

# The Placebo-nocebo conundrum

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*"You must know that the will is a powerful adjuvant of medicine."*  
(Paracelsus 1493-1541)

## Objectives

- To define placebos, placebo effect.
- To define social norms, placebo effect and the 'generalisability' and the placebo effect.
- To define expectations and the placebo, the placebo as a methodological tool, alternative therapies and the placebo effect.
- To define the significance of the relatively recently discovered nocebo effect.

## Competencies addressed

This article addresses the following competency standards: 1.3, 4.2, 7.1, 7.2, 7.3

The response to pharmacotherapy is more than the introduction of a medicine into the body. It represents the culmination of the health professional/patient relationship. The doctor prescribes the medicine in anticipation that it will induce the *expected* therapeutic effect and the patient fervently desires the drug to be effective and shares the professional's expectations that it will produce the desired effect (1).

Extraneous factors may considerably influence the size of a treatment effect. Factors such as the reputation of doctors, the patient's attitude towards the expected benefit, treatment mode, and credibility of the treatment might influence patients' expectancies and therefore therapeutic outcome (1,2). Consequently, administration of medicine takes place under circumstances characterised by *biased expectations* and *enhanced suggestibility* on the part of both the health professional and the patient (1-4).

In Latin placebo means literally "*I shall be acceptable or pleasing*", from the verb *placere*, to please. It came into medical terminology from liturgical Latin near the end of the eighteenth century.

The placebo was first defined as "any therapy, or that component of any therapy, that is deliberately used for its nonspecific, psychological, or psychophysiological effect or that is used for its presumed specific effect on a patient, symptom, or illness, but which, unknown to patient and therapist, is without specific activity for the condition being treated". The placebo effect is defined as "the nonspecific, psychological, or psychophysiological effect produced by a placebo"(2).

The placebo has so fired the imagination of the medical and lay world that there have now been hundreds of research papers and books on the subject. Four recent books on the placebo are listed in the reference list (5,6,7,8)

## The powerful placebo

The idea of the *powerful* placebo in modern times originated with Beecher back in 1955. He evaluated 24 studies and calculated that about 33 percent of those in the studies improved due to the placebo effect (3).

Other studies calculate the placebo effect as being even greater than Beecher claimed. For example, studies have shown that placebos are effective in 50 or 60 percent of subjects with certain conditions, e.g., "pain, depression, some heart ailments, gastric ulcers and other stomach complaints" As effective as the new psychotropic drugs seem to be in the treatment of various brain disorders, some researchers maintain that there is not adequate evidence from studies to prove that the new drugs are much more effective than placebos (4).

Recently, brain scan studies have shown that during the placebo effect, the brain turns down its own pain-responsive regions. (9)

**The influence of the mind?** A person's *beliefs* and *hopes* about a treatment, combined with their *suggestibility*, may have a significant biochemical effect. Sensory experience and thoughts can affect neurochemistry. The body's neurochemical system affects and is affected by other biochemical systems, including the hormonal and immune systems (1,4,10).

Thus, it is consistent with current knowledge that a person's *hopeful* attitude and *beliefs* may be very important to their physical well-being and recovery from injury or illness.

However, it may be that much of the placebo effect is not a matter of *mind* over *biochemistry*, but of *mind* over *behaviour*. A part of the behaviour of a "sick" person is learned. So is part of the behaviour of a person in pain. In short, there is a certain amount of *role-playing* by ill or hurt people. Role-playing is not the same as faking or malingering. The behaviour of sick or injured persons is socially and culturally based to some extent. The placebo effect may be a measurement of changed behaviour affected by a belief in the treatment. The changed behaviour includes a change in attitude, in what one says about how one feels, and how one acts. It may also affect one's body chemistry (11-13).

**Response expectations** have been proposed as the major determinant of placebo effects. However it has recently been shown that different expectations produce different analgesic effects which in turn can be harnessed in clinical practice. A fascinating study where thoracotomised patients were treated with buprenorphine on request for three consecutive days, together with a basal intravenous infusion of saline solution. However, the *symbolic* meaning of this basal infusion was changed in three different groups of patients:

- The first group was told nothing about any analgesic effect (*natural history*).
- The second group was told that the basal infusion was either a powerful painkiller or a placebo (*classic double-blind administration*).
- The third group was told that the basal infusion was a potent painkiller (*deceptive administration*).

Therefore, whereas the analgesic treatment was exactly the same in all three groups, the verbal instructions about the basal infusion differed. The placebo effect of the saline basal infusion was measured by recording the doses of buprenorphine requested over the three-days treatment. It was found that the *double-blind group* showed a reduction of buprenorphine requests compared to the *natural history* group. However, this reduction was even larger in the *deceptive administration* group. Overall, after 3 days of placebo infusion, the first group received 11.55 mg of buprenorphine, the second group 9.15 mg, and the third group 7.65 mg. Despite these dose differences, analgesia was the same in the three groups. These results indicate that *different verbal instructions about certain and uncertain expectations of analgesia produce different placebo analgesic effects, which in turn trigger a dramatic change of behaviour leading to a significant reduction of opioid intake*.

The patients who thought their IV contained a powerful pain reliever required 34% less of the analgesic than the patients who were not told anything about their IV and 16% less than the patients who were told the IV could be either a powerful pain killer or a placebo. Each group got exactly the same amount of buprenorphine but their requests for the analgesic differed dramatically. The only significant difference among the three groups was the set of *verbal instructions* about the basal infusion.

Several things are worth noting about this experiment.

The *setting* involves treatment being provided by medical personnel in a medical facility. This kind of setting usually involves a *strong desire for recovery* or relief on the part of the patient, as well as a *belief* that the treatment will be effective. The different verbal instructions about the basal IV would lead to different expectations. *Belief, motivation, and expectation* are essential to the placebo effect. Together, they are referred to as the *subject-expectancy effect*. (14)

*Classical conditioning* and suggestion by an authoritative healer seem to be triggering mechanisms for the placebo effect and this is also true for complementary medicines and other complementary treatments (15,16).

The **psychological** explanation seems to be the one most commonly believed. Perhaps this is why many people are dismayed when they are told that the effective drug they are taking is a placebo. This makes them think that their problem is "all in their mind" and that there is really nothing wrong with them. Yet, there are too many studies which have found objective improvements in health from placebos to support the notion that the placebo effect is entirely psychological.

Examples:

- Workers in one study successfully eliminated warts by painting them with a brightly coloured, inert dye and promising patients the warts would be gone when the colour wore off.
- In a study of people with asthma, researchers found that they could produce dilation of the airways by simply telling people they were inhaling a bronchodilator, even when they weren't.
- Patients suffering pain after wisdom-tooth extraction obtained just as much relief from a 'pseudo application' of ultrasound as from a real one, so long as both patient and therapist thought the machine was on.
- Fifty-two percent of patients with colitis treated with placebo in 11 different trials reported feeling better - and 50 percent of their inflamed intestines actually looked better when assessed with a sigmoidoscope (3,4,9-17).

### Why does the placebo work?

Some workers believe that at least part of the placebo effect is due to an illness or injury taking its natural course. We often heal spontaneously if we do nothing at all to treat an illness or injury. Furthermore, many disorders, pains and illnesses, wax and wane. What is measured as the placebo effect could be, in many cases, the measurement of natural regression. In short, the placebo may be given credit that is due to nature. However, spontaneous healing and spontaneous remission of disease cannot explain all the healing or improvement that takes place because of placebos. *People who are given no treatment at all often do not do as well as those given placebos or real medicine and treatment* (9-11,17). The use of a placebo could be particularly considered when a patient has to undergo a washout period when changing antidepressants. It is noted that in some cases practitioners use anxiolytic medications during this time.

A theory gaining popularity is that a process of treatment that involves showing attention, care, affection, etc., to the patient, a process that is encouraging and hopeful, may itself trigger physical reactions in the body which promote healing. There is certainly data that suggest that just being in the healing situation accomplishes something (18).

Depressed patients who are merely put on a waiting list for treatment do not do as well as those given placebos. This is very telling, when placebos are given for pain management, the course of pain relief follows what you would get with an active drug. The peak relief comes about an hour after it is administered, as it does with the active drug, and so on. If placebo analgesia was the equivalent of giving nothing, one would expect a more random pattern (9-11,17). What is seen here is the placebo *mimicking* the time-course of events of the active drug.

Brown et al (18) believe that the placebo effect is mainly or purely physical and due to physical changes which promote healing or feeling better. It is assumed that the physical changes are not caused by the placebo itself. So, what is the explanatory mechanism for the placebo effect? Some think it is the process of administering it. It is thought that the touching, the caring, the attention, and other interpersonal communication that is part of the controlled study process (or the therapeutic setting), along with the hopefulness and encouragement provided by the experimenter/healer, affect the mood of the subject, which in turn triggers physical changes such as release of endorphins. The process reduces stress by providing hope or reducing uncertainty about what treatment to take or what the outcome will be. The reduction in stress prevents or slows down further harmful physical changes from occurring. (15,16,18)

The process-of-treatment hypothesis would explain how homeopathic remedies and the questionable therapies of many "alternative" health practitioners are often effective or thought to be effective. It would also explain why medicines or procedures used by conventional medicine work until they are shown to be worthless. (15,16)

## Side effects from placebos?

Placebos have even been shown to cause unpleasant side effects. Dermatitis medicamentosa and angioneurotic oedema have resulted from placebo therapy. There are even reports of people becoming addicted to placebos (19).

Some believe the placebo effect is psychological, due to a belief in the treatment or to a subjective feeling of improvement. For example, the effectiveness of antidepressants may be attributed almost entirely to the placebo effect. An analysis of 19 clinical trials of antidepressants led to the conclusion that the expectation of improvement, not adjustments in brain chemistry, accounted for 75 percent of the drugs' effectiveness (20).

A meta-analysis of clinical trials with treatment, placebo, and no treatment arms suggested that placebos have small or no effects (20). However, even more recently (2005), a re-analysis of those studies showed that when disorders are amenable to placebos and the design is adequate to detect the effects, the placebo effect is robust and approaches the treatment effect, particularly for psychological disorders such as depression (21).

Patients can become dependent on non-scientific practitioners who employ placebo therapies. Here the placebo can be an open door to quackery (22).

## The nocebo effect

Administration of medicines is also often followed by harmful effects that are not always related to their known pharmacological effects. The "nocebo effect" is the lesser-known opposite number of the placebo effect, and describes any case where putting someone in a negative frame of mind has an adverse effect on their health or well-being. Tell people a medical procedure will be extremely painful, for example, and they will experience more pain than if you had kept the bad news to yourself. Similarly, experiences of side effects within the placebo groups of drug trials have shown that a doctor's warning about the possible side effects of a medicine makes it much more likely that the patient will report experiencing those effects.(23-25)

Unlike the placebo, the *nocebo* is a very modern word; it first appeared in the literature from the 1990s and until recently very little had been written about it. It is obviously modelled on placebo, but it comes instead from *nocere*, to harm, and so has a literal meaning of

*"I shall cause harm or be harmful".*

Influences such as beliefs, attitudes and cultural factors play a part in both the *placebo* and the *nocebo* effects. In one study, women who believed they were prone to heart disease were nearly four times as likely to die as women with similar risk factors who didn't believe (23-25).

A widely used (in the sixties and seventies) and highly respected text on poisoning by drugs and chemicals produced by the Royal Pharmaceutical Society of Great Britain seems to have unwittingly preempted the concept of the nocebo without mentioning the word in its alphabetical listing of substances causing poisonings with the following monograph:

*"Placebos*

*Although presumably pharmacologically inactive, placebos have been associated with "toxic reactions", including the following: nausea, excessive sweating, tachycardia, diarrhoea, dryness of mouth, severe headache, lack of concentration, fatigue, somnolence. Allergic type reaction such as itching, maculopapular erythema, angioneurotic oedema of lips, urticaria.*

*Suggested treatment: Withdraw placebo and use psychotherapy.*

*Allergic reactions may demand antihistamine treatment and local applications of hydrocortisone" (26).*

**The effect of colour.** A systematic review of many studies found that the colour of pharmaceuticals affect the perceived action of a medicine and seem to influence the effectiveness of that medicine. Remember, the not so good old days when we had Morphine and Aspirin Mixture, Codeine and Aspirin Mixture (coloured red for analgesic potency) and the wonderful, powerful placebo mixture, Compound Syrup of Glycerophosphates (also coloured red for potency). It has been shown that a relationship exists between the colouring of medications that affect the CNS and the indications for which they are used. *Some trends suggesting that green and blue may have more sedative effects and red and orange may have more stimulant effects have been found (27,28).*

## Placebo, ethics and legality?

The power of the placebo effect has led to an ethical dilemma. We should not deceive other people, but we should relieve the pain and suffering of our patients. Should health professionals use deception to benefit one's patients? Is it unethical for a prescriber to knowingly prescribe a placebo without informing the patient? If informing the patient reduces the effectiveness of the placebo, is some sort of deception warranted in order to benefit the patient? Some professionals think it is justified to use a placebo in those types of cases where a strong placebo effect has been shown and where distress is an aggravating factor. Others think it is always wrong to deceive the patient and that informed consent requires that the patient be told that a treatment is a placebo treatment. If this were the case the conduct of clinical trials would be in jeopardy. If the placebo effect is an illusion, then another ethical dilemma arises: should placebos be given if it is known that deception does not really reduce pain or aid in the cure of anything?

Recent work has addressed the question of the placebo in clinical practice. The authors argue, firstly, that the placebo can be an effective treatment, secondly, it is demonstrated that its use does not always entail deception and finally they produce guidelines according to which the placebo may be used for clinical purposes. They suggest that in select cases, use of the placebo may even be morally imperative (31).

While it may be unethical to knowingly package, prescribe, or sell placebos as magical cures, the Complementary and alternative medicine practitioners seem to think they are ethical because they *really believe* in their treatments (15,16)

Two studies investigated the views of both patients and medical practitioners as to the ethics of using placebos.

1. A study of 477 patients and 300 GPs from primary care practices utilising two questionnaires on responders' attitudes regarding non-specific therapies found that 87 per cent of patients and 97% of GPs thought that physical complaints can get better by believing in the effectiveness of the therapy. Overall, there was more support for placebo interventions among patients than among GPs (32)

2. Another recent study found that prescribing placebo treatments seems to be common and is viewed as ethically permissible among the surveyed US medical practitioners and rheumatologists. Vitamins and over the counter analgesics are the most commonly used treatments. Doctors might not be fully transparent with their patients about the use of placebos and might have mixed motivations for recommending such treatments.(33)

Although the available evidence is incomplete and confusing at times there can be little doubt that the prevalence of placebo use outside of clinical trials is not negligible and that views and attitudes on placebo use differs considerably among individuals, both health care professionals and patients.(34)

A fascinating study on perceived efficacy of a placebo based on cost carried out on 82 healthy volunteers who received identical placebos but half were informed that their 'painkiller' cost \$US2.50 per dose while the other half were told their drug had been discounted to \$US0.10. After being given light electric shocks to the wrist pre and post tablet, 85% of those taking the "full-priced" placebo reported a reduction in pain a compared with 61% of those taking the "cheaper" placebo (35).

Another area that has recently been studied is that of sexual dysfunction in women, where a substantial number of women experienced clinically significant improvement in sexual function during treatment with placebo. Changes in sexual behaviour during the trial, more so than participant age or symptom severity at baseline, appeared to be an important determinant of outcome. (36)



**Culture:** Moerman and Jonas in 2002 suggested that the term ‘the placebo effect’ should be replaced by ‘the meaning response’. They refer to studies that shows that the effects of treatment of duodenal ulcer with either active agents or with placebos varies enormously across different cultures. Cultures with a low rate of placebo response to anti-ulcer treatment also have a low rate of response to active treatment. Cultures with a high rate of response to placebo also has a high rate of response to active treatment. These studies also demonstrate that different cultures have varying placebo responses to different medical conditions.(37)

Table 1 summarises some key points that could be considered when reviewing a patient’s medication and their response or non-response.

**Table 1: Response or non- response to therapy**

- Response to drug therapy may be influenced by biased expectations and enhanced suggestions.
- Placebos are effective in 50-60% of people with certain conditions.
- Placebo effect may be a measurement of mind over behaviour which can validly show objective health changes.
- The nocebo effect where harmful effects occur may be related to beliefs, attitudes and cultural factors.
- Colour, size, brand, and shape of tablets may influence response.
- Cost may also be a factor.

It should be remembered that since patients’ beliefs and fears may be generated by just about anything they come in contact with, it may well be that many things that are unattended to by many if not most health professionals, such as the colour of the tablets/capsules they give, the type of uniform they wear, the words they use to give the patient information, the kind of room they place a patient in for recovery, etc., may be imbued with rich meaning for the patient and have profound effects for good or for ill on their response to treatment (25). These phenomena illustrate the power of words and careful and judicious counselling is strongly advocated(38).

The emphasis on autonomy in modern medical ethics provides little justification for the use of the placebo effect in its purest form. But the placebo effect should not be relinquished altogether. As we have seen throughout this article, patients are likely to respond better to any medication when the practitioner (doctor, dentist, practice nurse, podiatrist, optometrist or pharmacist) express optimism and confidence in the outcome. A degree of professional optimism is likely to be a large part of the practice of any health professional, but this must be constrained within the bounds of truth, even if this limits treatment effectiveness. (39)

## Scenario

Mary Poppins has a long-standing history of chronic daily headaches. She previously had been treated by numerous doctors and had tried a number of medications; all caused nonspecific side effects and resulted in her continually changing therapy. She also has a history of anxiety and depression.

She is 45 years old, single and is quite thin. She weighs 55 kg and is 172 cm tall (BMI = 18.6 kg/m<sup>2</sup>). She also complains that her antianxiety tablets are not working and her depression is certainly not good. She says to you as she hands you a prescription for Panadeine Forte 2 prn, “I knew I shouldn’t have let that chemist change my tablets last time; they don’t work, they might be cheaper, but they are different and the colours are not right and what’s more, they make me feel sick. I feel nauseous, I get palpitations, I’m constantly sweating, and I am having breathing difficulties as well as diarrhoea. I never had these problems before with my real medicine; nothing works for me, I always get things wrong”.

Current medications :

Panadeine Forte tablets (paracetamol 500 mg/codeine 30 mg) 2 prn  
 Alepam (oxazepam) tablets 15 mg tds (changed from Serepax two weeks ago)  
 Esipram (escitalopram) tablets 10 mg 1 daily (changed from Lexapro two weeks ago).

The brief clinical history provided by Ms Poppins raises the strong possibility that her nonspecific side effects represented are due to the *nocebo* effect, exacerbated by her anxiety state. Most practitioners (health professionals) have encountered patients who seem to have an adverse response to almost every medication prescribed. In such situations, both practitioner and patient come to *expect* an adverse outcome. This may be exacerbated by an anxious patient reading the Consumer Medicines Information (CMI) leaflet.

Typically, the side effects that occur are not commonly associated with the given medication. Even if they are, they may be disproportionately severe. In the *nocebo* response, the expectation is that the clinical outcome consequent to a given therapeutic intervention will be negative. The response is nonspecific and not based on any specific physiological properties of the treatment administered. This may well be the situation with Ms Poppins. The generic escitalopram and the oxazepam tablets are either different colours and/or have different brand names and are in different packages.

Table 2 lists brands, colours and doses of oxazepam and escitalopram tablets available in Australia as at 1/1/11 (40). This table represents just a small fraction of “generics” of differing colours and packaging. Similar situations exist for a wide range of products throughout the pharmaceutical armamentarium.

**Table 2: Brands, colours and doses of oxazepam and escitalopram in the strengths prescribed for Ms Poppins**

	Brand	Strength	Colour	Dose
<b>Oxazepam</b>	Alepam	15 mg	orange	7.5-30 mg tds/qid
	Serepax	15mg	white	
<b>Escitalopram</b>	Esipram	10 mg	white	10-20 mg, maintenance therapy rarely requires > 10 mg daily
	Lexapro	10 mg	white	
	Esitalo	10 mg	white	
	Lexam	10 mg	white	
	Loxellate	10 mg	white	
	Escitalopram CH, TW, TX	10 mg	white	

Due to her depression, she has a negative attitude to life and the *anxiety* caused by the changes in the brands of her medications may well have increased the non-specific side effects as well as the intensity of her headaches.

What is the effect of a history of mood disorders, such as Ms Poppins reported? Mood disorders may have significant impact in eliciting nonspecific side effects.

Depression is associated with a pessimistic and negative perception of self or events (note her negative comments to you). In the context of receiving a new medication, the expectation thus is that the drug is not likely to do anything positive and probably will make matters worse. An anxious person is hypervigilant for harmful dangerous situations and therefore may anticipate harm from medication.

Many anxious patients are excessively concerned with loss of control, and to them a tablet may represent a threat to their sense of control. There is good experimental evidence to support these patterns. Patients who are more anxious or who tend to *somatise* (the expressing of mental events as a body disorder or physical symptom) are more likely to experience nonspecific side effects, often the autonomic concomitants of anxiety itself (eg, tachycardia, dyspnoea, diaphoresis and/or diarrhoea). (41)

Another study found that an enduring tendency to experience psychological symptoms and emotional distress, such as hostility, guilt, low self-esteem, and fear was associated with placebo (read *nocebo*) side effects (42).

More anxious patients confronted with a change of regimen commonly generate anxiety symptoms that they attribute to the medication, i.e., the *nocebo* effect, perhaps especially if they have a tendency toward *somatisation* (43). Headaches are a special case. Patients with intractable chronic headaches typically have experienced many treatment failures and will likely have experienced more than a few “true”/specific side effects over the years. There are many conditioned positive and negative reactions to medications; emblematic of the latter is the phenomenon of medication overuse (44).

Ms Poppins has also reached a stage where she has entered the chronic pain cycle where her expectations of negative outcomes and increased anxiety levels will exacerbate her pain (45).

In dealing with Ms Poppins, we should establish if she has actually been taking her medications. As she is convinced that the substitute brands of the escitalopram and oxazepam are causing her the stated problems, why not let her have the original brands?

Some issues for consideration with respect to medication management for Ms Poppins are shown in Table 3.

### **Table 3: Key points for consideration when dealing with Ms Poppins**

- She is highly anxious.
- She is depressed and hence has a very negative attitude.
- She is totally suspicious of her generic branded and differently coloured products.
- She believes that her antidepressants and her anti-anxiety agents are not working.
- She seems to be displaying generalised symptoms that may be due to the *nocebo* effect.
- She needs a sympathetic ear and appropriate counselling.
- It should be established whether she would be happier going back to her original brands.
- She should be counselled with respect to the use of Panadeine Forte.
- She should be asked if she would be happy for you to talk to her prescriber.

This case illustrates the effects of anxiety and depression perceptions leading to the *nocebo* effect which is exacerbated by the brand changes. It would be important to discuss Ms Poppins' situation with her current doctor.

### **Questions**

In all the following questions, indicate the one incorrect answer or statement

- Drug administration takes place under circumstances characterised by biased expectations and enhanced suggestibility on the part of both the health professional and the patient.
  - \* Drug administration takes place under circumstances characterised by unbiased expectations and enhanced suggestibility on the part of both the health professional and the patient.
  - The reputation of the health professional(s) may influence patients' expectancies and therefore therapeutic outcome.
  - The patient's attitude towards the expected benefit may influence patients' expectancies and therefore therapeutic outcome.
- Treatment mode, and credibility of the treatment may influence patients' expectancies and therefore therapeutic outcome.
  - \* Depressed patients who are merely put on a waiting list for treatment do as well as those given placebos
  - Placebos used for pain management mimic the time course of events of active drugs
  - Touching, attention and caring and other interpersonal communication may account for some of the beneficial effects of the placebo.
- An analysis of 19 clinical trials of antidepressants led to the conclusion that the expectation of improvement, not adjustments in brain chemistry, accounted for 75 percent of the drugs' effectiveness.
  - Administration of drugs may also be followed by harmful effects that are not always related to their mechanism of action.
  - The *nocebo* may be seen as the reverse side of the placebo
  - \* The *nocebo* is another word for placebo



4. a The placebo may be responsible for numerous adverse effects unrelated to the known pharmacology of a given drug  
b The placebo may be influenced by beliefs, attitudes and cultural factors  
c\* The placebo is imaginary  
d The placebo is a relatively new concept
5. Colour of tablets, capsules and/or mixtures  
a may influence the perception of the efficacy of the medicine in the patient's mind  
b such as green may be seen to be more sedating  
c such as red may be seen to be stimulating  
d\* such as blue may be seen to be stimulating
6. Anxiety  
a may exacerbate pain  
b may exacerbate non-specific unwanted effects  
c is often associated with depression  
d\* may be relieved by ignoring it  
e may be increased with a change in regimen
7. Recent studies have found that of non-specific therapies (placebos)  
a 97% of GPs thought that physical complaints can get better by believing in the effectiveness of the therapy  
b\* 97% of patients thought that physical complaints can get better by believing in the effectiveness of the therapy  
c 87% of patients thought that physical complaints can get better by believing in the effectiveness of the therapy  
d both patient and GP groups expressed a high level of support for the use of placebos
8. In a study on the effect of the cost of placebo tablets on pain, it was found that  
a some 85% of those taking the "expensive" tablets reported a reduction in pain  
b some 61% of those taking the "expensive" tablets reported a reduction in pain  
c\* some 61% of those taking the "expensive" tablets reported a reduction in pain  
d price can have a significant effect on efficacy of the placebo
9. In the study where thoracotomised, patients were treated with buprenorphine on request, together with a basal intravenous infusion of normal saline  
a The first group was told nothing about any analgesic effect; this is called natural history.  
b The second group was told that the basal infusion was either a powerful painkiller or a placebo; this classic double-blind administration).  
c The third group was told that the basal infusion was a potent analgesic; this is deceptive administration  
d\* the fourth group was given nothing; this is the control group
10. In the study where thoracotomised, patients were treated with buprenorphine on request, together with a basal intravenous infusion of normal saline  
a The patients who thought their IV contained a powerful pain reliever required 34 percent less of buprenorphine than the patients who weren't told anything about it  
b The patients who thought their IV contained a powerful pain reliever required 16 percent less of buprenorphine than the patients who had been told that the infusion contained a powerful pain reliever OR a placebo  
c The only significant difference among the groups was the set of *verbal instructions* about the basal infusion.  
d\* Each group received varying amounts of buprenorphine

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Published in the *Australian Journal of Pharmacy* 2011 vol 92