Case Report

Nocebo Responses to Antihypertensive Medications

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A patient was seen in consultation for intolerance to multiple antihypertensive medications. She presented a list of her experiences, which is summarized in the Table. Although the cough she experienced while taking angiotensin-converting enzyme inhibitors was a typical side effect of this drug class and consistent on rechallenge, this was not the case with her other reported medication reactions. When the patient received the same medication labeled in the same way (Calan SR), she had diarrhea on both occasions. When she received the same medication labeled differently (Calan SR or Verelan and Cozaar or Hyzaar), her reactions differed. The patient listed valsartan, propranolol, hydralazine, and indapamide as ineffective, but it was not clarified whether they were tolerated.

The patient was taking one-fourth 100 mg metoprolol twice a day, but experienced headache and heartburn at higher doses, and clonidine 0.1 mg daily, but experienced a localized rash at higher doses. She had been hospitalized on one occasion for hypertension and on another occasion for hypertension and "stress." She was currently taking alprazolam. She summarized her view of antihypertensive medications as "I am scared of them." She added that statins raised her blood pressure, but she was tolerating levothyroxine.

After an explanation for the origin of these nonspecific side effects was provided to the patient, she stated that she did not believe this accounted for her reactions.

DISCUSSION

Physicians and patients are familiar with the placebo effect, an improvement mediated by an inert treatment believed to be beneficial. The less well-known nocebo response is the opposite, a worsening mediated by an inert treatment believed to be harmful. The literature sometimes considers adverse effects in placebo-treated patients as nocebo responses, but the belief that the treatment is harmful should be required. This patient's case provides an excellent example of nocebo responses. Although this phenomenon accounts for a significant fraction of unusual reactions to antihypertensive medications and of hypertension clinic referrals for medication intolerance, the term has not been mentioned in the hypertension literature to the best of our knowledge.

Barsky and coworkers[1] reviewed the relationship between the nocebo phenomenon and nonspecific medication side effects, which they characterize as unexplainable by pharmacology, idiosyncratic, and not dose-dependent. They point out that symptoms (eg, fatigue, difficulty concentrating, drowsiness/somnolence, headache, dizziness, weakness, nausea/gastrointestinal complaints) are common in healthy persons without medications or in placebo recipients in clinical trials of asymptomatic diseases and that these symptoms may be misattributed to a drug. Barsky and associates mention the role of negative expectations and suggestions, conditioning,

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Table. List of Adverse Drug Experiences in This Case

Class	Drug	Adverse Effect
ACE inhibitor	Enalapril/HCTZ	Cough
	Lisinopril	Cough, heartburn
	Lisinopril/HCTZ	Cough
	Quinapril	Cough
Aldosterone blocker	Spironolactone	Diarrhea
α-Blocker	Doxazosin	Head hurt, nervous
	Prazosin	Felt bad
	Terazosin	Blurry, very dry eyes
α/β-Blocker	Labetalol	Head, neck hurt
ARB	Candesartan	Head, neck, chest, back hurt
	Irbesartan	Bad heartburn
	Losartan	Heartburn
	Losartan/HCTZ	Constipated, felt horrible
	Olmesartan	Heartburn
	Telmisartan	Head, backache
β-Blocker	Atenolol	Diarrhea
	Betaxalol	Red, sore gums
	Metoprolol	Head hurt, heartburn
	Penbutolol	Really tired, eyes watered
Calcium channel blocker	Amlodipine	Stomach hurt, heartburn
	Diltiazem	Eyes watered
	Isradipine	Head, neck, chest, back hurt
	Nisoldipine	Neck, chest, back hurt
	Verapamil (brand 1)	Diarrhea
	Verapamil (brand 2)	Shoulders, back, neck hurt
Central α agonist	Clonidine (oral)	Rash
	Methyldopa	Head, ears felt like bursting
Diuretic	HCTZ/triamterene	Stomach hurt, diarrhea
Renin inhibitor	Aliskiren	Felt horrible

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HCTZ, hydrochlorothiazide.

and underlying psychological characteristics (anxiety, depression, and somatization) as important factors in producing nonspecific side effects.

The impact of psychiatric comorbidity on hypertension management was recently reviewed in this journal.[2] Misattribution of the symptoms of anxiety to medication adverse effects and reluctance to start medications viewed as potentially toxic were mentioned. A large study analyzing medication intolerance in a hypertension clinic found that about half of the episodes of intolerance due to symptoms were judged to be nonspecific.[3] These were associated with panic attacks, anxiety, and depression, whereas specific intolerances were not.

Although psychiatric comorbidity is strongly associated with nocebo responses, negative expectation and suggestion produce nocebo responses in volunteers and medical patients. Flaten and colleagues[4] gave a muscle relaxant and placebo to healthy volunteers, telling some they were getting a stimulant, others a relaxant, and others no information. Suggestion that participants were getting a stimulant increased reported tension. Silvestri and associates[5] reported that patients with hypertension who received atenolol had more erectile dysfunction if they were told that erectile dysfunction could occur but was uncommon than if they were not even told the name of the medication. Patients told only the name of the medication had an intermediate frequency of erectile dysfunction. Patients reporting erectile dysfunction were treated with sildenafil and placebo in a crossover study and described equivalent efficacy with the exception of one patient.

Negative expectations appear capable of producing a wide range of effects. Reeves and colleagues[6] describe a patient in a placebo-controlled, blinded antidepressant drug trial who overdosed on 29 placebo capsules believing that they contained a new experimental drug; hypotension developed that required intravenous fluids. When told he had taken a placebo, this abated. Benson[7] discusses

voodoo death, sudden death, and surgical mortality as responses to negative expectations. Hahn[8] mentions heart attacks and cardiovascular mortality, epidemic hysteria (globus/cough/laryngismus, abnormal movements, fainting, nausea, abdominal malaise, and headaches), asthma attacks, psychogenic seizures, and allergic reactions as responses to negative expectations.

The patient described here illustrates many of the issues relating to nocebo responses in patients with hypertension. Patients may exhibit typical adverse reactions combined with their nocebo responses. Patients may tolerate medications for other conditions or some antihypertensive medications, but at low doses. They may respond differently to the same medicine when labeled differently. This may contribute to reports of adverse responses specific to generic drugs. Many patients do not remain on a drug producing symptoms long enough to evaluate efficacy, but a lack of blood pressure lowering, and especially an increase in blood pressure, may reflect a response to the symptoms, rather than a lack of efficacy. This patient's increased blood pressure on statin therapy is an example.

Although recognizing nocebo responses is not difficult, especially by the time a patient is referred to a specialist for nonspecific reactions to multiple medications, the most effective approach to caring for these patients remains to be defined. Barsky and coworkers[1] suggest providing an explanation of the side effects and helping patients reattribute them to the patients' disease(s) or emotions or normal physiology. However, many patients with nocebo responses are not simply attributing preexisting symptoms or new coincidental symptoms to their medication. Often, patients acknowledge that the nocebo response may be a reasonable explanation of reactions in other patients, but not in them. Barsky and associates also suggest using collaborative strategies for prescribing; some of these patients are willing to experiment with low doses of well-tolerated medications, especially if this approach has not previously been explored. Emphasizing the importance of lifestyle changes is especially important. Further research on recognizing and managing nocebo responses is important, as they may be an important contributor to suboptimal blood pressure control.

References

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