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Nocebo effects with antidepressant clinical drug trial placebos

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Abstract

We describe an individual who experienced unusual negative effects while taking a placebo during a clinical drug trial. A 26-year-old male took 29 inert capsules, believing he was overdosing on an antidepressant. Subsequently, he experienced hypotension requiring intravenous fluids to maintain an adequate blood pressure until the true nature of the capsules was revealed. The adverse symptoms then rapidly abated. The nocebo effect (undesirable symptoms following administration of an inert substance that the patient believes to be an active drug) may have significant negative impacts on certain patients. Further research is warranted to better understand this phenomenon.

Keywords: Nocebo; Placebo; Adverse effects

Originally, "placebo" (Latin, "I will please") was used to refer to both pleasant and harmful effects of a treatment believed by the administrator to be inert or innocuous. By the 1980s "nocebo" (Latin, "I will harm") began to appear. This term referred to untoward effects of an inert treatment with many reserving placebo to refer only to positive effects. We describe the case of an individual who required emergency medical intervention after taking an overdose of placebos from a double-blind antidepressant trial. To our knowledge, this is the first report or such a phenomenon.

1. Case report

Mr. A, a 26-year-old male, presented to the receiving clerk of an emergency department stating, "Help me, I took all my pills" and then collapsed. As he fell, he dropped an empty prescription bottle. Assessment and treatment were initiated immediately. Mr. A was conscious but appeared drowsy and lethargic. He related that he had taken all of his medication, which he said was a new experimental drug for depression. The label confirmed that the bottle contained capsules to be taken as part of a clinical trial of an antidepressant medication but did not indicate whether the capsules were the active medication or placebo.

Mr. A was very fearful he would die of the overdose. He had received this bottle the previous day and had impulsively taken all of the remaining 29 capsules. He immediately felt that he had made a mistake and asked his neighbor to take him to the hospital. He denied taking any other medications or drugs.

Mr. A had been depressed for about 2 months after his girlfriend broke up with him because she felt he could not make decisions. Subsequently, he began to feel hopeless. When he saw an advertisement for a clinical trial for a new antidepressant at a large university, he thought it was probably a new breakthrough in depression treatment and decided to enroll. During the first month of the trial, he felt that his mood improved significantly and he had had no problems with the capsules. He had just started his second month in the trial when he took the capsules after an argument with his girlfriend. Mr. A had had one previous episode of depression at 22 years old. He had been treated with amitriptyline but stopped taking it because he found it to induce intolerable sedation and numbness of his body and felt it was "too strong" for him. Medical history was unremarkable. He had never abused alcohol or drugs.

Mr. A was pale and diaphoretic with a blood pressure of 80/40 and heart rate of 110. He was tremulous, and

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respirations were rapid. Examination was otherwise unremarkable. An intravenous line was inserted, blood drawn and infusion of normal saline begun. Acetaminophen and salicylate levels were zero, urine drug screen was negative and other laboratory studies were within normal limits. After receiving 2 L of normal saline, blood pressure rose but again dropped when the infusion was slowed. Over 4 h, he was given approximately 6 L of fluid. He remained lethargic with a blood pressure of 100/62 and heart rate of 106. At this point, a physician from the clinical trial arrived and determined that Mr. A had taken placebos. When informed of this, the patient expressed surprise then almost tearful relief. Within 15 min, he was fully alert, blood pressure was 126/80, heart rate was 80.

Mr. A was admitted to a psychiatric unit. Examination revealed him to be depressed. There was no evidence of psychosis. He had a strong desire for others to care for him, feared being alone, had difficulty making decisions without reassurance and was willing to go to extreme lengths to preserve relationships. He seemed highly suggestible and easily influenced by others. Psychological testing included an Minnesota Multiphase Personality Inventory, version II (MMPI-II) with elevation on the hypochondriasis, depression and conversion hysteria scales. Discharge diagnoses were depressive disorder, not otherwise specified, and dependent personality disorder. Mr. A subsequently did well with treatment with sertraline and psychotherapy.

2. Discussion

Mr. A's hypotension appears to have occurred as a result of the placebo overdose. Although other causes of hypotension cannot be entirely excluded, this would be the most likely explanation in view of his otherwise normal history, physical examination and laboratory studies at the time of presentation, particularly normal blood urea nitrogen (BUN), creatinine, electrolytes and hematocrit, suggesting a normovolemic state. The nature of placebo and nocebo effects are poorly understood, with some researchers feeling they represent positive and negative aspects of the same phenomenon [1], while others believe nocebo effects to be distinct [2]. Nevertheless, the nocebo phenomenon may have significant effects. Tension has been shown to increase in subjects given inert substances and even muscle relaxants if the subjects believed they were stimulants [3]. Paradoxical responses have been demonstrated to bronchoconstrictors and bronchodilators in asthmatic patients who thought they were receiving the opposite medications [4]. Allergic responses and decreases in allergic responses have occurred in subjects given saline injections, apparently related to the subjects' beliefs about what kind of injection they were being given [5]. Nocebo effects may be mild or serious, transient or chronic. "Voodoo death" has been hypothesized to represent an extreme form of the nocebo phenomenon [1,2].

Nocebo/placebo responses appear to have physiological as well as psychological bases. Placebo induced analgesia may be reversed by naloxone [6]. Cortisol has been shown to increase in subjects given inert preparations they believed would increase pain [7]. Activation of dopamine has been shown to occur in the striatum of parkinsonian patients given placebos they thought would improve their motor symptoms [8]. Placebos have even been shown to influence immune responses such as levels of interleukin 2 [9]. Placebo analgesia is associated with decreased activation in pain-sensitive brain regions, including the thalamus, but with increased activity in prefrontal areas [10]. Many cerebral metabolic changes occurring with fluoxetine treatment have also been observed in individuals receiving placebos they believed to be fluoxetine [11]. Leuchter et al. [12] described 51 subjects with major depression enrolled in one of two independent 9-week double-blind, placebo-controlled studies in which either fluoxetine or venlafaxine was the active medication. Serial quantitative electroencephalogram (EEG) recordings were performed during the course of treatment. Placebo responders showed a significant increase in prefrontal cordance (a measure of cerebral perfusion) starting early in treatment, in contrast to medication responders who showed decreased cordance, suggesting that placebo treatment induces changes in brain function that are distinct from those associated with antidepressant medication. Placebo-induced decreases in prefrontal EEG cordance during the placebo lead-in phase of clinical trials have been associated with better response among those later treated with antidepressants [13].

Nocebo effects may occur related to patient expectation, previous conditioning and psychological characteristics and to contextual influences [14]. Patients who expect side effects are more likely to attribute new sensations to their medication. If they have experienced them in the past, patients may manifest side effects later as a result of classical conditioning. Several psychological characteristics including anxiety, depression and somatization have been associated with nocebo symptoms. Nocebo effects are also influenced by the patient's perception of the medication and the context in which it is given. Mr. A had several characteristics which increased his risk of nocebo effects, including expectation of potent effect, previous medication side effects, somatization and his perceptions of the nature of the experimental drug trial.

This issue may be of importance in clinical drug trials because some of the effects of an active drug and its placebo comparator may be due to the nocebo/placebo effect. Approximately one fourth of patients taking placebos report side effects [14]. The response of patients with depression to placebo is especially strong with antidepressant clinical trials consistently showing placebo response rates of 30% to 50%, drug response rates of 45% to 70% and a drug-placebo response difference of 18% to 25% [15]. An analysis of 19,636 subjects participating in antidepressant studies [16] revealed symptom reduction in 40.7% of patients receiving investigational drugs, in 41.7% of those receiving active antidepressant comparators and in 30.9% of those receiving

placebo. A review of 19 antidepressant trials [17] found that placebo groups averaged 1.5 S.D. units of improvement, 75% of the overall progress shown by the drug groups, whose superiority over the placebo group was only 0.5 S.D. Less-than-impressive differences between drug and placebo response in clinical trials is not due to the ineffectiveness of antidepressants but to the degree of placebo response. Thus, double-blind trials must be carefully designed to take these factors into consideration. The question could be raised as to whether individuals with characteristics placing them at risk for placebo/nocebo responses should be excluded from such studies. Loebel et al. [18] demonstrated lower than typically expected placebo response rates of 13.1% in patients with anxiety and 6.7% in depressed patients in one cohort during 1 week of placebo treatment as part of an ongoing clinical trial. They concluded that much lower rates of placebo response than are currently encountered may be possible among rigorously selected patients.

The power of nocebo effects is well recognized theoretically but often ignored in clinical practice. Nocebo effects may be distressing and costly for patients who experience them and deserve greater clinical scrutiny. Future research should focus on identifying the personal characteristics and situational influences that make such side effects more likely to occur and on developing effective clinical strategies to ameliorate them [14].

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