The Nocebo Effect

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Most people are familiar with the Placebo Effect (Latin "I will please"). This occurs when an inert or ineffective substance produces a positive benefit. On the average, there is a 20-40% success rate to placebos in everything from depression to asthma to heart disease. The mechanism by which placebos exert such a consistent favorable outcome is not known. Explanations range from "the power of the mind to heal" to "positive expectations" to "the therapeutic doctor-patient relationship."

Lesser known is the Nocebo Effect (Latin "I will harm"). This is the complementary situation where an inert substance produces undesirable side effects. On the average there is also a 20-40% incidence of side effects to such substances, ranging from headaches to infections to arrhythmias.

Table 1 is a list of side effects from two different drugs. They were given as part of a double-blind placebo controlled trial to test a drug to prevent breast cancer in otherwise healthy women without cancer, ages 35 to 75.

Percentage of subjects reporting the following problems

Symptom	Drug A	Drug B	Significance*
Weight gain	40.1	47.1	no
Joint pains	36.3	43.1	no
Feeling bloated	34.2	39.1	no
Night sweats	43.1	28.7	A>B
Hot flashes	41.6	28.7	A>B
Fatigue	27.7	40.8	B>A
Muscle stiffness	29.8	32.6	no
Forgetfulness	30.6	28.7	no
Breast tenderness	23.0	36.6	B>A
Headaches	24.3	29.6	no
Anxiety	22.5	24.9	no
Mood swings	22.4	26.4	no
Increased appetite	19.2	25.1	no
Depression	16.9	21.4	no
Poor concentration	16.9	19.7	no
Irregular periods	21.6	16.1	no
Blurred vision	10.6	22.4	B>A
Vaginal discharge	17.7	10.3	A>B
Abdominal cramps	12.4	13.7	no
Diarrhea	7.8	8.6	no
Cold sweats	9.7	2.9	A>B
Vaginal bleeding	5.0	8.0	no
Weight loss	1.7	4.1	no

- Significant difference at .05 level; i.e., 5% chance that the result is random.

Can you guess which drug is active and which is placebo? Drug A is tamoxifen, which reduces the risk of breast cancer by 50%. Drug B is a placebo without any biological activity.

This study demonstrates several things. Firstly, there are many symptoms that occur commonly in this population. Other studies have shown that up to 73 % of healthy people who were not taking any medications had symptoms of some kind. The most common symptoms were fatigue (39%), difficulty concentrating (26%), drowsiness (23%), headaches (14%), and dizziness (5%).

Secondly, when symptoms occur while taking an identifiable substance, they are attributed to that substance, whether there is any cause-and-effect relationship. It is unlikely that placebos cause fatigue (40.8% of subjects) any more than tamoxifen prevents it (27.7%).

Thirdly, many patients, looking only at the side effects of a medication (36.3% incidence of joint pains), will refuse the drug to avoid the problem rather than view it in relationship to what happens naturally (43.1% with placebo). Such a decision would prevent them getting the benefit of the medicine (50% less breast cancer).

Some patients report "allergies" or side effects to many medications. They may confuse the very symptoms the drug is designed to treat with side effects from the medicine. This is particularly true for medications to treat depression, anxiety, and stress related disorders.

How should a prudent person, when confronting a treatment with possible side effects, make decisions to accept or decline it? The following questions can help.

1 What is the benefit of the treatment? How important is it?
2 Compared to placebo, what is the absolute chance of important side effects? You may choose to risk a 5% chance of something but not a 25% chance.
3 Are the side effects dangerous? Not all side effects are important, particularly the ones that disappear or you can "live with" if they do occur.
4 Is there a way to prevent or treat the side effects so you can reduce your chances of harm?
5 If something does happen while you're taking a treatment with an important benefit, how can you determine it is caused by the treatment and not by the disease it's treating?

<u>No one should take something with a good reason. Neither should you avoid a useful medication without a good reason.</u>

Ref: Barsky AJ, Saintfort R, Rogers MP, Borus JF Nonspecific Medication Side Effects and the Nocebo Phenomenon. JAMA 2002;287:622-627.