



The impact of framed side effect information on nocebo effect

Ioanna Belesioti¹, Victoria Alikari², Foteini Tzavella³, Sofia Zyga⁴, Maria Tsironi⁵, Paraskevi Theofilou⁶

¹ Department of Psychology, University of Central Lancashire, Preston, United Kingdom

² Department on Nursing, University of West Attica, Athens, Greece

³⁻⁵ Department on Nursing, University of Peloponnese, Tripolis, Greece

⁶ Ministry of Health, Aristotelous 17, Athens, Greece College of Humanistic Sciences, Filikon 56a Str, Athens, Greece

Abstract

This study examined the impact of framed side effect information on nocebo effect and anxiety levels. In this randomized, controlled study design participants (N=180) healthy volunteers completed a short demographic survey, the Q-No Questionnaire, and the Beck Anxiety Inventory. Participants were randomized to read a positive Patient Information Leaflet (PIL) or standard PIL or none PIL of analgesic. After reading the PIL, participants completed for second time the Beck Anxiety Inventory. Side effects of analgesic were assessed a month later through the report of symptoms in a diary. More participants who read the standard PIL reported symptoms (N=28, 47.5%) compared to participants who read the positive PIL (N=23, 38.3%). Moreover, participants with higher scores in Q-No (nocebo) were more likely to experience symptoms than those with lower scores (No Nocebo) (OR = 7.47, 95% CI: 3.78-14.79). There is a difference in the increase of anxiety levels in participants with high scores in Q-No between the three groups. The highest average increase of anxiety was in the standard framed group (6.00±4.27), while the positive framed follows (5.13± 3.42) and finally the control group (3.20±2.74). Results indicate that positive framed PIL reduced the likelihood of participants to attribute side effects to the treatment. Further research is needed in a patient population and in preventive treatment.

Keywords: nocebo, framing, side effects, expectations, patient information leaflet

Introduction

Nocebo effects include non-specific subjective complains such as fatigue, headache or dizziness, new or worsening pain, and any other harmful or unpleasant symptoms [1], which occur due to the patient's negative anticipation and usually lead to medication non-adherence and poor outcomes [2].

Research has demonstrated that many factors contribute to nocebo effect. Recently, a systematic review has revealed that women are more sensitive to nocebo [3] and mental disorder comorbidity also increases susceptibility to nocebo [4-6]. Moreover, personality traits have been associated with a higher likelihood of NEs, such as high levels of anxiety and somatization, which can impede the patient-physician interaction and increase pain perception [7]. Negative expectation is, also, a significant underlying mechanism that conduces to nocebo effects [8]. Symptoms are more likely to occur when physician warn patients of the possibility that they might experience a particular side effect or set of side effects [9]. Although it is considered unethical and unsafe for a doctor, according to the principles of respect for patient autonomy, to not provide information about potential AEs [10], the change of the way such information is provided to patients seems to determine the NEs [11]. Research has demonstrated that a Patient Information Leaflet (P.I.L.) may enhance the nocebo effect by the way the side effects framed. [12] Positively framing of the side effects, such as the number of people who will not be affected, causes lower expectations of side effects than negatively framing risk such as people who will be affected [13]. Studies showed that the focus on positive outcomes can lead to more positive

treatment expectations. [14] Although positive side effect information framing can decrease side effect symptoms compared with negative framing, medication side effect information is introduced with a negative focus because is usually represented as the percentage of patients who are likely to experience unpleasant side effects [15] rather than the percentage of patients who will remain free from side effects. [13] Therefore, positive framing of side effect information offers the potential to form positive treatment expectations that could reduce nocebo effects, while presenting statistically equivalent information about the likelihood of side effects. [16]

Few studies the last decades refer to the influence of framing on nocebo effects. Researchers [17] found a significant decrease in side effects following an influenza vaccination when using positive framing side effect risks. Others [18] found that a positive framing reduced the likelihood of participants to experience symptoms which they attribute to an inert treatment. Recently, a study [19] notice that in participants given an anti-hypertensive drug, positive framing of the side effect of dizziness using the words "a sign that the drug had started to work" decreased the perceived threat related with treatment side effects. However, the positive framing did not have an effect on the number or intensity of the side effects. Positive framing reduce side effects short term but the impact cannot be maintained over time [16]. In contrast, according to other studies [20] framing has no influence on side effects on the experience of headaches. Researchers told to the participants that the headaches are 70% likely or 30% unlikely to occur following sham transcranial direct current

stimulation. The last study is not similar to previous studies because it investigates different types of treatment and different framed and assessed side effects.

However, none of the empirical research conducted to date on framing and symptom experience has included a no-framed PIL control group condition to assess the symptoms that are caused by framed information versus those that would have occurred anyway because of the negative expectations.

The purpose of this study was to examine how the use of framed side effect information influences the nocebo effect and anxiety levels. This understanding will assist health providers to increase awareness and competence in their prevention, identification, and management of nocebo effects.

Materials and methods

Design

A randomized controlled research design was used. Healthy volunteers were recruited in the study through adverts on web. The adverts presented an outline of the study and a researcher's email address to contact for further information. Participants who interested in the study received an email with an information sheet and a screening questionnaire. The criteria for selecting the sample were the following: age ≥ 18 , speak fluently the Greek language, suffering from headache at least once per month and need to take analgesics to stop the pain. Participants with chronic or acute diseases, with psychiatric disorders and those who were taken any preventive or acute pharmaceutical treatment were excluded. Participants who met up with inclusion criteria arranged an appointment with the researchers to participate.

Participants were randomly assigned to one of three groups: participants who read a positively framed side effect information on analgesic (Positive Frame Group, N=60), those who read a standard framed side effect information (Standard Frame Group, N=59) as used in current practice and those who didn't read a framed side effect information (Control Group, N=61). Based on the demographic and medical history of the participants, a stratification test was performed to ensure that three groups were equivalent in terms of their characteristics. The three groups of the study were treated identically in all respects except for the intervention and for this reason participants and investigators were blinded to which group an individual is assigned. The only difference between the two leaflets was the part with possible side effects. The standard worded PIL reported side effect risk according to the current guidelines such as "12 out of 100 people will experience nausea." The intervention PIL reported positive framing to side effect risks, presenting the number of people who would not experience symptoms such as "88 out of 100 people will not experience nausea.

Phase I

After the classification of the participants into one of the three groups, the following questionnaires were followed (in this phase participants were given all of the questionnaires):

Q-No. This is a self-reporting questionnaire that scans participants for potential nocebo response. The questionnaire consists of 4 items with a Likert scale ranging from 1 (never) to 5 (always) and raw scores ranging from 4 to 20. The scores are classified as No Nocebo (<15) and

nocebo (≥ 15). The participants answer the questions "I read the summary of product characteristics (SPC) before taking a medication", "I have discontinued a medication because of adverse effects in the past", "I ask my physician for potential adverse effects of the medication he/she gives me" and "I take into account the adverse effects reported in the summary of product characteristics seriously. The Cronbach's alpha coefficient was 0.627 indicating acceptable internal consistency among the Q-No items. By using a cut-off at score 15, the Q-No predicts nocebo with 71.7% specificity, 67.5% sensitivity.^[6]

Beck Anxiety Inventory (BAI): This is a 21-question self-report inventory with a Likert scale ranging from 0 (not at all) to 3 (severely) and raw scores ranging from 0 to 63. Higher total scores indicate more severe anxiety symptoms. It is used in order to measure the severity of anxiety during the past week. It was developed in 1988 by Aaron Beck and a revised manual was published in 1993.^[21] The BAI discriminated anxious diagnostic groups such as panic disorder, generalized anxiety disorder, etc, from non-anxious diagnostic groups such as major depression, dysthymic disorder, etc. It takes 5 to 10 minutes to complete. The BAI scores are classified as normal to minimal anxiety (0 to 7), mild to moderate anxiety (8 to 15), moderate to severe anxiety (16 to 25), and severe anxiety (30 to 63). The instructions for the BAI are written at an 8.3-grade level, so oral instructions should be given to persons with lower reading skills (Beck, Epstein, Brown, Steer, 1988). The BAI showed high internal consistency ($\alpha = 0.92$) and test-retest reliability over 1 week, $r(81) = 0.75$.

Demographic data (age, gender, educational level) were, also, recorded.

Phase II

Immediately after the completion of the questionnaires, all participants were told to imagine that they were suffering from severe headaches, that they were at home and decided to go to the pharmacy to buy a well-known analgesic (same for all the participants). The researchers suggested to the participants to imagine that when they went home after the pharmacy, opened the medication and read the patient information leaflet. The researchers gave the PILs printed on an A4 sheet which was sealed in an opaque envelope. The envelopes were sealed by a research assistant and the researcher was blind to experimental conditions. Participants read the PILs and completed for second time the Beck Anxiety Inventory. After that, the researchers gave to the participants a diary for one month and suggested to the participants to record the days with headache, the intensity of the pain, if they took analgesic, what symptoms they had after the medication, if symptoms attributed to the analgesic and how long symptoms lasted.

Phase III

Participants returned one month later to give the completed diary to the researchers. In total, 180 participants completed the one-month follow-up.

Ethics

At the initial session participants were informed about the purpose of the study in accordance with ethical guidelines, that their participation is voluntary, the data will be kept

confidential. Then, they were asked to provide written informed consent. The researchers provided an opportunity for the participants to express questions and to withdraw their data if they wished. No one of the participants expressed any concern or chose to withdraw.

Statistical Analysis

Frequency tables to present the results for categorical variables were used. Continuous variables were presented the mean value, the standard deviation (SD), the range (Min, Max), and the median. The Chi-Square test of independence was used for comparison between categorical variables. The dependent t-test (paired samples t-test) was used to determine whether there is statistical evidence that the mean difference between paired observations on a particular outcome (2 measurements of BAI) is significantly different from zero significant. Furthermore, One Way ANOVA method was used for comparison between continuous and categorical variables (with more than 2 levels). All comparisons were two-sided and the significance level was set to $\alpha=0.05$ or 5%. For the statistical analysis we use the statistical software SPSS v20.

Results

The sample comprised 180 participants. The Q-No had a mean score of 10.75 (SD = 5.69). The participants who scored ≥ 15 (Nocebo) in Q-No were 66 (36.7%) while the

participants who scored < 15 (Non-Nocebo) were 114 (63.3%). Moreover, most participants had no symptoms (N = 102, 56.7%) after a month follow-up, while the mean number of symptoms was 0.97 (SD = 1.32). Finally, the scale of anxiety at the first measurement had an average score of 16.59 (SD = 8.55), while in the second measurement we see that it increased to 19.01 (s = 8.19) Tables 1 and 2).

Table 1: Baseline characteristics of the sample (qualitative) (N=180).

Gender	N	%
Male	40	22.2%
Female	140	77.8%
Education		
Primary school	19	10.6%
Secondary school	72	40.0%
Higher education	89	49.4%
Group		
Control Frame Group	61	33.9%
Positive Frame Group	60	33.3%
Standard Frame Group	59	32.8%
Nocebo		
Yes (≥ 15)	66	36.7%
No (< 15)	114	63.3%
Referred Symptoms		
Yes	78	43.3%
No	102	56.7%

Table 2: Baseline Characteristics of the sample (quantitative) (N=180).

Variable	Range (Min-Max)	Median	Mean \pm SD
Age	16-71	40.00	41.49 \pm 11.60
Q-No Score	4-20	10.00	10.75 \pm 5.69
Number of symptoms	0-5	0.00	0.97 \pm 1.32
Beck Anxiety Inventory (BAI) Score			
Measurement 1	1-40	16.50	16.59 \pm 8.55
Measurement 2	1-40	19.00	19.01 \pm 8.19

The results showed that twenty-eight (47.5%) participants, who received the standard framed PIL, experienced symptoms that they attributed to analgesic, compared to 23 (38.3%) participants in the positive framed group. There was no statistically significant difference in the percentage of participants who experienced symptoms between control

group (44.3%) and positive framed group (38.3%), ($\chi^2 = 0.228$, $df = 1$, p -value = 0.63). Moreover, there was no statistically significant difference in symptoms when comparing the two leaflet groups, ($\chi^2 = 0.673$, $df = 1$, p -value = 0.41) (Table 3).

Table 3: The difference in Symptoms Reporting between the two leaflets and control groups.

Groups	Symptoms		OR (95%)
	Did not experience	Experience	
Standard	31 (52.5%)	28 (47.5%)	1.14 (0.55-2.33)
Control	34 (55.7%)	27 (44.3%)	$z=0.35$, $p=0.73$
$\chi^2=0.028$, $df=1$ p value=0.87			
Positive	37 (61.7%)	23 (38.3%)	0.78 (0.38-1.62)
Control	34 (55.7%)	27 (44.3%)	$z=0.66$, $p=0.51$
$\chi^2=0.228$, $df=1$, p value=0.63			
Standard	31 (52.5%)	28 (47.5%)	1.45 (0.71-3.01)
Positive	37 (55.7%)	23 (44.3%)	$z=1.00$, $p=0.32$

There was a statistically significant difference between the scores in the Q-No questionnaire and the occurrence of the symptoms. In the overall sample, there was a statistically significant difference in the percentage of participants who experienced symptoms between those who scored higher in Q-No (72.7%) and those who scored lower (26.3%), $\chi^2 =$

$s36.667$, $df = 1$, p -value <0.001 . In other words, people with higher scores in Q-No (nocebo) are more likely to experience symptoms than those with lower scores (no nocebo) (OR = 7.47, 95% CI: 3.78-14.79). Detailed results are shown in Table 4 (Table 4).

Table 4: The difference in Symptoms reporting between the participants with high rates in Q-No (nocebo) and those with low rates (Non-Nocebo) in three conditions.

Symptoms			
Standard Group			
	No	Yes	OR (95%)
Nocebo	7 (29.2%)	17 (70.8%)	5.30 (1.71-16.45)
Non-Nocebo	24 (68.6%)	11 (31.4%)	$z=2.88, p=0.004$
$\chi^2=8.866, df=1, p \text{ value}=0.003$			
Positive Group			
	No	Yes	OR (95%)
Nocebo	3 (17.6%)	14 (82.4%)	17.63 (4.14-74.96)
Non-Nocebo	34 (79.1%)	9 (20.9%)	$z=3.89, p<0.0001$
$\chi^2=19.445, df=1, p \text{ value}<0.001$			
Control Group			
	No	Yes	OR (95%)
Nocebo	8 (32.0%)	17 (68.0%)	5.53 (1.82-16.81)
Non-Nocebo	26 (72.2%)	10 (27.8%)	$z=3.01, p=0.003$
$\chi^2=9.675, df=1, p \text{ value}=0.002$			
Total Sample			
	No	Yes	OR (95%)
Nocebo	18 (27.3%)	48 (72.7%)	7.47 (3.78-14.79)
Non-Nocebo	84 (73.7%)	30 (26.3%)	$z=5.77, p<0.0001$
$\chi^2=36.667, df=1, p \text{ value}<0.001$			

We used the t-test for dependent samples in order to investigate if the participants who scored higher in Q-No (>15), showed higher levels of anxiety after the intervention with leaflets. It was observed that the mean anxiety score in

the first measurement in participants with higher score in Q-No was 16.55 (SD=9.10), whereas in the second measurement was 21.17 (SD=8.09). This difference was statistically significant ($t=10.51, df=65, p<0.001$). This finding indicates that people with high rates in Q-No have an increase in anxiety level after reading the side effects leaflet (Table 5).

Table 5: The difference in anxiety levels before and after the intervention with leaflets in participants with high scores in Q-No.

Beck Anxiety Inventory	N	Mean± SD	Paired t-test
Measurement 1	66	16.55±9.10	$t=10.51, df=65, p<0.001$
Measurement 2	66	21.17±8.09	
SD: Standard Deviation			

It was also found that the effect of the group is overall significant ($F(2, 63) = 3.78, p = 0.028$). This means that there is a difference in the increase of anxiety levels in participants with high scores in Q-no between the 3 groups. The highest average increase was in the standard framed group (6.00 ± 4.27), while the second group was the positive framed (5.13 ± 3.42) and finally the control group (3.20 ± 2.74). According to the post-hoc tests (Bonferonni), the only statistically significant difference ($p = 0.035$) exists only between the control and standard groups, where the standard group compared with the control group had a higher average increase in anxiety (Table 6).

Table 6: Mean of increased anxiety levels in participants with high scores in Q-no between the 3 groups.

Group	N	Increase	Stable	Decrease	Mean ± SD	ANOVA
Positive	24	20	4	0	5.15±3.42	$F(2,63) = 3.78, p=0.028$
Standard	17	14	3	0	6.00±4.27	
Control	25	19	5	1	3.20±2.74	
SD: Standard Deviation						

Discussion

The results of this study show that positive framed PIL reduces the likelihood of participants occurring symptoms. The participants who read the standard framed PIL were more likely to attribute symptoms to the analgesic than participants who read the positive framed PIL. The findings are similar to other studies [16,17,18], which noticed that positive framing can decrease the experience of symptoms as medication side effects.

The results showed that the participants who scored higher in the Q-No (nocebo) were more likely to experience symptoms in comparison with those who scored lower (no nocebo). The questions in Q-No assess the expectancies and the behaviors of the participants on medication which have been formed by past experiences and revealed a nocebo effect. Moreover, between the participants who had higher scores in Q-No, those who read the standard PIL were more likely to experience symptoms in comparison with the participants who read the positive framed PIL. It has been known that negative expectancies of a medication can decrease its efficacy and that is a nocebo effect [21-23]. The patient information leaflet is an important way to provide information about medication to the patients but also it shapes the expectancies and as a result the effectiveness of the treatment. Every painkiller includes both a pharmacological and a psychological (placebo) part [21]. This psychological part can be affected by using positive instructions to create positive expectations or negative

instructions and no instructions to create negative expectations. As a result the negative expectations could reduce the treatment effectiveness [2,21,25].

In our study the results showed that anxiety levels were negatively affected when the participants read the standard framed PIL in comparison with positive framed PIL and control group. Unfortunately, we don't have a psychological theory to explain how expectancies are related to the intense of pain. Some researchers suggested that anxiety mechanism has an important role [26]. The medication decreases the anticipatory anxiety because patients believe that they can control the pain problem. As a result, they give more attention to improvement of pain and interpret ambiguous events positively [27]. Moreover, studies showed that negative information about treatment may increase anxiety and pain [28-30]. Negative information may lead to give attention to impairment of pain and interpret ambiguous events negatively. This may also lead to behaviors such as avoidance and anxiety. The negative framed PIL promote negative emotions such as anxiety resulting a decrease of the analgesic effect of the treatment. [9] When participants maintain in the negative thought that their pain will increase, anticipatory anxiety about the pain also increases. This triggers the activation of cholecystokinin that make easier pain transmission [7].

The current study has a number of strengths and limitations. In our study both researcher and participants were blind to the experimental condition. Also, the study conducted in

conditions of daily life and the sample was representative of the general public because we had participants of all the levels of educations and mean age of 40. Moreover, the follow up was after one month and all the participants had a diary to record any changes and behaviors. The limitation with that was that during this period the participants may misattribute unrelated symptoms to the painkiller after framing manipulation or maybe the impact of framing decreased after a long period of time and the participants forgot the information.

Research findings suggest how to enhance placebo and avoid nocebo effects. Patient-centered communication is a good strategy to decrease nocebo effect in clinical practice. In patient-centered communication the health care providers empower patients and make them feel autonomous. In that strategy the patient has a role in medication treatment. Research indicates that shared decision-making induced the way patients consider treatment decisions and may have an impact on outcomes.^[31]

Moreover, physicians must explore any pre-existing experiences and attitudes in treatments and they must educate patients on the existence of the nocebo effect. An important role in the management of nocebo effects is the education of patients about the nocebo response and guidance to reevaluation of side effects of treatment.

It is important for physicians to inform the patient thoroughly, provide the information of medication with verbal suggestion and not to leave patients to take information only from the PIL.^[32] The current study suggests to physicians to explain the mechanisms of action of the treatment without overemphasizing the side effects and provide positive framed information about the side effects, while they comply with the legal and ethical commitment to inform the patient.

Conclusions

Further research is needed in the diagnosis and management of the nocebo effect in clinical practice. Research, also, is required to explore how the words in package information leaflets can reduce anxiety levels and negative expectations and increase the positive expectations of the medication. Moreover further research is needed in a patient population and in preventive treatment.

References

1. Planès S, Villier C, Mallaret M. The nocebo effect of drugs. *Pharmacol Res Perspect*. 2016; 4(2):e00208.
2. Benedetti F, Lanotte M, Lopiano L, Colloca L. When words are painful: unraveling the mechanisms of the nocebo effect. *Neuroscience*. 2007; 147(2):260-271.
3. Vambheim SM, Flaten MA. A systematic review of sex differences in the placebo and the nocebo effect. *Journal Pain Res*. 2017; 10:1831-1839.
4. Dodd S, Schacht A, Kelin K, Duenas H, Reed VA, Williams LJ, *et al*. Nocebo effects in the treatment of major depression: results from an individual study participant-level meta-analysis of the placebo arm of duloxetine clinical trials. *J Clin Psychiatry*. 2015; 76(6):702-11.
5. Rojas-Mirquez JC, Rodriguez-Zuniga MJ, Bonilla-Escobar FJ, Garcia-Perdomo HA, Petkov M, Becerra L, *et al*. Nocebo effect in randomized clinical trials of antidepressants in children and adolescents: systematic review and meta-analysis. *Front Behav Neurosci*. 2014; 8:375.
6. Mitsikostas DD, Deligianni CI. Q-No: a questionnaire to predict nocebo in outpatients seeking neurological consultation. *Neurological Sci*. 2015; 36(3):379-381.
7. Colloca L, Benedetti F. Nocebo hyperalgesia: how anxiety is turned into pain. *Curr Opin Anaesthesiol*. 2007; 20(5):435-439.
8. Webster RK, Weinman J, Rubin GJ. A systematic review of factors that contribute to nocebo effects. *Health Psychol*. 2016; 35(12):1334-1355.
9. Colagiuri B, McGuinness K, Boakes RA, Butow PN. Warning about side effects can increase their occurrence: an experimental model using placebo treatment for sleep difficulty. *J Psychopharmacol*. 2012; 26(12):1540-1547.
10. Colloca L. Informed consent: hints from placebo and nocebo research. *Am J Bioeth*. 2015; 15(10):17-19.
11. Wells RE, Kaptchuk TJ. To tell the truth, the whole truth, may do patients harm: the problem of the nocebo effect for informed consent. *American J Bioeth*. 2012; 12(3):22-29.
12. Webster RK, Weinman J, Rubin GJ. Positively framed risk information in patient information leaflets reduces side effect reporting: a double-blind randomized controlled trial. *Ann Behav Med*. 2018; 52(11):920-929.
13. Peters E, Hart PS, Fraenkel L. Informing patients: the influence of numeracy, framing, and format of side effect information on risk perceptions. *Med Decis Making*. 2011; 31(3):432-436.
14. Bigman CA, Cappella JN, Hornik RC. Effective or ineffective: attribute framing and the human papillomavirus (HPV) vaccine. *Patients Educ Counsel*. 2010; 81:S70-S76.
15. Tan K, Petrie KJ, Faasse K, Bolland MJ, Grey A. Unhelpful information about adverse drug reactions. *BMJ*. 2014; 349:g5019.
16. Faasse K, Parkes B, Kearney J, Petrie KJ. The influence of social modeling, gender, and empathy on treatment side effects. *Ann Behav Med*. 2018; 52:560-570.
17. O'Connor AM, Pennie RA, Dales RE. Framing effects on expectations, decisions, and side effects experienced: the case of influenza immunization. *J Clin Epidemiol*. 1996; 49(11):1271-1276.
18. Wilhelm M, Rief W, Doering BK. Decreasing the burden of side effects through positive message framing: an experimental proof-of-concept study. *Int J Behav Med*. 2018; 25(4):381-389.
19. Caplandies FC, Colagiuri B, Helfer SG, Geers AL. Effect type but not attribute framing alters nocebo headaches in an experimental paradigm. *Psychology of Consciousness: Theory, Research and Practice*. 2017; 4(3):259-273.
20. Beck AT, Clark DA. Anxiety and depression: An information processing perspective, *Anxiety Research*. 1988; 1:123-36.
21. Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, Rainero I. Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *J Neurosci*. 2003; 23(10):4315-4323.
22. Klinger R, Flor H. Clinical and ethical implications of placebo effects: enhancing patients' benefits from pain treatment. *Handb Exp Pharmacol*. 2014; 225:217-235.

23. Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. *Annu Rev Psychol.* 2008; 59:565–590.
24. Colloca L, Finniss D. Nocebo effects, patient-clinician communication, and therapeutic outcomes. *JAMA.* 2012; 307(6):567–568.
25. Bingel U, Wanigasekera V, Wiech K, Mhuirheartaigh RN, Leem MC, Ploner MM, *et al.* The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanyl. *Sci Transl Med.* 2011; 3(70):70ra14.
26. Peiris N, Blasini M, Wright T, Colloca L. The Placebo phenomenon: a narrow focus on psychological models. *Perspect Biol Med.* 2018; 61(3):388-400.
27. Benedetti F. Placebo and the new physiology of the doctor-patient relationship. *Physiol Rev.* 2013; 93(3):1207-46.
28. Colloca L, Grillon C. Understanding placebo and nocebo responses for pain management. *Curr Pain Headache Rep.* 2014; 18(6):419.
29. Horing B, Weimer K, Muth ER, Enck P. Prediction of placebo responses: a systematic review of the literature. *Front Psychol.* 2014; 5:1079.
30. Weimer K, Colloca L, Enck P. Placebo effects in psychiatry: mediators and moderators. *Lancet Psychiatry.* 2015; 2(3):246–257.
31. Hughes TM, Merath K, Chen Q, Sun S, Palmer E, Idrees JJ *et al.* Association of shared decision-making on patient-reported health outcomes and healthcare utilization. *Am J Surgery.* 2018; 216(1):7-12.
32. Légaré F, Witteman HO. Shared decision making: examining key elements and barriers to adoption into routine clinical practice. *Health Aff.* 2013; 32(2):276-84.