance with treatment, including placebo therapy, had an increased survival. This increased survival was also described in patients in a 5-year study of the effects of lipid-influencing drugs on coronary heart disease. [67, 68, 77].

A different argument for the ethical basis of using placebo controls relies on the informed consent process. Before a patient's participation in a clinical trial, the patient is asked to participate in the trial. The informed consent process includes a description of the use of placebos along with other aspects of the trial. In this written agreement, the patient is responsible for notifying the physician of any medical problems and is informed of his or her right to withdraw from the study at any time, as described in the Nuremberg Code and the Declaration of Helsinki. During this disclosure, patients are presented with the risks and benefits of the study. On the basis of this information, a patient voluntarily decides to participate, knowing that he or she may receive a placebo or investigational medication.

All parties involved in research should be responsible for their research and accountable for its ethics. Clinical trials failing to comply with the Nuremberg Code and the Declaration of Helsinki should not be conducted and should not be accepted for publication. Yet, there is disagreement in determining which research

methods are in compliance with the Nuremberg Code and Declaration of Helsinki. Scientific needs should not take precedence over ethical needs. Clinical trials need to be carefully designed to produce a high quality of trial performance. In addition, in experimentation involving human subjects, the Nuremberg Code and Declaration of Helsinki must be used as universal standards. The Declaration of Helsinki addresses the selection of appropriate controls by stating 'the benefits, risks, burdens, and effectiveness of a new method should be tested against the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or of no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists.' Others have added that if the patient or subject is not likely to be harmed through exposure to placebo, and they can give voluntary informed consent, it is permissible to use placebo controls in some trials despite the existence of a know effective therapy.

Conclusions

Until the mechanism of the placebo action is understood and can be controlled, a clinical trial that does not include a placebo group provides data that should be interpreted with caution. The absence of a placebo group makes it difficult to assess the true efficacy of a therapy. It is easy to attribute clinical improvement to a drug therapy when there is no control group. As was found with heart failure, almost all chronic diseases have variable courses. In addition, because each clinical trial has a different setting and different study design within the context of the physician-patient relationship, a placebo group helps the investigator differentiate true drug effects from placebo effects.

More important than the inclusion of a placebo group is a careful study design that includes frequent review, by a data and safety monitoring board, of each patient's medical condition. This monitoring is crucial to protect the study participants. To protect the participants, trials must include provisions that require a patient to be removed from a trial when the patient or doctor believes that removal is in the patient's best interest. The patient can then be treated with currently approved therapies.

Patients receiving placebo may report subjective clinical improvements, and demonstrate objective clinical improvement, for instance on exercise tolerance testing or Holter monitoring of ischemic events. Findings such as these dispel the implication that placebo therapy is the same as no therapy and may occur because many factors are involved in the physician-patient relationship such as the psychological state of the patient; the patient's expectations and conviction in the efficacy of the method of treatment' and the physician's biases, attitudes, expectations, and methods of communication [2]. An explanation of improvement in patients participating in trials is the close attention received by patients from the investigators. Baseline laboratory values are checked to ensure the safety of the patient and compliance with the study protocol. This beneficial response by the patient is called a positive placebo effect when found in control groups of patients receiving placebo therapy [30, 33, 36, 37, 39, 44, 63, 78].

Conversely, the condition of patients receiving placebos has also in some cases worsened. Every drug has side effects. These side effects are also found with placebo therapy and can be so great that they preclude the patient's continuation with the therapy. This phenomenon is always reported by patients in clinical trials receiving placebo [14, 32, 44, 63, 79, 80]. Finally, placebos can act synergistically and antagonistically with other specific and nonspecific therapies. Therefore much is still to be discovered about the placebo effect.

The arguments in support of the use of placebo controls (placebo "orthodoxy") are numerous. The word "orthodoxy" is from the Greek ortho ('right', 'correct') and doxa ('thought', 'teaching', 'glorification'). Orthodoxy is typically used to refer to the correct theological or doctrinal observance of religion, as determined by some overseeing body. The term did not conventionally exist with any degree of formality (in the sense in which it is now used) prior to the advent of Christianity in the Greek-speaking world, though the word does occasionally show up in ancient literature in other, somewhat similar contexts. Orthodoxy is opposed to heterodoxy ('other teaching'), heresy and schism. People who deviate from orthodoxy by professing a doctrine considered to be false are most often called heretics. Some of the supporting arguments are that there are methodologic limitations of trials using active controls such as:

- Variable responses to drugs in some populations
- Unpredictable and small effects
- Spontaneous improvements

In addition, some believe that no drug should be approved unless it is clearly superior to placebo or no treatment, so that placebo is ethical if there is "no permanent adverse consequence" form its use; or, if there is "risk of only temporary discomfort", or if there "is no harm" consequent to its use. It should be noted that these latter two arguments are not equivalent; that is, patients may be harmed by temporary but reversible conditions, and that these criteria may in fact permit intolerable suffering. For example, in the 1990s several placebo-controlled trials of ondansetron for chemotherapy induced vomiting were performed when there were existent effective therapies (i.e. no permanent disability, but more than mere discomfort). Another example might be the use of placebo-controlled trials of antidepressants, in which there might occur instances of depression-induced suicide.

Others argue for the use of active-controls (Active-control "Orthodoxy") in lieu of placebo controls. They argue that whenever an effective intervention for a condition exists, it must be used as the control group; that is, the clinically relevant question is not whether a new drug is better than nothing, but whether it is better than standard treatment. The supporters of the use of active controls point to the most recent "Declaration of Helsinki" which states; "the benefits, risks, burdens, and effectiveness of a new method should be tested against those of the most current prophylactic, diagnostic, or therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists."

The problem with "Active-Control Orthodoxy" is that scientific validity constitutes a fundamental ethical protection, and that scientifically invalid research cannot

be ethical no matter how safe the study participants are. Thus, the almost absolute prohibition of placebo in every case in which an effective treatment exists is too broad, and that patients exposed to placebo may be better off than the group exposed to a new intervention. These authors agree with Emmanual and Miller in support of a "middle ground" as discussed above.

Summary

The effect of placebo on the clinical course of systemic hypertension, angina pectoris, silent myocardial ischemia, CHF, and ventricular tachyarrhythmia's has been well described. In the prevention of myocardial infarction, there appears to be a direct relation between compliance with placebo treatment and favorable clinical outcomes. The safety of short-term placebo-controlled trials has now been well documented in studies of drug treatment of angina pectoris. Although the ethical basis of performing placebo-controlled trials continues to be challenged in the evaluation of drugs for treating cardiovascular disease, as long as a life-saving treatment is not being denied it remains prudent to perform placebo-controlled studies for obtaining scientific information.

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