THE DARK SIDE OF THE PILLS

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Abstract:
Nocebo is "a harmless substance that when taken by a patient is associated with harmful effects due to negative expectations on the psychological condition of the patient."
Generally, approximately one quarter of patients taking placebo report adverse side effects (this can be assimilated to nocebo effect). Moreover, in a study 19% of healthy volunteers taking placebos spontaneously reported adverse side effects. Nocebo effects, seen as placebo side effects, are relatively high in psychiatric clinical trials.
The main mechanisms involved in nocebo effects are: expectations, prior conditioning, psychological characteristics and situational influences.
Most important anatomical structures hypothetically implicated in nocebo effect are: anterior cingulate cortex, prefrontal cortex, insula, and thalamus. Some neurotransmitters seem to be implicated in nocebo effect: endogenous opioids, cholecistokinine and dopamine.
Much remains to be known about nocebo effects. A better understanding of the neurobiology and psychology of the nocebo and placebo responses is of great importance, as it might have profound implications for basic and clinical research and clinical practice.
***Key words**: nocebo effect, psychiatric research.*

Rezumat:
Nocebo reprezintă :"o substanţă inofensivă care atunci când este administrată unui pacient determină efecte secundare deranjante pe baza expectaţiilor negative produse prin condiţionarea psihologică a pacientului. ". In general, circa un sfert din pacienţii cărora li se administrează placebo prezintă efecte adverse (acest fenomen fiind considerat ca efect nocebo). Mai mult, conform unui studiu, în jur de 19 % din voluntarii sănătoşi cărora li s-a administrat placebo raportează apariţia de efecte secundare. Efectul nocebo, definit ca apariţia de efecte secundare la administrarea de placebo, prezintă de asemenea o dimensiune importantă în psihiatrie.
Principalele mecanisme implicate în apariţia efectului placebo sunt: expectaţiile, condiţionările anterioare, caracteristicile psihologice şi influenţele situaţionale.
Cele mai importante structuri neuranatomice considerate a fi implicate în efectul nocebo sunt: cortexul cingulat anterior, cortexul prefrontal, insula şi talamusul. Neurotransmiţătorii posibil implicaţi în efectul nocebo sunt: opioidele endogene, cholecistokininele şi dopamine.
Efectul nocebo continuă să prezinte foarte multe necunoscute. O înţelegere mai bună a neurobiologiei efectului nocebo dar şi placebo ar putea avea implicaţii profunde pentru cercetarea fundamentală, dar şi în cercetarea şi activitatea clinică practică.
***Cuvinte cheie**: efectul nocebo, cercetare psihiatrică.*

In Latin "nocebo" means "I shall harm" and, according to the Merriam-Webster Online Dictionary (www.merriam-webster.com/dictionary/nocebo), nocebo is "a harmless substance that when taken by a patient is associated with harmful effects due to negative expectations on the psychological condition of the patient". Under a broader definition of nocebo effect usually go the negative consequences on health determined by the belief that a substance or an intervention is harmful. In 1938 W.R. Houston, in his paper "The Doctor Himself as a Therapeutic Agent" discussed the possibility that placebo procedures could become harmful, if not dangerous (1), and in 1961 W. Kennedy described the "nocebo reaction" in terms of a disagreeable response to the implementation of "placebo" intervention (2). From this moment on, the word nocebo became popular as the contrary of placebo. Many documented examples are reported in biomedical literature with reference to the onset of unpleasant symptomatology following the assumption, on the part of the patient, of a chemically inactive substance, considered an active intervention by the patient. After H. Basedow's report in 1925 of "voodoo" deaths (apparently healthy people inexplicably dying after having been hexed) (3), and the impressive confirmation of the same phenomenon by the outstanding physiologist W.B. Cannon in 1942 (4), an investigation of the Framingham Heart Study regarding 45–64 year old female participants, showed that women who believed they were more likely than others to suffer a heart attack were 3.7 times as likely to die of coronary conditions as were women who believed they were less likely to die of such symptoms, independent of commonly recognized risk factors for coronary death (e.g., smoking, systolic blood pressure, and the ratio of total to high-density lipoprotein cholesterol) (5). Since around 25% of patients assuming placebo refer adverse side effects (6), thereby documenting a nocebo phenomenon (if we are defining nocebo effects as placebo side effects). No medical encounter comes in emptiness. Expectations can be formed from information learned from the environment and social interactions, via personal experiences and from anticipation of benefit or harm. External inputs are

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dynamically connected with individual beliefs and internal states, leading to the formation of any response to each medical encounter and procedure. The way information about medical procedures or medications are processed by each individual is a matter of unique idiosyncrasy, results from each individual's general way of handling information, and is the end result of biological, social and cultural make-up of each of us. Physicians should be aware of the ambivalent power of placebos and need to be called upon to prevent and/or limit not only the side effects of active drugs but also those of inert substances and in general of each medical encounter. There are several major reasons for trying to understand nocebo. Understanding nocebo in its broader notion may contribute to clarifying deleterious "side effects" of each medical procedure (being that procedure taking a medication, having a major surgical procedure or simply getting a medical personal history). Although many drugs side effects result directly from these drugs' pharmacological activity, many others cannot be attributed to their specific pharmacological actions.

These nonspecific side effects distress patients, add to the burden of their illness, and increase the costs of their care. They may lead to nonadherence, confuse physicians and lead them to discontinue what is otherwise an appropriate therapy, or prompt attempts to treat these side effects with additional (useless or even harmful) drugs.

The results of clinical trials can be contaminated by nocebo effects (as well as by placebo effects). This can be done by, to say, inflating the dimension of drug side effects only by non-specific causes, which can became a major health issue if these information about side effects are incorporated in drugs' summary of product characteristics which information may further influence the patients' expectations about that drug, expectations which dramatically can modify both positive and negative drugs' actions (usually these kind of biases are being tried to be controlled by various means such double-blind randomization to active drug or placebo and so on, but is beyond the purpose of my article to review and discuss about potential biases of studies or types of designs of studies used in order to minimize potential biases). .

Despite the importance of understanding the dimension and mechanism of nocebo effects it is difficult to do studies to measure nocebo effects, especially in ill population, mainly due to ethical reasons. The result is that in present time there is a paucity of data about nocebo effect.

There is more data in literature concerning placebo response.

Placebo responses are common in clinical trials and practice. In clinical trials, a substantial proportion of patients in placebo control groups experience benefits which may be only apparent, because they are due to confounding factors (natural history, regression to the mean, response biases, co-interventions and so on) (7).

Placebo response is known to be especially elevated in clinical trials of psychiatric medications. In an investigation of placebo response in major depression, the mean percentage of placebo-treated patients who met response criteria was 30%, and the range was 13–52% (8). Observed responses to placebos in randomized controlled trials have been reported to be around a staggering 31% in bipolar mania (9). Such responses to placebo are comparable also in generalized anxiety disorder (10). For depression, the variation in the magnitude of the observed placebo responses depends on year of publication (11), study design (12, 13, 14), baseline severity (15), assessment methods (observer rating versus self-report) (16) and probability to receive a placebo (17). A similar comprehensive review of schizophrenia trials as had been done for depression clinical trials has not been performed; however, among recently published clinical trials conducted in patients with schizophrenia including a placebo arm and reporting response rates (18-25), the mean percentage of placebo responders was 25.0%, with a range of 0–41%. Although this was only a brief analysis, the placebo response rates for schizophrenia appeared to align with those from the depression studies.

I will briefly review in my article the nocebo effect as it appears in some clinical trials from psychiatric field. For doing this I will look into the adverse effects in patients who are allocated to the placebo arm of these randomized placebo controlled studies. Putatively by doing this we can have a glimpse of nocebo effect dimension in patients population. I will use some examples from studies of antidepressant in major depressive disorder and anxiety disorders, of antipsychotics in schizophrenia and bipolar disorder, and of antidementia drugs in Alzheimer disease. These examples are drawn from double blind placebo controlled studies. I will consider the placebo side effects as nocebo effects, while being aware that not all authors are agreeing with this assumption. According to Hahn (26) the "nocebo phenomenon is distinct from placebo side effects. Placebo side effects occur when expectations of healing produce sickness, i.e., a positive expectation has a negative outcome. For example, a rash that occurs following administration of a placebo remedy may be a placebo side effect. Diverse placebo side effects have been documented; one review reports an incidence of 19% in the subjects of pharmacologic studies (27). In the nocebo phenomenon, however, the subject expects sickness to be the outcome, i.e., the expectation is a negative one". Other authors (28) still use the broad definition: "the nocebo phenomenon refers to symptoms and/or physiological changes that follow the administration of an inert, chemically inactive substance that the patient believes to be an active drug", and this is also the definition I will use in my article.

The results of these examples do not represent a comprehensive analysis but a mere glimpse into the dimension of nocebo effects. The selection of the studies has been done after a literature search for relevant study in the above described illnesses, using studies with a proper methodology (double-blind placebo controlled) with a rather large number of people included.

In a study (29) which compare duloxetine (number of patients n=128) with placebo (n=139) for treatment of Major Depressive Disorder (MDD), the percent of side effects in placebo group was: nausea 11.5%, headache 22.3 %, dry mouth 6.5%, rhinitis 21.6%, insomnia 13.7%, dizziness 2.9%, asthenia 7.2 %, constipation 5.0%, anorexia 5.8 %, diarrhea 7.9%, somnolence 6.5%.

In a study (30) comparing sertraline (n=80) with placebo for treatment of panic disorder (n=88) subjects were required to have a minimum of four panic attacks, at least

one of which was unanticipated, during the 4 weeks before day 1 of the placebo lead-in and at least three, but no more than 100, DSM-III-R-defined panic attacks during the 2-week single-blind lead-in phase. The side effects in placebo arm were: nausea 17%, diarrhea 11 %, dry mouth 8 %, ejaculation failure (men) 0 %, decreased libido 0 %.

In a different study (31) which compare venlafaxine (n=166), paroxetine (n=166) and placebo (n=163) the percent of treatment-emergent side effects in placebo group was: sweating 4%, dry mouth 3%, anorexia 4 %, tremor 2%, constipation 1%, diarrhea 3%, somnolence 2%, back pain 2%.

In a study (32) comparing venlafaxine (n=129), escitalopram (n=127) and placebo (n=136) for the treatment of Generalized Anxiety Disorder the percent of adverse events with incidence greater than 10% in placebo arm was: ejaculation disorder (men) 0%, nausea 8.1 %, dry mouth 5.9 %, insomnia 13.2 %, somnolence 7.4 %, headache 15.4 % increased sweating 4.4 %, fatigue 3.7 %, impotence (men) 0 %.

The percent of a*dverse events with an incidence of ≥ 5% during the 24-week study period* of placebo treatment of patients with obsessive-compulsive disorder, according with a study (33) comparing escitalopram (n=227) with placebo (n=114) was: nausea 12.3%. headache 17.5%, fatigue 5.3%, somnolence 5.3%, insomnia 13.2%, ejaculation delayed (men) 0.0%, nasopharyngitis 8.8%, dizziness 6.1%, diarrhea 4.4%, libido decreased 0.9%, anxiety 6.1%, dry mouth 3.5%, hyperhidrosis 1.8%, anorexia 5.3%, constipation 2.6%, abdominal pain upper 7.0%, tremor 1.8%, influenza 6.1%, erectile dysfunction (men) 2.0%.

An important dimension of nocebo effects can be seeing in the study of more severe diseases such as bipolar disorder, schizophrenia, dementia and even Down syndrome.

In a study (34) comparing quetiapine (n=80) with placebo (n=38) in the treatment of patient of bipolar depression (type I and type II) the proportion of placebo side effects was: dry mouth 0%, sedation 7.9 %, dizziness 13.2 %, constipation 2.6 %, fatigue 5.3 %, somnolence 7.9 %, nasal congestion, 2.6 % blurred vision 2.6 %.

In a study (35) for acute mania comparing asenapine (n=185) with placebo (n=98), the proportion of side effects in placebo group was: somnolence 3.1 %, dizziness 2.0 %, sedation 3.1 %, weight increase 0.0 %, vomiting 2.0 %, appetite increase 1.0 %, akathisia 3.1 %, bradykinesia 0.0 %.

The proportion of placebo side-effects in schizophrenia is also quite high. Data presented here are from a pooled analysis (36) of safety and tolerability data from completed short-term, placebo-controlled trials in schizophrenia from the aripiprazole (n=926) clinical development program. The percent of side effects in placebo arm (n=413) is: headache 24.5 %, agitation 34.6 %, anxiety 24.0 %, insomnia 18.6 %, dyspepsia 15.5 %, nausea 9.7 %, vomiting 7.0 %, lightheadedness 6.5 %, somnolence 8.0 %, constipation 7.7 %, akathisia 6.8 %, extrapyramidal syndrome 5.8 %.

The nocebo effects can be observed even in people with severe Alzheimer disease (Mini mental State Examination- MMSE 5–12 points) (37). According to this study the percent of people with severe Alzheimer diseases treated with placebo was: urinary tract infection 22%, vomiting 15%, diarrhoea 19%, nausea 7%, fall 11%, agitation 5%, arthralgia 4%, constipation 5%, aggression 4%, depression 3%, cystitis 2% pyrexia 5%, anorexia 3%, peripheral oedema 2%, bronchitis 8%, headache 7%, cough 6%, hypertension 6%.

In a study (38) comparing donepezil (n=62) with placebo (n=61) in patients with Down syndrome the percent of placebo treated patients is: abdominal pain 4.9 %, asthenia 0 %, headache 4.9 %, sinus bradycardia 0 % , anorexia 0 %, diarrhea 9.8 %, dyspepsia 1.6 %, nausea 0 %, vomiting 1.6 %, agitation 0 %, insomnia 0 %, somnolence 0 %, cough increased 0 % , respiratory tract infection 8.2 %, urinary incontinence 0 %, vaginitis 0 %.

However, data from these studies should be seen with some caution since some adverse effects may be simple various symptoms of different diseases (being that disease a somatic or psychiatric illness) or vague somatic symptoms which appear quite often in normal population.

Obviously the best type of study in order to quantify the dimension of nocebo effects (considered as placebo side-effects) would be a meta-analysis done for each class of medication or disease. At the moment I'm not aware by the existence of such meta-analysis. However, it is quite clear that nocebo effect has an important dimension. The phenomenon of getting side effects on placebo is by no means confined to psychiatry. Approximately one quarter of patients taking placebo report adverse side effects (39, 40). Moreover, placebo side effects do appear in normal populations-volunteers in phase 1 clinical trials. Rosenzweig et al. (41) found that 19% of healthy volunteers taking placebos in 109 double-blind, placebo-controlled trials spontaneously reported adverse side effects.

There are several ways these nonspecific symptoms may arise.

Firstly, the symptoms of the underlying disease for which the patient is being treated may be mistakenly ascribed to the medication. People entering trials have many preexisting, vague somatic symptoms available for attribution to a newly instituted medication.

Second, the symptoms may be the somatic concomitants of emotion (such as anxiety or depression-especially in clinical trials in depression or anxiety disorders). Third, patients may erroneously assign the symptoms of mild infirmities or benign, self-limited ailments (such as headaches or cramps) or of normal physiological functioning (eg, orthostatic dizziness) to the medication. According to Barsky (28) this misattribution is more likely to occur in: "(1) patients who expect to experience side effects; (2) patients who have been previously conditioned to experience side effects; (3) patients who have particular psychological characteristics; and (4) certain circumstances and conditions".

Patients who expect distressing side effects before taking a medication are more likely to develop them.

In a multicenter, placebo-controlled trial of aspirin treatment for unstable angina, the informed consent form at 2 of the participating centers specifically listed "gastrointestinal irritation" as a possible side effect, while the consent form at the third center did not (42). Patients at the former institutions reported a significantly higher incidence of gastrointestinal symptoms, but did not have a higher incidence of confirmed gastrointestinal disease than the patients whose consent forms did not mention these side effects and 6 times as many patients in the former group withdrew from the study because of gastrointestinal distress.

Patients may manifest side effects to a prescribed medication not because of its specific pharmacological actions, but rather because they have experienced side effects to other drugs in the past. This occurs as a result of classical conditioning in which a neutral or inactive stimulus (such as a substance, person, procedure or place) obtains the capacity to elicit a physiological change if it has previously been repeatedly paired with a provocative stimulus (43).This may be one way patients can become conditioned to develop medication side effects.

Several psychological characteristics, including anxiety, depression, and somatization, have been associated with side effects to active drugs and with nocebo symptoms (44).

Side effects reported by people with anxiety disorders are often the somatic concomitants of anxiety itself (eg, tachycardia, dyspnea, sweating and so on) (45). Neuroticism (a generalized and enduring tendency to experience a wide range of psychological symptoms and emotional distress) appears to be associated with the nocebo effect (46).

Finally, again according to Barsky (28) nonspecific side effects reporting is influenced by the context and environment in which the medication is given, and by the physical and symbolic characteristics of the medication itself. Clinical experience and some small studies (47, 48) supports this widespread conviction that situational characteristics (eg, the setting and environment in which medication is prescribed) and interpersonal factors (such as the nature of the patient-physician relationship) influence the incidence and nature of side effects.

A major insight from the recent publications (49) on placebo and nocebo is that there seems not to be a single neurobiological or psychobiological mechanism which is able to explain placebo and nocebo phenomena in general. Instead, it seems that different mechanisms exist by which placebo or nocebo responses are steered across diseases and experimental conditions.

Compared to the placebo effect, much less is known about the nocebo effect, since the induction of a nocebo response represents a stressful and anxiogenic procedure, thus limiting its ethical investigation.

Brain imaging techniques have been crucial to understanding the neurobiology of negative expectations, and most of this research has been performed in the field of pain.

Overall, negative expectations may result in the amplification of pain (50) and several brain regions, like the anterior cingulate cortex (ACC), the prefrontal cortex (PFC), and the insula, have been found to be activated during the anticipation of pain (51, 52).

In another study by Koyama et al. (53), as the magnitude of expected pain grew, activation increased in the thalamus, insula, PFC, and ACC. By contrast, expectations of decreased pain reduced activation of pain-related brain regions, like the primary somatosensory cortex, the insular cortex, and ACC. Likewise, Keltner et al. (52) found that the level of expected pain intensity altered the perceived intensity of pain along with the activation of different brain regions, like the ipsilateral caudal ACC, the head of the caudate, the cerebellum, and the contralateral nucleus cuneiformis (nCF).

Besides neuroimaging, pharmacological studies give us insights into the biochemistry of the nocebo effect and of negative expectations. For example, the antagonist action of cholecistokinine (CCK) on endogenous opioids (54) is particularly interesting in the light of the opposing effects of placebos and nocebos. A model has recently (55) been proposed whereby the opioidergic and the CCK-ergic systems may be activated by opposite expectations of either analgesia or hyperalgesia, respectively. In other words, verbal suggestions of a positive outcome (pain decrease) activate endogenous m-opioid neurotransmission, while suggestions of a negative outcome (pain increase) activate CCK-A and/or CCK-B receptors. This neurochemical view of the placebo-nocebo phenomenon, in which two opposite systems are activated by opposite expectations about pain, is in keeping with the opposite action of opioids and CCK in other studies (55). Interestingly, the CCK-antagonist proglumide has been found to potentiate placebo-induced analgesia, an effect that is probably due to the blockade of the anti-opioid action of CCK (56, 57). Therefore, CCK appears to play a pivotal role in the psychological modulation of pain, antagonizing placebo-induced opioid release on the one hand and mediating nocebo-induced facilitation of pain on the other hand. The involvement of CCK in nocebo hyperalgesia is likely to be mediated by anxiety, as benzodiazepines have been found to block both nocebo-induced hyperalgesia and the typical anxiety-induced hypothalamus-pituitary-adrenal hyperactivity. Conversely, the CCK antagonist, proglumide, has been found to prevent nocebo hyperalgesia but not the hypothalamuspituitary-adrenal hyperactivity, which suggests two independent biochemical pathways activated by nocebo suggestions and anxiety.

More recent studies have found that nocebo effect is also associated with a decrease in dopamine and opioid activity in the nucleus accumbens, thus underscoring the role of the reward and motivational circuits in nocebo effects as well (58) . In other words, the activation/deactivation balance of both dopamine and opioids in the nucleus accumbens would account for the modulation of placebo and nocebo responses.

Therefore, a complex interaction among different neurotransmitters, such as CCK, dopamine, and opioids, occurs when either placebos or nocebos are administered.

A better understanding of the neurobiology and psychology of the placebo and nocebo responses is of great importance, as it might have profound implications for basic and clinical research and clinical practice. In basic research, we can learn more about how psychological processes affect Central Nervous System neurochemistry and how these alterations subsequently shape peripheral physiology and end organ functioning. The growing knowledge on the neurobiology of the placebo/nocebo response will also affect the design of clinical trials in which treatment is tested against a placebo. Finally, concerning clinical practice, if nonspecific side effects occur, it is helpful to discuss with patients the process of symptom misattribution described and to explore whether the patient may have relabeled or misattributed the symptoms of his/ her disease, or the somatic concomitants of emotion or of normal physiology, to the new medication with the goal of improving patients' care by helping the patient to better

understand and tolerate the nonspecific side-effects.

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